INFLUENCE OF ISOSTERIC REPLACEMENTS UPON BIOLOGICAL ACTIVITY

by

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PART 1

INTRODUCTION

To the synthetic organic chemist interested in medicinal chemistry, every physiologically active compound of known structure is a challenge - a challenge either to better it, or perhaps merely to equal it. For it must be remembered that even the most innocuous drug is not tolerated by some people.

There are numerous ways of attacking such a problem, and this audience is certainly familiar with them. One of the methods which has been used frequently, very often with success, is that of isosteric replacement. The examples of this type of replacement in the literature are very numerous, and the fruitful results in the fields of sulfonamides, antimetabolites, and antihistamines are well known.

The concept of isosterism, first introduced by Langmuir,[13] has been changed over the years by the work of many others. It will be the object of this paper to survey the history of isosterism, to classify the varieties of isosteric replacements which are recorded in the literature, and to note the influence of these replacements on the biological activity of compounds. We shall then be able to see if any general relationships apply, and what conclusions may be drawn from such data.

PART 2

THEORETICAL

Langmuir in 1919[13] pointed out the remarkably similar physical properties of carbon dioxide and nitrous oxide. He deduced from the octet theory that the number and arrangement of electrons in these molecules are the same. Compounds showing such relationship to one another were termed isosteric compounds or isosteres. These terms were not restricted to compounds, but were extended to groups of atoms which hold pairs of electrons in common (termed by Langmuir comolecules). Comolecules were likewise considered isosteric if they contained the same number of atoms and possessed the same number and arrangement of electrons.

Langmuir predicted twenty-one types of isosteric groups of which only a few will be mentioned here:

CHART 1

Langmuir Type	
2	$O^{=}$, F^{-}, Ne, Na^{+}, Mg^{++}, Al^{+++}
3	$S^{=}$, Cl^{-}, A, K^{+}, Ca^{++}
5	Br^{-}, Kr, Rb^{+}, Sr^{++}
8	N_2, CO, CN^{-}
9	CH_4, NH_4^{+}
10	CO_2, N_2O, N_3^{-}, CNO^{-}

Langmuir postulated that when isosteric comolecules are also isoelectric, that is when they have the same total charge, all their physical properties should be closely similar. Only three such pairs occurred in Langmuir's tables:

N_2 and CO; CO_2 and N_2O; N_3^{-} and NCO^{-}

However, no direct comparison can be made of the physical properties of isosteres having different electrical charges.

Even though the classes are distinct from one another, it was demonstrated that comparisons of comolecules in different groups could still be made. If any two substances are very much alike in physical properties, then any isoelectric isosteres of these substances should show close relationships with one another. Thus in types 3 and 8, argon and nitrogen resemble each other closely, therefore chloride ion (isosteric with argon) should resemble the cyanide ion (isosteric with nitrogen). Likewise the similarity between K^{+} and NH_4^{+} can be derived from argon and methane. It is to be emphasized that in Langmuir's terminology K^{+} and NH_4^{+} are not isosteres of one another.

Whereas Langmuir compared only physical properties, Seifriz[17] showed in 1948 that CO_2 and N_2O are both reversibly anesthetic to the slime mold Physarum polycephalum.

In 1921, W. Huckel[11] pointed out that the imino group (=NH) in homopolar compounds corresponds to the oxygen atom and that the $-NH_2$ and -OH groups correspond to the F atom.

Somewhat later (1925) Grimm[8] very markedly extended the concept of isosterism. In place of Langmuir's term "isosteric comolecule", Grimm preferred the term pseudoatom. His hydride displacement law states:

> "Atoms anywhere up to four places in the periodic system before an inert gas change their properties by uniting with 1 to 4 hydrogen atoms, in such manner that the resulting combinations behave like pseudoatoms, which are similar to elements in the groups 1 to 4 places, respectively, to their right."

Grimm showed this relationship by the following chart:

CHART 2

	Group	4	5	6	7	0	1
Number of	0	C	N	O	F	Ne	Na
Hydrogens	1		CH	NH	OH	FH	
	2			CH_2	NH_2	OH_2	FH_2^+
	3				CH_3	NH_3	OH_3^+
	4					CH_4	NH_4^+

Beginning in 1932, Professor Erlenmeyer[5] at the University of Basel in Switzerland has published a series of papers on isosteric compounds. He has given great impetus to the modern concept of isosterism in organic chemistry, particularly in relation to biological activity. Erlenmeyer accepted Grimm's classification and has broadened it even further. His definition of isostere is:

> "Atoms, ions, or molecules in which the peripheral layers of electrons can be considered to be identical are termed isosteres."

By Erlenmeyer's definition all elements in the same group of the periodic table are isosteric so long as they have the same number of electrons in their outermost shell. In a unique application of this concept, Erlenmeyer in 1933[6] considered S and CH=CH in an aromatic nucleus to be isosteric by counting only the "peripheral" electrons in the C=C pseudoatom (whether it be written -CH=CH- or =CH-CH=).

In 1946, Mentzer[14] demonstrated that, in certain circumstances, the group $-CH_2-CH_2-$ could be replaced by -CO-O- with no change in biological activity of the parent compound. He did not term these isosteric pairs.

Some authors, as Mentzer[14] and Erlenmeyer[3] use the term potential-cycle or pseudocycle to bring out the steric relationships between the ring and opened form of physiologically active molecules.

Occasionally the term "isolog" is used by some authors (as Fieser[7] in the United States and Steinkopf[18] in Europe) where "isostere" is usually designated. Isologous compounds, however, need not be isosteric.

It is obvious from this brief survey that the term "isosteric" has varied in meaning with different writers - from a narrow to a very broad concept. In this discussion we shall accept the term in its broadest meaning and study the influence of isosteric replacements on the biological activity of molecules. We shall not consider physical properties, although it is not implied that such properties as mixed-crystal formation are not of great significance for isosteric relationships.

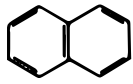
We shall term compounds "bio-isosteric" if they fit the broadest definition for isosteres and have the same type of biological activity.

The biological equivalence of isosteric groups receives support from immunological studies. Landsteiner[12] was able to prepare artificial antigen-antibody systems by coupling diazotized aromatic amines with proteins, and injecting these protein complexes into animals to form antibodies. He discovered that these antibodies have the specific power of combining with the group attached by the azo linkage. This group, which is of known structure, he termed the haptenic group. The specificity of the antibody in any serum could be tested, by means of the precipitin reaction, with related complex proteins. In general, the combining power is highly,

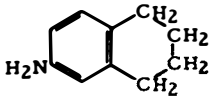
but not completely, specific.

Erlenmeyer,[4,19] using Landsteiner's method, demonstrated the serological similarity of several isosteric atoms and pseudoatoms. The following are illustrations of several types of isosteric replacement, where the resulting compounds give cross-reactions:

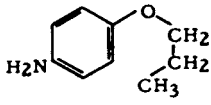
CHART 3

SEROLOGICAL SPECIFICITY	
C_6H_5-O-C_6H_4-N=N-Protein C_6H_5-NH-C_6H_4-Protein C_6H_5-CH_2-C_6H_4-Protein	-C_6H_4-PO_3H_2 -C_6H_4-AsO_3H_2 not -C_6H_4-SbO_3H_2
-C_6H_4-SO_3H -C_6H_4-SeO_3H not -C_6H_4-SO_2H	 -CO-NH-C_6H_4-  -CO-NH-C_6H_4- not  -CO-NH-C_6H_4-

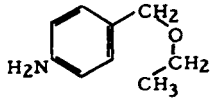
I



II



III



I and II +++

I and III ±

II and III ++

From Erlenmeyer[4,19]

While this work is not necessarily foolproof, and indeed has been criticized by Heidelberger[10] as requiring more and better support, it is in good agreement with Pauling's views.

Pauling[15] has also studied serological reactions to provide information about the molecular structure and configuration of simple substances. He compared the process of antibody formation to the production of a replica by pressing a plastic material against a mold and permitting it to harden. The polypeptide chain, with its power of assuming alternative configurations, is the plastic material, and the surface of the antigen serves as the die or mold. The complementariness of antigen and antibody includes not only surface configuration, but also juxtaposition of special combining groups, such as a negatively charged group in the antibody with a positively charged group in the antigen, and a hydrogen-bond-forming group carrying the proton with a similar group presenting an electron pair. Thus, isosteric replacements in an antigen which do not affect the shape or polarity of the molecule should not interfere with its reaction with the antibody.

Pauling has extended this concept of spatial surface configuration to include biological specificity in general.

Deductions from serological reactions are limited because strongly polar groups have predominant effects. However, this type of study should show when parts of a molecule are simple "space fillers", that is occupy specified geometrical bulk.

Since the discovery that the antagonism of the sulfonamides to p-amino benzoic acid is an antimetabolite effect, due to the close similarity of structure, isosteric replacements in other essential nutrients have yielded many compounds of interest. This field has been thoroughly reviewed in the literature,[16] and is the subject of a separate part of the symposium. We shall merely mention some of the types of isosteric replacement in the numerous antimetabolites which have been made, and only a few specific examples will be given in this paper:

CHART 4

Essential Nutrient	Atom or Group Replaced	Replacement
Riboflavin	2-CH_3	2-Cl
Thymine	-CH_3	-OH, -Br, or -NH_2
Mesoinositol	6-OH	6-Cl
Thymine, lysine, folic acid	-NH_2	-OH
Folic acid	-OH	-NH_2
p-Amino benzoic acid, glutamic acid	-COOH	-$CONH_2$
p-Amino benzoic acid, niacin	-COOH	-$COCH_3$
Arginine	-O-	-CH_2-
Uracil, thymine, niacin amide	-O-	-S-
Methionine	-S-	-O-, or -CH_2-
Purines	-CH=	-N=
Phenyl alanine, p-aminobenzoic acid	benzene	pyridine

CHART 4 (Cont.)

Essential Nutrient	Atom or Group Replaced	Replacement
Phenyl alanine	benzene	thiophene, furan, pyrrole
Niacin	pyridine	thiazole
Thiamine	thiazole	pyridine
Methionine	-S-	-CH=CH-
Valine, niacin, pantothenic acid, aspartic acid, oxybiotin, heteroauxin	-COOH	$-SO_3H$
p-Amino benzoic acid	-COOH	$-AsO_3H_2$
p-Amino benzoic acid	-COOH	$-PO_3H_2$

The isosteric compound formed may have either the same activity as the original, or more usually it may have an antagonistic effect. In either case, it is proof that isosteric replacement gives compounds acting by the same mechanism, that they are truly bio-isosteric.

Ideally, to make comparisons between structure and biological activity, two criteria are necessary: (1) Substances compared must act by the same mechanism and (2) The structure involved in the test should be the structure of the compound under study. However, in practice, for many types of biological activity only in vivo tests can be used, and even when using in vitro tests, we cannot be sure that the above criteria apply. In so far as possible, examples have been chosen which are based on in vitro activity, and mainly those using an isolated tissue or micro-organism. It is not claimed that the in vitro tests will necessarily correlate with in vivo or clinical studies; nonetheless the data obtained may be a useful guide for further work and may be adaptable to other series of compounds.

Activities found in one screening test need not parallel the relative activities of the compounds in another test. Since data in the literature are usually lacking for tests other than those in which the authors were most interested, it is seldom possible to make such alternate lists.

Biological activities, as absorption, distribution, conjugation (detoxification), taste, odor, side effects of drugs, will not be discussed.

PART 3

TABLES OF DATA

In order to classify the data for presentation, the following chart is pertinent for organic compounds.

CHART 5

Class 4	Class 3	Class 2	Class 1	
	Sb	Te	I	
	As	Se	Br	
	P	S	Cl	
C	N	O	F	Ne
N^+ P^+ S^+	-CH-	-NH- -PH-	-OH -SH	
		$-CH_2-$	$-NH_2$ $-PH_2$	
			$-CH_3$	

Table modified from Grimm[8]

We have designated these four types from the number of covalent bonds. Above are the elements of the same periodic group, below are the isosteric hydrides. The following tables will show the effect of isosteric replacement on biological activity within each type. The -S- and -C=C-, and other special cases do not fit into this chart and will be treated separately.

Discussion of Tables

Class 1 - Halogens and Hydrides (OH, NH_2, CH_3)

Tables 1-4 list examples of comparisons of Class 1 of the chart previously shown. Table 1 contains examples of multiple comparisons, Table 2 compares halogens only, Table 3 compares halogens with hydrides, Table 4 compares hydride with hydride. An attempt has been made to select examples from fields of current interest.

Table 1. If one were to judge results of isosteric replacements from Table 1, it would be difficult to arouse enthusiasm. The most unusual case is the replacement of the chain -OH of epinephrine by NH_2; the activities of other members of this series should be of great theoretical interest.

Table 2. In general the results are what would be expected, activities usually showing a gradient with the molecular weights. There are exceptions, mostly with the extreme members F and I.

Tables 3 and 4. These again show unpredictability of response. The α-hydroxy-β-phenylethylamine examples have been amply discussed by Hartung.[9]

General Conclusions to Class 1. It is not possible to predict when members of this class will be bio-isosteric; in most instances they will not be. Very often activity is specific to one member which would be called, in Ehrlich's terminology, an anchoring group. Differences in activities may be attributable to differences in polarity of the groups, to solubility differences, or to chemical reactivity. The most likely pairs of bio-isosteres are:

halogen and CH_3

halogen and OH,

the most unlikely pairs are:

OH and NH_2.

Class 2 - (S, O, NH, CH_2)

Tables 5 - 7 inclusive list examples of Class 2 replacements. For convenience, the examples have been divided into structural types: ether, ketone, and ester.

Table 5: Ether Type. These show a better probability of bio-isosterism than Class 1 types. The member which fits in the least is -NH. Sulfur is not always bio-isosteric with oxygen, in fact surprisingly less than might be anticipated. Probably polarity differences play a predominant role.

Table 6: Ketone Type. The most interesting examples are probably the thio-barbiturates. In general, these types have restricted comparability.

Table 7: Ester Type. Many amides and thioesters related to the local anesthetic and antispasmodic esters are known, but practically none have come into use. More thought should be given to the replacement of ester oxygen by the CH_2 group.

General Conclusions to Class 2. Isosteric replacement in this group has better promise of usefulness than in Class 1. While methoxy and ethyl often do not show similarity, in other cases interchanging O and CH_2 yields compounds of similar activity. Here, as in Class 1, polarities probably play a dominant role.

Class 3 - Tertiary N and Tertiary C

Tables 8 and 9 list examples of Class 3. Most of the known examples of this class occur in the aromatic ring systems (Table 8). No attempt has been made to list the numerous examples in well-known fields as the sulfonamides and antihistamines but a few are given to refresh memories. Commercially this has been the most valuable application of bio-isosterism.

Table 9 contains non-aromatic examples. Because of polarity differences the aliphatic types can seldom be expected to display bio-isosterism, but it is a more likely assumption that diphenylamine and benzhydryl derivatives would show such similarity. More examples are desirable.

While tertiary P, As and Sb theoretically are electronically isosteric with N and CH, practically, except between As and Sb, they show little bio-isosterism.

Class 4 - Quaternary C, N, S, Etc. (Table 10)

The spatial tetrahedral geometry and the positive charge are of paramount importance for this class. In general, a quaternary carbon, because it lacks a charge, is not interchangeable with quaternary nitrogen.

The Special Classes

Table 11 - Aromatic C=C and O, S, NH. Following Erlenmeyer, it is generally agreed that the pairs, benzene and thiophene, and pyridine and thiazole, are isosteric. Furan and pyrrole differ markedly from benzene in both physical and chemical properties. Indeed, Bradlow, Vanderwerf and Kleinberg[2] in a brief discussion of the concept of isosterism, state that "Proponents of the principle of isosterism do not point out the fact that by definition pyrrole is also isosteric with benzene, thiophene and furan." There are sufficient examples, however, to indicate that these rings may be bio-isosteric although the furan and pyrrole compounds are usually weaker in activity than those containing benzene and thiophene. The activity of furan isosteres in the antihistamine field indicates that such replacements cannot be ignored.

The latter part of the table contains comparisons of an ethylenic bridge between two aromatic rings with S, O and NH. Not enough examples are available to draw conclusions, but this should be an interesting replacement type.

Table 12 - Carbonyl and Sulfone (or Sulfoxide). The structural relationship between p-aminobenzoic acid and sulfanilamide has been emphasized by Bell and Roblin[1] in explaining the mode of action of sulfonamides. The exchange of -COOH for $-SO_3H$ in many metabolites to produce antagonistic substances has shown this to be a general phenomenon. Therefore, a comparison has been made in this table of compounds with carbonyl and sulfone groups. The sulfoxide has been added since spatially it more nearly resembles the carbonyl than does the sulfone grouping. Electronically neither the sulfoxide nor the sulfone group is isosteric with the carbonyl group. The ionic bond of the sulfur groups further emphasizes the difference.

The table does not indicate any striking resemblances except for the amidone type example.

Table 13 - $-CO-O-$ and $-CH_2-CH_2-$. These groups are not electronically isosteric; it is most likely that they owe their activity to similar spatial fixation (as discussed in the following type).

Table 14 - Spatial Fixation by Ring or Double Bond. That three dimensional spatial characteristics play a highly important role in biological activity is known to everyone. The vastly different activities often noted in optical or cis-trans isomers must be considered in any attempt to explain the mechanism of biological activity. When two molecules are almost identical spatially, that is, are superimposable in three dimensions, we may expect similar activity provided the polarities are situated in corresponding parts of the molecules.

Table 14 lists examples of ring and open forms. In many cases there is striking agreement; often however, one form is completely inactive. Where agreement between activities is found, it is interesting to assume that the open and closed forms can be superimposed in three dimensions.

Benadryl is an interesting example. When the rings are forced into the planar form of the fluorene ring, activity is lost; one might speculate therefore that in the "active" form of Benadryl the two benzene rings do not lie in the same plane. From the example of Trasentin and Pavatrine the opposite appears to be the case.

Table 15.- Polarity Shift, Exo-Endo Cyclic. This and the following table are offered in an attempt to systematize data scattered throughout the literature. This table demonstrates the effect of moving a polarity from without to within a ring, the shift being to the adjacent position. The probability is that the polarity of the atom must remain quite similar in order to retain the same activity.

Table 16 - Reversed Adjacent Polarity. This table illustrates the effect of reversing adjacent polar groups. Many instances are of great interest; this is a transformation to be kept in mind in seeking new compounds.

CONCLUSIONS

We have seen that similarity in biological action need not result from isosteric replacement - isosteres need not be bioisosteres. This is not surprising in view of the complexity of the simplest living systems.

As we all know, simple isosteric replacements often give compounds of interest and value. In addition, there are two important types of information to be learned from such replacements. One is that we discover which groups cannot be eliminated in order to retain the desired activity (i.e., the anchoring groups); the other is that we learn which parts of the molecule are important because of their bulk space characteristics. These facts enable a more intelligent approach to the synthesis of new compounds.

The similarity of biological activity in so many instances, and the successful results already achieved through isosteric replacements, show that this is a type of variation which the synthetic chemist must keep in mind. If chemical reactivity and polarities are considered, the predictability of bio-isosteric replacement is quite high.

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EXPLANATION OF TABLES

In the first column the structural formulas of the compounds under consideration are written with the variable isosteric group represented as X.

In the second column the biological list is stated (e.g. anti-tubercular, narcotic, anesthetic, etc.) together with other pertinent data necessary - as to whether in vitro or in vivo, what organ, organism, or animal was used, what challenging agent, if any, was used, and in what terms the activity data are expressed with a designation of the reference compound if such was used. Below, in parenthesis, the references to the literature are given. This list is found immediately following the tables.

The remaining column headings usually designate the atom or group represented by X. In cases where this is not so, the heading is self evident. The data in these columns are the activities of the compounds in the terms used by the original workers; this varies with different authors from quantitative figures, a system of plusses, to mere statements of activity or non-activity.

TABLE 1

CLASS 1

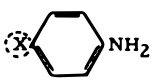
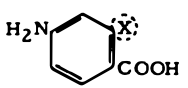
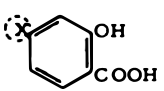
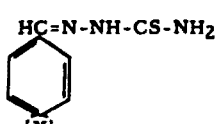
Compound	Biological Test (Reference)	Halogen	-OH	$-NH_2$	$-CH_3$
	Anti-tubercular In vitro Salicylate No. (16)	F < 1 Cl 6 Br 7 I 20	< 1	< 1	27
	Anti-tubercular % curative in guinea pigs (111)	Cl 19%	16%	-	inactive
	Anti-tubercular In vitro (94)	Cl inactive	most active	inactive	weak
	Anti-tubercular In vitro Molar conc. for stasis (72)	Cl 1/500	1/1,000	1/40,000	
	Anti-tubercular In vivo (mouse) (74)	Cl slight	definite	slight	

TABLE 1 (Cont.)

CLASS 1

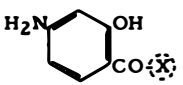
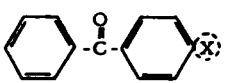
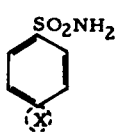
Compound	Biological Test (Reference)	Halogen	-OH	$-NH_2$	$-CH_3$
	Phenol Coefficient vs. B. Thyphosus Phenol = 1 (140)	F 1 Cl 3.9 Br 5.4	12	?	2.5
	Anti-tubercular In vitro Molar Conc. for Stasis (72)		1/40,000	1/80	1/17
	Anti-tubercular In vitro Stasis - mg % (57)	Cl 2.5	10		2
	Antibacterial (120)	inactive	inactive	active	inactive

TABLE 1 (Cont.)

CLASS 1

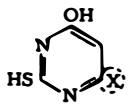
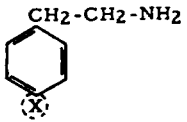
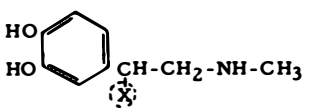
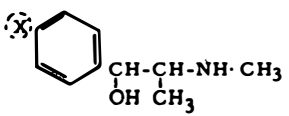
Compound	Biological Test (Reference)	Halogen	-OH	$-NH_2$	$-CH_3$
	Antithyroid (109, 138)		inactive	weak	potent
	Pressor Activity Epinephrine = 1 (66, 103)	F or Cl "weak"	1/70		"weak"
	Pressor Activity (66, 143, 64, 81, 67)	F, Cl "possess pressor activity"	1/50 epi	? activity unpublished	1/200 epi
	Pressor Activity (18, 152, 93)	Cl - known ?	OH - epi SH - "epi-like"	1/10 epi	?
	Pressor Ephedrine = 1 (66)		< 1	2	< 1

TABLE 1 (Cont.)

CLASS 1

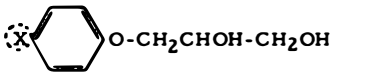
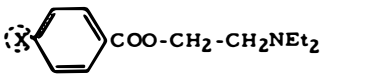
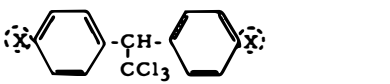
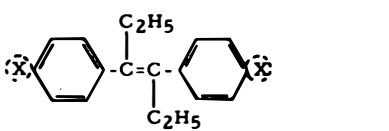
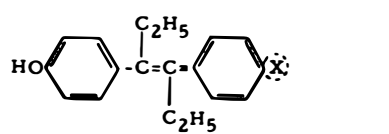
Compound	Biological Test (Reference)	Halogen	-OH	$-NH_2$	$-CH_3$
	Muscle relaxant ø-O-CH_2-CHOH-CH_2OH = 1 (99)	Cl 2.1		0.2	1.2
	Local anesthetic Procaine = Standard (27, 128)	F comparable	comparable	(standard)	
	Insecticidal vs. Lice Standard = DDT (113)	F 1/4 DDT Cl DDT Br 1/2 DDT	inactive	inactive?	1/5 DDT
	Estrogenic (135)	Br very weak	potent 0.4 gamma	very weak	inactive?
	Estrogenic (135)	Br 100 gamma	0.4 gamma	7.5 gamma	

TABLE 1 (Cont.)

CLASS 1

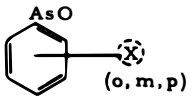
Compound	Biological Test (Reference)		Halogen	-OH	$-NH_2$	$-CH_3$
AsO  (o, m, p)	vs. T. pallidum		Cl			
	in vitro	ortho	83	84	88	84
		meta	110	79	104	97
	Ø AsO = 100	para	85	72	83	102
	(38)					

TABLE 2

CLASS 1

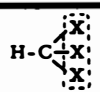
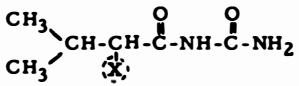
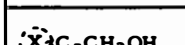
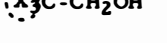
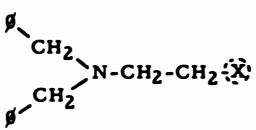
Compound	Biological Test (Reference)	I	Br	Cl	F
	Narcosis (56, 70)	narcotic	narcotic	narcotic	inactive
	Hypnosis (56)	inactive	hypnotic	hypnotic	
 	Narcosis (91)		narcotic (2 x Cl cmpd) inactive	narcotic narcotic	
	Adrenergic blocking (119)		active (same as Cl)	active	
	vs. Vaccinia virus (144)			active	inactive

TABLE 2 (Cont.)

CLASS 1

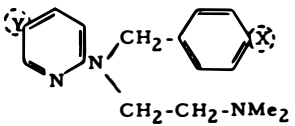
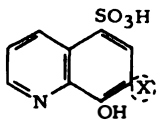
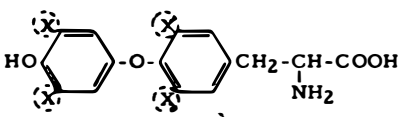
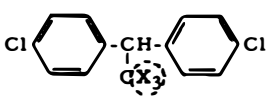
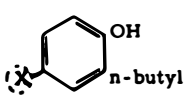
Compound	Biological Test (Reference)	I	Br	Cl	F
	Antihistamine X PBZ = 1 Y (147)	- 1/2 -	1 1/2	2 1/2	3
	Amebic Dysentery (149)	active	inactive	inactive	
	vs. Myxedema in humans (95)	1	1/17	1/250	
	Insecticidal (113)		good	excellent	weak
	Phenol coefficient vs. S. aureus (140)		313	257	60

TABLE 3

CLASS 1

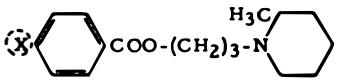
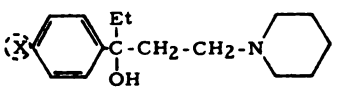
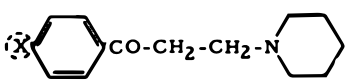
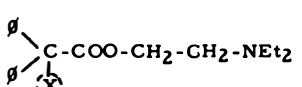
Compound	Biological Test (Reference)	I	Br	Cl	F	OH	NH_2	CH_3
	Local anesthesia minutes (107)	12	15	10			?	9
	Local anesthesia Procaine = 1 (84)			2				4
	Antispasmodic vs. Furmethide Trasentin = ++ (37)		+++	+++				+++
	Ditto (37)		+	0				+
	Antispasmodic vs. acetylcholine, Ba, or histamine (92)			+++		+++		

TABLE 3 (Cont.)

CLASS 1

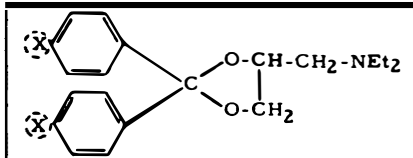
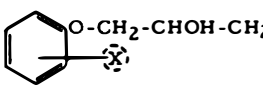
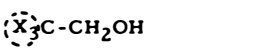
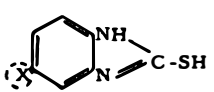
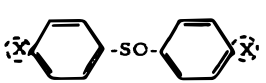
Compound	Biological Test (Reference)	I	Br	Cl	F	OH	NH_2	CH_3
	Antispasmodic vs. acetylcholine, Ba (19)			+				++
	Muscle relaxant Ø-O-CH_2-CHOH-CH_2OH = 1 ortho meta para (9,99)		1.3	1.7 2.4 2.1				2.2 2.1 1.2
	Narcotic (91,101)		strong-est	strong				very weak
	Antithyroid Thiouracil = 100 (26)	11	27	44				12
	Insecticidal vs. clothes moth (88)		effective	effective				inactive

TABLE 3 (Cont.)

CLASS 1

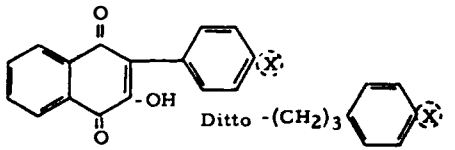
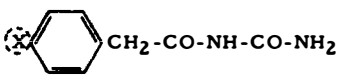
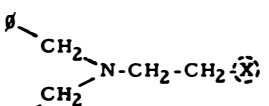
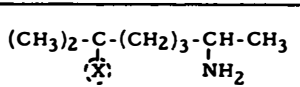
Compound	Biological Test (Reference)	I	Br	Cl	F	OH	NH_2	CH_3
	Antimalarial in ducks ED_{95} in mg/kg (54)	>40 28	29 19	45 20	>60 60			73 15
	Anticonvulsant vs. electroshock (136)			±				++
	Adrenergic blocking (119)		active	active		inactive		
	Cardiac action (100)			+		+		
Vitamin D 3-substituent	(10)		inactive	inactive		active		

TABLE 3 (Cont.)

CLASS 1

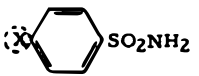
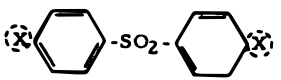
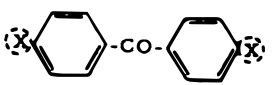
Compound	Biological Test (Reference)	I	Br	Cl	F	OH	NH_2	CH_3
	(88)			insect-icidal			bacter-icidal	
	(88)			ditto			ditto	
	(88)			ditto			ditto (weak)	

TABLE 4

CLASS 1

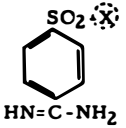
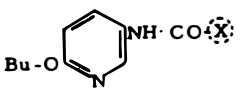
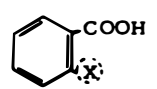
Compound	Biological Test (Reference)	SH	OH	NH_2	CH_3
	(36)			Active vs. bacteria (both have same effect on blood pressure and respiration)	Active vs. rickettsia
	Antitubercular in vitro vs. 607 stasis in mg % (58)			16	1/16
$H_2N\text{-}CS\text{-}NH\text{-}X$	Antithyroid (7)			+	++
$Me_3\overset{+}{N}\text{-}CH_2\text{-}CH_2\text{-}O\text{-}CO\text{-}X$	Parasympathomimetic (117,20)			active	active
	vs. E. coli in vitro Sulfadiazine = 1 (8)			1/125	1/9
	Analgesic (56)		active	inactive	-

TABLE 4 (Cont.)

CLASS I

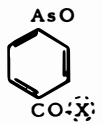
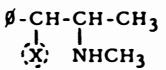
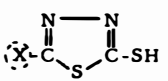
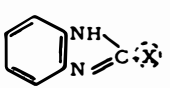
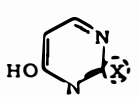
Compound	Biological Test (Reference)	SH	OH	NH_2	CH_3
	vs. T. pallidum in vitro ØAsO = 100 (40)		7	45	
	Pressor CNS stimulation (93)		1 ++	1/3 +	
	Antithyroid Thiouracil = 100 (26, 108)	7		156	
	Ditto	116		6	
	Antithyroid (7)	active	inactive		

TABLE 4 (Cont.)

CLASS 1

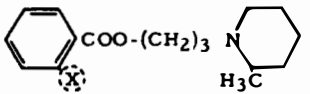
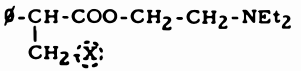
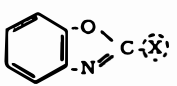
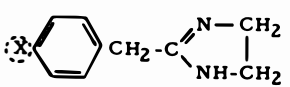
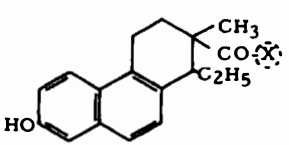
Compound	Biological Test (Reference)	SH	OH	NH_2	CH_3
	Local anesthesia (107)	inactive	active		
	Antispasmodic vs. Acetylcholine Atropine = 1 (21, 63)		1/7		1/10
	Anticonvulsant (25)		inactive		++++
	Effect on blood pressure (130)		pressor		depressor
	Estrogenic (115)		active		inactive

TABLE 4 (Cont.)

CLASS 1

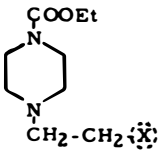
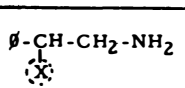
Compound	Biological Test (Reference)	SH	OH	NH_2	CH_3
	vs. Filariasis (139)		inactive		active
	Pressor (66)		1		1

TABLE 5

CLASS 2

Type R-X-R

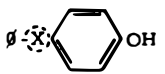
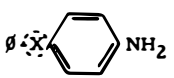
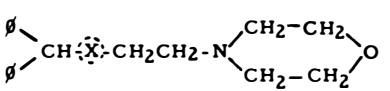
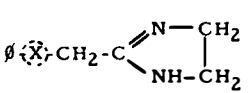
Compound	Biological Test (Reference)	S	O	NH	CH_2
	Phenol Coefficient vs. Staph. aureus (140)	S 100 Se 100	40	10	100
	Antitubercular Salicylate No. (16)		40	2	160
	Antihistamine (17, 97, 127)	weak ?	active	very weak	active
	Blood pressure effect (130)		pressor	pressor	depressor
	Trypanocidal (6)	±	+++	+	++

TABLE 5 (Cont.)

CLASS 2

Type R-X-R

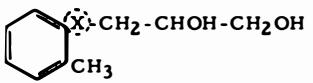
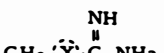
Compound	Biological Test (Reference)	S	O	NH	CH_2
	Muscle relaxant Ø-O-CH_2-CHOH-CH_2OH = 1 (99)	1.3	2.2	0.3	
	Pressor effect (51)	++	+	+	+
	Narcosis (56)	inactive	narcotic	inactive?	narcotic
	Local anesthesia (75,118)	inactive	active	active	
	Lipotropic activity (133)	active	active		

TABLE 5 (Cont.)

CLASS 2

Type R-X-R

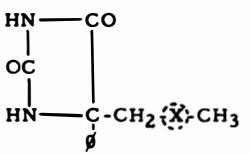
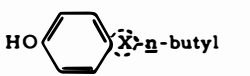
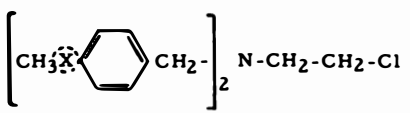
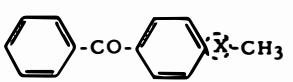
Compound	Biological Test (Reference)	S	O	NH	CH_2
	Antivonvulsant vs. electroshock (98)	+++	+++		++++
	Estrogenic (135, 106)		100 mg.		100 mg.
	Phenol coefficient vs. Staph. aureus (140)	60	9		20
	Adrenergic blocking (119)		++		inactive
	Antitubercular stasis in mg % (57)		1.7		20

TABLE 5 (Cont.)

CLASS 2

Type R-X-R

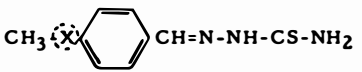
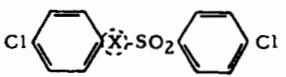
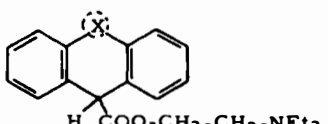
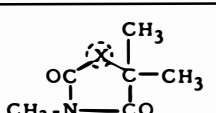
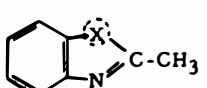
Compound	Biological Test (Reference)	S	O	NH	CH_2
	Antitubercular in mice (74)	slight	active	slight	
	Insecticidal (88)		active	inert	
	Antispasmodic vs. acetylcholine Atropine = 1 vs. Ba Papaverine = 1 (22)	1/45 3/4	1/3 3	1/21 3/4	1/35 1.5
	Anticonvulsant (136)	inactive	active	inactive	
	Anticonvulsant (25)	very little	active		

TABLE 5 (Cont.)

CLASS 2

Type R-X-R

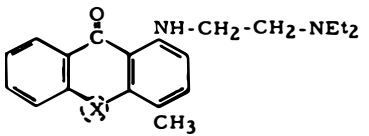
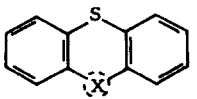
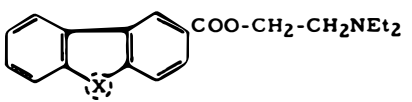
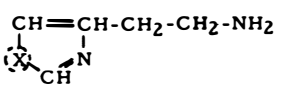
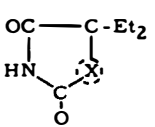
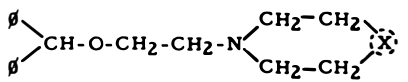
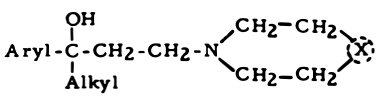
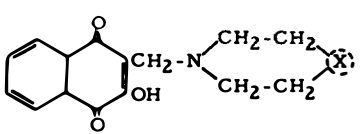
Compound	Biological Test (Reference)	S	O	NH	CH_2
	Schistosomiasis in humans in mice (12)	 active active	 inactive active		
	Insecticidal (113)		active	active	
	Local anesthesia rabbit cornea (23)	 +	 ++	 +++	
	Effect on blood pressure (49)	 depressor		 depressor	
	Narcotic (47)	++	+		

TABLE 5 (Cont.)

CLASS 2

Type R-X-R

Compound	Biological Test (Reference)	S	O	NH	CH_2
	Antihistamine Benadryl = 1 (97)	weak ?	1/2	inactive	1
	Antispasmodic (37)		+		++
	Antimalarial in ducks (54)		inactive		active

Aromatic rings are treated under "Special Cases".

TABLE 6

CLASS 2

Type R-C(=X)-R

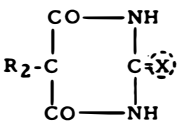
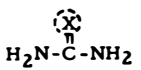
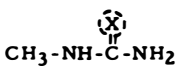
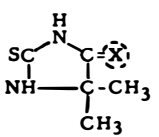
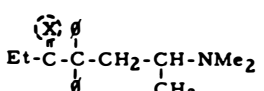
Compound	Biological Test (Reference)	S	O	NH	CH_2
	Hypnotic effect duration (32, 141, 142, 56, 116)	 ++ +	 + ++	 inactive	 weak
	Diuretic (96)	1	1	(toxic)	
	Ditto (96)		0.8	13.4	
	Anticonvulsant % protection from metrazol (68)	 100%	 44%	 0	
	Analgesic mg/kg (29)		12.5	12.5	

TABLE 6 (Cont.)

CLASS 2

Type R-C(=X)-R

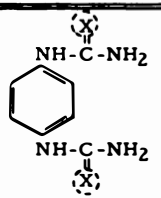
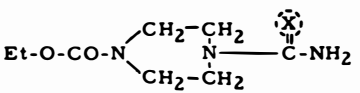
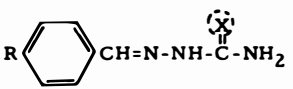
Compound	Biological Test (Reference)	S	O	NH	CH_2
	Trypanosomiasis (71)		inactive	active	
	Filariasis (86)		inactive	active	
	Antitubercular in mice (74)	active	inactive	inactive	

TABLE 7

CLASS 2

Type R-CO-X-R

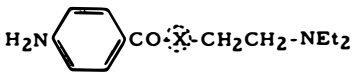
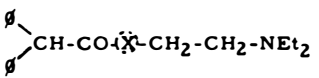
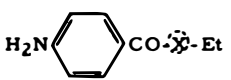
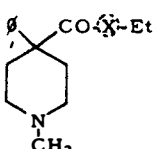
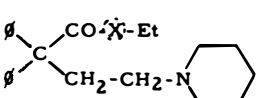
Compound	Biological Test (Reference)	S	O	NH	CH_2
	Local anesthesia (118, 65)	active	active	weak?	
	Antispasmodic vs. acetylcholine Trasentin = 1 (21, 110, 124)	4	1	7/10	
	Antitubercular salicylate no. (16)		40	1	80
	Analgesic (84)		1		1
	Analgesic (84)		1		1/5

TABLE 8

CLASS 3

Aromatic Rings

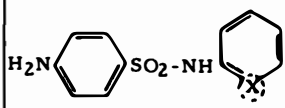
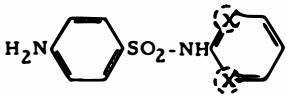
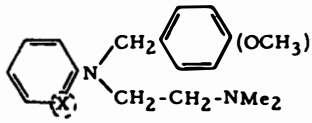
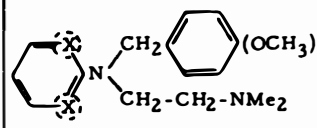
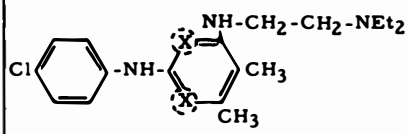
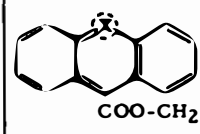
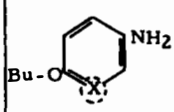
Compound	Biological Test (Reference)	=CH-	=N-
	Antibacterial (8, 120)	moderate	active
	Ditto	moderate	very active
	Antihistamine (148, 78, 80, 59)	active	active
	Ditto	active	active
	Antimalarial (102)	inactive	active
	Antispasmodic vs. acetylcholine Atropine = 100 (92)	15	5
	Antitubercular vs. 607 mg. % stasis (52)	1/16	1/32

TABLE 8 (Cont.)

CLASS 3

Aromatic Rings

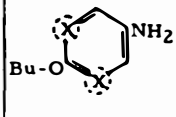
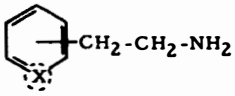
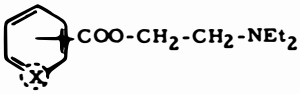
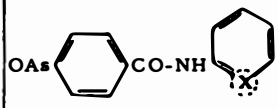
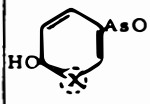
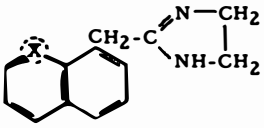
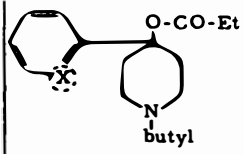
Compound	Biological Test (Reference)	=CH-	=N-
	Antitubercular vs. 607 mg. % stasis (52)	1/16	1/16
	Effect on blood pressure (66, 77, 60)	pressor	α depressor β pressor γ pressor (weak)
	Local anesthesia (30)	active	α inactive β active (weak) γ inactive
	vs. T. pallidum in vitro ØAsO = 100 (41)	97	74
	Syphilis (56, 123)	active	active
	Effect on blood pressure (130)	pressor	depressor
	Analgesic (125)	strong	weak

TABLE 8 (Cont.)

CLASS 3

Aromatic Rings

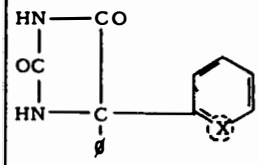
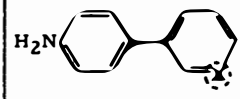
Compound	Biological Test (Reference)	=CH-	=N-
	Anticonvulsant vs. electroshock (98)	++++	++++
	Antitubercular salicylate no. (44)	1600	600

TABLE 9

CLASS 3

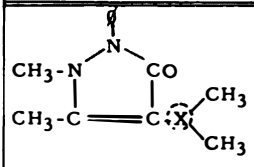
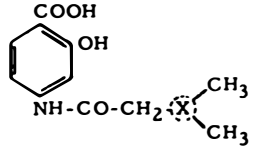
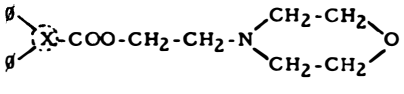
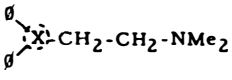
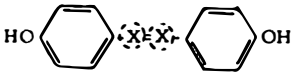
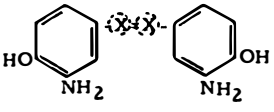
Compound	Biological Test (Reference)	=CH-	=N
	Antipyretic (50, 121)	+	+
	Antitubercular stasis at mol. conc. (72)	1/1200	1/160
	Antispasmodic intestinal strip Papaverine = 100 (28)	75	30
	Antihistamine Benadryl = 1 (126, 104)	1	1.25
	Estrogenic (131, 135)	10 mg.	10 mg.
	Syphilis (149)	Sb unstable	As Salvarsan

TABLE 10

CLASS 4

Compound	Biological Test (Reference)	C	N	S	P	As	Sb
$Me_{3,4}X^+$	Muscarine-like (depressor) (76)		+++	++	++	+	+
$Me_{2,3}X^+-CH_2-CH_2-OAc$	Depressor Acetylcholine = 100% (151, 122)		100	10	10	2	
$Me_3X^+-CH_2-CH_2-OH$	Lipotropic activity Methyl donor (150)		+ yes			+ no	
$Me_3X^+-CH_2-CH_2-OAc$	Rate of hydrolysis by cholinesterase (2)	fast	fast				

TABLE 11

SPECIAL CLASS

Aromatic C=C, S

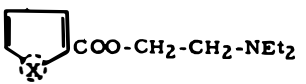
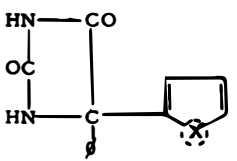
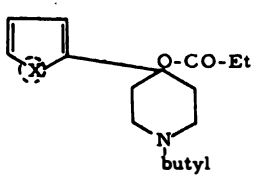
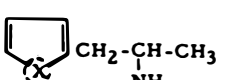
Compound	Biological Test (Reference)	-HC=CH-	S	O	NH
	Local anesthesia Cocaine = 10 (62)	4	1	trace	2
	Anticonvulsant (98)	++++	++++		+
	Analgesic (125)	strong	weak	weak	
	Pressor in dogs stimulatory in humans (4)	++ +	++ 0	+ 0	
	Anticonvulsant Electroshock Metrazole (136)	 +++ ++	 + 0	 0 0	

TABLE 11 (Cont.)

SPECIAL CLASS

Aromatic C = C, S

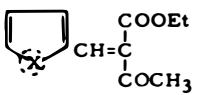
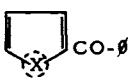
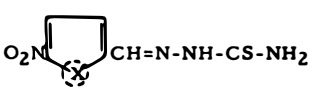
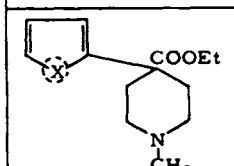
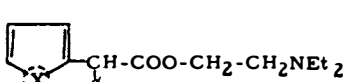
Compound	Biological Test (Reference)	-CH=CH-	S	O	NH
	Insecticidal vs. clothes moth (88)	excellent		excellent	
	Antitubercular mg. % stasis (57)	5		10	
	Antitubercular in mice (74)	active		inactive	
	Analgesic (13)	++		+	
	Antispasmodic vs. acetylcholine Atropine = 1 (15, 53)	1/40	1/20		

TABLE II (Cont.)

SPECIAL CLASSES

Aromatic C= C, S

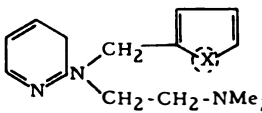
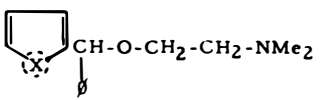
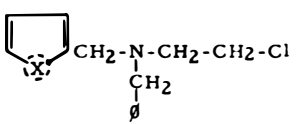
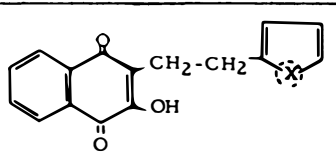
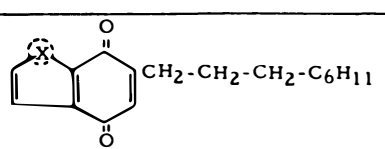
Compound	Biological Test (Reference)	-CH=CH-	S	O	NH
	Antihistamine, ileum PBZ = 1 (104, 80, 89, 11)	1	1	1	
	Ditto Benadryl = 1 (97, 104, 11)	1	1/4	ca. 2	
	Adrenergic blocking (119)	++	++		
	Antimalarial in ducks ED_{95} in mg/kg (54)	>100	85		
	Ditto (54)	20	weak		

TABLE 11 (Cont.)

SPECIAL CLASSES

Aromatic C = C, S

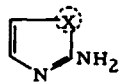
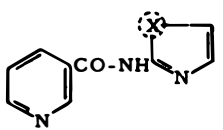
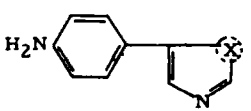
Compound	Biological Test (Reference)	-CH=CH-	S	O	NH
	Antithyroid (132)	0	++		
	Antitubercular ++ corresponds to 50% of streptomycin activity (87)	0	++		
	Analeptic (48)	+	+		
	Antitubercular salicylate No. (44)	600	2,000		
	Antibacterial (120)	inactive ?	weak		

TABLE 11 (Cont.)

SPECIAL CLASSES

Aromatic C = C, S

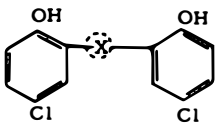
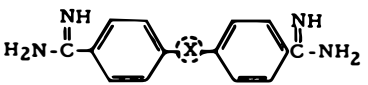
Compound	Biological Test (Reference)	-CH=CH-	S	O	NH
	Fungicidal (105)	++	++		
	Trypanocidal mice (6)	+++	+	+++	++
	Estrogenic dose in mg. (135, 106)	10		100	

TABLE 12

SPECIAL CLASS

CO, SO, SO_2

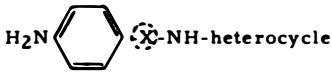
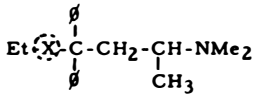
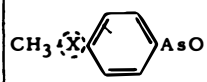
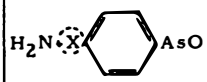
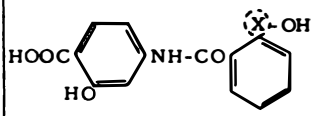
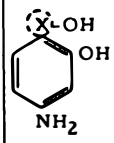
Compound	Biological Test (Reference)	CO	SO	SO_2
	Insecticidal vs. clothes moth (88)	inactive	active	active
	Antibacterial vs. pneumococcus (120)	inactive	weak	active
	Antibacterial (83, 120)	inactive		active
	Analgesic Amidone = 100 (42)	100		120
	vs. T. pallidum ØAsO = 100 (39)	42		49
 HO- Me_2N-	vs. T. pallidum ØAsO = 100 (41)	45 7 8		29 3 112
	Antitubercular in vitro (72)	active		inactive
	Ditto (94)	active		inactive

TABLE 13

SPECIAL CLASS

-COO-, CH_2-CH_2

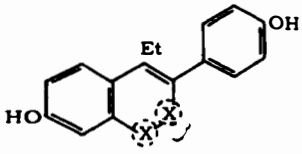
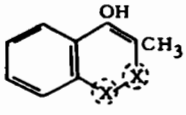
Compound	Biological Test (Reference)	-CO-O	-CH_2-CH_2-
	Estrogenic (112)	100 gamma 	100 gamma
	Vitamin K activity (112)	active 	active

TABLE 14

SPECIAL CLASS

Spatial Fixation by Ring or Double Bond

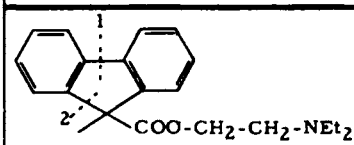
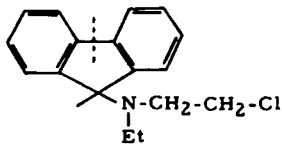
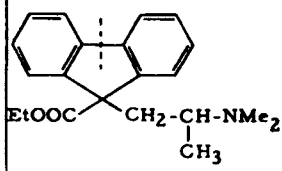
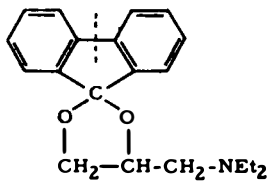
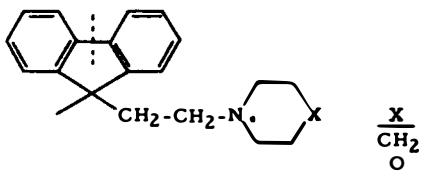
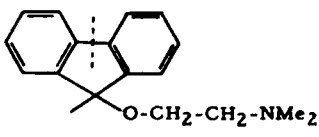
Compound	Biological Test (Reference)	Open Form	Ring Form
	Antispasmodic vs. acetylcholine Atropine = 100 (22,92)	1 2.3 2 0.7	14
	Adrenergic blocking (119)	++	+++
	Analgesia (134)	strong	weak
	Antispasmodic vs. acetylcholine (19)	active	weak
	Antispasmodic vs. acetylcholine, Ba, histamine (84,17)	active	less active
	Antihistamine (126)	active	inactive

TABLE 14 (Cont.)

SPECIAL CLASS

Spatial Fixation by Ring or Double Bond

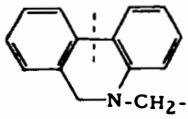
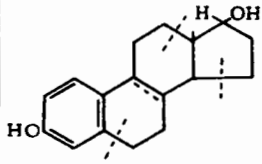
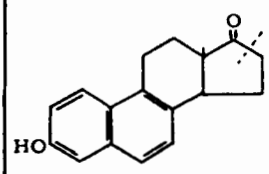
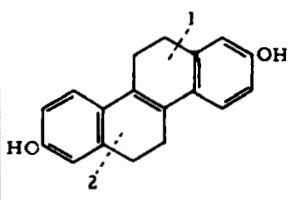
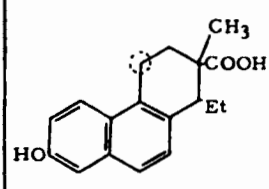
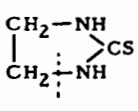
Compound	Biological Test (Reference)	Open Form	Ring Form
	Antihistamine (79)	active	inactive
	Estrogenic (31)	1/40,000 of stilbestrol	active
	Estrogenic in gammas (115)	0.4	1
	Estrogenic (135)	1 ++ 1 and 2 +++	+
	Estrogenic in gammas (115)	0.5	0.4
	Antithyroid Thiouracil = 100 (26)	35	63

TABLE 14 (Cont.)

SPECIAL CLASSES

Spatial Fixation by Ring or Double Bond

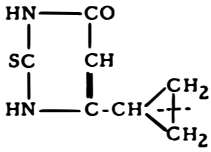
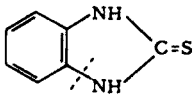
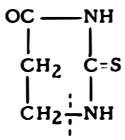
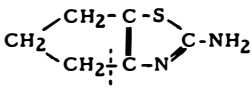
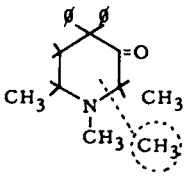
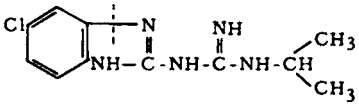
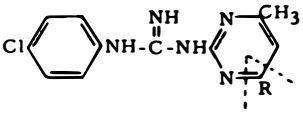
Compound	Biological Test (Reference)	Open Form	Ring Form
	Antithyroid Thiouracil = 100 (137)	100	100
	Antithyroid Thiouracil = 100 (109)	14	116
	Ditto (109)	14	10
	Effect on blood pressure (45)	depressor	pressor
	Analgesic (14)	active (Amidone)	inactive
	Antimalarial (1)	active (Paludrine)	inactive
	Antimalarial (34)	+++	++

TABLE 14 (Cont.)

SPECIAL CLASS

Spatial Fixation by Ring or Double Bond

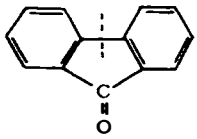
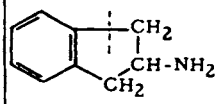
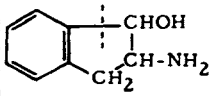
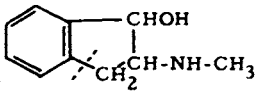
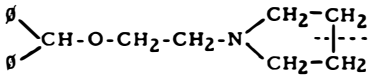
Compound	Biological Test (Reference)	Open Form	Ring Form
	Antitubercular (57)	active	inactive
	Sympathomimetic Vasoconstrictor Pressor (66)	+ weak	+ weak
	Ditto Vasoconstrictor Pressor (66)	+ +	+ weak
	Bronchodilator (69)	good	good
	Antihistamine Benadryl = 1 (153)	0.1	2

TABLE 15

SPECIAL CLASS

Polarity Shift

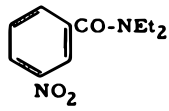
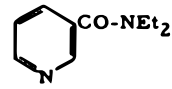
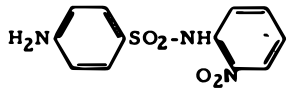
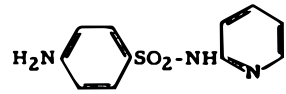
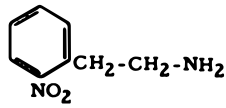
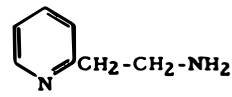
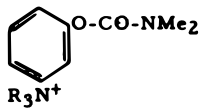
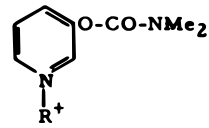
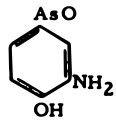
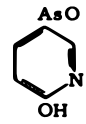
TEST	Exocyclic	Endocyclic
Analeptic activity (46)	 Active	 Active
vs. Hem. strep. in mice (43)	 15% greater activity than Sulfanilamide	 (Sulfapyridine)
Histamine-like activity (90)	 None (pressor compound)	 Weak (0.02 x histamine)
Parasympathomimetic (154, 73, 3)	 Active	 Active
vs. Syphilis (123)	 Active	 Active

TABLE 15 (Cont.)

SPECIAL CLASS

Polarity Shift

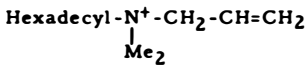
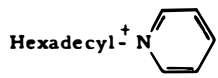
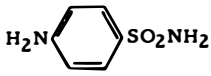
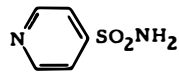
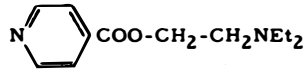
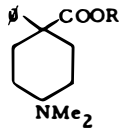
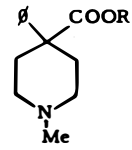
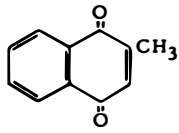
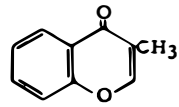
TEST	Exocyclic	Endocyclic
Antibacterial vs. Staph. aureus (146)	 1/25,000	 1/25,000
Antibacterial (145)	 Active	 Inactive?
Local anesthetic (30)	 Active	 Inactive
Analgesic (129)	 Weak	 Strong
Vit. K. activity (114)	 Potent	 Weak, but active

TABLE 16

SPECIAL CLASS

Reversed Polarity

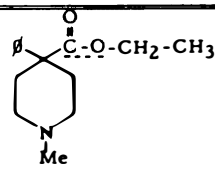
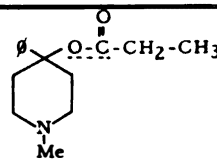
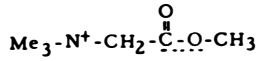
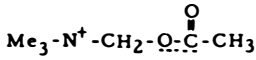
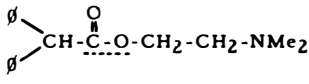
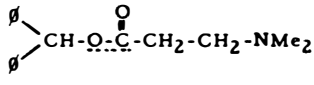
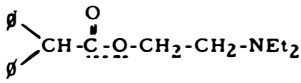
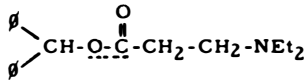
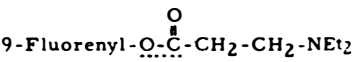
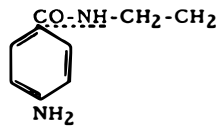
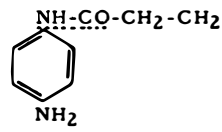
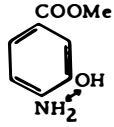
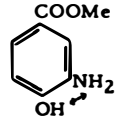
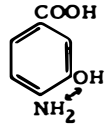
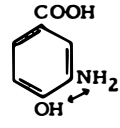
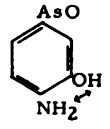
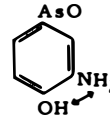
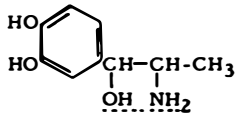
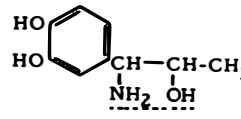
TEST		
Analgesic (82, 55)	 Demerol	 30 x Demerol
Choline-like (Muscarinic) Acetylcholine = +++ (33)	 (Betaine ester) ++	 (Acetyl - formocholine) ++
Antispasmodic vs. Histamine vs. Acetylcholine (5)	 very weak moderate	 very weak moderate
Antispasmodic (35)	 (Trasentin)	 Activity?
Ditto (35)	 (Pavatrine)	 Activity?
Local anesthetic (61)	 weak?	 Activity?

TABLE 16 (Cont.)

SPECIAL CLASS

Reversed Polarity

TEST		
Local anesthetic (56)	 (Orthoform) Active	 (Orthoform new) Active
Antitubercular molar conc. for stasis (72)	 1/200	 1/200
vs. T. pallidum in vitro ØAsO = 100 (40)	 40	 38
Pressor (85,66)	 1/12 epi	 Inactive

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