ANTIHISTAMINE DRUGS

BERNARD IDSON

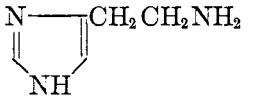
Polytechnic Institute of Brooklyn, Brooklyn 2, New York

Received September 12, 1950

CONTENTS

I. Introduction

Proof of the concept that histamine (I) or a histamine-like substance is responsible for the various symptoms associated with allergic reactions has



I

Histamine

prompted a vigorous search for substances which would antagonize this powerful agent. Several compounds have been developed which are extremely useful in the symptomatic amelioration of these many allergic phenomena (195).

The chemical structures of these antihistaminic drugs vary, yet the prominent compounds exert similar pharmacological and therapeutic action. There is considerable difference in potency, in both animal experiments and clinical tests.

The therapeutic effects of the antihistamine compounds are most evident in the nasal allergies, such as seasonal hay fever and vasomotor rhinitis. Urticaria, angioneurotic edema, motion sickness, the nausea of pregnancy, and serum sickness are other indications which have been relieved (258). Considerable publicity has been given reports of the abortion of the "common cold" (119).

Undesirable side effects, such as sedation, lassitude, and muscular weakness, are produced, the incidence of which varies with the individual drug and the individual patient.

Loew (257) defines antihistaminics as "drugs which are capable of diminishing or preventing several of the pharmacological effects of histamine and do so by a mechanism other than the production of pharmacological responses diametrically opposed to histamine." Consequently, antihistaminic drugs are a special category of spasmolytic drugs, and justification for the name is found in the extraordinarily high specificity of these compounds in antagonizing histamine-induced physiological effects. This specificity is relative and not absolute, for pharmacological experience has proved that absolute specificity is rare and practically unattainable. To a varying extent antihistaminics exert anti-acetylcholine, local anesthetic, sympathomimetic, sympatholytic, antispasmodic, analgesic, and quinidine-like actions (274).

Excellent reviews have appeared (39, 41, 49, 76, 93, 97, 108, 133, 135, 136, 147, 161, 179, 182, 197, 210, 219, 223, 227, 236, 268, 272, 276, 292, 314, 315, 322, 388, 402, 414, 421, 422, 435, 445, 447), outstanding among which are those of Loew (257, 258), Haley (169), Huttrer (200, 201), Dunlop (117a), Viaud (443), the book of Bovet and Bovet-Nitti (32), and the Annals of the New York Academy of Sciences (10).

II. Historical

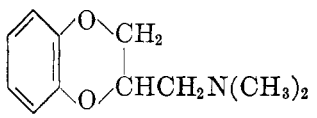
Dale (105) in 1929 noted that the effects of histamine in animals resembled those of anaphylactic shock and advanced the theory that histamine is liberated from the tissues of animals by cell stimulation due to the interaction of an antigen and antibody. Dragstedt (116) compared the physiological effects of histamine with the symptoms observed in asthma, anaphylaxis, and other allergic and pathological conditions and reached the conclusion that, although histamine may not always be the main causative agent, any prevention of its effects would be of great benefit. Rosenthal (233, 234, 372, 374, 375, 376) has published a series of studies designed to prove that histamine or a histamine-like substance is the chemical mediator for cutaneous pain. Thus a large body of evidence has accumulated to indicate that histamine is released in anaphylactic shock and similar reactions in amounts adequate to account for many features of these phenomena (116, 191, 194, 330, 387, 437).

Therapeutic efforts to combat the action of histamine resulted in the use of gradual doses of histamine to desensitize patients and the conjugation of histamine with proteins through azo linkages (138, 389, 450). Feinberg (134), in a report to the Council of Pharmacy and Medicine of the American Medical Association, concluded that the treatments were ineffective. Diamine oxidase (histaminase, Torantil), a kidney enzyme, proved effective in the prevention of the toxic effects of histamine (23, 24, 121, 122), but recent highly purified extracts of this enzyme (318, 417) proved too toxic for clinical use (24, 130, 134, 167, 318, 348, 368). The destruction of histamine appears to be an oxidation phenomenon, but disagreement exists as to whether the enzyme leaves the imidazole ring of histamine intact (417, 418, 451). Several amino acids, including arginine, histidine, and cysteine, inhibit the characteristic action of histamine in laboratory experiments (120). Since 5–10 mg. of arginine monohydrochloride was needed to counteract the effect of 0.02–0.05 microgram of histamine (177, 369, 380), no clinical tests were performed. Amino acids, such as arginine and spermine, are 100,000 to 1,000,000 times less effective than the present synthetic antihistamine substances.

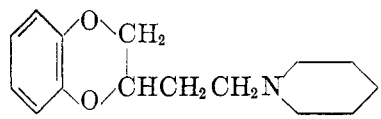
Over 200 compounds other than those included in this review have been tested for activity. Hill and Martin (189) published an extensive review in 1932 which served to emphasize the fact that, although numerous substances had been tested, there were none which could be considered ideal agents for alleviating anaphylactic shock in experimental animals. Some of the more recent substances tested include the following: cardiazole (416), pyridinesulfonamide (410), ascorbic acid, and ascorbates (153, 379), bile acids (128), procaine and quinidine

(118), 2-diethylaminoethanol (89), imidazole (293), nicotinamide (57, 151), pyridylbenzamide (275), cocaine, novocaine, percaine (118, 152, 324, 345), xanthines (129), coramine (164), folic acid (428), vitamin A (13), formaldehyde (217, 218), and various hypotensive agents (14). The claim that ferrous ion is an aid in the prevention of the side effects and potentiates the activity of antihistamines (409) has been disputed (386). Sympathomimetic and sympatholytic substances have been tested and found relatively active, but their primary action is not against histamine (19, 26, 58, 420).

In 1937 Bovet (38, 408, 433) issued preliminary reports concerning the first effective synthetic antihistaminic drugs. Previous studies of sympathomimetic and sympatholytic poisons, carried out in the Pasteur Institute, had shown that a relationship exists in the pharmacodynamic response between the different series of alkyl aromatic amines: 2-(phenylthio)ethylamine, phenethylamine, 2-phenoxyethylamine, and *N*-phenylethylenediamine. Neither phenylethylamines nor thioethylamines counteracted histamine, but the benzodioxans F 883 (II) (33, 140, 141, 145) and F 933 (III) exhibited mild antagonism, prompting further

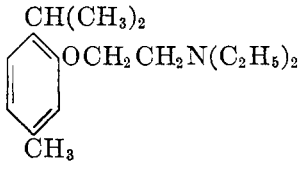


II
F 883

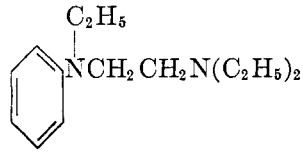


III
F 933

studies of related phenolic ethers. In a series of twenty-one ethers, F 929 (2-isopropyl-5-methylphenoxydiethylamine or 2-thymyloxytriethylamine) (IV) proved to be the most active in alleviating the symptoms of histamine shock in guinea pigs. *N*-Phenylethylenediamines behaved in a similar fashion. Within a series of seventeen amines, F 1571 (*N*,*N*-diethyl-*N'*-phenyl-*N'*-ethylethylenediamine) (V) proved to be the most active (407), but diverse toxic effects, such as cyanosis, prostration, and convulsions, prohibited the clinical use of these substances. More potent antihistamines resulted from a study of twenty-four



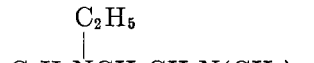
IV
F 929



V
F 1571

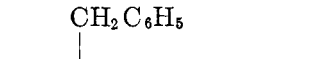
derivatives of F 1571 which had been synthesized by Mosnier (176, 434). The dimethyl homolog of F 1571, *N*-phenyl-*N*-ethyl-*N'*,*N'*-dimethylethylenediamine (VI) (RP 2325), had greater antiasthmatic activity than F 1571 and reduced toxicity. The replacement of the ethyl group by benzyl, giving *N*-phenyl-*N*-benzyl-*N'*,*N'*-dimethylethylenediamine (RP 2339 or Antergan) (VII), resulted

in sufficient improvement to justify the first human therapy. The clinical introduction of this drug was marked with great success and represented, after epinephrine, the first significant step in the chemotherapy of allergic diseases. In



VI

RP 2325



VII

Antergan

spite of its increased activity and tolerance, Antergan produced a number of unpleasant side effects and was, moreover, ineffective in many patients.

From 1942 on, research in France shifted to the investigation of heterocyclic compounds. Definite progress was made by Horclois (40), who substituted pyridyl for the phenyl group in Antergan. Around 1943 research on heterocycles started in the United States. To American investigators, working mainly with aminopyridines, the appearance of Bovet's publication (35) dealing with these compounds was a complete surprise. Neoantergan (RP 2786) was shown to possess a remarkable degree of antihistamine potency (34, 35, 40).

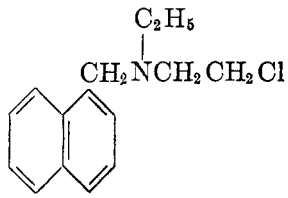
Several American publications appeared shortly thereafter. In 1945 Loew (263) reported tests on a series of benzhydryl alkamine ethers which had been synthesized by Rieveschl and Huber (367). 2-Dimethylaminoethyl benzhydryl ether (Benadryl) and several related tertiary amines were found to exert definite antihistaminic and antianaphylactic action.

Also in 1945 Mayer (277, 278) reported the considerable activity of *N*-(α pyridyl)-*N*-benzyl-*N'*,*N'*-dimethylethylenediamine (Pyribenzamine). Benadryl and Pyribenzamine were immediately and widely used by the medical profession, and many pharmacological and clinical reports on their use have been published.

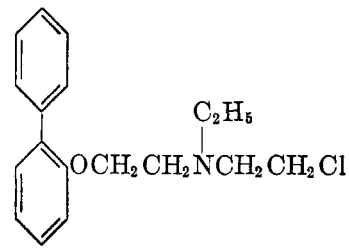
A multitude of compounds have been prepared and tested for antihistaminic potency. In many cases, patents and publications are extremely vague as to the latter. The structures and activity of all synthetic antihistamines will be noted in the subsequent portions of this paper.

About twenty compounds have been offered for clinical use (195). Table 1 lists these and recently published active compounds in alphabetical order. Their syntheses and properties will appear in the main body of the review.

Aryl-substituted β-haloalkylamines have been demonstrated to be potent antihistaminics; in contrast to other agents which enhance the pressor action of epinephrine, these compounds block and reverse this pressor action (257). *N*-2-Chloroethyl-*N*-ethyl-1-naphthalenemethylamine (VIII) and 2-(2-biphenylyloxy)-2'-chlorotriethylamine (IX) exert this dual action. Chemically, these compounds are related (177) to Dibenamine [*N*-(2-chloroethyl)-dibenzylamine], a compound which exerts adrenergic blocking action but which is almost devoid of antihistamine action (302, 303, 305). Nickerson (301) has covered the pharmacology of "adrenergic blockade" in an excellent review. The principal clinical



VIII

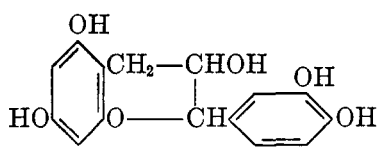


IX

application of these drugs appears to be in the group of peripheral vascular diseases.

The adrenocorticotropic hormone (ACTH) has been used with remarkable success in treatment of the allergic reactions of asthma, hay fever, and drug sensitivity (149a). This work was based on the experimental studies of Rich and Gregory (346, 347), which suggested a relationship between the hypersensitive state and rheumatic diseases.

Based upon the hypothesis that greater therapeutic value would result from the prevention of the formation of histamine than from prevention of its action, as occurs with standard antihistamines, studies were made of the inhibition of histidine decarboxylase, an enzyme in animal tissues which is capable of forming histamine from histidine. Flavonoids proved to be the most effective inhibitors. Catechin (X) protected guinea pigs against anaphylactic shock, but not from



X

Catechin

histamine shock (296). The results were interpreted as reflecting *in vivo* inhibition of histidine decarboxylase.

III. Testing

A. Pharmacological

Antihistaminic drugs are assayed by observing whether or not they will inhibit or block one or more of the easily demonstrable pharmacological effects of histamine. In one test, the lethal dose of histamine injected intravenously is determined for a group of guinea pigs. The compound to be tested is injected subcutaneously and increasing doses of histamine are thereafter given to determine the maximum dose which the animal survives and thus the protective effect of the drug. A second test is designed to measure the protective action of

the drug against the lethal effect of histamine inhaled by a guinea pig. If the animal is subjected to a fine mist of histamine solution, respiratory distress occurs within a short time. On removal from the spray the animal will recover, but if it is allowed to remain exposed to histamine, death will occur from asphyxiation due to a muscular spasm of the bronchioles, which prevents sufficient ventilation of the lungs. Guinea pigs that have received a sufficiently large oral or parenteral dose of an antihistaminic are able to resist the asphyxial action of histamine for much longer times. The dose of the drug that is necessary for this protective effect is a measure of its antihistaminic potency. Since protected animals can be exposed repeatedly to the histamine spray at regular time intervals, the return of the asphyxial signs may be observed as the drug is eliminated by the animal; thus a measure of the duration of activity may be obtained. The third general test determines the power of the antihistamine to prevent contraction of the isolated ileum of the guinea pig. By appropriate adjustment of the concentrations of histamine and the antagonist, an assay method is devised whereby one antihistaminic may be compared with another. The estimate of activity is derived from the ratio of the concentrations of the antihistaminics that cause equal inhibition of the histamine spasm. A fourth test determines the effect of a drug in preventing the depressor action of histamine on the blood pressure of a dog or cat. The final major test measures the capacity of the antihistaminic to abolish or diminish the size of a wheal caused by an intradermal injection of histamine (344).

Other more precise methods have been developed, including the use of the tracheal chain (66, 67, 68), canine spinal fluid pressure (390), and area changes in the bronchi of dogs and cats (132). An equation relating the affinity of histamine and the antihistamine for the cell receptor has been proposed (449). Precise results were obtained (289, 381, 382), utilizing an older idea (91) of measuring drug antagonism through the concentration which would neutralize the effects of a tenfold increase of the drug. The dynamics of recovery for the isolated intestinal strip was considered a reliable quantitative assay (21, 370). Antihistaminic activity can be measured *in vivo* by means of fluorescein (50). In *normal* subjects fluorescein disappears rapidly under the influence of histamine, and antihistaminic substances always neutralize this effect. In *allergic* subjects fluorescein alone is visible only for a short time, but when antihistaminics are added fluorescence is visible for a prolonged period of time. Avoidance of large standard errors of group assays is proposed through the equations of S. Loewe (266, 267), while time–per cent curves give rapid nomographic solutions (255). The inhibition of the spasmogenic effect of histamine or acetylcholine following a short exposure is used as a differentiation of the two innervators (174, 271). Histamine iontophoresis has been used to determine comparative activity in man. The initial threshold is determined by the highest dilution of histamine base producing diffuse punctate whealing. The threshold of the drug is redetermined by administering it orally and the difference between the two determinations is a measure of activity (412).

B. CHEMICAL

1. Histamine

The normal histamine content of human blood as determined by bioassay ranges from 1 to 8 gammas (γ) per 100 ml., with an average value of about 4 γ (186, 371). These low levels have limited the development of chemical analysis until suitable micro methods could be developed.

Two chemical methods which have become available for the analysis of histamine in biological fluids involve the coupling of imidazoles with 4-nitroaniline (378, 419) and with 2,4-dinitrofluorobenzene (280, 281). The two methods were combined and modified (269) to permit the colorimetric analysis of 0.1–1.0 γ of histamine in a 5–10 ml. specimen of whole blood. Chromatography has been successfully applied to the problem (437). Sodium 1,2-naphthoquinone-4-sulfonate (270) and *p*-bromoaniline (20, 436, 437, 438) have been recommended as colorimetric reagents.

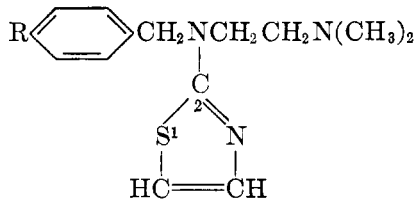
2. Antihistamines

Specifications and identifying tests for Benadryl (298), Pyribenzamine (337), Thenylene (334), Neohetramine (336), Decapryn (333), Trimeton (335), Dramamine (297), and Antistine (332) have been reported in *New and Non-Official Remedies*. The tests described are nonspecific.

Haley and Keenan (168, 171, 172, 173, 174, 221) studied the reactivity of several antihistaminic drugs with simple alkaloidal precipitants and color reactions to see if such tests could serve as means of identification. Benadryl and Pyribenzamine gave the same type of precipitate with most of the precipitation reagents. The only reagent useful in their identification was chloroplatinic acid (168, 221), with which different crystalline precipitates were obtained. The results of precipitation and colorimetric tests on several different antihistaminic drugs brought forth many distinctive differentiations and identifications (table 2).

Crystallographic properties, also determined by Haley and Keenan, pointed out even better means of identification. Excellent photomicrographs were obtained, using the immersion method with the polarizing microscope (171, 172, 173).

The effect of radical substitution on the optical properties of derivatives of *N*-2-thiazolylethylenediamine (White 194B; table 1, No. 27)



where R represented hydrogen, chlorine, or methoxy, yielded interesting observations (222). The crystal habits of the three substances appeared essentially

identical in ordinary light. However, there was a very marked difference in the axial angles. The angle was quite large where hydrogen substitution occurred and was much smaller when chlorine was in position. Cavallini recorded the effect of various alkaloidal reagents on benzhydryl 2-imidazolin-2-ylmethyl ether (71).

The analytical method of Brodie (43, 44, 45, 46, 47) for the analysis of organic bases was utilized for the determination of the changes in concentration of Benadryl and Pyribenzamine in blood, urine, and spinal fluid (160). The method depends on the reaction of the organic base with methyl orange to form a colored complex salt which is soluble in ethylene dichloride. Dill (111) noted that the above procedure gave high blanks in the analysis of urine and tissues and therefore utilized a double-extraction technique to eliminate interferences. The identity of Benadryl in the urine was established by counter-current extraction with the Craig technique (96) and by the ultraviolet absorption spectrum (162a).

The red color with concentrated sulfuric acid gave a sensitivity of 20 mg./l. of Neoantergan (117). The turbidity of an ether extract of a protein-free blood filtrate after treatment with iodine allowed measurement of 5 γ of Pyribenzamine and 3 γ of Antistine per milliliter of human blood (321).

A colorimetric method for the determination of *N*-(2-pyridyl)-substituted antihistamine drugs consists in the opening of the pyridine ring by cyanogen bromide and the coupling of the intermediate compound with aniline, resulting in the formation of a yellow complex which follows Beer's law (213, 316). Ammonium reineckate, in aqueous solution, quantitatively precipitated most of the antihistamine compounds. The precipitates are isolated, dissolved in acetone, and determined colorimetrically (17). Various sympathomimetic amines, such as ephedrine, amphetamine, and desoxyephedrine, did not interfere.

The ultraviolet absorption spectra of a large series of antihistaminic compounds were determined (148, 149) to ascertain whether adequate sun screening could be obtained. Characteristic spectra with well-defined maxima were found for *N*-(2-pyridyl)ethylenediamines and form the basis for excellent determinations (9, 88, 273). Four micrograms of Thenylene or Neoantergan was determined with an accuracy of ± 0.5 per cent.

Compounds containing nitrogen, sulfur, and halogens may be analyzed, after combustion, by standard methods. The bases can be titrated with standard acid and the acid salts with standard alkali, but these methods are nonspecific.

IV. Histamine Antagonists

Bovet and Bovet-Nitti (32), in their book on drugs affecting the autonomic nervous system, classify antihistaminic agents according to their mode and site of action. The compounds are separated into two groups, dependent on whether their pharmacological action resembles that of sympathomimetic and sympatholytic agents or whether their antagonism is mainly directed toward the parasympathetic nervous system. In the first group are placed the phenolic ethers and derivatives of aniline, α-aminopyridine, aminopyrimidine, phenylaminomethylimidazoline, aminochloroethane, and phenyltetrahydropyridindene. In

the latter spasmolytic grouping are placed the benzhydryl ethers, derivatives of phenothiazine, and esters of phenyl-α-thenylglycolic acid.

This review will not utilize a pharmacological division, but will employ a broader structural classification, dividing the histamine antagonists into derivatives of ethanolamine, derivatives of ethylenediamine, derivatives of aminopropane, derivatives of phenyltetrahydropyridindene, and amino esters.

A. DERIVATIVES OF ETHANOLAMINE

1. Phenolic ethers

2-Thymyloxytriethylamine (IV) was the first synthetic substance which was found to exhibit potent antihistaminic properties (38). The weak sympatholytic properties of the compound had been noted previously (7, 8). Staub described (407) the antihistaminic properties of the phenoxyethylamines prepared by Maderni (36) (table 3).

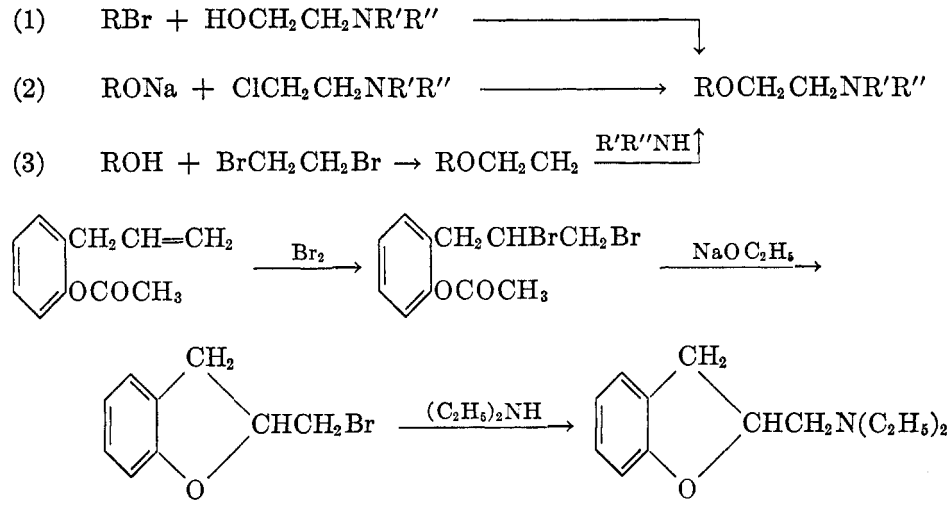
Various relationships between chemical constitution and antihistaminic activity were observed. The nitrogen atom in the alkyl side chain must be tertiary, for replacement of one of the ethyl groups in the amine radical, to yield the secondary amine (F 1482), suppressed all activity. Replacement of the diethylamino group by piperidine (F 1462) caused a large decrease in activity. Isomeric compounds had practically identical actions (F 929 and F 1379; F 1482 and F 1483; F 1464 and F 1465). Of the various derivatives of (2-phenoxyethyl)-diethylamine or F 928 (F 940, F 1274, F 1262, F 1306, F 1323, F 1655), only 2-(2-biphenylyloxy)triethylamine (F 1262) possessed activity, but its cardiac activity precluded any further study. Tastromine, the dimethyl analog of F 929, is probably slightly superior to the latter, but its histaminolytic properties have not been fully investigated.

Monobasic and polybasic aryl ethers, prepared and studied by Protiva (327), exhibited very mild activity (table 4, Nos. 1–13). The ortho-disubstituted phenol possessed 10–30 times the activity of the meta- and para-substituted (Nos. 2 and 3) and the trisubstituted ethers (Nos. 4 and 5). The aminoalkyl benzyl and benzhydryl ethers (Nos. 6–9) were appreciably more active, while the benzhydryl thioethers (Nos. 12 and 13) were of the same order of activity, with diminished toxicity (No. 13). The diphenyl derivatives (Nos. 11 and 12) are relatively inactive, compared to the benzhydryl ether derivatives (table 5) and the recent potent derivatives of benzylphenol (table 19).

Dialkylaminoalkyl thioethers were prepared to study the effect of replacement of oxygen and nitrogen in compounds of the type of Benadryl and Pyribenzamine (table 4, Nos. 14–21) (31). The pharmacological properties were not reported.

The amino ethers were prepared either by the condensation of the aryl bromide with a dialkylamino alcohol, or by that of the sodium salt of the cyclic alcohol with a dialkylaminoalkyl halide. A variation of the latter method consists in reacting the cyclic alcohol with ethylene bromide and treating the resultant

bromo ether with a dialkylamine. F 929 was initially synthesized by the vacuum distillation of β-diethylaminoethylthymyl carbonate (124, 125). Fourneau and Lestrange (*cf.* 407) heated sodium thymolate in a sealed tube with 2-chlorotriethylamine. The same result has been obtained in open reflux (106). Thymoxyethyl bromide (from thymol and ethylene dibromide) and diethylamine give the desired product (373). F 883 (II) was obtained from the condensation of catechol and epichlorhydrin in the presence of alkali and reaction of the product with dimethylamine (145). The ring closure of the substituted allylphenol yielded the corresponding coumaran. The benzodioxan was relatively inactive, protecting only 30 per cent of test animals from a single toxic dose of histamine (433).



The dialkylaminoalkyl aryl ethers and thioethers (table 4) resulted from the condensation of sodium phenates and thiophenates with chloroalkylamines (31, 327).

2. Benzhydryl ethers

The ethers of benzhydrol represent the first potent histamine-antagonizing drugs which originated in the United States. The most active of an initial series of seventeen benzhydryl ethers tested by Loew, Kaiser, and Moore (263) (table 5) was the dimethylaminoethyl derivative, Benadryl (table 1, No. 3), synthesized by Rieveschl and Huber (354, 367), which protected guinea pigs against seventy-

$(C_6H_5)_2CHCOOCH_2CH_2N(C_2H_5)_2$

XII

Trasentin

five toxic doses of histamine. The benzhydryl ethers are closely related to the spasmolytic agents and the acetylcholine antagonists of the Trasentin (XII) type, which are benzhydryl esters. Loew (264) compared the antispasmodic and antihistaminic activity of atropine, papaverine, Trasentin, Pavatrine, Benadryl, and F 1571. Benadryl was a much more potent antispasmodic than Pavatrine and Trasentin, the most effective antispasmodics. It exerted weak antagonism against barium, and moderate antagonism against acetylcholine, the latter being one-half to one-tenth that exhibited by Trasentin and Pavatrine. F 1571 (V) was comparatively impotent in antagonizing barium and acetylcholine.

The three most potent compounds in table 5, listed therein in descending order of activity, were the 2-dimethylaminoethyl, 2-piperidinoethyl, and 2-morpholinoethyl benzhydryl ethers. The first two are at least twice as potent as benzhydryl 2-morpholinoethyl ether, which has an activity comparable to that of F 1571, the most active Fourneau antagonist.

Several conclusions can be drawn concerning the relationship between molecular structure and antihistamine activity (263). A chain length of two carbon atoms is found in the five most active compounds (table 5, Nos. 1–5). Compounds with longer or branched carbon chains are less active. This is apparent in comparing No. 3 with Nos. 8, 12, and 14; however, the relative potency of Nos. 6 and 7 opposes this view. An increase in chain length obtained by an oxygen-interrupted chain (No. 15) also decreased the activity. The character of the substitution on the nitrogen atom is seen by comparing Nos. 1, 4, and 9, in which the activity is in the order of the tertiary > secondary > primary amine. In general, the data indicate that an increase in the size of the group on the nitrogen atom leads to less active compounds in both the secondary and the tertiary amines (compare Nos. 4, 5, and 13; also Nos. 1, 6, 16, and 17). No. 11 represents one example of substitution on the benzene rings of the benzhydryl group. On comparison with the analogous unsubstituted compound (No. 3) the 4,4′-dichlorobenzhydryl 2-morpholinoethyl ether is seen to be much less active, but also less toxic. Substitution in the benzhydryl part of Benadryl resulted in major loss of activity. Simple substitution of halogen, or rearrangement of phenyl rings to give fluorene or naphthalene derivatives, resulted in agents with little activity. Lesser toxicity was claimed for the *p*-methoxy derivatives (159).

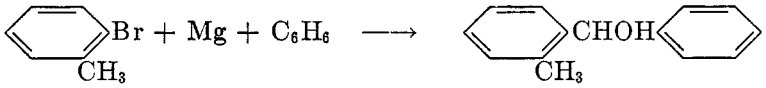
Rieveschl, in a series of patents (349, 350, 351, 352, 353, 354, 355, 356, 358, 366, 367), has described an extensive series of benzhydryl ethers prepared by the condensation of a benzhydryl halide with the appropriate dialkylamino alcohol, usually in the presence of an acid-binding agent, such as an alkali carbonate.

$$(C_6H_5)_2CHBr + HOCH_2CH_2NRR' \rightarrow (C_6H_5)_2CHOCH_2CH_2NRR'$$

Alternate methods of preparation included the reaction of an alkali metal salt of benzhydrol with a 2-dialkylaminoethyl halide or the reverse condensation of the alkali metal salt of a 2-dialkylaminoethanol with a benzhydryl halide.

$$(C_6H_5)_2CHONa + XCH_2CH_2NRR' \searrow$$
$$(C_6H_5)_2CHOCH_2CH_2NRR'$$
$$(C_6H_5)_2CHBr + NaOCH_2CH_2NRR' \nearrow$$

Substituted benzhydrols have been made *via* the Grignard addition compound (326).



Benzhydryl bromide was obtained when diphenylmethane and bromine were heated together, with illumination (354). The benzhydrols are readily obtained by the reduction of the benzophenone with either aluminum isopropoxide or zinc dust and alcoholic caustic (165). The ethers of the 1-alkyl-4-piperidinols were obtained from either the benzhydryl halide and the piperidinol or the 1-alkyl-4-halopiperidine with the alkali salts of benzhydrol (226).

Table 6 lists reported benzhydryl ethers according to structural similarities. Methods of synthesis are not reported, since practically all preparations are performed as previously described.

A number of benzhydryl sulfones, synthesized by Klenk and Suter (225), have been tested as analgesics.

The studies of Alles and Redemann (6) on the comparative spasmolytic activities of the salts of Nos. 6, 7, 8, 12, 13, 14, 15, and 73 (of table 6) are shown in table 6A. Examination of the results of table 6A shows that single or double branching of the chain with a methyl group, in either the 1- or the 2-position of the ethyl group in benzhydryl dimethylaminoethyl ether, diminishes the antihistamine activity. This diminution can also be viewed in the light of changing the oxygen function of the α-carbon of the alkyl part of the ether from that of a primary carbinol to that of a secondary and tertiary carbinol, and of changing the nitrogen function of the β-carbon of the alkyl part of the ether from that of a primary carbindimethylamine to that of a secondary and tertiary carbindimethylamine.

The lengthening of the alkyl group of the ether from that of a 2-dimethylaminoethyl ether to a 3-dimethylaminopropyl ether also diminishes the antihistamine activity. The introduction of a triphenylmethyl radical rather than the diphenylmethyl radical, with the increase in the electronegative character of the carbon adjacent to the ether link, diminished activity, though this may also (and more probably) be related to the very considerable concomitant increase in the size of the molecule.

A comparison of the *m*-chloro derivative of Benadryl (table 6, No. 63) with Benadryl revealed it to be three times as active and less toxic (290).

Wright, Koloff, and Hunter (463) prepared two alkamine ethers (table 6, Nos. 20 and 29) by the reaction of the disubstituted methyl bromide with the

requisite amino alcohol in the presence of anhydrous potassium carbonate. The hydrochloride of benzhydryl 2-pyrrolidylethyl ether (No. 20) possessed 1.5–2 times the activity of Benadryl, while that of benzhydryl 2-(4-methylpiperazyl) ethyl ether had only 0.1 the activity.

To aid in metabolic studies (163), Fleming and Rieveschl (139) prepared Benadryl containing isotopic C^{14}. The $C^{14}O_2$ was generated from barium carbonate containing 6.88 mc. of C^{14}. The overall yield based on barium carbonate was 55 per cent.

$$C_6H_5MgBr + C^{14}O_2 \longrightarrow C_6H_5C^{14}OOH \xrightarrow{SOCl_2} C_5H_{15}C^{14}OCl$$

$$\xrightarrow[(AlCl_3)]{C_6H_6} (C_6H_5)_2C^{14}O \xrightarrow[i\text{-}C_3H_7OH]{Al(O\,C_3H_7\text{-}i)_3} (C_6H_5)_2C^{14}HOH \xrightarrow[C_6H_6]{CH_3COBr}$$

$$(C_6H_5)_2C^{14}HBr \xrightarrow{HO\,CH_2\,CH_2N(CH_3)_2} (C_6H_5)_2C^{14}OCH_2\,CH_2N(CH_3)_2$$

To offset the drowsiness caused by certain antihistamines, attempts were made to combine the bases with the methylxanthines, selected because of their stimulation of the central nervous system. Because of the low ionization constants of the methylxanthines, however, no stable salts were obtained. The problem was solved by the use of 8-chlorotheophylline, which has a high enough ionization constant to form a stable salt (100). Dramamine (table 1, No. 10), the 8-chlorotheophylline salt of Benadryl, has received wide publicity in the treatment of motion sickness. Its antihistaminic potency and spasmolytic activity are respectively 1.5 and <1 times that of the ether on a molar basis (158). Cusic (101) prepared various xanthine salts of 2-dimethylaminoethyl ether by the action of a haloxanthine on a diarylalkyl ether of an amino alcohol (table 7).

3. Quaternary ammonium salts of benzhydryl alkamine ethers

Conversion of the tertiary amines derived from benzhydryl ethers to quaternary ammonium salts does not alter the antihistaminic action to a great degree, but greater antispasmodic qualities become evident. The methiodide of Benadryl [(2-benzhydryloxyethyl)trimethylammonium iodide] was approximately one-half as effective as Benadryl against histamine and barium, but four times more potent with respect to the antagonism of acetylcholine action, on intestinal muscle (264). Thus, atropine-like qualities were increased at the expense of antihistamine properties. Winder, Kaiser, Anderson, and Glassco (459) present an excellent discussion of the resultant of the influences of molecular structure at both ends of two carbon alkylamine bridges, which are of primary importance in the physiology and pharmacology of the autonomic nervous system (32). In the adrenergic system an optimal circumstance of the aminoethyl chain appears to be extension or attachment to the aryl structure; in the histaminic system, attachment to a heterocyclic structure for activation or through an ether or nitrogen linkage to an aryl or aralkyl group for interference; in the cholinergic

system, either ester or ether linkage, with quality and quantity of action influenced by the state of both molecular extremities. In the structure of Benadryl, as compared with that of histamine (I), the 2-imidazolyl structure of the latter is replaced by a benzhydryl ether group, and as the function of the nitrogen is changed from primary to tertiary the histamine interference increases (263). Thus, in the presence of the benzhydryl ether group, as histamine interference increases, the function of the nitrogen progressively deviates from that in histamine. From this view it is not surprising to find essential maintenance of interfering potency in passing on to the quaternary amines. These are now in the class of choline derivatives, in the cholinergic system (459). Ing (205) found that atropine-like action was sharply increased by substituting ethyl for one of the three *N*-methyl groups of the benzilic acid esters of quaternary ethanolamines. The presence of the quaternary function is associated with curariform, parasympathomimetic, nicotinic, and adrenergic activities (204).

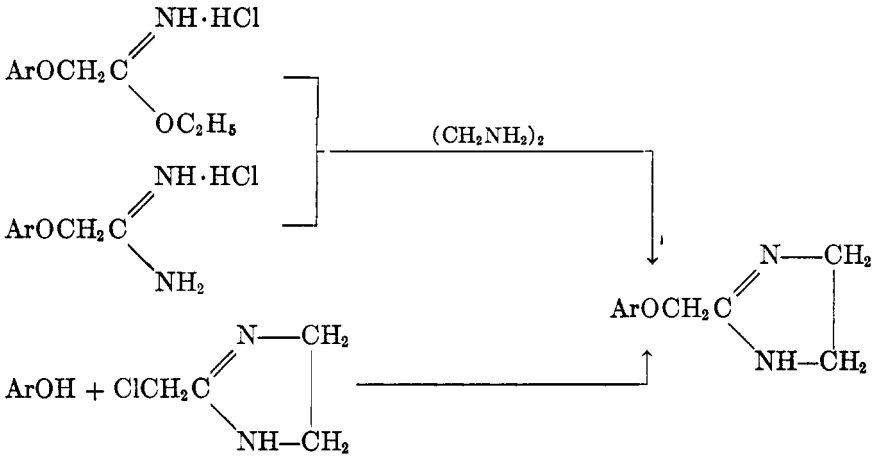
Table 8 lists some quaternary salts of benzhydryl ethers which were synthesized by treating the substituted aminoalkyl or chloroalkyl benzhydryl ether with the appropriate alkyl halide or alkylamine (351). The methiodide (No. 3), methochloride (No. 1), methyl *p*-toluenesulfonate (No. 5), and methosulfate (No. 4) were the most active of a series of quaternary salts initially tested (262). The failure of the present compounds to show any remarkable difference in histamine-interfering potency suggests that the ionic state is not of the order of importance that it is in the cholinergic system. The quaternary compounds do not appear promising as visceral spasmolytics because of a lack of good myotropic action to accompany the atropine-like action (458). There is a suggestion of increased toxicity in the ethyldimethylammonium derivatives (Nos. 6, 7, 8, and 9). This may be due to the approach to the curariform action of the triethylammonium ethers. A series of quaternary benzhydryl ethers have been patented for this activity (359), while long-chain molecules have been advanced as germicides (365).

4. Aryloxyimidazolines and amidines

The desirable features of 2-(*N*-benzyl-*N*-phenylaminomethyl)-2-imidazoline (Antistine, table 1, No. 2) prompted substitution searches in the ether series. In addition to their antihistaminic action, the imidazoline agents appear to have some direct effect upon almost every organ of the body.These effects are highly varied. This lack of specificity is not surprising, since only slight changes in the structure of Antistine produce the sympathomimetic drugs Privine [2-(1-naphthylmethyl)-2-imidazoline] and Otrivine [2-(anilinomethyl)-2-imidazoline] (301). Djerassi and Scholz (113, 115, 365) noted the similarity in the side chain of Antistine to that of Antergan (VII), 2-methylimidazolyl replacing the dimethylaminomethyl moiety. Since this change enhanced the desirable activity, the observation was extended to variations of the side chain of ring-alkylated aryloxyethyldialkylamines, of which F 929 (IV) is the best-known example. Since imidazolines can be considered to be cyclized amidines, aryloxyacetamidines were added to the investigation of the 2-(aryloxymethyl)imidazolines (113).

The amidines (table 9) were prepared by condensing ring-acylated phenols with chloroacetonitrile by a modification of the conventional Claisen *O*-alkylation of phenols. Treatment with ethanolic hydrochloric acid gave the ethyl aryloxyacetimidate hydrochlorides, from which the desired amidines were obtained with ammonia or substituted amines.

The aryloxymethylimidazolines (table 10) were synthesized by three different methods. The method of choice was the condensation of the imidic ester hydro-

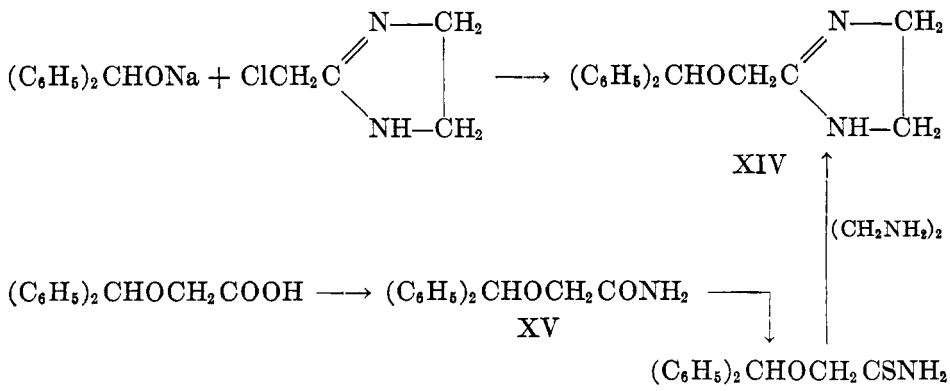


chloride (XI) with ethylenediamine (401).

Inspection of the pharmacological results (201) reveals that all the phenoxy compounds (table 9) were relatively inactive; this confirms Staub's rule to the effect that in the ether series the ring should be substituted. The 2-(thymyloxymethyl)-2-imidazoline was found to be at least as effective as F 929 (407), indicating that in this series the 2-imidazolylmethyl group was equal or superior to the diethylaminoethyl side chain. Most of the imidazolines were strong vasopressors with the exception of the 2-(*p*-cresoxymethyl)-2-imidazoline (table 10, No. 27), which showed adrenolytic action.

The analogy approach was applied to 2-dimethylaminoethyl benzhydryl ether (114). 2-(Benzhydryloxymethyl)-2-imidazoline (XIV) was synthesized and found to be a strong histamine antagonist (170). The same compound was prepared almost simultaneously in other laboratories (70, 71, 104, 328). The compound could be made either by the direct condensation of sodium benzhydrolate and 2-(chloromethyl)-2-imidazoline hydrochloride in toluene suspension (224) or by the conversion of benzhydryloxyacetamide (XV) to the thioamide, which reacted with ethylenediamine to afford the desired imidazoline (XIV).

All the various imidazoline derivatives subsequently prepared were made by either of these procedures. Reduction of 2-benzoylthiophene with aluminum isopropoxide gave 2-thienylphenylcarbinol, which was condensed with 2-(chloromethyl)-2-imidazoline, in the presence of sodium amide, to give 2-(thienylphenyloxymethyl)-2-imidazoline (*cf.* *p*-methoxyphenyl derivative: table 11, No. 15).



The pyridylmethylcarbinol (table 11, No. 16) resulted from a similar procedure (103). The compounds possessed only weak antihistamine action.

2-(Benzhydryloxymethyl)-2-imidazoline was about one-half as toxic as Pyribenzamine (table 1, No. 19) in rats and demonstrated antihistaminic and antianaphylactic properties comparable to those of Benadryl and Pyribenzamine. In contrast to most antihistaminic drugs, this substance relaxes the bronchiolar muscles of the guinea pig (114). Table 11 gives a list of aryloxyalkylimidazolines other than those initially prepared by Djerassi and Scholz (114).

5. Dioxolanes

Certain 1,3-dioxolanes have exhibited a high degree of spasmolytic activity. Brown and Werner (48) studied the parasympathetic depressant and antihistamine action of certain substituted 1,3-dioxolanes prepared by Blicke and Anderson (27) and by Blicke and Schumann (*cf.* 48) (table 12). The antihistamine activity was generally weak for all compounds; however, No. 10 had activity similar to that of certain antihistamines used clinically, while No. 5 was a potent parasympathetic depressant. The change to quaternary ammonium salts from halogen acid salts generally resulted in increased antiacetylcholine activity.

6. Heterocyclic substituted alkamine ethers

The extremely favorable change in therapeutic index which resulted from the replacement of the phenyl group in the Fourneau ethers (table 3) by the benzhydryl group (tables 5 and 6) prompted various investigators to substitute heterocyclic groups for phenyl in the benzhydryl portion.

The effect of heterocyclic replacement of one or both of the aryl functions (tables 13, 14, 15, 16, and 17) resulted in extreme limits of variation in toxicity and potency. The 1-pyrrolidyl and 4-methylpiperazyl benzhydryl ethers were appreciably more active (table 6, Nos. 20 and 30) than Benadryl. They were synthesized by treatment of the sodium (lithium) salt of the appropriate disubstituted carbinol with the aminoalkyl chloride.

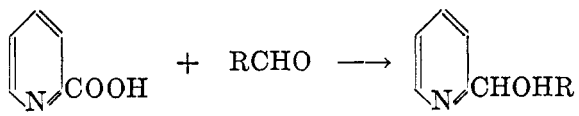
$$RR'CHONa(Li) + R''_2NCH_2CH_2Cl \rightarrow RR'CHOCH_2CH_2NR''_2$$

The use of one equivalent of 2-dimethylaminoethyl chloride resulted in low yields. This may be attributed to the ease with which the halide forms a cyclic piperazinium salt. The use of a large excess of the chloride did not materially improve the yield. Satisfactory results were obtained by treatment of the disubstituted carbinol with one equivalent of sodium or lithium amide to liberate the dimethylaminoethyl chloride from its salt.

A number of substituted dialkylaminoalkyl pyridylalkyl ethers were synthesized by Schwenk and coworkers (table 14) (405). The most active compounds were the 2-pyridyl derivatives in which R′ is phenyl or an alkoxy, alkyl, halogen, or dimethylamino substituted phenyl group, R″ is hydrogen or a methyl group, and R‴ is methyl. These compounds (Nos. 1, 3, 4, 5, 6, 7, 10, 19, and 20), referred to as group 1, exhibited antihistaminic activity comparable to that of Benadryl. The oral L.D.50 in mice was approximately 300–400 mg./kg.

Lower antihistaminic activity is exhibited by the 3-pyridyl compounds (Nos. 2, 8, and 21) and the 2-pyridyl compounds wherein R′ is 3,4-methylenedioxyphenyl (No. 8), benzyl (No. 11), phenethyl (No. 12), 2-thienyl (No. 13), *n*-propyl (No. 14); or wherein R‴ is C_2H_5 (Nos. 15 and 16). Variations in the length of the carbon chain of the ether also result in decreased potency (No. 17). In general, these compounds possess 1/5 to 1/100 the activity of the compounds in group 1.

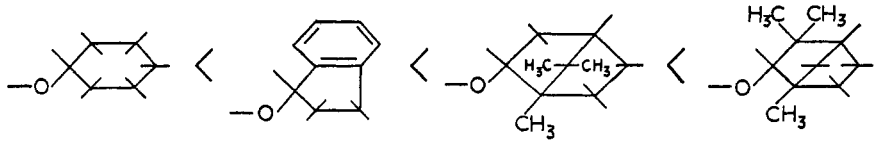
The pyridyl-substituted alkamine ethers were synthesized by the condensation of the appropriately substituted carbinols with dialkylaminoalkyl halides and sodium amide in toluene. The yields varied from 45 to 88 per cent. The secondary substituted 2-pyridylcarbinols were made by the decarboxylation of picolinic acid in the presence of an aromatic aldehyde at a temperature above 140°C. The products of the reaction are the desired carbinol, pyridine, and carbon dioxide.



A large group of similar basically substituted pyridine derivatives was synthesized by Tilford, Shelton, and Van Campen (423, 424, 425) (table 15). The antihistaminic activities showed that Nos. 1 and 7 were the most active of these tested. Substitution on the phenyl group of either of these compounds with alkyl, alkoxy, or halogen groups does not increase the activity, although Nos. 7, 9, 16, 17, 19, 20, and 21 have about equal potency. When a naphthyl (Nos. 14 and 15), pyridyl (No. 33), thienyl (No. 34), or cyclohexyl (No. 28) group replaced the phenyl group of No. 7, the activity was diminished considerably. The greater the degree of hydrogenation of the R group of No. 7, the lower the activity (No. 28 < No. 27 < No. 7). Replacement of the pyridine ring with a piperidine group has no apparent beneficial antihistaminic effect, as shown by the low order of activity of Nos. 53 and 54.

As the length of the carbon chain of group R′ increased beyond one carbon

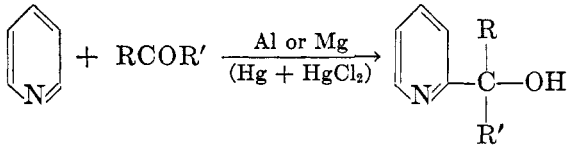
atom, the potency decreased: thus No. 23 < No. 22 < No. 7. Substitution on the chain with basic groups (Nos. 24 and 32) also lowered the activity. The antihistaminic effect of cyclic compounds (group B in table 15) seems to increase with branching on the carbon atoms near the ether linkage.



Compounds of group C (table 15), in which the point of attachment to the pyridine ring is at the 3- or 4-position, are not within the range of potency of Nos. 1 and 7. An additional methylene group separating the phenyl or the pyridyl ring from the ether linkage is detrimental to the antihistaminic activity, as shown by Nos. 8 and 42. Any variation of the dimethylaminoethyl side chain of No. 7 decreases the potency.

The most active compounds (Nos. 1, 7, and 9), when administered intravenously to guinea pigs at levels of 4–32 mg./kg., gave complete protection against 50–300 fatal doses of histamine injected intravenously.

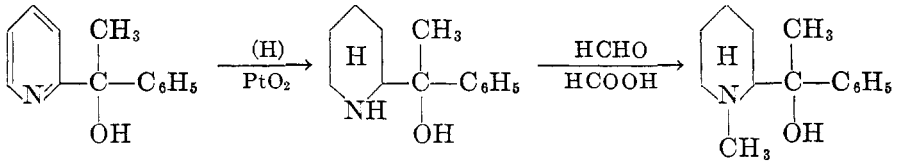
The most convenient method for the preparation of the α-substituted pyridinemethanols was through the condensation of a ketone with pyridine in the presence of aluminum or magnesium, mercuric chloride, and iodine.



Magnesium was a superior agent for condensing benzaldehyde with pyridine, whereas with substituted benzaldehydes the yields with aluminum were about the same as those with magnesium.

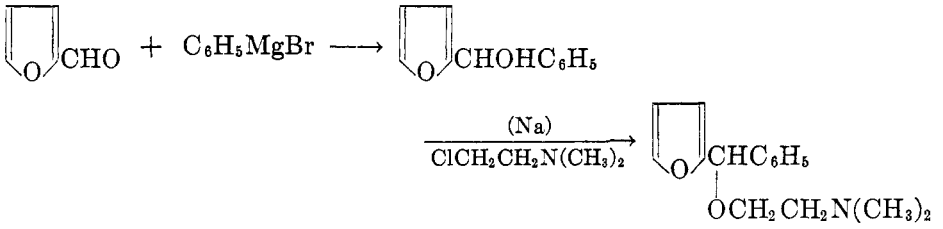
Preparation of these types of carbinols have been reported, using either pyridylmagnesium bromide (308, 325) or picolinic acid (11) and the carbonyl compound, as well as phenylmagnesium bromide and a pyridylcarbonyl derivative (430). A 3-pyridinemethanol (232) resulted from the reaction of 3-pyridylmagnesium bromide and benzaldehyde.

Several of the pyridinemethanol hydrochlorides were reduced catalytically to the piperidinemethanols. A compound where R is methyl (table 15, No. 54) was treated with formalin and formic acid and the *N*-methyl derivative was obtained.



The synthesis of 2-pyridinemethanol has recently been simplified (123). 2-Picoline was converted to the lithium salt by the hydrogen–metal interchange reaction between 2-picoline and phenyllithium. The picolyllithium was oxidized with a slow current of air to form the 2-pyridinemethanol. The effectiveness of Decapryn (table 1, No. 8; table 15, No. 7) as an antihistaminic agent prompted the preparation of the 2-pyrimidine- and 2-imidazoline-methanols (425) and their dimethylaminoethyl ethers (table 16, Nos. 1 and 2) (425), which were about 0.0025 as active as Decapryn.

The furyl isostere of Benadryl (table 16, No. 3) was prepared from furfural and the phenyl Grignard reagent (25).



This phenyl-2-furylmethyl 2-dimethylaminoethyl ether proved to be less than twice as active as Benadryl.

2-Diethylaminopropyl sulfides were prepared in an attempt to synthesize sulfur compounds analogous to Benadryl and Pyribenzamine with sulfur replacing the oxygen and the nitrogen linkage, respectively. The general structure of the molecule differs from these antihistamine drugs in that only one aryl group is present instead of the diaryl groups (table 17).

The 3-diethylaminopropyl derivatives were prepared by condensing the potassium arylthiolate with 3-diethylaminopropyl chloride. The derivatives of 1-diethylamino-2-propanol were prepared from the sodium salt of the aryl mercaptan with 1-diethylamino-2,3-epoxypropane. No pharmacological data were presented (31).

A large variety of *N*-2-pyridylalkanolamines were prepared by Weiner and Kaye (448) by heating 2-bromopyridine with the appropriate amino alcohol. Moffett (291) synthesized a series of pyrrolidylalkanols by a variety of methods. Lithium aluminum hydride was found to be very satisfactory for the reduction of pyrrolidyl-substituted esters or ketones to pyrrolidyl alcohols, and for the reduction of substituted pyrrolidones and succinimides to pyrrolidines.

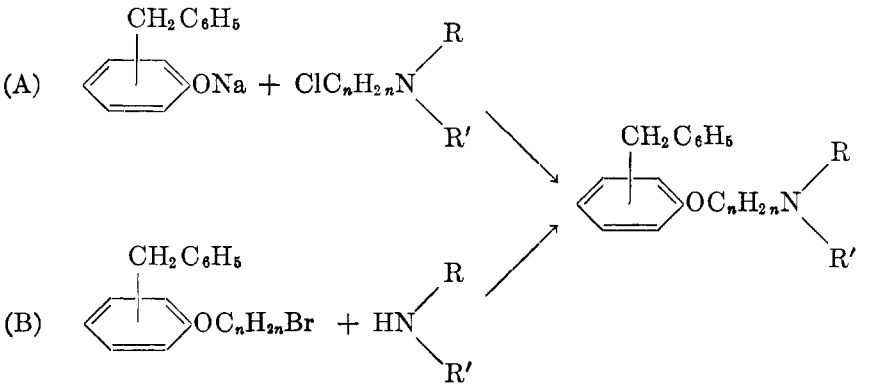
Heterocyclic ethers were prepared as part of a larger study by Sutherland and coworkers (415) (table 18), by modifications of the Williamson ether synthesis. Each of the dimethylaminoethoxy compounds was made by dissolving sodium metal in an excess of dimethylaminoethanol and then treating with the appropriate aromatic halide. None of the compounds was more active than Benadryl.

7. Benzylphenols

The effectiveness of F 929 (IV) and Benadryl (table 1, No. 3) led Binkley and coworkers (81, 453, 454, 456) to investigate the effect of the substitution of the benzyl group in the phenolic ethers (table 19). The hydrochloride of 2-benzyl-

phenyl 2-dimethylaminoethyl ether (C-5581-H, No. 4 in table 1) proved relatively nontoxic and elicited the highest order of antihistaminic and local anesthetic activity in animals. In contrast, the isomeric 4-benzyl (338-20) compound exhibited a low order of antihistaminic action. In general, branching or lengthening the alkylene chain, $—C_nH_{2n}—$, or replacing the dimethylamino group with other secondary amines did not lead to increased potency.

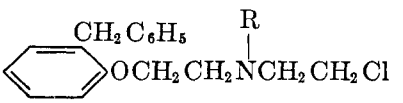
With the exception of the two hydrogenated derivatives (489-1 and 489-2), all of the compounds in table 19 were prepared by condensing sodium benzylphenoxide with the appropriate aminoalkyl chloride (A). Where low yields resulted, an ω-bromoalkyl ether of a benzylphenol was reacted with the appropriate amine (B). This proved to be the procedure of choice for the synthesis of an ether bearing a secondary amino group. Owing to the tendency for free alkylaminoalkyl chlorides to polymerize when heated in the presence of polar solvents, toluene was employed as a reaction medium and sodium or sodium hydride



was selected instead of sodium alkoxides for preparing the sodium salts of the phenols.

Pure 2-benzylphenol and 4-benzylphenol were readily separated from a commercial mixture (Santophen 7) by utilizing the marked difference in the water solubility of their barium salts. The method of Claisen (87) for the *C*-alkylation of phenols was used for the preparation of the intermediate substituted 2-benzylphenols, with extension to heterocyclic systems (table 19, Nos. 42–55). Conversion of the various substituted phenols to the 2-dimethylaminoethyl ethers proceeded smoothly *via* the Williamson ether synthesis.

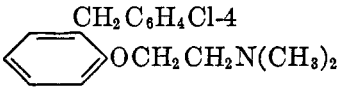
A series of 2–(2-benzylphenoxy)ethyl-2′-chloroethylamines (Nos. 56–79) were prepared for testing as spasmolytics (456).



Many of the members possess antihistaminic properties in various degrees, but their primary action is to reverse the pressor effect of epinephrine (*cf.* page 311).

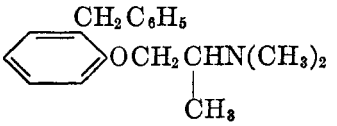
Attachment of the ethanolamine residue directly to a diphenylethane system resulted in quite inactive agents (table 4, Nos. 10 and 11).

The 2-(4-chlorobenzyl)phenyl 2-dimethylaminoethyl ether (Lilly 01780) is an extremely active antagonist (137, 155).



Lilly 01780

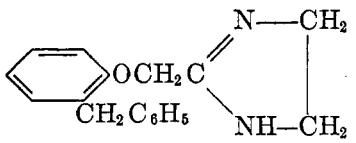
Branching of the side chain at the α-carbon atom more than doubled the activity (460 per cent Benadryl) and prolonged the action (Lilly 03875). Side-chain substitution at the β-carbon atom destroyed antihistaminic activity (344).



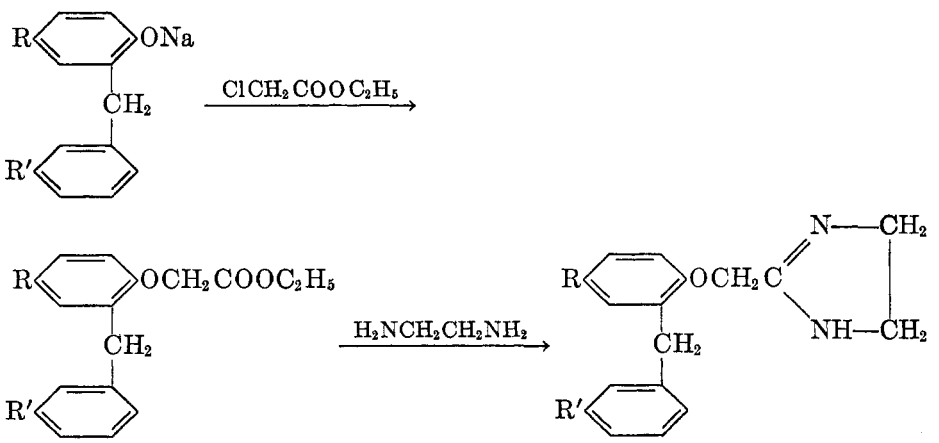
Lilly 03875

All of the benzylphenols have a sedative effect, which is due to the dialkylaminoethoxy side chain.

The imidazoline analogs of 2-benzylphenyl 2-dimethylaminoethyl ether were recently announced (455). None of the compounds prepared was more active



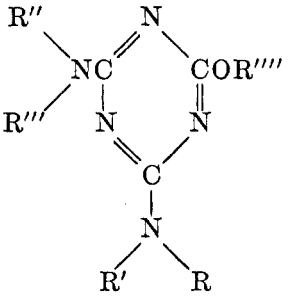
than the dimethyl derivative. They were prepared by converting the appropriate 2-benzylphenols to the sodium derivatives by means of sodium hydride, condensing with chloroethyl acetate, and treating the product with ethylenediamine.



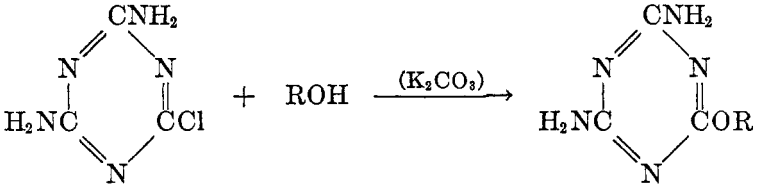
The effect of quaternization on the benzylphenols revealed powerful antihistaminic activity, but less than that of the tertiary bases (455).

8. Alkoxy-s-triazines

In the search for improved ether antagonists, a large series of triazinyl ethers were synthesized and tested (table 19) (94, 261, 312, 313). The pharmacological properties exhibited by the triazine arsenicals (18) were the impetus for the preparation of the series of alkyl 2,4-diamino-6-*s*-triazinyl ethers.



The reaction of 2-chloro-4,6-diamino-*s*-triazine with various alcohols in the presence of potassium carbonate was unsatisfactory. The conditions of the classical Williamson reaction were found suitable.



Of the various types of alcohols employed it was found that the isoalkyl and *sec*-alkyl alcohols took part in the reaction as readily as the primary alcohols. No ether type of product was obtained from the action of the halotriazine on sodium *tert*-butoxide. This was also the case with the sodium derivatives of benzhydrol, fluorenol, xanthhydrol, and menthol. Whether or not this phenomenon was due to steric hindrance was not determined. Since the tautomeric possibilities of the triazine nucleus are limited by the number and arrangement of alkyl substituents on nitrogen, a series of ethers was prepared in which one to four of the hydrogens on the two amino groups were replaced by alkyl groups (table 20, Nos. 24–81).

Examination of the data shows all the triazinyl ethers to be much weaker histamine antagonists than the benzhydryl ethers. The potency of the compounds at first increases with molecular weight and then decreases. The peak lies in the vicinity of the propyl and butyl derivatives (Nos. 3–7) and then decreases (261). Higher homologs, pentoxy to decoxy (Nos. 8–13), were less active. Incorporation of a tertiary amine in the aliphatic chain resulted in inactive compounds, i.e., 2-dimethylaminoethoxy and 2-morpholinoethoxy (Nos. 19 and 21). Of the

two aryloxy derivatives (Nos. 16 and 18), only the phenoxy exhibited some activity. Perhaps the activity of the cyclohexyl ether may be explained on the basis of a similarity in length of the molecule to that of the propyl and butyl ethers. The antihistamine effect of 2-isopropylthio-4,6-diamino-*s*-triazine (No. 22) is about the same as that of the oxygen analog. Substitution of the amino groups in the 4- and 6-positions of the ring (Nos. 23–25) did not appreciably alter the activity of the unsubstituted compounds.

It is of interest to note that melamine itself, and its derivatives devoid of an ether linkage, were found to be ineffective antihistamine agents. Thus, it is apparent that an ether linkage was necessary within this series. The acute toxicity of the propoxy and butoxy compounds (Nos. 3, 4, 6, and 7) was nearly one-half that of aminophylline, which was used as a reference. Lower homologs possessed low toxicity and activity, whereas higher homologs are more toxic and exhibit low activity, if any.

No orderly variation in activity was noted in the methyl and butyl ethers or with multiple substitution on the amine groups (Nos. 26–83) (312). Nos. 84–99 were prepared to fill in the gaps to determine if any products of appreciable activity had been overlooked. No potent compounds were noted therein (313).

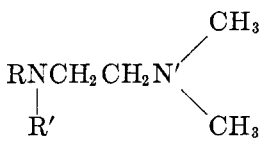
9. 2-(2-Biphenylyloxy)ethyl-2-haloalkylamines

Divergent in structure from the previously described antihistaminics are the substituted 2-haloalkylamines. Although their primary action is to block and reverse the pressor action of epinephrine (*cf.* page 311), their powerful sympatholytic and antihistaminic effect warrants the listing of the series of 2-(2-biphenylyloxy)ethyl-2-haloalkylamines (table 21) (364).

Antihistamine action was greatest with the methyl homolog (No. 2), which was effective in a dose of 1.5 mg./kg. Activity decreased progressively as methyl groups were added to the alkyl chain (Nos. 1, 3, 5, 7–12) and was decreased by substitution of the 2-chloroethyl group (compare Nos. 20 and 3). None of these compounds exerted an antihistamine action comparable in degree to that of Benadryl.

B. DERIVATIVES OF ETHYLENEDIAMINE

Isocyclic and heterocyclic derivatives of ethylenediamine comprise the bulk of and represent the most potent compounds of the antihistaminic drugs. The basis for the present differentiation into isocyclic and heterocyclic derivatives in the typical formula



rests in the *N*-substituents. The structure of the *N'*-substituents does not affect the present classification.

The isocyclic derivatives are subdivided into the *N*-phenylethylenediamines (Fourneau amines), the Rhône-Poulenc isocyclic amines, other isocyclic ethylenediamines, benzhydrylamines, isocyclic-substituted heterocyclics, amides of ethylenediamine, and isocyclic aminomethylimidazolines. The heterocyclic compounds are grouped into monocyclic amines, polyheterocyclic ring structures, and heterocyclic methylimidazoles and methylimidazolines.

1. N-Isocyclic derivatives of ethylenediamine

a. Fourneau amines

After investigating the phenoxyethylamines (table 3), Bovet and Staub (38) turned their improved techniques of antihistamine assays to the study of the *N*-phenylethylenediamines.

Synthetic research in Fourneau's laboratory (142, 143, 144) had disclosed that sympathomimetic, sympatholytic, and antihistaminic actions are found side by side in these aniline compounds. Staub (407) studied the different ethylenediamines and reached almost the same conclusions as with the phenoxyethylamines (table 22) (*cf.* page 16). Secondary amines were very inferior to the tertiary bases. *N*-(2-Aminoethyl)aniline or *N*-phenylethylenediamine (F 1540) is inactive against histamine, although it is a hypertensor and a bronchodilator. The effects of modifications of F 1571 (V), the most active Fourneau amine, were noted. When the ethyl group was replaced by hydrogen (F 1167), the product was totally inactive. If methyl replaced ethyl (F 1335), the result was rather weak activity. When isopropyl replaced ethyl (F 1709), the compound was distinctly less active. Studies were made of nuclear changes in F 1167 and F 1571. In F 1167, the results were almost exactly as in the phenoxyethylamines. The introduction of a methyl group (F 1332) into the ring did not augment the activity. Further introduction of an isopropyl function (F 1691) to give the *N*-analog of F 1379 (table 3) gave increased potency. The isomer of F 1691 corresponding to F 929 was not investigated, owing to the difficulties of its preparation, but it was supposed that it would correspond, as did F 1167 and F 1379. The parallels noted between the ethers and amines led to the hope that derivatives of F 1699 would be very active, but no activity was found. The modifications of the nucleus of F 1571 did not increase activity, but ring substitution instead decreased the potency in the following order: methylphenyl, dimethylphenyl, isopropylphenyl (F 1599, F 1670, F 1699). At the same time, the antispasmodic activity (as measured by the relaxation of acetylcholine-induced spasm) was increased. Exactly the opposite effect was found by Staub (407) to hold true for the phenoxyethylamines. In the latter series, the introduction of methyl, dimethyl, or isopropyl in the phenyl ring increased the antihistamine activity (F 928, F 1655, F 929), while spasmolytic activity was decreased in the same order.

The minimum active dose of F 1571 is 10–15 γ/ml. Five milligrams protected guinea pigs against four to six lethal doses of histamine (38, 51, 109, 170, 175, 311, 329, 407).

N-Phenyl-*N'*,*N'*,*N'*-triethylethylenediamine (F 1571) was first prepared by v. Braun (42) and reported by Schulemann (383).

A series of di- and tri-substituted aryldiamines, among which was F 1571, were prepared for study by J. P. Fourneau and Lestrange (144) (table 23). The disubstituted bases were prepared *via* the *N*-substituted phthalimides, which were cleaved by hydrochloric acid, except for the methoxyaryls which required hydrazine for cleavage. The trisubstituted diamines were synthesized by heating the arylamine in a sealed tube with the appropriate dialkylaminoalkyl halide.

Alternate methods of synthesis involve the condensation of a dialkylaminoalkyl-substituted amine with an alkyl, aryl, or aralkyl halide or the reaction of the aryl halide with an asymmetrically trisubstituted alkylenediamine. The

$$C_6H_5Br + RNHCH_2CH_2N(C_2H_5)_2 \longrightarrow C_6H_5\underset{\displaystyle R}{\underset{|}{N}}CH_2CH_2N(C_2H_5)_2$$

reactions are best carried out at higher temperatures in solvents like benzene and toluene and in the presence of a neutralizing agent such as potassium carbonate or sodium amide.

b. Rhône-Poulenc isocyclic amines

Research in the laboratories of the Société des usines chimiques Rhône-Poulenc (Paris) soon revealed that the changing of the diethyl group in F 1571 to dimethyl (RP 2325, VI) improved the antihistaminic activity (histamine aerosol test) fourfold and decreased the toxicity considerably. Furthermore, it was found that further improvement could be obtained by replacing the ethyl of the dimethyl homolog by benzyl (RP 2339, Antergan, VII). This change produced an increase in the antiasthma activity of twenty times over that of F 1571 (175). From there research led to the synthesis of a number of compounds (tables 24 and 24A), the majority of which are homologs of RP 2325 (VI) and RP 2339 (VII).

Viaud (443), in a review of the RP compounds, drew the following conclusions regarding structure and activity: variations at the end of the aliphatic side chain of RP 2325 and RP 2339 (substituting for dimethylamino, amino, diethylamino, etc.) resulted in almost complete loss of activity (RP 2315, 2358, 2650, 2323, 2762, 2835); replacement of the benzyl group in RP 2339 by hydrogen, methyl, ethyl, allylphenyl, *p*-ethylbenzyl, and phenethyl resulted in decisive loss of activity (RP 2236, 2337, 2325, 2342, 2347, 2338, 2757, 2612, 2614, 2349, 2744, 2355, 2637, 2354, 2768, 2565, 2352, 2621).

Substitution of the benzyl group in RP 2339 by certain oxygen-interrupted aliphatic chains, such as $-CH_2CH_2OCH_3$ (RP 2887) or $-CH_2CH_2OC_2H_5$ (RP 2796) gave compounds of still considerable activity, while substitution by $-CH_2COOC_2H_5$ (RP 2846) or $-CH_2CH_2N(CH_3)_2$ (RP 2368) gave inactive compounds. A compound with a sulfur-interrupted side chain, $-CH_2COCH_2SCH{=}NH$ (RP 2776), had considerable activity.

The length of the aliphatic side chain was found not to be the sole determinant of activity, but potency is dependent on other parts of the molecule.

Substitution in the phenyl ring of RP 2339 by *p*-methyl (RP 2639) maintained the original activity, while amino substitution in the para position (RP 2378) or substitution of the phenyl by cyclohexyl (RP 2497) or benzyl (RP 2503) resulted in complete loss of activity.

Several other far-reaching changes, such as substitution of the phenyl group in RP 2325 by the *p*-*N*-ethyl-*N*-(2-dimethylaminoethyl)amino group (RP 2902) and others (RP 2889, RP 3110) gave only inactive compounds.

RP 2339 (VII) was prepared by condensing *N*-benzylaniline with 2-(dimethylamino)ethyl chloride in the presence of potassium carbonate (64). The others were synthesized by the proper modification of the previously mentioned methods.

c. Other isocyclic ethylenediamines

Early European and American investigators, unaware of the various Rhône-Poulenc isocyclic compounds, synthesized many of the RP compounds (table 24), among other structures.

Table 25 lists the constants of the other isocyclic ethylenediamines. The pharmacological data are slight. *N*-Phenyl-*N*-benzyl-*N'*-(1-piperidyl)ethylenediamine (No. 23) possessed 0.2 of the activity of Antergan, while the *N*-methyl analog (No. 51) had only 0.05 of the activity of Antergan. With the exception of the *N*-(2-haloalkyl)-1-naphthalenemethylamine derivatives (Nos. 34–47), none of the compounds are more active than Antergan. The 3,4-dioxymethylene aryls (Nos. 53 and 54) are much less effective than Benadryl (307).

The series of *N*-(2-haloalkyl)naphthalenemethylamine derivatives (Nos. 34–50) tested by Loew and Micetich (265) and synthesized by Rieveschl and coworkers (361) belong in the class of adrenergic blocking drugs (*cf.* pages 311–312). They are also quite potent antihistamine drugs. Activity was greatest with the lower alkyl homologs (Nos. 34–36) which contained a 2-chloroethyl or 2-bromoethyl group, the ethyl homologs being the most active. Diminution of histamine-induced bronchospasm was progressively lessened as additional carbon atoms were added to the alkyl groups (Nos. 37–44). Activity was lost if the 2-chloroethyl was replaced by 2-hydroxyethyl (No. 47). The bis-(2-chloroethyl) compound (No. 46) was quite weak. Substitution of chlorine in the 4-position of the naphthalene ring (No. 50) decreased activity. The two *N*-ethyl compounds (Nos. 35 and 36) proved to be about as effective as Pyranisamine, an extremely potent agent (table 1, No. 15).

The antihistaminic activity of seventy-five congeners of Dibenamine [*N*-(2-chloroethyl)dibenzylamine] revealed (304) that the antihistaminic properties

$$(C_6H_5CH_2)_2NCH_2CH_2Cl$$

Dibenamine

were independent of significant cholinergic blocking activity. Antihistaminic activity was not parallel to adrenergic blocking activity. The 2-haloalkyl group is essential for high activity. Substitution of a 2-dimethylaminoethyl radical, which provides maximal activity in most series of antihistaminics, leads to inactivation. Phenoxyethyl- (particularly 2-substituted) and 1-naphthalene-

methylamines are the most active. Unsymmetrical *N*-phenoxyethyl-*N*-benzylamines are almost always more active than the *N*-diphenoxyethylamine or *N*-phenoxyethyl-*N*-ethylamine analogs.

The use of sodium iodide, copper powder, and cupric chloride catalysts proved advantageous for the preparation of some of the tertiary amines (396).

d. Benzhydrylamines

The replacement of the ether linkage by —NH in benzhydryl compounds (*cf.* pages 317–321) (tables 5 and 6) has usually led to weaker and inactive compounds.

$$(C_6H_5)_2CHNHR$$

Table 26 lists the amine analogs of the ethers, studied by Loew, Kaiser, and Moore (263) (table 5, Nos. 3, 6, 7, and 9), which proved practically inactive. In a series of ring-substituted benzhydrylamines tested the *p*-phenoxy compounds (table 27, Nos. 16 and 17) were the most active. No physical constants were given (4).

N-Substituted benzhydrylamines were synthesized by the reaction of benzhydryl bromide with ethanolamines in benzene solution, and then conversion of the *N*-benzhydrylethanolamines to the 2-chloroethylamines by reaction with thionyl chloride in chloroform solution. The 2-chloroethylamines were condensed with secondary amines to give the substituted ethylenediamines (98) (table 28).

$$2(C_6H_5)_2CHBr + RNHCH_2CH_2OH \rightarrow (C_6H_5)_2CHNCH_2CH_2OH \xrightarrow{SOCl_2}$$

$$(C_6H_5)_2CHNCH_2CH_2Cl \xrightarrow{R'NHR''} (C_6H_5)_2CHNCH_2CH_2NR''$$

It is necessary to run the initial condensation in a nonpolar medium, for in a reactive solvent such as ethanol it is possible for the benzhydryl ether to form instead of the desired benzhydrylamine (98).

Pharmacological data for the various *N*-substituted benzhydrylamines (table 28) were not reported.

Alles and Redemann (6) (*cf.* page 319) studied three benzhydrylamines: (β-diphenylmethylaminoethyl)dimethylamine and the *N*-methyl and *N*-ethyl analogs (R = H, CH_3, C_2H_5). Their results showed that the compounds of the di-

$$(C_6H_5)_2CHNCH_2CH_2N(CH_3)_2$$

amine system were not quite as active as the ethers (table 6A). The activity of the methosulfate of the ethyl compound was close to that of the tertiary methyl derivative.

An alternate method of synthesis involves the condensation of benzhydrylamine and an appropriately substituted halide. Benzhydrylamine has recently been prepared from benzophenone oxime, both by reduction with sodium in ethanol and by hydrogenation over Raney nickel (185).

The lower alkyl members of the series of benzhydryl-2-haloalkylamines

$$(C_6H_5)_2CH\underset{\displaystyle R}{N}CH_2CH_2X$$

(table 28, No. 4, and table 29) have both very slight antihistaminic activity and moderate epinephrine-blocking activity (259). Those with higher alkyl groups had only the latter activity. Table 29 lists a series of haloamines synthesized by Rieveschl and Fleming (363) and investigated by Loew and coworkers (259). The haloamines were prepared by heating substituted benzhydrylethanolamines with thionyl chloride or phosphorus oxychloride (362).

The 2-haloalkylnaphthalene derivatives (table 25, Nos. 34–47) were much more potent antihistaminics than the benzhydryl analogs, while the *N*-alkyl-2-(2-biphenylyloxy)-2′-diethylamines (table 21) exerted a moderate degree of antihistamine action and stronger adrenergic blocking action than the benzhydryl derivatives (265).

Nickerson and Gump (303) have brilliantly covered the chemical basis for adrenergic blocking activity in compounds related to Dibenamine.

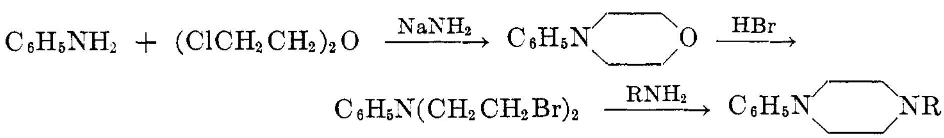
The benzhydrylpiperazine derivatives are the most potent of the benzhydrylamine derivatives, and will be discussed in the succeeding section.

e. *N*-Isocyclic substituted heterocycles

Among the different heterocyclic nitrogen groups, piperazine and piperidine are the only ones in which a significant amount of work has been done with isocyclic substituents, with a view toward antihistaminic action.

Cerkovnikov and coworkers (73, 74, 75) prepared a number of mono- and 1,4-disubstituted derivatives (table 30) whose activities varied from nil to moderate. The most active initial compound was 1-phenyl-4-(2-dimethylaminoethyl)piperazine (No. 6). Fifty milligrams protected guinea pigs against eight lethal doses of histamine. This effect is very weak as compared to that of the more potent antihistamines (table 1). The benzyl analog (No. 19) was a weaker antagonist.

The 1-phenylpiperazine derivatives were synthesized from 4-phenylmorpholine, prepared from aniline and bis(2-chloroethyl) ether. The morpholine compound yielded *N*,*N*-bis(2-bromoethyl)aniline on hydrolysis in a sealed tube with hydrobromic acid. Treatment with substituted amines yielded the phenylpiperazine derivatives.



The 1-benzylpiperazine (No. 19) was prepared in a like manner from 4-benzylmorpholine.

1-Phenyl-4-(2-dimethylaminoethyl)piperazine (No. 6) having been found to possess considerable activity, a number of other *N*-heterocyclic compounds containing an ω-dimethylaminoalkyl group attached to the nitrogen atom were synthesized and their pharmacological properties compared (table 30, Nos. 22–28) (75).

All the substances were prepared by boiling the desired amine with the corresponding heterocyclic compound in the form of a halo derivative. The tertiary bases were isolated as the *p*-toluenesulfonyl chlorides.

Comparison of the data in table 30 shows certain definite regularities. Activity is present where the aliphatic substituent contains an ethyl or propyl chain. However, an increase in length by one methylene group lowered the potency (*cf.* Nos. 6 and 22). When the ethyl chain carries a dimethylamino group in the 2-position, the antihistaminic activity is present to a higher degree than when the —CH_2CH_2— group is joined to an oxygen atom (ether), as seen from a comparison of Nos. 6 and 29. On the other hand, the effect of a heterocyclic nucleus is also very great. When the 2-dimethylaminoethyl group is attached to a morpholine nucleus (No. 28), the activity is abolished. When it is attached to a piperidine nucleus, slight activity results (No. 27). Introduction of a piperazine nucleus raises the potency considerably (sixteen times), as can be noted by comparing Nos. 27 and 6. The dimethylamino group is important with regard to both its presence and its relative position. Thus, when this group is attached directly to the heterocyclic nucleus, activity is present, while if a methylene group is interposed, the potency is zero (*cf.* Nos. 24 and 26). Introduction of two dimethylamino groups increases the antihistaminic activity nearly twice, as seen from comparing No. 22 and No. 23. The nature of the second substituent on the heterocyclic nucleus is also of significance. Nos. 24 and 25 have the same aliphatic substituent in the same position, but one carries a phenyl group and is active, while the methyl-containing compound has zero potency.

The toxicity is also greatly influenced by constitution. The phenyl group on the heterocyclic nucleus definitely increases toxicity (*cf.* Nos. 24, 25, and 27). The position of the dimethylamino group, as well as the number of groups, also influences the toxicity. When the group is attached directly to the heterocyclic nucleus, the compound (No. 24) is toxic to mice. When a methylene group is interposed, the toxicity increases (No. 26), and when an ethyl group replaces a methyl group the tolerance is much higher (Nos. 6 and 27). When a propyl group is used instead, the lethal dose for mice is slightly higher than when the ethyl group is used (Nos. 6 and 22). Introduction of a second dimethylamino group into the same (ethyl) chain increases the toxicity more than fivefold (Nos. 6 and 23).

4-Dimethylamino-1-phenylpiperidine (Irenal) (No. 24) had previously been shown to be a relatively potent spasmolytic (411). It was prepared from 1,5-dibromo-3-dimethylaminopentane hydrobromide and aniline by heating in a sealed tube (72).

The antihistaminic activity of a series of dibenzylpiperazines (table 31) (243, 284) did not reveal potent antihistamines. Antergan (RP 2339) is three times more active than the most active derivative (No. 1). The activities of Nos. 1 and 4 are comparable and four times that of No. 3.

Two independent investigations of substituted piperazines, simultaneously proceeding in the laboratories of Burroughs Wellcome and Company, Tuckahoe, New York, and the Abbott Company, Chicago, Illinois, reached the identical conclusion that *N*-methyl-*N'*-benzhydrylpiperazine (table 33, No. 1) was an active histamine antagonist, equal to Benadryl in potency.

Benzylmethyl- and benzylethyl-piperazines, when tested by the tracheal chain method (*cf.* page 313) at the laboratories of Burroughs Wellcome and Company, were found to have 1 per cent and 0.4 per cent, respectively, of the antihistaminic activity of Benadryl (15). This suggested that *N*-methylpiperazines having *N'*-substituents containing two or three rings would be active antagonists and prompted the preparation of a variety of derivatives of methylpiperazine (table 32) (5).

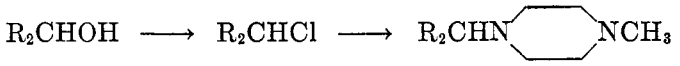
The α-phenylphenacyl derivative (No. 10) was much less potent than 1-benzhydryl-4-methylpiperazine (table 33, No. 1) and the 1-phenyl-2-hydroxyphenethyl and 1-phenyl-1-(4-hydroxyphenacyl) compounds (Nos. 11 and 12) had only vestigial activity. Nos. 1–5 had activities intermediate between those of 1-benzyl-4-methylpiperazine (No. 13) and 1-benzhydryl-4-methylpiperazine. Nos. 6–9 showed little or no activity.

The benzhydryl group appeared, from the above, to be close to the optimal size desired for antihistaminic activity.

With the exception of Nos. 3 and 11, all the substances listed in table 32 were prepared by the direct action of methylpiperazine with the appropriate halide. No. 3 was prepared by catalytic hydrogenation of the nitro compound (No. 2), while No. 11 resulted from reduction of the phenacyl precursor with aluminum isoproproxide. Hydrogenation of the phenacyl derivative with Adams' catalyst resulted in debenzylation.

N-Benzhydryl-*N'*-methylpiperazine (table 33, No. 1) was found to possess the same activity as Benadryl (66, 67, 68). Its toxicity was also very similar to that of Benadryl.

Table 33 lists the series of *N*-benzhydryl-*N'*-methylpiperazines prepared by Baltzly and coworkers (16). Synthesis of the benzhydrylmethylpiperazines proceeded from the benzhydrol through the halide and final reaction with methyl-



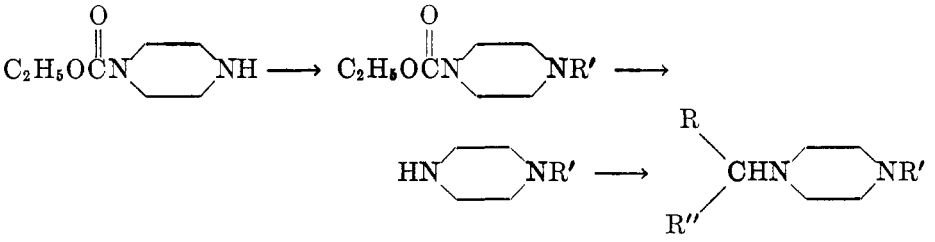
piperazine. Some of the required carbinols were prepared directly from the appropriate aldehydes and Grignard reagents. The others resulted from the reduction of the corresponding ketones.

Quaternization of the methyl-bearing nitrogen atom (No. 2) largely abolished activity. Nos. 3 and 18, in which one cyclohexyl replaces phenyl, also showed diminished potency.

Nos. 6, 15, and 17, wherein the benzhydryl substitution was *p*-chloro, *o*-methoxy, and *p*-methoxy, respectively, were less toxic than the parent substance (No. 1), No. 6 being about one-half and No. 17 about one-third as toxic. Nos. 15 and 18 appeared respectively to be slightly less and slightly more potent than No. 1. No. 6 (Perazil, table 1, No. 17) was very potent and persistent in action. No. 17 was virtually impotent when tested *in vivo*. This is probably due to instability, since it is rapidly cleaved in warm aqueous and alcoholic solutions to methylpiperazine and neutral fragments. The *o*-methoxy compound (No. 15) is considerably more stable. Table 34 lists the antihistamine activities of some of the aforementioned substituted piperazines (68).

Independent investigation in the Abbott Laboratories verified the activity of 1-(*p*-chlorobenzhydryl)-4-methylpiperazine. Table 35 lists the group of 1-substituted and 1,4-disubstituted piperazines prepared there by Hamlin and coworkers (183, 184).

The unsymmetrical 1,4-disubstituted piperazines were prepared through the use of 1-carbethoxypiperazine. The low-molecular-weight group was added and then the ester group removed with concentrated hydrochloric acid. The final alkylation was accomplished with the appropriate halide, with the aid of an

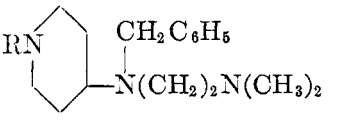


acid-binding agent. With the more stable benzhydryl chlorides and 1-methylpiperazine the yields were good. As R′ (table 35) increased in molecular weight, the yields progressively decreased, as was the case for the less stable benzhydryl halides.

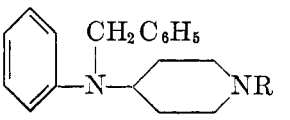
With the exception of the 1-(9-fluorenyl)piperazines (Nos. 34–37), all the 1-substituted and 1,4-disubstituted piperazines (Nos. 23–33, 38, 39) were prepared in a manner essentially parallel to that of Baltzly and coworkers (15), where the appropriate halide was reacted with anhydrous piperazine. 1-(9-Fluorenyl)piperazine was made *via* the carbethoxypiperazine method.

A series of 1,4-diheterocyclic substituted piperazines recently proved to be potent analgesics (110), while sym-dialkylpiperazines, containing long-chain alkyl radicals, were made for testing as germicides (391).

Certain 4-aminopiperidines were prepared as potential antihistaminic agents, on the basis of their structural analogy to *N*,*N*-dialkyl-*N*′-benzyl-*N*′-aryl(or heterocyclic)ethylenediamines (342). The 4-aminopiperidines could be classified with both the isocyclic and the heterocyclic derivatives, for the piperidine group has been subtituted for the phenyl group in A and for the ethylenediamine group in B (table 36).



A



B

All the alkyl and isocyclic derivatives showed rather weak activity. The necessary piperidones were made by condensation of methylamine or ethylamine with methyl acrylate and subsequent cyclization. Reductive alkylation of primary amines with the piperidones yielded the substituted 4-aminopiperidines. The secondary amines were alkylated with benzyl bromide to yield No. 5 (in table 36).

f. Amides of ethylenediamine

The effect of substituting $R\overset{|}{C}O$ for the R radical in the general formula

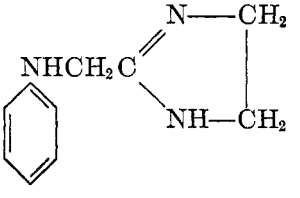
$$RC(=O)NR'CH_2CH_2N(R'')_2$$

to produce a series of amides of ethylenediamine was studied by Villani and coworkers (table 37) (444). The amides were prepared by the reaction of aryl or heterocyclic acid chlorides with the appropriately substituted ethylenediamines. The condensations were carried out in the presence of a tertiary amine such as pyridine, triethylamine, or dimethylaniline. In the case of the picolinoyl amides, pyridine could not be employed as the solvent because of the ease with which picolinoyl chloride forms colored complexes with pyridine. A mixture of triethylamine and anhydrous benzene was suitable.

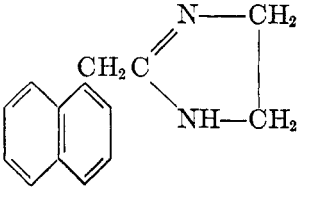
Nos. 24–27 had an activity approximately 0.1 that of Trimeton (table 1, No. 26). Nos. 2, 3, 9, 12, and 23 had 0.2 the activity orally and subcutaneously. No. 22 possessed 0.4–0.5 the potency by either route of administration. The remainder of the substances showed approximately 0.01 the activity orally and 0.01–0.02 subcutaneously. The amides might have been classified with the heterocyclics.

g. *N*-Isocyclic aminomethylimidazolines

2-(*N*-Benzylanilinomethyl)-2-imidazoline, Antistine (table 1, No. 2), is the most prominent of the chemical family where the dialkylaminoethyl side chain is replaced by the more complex imidazoline (dihydroglyoxaline) function. Antistine is similar to the sympathomimetic drugs Otrivine [(2-anilinomethyl)-2-imidazoline] and Privine [2-(1-naphthylmethyl)-2-imidazoline].



Otrivine

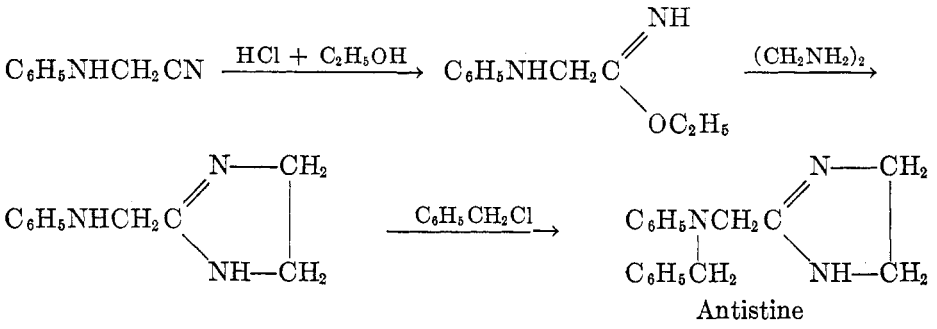


Privine

Antistine appears to exercise an antihistaminic action slightly less than that of Antergan (table 25, No. 1). Although the substitution of an imidazoline group slightly reduces the pharmacological activity, there is such clinical tolerance that it can be used for local administration to sensitive organs such as the eye, ear, and nose.

Antistine is synthesized from anilinomethylimidazoline, which is prepared from anilinoacetimidoester and ethylenediamine (110). The 2-(*N*-benzylanilinomethyl)-2-imidazoline is then formed by the reaction with benzyl chloride

Method A

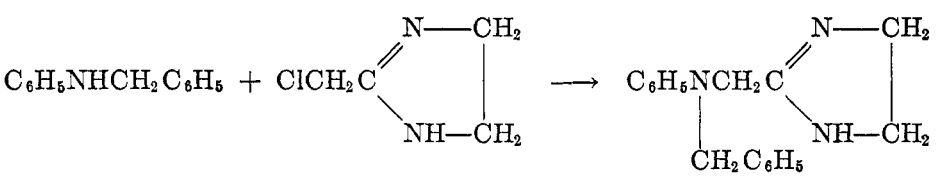


Antistine

(method A) (86). The 2-imidazolines can be prepared directly from the nitrile and an aliphatic diamine, if the two amino groups of the latter are attached to vicinal carbon atoms. Hydrogen sulfide, carbon disulfide, phosphorus pentasulfide, aluminum trisulfide, ferrous sulfide, and sodium sulfide are catalysts for the reaction (206). A recent patent claims the production of imidazolines when *N*-aryl-*N*-aralkylaminoalkylcarboxylic acids or their derivatives are treated with an aliphatic 1,2-diamine (207).

An alternative synthetic method for the *N*-substituted imidazolines involves the condensation of 2-(chloromethyl)-2-imidazoline and the appropriate isocyclic

Method B



secondary amine (method B) (285). 2-(Chloromethyl)-2-imidazoline is prepared from the 2-chloroethylimidoester and ethylenediamine at 0°C. (397a).

Table 38 lists the series of *N*-isocyclic substituted imidazolines prepared for testing. The ether analogs (table 11) appear to be more potent, but this is overshadowed by their toxicity. Practically all the compounds were synthesized by Miescher and coworkers in Switzerland. The pharmacological data on all except Antistine (No. 8) are nil, but no improvements in activity seem to have been achieved by ring substitutions or variations in the side chain. 2-*N*-*p*′-Tolyl-

N-(*m*-hydroxyphenyl)aminomethyl-2-imidazoline (No. 6) possesses weak antihistaminic activity but is a potent adrenergic drug (188) (*cf.* pages 311–312).

The series of diphenylaminomethylimidazolines (Nos. 3–7) was prepared by heating substituted diphenylamines with 2-(chloromethyl)-2-imidazoline in an atmosphere of nitrogen (287).

The tetrahydropyrimidine analog of Antistine (No. 26) has insignificant activity (230). The compound was prepared from the condensation of ethyl *N*-phenylaminoacetate and benzyl chloride to yield ethyl *N*-benzyl-*N*-phenylaminoacetate, which was then refluxed with trimethylenediamine.

In the course of an extensive investigation of amidines, Oxley and Short (310) found that 2-substituted imidazolines and their ring homologs were obtained in good yield by heating *N*-substituted amidinium salts with an alkylenediamine. An extensive series of imidazoline intermediates, valuable in the synthesis of the types found in table 37, were prepared. 2-Arylmethyl-1-alkylimidazolines were likewise prepared by the interaction of the appropriate cyanide with a salt of *N*-methyl- or *N*-ethyl-ethylenediamine.

h. Anilino-*s*-triazines

The weak antihistaminic properties exhibited by the alkoxy-*s*-triazines (*cf.* page 329, table 19) suggested the investigation of anilino-*s*-triazines (446). Table 39 lists the prepared triazines, in which extremely small potency appeared.

2. N-Heterocyclic derivatives of ethylenediamine

The majority of potent histamine antagonists are found in this group, wherein the aryl functions are replaced by various mono- and poly-cyclic heterocyclic groups. An analogous situation resulted when heterocyclic nitrogen moieties were introduced into the sulfanilamide derivatives (306).

Since the initial and most productive work was performed at the Rhône-Poulenc laboratories, a special section is devoted to this research. Various heterocyclic functions are included in the "RP" investigations and will be grouped together in tables 40 and 50. The remainder of the monocyclic hetero functions will be classified according to individual structures.

a. *N*-Monoheterocyclic derivatives of ethylenediamine

(1) Rhône-Poulenc monoheterocyclic diamines

In 1944 Bovet and coworkers (34, 35, 40) described the properties of derivatives of 2-aminopyridine culminating in Neoantergan (table 1, No. 15), which still remains among the most potent of the antihistaminic drugs.

Table 40 lists the various *N*-heterocyclic derivatives of ethylenediamine, prepared at the laboratories of the Société des usines chimiques Rhône-Poulenc (*cf.* isocyclic amines, pages 332–333, table 24).

Viaud (443) drew the following relationships between structure and activity (*cf.* 200): replacement of the benzyl group in Antergan (RP 2339) by various heterocyclic groups resulted in either loss of activity, or similar potency. The 2-thenyl derivative (RP 2740) was inactive. The 2-furfuryl analog (RP 2747)

possessed little activity. The 2-tetrahydrofurfuryl (RP 2749) and the 2-methylthiazole (RP 2764) compounds had the same activity as Antergan. The pyridine analog (RP 2972) and others (RP 2758, 2764, 2765, 2788, 2880, 2895) were compounds of little pharmacological interest.

The replacement of the phenyl group in Antergan by heterocycles resulted in major improvements. The 2-pyridyl compound (RP 2750) was twice as active as Antergan. Further substitution in the benzyl group by *p*-methoxy gave Neoantergan (RP 2786) with fivefold the activity of the 2-pyridyl derivative (RP 2750) and ten times that of Antergan. If the methoxy group was in the ortho position (RP 2855) or meta position (RP 3325), the activity disappeared completely. Substitution by *p*-methyl (RP 2932) lowered the activity to that of Antergan, while *p*-ethyl (RP 2910) caused almost complete disappearance of activity. Branching of the aliphatic side chain in Neoantergan (RP 3420, RP 3427) or increase of the length of the chain (RP 2800) lowered the activity considerably. Substitution in the pyridine ring of Neoantergan by one (RP 2890) or two methyl groups (RP 2933) suppressed the activity. The 3- (RP 2938) and 4-pyridyl (RP 2958) compounds were almost completely inactive. The 2-pyrimidyl (RP 2971) and 2-thiazolyl (RP 2909) derivatives were inactive. The replacement of the *p*-methoxybenzyl group in Neoantergan by furfuryl (RP 2803) lowered the activity to that of RP 2750. Many of the observations have been disputed by American investigators. Compounds which have been declared almost impotent by the Rhône-Poulenc pharmacologists have appeared among the prominent commercial drugs (RP 2740, 2971, 2764; table 1, Nos. 9, 12, 27).

Neoantergan was prepared by the reaction of 2-(2-dimethylaminoethylamino)-pyridine with *p*-methoxybenzyl chloride in the presence of sodium amide or by the reaction of 2-(*N*-*p*-methoxybenzyl)aminopyridine with 2-dimethylaminoethyl chloride (443).

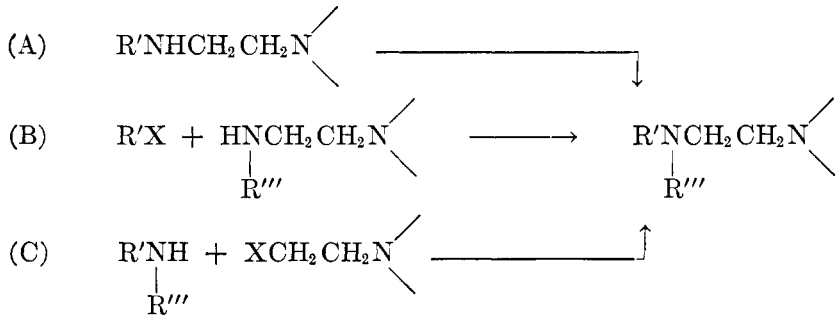
(2) Monoheterocyclic compounds other than Rhône-Poulenc compounds

(a) Pyridine derivatives

The extensive work of the Rhône-Poulenc investigators (pages 341–342) not being known, research on the replacement of the aryl groups of the Fourneau diamines (pages 331–332) by heterocyclic radicals progressed independently at the laboratory of the Ciba Pharmaceutical Company in New Jersey (112, 203, 278) and culminated in the preparation and testing of Pyribenzamine (table 1, No. 19).

Various basically substituted tertiary pyridine compounds (table 41, Nos. 1, 2, 4, 14, 35–37, 39, 40, 45–49, 59, 60, 62, 69, 100–109) were prepared by condensing the dialkylaminoethyl substituted-amino heterocyclic compound with an alkyl or aralkyl halide (A), by condensing the halogenated heterocyclic substance with an asymmetrically trisubstituted alkylenediamine (B), or by condensing the alkyl- or aralkyl-amino heterocyclic derivative with a dialkylaminoethyl halide (C).

The necessary secondary amines were prepared by condensing primary amines with a dialkylaminoethyl halide in toluene solution in the presence of sodium or



lithium amide (203, 457). This method was preferred to that of condensing the asymmetrically substituted diamine with a halogen-substituted heterocyclic compound. All the secondary amines were found to be inactive, in contrast to the tertiary bases, which exhibited considerable range of activity (table 41).

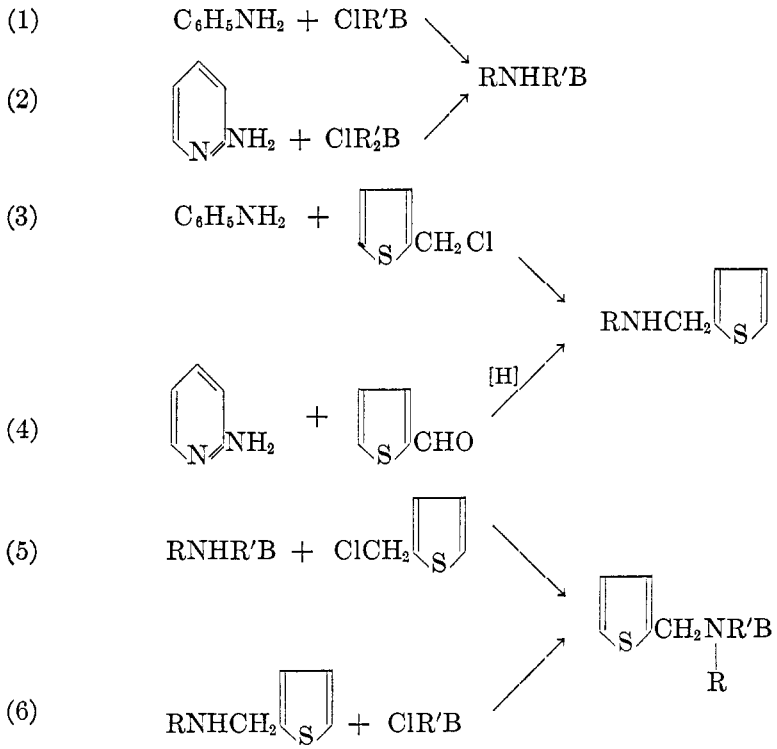
The research of Huttrer and coworkers confirmed many of the findings of Viaud (443) with the RP compounds. The 2-pyridyl-substituted compounds were the most active (table 41, Nos. 1, 4, 14, 35–37, 39, 40, 45–49, 59, 60, 62, 69), with the benzyl derivatives being the most potent (Nos. 1, 4, 59, 60, 101, 103, 104, 106, 108). The dimethylaminoethyl side chain was by far the most reactive, for replacement by diethyl (Nos. 37, 40, 43, 48, 108), piperidyl (Nos. 59, 60), or morpholinyl (No. 62) caused severe decreases in activity. Alkyl substituents (Nos. 35–38, 59), acyl (No. 46), aryl (Nos. 39, 40, 69, 100, 109), or the dipyridyl-substituted derivatives (Nos. 47, 48, 49, 105, 107) were all ineffective as compared with Pyribenzamine (No. 1) or Neoantergan (No. 4). The phenethyl compound (No. 2) was practically inactive. The introduction of chlorine in the pyridine ring almost doubled the activity of the Pyribenzamine type (No. 71), while the toxicity was only slightly elevated. A simultaneous introduction of chlorine and methoxy in the pyridine and phenyl ring, respectively (No. 73), resulted in decreased activity, but also in an appreciable lowering of acute toxicity. A *p*-isopropoxy substituent in the benzyl moiety of Pyribenzamine (No. 6) markedly enhanced the antihistaminic activity and lowered the acute toxicity of the parent compound (25). This follows the effect of the *p*-methoxy group in Neoantergan. However, an ethoxy group in the same position (RP 2843) did not seem to bring about any change in activity (443).

The replacement of the benzyl group by 2,2-dibutylhexyl (table 41, Nos. 66 and 67) was investigated (403) to determine whether this highly branched group would show greater activity than the lower alkyl groups (table 41, Nos. 35, 36, 59). The dimethyl derivative (No. 66) had approximately 1/250 the antihistaminic activity of Pyribenzamine, while the diethyl homolog (No. 67) was 1/5–1/10 as active as No. 66. The synthesis was carried out by the condensation of 2-bromopyridine and (2,2-dibutylhexyl)amine in xylene or cymene solution in the presence of anhydrous sodium carbonate. The *N*-(2,2-dibutylhexyl)-2-aminopyridine was alkylated with the dialkylaminoethyl chloride. Attempts to condense *N*,*N*-diethyl-*N'*-(2,2-dibutylhexyl)ethylenediamine and 2-bromopyridine with sodium amide were unsuccessful.

Quaternization of Pyribenzamine, Neoantergan, or Antergan did not affect their activity, but their toxicity seems to have been slightly decreased (211).

The principle of isosterism was applied in the preparation of the thiophene analogs (table 41, Nos. 21–32, 51–53, 57, 58, 61, 65, 68, 74–77; table 42). These compounds proved practically as potent as their benzyl or pyridyl analogs.

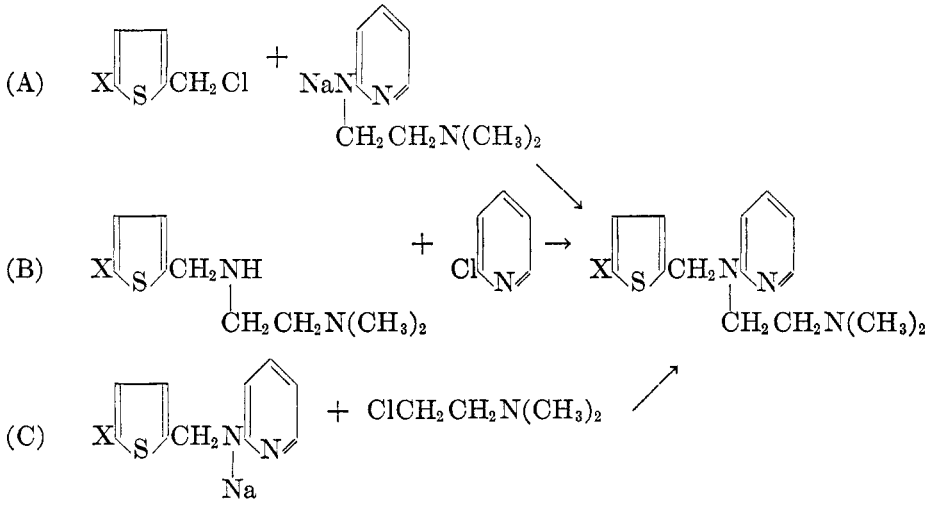
The preparation of the 2-thienyl analog of Pyribenzamine (table 41, No. 21; Table 1, No. 24; Thenylene, Histadyl) was prepared practically simultaneously by a number of laboratories (90, 228, 242, 452). The tertiary amine was obtained by the alkylation of the appropriate secondary amine in benzene or toluene solution in the presence of sodium amide (90, 242, 452) (procedures 5 and 6). The intermediate secondary amines were prepared by condensing aniline with a dialkylaminoalkyl chloride or 2-thenyl chloride (procedures 1 and 3) and 2-aminopyridine with a dialkylaminoalkyl chloride or 2-thiophenealdehyde, followed by reduction (procedures 2 and 4).



The effects of substitution in the thiophene and pyridine rings were studied by a research group at the American Cyanamid Company (88, 90, 442). The 5-halogenated thiophenes (Chlorothen and Bromothen; Table 41, Nos. 24 and 25; Table 1, Nos. 22 and 5) were more active than Pyribenzamine, being twice as active and possessing one-half the acute toxicity on a weight basis. When equal doses of the drugs were administered, Chlorothen and Bromothen protected against histamine shock twice as long as Pyribenzamine (256). In a series

of *N*,*N*-dimethyl-*N'*-2-pyridyl-*N*-thenylethylenediamines, prepared by Clark and coworkers (90) (table 41, Nos. 23, 24, 27, 28, 32, 51, 52, 74–77), none was as active as Bromothen or Chlorothen.

The compounds were synthesized by the reaction of the 5-halo-2-thenyl halides with the sodium salt of *N*,*N*-dimethyl-*N'*-2-pyridylethylenediamine (A), by the condensation of 2-chloropyridine with *N*,*N*-dimethyl-(*N'*-5-chloro-2-thenyl)-ethylenediamine (B), and by the reaction of *N*,*N*-dimethylaminoethyl chloride and 2-(5-bromo-2-thenyl)aminopyridine (C).



The thenyl halides were usually prepared by chloromethylation in the 1-position. If both 1-positions were substituted, chloromethylation occurred in the 2-position. Alternate methods involved the bromination of various 2-methylthiophenes with *N*-bromosuccinimide and treatment of alkyl 2-thienyl carbinols with hydrogen bromide in benzene.

In view of the increased activity brought about by introduction of the halogen into the thiophene group, it was decided to investigate the effect of halogenation on the antihistamine activity of *N*,*N*-dimethyl-*N'*-benzyl-*N'*-(2-pyridyl)ethylenediamine (442). The compounds (table 41, Nos. 7–12) where pyridine is unsubstituted were prepared by the condensation of *N*,*N*-dimethyl-*N'*-(2-pyridyl)ethylenediamine with the appropriate halogenated benzyl halide in the presence of alkali amide or hydride. The highest activity is found in those derivatives halogenated in the 4-position of the benzyl group, and this activity increases as the electronegativity of the substituent increases and its atomic weight decreases from iodo to fluoro. The 4-bromobenzyl derivative has approximately the same activity as Pyribenzamine but the 4-fluorobenzyl derivative is three to four times as active. Halogen substituents in the 2- or 3-position of the benzyl group or in the 5-position of the pyridyl group (table 41, Nos. 70, 71) led to essentially inactive compounds. In the dihalogenated compound (No. 72), the same disadvantageous result occurred.

The replacement of the dimethylaminoethyl group by a dialkylaminoacetyl group (table 41, Nos. 78 and 79) resulted in inactive compounds, as did the 1-naphthalenemethyl derivative (table 41, No. 34) and the *n*-hexyl compound (table 41, No. 17).

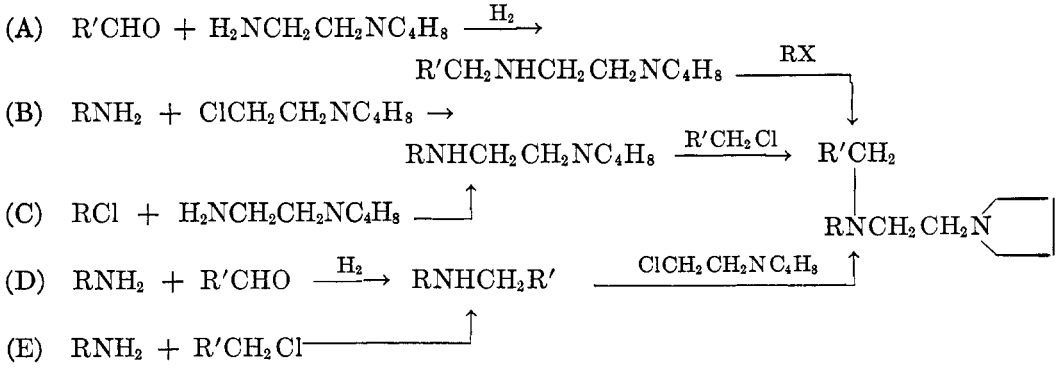
Campaigne and coworkers (59, 60, 61) studied the synthesis and reactions of 3-substituted thiophenes and prepared four *N*-substituted dimethylaminoethylpyridines containing the 3-thenyl and halogen-substituted 3-thenyl nucleus (table 41, Nos. 28–31). The compounds were synthesized by the reaction of the sodium derivative of 2-(dimethylaminoethylamino)pyridine with the appropriate 3-thenyl bromide, obtained when the proper 3-methylthiophene reacted with *N*-bromosuccinimide (60).

The 3-thenyl compounds all possessed activities about equal to those of Thenylene (the 2-thenyl analog) and Pyribenzamine. The unsubstituted derivative (Thenfadil, table 1, No. 23; table 41, No. 29) is more potent than the chloro- and bromo-substituted analogs. The three compounds (No. 29–31) appear to be of the same order of toxicity as Pyribenzamine when administered intravenously in mice, while Benadryl is approximately one-half as toxic. The two halogenated derivatives appear to be less toxic than the parent compound, the chloro (No. 31) being less toxic than the bromo (No. 30) by subcutaneous injection (192, 235).

The difference between the increased activity on halogenation in the 2-thenyl series and the lack of this in the 3-thenyl analogs is attributed to the difference in the position of the halogen atoms, being 5- in the former and 2- in the 3-thenyl series (235).

The derivatives of 4-aminopiperidine (*cf.* table 36 and page 338) demonstrated that these compounds (table 41, Nos. 85 and 86) were three-fourths as active as Benadryl (342). The same compounds were prepared by the alkylation of a 1-alkyl-3(or 4)-benzylaminopyridine with a 2-halopyridine (341).

Tertiary pyrrolidylethylamine derivatives (table 41, Nos. 54–58) were synthesized *via* the secondary amino compounds by one of the following procedures (244):



In general, the order of activity of these pyrrolidylethylamine compounds is low. The most active members, the *p*-methoxybenzyl derivative (table 41, No.

54) and the 5-chloro-2-thenyl compound (No. 58), had an effectiveness equal to approximately one-fourth that of Pyribenzamine (244).

The pyridylarylmethanes (table 41, Nos. 96–98) were obtained from 2-benzoylpyridine and the substituted amine, using formic acid as the reducing medium (423). None of the compounds was an active histamine antagonist.

(b) Pyrimidine derivatives

The derivatives of pyrimidine are all characterized by reduced activity (RP 3015), but decreased toxicity results in most cases. The most prominent members of this group are Hetramine (table 1, No. 12; table 42, No. 3) and Neohetramine, the *p*-methoxy analog (table 1, No. 16; table 42, No. 4).

The thienyl isostere of Hetramine (table 42, No. 1), produced a compound of very low activity. Introduction of methoxy in the pyrimidine ring of Hetramine (table 42, No. 9) afforded a compound comparable to Pyribenzamine in activity and acute toxicity.

The preparations of the pyrimidines are almost identical with those of the pyridines. Aromatic aldehydes are condensed with 2-aminopyrimidine in the presence of formic acid to form the secondary amines (25, 150). An alternate method involves the treatment of 2-aminopyrimidines with sodium amide and reaction of the sodium salt with the proper halide (150). Another preparation involves condensing 2-aminopyrimidines with the corresponding chloromethyl compound in toluene, using lithium amide as the condensing agent (25).

(c) Thiophene derivatives

The pyridylthienyl compounds (table 41, Nos. 21–32, 51–53, 57, 58, 61, 65, 68, 74–77) have already been discussed. Table 44 lists other thienyl derivatives.

Diatrin (table 1, No. 9; table 43, No. 1), the phenyl analog of Thenylene, had been reported as being completely inactive by Viaud (443) (RP 2740), while Kyrides (228) reported an activity approximately two-thirds that of Antergan and Ercoli (131) claimed about equal potency and considerably lower toxicity. It was synthesized by condensing *N*,*N*-dimethyl-*N'*-phenylethylenediamine (prepared from aniline and dimethylaminoethyl chloride) and 2-thenyl chloride (242).

In a series of arylthiophene derivatives synthesized by Kyrides and coworkers (228, 230) (table 43, Nos. 1, 2–10, 15, 18), *N*,*N*-dimethyl-*N'*-(5-chloro-2-thenyl)-*N'*-phenylethylenediamine (table 43, No. 6) proved to be the most potent, approximately 125 per cent as active as Antergan in animal tests. The introduction of chlorine into the thiophene ring had a potentiating effect on antihistaminic activity, similar to that observed in the pyridine series (90). When chlorine was introduced into the phenyl ring, the activity dropped markedly (table 43, Nos. 2–4, 8, 9). The *o*-chlorophenyl derivatives (Nos. 2 and 7) had negligible activity, the *m*-chlorophenyl compounds (Nos. 3 and 8) were slightly active, and the *p*-chlorophenyl members (Nos. 4 and 9) were the most active, but the best compound in this series (No. 4) was only one-half as active as Antergan.

Introduction of a third methyl group in place of the aryl group (table 43, No.

15), or replacement of the 2-thenyl group by methoxybenzyl, practically eliminated activity. Substitution of chlorine or the 4-morpholinyl group for the dimethylamino group produced inactive compounds (230).

(d) Thiazole derivatives

Viaud (443) found the thiazolyl derivative of Neoantergan to be practically inactive (RP 2909), but Feinberg found it to be quite active (22, 137) (table 1, No. 27; table 44, No. 2).

The parent arylthiazole compound (table 44, No. 1) was synthesized by reacting benzylamine with dimethylaminoethyl chloride in the presence of potassium acetate and treating the *N*-benzyl-*N*-(2-dimethylaminoethyl)amine with 2-bromothiazole (400). It was found to possess 0.1 the activity of Neoantergan by Viaud (443) (RP 2764).

(e) Furan derivatives

The furyl isosteres of Pyribenzamine proved effective histamine antagonists. The pyridyl-substituted furans are listed in table 41 (Nos. 18–20, 50, 56), while the arylfurfuryldiamines are tabulated in table 45.

The unsubstituted furfuryl derivative, Foralamin (table 1, No. 11; table 41, No. 18), proved as effective an antagonist as Pyribenzamine when tested in guinea pigs against histamine aerosol or intravenous injection of histamine (187, 441). The bromofurfuryl derivative (No. 20) was only slightly less effective. These results are in agreement with those reported by Viaud (443) (RP 2803), but Biel (25) claimed the furyl isostere of Pyribenzamine to be twice as active. The toxicity of the furfuryl compound was the same as that of Pyribenzamine, whereas the bromofurfuryl derivative was approximately 50 per cent less toxic (441).

In a general study of the pharmaceutical applications of furan derivatives, Hayes and coworkers (187) prepared the two aforementioned derivatives plus the chloro- and methyl-furfuryl compounds (table 41, Nos. 19 and 50). The latter was practically inactive, while the 5-chloro member had approximately one-half the activity of the bromo compound. In contrast to the report of Vaughan and Anderson (441), the acute toxicity of the furfuryl derivative (as the fumarate salt) was observed to be approximately two-thirds the toxicity of Pyribenzamine.

Methoxy or isopropyl substitution in the para position of the phenyl ring of the furyl isostere of Antergan (table 45, Nos. 2 and 3) resulted in appreciable lowering of activity, coupled with an increase of acute toxicity in the case of the isopropyl derivative (25).

Foralamin (table 41, No. 18) was synthesized by an initial reaction of 5-bromofurfuryl alcohol with thionyl chloride in toluene solution at low temperature. The unstable intermediate furfuryl chlorides were treated directly with the sodium salt of *N*,*N*-dimethyl-*N'*-(2-pyridyl)ethylenediamine (441). The lithium salt of the latter has been employed (229), as has been lithium amide for the condensation (25). Hayes and coworkers (187) condensed furfural or 5-halo-2-furaldehydes with 2-aminopyridine to yield the azomethines. The latter were

catalytically hydrogenated to yield the *N*-furylmethyl-2-aminopyridines. The Schiff bases were either reductively alkylated with a Grignard reagent or lithiated with lithium amide in benzene and treated with 2-dimethylaminoethyl chloride to yield the desired base.

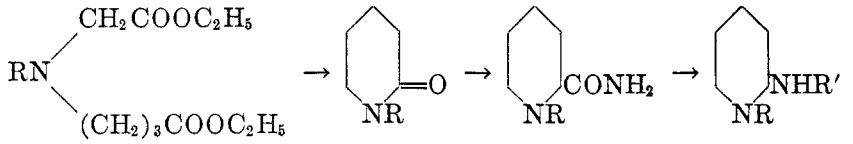
(f) Piperidine and pyrrolidine derivatives

These groups are usually met as part of the side chain in the replacement of the usual $-N(CH_3)_2$; however, molecular species have been prepared in which these nitrogen heterocycles are in the "front" of the structure.

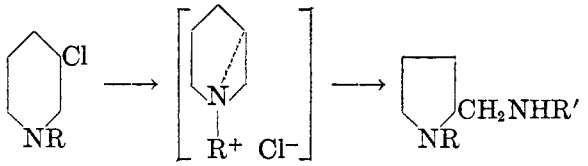
The 4-aminopiperidines containing isocyclic (table 36) and pyridyl moieties (table 41, Nos. 85 and 86) have been discussed. *N*-Benzyl-*N*-4-piperidylethyl-*N'*-pyrrolidylethylamine (table 46, No. 6) was prepared from pyrrolidylethylamine (obtained by catalytic reduction of pyrrolidylacetonitrile), which was condensed with benzyl-1-alkyl-4-piperidine in toluene solution with potassium carbonate and copper powder catalysts (342).

N-Substituted piperidines without any nuclear substitution (table 46, Nos. 1–3) and the piperidone (No. 4) were all inactive.

The replacement of the ethylenediamine unit by a 3-aminopiperidine group was shown to yield weakly active compounds (341, 343) (table 41, Nos. 80–84). They were synthesized through reductive alkylation of amines with 1-alkyl-3-piperidones. 1-Methyl- and 1-ethyl-3-piperidone were prepared from the alkylaminodicarboxylic esters (343).



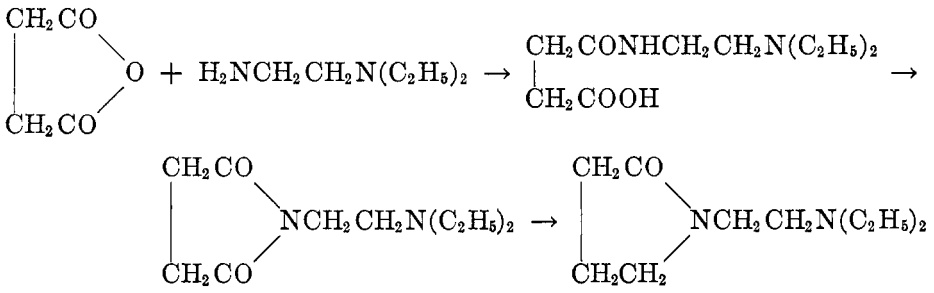
2-Aminomethylpyrrolidines resulted from a novel rearrangement of the piperidine ring. Treatment of 1-ethyl-3-chloropiperidine with benzylamine did not give the expected 3-benzylaminopiperidine; instead, 2-aminomethylpyrrolidines were obtained. Since 1,2-chloroamines react as though an intermediate cyclic imonium salt is formed, the formation of a similar intermediate from 3-chloropiperidine would explain the formation of 2-aminomethylpyrrolidines.



The direction of the imonium ring opening is dependent upon the nature of the attacking nucleophilic agent, and a strongly basic group evidently favors the formation of the pyrrolidine structure (339).

(g) Pyrrolidone, pyrazine, and pyridazine derivatives

Pyrrolidones (table 47, Nos. 1 and 2), prepared recently in Japan, were inactive (307). Succinic anhydride and diethylethylenediamine yielded the succinamide, which on electrolytic reduction produced 1,2-(diethylaminoethyl)-2-pyrrolidone.



The pyrazine (table 47, No. 3) and the pyridazine were very weak antagonists.

(h) Imidazole and imidazoline derivatives

In a study of imidazole compounds resembling histamine in structure, 4-methylimidazole, 4-ethylimidazole, and related compounds were synthesized (196, 432) (table 48). Some of the 4-(substituted aminomethyl)imidazoles showed a weak antihistaminic action, while others imitated histamine.

4-(Benzylphenylaminomethyl)imidazole (No. 9) is of interest because it is a position isomer of 2-(benzylphenylaminomethyl)imidazoline (Antistine, table 1, No. 2). The imidazole possesses about one-half the antihistaminic action of Antistine.

In the ethyl series, antihistamine activity was shown by No. 25, which possessed 0.5 of the activity of Pyribenzamine. The rest of the compounds in table 48 displayed various degrees of histamine-like activity.

The thiophene analog of Antistine (table 49, No. 1) had approximately 5 per cent of the activity of Antergan (228), while the tetrahydropyrimidine analog (No. 2) possessed insignificant activity (230).

A brief study was made by Turner of substances containing the imidazole nucleus (Nos. 3–6). None had any antihistaminic activity (431).

Jones (214, 215, 216) synthesized a series of 2-substituted imidazoles and 3- and 4-substituted pyrazoles in a broad study of the possible relationships of chemical structure to biological activity. None of the compounds are histamine antagonists, but rather resemble histamine in action. An excellent concise table correlating the structure of 2-aminoethyl heterocyclic nitrogen compounds and histamine activity was drawn up by Lee and Jones (468).

b. *N*-Polycyclic derivatives of ethylenediamine

Modifications of the linkages between the aryl groups in the Antergan molecule were of little avail (*cf.* tables 24 and 25). The diphenylamine derivative, RP 2565 (table 25, No. 3), had only about 1/50th the activity of Antergan. Polycyclic derivatives, such as carbazoles and phenoxazines (tables 50 and 53), possessed slight activity. A search for antimalarials among the phenothiazines and their testing as antihistamines led to the discovery of extreme potency in a bridged structure (178, 181).

By far the most active antihistaminic compounds known belong to the series of phenothiazines or thiodiphenylamines, which have been thoroughly investi-

gated by the Rhône-Poulenc research group. Only in this series and in the acridines have especially potent antagonists been found.

The potency of the active phenothiazines (RP 3015, RP 3277) is about fifteen times that of Pyribenzamine and the duration of action is three times that of Antergan or Pyribenzamine.

(1) Rhône-Poulenc *N*-polycyclic diamines

Table 50 lists the various polycyclic derivatives prepared for testing as histamine antagonists by Charpentier and described by Viaud (443) of the Rhône-Poulenc laboratories. The latter noted that the 3-aminoquinolyl derivative (RP 2970) was inactive. In the phenothiazine series, the dimethylaminoethyl side chain (RP 3015) gave antiasthma activity similar to that of Antergan, but considerably higher protection against intravenous histamine. While 20 mg./kg. of Antergan protected against 120 lethal doses, a similar dosage of RP 3015 protected against 700 lethal doses. Branching of the side chain by adding one methyl group (RP 3277, RP 3389) yielded further improvement. However, two other branched-chain compounds having two methyl groups (RP 3300, RP 3349) were completely inactive. Both the diethyl analog of RP 3015 (RP 2987) and the trimethylene analog (RP 3276) were almost inactive. When methoxyl groups were introduced into the phenothiazine nucleus (RP 3298, RP 3299), no particular advantage accrued.

Replacement of the phenothiazine molecule by related nuclei led only to compounds of inferior activity (RP 3283, 3289, 3040, 3041, 3192, 3390, 3398). Variations within this group of compounds, such as the formation of the sulfoxide (RP 3283) and the sulfone (RP 3289), led to the interesting observation that the sulfoxide was inactive, while the sulfone was as active as Antergan. The most active antagonist in the series was RP 3277 or Phenergan (table 1, compound 18), which is able to protect guinea pigs against 1500 lethal doses of histamine (181). These high doses led shortly afterwards to death, due to perforating stomach ulcers (180).

(2) Individual polycyclic groupings

(a) Phenothiazines

Charpentier (77, 394) prepared RP 3015 (table 51, No. 1) by reacting phenothiazine with dimethylaminoethyl chloride in the presence of an agent binding halogen acid, preferably sodium amide. The diethyl analog had been prepared, for other purposes, by Gilman and Shirley (162), by condensing phenothiazine with 2-chloroethyl *p*-toluenesulfonate in the presence of butyllithium and reacting the 10-chloroethylphenothiazine with dimethylamine in the presence of copper powder. The diethyl compound (Diparcol) was found to be useful in the treatment of Parkinsonism.

The quaternary ammonium salts (table 51, Nos. 31–39) were prepared by heating the tertiary base with the appropriate alkylene dihalides (78). The 8-chlorotheophylline salt of RP 3015 has been described as extremely potent (91, 146, 157, 317).

In the series of *N*-(pyrrolidylalkyl)phenothiazines (table 51, Nos. 17–22), *N*-pyrrolidylethylphenothiazine (No. 17; Pyrrolazote, table 1, No. 20) showed the highest level of antihistaminic activity (338). They were synthesized by hydrogenating pyrrole and its dimethyl homologs over Raney nickel and treating the resulting pyrrolidines with the appropriate alkylene chlorohydrin. The *N*-pyrrolidylalkanols thus formed were converted into the corresponding *N*-pyrrolidylalkyl chlorides with thionyl chloride. *N*-Alkylation of phenothiazine with the chlorides in the presence of sodium amide proceeded smoothly (198, 199, 338).

The *N'*-(2-hydroxyethyl)-*N'*-methyl derivative (table 51, No. 7) appears to possess about 1.5 times the activity of Benadryl (99).

The acylphenothiazine derivatives (table 51, Nos. 8–16) have weak antihistaminic power. They were prepared by heating phenothiazine with an excess of the appropriate haloacyl halide (126).

Miescher (286) described the imidazolyl derivative (No. 25) and the 2-methoxy compound (No. 28), prepared from the thiodiphenylamine and 2-chloromethyl-2-imidazoline, or from 10-(cyanomethyl)phenothiazine and ethylenediamine. No activity data are given.

An extensive series of *N*-(dialkylaminoalkyl)phenothiazines (table 52) were synthesized by Wright and coworkers (464). The pharmacological results (table 52) demonstrated that the introduction of groups larger than methyl on the terminal amino nitrogen does not increase the antihistamine effectiveness; more often the activity is lowered (464).

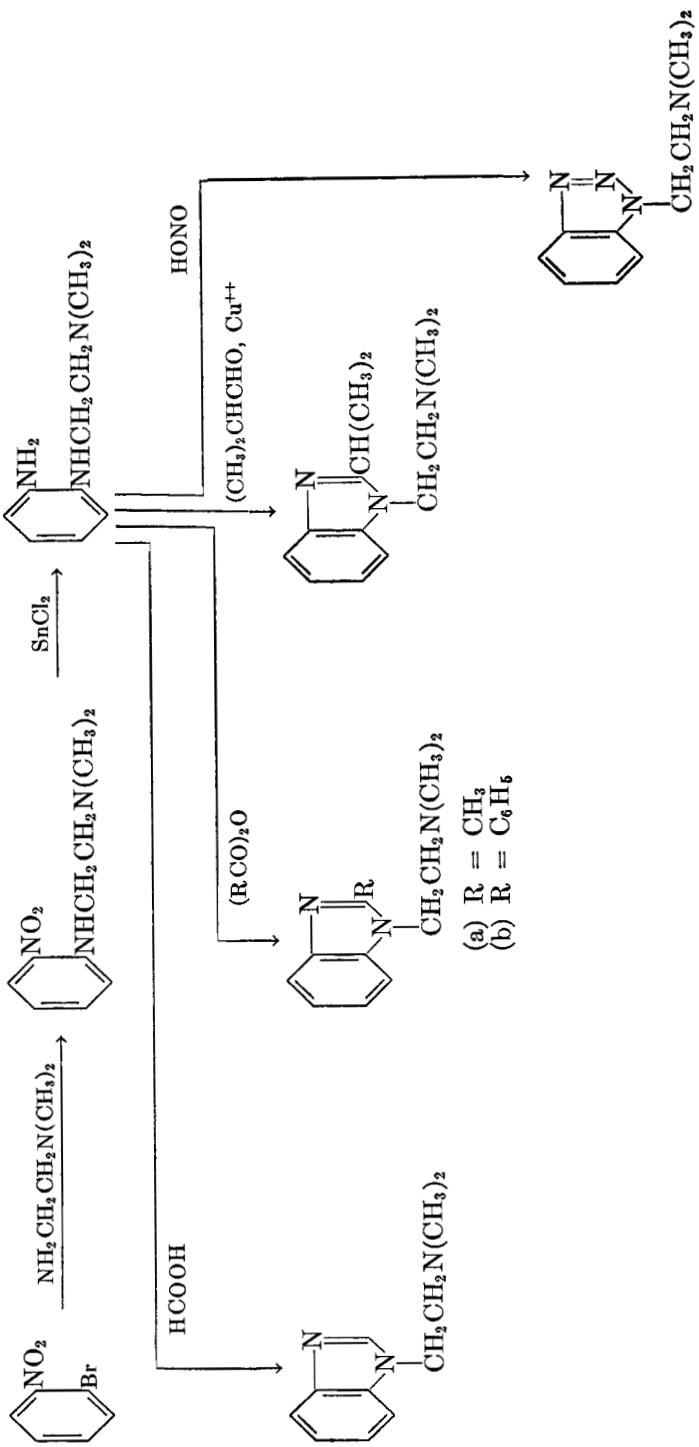
(b) Polycyclic functions other than phenothiazines

The indole and carbazole derivatives (table 53, Nos. 1–5, 39–41) were prepared by heating the appropriate sodium salts with the dialkylaminoethyl chloride. The compounds possess weak to moderate antihistaminic activity. 1-[2-(1-Pyrrolidyl)ethyl]indoline (No. 2) and the phenylindole (No. 3) had 0.1–0.01 the spasmolytic activity of Benadryl, while the phenylindolines (Nos. 4 and 5) had about one-half the activity. The carbazole and tetrahydrocarbazole (Nos. 39 and 40) were 0.1–0.01 as active and the hexahydro derivative possessed one-third to one-sixth the activity of Benadryl (460). The dimethylaminoethyl carbazole derivative (No. 36) was practically inactive (52).

Benzimidazole derivatives (Nos. 6–9) appeared to be of interest because they have the —N—C=N— grouping present in Pyribenzamine and other agents, as well as structures analogous to the imidazole ring of histamine (461).

The benzimidazole derivatives and the benzotriazole (No. 10) were prepared from *o*-(2-dimethylaminoethylamino)nitrobenzene. Reduction with stannous chloride gave a diamine which, upon treatment with formic acid, acetic anhydride, benzoic anhydride, isobutyraldehyde, and cupric acetate and nitrous acid gave the respective benzimidazole and benzotriazole derivatives (461, 462) (see page 353). These compounds possess only slight antihistaminic activity.

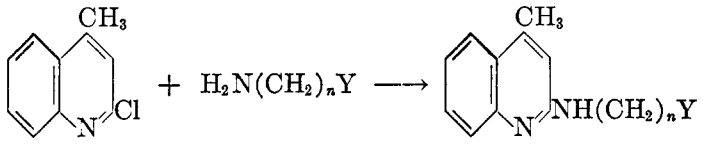
The quinoline derivatives (Nos. 13–20) are all practically inactive, agreeing with the results of Viaud (443), who found RP 2756 inactive. The lack of activity in Nos. 11, 12, 14–18 suggested that the presence of at least one aromatic nucleus


NO2
Br
NH2CH2CH2N(CH3)2
NO2
NHCH2CH2N(CH3)2
SnCl2
NH2
NHCH2CH2N(CH3)2
HCOOH
(RCO)2O
(CH3)2CHCHO, Cu++
HONO
CH2CH2N(CH3)2
(a) R = CH3
(b) R = C6H5
CH(CH3)2

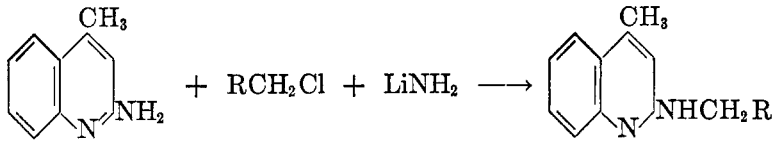
or its isostere is desirable for potency (307), but the furyl and thenyl derivatives (Nos. 19 and 20) possessed about 0.01 the activity of Pyribenzamine (244). The lepidyl-substituted diamines (Nos. 21–34) seem to be mildly active (5, 220).

The intermediate 2-lepidyl secondary amines were prepared either by heating 2-chlorolepidine with excess alkylenediamine (method A) or treating 2-lepidylamine with a halide in the presence of lithium amide (method B). An alternate method involved condensation of the aminolepidine with benzaldehyde, using formic acid as a solvent, and reduction (method C). The tertiary amines were prepared by standard procedures (methods D and E) (220).

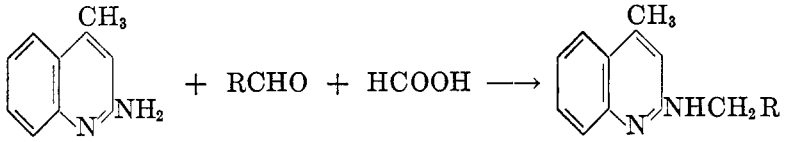
Method A



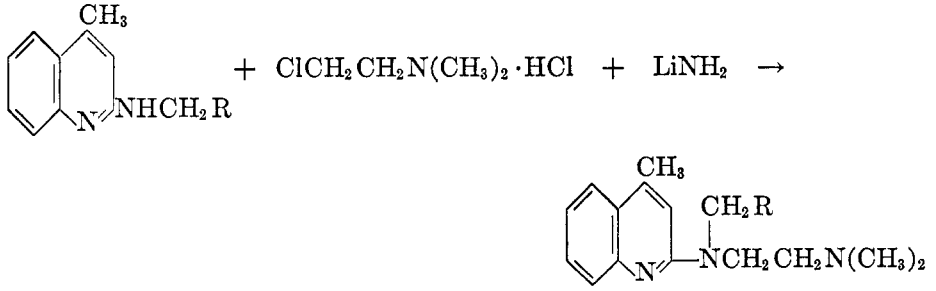
Method B



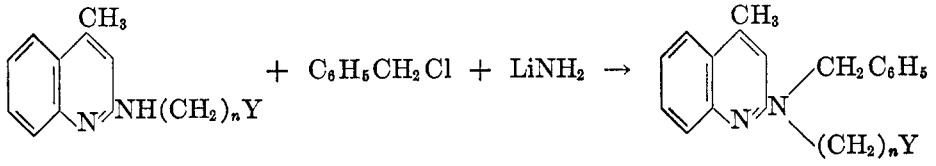
Method C



Method D

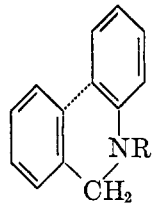


Method E



The quinoxaline derivative (No. 35) was synthesized by condensing dimethylaminoethyl chloride with *N*-benzylbenzamide to give *N*-benzoyl-*N*-benzyl-*N'*,*N'*-dimethylethylenediamine, which was hydrolyzed to the benzyl derivative. This was condensed with 2-chloroquinoxaline to form the desired compound. No pharmacological data were given (156).

Huttrer (202) noted that the 5,6-dihydrophenanthridine derivatives (Nos. 42–45) differed from the Antergan type compounds only in the existence of the linkage represented by the dotted line.



Nos. 42 and 45 were completely inactive, while No. 43 had very slight activity (202). It thus appears that ring closure does not aid in the antihistamine field, as it does with antispasmodics (e.g., Trasentin and Pavatrine).

The acridine derivative (No. 47) is an extremely potent antagonist, possessing variously 7.5 times the activity of Benadryl (290) or 16 times the potency (146). It appears too toxic for clinical usage (95, 146), though claims for low toxicity have been made (290).

3. Conclusions

Table 54 represents a compilation by Scholz (384) which illustrates lucidly the relationships between structure and activity in the ethylenediamine derivatives. Even though exceptions exist, one can conclude from the experimental findings that in order to get active compounds both nitrogen atoms of the ethylenediamine moiety should be completely substituted with organic radicals. For highest activity one nitrogen usually should be dimethylated and the other should carry an aryl radical and an aralkyl radical.

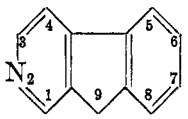
As far as the aryl radical is concerned maximum effect has been observed with α-pyridyl; phenyl, β- or γ-pyridyl, picolyls, pyrimidyl, thiazolyl, etc. show less activity. In the case of the aralkyl radical, the alkyl chain should be a methylene group, whereas the aryl part may be phenyl, substituted phenyl, furyl, thienyl, substituted thienyls, thiazolyl, etc. Substitution of a propylene or a branched-chain alkylene radical for the ethylene portion results, in most cases, in lowered effectiveness (384). The fusion of the aryl and aralkyl portions into a polycyclic ring is only effective in the case of the thiodiphenylamines, where the branching of the side chain plays an important role which is lacking in the other series.

In the ether series, substituents on the benzene nucleus play a part which does not have any significance in the aniline compounds. Indeed, the *p*-methoxy group has a great importance when attached to the benzyl group of Neoantergan but is of no importance if present in the benzyl group of Antergan.

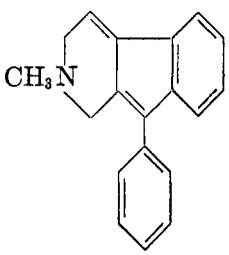
Bovet (32) stresses the significant fact that antihistaminic activity could always be detected in those substances which are structurally related to adrenolytic or spasmolytic compounds. It should again be emphasized that the compound with the highest activity is not always so superior in clinical trials.

C. DERIVATIVES OF PYRIDINDENE

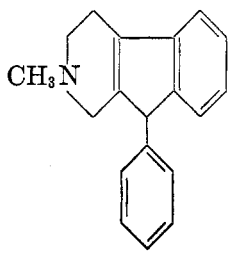
A class of compounds seemingly unrelated to the ethylenediamines is that of the derivatives of pyridindene (indenopyridine), which contain the novel fusion of the indene and pyridine rings.



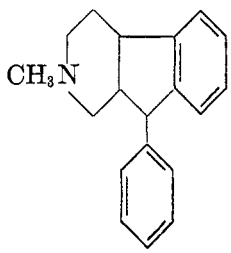
From a number of pyridindenes (table 55), 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (Thephorin; table 1, No. 25; table 55, No. 9) showed promising antihistamine activity. In a study of three derivatives of pyridindene which differed only in the number of double bonds, the dihydro (Nu 1326), tetrahydro (Nu 1504), and hexahydro (Nu 1525), Lehmann (237) concluded that Thephorin (Nu 1504) was about one-half as effective as Pyribenzamine in



Nu 1326



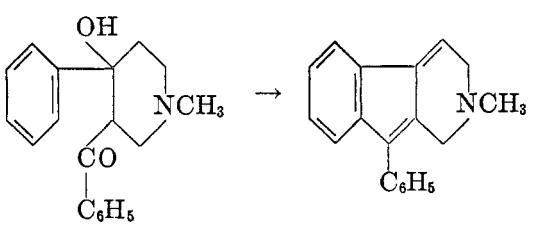
Thephorin
Nu 1504



Nu 1525

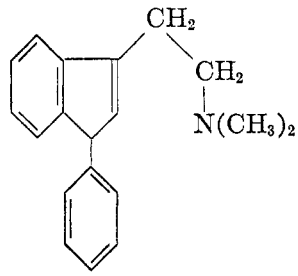
aerosol testing and protection against intracardially injected histamine. Of the two other derivatives, Nu 1326 only showed some antihistamine activity, showing that double bond changes cause striking decreases in activity.

The pyridindenes or 1*H*-indeno[2,1-*c*]pyridines result from the cyclodehydration of 1,3,4-trisubstituted piperidines by heating with strong hydrobromic or sulfuric acid. Thus, 2-methyl-9-phenyl-2,3-dihydro-1*H*-pyridindene is produced from 3-benzoyl-4-hydroxy-1-methyl-4-phenylpiperidine (319, 320).



Treatment of Mannich products, such as $C_6H_5COCH_2CH_2NRCH_2CH_2COC_6H_5$, with hydrobromic acid gives initially the piperidine derivative, which undergoes further cyclization to the above pyridindene derivative (319). Thus, derivatives of dihydro-1-pyridindenes have become one of the most easily accessible classes of polynuclear heterocyclic compounds.

The pyridindenes are placed immediately after the ethylenediamine derivatives, since Thephorin can be interpreted as a substance in which the aliphatic side chain $—CH_2CH_2N(CH_3)_2$ has participated in ring closure, somewhat similar to the imidazoline side chain of Antistine (201). The relationship is shown in the open-ring analog of Thephorin.



D. DERIVATIVES OF AMINOPROPANE

Dialkylaminopropanes

Two groups, one working at the Burroughs Wellcome Research Laboratories in Kent, England (1, 2), and the other at the laboratory of the Schering Corporation in Bloomfield, New Jersey (429, 231), investigated the effect of replacement of the oxygen and nitrogen functions in the ethanolamine and ethylenediamine derivatives by a methylene group to yield *C*-substituted dialkylaminoalkanes (tables 56, 57, 58).

The United States group announced the effectiveness of 3-phenyl-3-(2-pyridyl)-*N*,*N*-dimethylpropylamine (Trimeton, table 1, No. 26), which was estimated to possess four times the therapeutic index (effective dose/toxicity) of Pyribenzamine (427).

Chlorination of Trimeton in the phenyl ring produced a twentyfold increase in potency, yielding Chlortrimeton (table 1, No. 7), which appears to be the most potent oral antihistamine known. Halogenation produced no appreciable change in toxicity.

Tislow (426) has discussed the effect of halogenation on antihistamine activity. The tremendous change in Trimeton has been noted. However, halogenation does not always produce more potent compounds. Chlorobenzhydryl ethers (table 6, Nos. 63–68) are listed without any pharmacological data. Chlordecapyryn (table 14, No. 20) does not appear to be more active than the parent compound. Chlorination of the phenyl group in the benzhydrylpiperazines (table 33, No. 6) gave increased potency and lengthened duration of action. The *p*-chloro derivative of Pyribenzamine (table 41, No. 8) appears to be slightly more potent than the parent compound. The fluoro analog (table 41, No. 7) is

more active than the chloro, while the bromo compound (table 41, No. 10) is slightly less active. Halogenation of the 2-thenyl groups in Thenylene or Histadyl gave three times the activity of the unsubstituted compound (table 41, Nos. 24 and 25). In the 3-thenyl series, halogenation did not produce the desired effect (table 41, Nos. 28, 30, and 31), achieved in 2-thenyl isosteres. The bromofurfuryl derivative (table 41, No. 20) was slightly less effective than the unsubstituted derivative.

The propylamines were prepared by the condensation of 2-tertiary aminoethyl halides with (2-pyridyl)benzyl cyanide and subsequent removal of the cyano group or alkylation of the appropriately substituted dihydrostilbazoles with dialkylaminoalkyl halides (404, 406).

Unaware of the work at the Schering laboratory, Adamson (1, 2) prepared a large series of aminoalkyl tertiary carbinols, esters, propenes, and propanes (table 56). Several of the 3-tertiary-amino-1,1-diphenyl-1-propenes and -propanes exerted a moderate antihistamine action, in addition to surface anesthetic, spasmolytic, and mydriatic properties.

Since the replacement of the *N*-phenyl ring of Antergan by the 2-pyridyl group of Pyribenzamine and others increased the potency, it was sought to increase the antihistamine potency of the substituted allylamines by replacing one of the phenyl rings by 2-pyridyl (table 57) (2).

The aminopropanols were prepared by treating the appropriate aryl-2-tertiary-aminoethyl ketones (prepared by the Mannich reaction) with 2-pyridyllithium, and were converted into water-soluble neutral oxalates for pharmacological testing. The pyridylcarbinols, in contrast to the analogous diphenylcarbinols, were resistant to moderately severe dehydration conditions. This relative stability is in accord with the electrophilic nature of the 2-pyridyl group. Dehydration to the 1-propenes was effected by heating with aqueous sulfuric acid.

The activities of the carbinols were nil. The allylamines, like the propylamines, were outstanding for their antihistamine activity. The influence of the tertiary-amino substituent did not appear to run parallel in the two series. In the allylamine series, the pyrrolidino group had the most favorable effect, while in the propylamine series the highest activity is found in the dimethylamino compounds, as in Chlortrimeton.

In a series of bridged-ring propylamine hydrochlorides and 8-chlorotheophyllinates (table 58), the most active compounds were the thioxanthene (No. 2) and the dihydroanthracene derivatives (No. 5) (95, 146, 317).

In view of the similarity in the pharmacological properties between the ethyldialkylamines and the 2-imidazoline derivatives (*cf.* tables 6 and 11), a series of amidine and dihydroglyoxaline analogs of 3,3-diphenylpropylamines were prepared (212). This group of compounds is characterized by 3,3-diphenyl-*N*,*N*-dimethylpropylamine (Aspasan, table 58, No. 7), which had been prepared for testing as an antispasmodic and analgesic (28, 29). Aspasan possessed 0.1 the activity of Benadryl. The imidazoline analog of Aspasan (table 59, No. 1) was obtained from 2,2-diphenylpropionitrile either through the imidate hydrochloride (224) or by fusion with 2-aminoethylammonium toluene-*p*-sul-

fonate (309). The amidines (Nos. 2–4) were prepared by the action of an excess of ammonia or of the appropriate amine on ethyl 2,2-diphenylpropionimidate hydrochloride. For comparison diphenylacetamidine (No. 5) and 2-benzhydryl-2-imidazoline (No. 6) were prepared by standard methods. Only 2,2-diphenylpropionamidine (No. 3) had approximately one-tenth the activity of Benadryl.

The benzylimidazoline (No. 7), 1-naphthalenemethyl (No. 8), and biphenyl (No. 10) derivatives were prepared from the arylacetamide and excess ethylenediamine (283).

E. DERIVATIVES OF BUTENE AND STILBENE

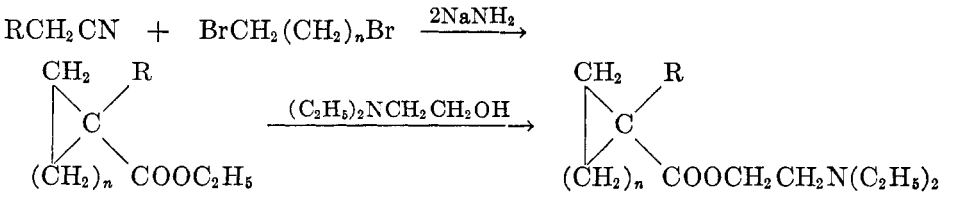
The antihistamine activity of basic propenes has already been discussed (tables 56 and 57). A series of 3-tertiary-amino-1,1-(2-thienyl)-1-butenes (table 60) has recently been announced (3), which exhibit considerable antihistaminic, spasmolytic, local anesthetic, and particularly analgesic activity. The butenes were prepared by the action of 2-thienyllithium on the appropriate ethyl 2-aminobutyrate.

Basic stilbenes, synthesized by Rohrmann (*cf.* 344), are unusual in that maximum activity (twice that of Benadryl) is obtained with a piperidinoethyl side chain (Lilly 01003, table 1, No. 14). The substitution of a dimethylamino group for the piperidino function cuts the activity in half.

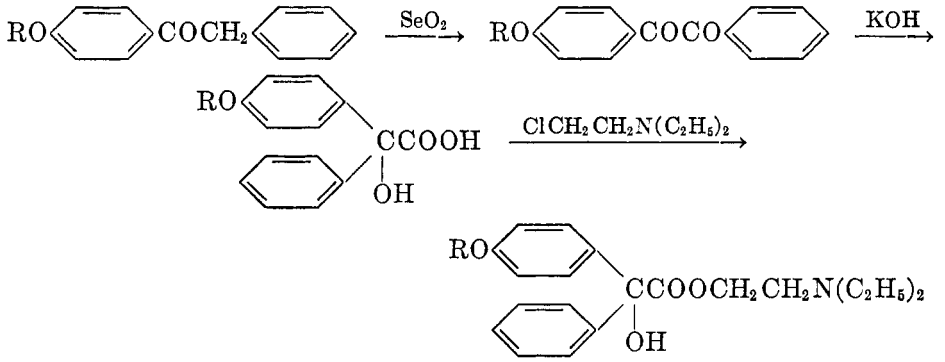
F. DERIVATIVES OF AMINOPROPIONIC ACID

Basic esters of alicyclic and heterocyclic acids have been tested as histamine antagonists, but usually this evaluation is adjunct to investigations of antispasmodic and anesthetic properties. Many of these early compounds (prior to about 1942) were tested against histamine, but cannot be mentioned here.

Tilford and coworkers (424, 440) synthesized a series of amino esters of substituted cycloalkanecarboxylic acids (table 61) for antihistamine and antispasmodic testing. No definite conclusions can be drawn in regard to relationship between structure and activity. However, a cyclohexyl or benzyl group in the 1- or 2-position of the cyclohexane ring was the most active of the series, but even the most active compound (No. 7) was less than one-half as active as Benadryl. The compounds were more effective as antispasmodics. The amino esters were prepared from the corresponding cyanides. Thus, phenylacetonitrile was condensed with an alkylene dihalide using two equivalents of sodium amide in a mixture of liquid ammonia and ether at low temperatures. Alcoholysis of the substituted nitriles by a sulfuric acid–ethanol mixture resulted in crude ethyl esters which were reësterified with the desired amino alcohol in toluene, using sodium as a catalyst.

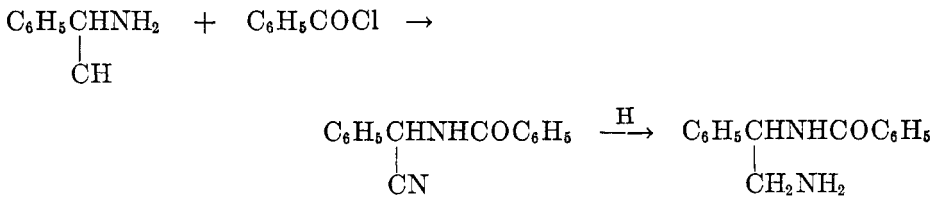


A study of diethylaminoethyl 4-alkoxybenzilates, primarily investigated for local anesthetic and antispasmodic action, yielded compounds of minor antihistamine activity (30) (table 62). The esters were obtained from appropriately substituted desoxybenzoins by the following route:



A peak activity is reached with the *n*-amoxy derivative (No. 8), with a potency equal to that of the unsubstituted benzilate.

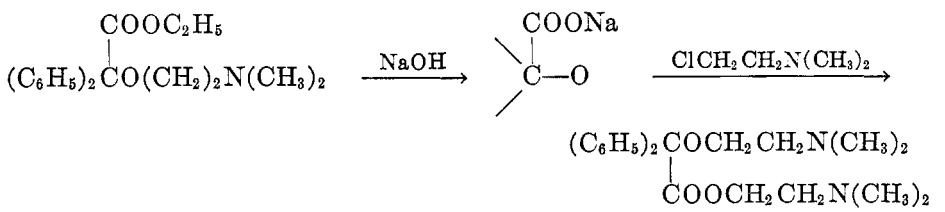
Funke and Kornmann (154) prepared a long series of ester derivatives of ethylenediamine by condensing arylaminonitriles with arylacyl halides to give the arylbenzamidoacetonitriles, which were reduced over Raney nickel to give the ethylenediamines.



The amines are not described as antihistamines, but could be valuable in the preparation of antagonists.

In a study of the comparative spasmolytic activities of benzhydryl alkamine ethers, Alles and Redemann (6) (*cf.* page 319, table 6A) noted that keto and ester compounds of essentially the same molecular size as the dialkylaminoethyl benzhydryl ethers are relatively much less active in their antihistamine activities and no more active in their antiacetylcholine activities (table 63, Nos. 1–3).

Ether-esters of hydroxydiphenylacetic acid were prepared, for testing, by treating a dialkylaminoalkyl halide with an alkali metal derivative of an ester (table 63, Nos. 4 and 5) (294, 295).



The replacement of one of the benzene rings of the Benadryl molecule (table 1, No. 3) with various ester groups and altering the structure of the dialkylaminoalkyl group yielded compounds of negligible activity (table 64) (429).

The esters, derivatives of phenylacetic acid, were prepared as shown by the following continuous equation:

$$C_6H_5CH_2COOH \xrightarrow{SOCl_2} C_6H_5CH_2COCl \xrightarrow{Br_2} C_6H_5CHBrCOCl \xrightarrow{ROH}$$

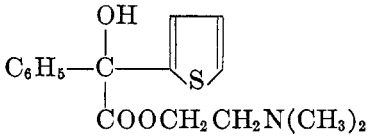
$$C_6H_5CHBrCOOR \xrightarrow{NR'_2CH_2CH_2ONa} C_6H_5\underset{\displaystyle O(CH_2)_nNR'_2}{\underset{|}{C}}HCOOR$$

Ethers of 2-hydroxypyridine were investigated to ascertain the effect of introducing the 2-pyridyl group into compounds for possible antihistaminic and antispasmodic action (190). The 2-pyridylaryl ethers were prepared by heating 2-bromopyridine and the phenol in the presence of anhydrous potassium carbonate. Where this method was inapplicable, the compounds were synthesized by heating the appropriate dry sodium phenoxide with 2-bromopyridine in the presence of copper powder. The 2-pyridyl ethers of ethyl glycolate, ethyl lactate, and ethyl mandelate were prepared through interaction of the sodium alkoxide of the ester with an excess of 2-bromopyridine. When applied to ethyl benzilate, this method failed, but the ethyl diphenyl(2-pyridoxy)acetate was prepared by heating dry sodium benzhydrolate with 2-bromopyridine and copper powder. The esters were converted to the alkamine esters of 2-diethylaminoethanol and 3-diethylamino-1-propanol through alcoholysis of the alkyl esters with excess amino alcohol containing a small quantity of dissolved sodium metal (table 65). Pharmacological evaluation was not given (190).

A series of esters of bridged compounds were prepared in 1942 by Burtner and Cusic (53–56) and tested by Lehmann and Knoefel (239, 240, 241) to determine the influence of the bridge on physiological activity (table 66). It was found that the replacement of the C—C (fluorene, No. 1) bridge by —CH_2— (dihydroanthracene, No. 2) led to much stronger antihistaminic activity, while substitution of the —CH_2— by oxygen (xanthene, No. 4) caused greater spasmolytic potency, and the substitution of sulfur (thioxanthene, No. 5) for the oxygen caused lesser activity. Substitution by an imino group (acridine, No. 4) reduced the histamine antagonism.

The 2-diethylaminoethyl fluorene-9-carboxylate was prepared from fluorenecarboxylic acid and diethylaminoethyl chloride, while the dihydroanthracene derivative was made from 9,10-dihydroanthracene-9-carboxylate and the diethylaminoethyl chloride. The carboxylic acids were prepared by carbonation of the lithium derivatives of the hydrocarbons.

Within a series of esters of phenyl-α-thienylglycolic acid, the dimethylamino derivative was reported to have some activity (467). The piperidine analog was



one-half as active as Benadryl against histamine (79). However, it was quite toxic and produced convulsions.

V. Summary and General Conclusions

An attempt has been made to present most of the salient facts relative to the chemistry of the present antihistamine agents. The search for the pharmacological and clinical results of the well-known antihistaminics, which have had wide usage, were not included here, since these data are excellently covered in several papers (*cf.* page 309), notably in the annual reviews, entitled "Progress in Allergy," which are published in the Annals of Allergy.

The following conclusions as to correlation of structure and chemotherapeutic activity are based on such scanty and variable pharmacological data that they are of little scientific value. They are offered as a guide to future research, and not as a sign that negative conclusions invalidate further work.

The basic unit for all effective agents has been the ethylamine skeleton. Essentially all the compounds contain this group, whether it be a "straight-chain" compound such as Antergan or part of a ring compound such as Antistine. Thus such widely differing (structurally) compounds as Thephorin, Antistine, Perazil, Trimeton, and Phenergan show a common factor. It is interesting that the ethylamine skeleton also corresponds to the side chain of the histamine molecule and to part of the imidazole chain.

With the exception of the 2-methyl-2-imidazoline side chain, the terminal nitrogen should be a tertiary nitrogen, for secondary and primary amino derivatives are inactive. It is interesting that while the *N*-diethylalkyl group seems characteristic of antispasmodic compounds, the *N*-dimethylalkyl group appears to be the optimal grouping in the antihistamine compounds. Branching of the side chain, with methyl attached to the α-carbon, seems to have had a beneficial effect, but β-methyl substituents sharply reduce activity. Larger alkyl groups cause decreased activity (tables 5 and 52). When the methyl groups are part of a heterocyclic side chain, such as pyrrolidino, piperidino, and morpholino, less active compounds are usually produced, although the pyrrolidine derivatives in the benzhydryl ethers and phenothiazines have been reported to possess at least as great activity as the dimethyl analogs. No such effect was noted in the *N*-pyridyl series (*cf.* table 41, Nos. 54–58). The methylpiperazyl ether is also a decided improvement. Substitutions in the pyrrolidyl portions of the pyrrolidinophenothiazines (table 51, Nos. 17–22) were of no advantage.

An increase in side-chain length from ethylene to trimethylene or greater has usually produced a sharp drop in activity. Quaternization in the ethers has led to decreased antihistaminic activity but increased antispasmodic activity (*cf.* page 320 and table 32). There is sometimes a notable difference in potency of the various salts of a particular compound. This is probably due to increased solubility or absorption in the animal. Thus, Chlortrimeton maleate appears more active than the hydrochloride. Various dicarboxylic acid salts, such as the acid succinates, fumarates, malates, citrates, acid tartrates, and maleates have been found suitable.

The nucleus of all the antihistaminic agents should have a minimum of two

aryl or aralkyl groups or their equivalent in a polycyclic ring system. Monoaryls, such as the phenoxyethyl ethers (table 3), triazines (tables 20, 39), Fourneau amines (table 22), and imidazoles (table 48), were all weak antagonists. A minimum molecular weight of about 150 seems necessary.

Ether linkages on the carbon of the basic ethylamine skeleton appear to lead to relatively more toxic and sedative properties, although the groups attached to the ether oxygen exert severe modifying effects. Thus, Benadryl is less toxic than F 929 and Decapryn, while the benzylphenols are more potent and much less toxic than any of these. The great increases in potency found in the diamines by replacement of alicyclic by heterocyclic groups were noted, but the effect was not as great as in the ethers. Substitution in the aryl groups has yielded some improvement in the benzhydryl ethers. The phenoxyethyl ethers have to be substituted in the ring for any adequate activity. Trisubstitution in the nuclei was disadvantageous, for the 2-dimethylaminoethyl triphenylmethyl ether was practically inactive. Diheterocyclic substitution in the ether nuclei led to inactive compounds, as did hydrogenated rings (*cf.* table 15). It is interesting that the benzyl group does not have the same favorable effect with the pyridyl-substituted ethers (table 14, No. 11) as with the diamines, nor does *p*-methoxy substitution help (*cf.* page 316 and table 11). Peroxides, such as the dioxolanes (table 12), were quite weak.

The effect of halogenation has been discussed (*cf.* page 357). Isoteric principles have been effectively used, for the replacement of the aryl group by thenyl and furfuryl in the pyridyl series (table 41) has left essentially the same activity. The same did not seem to apply to the pyrimidine-aryls (*cf.* page 347). The addition of the benzyl radical increased the basicity and the activity. *p*-Methoxy substitution in the benzyl radical improved the pharmacological activity in Neoantergan. However, clinically, there is often little difference between the action of Neoantergan and that of Pyribenzamine. The substitution of the pyrimidyl group in the diamines lowers the potency but also reduces the toxicity. Clinically, Neohetramine is not as potent as other drugs, but it also has fewer side actions. The aminopropane derivatives, such as Trimeton, are not as active pharmacologically or clinically. However, Trimeton is also neither as toxic nor as likely to cause drowsiness. The *p*-chloro derivative is extremely active and has no increased toxicity.

Thephorin, a pyridindene derivative, is as effective as most of the previous drugs. Its greatest advantage is that it enervates, rather than sedates, the patient.

Attempts to correlate physical properties with chemotherapeutic activity have been rare. Baltzly and coworkers (16) suggested that the prolonged action of Perazil (*cf.* page 338) might be due to inhibition of metabolic oxidation, and that the electron-releasing or -attracting effect of the polar *p*-halogen groups ought to be reflected in the pK_a values. Certain trends were noted in the compounds of table 33, although the effects of variations on the basicity of the benzhydrylamino nitrogen tend to be masked by the presence of the more strongly basic methylamino group.

The influence of methoxy substitution on the pK_a was less than expected. The resonance of a methoxyl group could be expected to increase electron con-

centration para to itself and thus increase basicity. This tendency seems of minor importance here, and the methoxyl group seems to function mainly through its inductive action, electron attraction being dominant. This suggests that the methoxyl resonance, while important in activated or transition states, has little influence on continuing unactivated properties of the molecule. Yet it is evident that the nucleus of antihistamine agents must include an unsaturated ring structure attached to oxygen, nitrogen, or carbon in such a way as to allow resonance stabilization of the active intermediate, for all compounds with saturated substituents are practically inactive. Substitutions on the aromatic rings themselves which interfere with, but probably would not completely prevent, stabilization through hyperconjugation usually cause relative inactivation. Methyl substitutions in the 4- and 2-positions have not increased potency, but in the 3-position (Toladryl), where it would not interfere with conjugation, there appears to be a favorable effect. It is probable that steric forces are added factors in the reduced activity of ortho-substituted compounds. The extra potency of benzyl compounds and similar methylene separations between the aromatic rings and nitrogen lends support to resonance ideas, for direct apposition of the ring and the nitrogen, which would reduce but not prevent stabilization, yields lowered activity. The interposition of one carbon atom permits effective resonance. The replacement of the benzyl group in Antergan by heterocyclic functions yielded little improvement, but change of the phenyl group caused great changes. Two-carbon interposition between the aryl group and nitrogen reduces activity, possibly owing to inhibition of resonance. The phenoxyethyl derivatives which favor hyperconjugation are improved in the benzhydryl series, where the stability of the ion decreases with the increase of aromatic rings. The sharp differences in the dimethyl and diethyl derivatives could not be expected on the basis of resonance; possibly planarity is involved. The possible anomaly in the case of the *p*-halogen derivatives may lie in that these antihistaminics function by being absorbed on some enzyme whose matrix admits the presence of para substituents only (16).

No correlations can be drawn between activity and the intrinsic chemical properties of the aromatic nuclei. The pyridine, pyrimidine, pyrazine, pyridazine, and certain of the bridged-ring systems are relatively weakly nucleophilic, while the thienyl, imidazolyl, and phenyl systems are relatively strongly nucleophilic. All types are found among the active and inactive compounds. Possibly studies of spatial dispositions, bond angles, and distances may reveal fruitful correlations.

Since very few drugs act by a single mechanism, the clinical relief which is obtained upon their use is the result of the accumulation of various activities and of attacks upon different cell and enzyme systems. This is probably true with the antihistaminic drugs. Some sort of easily reversible union probably occurs between the competing drug and a receptor in the tissue for which both have an affinity. Such a union might be in the nature of a loose chemical bond or a process of adsorption. Thus, the physicochemical principles governing chemical or adsorptive equilibria may be the keys for the interpretation of this system of

antagonists. Wells (449) has presented fascinating hypothetical kinetic equations for histamine antagonism.

The author is indebted to Mrs. Rita A. Idson and Miss Katharine K. Frisbie for invaluable assistance in the preparation and editing of the manuscript.

VI. References

(1) Adamson, D. W.: J. Chem. Soc. **1949,** Suppl. Issue, No. 1, S144.
(2) Adamson, D. W., and Billinghurst, J. W.: J. Chem. Soc. **1950,** 1039.
(3) Adamson, D. W., and Green, A. F.: Nature **165,** 122 (1950).
(4) Aiman, R., and Gharpure, M. B.: Current Sci. (India) **18,** 303 (1949); Chem. Abstracts **44,** 1201 (1950).
(5) Albro, L. P., Baltzly, R., and Phillips, A.: J. Org. Chem. **14,** 771 (1949).
(6) Alles, G. A., and Redemann, M. A.: J. Pharmacol. **96,** 338 (1949).
(7) Anan, S.: Folia Pharmacol. Japon. **9,** 53 (1929).
(8) Anan, S.: Ber. ges. Physiol. **35,** 430 (1930).
(9) Anderson, L. T., Gakenheimer, W. C., Rosenblum, C., and Smith, E. H.: J. Am. Pharm. Assoc. **38,** 373 (1949).
(10) Annals of the New York Academy of Science **50,** 1013 (1950).
(11) Ashworth, M. R. F., Daffern, R. P., and Hammick, D. L.: J. Chem. Soc. **1939,** 811.
(12) Aspinall, S. R.: J. Am. Chem. Soc. **61,** 3195 (1939).
(13) Balakhovskiĭ, S. D., Borodatov, V. V., and Budnitskaya, E. V.: Compt. rend. acad. sci. U.R.S.S. **54,** 243 (1946); Chem. Abstracts **41,** 5176 (1946).
(14) Balakhovskiĭ, S. D., and Troitskaya, N. A.: Doklady Akad. Nauk S.S.S.R. **67,** 691 (1949); Chem. Abstracts **44,** 1200 (1950).
(15) Baltzly, R., Buck, J. S., Lorz, E., and Schoen, W.: J. Am. Chem. Soc. **66,** 263 (1944).
(16) Baltzly, R., DuBreuil, S., Ide, W., and Lorz, E.: J. Org. Chem. **14,** 775 (1949).
(17) Bandelin, F. J., Slifer, E. D., and Pankratz, R. E.: J. Am. Pharm. Assoc. **39,** 277 (1950).
(18) Banks, C. K., Gruhzit, O. M., Tillitson, E. W., and Controulis, J.: J. Am. Chem. Soc. **66,** 1771 (1944).
(19) Bariety, M., and Kohler, D.: Compt. rend. soc. biol. **135,** 161 (1941).
(20) Barraud, J., and Genevoise, L.: Compt. rend. acad. sci. **222,** 760 (1946).
(21) Beraldo, W. T., and Rocha e Silva, M.: J. Pharmacol. **89,** 167 (1947).
(22) Bernstein, T. B., and Feinberg, S. M.: J. Lab. Clin. Med. **34,** 1007 (1949).
(23) Best, C. H.: J. Physiol. **67,** 256 (1929).
(24) Best, C. H., and McHenry, E. W.: Can. Med. Assoc. J. **43,** 163 (1940).
(25) Biel, J.: J. Am. Chem. Soc. **71,** 1306 (1949).
(26) Binet, L., and Kohler, D.: Compt. rend. soc. biol. **135,** 345 (1941).
(27) Blicke, F. F., and Anderson, F. E.: Abstracts of Papers Presented at the 114th Meeting of the American Chemical Society, September, 1948, p. 14K.
(28) Bockmuhl, M., and Erhart, G.: Ann. **561,** 62 (1948).
(29) Bockmuhl, M., Erhart, G., Eisleb, O., and Stein, L.: U. S. patent 2,446,552 (August 10, 1948); Chem. Abstracts **43,** 1810 (1949).
(30) Bockstahler, E. R., and Wright, D. L.: J. Am. Chem. Soc. **71,** 3760 (1949).
(31) Boenigk, J. W., Christian, J. E., and Jenkins, G. L.: J. Am. Pharm. Assoc. **38,** 357 (1949).
(32) Bovet, D., and Bovet-Nitti, F.: *Medicaments du systeme nerveux vegetatif*, Chapter 22. S. Karger, Basel (1948).
(33) Bovet, D., and Fourneau, E.: Arch. intern. pharmacodynamie **46,** 148 (1933).
(34) Bovet, D., Horclois, R., and Fournel, J.: Compt. rend. soc. biol. **138,** 185 (1944).
(35) Bovet, D., Horclois, R., and Walthert, F.: Compt. rend. soc. biol. **138,** 99 (1944).

(36) BOVET, D., AND MADERNI, P.: Compt. rend. soc. biol. **114,** 980 (1933).
(37) BOVET, D., AND SIMON, A.: Arch. intern. pharmacodynamie **55,** 15 (1937).
(38) BOVET, D., AND STAUB, A. M.: Compt. rend. soc. biol. **124,** 547 (1937).
(39) BOVET, D., AND VIAUD, P.: Intern. Congr. Pure Applied Chem., 11th Congr., London, 1947.
(40) BOVET, D., AND WALTHERT, F.: Ann. pharm. franc. **2,** supplement to No. 4, 1 (1944).
(41) BOWEN, R.: Texas State Med. J. **42,** 188 (1946).
(42) BRAUN, J. V., HEIDER, K., AND MUELLER, E.: Ber. **50,** 1637 (1917).
(43) BRODIE, B. B., AND BAER, J. E.: J. Biol. Chem. **168,** 299 (1947).
(44) BRODIE, B. B., AND UDENFRIEND, S.: J. Biol. Chem. **158,** 705 (1945).
(45) BRODIE, B. B., AND UDENFRIEND, S.: Federation Proc. **5,** 124 (1946).
(46) BRODIE, B. B., AND UDENFRIEND, S.: J. Biol. Chem. **168,** 327, 335 (1947).
(47) BRODIE, B. B., AND UDENFRIEND, S.: J. Biol. Chem. **168,** 341 (1947).
(48) BROWN, B. B., AND WERNER, H. W.: J. Pharmacol. **97,** 157 (1949).
(49) BUCHI, J.: Galenica Acta Ano (Madrid) **1,** 119 (1949).
(50) BUKANTZ, S. C., AND DAMIEN, G.: Science **107,** 224 (1948).
(51) BURCHELL, H. B., AND VARCO, R. L.: J. Pharmacol. **75,** 1 (1942).
(52) BURCKHALTER, J. H., STEPHENS, V. C., AND HALL, L. A. R.: J. Am. Pharm. Assoc. **39,** 271 (1950).
(53) BURTNER, R. R.: U. S. patent 2,262,754 (November 18, 1941): Chem. Abstracts **36,** 1738 (1942).
(54) BURTNER, R. R.: U. S. patent 2,334,310 (November 16, 1943); Chem. Abstracts **38,** 2794 (1944).
(55) BURTNER, R. R., AND CUSIC, V. W.: J. Am. Chem. Soc. **65,** 262 (1943).
(56) BURTNER, R. R., AND CUSIC, V. W.: J. Am. Chem. Soc. **65,** 1582 (1943).
(57) BUSINCO, L.: Boll. soc. ital. biol. sper. **15,** 826 (1940); Chem. Abstracts **40,** 5834 (1945).
(58) CAMERON, W. M., AND TAINTER, M. L.: J. Pharmacol. **51,** 371 (1934).
(59) CAMPAIGNE, E., AND LESUER, W. M.: J. Am. Chem. Soc. **70,** 415 (1948).
(60) CAMPAIGNE, E., AND LESUER, W. M.: J. Am. Chem. Soc. **70,** 1555 (1948).
(61) CAMPAIGNE, E., AND LESUER, W. M.: J. Am. Chem. Soc. **70,** 3498 (1948).
(62) CAMPAIGNE, E., AND LESUER, W. M.: J. Am. Chem. Soc. **71,** 333 (1949).
(63) CAMPBELL, K. N., ACKERMAN, J. F., AND CAMPBELL, B. K.: J. Am. Chem. Soc. **71,** 2905 (1949).
(64) CARRARA, G., D'AMATO, V., AND PAGANI, R.: Chimica e industria (Milan) **28,** 9 (1946); Chem. Abstracts **40,** 7241 (1946).
(65) CARRARA, G., D'AMATO, V., AND PAGANI, R.: Farm. sci. e tec. (Pavia) **3,** 178 (1948); Chem. Abstracts **42,** 6988 (1948).
(66) CASTILLO, J. C., AND DEBEER, E. J.: J. Pharmacol. **90,** 104 (1947).
(67) CASTILLO, J. C., AND DEBEER, E. J.: Federation Proc. **6,** 315 (1947).
(68) CASTILLO, J. C., DEBEER, E. J., AND JAROS, S. H.: J. Pharmacol. **96,** 388 (1949).
(69) CASTORINA, G.: Farm. sci. e tec. (Pavia) **4,** 45 (1949); Chem. Abstracts **43,** 4657 (1949).
(70) CAVALLINI, G., MASSARINI, E., RAVENNA, F., AND MAZZUCCHI, F.: Farm. sci. e tec. (Pavia) **2,** 265 (1947); Chem. Abstracts **42,** 4574 (1948).
(71) CAVALLINI, G., AND MAZZUCCHI, F.: Farm. sci. e tec. (Pavia) **2,** 273 (1947); Chem. Abstracts **42,** 1664 (1948).
(72) CERKOVNIKOV, E., AND PRELOG, V.: Ber. **74,** 1648 (1941).
(73) CERKOVNIKOV, E., SKARICA, N., AND STERN, P.: Arkiv. Kemi, Mineral. Geol. **18,** 37 (1946); Chem. Abstracts **42,** 1942 (1948).
(74) CERKOVNIKOV, E., AND STERN, P.: Arkiv. Kemi, Mineral. Geol. **18,** 12 (1946); Chem. Abstracts **42,** 1938 (1948).
(75) CERKOVNIKOV, E., STERN, P., AND MARIJAN, N.: Arkiv. Kemi, Mineral. Geol. **18,** 87 (1946); Chem. Abstracts **42,** 3394 (1948).
(76) CHAMINGS, A. R. G.: Pharm. J. **159,** 83 (1947).

(77) CHARPENTIER, P.: Compt. rend. **225,** 306 (1947).
(78) CHARPENTIER, P.: U. S. patent 2,480,355 (August 30, 1949); Chem. Abstracts **44,** 1145 (1950).
(79) CHEN, J. V. P., AND ABREU, B. F.: Federation Proc. **6,** 316 (1947).
(80) CHEN, G., AND ENSOR, C. R.: J. Pharmacol. **98,** 245 (1950).
(81) CHENEY, L. C., SMITH, R. R., AND BINKLEY, S. B.: J. Am. Chem. Soc. **71,** 60 (1949).
(82) CIBA LTD.: British patent 608,296 (September 13, 1948); Chem. Abstracts **43,** 5048 (1949).
(83) CIBA LTD.: Swiss patent 242,839 (June 15, 1946); Chem. Abstracts **43,** 3979 (1949).
(84) CIBA LTD.: Swiss patents 245,894–900 (August 1, 1947); Chem. Abstracts **43,** 5049 (1949).
(85) CIBA LTD.: Swiss patent 246,579 (October 1, 1947); Chem. Abstracts **43,** 6240 (1949).
(86) CIBA LTD.: Swiss patent 258,585 (May 16, 1949); Chem. Abstracts **44,** 2037 (1950).
(87) CLAISEN, L., KREMERS, F., AND ROTH, F.: Ann. **442,** 210 (1925).
(88) CLAPP, R. C., CLARK, J. H., VAUGHAN, J. R., ENGLISH, J. R., AND ANDERSON, G. W.: J. Am. Chem. Soc. **69,** 1549 (1947).
(89) CLARK, B. B., AND HELPERN, M. M.: Federation Proc. **8,** 282 (1949).
(90) CLARK, J. H., CLAPP, R. C., VAUGHAN, J. R., JR., SUTHERLAND, L. H., WINTERBOTTOM, R., ANDERSON, G. W., FORSYTHE, J. D., BLODINGER, J., EBERLIN, S. L., AND ENGLISH, J. P.: J. Org. Chem. **14,** 216 (1949).
(91) CLARK, A. J., AND RAVENTOS, J.: Quart. J. Exptl. Physiol. **26,** 375 (1937).
(92) CLAUSER, H., MAIER-HUSER, H., AND FROMAGEOT, C.: Compt. rend. **230,** 879 (1950).
(93) CODE, C. F.: Proc. Staff Meetings Mayo Clinic **20,** 439 (1945).
(94) CONTROULIS, J., AND BANKS, C. K.: J. Am. Chem. Soc. **67,** 1946 (1945).
(95) COOK, D. L., HAMBOURGER, W. E., AND WARBURY, M. M.: Federation Proc. **7,** 212 (1948).
(96) CRAIG, L. C.: J. Biol. Chem. **150,** 33 (1943).
(97) CRIEP, L. H.: Lancet **68,** 55 (1948).
(98) CROMWELL, N. H., AND FITZGIBBON, W. E.: J. Am. Chem. Soc. **70,** 387 (1948).
(99) CUSIC, J. W.: J. Am. Chem. Soc. **71,** 3237 (1949).
(100) CUSIC, J. W.: Science **109,** 574 (1948).
(101) CUSIC, J. W.: U. S. patent 2,499,058 (February 28, 1950); Chem. Abstracts **44,** 4926 (1950).
(102) DAHLBOM, R.: Acta Chem. Scand. **3,** 32 (1949); Chem. Abstracts **43,** 6619 (1949).
(103) DAHLBOM, R.: Acta Chem. Scand. **3,** 93 (1949).
(104) DAHLBOM, R., AND SJÖGREN, B.: Acta Chem. Scand. **1,** 177 (1948); Chem. Abstracts **42,** 5450 (1948).
(105) DALE, H. H.: Lancet **1,** 233 (1929).
(106) DALGLIESH, C. E.: J. Chem. Soc. **1944,** 677.
(107) DAWES, G. S.: Brit. Med. J. **1,** 43 (1946).
(108) DECKENBROCK, W.: Pharmazie **3,** 495 (1948).
(109) DECOURT, M. J.: Presse méd. **50,** 773 (1943).
(110) DENTON, J. J., AND HOWARD, K. L.: U. S. patent 2,459,367 (January 18, 1949); Chem. Abstracts **43,** 4704 (1949).
(111) DILL, W. A., AND GLAZKO, A. J.: J. Biol. Chem. **179,** 395 (1949).
(112) DJERASSI, C., HUTTRER, C. P., AND SCHOLZ, C. R.: U. S. patent 2,406,594 (August 27, 1946); Chem. Abstracts **41,** 489 (1947).
(113) DJERASSI, C., AND SCHOLZ, C. R.: J. Am. Chem. Soc. **69,** 1688 (1947).
(114) DJERASSI, C., AND SCHOLZ, C. R.: J. Org. Chem. **13,** 830 (1948).
(115) DJERASSI, C., SCHOLZ, C. R., CRAVER, B. N., AND YONKMAN, F. F.: Abstracts of Papers Presented at the 110th Meeting of the American Chemical Society, September, 1946, page 12K.
(116) DRAGSTEDT, C. A.: J. Allergy **16,** 69 (1945).
(117) DUBOST, P.: Ann. pharm. franç. **7,** 139 (1949).

(117a) DUNLOP, D. M.: J. Pharm. Pharmacol. **1,** 1 (1949).
(118) DUTTA, N. K.: Brit. J. Pharmacol. **4,** 197 (1949).
(119) Editorial: J. Am. Med. Assoc. **142,** 566 (1950).
(120) EDLBACHER, S., JUCKER, P., AND BAUR, H.: Z. physiol. Chem. **247,** 63 (1937).
(121) EDLBACHER, S., AND ZELLER, A.: Helv. Chim. Acta **20,** 717 (1937).
(122) EDLBACHER, S., AND ZELLER, A.: Helv. Chim. Acta **21,** 880 (1938).
(123) EDWARDS, W. M., AND TEAGUE, P. C.: J. Am. Chem. Soc. **71,** 3548 (1949).
(124) EINHORN, A.: German patent 224,160 (October 16, 1908); Chem. Abstracts **4,** 3283 (1910).
(125) EINHORN, A., AND ROTHLAUF, L.: Ann. **382,** 256 (1911); Chem. Abstracts **5,** 3459 (1911).
(126) EKSTRAND, T.: Acta Chem. Scand. **3,** 302 (1949).
(127) ELLIS, F. W., AND NEWSOME, J. F.: Federation Proc. **5,** 176 (1946).
(128) EMMELIN, N.: Acta Physiol. Scand. **5,** 372 (1943).
(129) EMMELIN, N., KAHLSON, G. S., AND LINDSTROM, K.: Acta Physiol. Scand. **3,** 39 (1941).
(130) ERCKLENTZ, W., AND ERCKLENTZ, B. W.: Münch. med. Wochschr. **83,** 17 (1936).
(131) ERCOLI, N., SCHACHTER, R. J., LEONARD, F., AND SOLMSSEN, U. V.: Arch. Biochem. **13,** 487 (1947).
(132) EWING, P. L., NASH, J., AND EMERSON, G. A.: J. Pharmacol. **98,** 8 (1950).
(133) FEINBERG, S. M.: J. Allergy **17,** 217 (1946).
(134) FEINBERG, S. M.: J. Am. Med. Assoc. **132,** 702 (1946).
(135) FEINBERG, S. M.: J. Am. Pharm. Assoc., Pract. Pharm. Ed. **8,** 547 (1947).
(136) FEINBERG, S. M.: Chem. Eng. News **25,** 2134 (1947).
(137) FEINBERG, S. M., MALKIEL, S., BERNSTEIN, T. H., AND HARGIS, B. J.: J. Pharmacol. **99,** 195 (1950).
(138) FELL, N., RODNEY, G., AND MARSHALL, D. E.: J. Immunol. **47,** 237 (1943).
(139) FLEMING, R. W., AND RIEVESCHL, G., JR.: Abstracts of Papers Presented at the 112th Meeting of the American Chemical Society, September, 1947, p. 16K.
(140) FOURNEAU, E., AND BOVET, D. Arch. intern. pharmacodynamie **46,** 178 (1933).
(141) FOURNEAU, E., AND BOVET, D.: Compt. rend. soc. biol. **113,** 388 (1933).
(142) FOURNEAU, J. P.: Bull. soc. chim. France **7,** 603 (1940).
(143) FOURNEAU, J. P.: Bull. soc. chim. France **11,** 141 (1944).
(144) FOURNEAU, J. P., AND LESTRANGE, Y.: Bull. soc. chim. France **14,** 827 (1947).
(145) FOURNEAU, E., MODERNI, P., AND LESTRANGE, Y.: J. pharm. chim. **18,** 185 (1933).
(146) FREESE, H. B., HAMBOURGER, W. E., AND MICHIELS, P. M.: Federation Proc. **7,** 219 (1948).
(147) FRIEDLAENDER, A. S., AND FRIEDLAENDER, S.: Ann. Allergy **7,** 83 (1949).
(148) FRIEDLAENDER, A. S., FRIEDLAENDER, S., AND VANDENBELT, J. M.: J. Invest. Dermat. **11,** 397 (1948).
(149) FRIEDLAENDER, A. S., FRIEDLAENDER, S., AND VANDENBELT, J. M.: J. Allergy **20,** 229 (1949).
(149a) FRIEDLAENDER, S., AND FRIEDLAENDER, A. S.: J. Allergy **21,** 303 (1950).
(150) FRIEDMAN, H. L., AND TOLSTOOUHOV, A. V.: U. S. patent 2,465,865 (March 29, 1949); Chem. Abstracts **43,** 6244 (1949).
(151) FROMMEL, E., BISCHLER, A., BECK, I. T., VALLETTE, F., AND FAVRE, M.: Intern. Z. Vitaminforsch. **19,** 193 (1947).
(152) FROMMEL, E., FAVRE, M., AND VALLETTE, F.: Arch. intern. pharmacodynamie **73,** 355 (1947).
(153) FROMMEL, E., AND GOLDFEDER, A.: Arch. intern. pharmacodynamie **72,** 321 (1946).
(154) FUNKE, A. F., AND KORNMANN, P. K.: Bull. soc. chim. France **1949,** 241.
(155) GAIR, D. S., AND DUCEY, J.: Arch. Internal Med. **85,** 284 (1950).
(156) GARDNER, J. H., AND STEVERS, J. R.: J. Am. Chem. Soc. **71,** 1868 (1949).
(157) GAY, L. N., AND CARLINER, P. E.: Bull. Johns Hopkins Hosp. **83,** 356 (1948).
(158) GAY, L. N., AND CARLINER, P. E.: Bull. Johns Hopkins Hosp. **84,** 470 (1949).

(159) GEIGY, J. R.: Swiss patent 260,996 (August 1, 1949); Chem. Abstracts **44,** 2563 (1950).
(160) GELVIN, E. P., MCGAVACK, T. H., AND DREKTER, I. J.: Bull. N. Y. Med. Coll. **9,** 51 (1946).
(161) GILMAN, A.: J. Allergy **19,** 281 (1948).
(162) GILMAN, H., AND SHIRLEY, D. A.: J. Am. Chem. Soc. **66,** 888 (1944).
(162a) GLAZKO, A. J., AND DILL, W. A.: J. Biol. Chem. **179,** 403 (1949).
(163) GLAZKO, A. J., MCGINTY, D. A., DILL, W. A., WILSON, M. L., AND WARD, C. S.: J. Biol. Chem. **179,** 409 (1949).
(164) GORDONOFF, T.: Helv. Physiol. Pharmacol. Acta **3,** 11 (1945).
(165) GREEN, G. H., AND KENYON, J.: J. Chem. Soc. **1950,** 751.
(166) GUIMARAES, N.: Pubs. farm. (São Paulo) **14,** 5 (1949); Chem. Abstracts **43,** 7140 (1949).
(167) HAAG, F. E., AND LATZ, L.: Z. Immunitätsforsch. **96,** 117 (1939).
(168) HALEY, T. J.: J. Am. Pharm. Assoc. **37,** 294 (1948).
(169) HALEY, T. J.: J. Am. Pharm. Assoc. **37,** 383 (1948).
(170) HALEY, T. J., AND HARRIS, D. H.: J. Pharmacol. **95,** 293 (1949).
(171) HALEY, T. J., AND KEENAN, G. L.: J. Am. Pharm. Assoc. **38,** 85 (1949).
(172) HALEY, T. J., AND KEENAN, G. L.: J. Am. Pharm. Asoc. **38,** 381 (1949).
(173) HALEY, T. J., AND KEENAN, G. L.: J. Am. Pharm. Assoc. **38,** 384 (1949).
(174) HALEY, T. J., AND KEENAN, G. L.: J. Am. Pharm. Assoc. **39,** 212 (1950).
(175) HALPERN, B. N.: Arch. intern. pharmacodynamie **68,** 339 (1942).
(176) HALPERN, B. N.: J. Med. Lyon **23,** 409 (1942).
(177) HALPERN, B. N.: Compt. rend. soc. biol. **139,** 625 (1945).
(178) HALPERN, B. N.: Bull. soc. chim. biol. **29,** 309 (1947).
(179) HALPERN, B. N.: Acta Allergologica **1,** 3 (1948).
(180) HALPERN, B. N., AND MARTIN, J.: Compt. rend. soc. biol. **140,** 830 (1946).
(181) HALPERN, B. N., AND WALTHERT, F.: Compt. rend. soc. biol. **140,** 361 (1946).
(182) HALPIN, L. J.: Ann. Allergy **7,** 820 (1949).
(183) HAMLIN, K. E., WESTON, A. W., FISCHER, F. E., AND MICHAELS, R. J., JR.: J. Am. Chem. Soc. **71,** 2731 (1949).
(184) HAMLIN, K. E., WESTON, A. W., FISCHER, F. E., AND MICHAELS, R. J., JR.: J. Am. Chem. Soc. **71,** 2734 (1949).
(185) HAUSER, C. R., FLUR, I. C., AND KANTOR, S. W.: J. Am. Chem. Soc. **71,** 294 (1949).
(186) HAWORTH, E., AND MACDONALD, A. D.: J. Hygiene **37,** 234 (1937).
(187) HAYES, K., GEVER, G., AND ORCUTT, J.: J. Am. Chem. Soc. **72,** 1205 (1950).
(188) HERROLD, E. A., CAMERON, A., EARL, A., ROTH, F., SMITH, J., SMITH, N., SORRENSEN, E., AND CRAVER, B. N.: Federation Proc. **8,** 302 (1949).
(189) HILL, J. H., AND MARTIN, L., Medicine **11,** 141 (1932).
(190) HILL, A. J., AND MCGRAW, W. J.: J. Org. Chem. **14,** 783 (1949).
(191) HOLMES, C. A., OJERS, G., AND DRAGSTEDT, C. A.: Proc. Soc. Exptl. Biol. Med. **46,** 576 (1941).
(192) HOPPE, J. O., AND LANDS, A. M.: J. Pharmacol. **97,** 371 (1949).
(193) HORCLOIS, R. J.: U. S. patent 2,502,151 (March 28, 1950); Chem. Abstracts **44,** 5921 (1950).
(194) HORTON, B. T.: Proc. Staff Meetings Mayo Clinic **20,** 417 (1945).
(195) HOWARD, M. E.: *Modern Drug Encyclopedia,* 4th edition. Drug Publications, Inc., New York (1949).
(196) HUEBNER, C. F., TURNER, R. A., AND SCHOLZ, C. R.: J. Am. Chem. Soc. **71,** 3942 (1949).
(197) HUNTER, R. B., AND DUNLOP, D. M.: Quart. J. Med. **17,** 271 (1948).
(198) HUNTER, J. H., AND REID, W. B., JR.: U. S. patent 2,483,998 (October 4, 1949); Chem. Abstracts **44,** 2573 (1950).
(199) HUNTER, J. H., AND REID, W. B., JR.: U. S. patent 2,483,999 (October 4, 1949); Chem. Abstracts **44,** 2573 (1950).

(200) HUTTRER, C. P.: Enzymologia **12,** 277 (1948).
(201) HUTTRER, C. P.: Experientia **5,** 53 (1949).
(202) HUTTRER, C. P.: J. Am. Chem. Soc. **71,** 4147 (1949).
(203) HUTTRER, C. P., DJERASSI, C., BEEARS, W. L., MAYER, R. L., AND SCHOLZ, C. R.: J. Am. Chem. Soc. **68,** 1999 (1946).
(204) ING, H. R.: Physiol. Revs. **16,** 527 (1936).
(205) ING, H. R., DAIVER, G. S., AND WAJDA, I.: J. Pharmacol. **85,** 85 (1945).
(206) ISLER, H.: U. S. patent 2,505,247 (April 25, 1950); Chem. Abstracts **44,** 6888 (1950).
(207) ISLER, H., SCHELLENBER, H., AND URECH, E.: U. S. patent 2,505,248 (April 25, 1950); Chem. Abstracts **44,** 6888 (1950).
(208) JALON, G.: Farmacoterap. actual Madrid **2,** 35 (1945); Chem. Abstracts **40,** 5136 (1946).
(209) JALON, G.: Farmacoterap. actual Madrid **3,** 98 (1946); Chem. Abstracts **40,** 3829 (1946).
(210) JANSSEN, G.: Süddeut. Apoth. Ztg. **89,** 899 (1949).
(211) JENSEN, K. A., LAURIDSEN, M., AND CHRISTENSEN, J. A.: Acta Chem. Scand. **2,** 381 (1948).
(212) JILEK, J. O., AND PROTIVA, M.: J. Chem. Soc. **1950,** 188.
(213) JONES, H. M., AND BRODY, E. S.: J. Am. Pharm. Assoc. **38,** 579 (1949).
(214) JONES, R. G.: J. Am. Chem. Soc. **71,** 383 (1949).
(215) JONES, R. G.: J. Am. Chem. Soc. **71,** 644 (1949).
(216) JONES, R. G.: J. Am. Chem. Soc. **71,** 3994 (1949).
(217) KAMIMURA, S.: Proc. Japan. Pharmacol. Soc. **13,** 148 (1940); Chem. Abstracts **34,** 7430 (1940).
(218) KAMIMURA, S.: Hukuoka Acta Med. **33,** 116, 1269 (1940); Chem. Abstracts **36,** 1338 (1942).
(219) KAPLAN, M. A., AND EHRLICH, N. J.: Ann. Allergy **7,** 689 (1949).
(220) KAYE, I. A.: J. Am. Chem. Soc. **71,** 2322 (1949).
(221) KEENAN, G. L.: J. Am. Pharm. Assoc. **36,** 281 (1947).
(222) KEENAN, G. L., AND HALEY, T. J.: J. Am. Pharm. Assoc. **39,** 333 (1950).
(223) KEENEY, E. L.: Calif. Med. **72,** 377 (1950).
(224) KLARER, W., AND URECH, E.: Helv. Chim. Acta **27,** 1762 (1944).
(225) KLENK, M. M., AND SUTER, C. M.: J. Am. Chem. Soc. **70,** 3846 (1948).
(226) KNOX, L. H., AND KAPP, R.: U. S. patent 2,479,843 (August 23, 1949); Chem. Abstracts **44,** 1144 (1950).
(227) KOELZER, P. P.: Z. Naturforsch. **56,** 1 (1950).
(228) KYRIDES, L. P., MEYER, F. C., AND ZIENTY, F. B.: J. Am. Chem. Soc. **69,** 2239 (1947).
(229) KYRIDES, L. P., AND ZIENTY, F. B.: J. Am. Chem. Soc. **71,** 1122 (1949).
(230) KYRIDES, L. P., MEYER, F. C., ZIENTY, F. B., HARVEY, J., AND BANNISTER, L. W.: J. Am. Chem. Soc. **72,** 745 (1950).
(231) LA BELLE, A., AND TISLOW, R.: Federation Proc. **7,** 236 (1948).
(232) LAFORGE, F. B.: J. Am. Chem. Soc. **50,** 2484 (1928).
(233) LAMBERT, E. H., AND ROSENTHAL, S. R.: Proc. Soc. Exptl. Biol. Med. **44,** 235 (1940).
(234) LAMBERT, E., AND ROSENTHAL, S. R.: Proc. Soc. Exptl. Biol. Med. **52,** 302 (1943).
(235) LANDS, A. M., HOPPE, J. O., SIEGMUND, O. H., AND LUDUENA, F. P.: J. Pharmacol. **95,** 45 (1949).
(235a) LANDS, A. M., NASH, V. L., AND HOOPER, K. T.: J. Pharmacol. **86,** 129 (1946).
(235b) LEE, H. M., AND JONES, R. G.: J. Pharmacol. **95,** 71 (1949).
(236) LEGER, J.: Union med. Canada **77,** 5 (1948).
(237) LEHMANN, G.: J. Pharmacol. **92,** 249 (1948).
(238) LEHMANN, G., HAGAN, E., BARBAROW, G., AND ROE, M.: Federation Proc. **6,** 350 (1947).
(239) LEHMANN, G., AND KNOEFEL, P. K.: J. Pharmacol. **74,** 274 (1942).
(240) LEHMANN, G., AND KNOEFEL, P. K.: J. Pharmacol. **80,** 335 (1944).

(241) LEHMANN, G., AND KNOEFEL, P. K.: J. Pharmacol. **83,** 86 (1945).
(242) LEONARD, F., AND SOLMSSEN, U. V.: J. Am. Chem. Soc. **70,** 2064 (1948).
(243) LESPAGNOL, A., ROTRU, F., AND VANLERENBERGHE, J.: Bull. soc. pharm. Lille **1947,** No. 4, 27; Chem. Abstracts **43,** 1484 (1949).
(244) LINCOLN, E. H., HEINZELMANN, R. V., AND HUNTER, J. H.: J. Am. Chem. Soc. **71,** 2902 (1949).
(255) LITCHFIELD, J. T., JR.: J. Pharmacol. **97,** 399 (1949).
(256) LITCHFIELD, J. T., JR., ADAMS, M. R., GODDARD, L., JAEGER, M. S., AND ALONSO, L.: Bull. Johns Hopkins Hosp. **81,** 55 (1947).
(257) LOEW, E. R.: Physiol. Revs. **27,** 542 (1947).
(258) LOEW, E. R.: Med. Clinics N. Amer. **34,** 1 (1950).
(259) LOEW, E. R., ACHENBACH, P., AND MICETICH, A.: J. Pharmacol. **97,** 441 (1949).
(260) LOEW, E. R., AND KAISER, M. E.: Proc. Soc. Exptl. Biol. Med. **58,** 235 (1945).
(261) LOEW, E. R., KAISER, M. E., AND ANDERSON, M.: J. Pharmacol. **86,** 7 (1946).
(262) LOEW, E. R., KAISER, M. E., AND ANDERSON, M.: Federation Proc. **5,** 190 (1946).
(263) LOEW, E. R., KAISER, M. E., AND MOORE, V.: J. Pharmacol. **86,** 1 (1945).
(264) LOEW, E. R., MACMILLAN, R., AND KAISER, M. E.: J. Pharmacol. **86,** 289 (1946).
(265) LOEW, E. R., AND MICETICH, A.: J. Pharmacol. **94,** 339 (1948).
(266) LOEWE, S.: Science **106,** 89 (1947).
(267) LOEWE, S., WOODBURY, L. A., AND PUTTUCK, S. L.: Federation Proc. **8,** 316 (1949).
(268) LOVELESS, N. H., AND DWORIN, M.: Bull. N. Y. Acad. Med. **25,** 473 (1949).
(269) LUBSCHEZ, R.: J. Biol. Chem. **183,** 731 (1950).
(270) MADER, W. J., STERNE, H. S., JR., ROSIN, J., AND FREDIANI, H. A.: J. Am. Pharm. Assoc. **39,** 175 (1950).
(271) MARGOLIN, S., MAKOVSKY, A., AND TISLOW, R.: Federation Proc. **9,** 300 (1950).
(272) MARSH, D. F.: West Va. Med. J. **44,** 10 (1948).
(273) MARTIN, E. W., AND HARRISON, J. W. E.: J. Am. Pharm. Assoc. **39,** 390 (1950).
(274) MARTLAND, H. S., JR., AND GUCK, J. K.: J. Am. Med. Assoc. **143,** 742 (1950).
(275) MAYER, R. L.: J. Allergy **17,** 153 (1946).
(276) MAYER, R. L.: Trans. N. Y. Acad. Sci. **9,** 207 (1947).
(277) MAYER, R. L., HUTTRER, C. P., AND SCHOLZ, C. R.: Federation Proc. **4,** 129 (1945).
(278) MAYER, R. L., HUTTRER, C. P., AND SCHOLZ, C. R.: Science **102,** 93 (1945).
(279) MCGAVACK, T. H., SHERMAN, A. M., WEISSBERG, J., FUCHS, A. M., SCHULMAN, P. M., CHEVALLEY, J., DREKTER, I. J., AND BOYD, L. J.: J. Allergy **21,** 353 (1950).
(280) MCINTIRE, F. C., ROTH, L. W., AND SHAW, J. L.: J. Biol. Chem. **170,** 537 (1947).
(281) MCINTIRE, F. C., SPROULL, M., AND WHITE, F. B.: Federation Proc. **8,** 102 (1949).
(282) MEIER, R., YONKMAN, F. F., CRAVER, B. N., AND GROSS, F.: Proc. Soc. Exptl. Biol. Med. **71,** 70 (1949).
(283) MELANDER, B. O., AND ASKELÖF, E. E. A.: Swedish patent 121,537 (April 27, 1948); Chem. Abstracts **43,** 3467 (1948).
(284) MERCIER, F., LESPAGNOL, A., AND MERCIER, J.: Compt. rend. soc. biol. **142,** 364 (1948).
(285) MIESCHER, K., AND KLARER, W.: U. S. patent 2,449,241 (September 14, 1948); Chem. Abstracts **43,** 692 (1949).
(286) MIESCHER, K., AND MARXER, A.: U. S. patent 2,485,212 (October 18, 1949); Chem. Abstracts **44,** 2572 (1950).
(287) MIESCHER, K., MARXER, A., AND URECH, E.: U. S. patent 2,503,059 (April 4, 1950); Chem. Abstracts **44,** 6889 (1950).
(288) MIESCHER, K., AND KLARER, W.: U. S. patent 2,505,133 (April 25, 1950); Chem. Abstracts **44,** 6880 (1950).
(289) MILLER, L. C., BECKER, T. J., AND TAINTER, M. L.: J. Pharmacol. **92,** 260 (1948).
(290) MILLS, J. ROHRMANN, E., DINWIDDIE, W. G., AND LEE, H. M.: Arch. intern. pharmacodynamie **80,** 119 (1949).
(291) MOFFETT, R. B.: J. Org. Chem. **14,** 862 (1949).

(292) MOLLER, K. O.: Arch. Pharm. Chemi **56,** 1 (1949).
(293) MORRIS, H. C., AND DRAGSTEDT, C. A.: Proc. Soc. Exptl. Biol. Med. **59,** 311 (1945).
(294) MORRISON, A. L., AND KONIGSTEIN, M.: British patent 610,198 (October 12, 1948); Chem. Abstracts **43,** 3462 (1949).
(295) MORRISON, A. L., AND KONIGSTEIN, M.: U. S. patent 2,437,035 (March 2, 1948); Chem. Abstracts **42,** 4610 (1948).
(296) MOSS, J. M., BEILER, J. M., AND MARTIN, G. J.: Science **112,** 16 (1950).
(297) *New and Non-Official Remedies:* J. Am. Med. Assoc. **143,** 814 (1950).
(298) *New and Non-Official Remedies,* p. 30. J. B. Lippincott Company, Philadelphia, Pennsylvania (1950).
(299) NEWTON, E. P.: British patent 605,915 (August 3, 1948); Chem. Abstracts **43,** 1064 (1949).
(300) NEWTON, E. P.: British patent 605,916 (August 3, 1948); Chem. Abstracts **43,** 1064 (1949).
(301) NICKERSON, M.: J. Pharmacol. **95,** 27 (1949).
(302) NICKERSON, M., AND GOODMAN, L. S.: J. Pharmacol. **89,** 167 (1947).
(303) NICKERSON, M., AND GUMP, W. S.: J. Pharmacol. **97,** 25 (1949).
(304) NICKERSON, M., AND HARRIS, F. B.: Federation Proc. **8,** 321 (1949).
(305) NICKERSON, M., GOODMAN, L. S., AND NOMAGUCHI, G.: J. Pharmacol. **89,** 167 (1947).
(306) NORTHEY, E. H.: Chem. Revs. **27,** 85 (1940).
(307) OHKI, S.: J. Pharm. Soc. Japan **70,** 92 (1950); Chem. Abstracts **44,** 5867 (1950).
(308) OVERHOFF, J., AND PROOST, W.: Rec. trav. chim. **57,** 179 (1938); Chem. Abstracts **32,** 3402 (1938).
(309) OXLEY, P., AND SHORT, W. F.: J. Chem. Soc. **1947,** 497.
(310) OXLEY, P., AND SHORT, W. F.: J. Chem. Soc. **1950,** 859.
(311) PARROT, J. L.: Presse méd. **50,** 777 (1942); Chem. Zentr. **1943, I,** 2217.
(312) PEARLMAN, W. M., AND BANKS, C. K.: J. Am. Chem. Soc. **71,** 1128 (1949).
(313) PEARLMAN, W. M., MITULSKI, J. D., AND BANKS, C. K.: J. Am. Chem. Soc. **71,** 3248 (1949).
(314) PELLERAT, J.: Gaz. méd. France **53,** 147 (1946).
(315) PELLERAT, J.: Nord. Med. **40,** 2189 (1948).
(316) PERLMAN, E.: J. Pharmacol. **95,** 465 (1949).
(317) PERRY, D. J., AND LEVAN, P.: J. Allergy **21,** 73 (1950).
(318) PESHKIN, M. M., AND RAPPAPORT, H. G.: J. Pediat. **22,** 428 (1943).
(319) PLATI, J. T., AND WENNER, W.: J. Org. Chem. **15,** 209 (1950).
(320) PLATI, J. T., AND WENNER, W.: U. S. patents 2,470,108–9 (May 17, 1949); Chem. Abstracts **43,** 5808 (1949).
(321) PLUMMER, A. L.: Federation Proc. **8,** 325 (1949).
(322) POST, C. F.: J. Med. Soc. N. J. **44,** 317 (1947).
(323) PRATESI, P., AND DE CARO, L.: Bull. soc. chim. biol. **31,** 520 (1949); Chem. Abstracts **44,** 1607 (1950).
(324) PRATT, H. J., AND BEUTNER, R.: Federation Proc. **6,** 363 (1947).
(325) PROOST, W., AND WIBAUT, J. P.: Rec. trav. chim. **59,** 971 (1940); Chem. Abstracts **35,** 4771 (1941).
(326) PROTIVA, M., AND BOROVICKA, M.: Collection Czechoslov. Chem. Commun. **13,** 582 (1948); Chem. Abstracts **43,** 3810 (1949).
(327) PROTIVA, M., JILEK, J., KOLINSKY, J., RERICHA, V., AND URBAN, J.: Collection Czechoslov. Chem. Commun. **13,** 326 (1948); Chem. Abstracts **42,** 8189 (1948).
(328) PROTIVA, M., AND URBAN, J.: Collection Czechoslov. Chem. Commun. **13,** 340 (1948); Chem. Abstracts **42,** 8188 (1948).
(329) RAMANAMANJARY, W.: Compt. rend. soc. biol. **138,** 480 (1944).
(330) RAMIREZ DE ARELLANO, M., LAWTON, H. H., AND DRAGSTEDT, C. A.: Proc. Soc. Exptl. Biol. Med. **43,** 360 (1940).
(331) REDEMANN, C. E.: Personal communication.

(332) Ref. 298, p. 30.
(333) Ref. 298, p. 31.
(334) Ref. 298, p. 32.
(335) Ref. 298. p. 33.
(336) Ref. 298, p. 34.
(337) Ref, 298, pp. 34–5.
(338) REID, W. B., JR., WRIGHT, J. B., KOLLOFF, H. G., AND HUNTER, J. H.: J. Am. Chem. Soc. 70, 3100 (1948).
(339) REITSEMA, R. H.: J. Am. Chem. Soc. **71,** 2041 (1949).
(340) REITSEMA, R. H.: U. S. patent 2,476,912 (July 19, 1949); Chem. Abstracts **44,** 1143 (1950).
(341) REITSEMA, R. H.: U. S. patent 2,496,957 (February 7, 1950); Chem. Abstracts **44,** 5397 (1950).
(342) REITSEMA, R. H., AND HUNTER, J. H.: J. Am. Chem. Soc. **70,** 4009 (1948).
(343) RIETSEMA, R. H., AND HUNTER, J. H.: J. Am. Chem. Soc. **71,** 1680 (1949).
(344) *Research Today* **5,** 31 (1949). Eli Lilly and Company.
(345) REUSE, J. J.: Brit. J. Pharmacol. **3,** 174 (1948).
(346) RICH, A. R.: Bull. Johns Hopkins Hosp. **77,** 43 (1945).
(347) RICH, A. R., AND GREGORY, J. E.: Bull. Johns Hopkins Hosp. **73,** 329 (1943).
(348) RIEFLER, F., AND SCHMID, J.: Gastroenterologia **74,** 134 (1948–49).
(349) RIEVESCHL, G., JR.: British patent 606,317 (August 11, 1948); Chem. Abstracts **43,** 3462 (1949).
(350) RIEVESCHL, G., JR.: British patent 609,454 (September 30, 1948); Chem. Abstracts **43,** 2640 (1949).
(351) RIEVESCHL, G., JR.: British patent 609,455 (September 30, 1948); Chem. Abstracts **43,** 2641 (1949).
(352) RIEVESCHL, G., JR.: British patent 611,242 (October 27, 1948); Chem. Abstracts **43,** 3463 (1949).
(353) RIEVESCHL, G., JR.: Symposium held by the American Association for the Advancement of Science at Gibson Island, Maryland, 1945.
(354) RIEVESCHL, G., JR.: U. S. patent 2,421,714 (June 3, 1947); Chem. Abstracts **41,** 5550 (1947).
(355) RIEVESCHL, G., JR.: U. S. patent 2,427,878 (September 23, 1947); Chem. Abstracts **42,** 605 (1948).
(356) RIEVESCHL, G., JR.: U. S. patent 2,453,729 (November 16, 1948); Chem. Abstracts **43,** 2234 (1949).
(357) RIEVESCHL, G., JR.: U. S. patent 2,454,092 (November 16, 1948); Chem. Abstracts **43,** 5803 (1949).
(358) RIEVESCHL, G., JR.: U. S. patent 2,455,949 (December 14, 1948); Chem. Abstracts **43,** 3463 (1949).
(359) RIEVESCHL, G., JR.: U. S. patent 2,464,260 (March 15, 1949); Chem. Abstracts **43,** 5045 (1949).
(360) RIEVESCHL, G., JR.: U. S. patent 2,483,671 (October 4, 1949); Chem. Abstracts **44,** 6438 (1950).
(361) RIEVESCHL, G., JR., AND FLEMING, R. W.: Abstracts of Papers Presented at the 112th Meeting of the American Chemical Society, September, 1947, p. 17K.
(362) RIEVESCHL, G., JR., AND FLEMING, R. W.: U. S. patent 2,490,834 (December 13, 1949); Chem. Abstracts **44,** 2563 (1950).
(363) RIEVESCHL, G., JR., AND FLEMING, R. W.: U. S. patent 2,490,835 (December 13, 1949); Chem. Abstracts **44,** 2562 (1950).
(364) RIEVESCHL, G., JR., AND FLEMING, R. W.: U. S. patent 2,495,772 (January 31, 1950); Chem. Abstracts **44,** 5393 (1950).
(365) RIEVESCHL, G., JR., AND FLEMING, R. W.: U. S. patent 2,499,417 (March 7, 1950); Chem. Abstracts **44,** 4932 (1950).

(366) RIEVESCHL, G., JR., AND GRUZHIT, O. M.: Federation Proc. **4**, 150 (1945).
(367) RIEVESCHL, G., JR., AND HUBER, W. F.: Abstracts of Papers Presented at the 109th Meeting of the American Chemical Society, April, 1946, p. 50K.
(368) RIGLER, R.: Münch. med. Wochschr. **83**, 15 (1936).
(369) ROCHA E SILVA, M.: J. Pharmacol. **80**, 399 (1944).
(370) ROCHA E SILVA, M., AND BERALDO, W. T.: J. Pharmacol. **93**, 457 (1948).
(371) ROSE, B., AND BROWNE, J. S. L.: Proc. Soc. Exptl. Biol. Med. **44**, 182 (1940).
(372) ROSENTHAL, S. R.: Proc. Soc. Exptl. Biol. Med. **74**, 167 (1950).
(373) ROSENTHAL, S. R.: U. S. patent 2,337,572 (December 28, 1943); Chem. Abstracts **38**, 3422 (1944).
(374) ROSENTHAL, S. R., AND MINARD, D.: J. Exptl. Med. **70**, 415 (1939).
(375) ROSENTHAL, S. R., AND MINARD, D.: Proc. Soc. Exptl. Biol. Med. **44**, 237 (1940).
(376) ROSENTHAL, S. R., MINARD, D., AND LAMBERT, E.: Proc. Soc. Exptl. Biol. Med. **52**, 317 (1943).
(377) ROSENTHAL, S. R., AND SONNENSCHIEN, R. R.: Am. J. Physiol. **155**, 186 (1948).
(378) ROSENTHAL, S. R., AND TABOR, J. H.: J. Pharmacol. **92**, 425 (1948).
(379) RUSKIN, S. L.: Arch. Otolaryngol. **36**, 853 (1942).
(380) SAVAGNONE, L.: Boll. ist. sieroterap. milan. **27**, 172 (1948); Chem. Abstracts **43**, 6730 (1949).
(381) SCHILD, H. O.: Brit. J. Pharmacol. **2**, 189 (1947).
(382) SCHILD, H. O.: Brit. J. Pharmacol. **4**, 277 (1949).
(383) SCHULEMANN, W., MIETZSCH, F., AND WINGLER, A.: German patent 488,945 (September 12, 1924); Chem. Abstracts **24**, 2242 (1930).
(384) SCHOLZ, C. R.: First National Medicinal Chemistry Symposium of the American Chemical Society, held at Ann Arbor, Michigan, June 17-19, 1948.
(385) SCHULMAN, P. M., AND FUCHS, A. M.: Ann. Allergy **7**, 502 (1949).
(386) SCHULMAN, P. M., AND FUCHS, A. M.: J. Allergy **20**, 443 (1949).
(387) SELLE, W. A.: Texas Repts. Biol. Med. **4**, 138 (1946).
(388) SHANNON, W. R.: Minnesota Med. **28**, 993 (1945).
(389) SHELDON, J. M., FELL, N., JOHNSTON, J. M., AND HOWES, H. A.: J. Allergy **13**, 18 (1941).
(390) SMITH, D. R., CURRY, J. W., AND EIFFERT, R. L.: J. Am. Chem. Soc. **72**, 2969 (1950).
(391) SMITH, J., CAMERON, A., AND CRAVER, B.: Federation Proc. **7**, 256 (1948).
(392) SOCIÉTÉ DES USINES CHIMIQUES RHÔNE-POULENC: British patent 606,181 (August 10, 1948); Chem. Abstracts **43**, 3471 (1949).
(393) SOCIÉTÉ DES USINES CHIMIQUES RHÔNE-POULENC: British patent 606,182 (August 10, 1948); Chem. Abstracts **43**, 3471 (1949).
(394) SOCIÉTÉ DES USINES CHIMIQUES RHÔNE-POULENC: British patent 608,208 (September 10, 1948); Chem. Abstracts **43**, 2647 (1949).
(395) SOCIÉTÉ DES USINES CHIMIQUES RHÔNE-POULENC: British patent 632,277 (November 18, 1949); Chem. Abstracts **44**, 5399 (1950).
(396) SOCIÉTÉ POUR L'INDUSTRIE CHIMIQUE À BÂLE:British patent 604,363 (July 2, 1948); Chem. Abstracts **43**, 682 (1949).
(397) SOCIÉTÉ POUR L'INDUSTRIE CHIMIQUE À BÂLE: Swiss patent 221,216 (August 1, 1942); Chem. Abstracts **43**, 692 (1949).
(397a) SOCIÉTÉ POUR L'INDUSTRIE CHIMIQUE À BÂLE: Swiss patent 229,606 (November 15, 1943); Chem. Abstracts **43**, 3042 (1949).
(398) SOCIÉTÉ POUR L'INDUSTRIE CHIMIQUE À BÂLE: Swiss patent 235,951 (June 16, 1945); Chem. Abstracts **43**, 4303 (1949).
(399) SOCIÉTÉ POUR L'INDUSTRIE CHIMIQUE À BÂLE: Swiss patents 235, 952-3 (June 16, 1945); Chem. Abstracts **43**, 4304 (1949).
(400) SONDERN, C. W., AND BREIVOGEL, P. J.: U. S. patent 2,440,703 (May 4, 1948); Chem. Abstracts **43**, 1914 (1949).
(401) SONN, A.: U. S. patent 2,149,473 (March 7, 1939); Chem. Abstracts **33**, 4380 (1939).

(402) SPAIN, W. C., AND PFLUM, F. A.: N. Y. State J. Med. **48,** 272 (1948).
(403) SPERBER, N., AND PAPA, D.: J. Am. Chem. Soc. **71,** 886 (1949).
(404) SPERBER, N., PAPA, D., SCHWENK, E., AND SHERLOCK, M.: Abstracts of Papers Presented at the 113th Meeting of the American Chemical Society, April, 1948, p. 4K.
(405) SPERBER, N., PAPA, D., SCHWENK, E., AND SHERLOCK, M.: J. Am. Chem. Soc. **71,** 887 (1949).
(406) SPERBER, N., PAPA, D., SCHWENK, E., SHERLOCK, M., AND FRICANO, R.: British patent applications 25,947, 26,873, 27,020, and 27,048.
(407) STAUB, A. M.: Ann. Inst. Pasteur **63,** 400, 420, 485 (1939).
(408) STAUB, A. M., AND BOVET, D.: Compt. rend. soc. biol. **125,** 818 (1937).
(409) STAVRACKY, G. W.: Federation Proc. **7,** 257 (1948).
(410) STEFFENONI, S.: Arch. farmacol. sper. **72,** 44 (1941); Chem. Abstracts **36,** 1087 (1942).
(411) STERN, P.: Arch. exptl. Path. Pharmakol. **199,** 251 (1942); Chem. Abstracts **37,** 6033 (1943).
(412) STERNBERG, T. H., PERRY, D. J., AND LEVAN, P.: J. Am. Med. Assoc. **142,** 969 (1950).
(413) STERZL, J., AND KRECEK, J.: Nature **164,** 700 (1949).
(414) STRAUSS, W. T.: J. Am. Pharm. Assoc., Pract. Pharm. Ed. **9,** 728 (1948).
(415) SUTHERLAND, L. H., EBERLIN, S. L., FORSYTHE, J. D., HALVERSTADT, I. F., VAUGHAN, J. R., JR., AND CLAPP, R. C.: J. Org. Chem. **14,** 235 (1949).
(416) SZAKALL, A.: Arch. exptl. Path. Pharmakol. **148,** 218 (1930).
(417) TABOR, H.: Federation Proc. **8,** 335 (1949).
(418) TABOR, H.: Federation Proc. **9,** 319 (1950).
(419) TABOR, H., AND ROSENTHAL, S. M.: Federation Proc. **7,** 258 (1948).
(420) TAINTER, M. L., REDDEN, J. R., AND JAMES, M.: J. Pharmacol. **51,** 371 (1934).
(421) THIENES, C. H.: Ann. West Med. **1,** 128 (1947).
(422) THIENES, C. H.: Calif. Med. **67,** 1 (1947).
(423) TILFORD, C. H., SHELTON, R. S., AND VAN CAMPEN, M. G., JR.: J. Am. Chem. Soc. **70,** 4001 (1948).
(424) TILFORD, C. H., VAN CAMPEN, M. G., JR., AND SHELTON, R. S.: J. Am. Chem. Soc. **69,** 2902 (1947).
(425) TILFORD, C. H., VAN CAMPEN, M. G., JR., AND SHELTON, R. S.: J. Am. Chem. Soc. **71,** 1885 (1949).
(426) TISLOW, R.: Paper presented before the 116th Meeting of the American Association for the Advancement of Science, New York, December 31, 1949.
(427) TISLOW, R., LABELLE, A., MARKOVKSY, A. J., REED, M. A. G., CUMMINGHAM, M. D., EMELE, J. F., GRANDAGE, A., AND ROGGENHOFFER, R. J. M.: Federation Proc. **8,** 338 (1949).
(428) TRAINA, V.: Nature **163,** 364 (1949).
(429) TRUITT, P., MARK, D., LONG, L. M., AND JEANES, J.: J. Am. Chem. Soc. **70,** 4214 (1948).
(430) TSCHITSCHIBABIN, A. E., AND BENEWALINSKAJA, S. V.: Ber. **61B,** 547 (1928); Chem. Abstracts **22,** 2166 (1928).
(431) TURNER, R. A., HUEBNER, C. F., AND SCHOLZ, C. R.: J. Am. Chem. Soc. **71,** 2801 (1949).
(432) TURNER, R. J.: J. Am. Chem. Soc. **70,** 3523 (1948).
(433) UNGAR, G., PARROT, G. L., AND BOVET, D.: Compt. rend. soc. biol. **124,** 53, 445 (1937).
(434) UNGAR, G., PARROT, G. L., AND BOVET, D.: Compt. rend. soc. biol. **136,** 385 (1942).
(435) UNGER, L., AND GORDON, B. J.: Ann. Allergy **7,** 551 (1949).
(436) URBACH, K. F.: Proc. Soc. Exptl. Biol. Med. **70,** 146 (1949).
(437) URBACH, K. F.: Proc. Soc. Exptl. Biol. Med. **72,** 626 (1949).
(438) URBACH, K. F., AND GISCAFRÉ, L.: Proc. Soc. Exptl. Biol. Med. **68,** 430 (1948).
(439) VALLERY-RADOT, P., BOVET, D., MAURIC, G., AND HOLTZER, A.: Compt. rend. soc. biol. **136,** 354 (1942).

(440) VAN CAMPEN, M. G., JR., AND TILFORD, C. H.: U. S. patent 2,474,796 (June 28, 1949); Chem. Abstracts **44,** 3017 (1950).
(441) VAUGHAN, J. R., JR., AND ANDERSON, G. W.: J. Am. Chem. Soc. **70,** 2607 (1948).
(442) VAUGHAN, J. R., JR., ANDERSON, G. W., CLAPP, R. C., CLARK, J. H., ENGLISH, J. P., HOWARD, K. L., MARSON, H. W., SUTHERLAND, L. H., AND DENTON, J. J.: J. Org. Chem. **14,** 228 (1949).
(443) VIAUD, P.: Produits pharm. **2,** 53 (1947).
(444) VILLANI, F. J., SPERBER, N., LANG, J., AND PAPA, D.: J. Am. Chem. Soc. **72,** 2724 (1950).
(445) WALDBOTT, G. L.: J. Am. Med. Assoc. **135,** 207 (1946).
(446) WALKER, D. F., L'ITALIEN, Y. L., PEARLMAN, W. M., AND BANKS, C. K.: J. Am. Pharm. Assoc. **39,** 393 (1950).
(447) WALTON, C. H. A.: Can. Med. Assoc. J. **57,** 315 (1947).
(448) WEINER, N., AND KAYE, I. A.: J. Org. Chem. **14,** 868 (1949).
(449) WELLS, J. A.: Am. N. Y. Acad. Sci. **50,** 1202 (1950).
(450) WENT, I., AND KESTYUS, L.: Orvosok Lapja Népegészségügy **2,** 257 (1946); Chem. Abstracts **42,** 3062 (1948).
(451) WERLE, E.: Biochem. Z. **311,** 329 (1942).
(452) WESTON, A. W.: J. Am. Chem. Soc. **69,** 980 (1947).
(453) WHEATLEY, W. B., CHENEY, L. C., AND BINKLEY, S. B.: J. Am. Chem. Soc. **71,** 64 (1949).
(454) WHEATLEY, W. B., CHENEY, L. C., AND BINKLEY, S. B.: J. Am. Chem. Soc. **71,** 3795 (1949).
(455) WHEATLEY, W. B., FITZGIBBON, W. E., AND CHENEY, L. C.: Abstracts of Papers Presented at the 118th Meeting of the American Chemical Society, September, 1950, p. 20M.
(456) WHEATLEY, W. B., FITZGIBBON, W. E., CHENEY, L. C., AND BINKLEY, S. B.: J. Am. Chem. Soc. **72,** 1655 (1950).
(457) WHITMORE, F. C., MOSHER, H. S., GOLDSMITH, D. P. J., AND RYTINA, A. W.: J. Am. Chem. Soc. **67,** 393 (1945).
(458) WILCOX, H. B., AND SEEGAL, B. C.: J. Immunol. **44,** 219 (1942).
(459) WINDER, C. V., KAISER, M. E., ANDERSON, M. M., AND GLASSCO, E. M.: J. Pharmacol. **87,** 121 (1946).
(460) WRIGHT, J. B.: J. Am. Chem. Soc. **71,** 1028 (1949).
(461) WRIGHT, J. B.: J. Am. Chem. Soc. **71,** 2035 (1949).
(462) WRIGHT, J. B.: U. S. patent 2,501,649 (March 21, 1950); Chem. Abstracts **44,** 5919 (1950).
(463) WRIGHT, J. B., KOLLOFF, H. G., AND HUNTER, J. H.: J. Am. Chem. Soc. **70,** 3098 (1948).
(464) WRIGHT, J. B., LINCOLN, E. H., HEINZELMANN, R. V., AND HUNTER, J. H.: J. Am. Chem. Soc. **72,** 3536 (1950).

TABLE 1

Prominent antihistamines

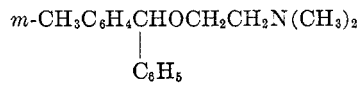
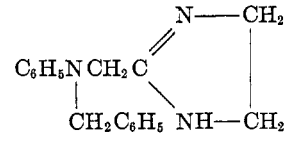
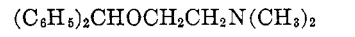
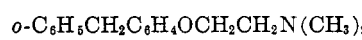
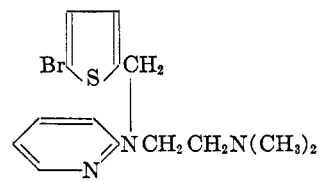
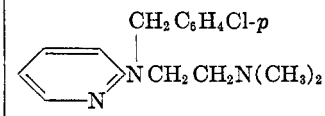
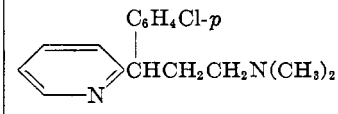
COMMON NAME AND/OR CODE NUMBER	CHEMICAL NAME	FORMULA
1. AH 853, Toladryl, Neobenodine	β-(*m*-Methyl)benzhydryloxyethyldimethylamine	
2. Antistine, Antazoline, Phenazoline	2-(*N*-Benzylanilinomethyl)-2-imidazoline* 2-(*N*-Benzyl-*N*-phenylaminomethyl)-imidazoline	
3. Benadryl, Diphenhydramine, A 424, S 51	2-(Benzhydryloxy)-*N*,*N*-dimethylethylamine* β-Dimethylaminoethyl benzhydryl ether	
4. Bristol C-5581-H, Lilly 01500	[2-(*o*-Benzylphenoxy)-ethyl]dimethylamine* 2-Benzylphenyl-β-dimethylaminoethyl ether	
5. Bromothen	2-[(5-Bromo-2-thenyl)-(2-dimethylaminoethyl)amino]pyridine* *N'*-2-Pyridyl-*N'*-5-bromothenyl-*N*,*N*-dimethylethylenediamine	
6. Chlorneoantergan	2-[(4-Chlorobenzyl)(2-dimethylaminoethyl)amino]pyridine* *N'*-*p*-Chlorobenzyl-*N'*-2-pyridyl-*N*,*N*-dimethylethylenediamine	
7. Chlortrimeton, Chlorprophenpyridamine	2-[(4-Chlorophenyl)-(2-dimethylaminoethyl)amino]pyridine* 1-(*p*-Chlorophenyl)-1-(2-pyridyl)-3-*N*,*N*-dimethylpropylamine	

TABLE 1—*Continued*

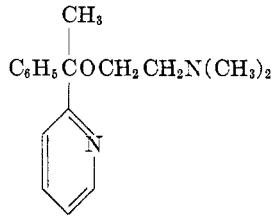
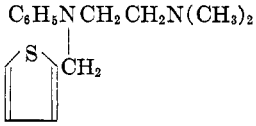
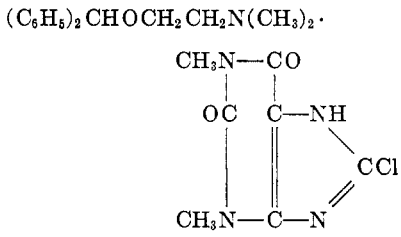
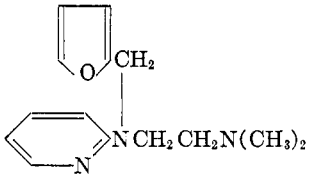
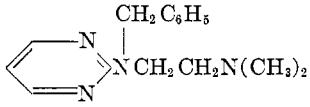
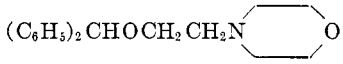
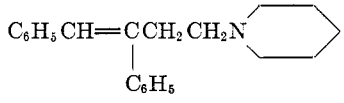
COMMON NAME AND/OR CODE NUMBER	CHEMICAL NAME	FORMULA
8. Decapryn, Doxylamine	2-[α-(2-Dimethylaminoethoxy)-α-methylbenzyl]pyridine	
9. Diatrin	*N*,*N*-Dimethyl-*N*′-phenyl-*N*′-2-thenylethylenediamine* *N*,*N*-Dimethyl-*N*′-phenyl-*N*′-(2-thienylmethyl)ethylenediamine	
10. Dramamine, Dimenhydrinate	β-Dimethylaminoethyl benzhydryl ether 8-chlorotheophyllinate	
11. Foralamin, Methafurylene, F 150	*N*-2-Furylmethyl-*N*-2-pyridyl-*N*′,*N*′-dimethylethylenediamine	
12. Hetramine	2-[Benzyl(2-dimethylaminoethyl)amino]-pyrimidine* *N*′-Benzyl-*N*′-2-pyrimidyl-*N*,*N*-dimethylethylenediamine	
13. Linadryl, A 446	β-Morpholinylethyl benzhydryl ether	
14. Lilly 01003	1,2-Diphenyl-4-piperidyl-1-butene	

TABLE 1—*Continued*

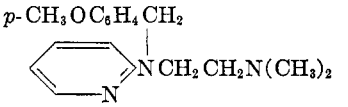
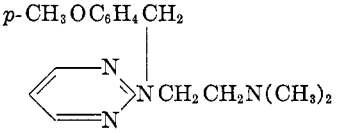
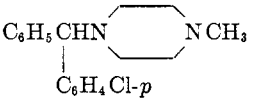
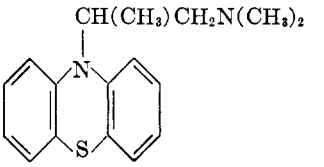
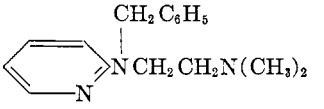
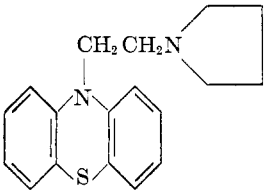
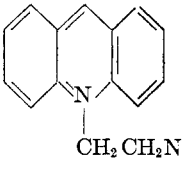
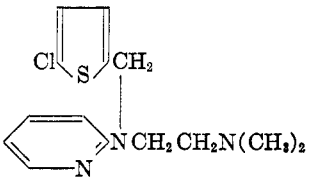
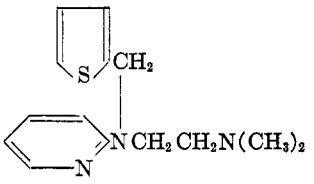
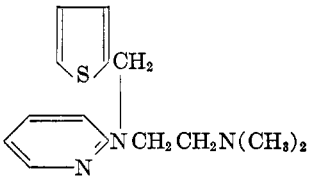
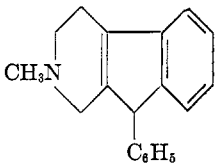
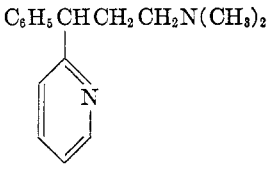
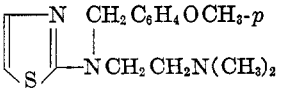
COMMON NAME AND/OR CODE NUMBER	CHEMICAL NAME	FORMULA
15. Neoantergan, Mepyramine, Pyranisamine, Anthisan, RP 2786	2-[(2-Dimethylaminoethyl)(p-methoxybenzyl)amino]pyridine* N′-*p*-Methoxybenzyl-*N*′-pyridyl-*N*,*N*-dimethylethylenediamine	
16. Neohetramine, Thonzylamine, Anahist	2-[(2-Dimethylaminoethyl) (*p*-methoxybenzyl)amino]pyrimidine* N′-*p*-Methoxybenzyl-*N*′-2-pyrimidyl-*N*,*N*-dimethylethylenediamine	
17. Perazil, Chlorcyclizine, Diparalene, 47-282, AH 289	*N*-Methyl-*N*′-(4-chlorobenzhydryl)piperazine	
18. Phenergan, RP 3277	10-(2-Dimethylaminoisopropyl)phenothiazine* *N*,*N*-Dimethylaminoisopropylthiodiphenylamine	
19. Pyribenzamine, Tripelennamine, C 63	2-[Benzyl(2-dimethylaminoethyl)amino]pyridine* *N*,*N*-Dimethyl-*N*′-benzyl-*N*′-(2-pyridyl)-ethylenediamine	
20. Pyrrolazote, Pyrathiazine	10-(2-Pyrrolidylethyl)-phenothiazine* (β-Pyrrolidylethyl)-phenothiazine	
21. Searle 1675	*N*-(2-Dimethylaminoethyl)acridine *N*-(β-Dimethylaminoethyl)acridine	

TABLE 1—*Concluded*

COMMON NAME AND/OR CODE NUMBER	CHEMICAL NAME	FORMULA
22. Tagathen, Chlorothen (citrate)	2-[(5-Chloro-2-thenyl)-(2-dimethylaminoethyl)amino]pyridine* (citrate) *N'*-2-Pyridyl-*N'*-2-chlorothenyl-*N*,*N*-dimethylethylenediamine	
23. Thenfadil, WIN 2848	2-[(2-Dimethylaminoethyl)-3-thenylamino]pyridine *N*,*N*-Dimethyl-*N'*-(3-thenyl)-*N'*-(2-pyridyl)ethylenediamine	
24. Thenylene, Histadyl, Pyrathyn, Methapyrilene, Thenylpyramine, AH 42, Lilly 01013	2-[(2-Dimethylaminoethyl)-2-thenylamino]pyridine *N'*-2-Pyridyl-*N'*-2-thenyl-*N*,*N*-dimethylethylenediamine	
25. Thephorin, Phenindamine, Nu 1504	2-Methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene	
26. Trimeton, Prophenpyridamine	1-Phenyl-2-(2-pyridyl)-3-dimethylaminopropane	
27. White 194B	*N'*-2-Thiazolyl-*N'*-*p*-methoxybenzyl-*N*,*N*-dimethylethylenediamine	

* Name given in *Chemical Abstracts.*

TABLE 2

Color reactions of antihistamines (168, 171, 172, 173, 174, 221)

REAGENT	BENADRYL HYDROCHLORIDE	PYRIBENZAMINE HYDROCHLORIDE	HISTADYL HYDROCHLORIDE	BROMOTHEN HYDROCHLORIDE	CHLOROTHEN HYDROCHLORIDE	TAGATHEN (CHLOROTHEN CITRATE)
H_2SO_4 (concd.)	Orange	Greenish yellow	Burnt orange, changing to blood-red; finally deep purple	Magenta; then deep purple	Magenta; then deep purple	Magenta; then deep purple
HNO_3 (concd.)	No reaction	No reaction	Purple-pink, changing to brown	Orange, changing to lemon-yellow	Yellow	Orange-red
Mandelin's	Red with oily red globules	Chocolate-brown	Burnt orange	Deep reddish orange	Deep reddish orange	Deep reddish orange
Marquis'	Canary-yellow, reddish orange, then chocolate-brown	Red, then deep reddish brown	Orange-brown, changing to purplish pink	Bright red	Carmine red with a slight purple cast	Brilliant magenta
Frohde's	Canary-yellow, orange, then orange-red	Pale pink, then rust-red	Dark brown with black streaks	Deep reddish purple	Deep reddish purple	Deep reddish purple
Chloroplatinic acid	Granular orange precipitate; leaf-like crystals in crosses; cigar shape for some of the crystals	Granular orange precipitate; rosettes and sheaves of flat plates on drying	Branched bundles of rods in feather-like agglomerates	Amorphous precipitate	Amorphous precipitate	Amorphous precipitate
Chloroauric acid	Granular yellow precipitate	Granular yellow precipitate	Amorphous precipitate	Amorphous precipitate	Amorphous precipitate	Amorphous precipitate
Picric acid (saturated aqueous solution)	Granular yellow precipitate	Granular yellow precipitate	Amorphous precipitate	Amorphous precipitate	Amorphous precipitate	Amorphous precipitate
Buckingham's			Brown; then black	Deep reddish purple	Deep reddish purple	Deep reddish purple

TABLE 2—*Continued*

REAGENT	TRIMETON	THEPHORIN	SC 887[a]	F 929	F 1571	DIATRIN
H_2SO_4 (concd.)	Colorless	Canary-yellow	Deep orange-yellow	Yellow then pink	Orange	Orange-yellow
HNO_3 (concd.)	Canary-yellow	Colorless	Very faint yellow	Deep blue	Lemon-yellow; then orange	Brownish red
Mandelin's	Colorless	Greenish blue; then deep blue	Faint greenish yellow	Pale brown with purple center	Bright orange	Orange-red, changing to pale yellow
Marquis'	Colorless	Pale brown	Pale brown	Carmine	Pale yellow	Pale yellow
Frohde's	Colorless	Greenish yellow	Greenish yellow to orange	Pale green; then red-violet	Colorless	Orange
Chloroplatinic acid	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous
Chloroauric acid	Amorphous	Amorphous	Amorphous	Square flat plates of varying sizes	Broad leaf-like crystals; reagent turns blue green	Amorphous
Picric acid (saturated aqueous solution)	Thin small needles in crosses and bundles	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous
Buckingham's	Colorless	Olive-green	Green to bluish green	Bluish green; then red-brown to black	Colorless	Orange-red

[a] Diethylaminoethyl 9,10-dihydroanthracene-10-carboxylate.

REAGENT	DRAMAMINE	NEOHETRAMINE	NEOANTERGAN	DECAPRYN	LINADRYL HYDROCHLORIDE A 446	ANTISTINE	NO. 204[b]
H_2SO_4 (concd.)	No change	Red	Magenta	Canary-yellow	Canary-yellow with oily orange-red droplets	Colorless	Bright orange
HNO_3 (concd.)	No change	Colorless	Colorless	Colorless	Colorless	Magenta	Colorless
Mandelin's	Cloudy bluish	Deep pink	Magenta	No change	No change	Brick-red	No change
Marquis'	Cloudy tan	Magenta	Magenta	No change	No change	No change	Pale yellow
Frohde's	No change	Magenta	Magenta	Canary-yellow; then orange	Canary-yellow with oily orange-red droplets	Colorless	Canary-yellow with oily orange droplets
Chloroplatinic acid	Amorphous	Amorphous	Amorphous; then oily globules	Leaf-like agglomerates in bundles	Amorphous	Amorphous	Amorphous
Chloroauric acid	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous
Picric acid (saturated aqueous solution)	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous
Buckingham's	No change	Magenta	Magenta	Canary-yellow; then dirty green	Canary-yellow with oily orange-red droplets	Colorless	Canary-yellow with oily orange drops

[b] 2-Imidazolyl-2-methyl benzhydryl ether.

TABLE 2—*Concluded*

REAGENT	SC 1627, RP 3015[c]	SC 1742[d]	SC 1898[e]	SC 1923[f]	PHENERGAN, RP 3277	PYRROLAZOTE
H_2SO_4 (concd.)	Pink	Pink	Magenta	Pink	Fuchsia	Magenta
HNO_3 (concd.)	Magenta, changing immediately to orange-yellow	Brilliant red, changing immediately to orange-yellow	Magenta, changing immediately to orange-yellow	Magenta, changing immediately to orange-yellow	Magenta, changing immediately to orange-yellow	Magenta, changing immediately to greenish yellow
Mandelin's	Pink	Pink	Pink	Pink	Pink	Pink
Marquis'	Magenta	Magenta	Magenta	Magenta	Magenta	Magenta
Frohde's	Pink	Pink	Magenta	Pink	Pink	Magenta, changing to orange-red with greenish edges
Chloroplatinic acid	Black amorphous mass; reagent turns blue-green	Black amorphous mass; reagent turns blue-green	Black amorphous mass; reagent turns blue-green	Black amorphous mass; reagent turns blue-green	Flat purple leaf-like crystals, single or in crosses; reagent turns blue-green	Purple, pointed rods; reagent turns blue-green
Chloroauric acid						
Picric acid (saturated aqueous solution)	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous
Buckingham's	Deep red	Chocolate-brown	Reddish brown	Brownish black	Brilliant red, changing to magenta	Magenta; then brown; finally black

[c] *N*-Dimethylaminoethylthiodiphenylamine hydrochloride.
[d] *N*-Trimethylaminoethylthiodiphenylamine chloride.
[e] *N*-Dimethylethanolaminoethylthiodiphenylamine bromide.
[f] *N*-Methylethanolaminoethylthiodiphenylamine hydrochloride.

TABLE 3

Phenolic ethers

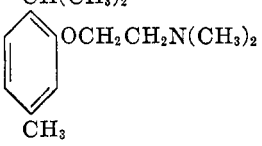
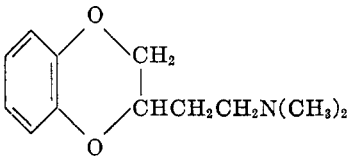
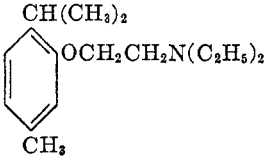
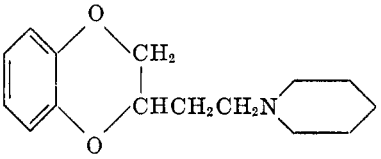
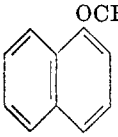
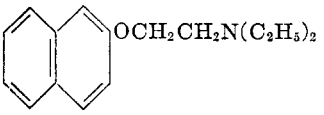
FOURNEAU CODE NO.	STRUCTURE	A.H. INDEX*	TOXICITY FOR RABBITS		REMARKS	REFERENCES
			M.T.D.†	M.L.D.‡		
			g./kg.	*g./kg.*		
Tostramine..		4			Better tolerated by humans than F 929	(7, 8)
F 883, Prosympal...		1			Less active and less toxic than F 929	(33, 36, 37, 38, 140, 141, 145, 439)
F 928...	$C_6H_5OCH_2CH_2N(C_2H_5)_2$	1	0.015	0.055	Less active than F 929	(38, 407)
F 929...		3	0.005	0.025	Most active ether	(*cf.* 235)
F 933...					Solution of $1:10^5$ inhibited 1 γ/10 ml. histamine	(38, 433, 434)
F 936...	p-$CH_3C_6H_4OCH_2CH_2N(C_2H_5)_2$.....	1	0.010	0.040	Inactive	(407)
F 937...					Almost inactive; delayed but did not prevent death	(38)
F 939...					Less active than F 929; 30–60 per cent of animals saved from death	(38)

TABLE 3—*Continued*

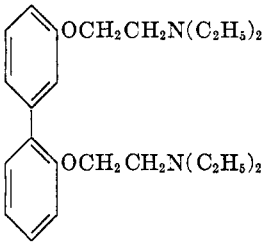
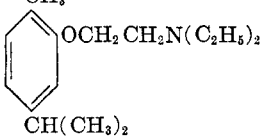
FOURNEAU CODE NO.	STRUCTURE	A.H. INDEX*	TOXICITY FOR RABBITS		REMARKS	REFERENCES
			M.T.D.†	M.L.D.‡		
			g./kg.	*g./kg.*		
F 940...	*p*-$CH_3OC_6H_4OCH_2CH_2N(C_2H_5)_2$				Less active than F 929; 30–60 per cent of animals saved from death	(38)
F 1262..	*o*-$C_6H_5C_6H_4OCH_2CH_2N(C_2H_5)_2$				Prevents anaphylactic shock in rabbits; nontoxic	(407, 439)
F 1271..					Less active than F 929; 30–60 per cent of animals saved from death	(38)
F 1274..	*p*-$CH_2{=}CHCH_2C_6H_4O$-$CH_2CH_2N(C_2H_5)_2$				Inactive	(407)
F 1306..	*p*-$C_6H_5C_6H_4OCH_2CH_2N(C_2H_5)_2$				Almost inactive; 30–60 per cent of animals saved from death	(38, 407)
F 1323..	*m*-$C_6H_5C_6H_4OCH_2CH_2N(C_2H_5)_2$				Inactive	(407)
F 1379..		3	0.005	0.025	Same activity as F 929	(407)

TABLE 3—*Continued*

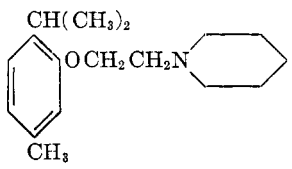
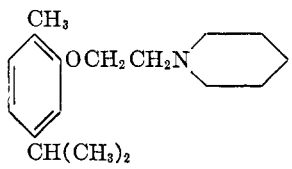
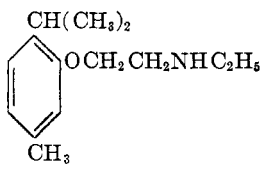
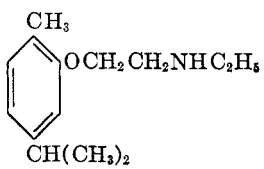
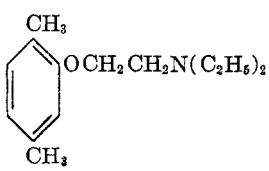
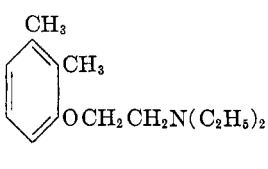
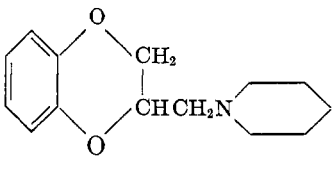
FOURNEAU CODE NO.	STRUCTURE	A.H. INDEX*	TOXICITY FOR RABBITS		REMARKS	REFERENCES
			M.T.D.†	M.L.D.‡		
			g./kg.	*g./kg.*		
F 1464..		2	0.010	0.030	Less active than F 929	(407)
F 1465..		2			Same activity as F 1464	(407)
F 1482..		1	0.010	0.035	Inactive	(407)
F 1483..					Inactive	(407)
F 1655..		2	0.010	0.020	Less active than F 929	(407)
F 1702..	*o*-$CH_3C_6H_4OCH_2CH_2N(C_2H_5)_2$	1			Inactive	(407)
F 1703..	*m*-$CH_3C_6H_4OCH_2CH_2N(C_2H_5)_2$				Inactive	(407)
					Inactive	(407)
					Augmented the action of histamine	(26)

TABLE 3—*Concluded*

FOURNEAU CODE NO.	STRUCTURE	A.H. INDEX*	TOXICITY FOR RABBITS		REMARKS	REFERENCES
			M.T.D.†	M.L.D.‡		
			g./kg.	*g./kg.*		
	m-$HOC_6H_4OCH_2CH_2NHCH_3$				Augmented the vasodilating action of histamine	(19)
	p-$HOC_6H_4OCH_2CH_2NHCH_3$				Augmented the vasodilating action of histamine	(19)
	p-$C_6H_5C_6H_4OCH_2CH_2NH_2$				Augmented the action of histamine	(26)
	$C_6H_5OCH_2CHOCH_2CH_2NH_2$				Augmented the action of histamine	(26)
	o-$CH_3OC_6H_4O$-$CH_2CH_2OCH_2CH_2NH_2$				Augmented the action of histamine	(26)
	$C_4H_9OCH_2CH_2N(CH_3)_2$				Augmented the action of histamine	(26)
	$C_4H_9OCH_2CH_2N(C_2H_5)_2$				Augmented the action of histamine	(26)
	$C_6H_5OCH_2CH_2N(CH_3)_2$				Ineffective; activity resembled that of nicotine	(26)

* Antihistamine index for histamine shock.
† Maximum tolerated dose.
‡ Minimum lethal dose.

TABLE 4

Ethers

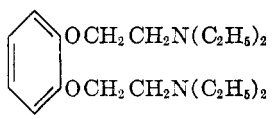
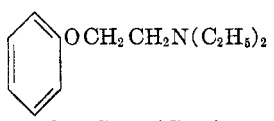
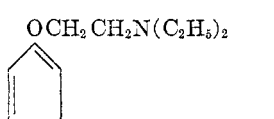
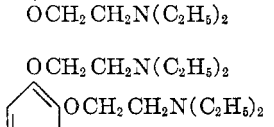
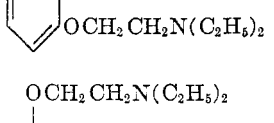
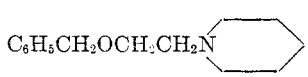
NO.	FORMULA	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY*	TOXICITY†
	Basic aryl ethers (327)				
		°C.	°C.	mg.	mg./kg.
1..		165–175/1–3 mm.	145 (2HCl)	2–4	
2..		194–200/5 mm.	133 (2HCl) 117–118 (dipicrate)	20	
3..		178–182/102 mm.	155 (2HCl) 184 (dipicrate)	60	
4..			197 (3HCl) 156–157 (tripicrate)	40	
5..			161–162 (tripicrate)	55	
6..	$C_6H_5CH_2OCH_2CH_2N(C_2H_5)_2$	134–136/1 mm.	63–64 (picrate)	16.5	
7..		184–185/1 mm. 167–168/0.4–0.5 mm.	169 (HCl) 144.5 (HBr) 188 (CH_3I) 123–125 (C_2H_5Br)	0.210	100
8..	$(C_6H_5)_2CHOCH_2CH_2N(C_2H_5)_2$		144 (HCl)	0.06	87.5

TABLE 4—*Concluded*

NO.	FORMULA	BOILING POINT	MELTING POINT OF SALT	ANTI-HISTAMINE ACTIVITY*	TOXICITY†
	Basic aryl ethers (327)				
		°C.	°C.	*mg.*	*mg./kg.*
9. .	$(C_6H_5)_3COCH_2CH_2N(C_2H_5)_2$	200–206/1 mm.	158–160 (HCl)	1	
10. .	$C_6H_5CH_2CHOCH_2CH_2N(CH_3)_2$ C_6H_5	169–171/2–3 mm.	116–117 (HCl)	1	
11. .	$C_6H_5CH_2CHOCH_2CH_2N$ C_6H_5	190–195/3 mm.	123–124 (hydrochloride)	0.220	86
	Thioethers (327)				
12. .	$(C_6H_5)_2CHSCH_2CH_2N$		176–177 (hydrochloride)	1	
13. .	$(C_6H_5)_2CHSCH_2CH_2N(C_2H_5)_2$		100–105 (hydrochloride)	0.5	242
	Thioethers (31)				
14. .	$C_6H_5SCH_2CH_2CH_2N(C_2H_5)_2$	190–193/12 mm.	83–84 (hydrochloride)		
15. .	$C_6H_5SCH_2CHOHCH_2N(C_2H_5)_2$	168–171/4 mm.			
16. .	o-$CH_3C_6H_4SCH_2CH_2N(C_2H_5)_2$	150–153/5 mm.	126–127 (hydrochloride)		
17. .	o-$CH_3C_6H_4SCH_2CHOHCH_2N(C_2H_5)_2$	153–157/1 mm.			
18. .	m-$CH_3C_6H_4SCH_2CH_2CH_2N(C_2H_5)_2$	168–173/13 mm.	65–66 (hydrochloride)		
19. .	m-$CH_3C_6H_4SCH_2CHOHCH_2N(C_2H_5)_2$	168–172/3 mm.			
20. .	p-$CH_3C_6H_4SCH_2CH_2CH_2N(C_2H_5)_2$	155–158/7 mm.	97–98 (hydrochloride)		
21. .	p-$CH_3C_6H_4SCH_2CHOHCH_2N(C_2H_5)_2$	168–172/3 mm.			

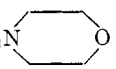
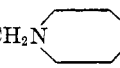
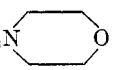
* Milligrams necessary to neutralize contraction of isolated guinea-pig intestine caused by 0.01 mg. histamine.

† Milligrams per kilogram necessary to kill 50 per cent of the test animals.

TABLE 5

Efficacy of benzhydryl alkamine ethers in preventing fatal histamine-induced bronchoconstriction in guinea pigs (263)

$(C_6H_5)_2CHOR$

NO.	R	ANTIHISTAMINE ACTIVITY INDEX*	L.D.$_{50}$†
			mg./kg.
1....	$-CH_2CH_2N(CH_3)_2$	33	82
2....	$-CH_2CH_2N$ 	33	80
3....	$-CH_2CH_2N$ 	16	185
4....	$-CH_2CH_2NHCH_3$	8	85
5....	$-CH_2CH_2NHCH(CH_3)_2$	8	72
6....	$-CH_2CH_2CH_2N(C_2H_5)_2$	8	85
7....	$-CH_2CH_2N(C_2H_5)_2$	4	55
8....	$-CH_2CH_2CH_2N$ 	4	
9....	$-CH_2CH_2NH_2$	2	50
10....	$-CH_2CH_2NHCH_2CH_2N$ 	2	92
11....	$(p\text{-}ClC_6H_4)_2CHOCH_2CH_2N$  ‡	2	390
12....	$-CH_2CH_2CH_2CH_2CH_2CH_2N$ 	1	254
13....	$-CH_2CH_2NHCH_2CH_2CH_2CH_3$	<4	50
14....	$-CH_2C(CH_3)_2N$ 	<2	
15....	$-CH_2CH_2OCH_2CH_2N(C_2H_5)_2$	<1	71
16....	$-CH_2CH_2N(\text{cyclo-}C_6H_{11})_2$	Very weak	
17....	$-CH_2CH_2N(n\text{-}C_4H_9)_2$		

* Efficacy in the prevention of fatal histamine-induced bronchoconstriction in guinea pigs. Aminophylline = 1.

† Dose administered intraperitoneally to kill 50 per cent of test animals.

‡ Formula of compound.

TABLE 6

Benzhydryl ethers and thioethers

NO.	R	BOILING POINT	MELTING POINT OF SALT (OR BASE)	REFERENCES
	$(C_6H_5)_2CHOR$			
		°C.	°C.	
1.....	$-CH_2CH_2NH_2$	150–153/0.3 mm.	74	(263, 415)
2.....	$-CH_2CH_2NHCH_3$		159 (HCl)	(349)
3.....	$-CH_2CH_2NHC_4H_9$			(263)
4.....	$-CH_2CH_2NHC_6H_5$		100 (base) 210 (HCl)	(98)
5.....	$-CH_2CH_2NHCH_2C_6H_5$	182–184/0.4–0.6 mm.	182 (HBr)	(415)
6.....	$-CH_2CH_2N(CH_3)_2$	150–165/2 mm.	167 (HCl) 131 (picrate) 140 (oxalate) For haloxanthinates see table 7	(299, 349, 354, 356, 459)
7.....	$-CH_2CH_2N(C_2H_5)_2$	199–202/11 mm. 155–158/1.5 mm.	146 (HCl)	(6, 299, 327, 331, 349, 354)
8.....	$-CH(CH_3)CH_2N(CH_3)_2$	122/0.5 mm. 138–140/1.5 mm.	150 (HCl) 162 (oxalate)	(6, 331, 356, 358)
9.....	$-CH_2CH_2NHCH(CH_3)_2$	138–140/1.5 mm.	169 (HCl)	(127, 349)
10.....	$-C(CH_3)_2CH_2N(C_2H_5)_2$			(358)
11.....	$-CH(C_2H_5)CH_2N(CH_3)_2$			(358)
12.....	$-CH_2C(CH_3)_2N(CH_3)_2$	154–158/1 mm.	216 (HCl)	(6, 331)
13.....	$-CH_2CH(CH_3)N(CH_3)_2$	158/2 mm.	180 (HCl)	(6, 331)

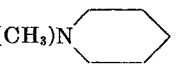
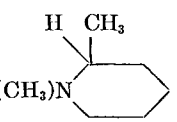
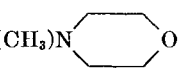
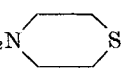
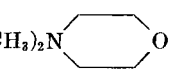
14.....	$-C(CH_3)_2CH_2N(CH_3)_2$	140–143/2 mm.	200 (HCl)	(6, 331)
15.....	$-CH_2CH_2CH_2N(CH_3)_2$	148/2 mm.	98 (acid succinate)	(6, 290, 331, 355)
16.....	$-CH(CH_3)CH_2CH_2CH_2N(C_2H_5)_2$			(355)
17.....	$-CH_2CH_2CH_2N(C_2H_5)_2$	182–183/4.5 mm.		(355)
18.....	$-CH_2C(CH_3)_2CH_2N(C_2H_5)_2$			(358)
19.....	$-CH_2CH_2CH_2N(C_4H_9)_2$			(355)
20.....		161–165/0.7 mm.	132 (HCl) 165 (CH_3I)	(356, 463)
21.....		205/6 mm.	169 (HCl)	(80, 299, 349, 356, 413)
22.....				(357)
23.....				(357)
24.....			183 (HCl)	(170, 260, 263, 299, 349, 356)
25.....				(357)
26.....				(356)
27.....				(263)

TABLE 6—*Continued*

NO.	R	BOILING POINT	MELTING POINT OF SALT (OR BASE)	REFERENCES
		°C.	°C.	
28.....	—$CH_2C(CH_3)_2N$⟨O⟩			(357)
29.....	—$CH_2CH_2CH_2CH_2N$⟨CH_3, CH_3⟩			(357)
30.....	—CH_2CH_2N⟨NCH_3⟩		53 190 (2HCl)	(463)
31.....	—$CH_2CH_2N(C_6H_5)_2$			(263, 356)
32.....	—$CH_2CH_2CH_2N$⟨⟩			(356)
33.....	—$CH_2CH_2CH_2N$⟨O⟩			(356)
34.....	—⟨NCH_3⟩		206 (HCl)	(226)
35.....	—⟨NC_2H_5⟩			(226)
36.....	—⟨NC_3H_7⟩			(226)

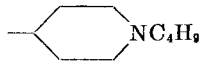
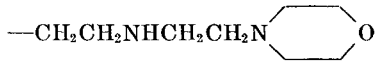
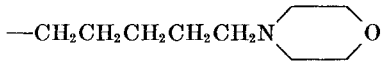
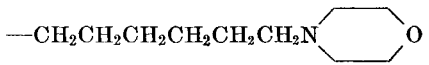
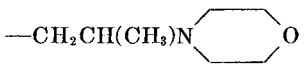
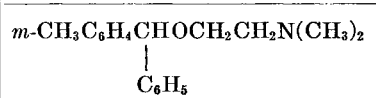
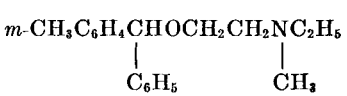
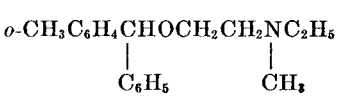
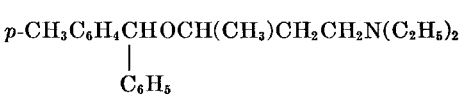
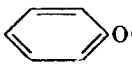
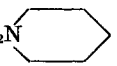
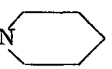
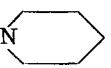
37.....				(226)
38.....				(263)
39.....				(357)
40.....				(263, 357)
41.....	$-COCH_2N(CH_3)_2$	155–157/2 mm.	179 d. (HCl)	(6, 331)
42.....	$-COCH_2CH_2N(CH_3)_2$	161–162/1.5 mm.	160 (HCl)	(6, 331)
43.....				(357)
	FORMULA			
44.....				(279, 385)
45.....				(349)
46.....				(349)
47.....				(358)

TABLE 6—*Continued*

NO.	FORMULA	BOILING POINT	MELTING POINT OF SALT (OR BASE)	REFERENCES
		°C.	°C.	
48.....	$(CH_3)_3CCH_2C(CH_3)_2$  $OCH_2CH_2OCH_2CH_2N$ 			(127)
49.....	$(p\text{-}CH_3C_6H_4)_2CHOCH_2CH_2N(C_3H_7)_2$			(299, 349)
50.....	$o\text{-}CH_3C_6H_4CHOCH(CH_3)CH_2CH_2N$  C_6H_5			(357)
51.....	$o\text{-}CH_3C_6H_4CHOCH_2CH_2N$  C_6H_5	75–83/7 mm.	159 (HCl)	(326)
52.....	$m\text{-}CH_3C_6H_4CHOCH_2CH_2N$  C_6H_5	196–200/1.3 mm.	142 (HCl)	(326)
53.....	$p\text{-}CH_3C_6H_4CHOCH_2CH_2N$  C_6H_5	190–192	137 (HCl)	(326)
54.....	$p\text{-}CH_3OC_6H_4CHOCH_2CH_2NHCH(CH_3)_2$ C_6H_5			(4)
55.....	$p\text{-}CH_3OC_6H_4CHOCH_2CH_2N(CH_3)_2$ C_6H_5	137–139/0.1 mm.		(159)

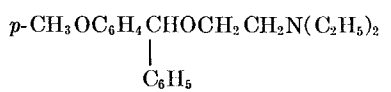
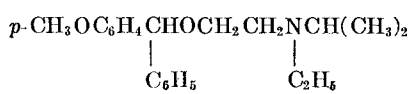
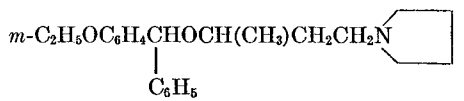
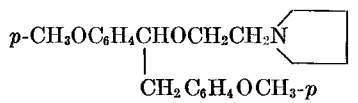
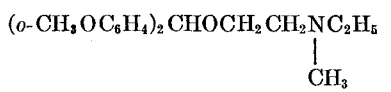
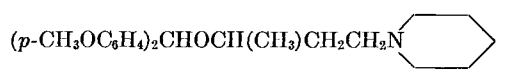
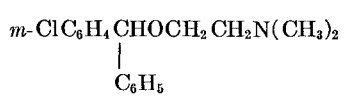
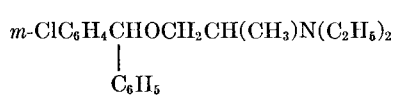
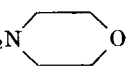
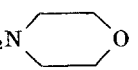
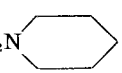
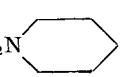
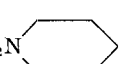
56.....				(4)
57.....				(4)
58.....				(357)
59.....		218-220/0.35 mm.	144 (CH_3I)	(463)
60.....				(299)
61.....				(358)
62.....				(357)
63.....				(290)
64.....				(358)

TABLE 6—*Continued*

NO.	FORMULA	BOILING POINT	MELTING POINT OF SALT (OR BASE)	REFERENCES
		°C.	°C.	
65.....	m-$ClC_6H_4CHOCH_2CH(CH_3)CH_2N(i\text{-}C_3H_7)_2$ C_6H_5			(358)
66.....	o-$CH_3C_6H_4CHOCH_2C(CH_3)_2N$  C_6H_4Cl-p			(357)
67.....	(p-$ClC_6H_4)_2CHOCH_2CH_2N$ 			(263)
68.....	(p-$ClC_6H_4)_2CHOCH_2CH_2CH_2N$ 			(357)
69.....	$(C_6H_5)_2C(CH_3)OCH_2CH_2N(C_2H_5)_2$	198–199/13 mm.		(69)
70.....	$(C_6H_5)_2C(CH_3)OCH_2CH_2N$ 	222/13 mm.		(69)
71.....	$(C_6H_5)_2C(C_2H_5)OCH_2CH_2N(C_2H_5)_2$	236/14 mm.		(69)
72.....	$(C_6H_5)_2C(C_2H_5)OCH_2CH_2N$ 	231/760 mm.		(69)
73.....	$(C_6H_5)_3COCH_2CH_2N(CH_3)_2$			(6)
74.....	$(C_6H_5)_3COCH_2CH_2N(C_2H_5)_2$	248–250/14 mm.	140 (HCl)	(69, 327)
75.....	$(C_6H_5)_2COCH_2CH_2N$ 		97	(69)

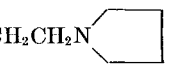
76.....	$(C_6H_5)_2CHSCH_2CH_2N(C_2H_5)_2$	175–178/1–2 mm.	100–105 (HCl)	(65, 327)
	R			
77.....	$-CH_2CH_2N(CH_2C_6H_5)CH(C_6H_5)_2$		109	(98)
	FORMULA			
78.....	$(n\text{-}C_4H_9)_2CHOCH_2CH_2N$ 	124–127/2.3 mm.		(463)
	$(C_6H_5)_2CHSR$ (360)			
79.....	$-CH_2CH_2N(CH_3)_2$		183 (HCl)	(360)
80.....	$-CH_2CH_2N$ 		180 (HCl)	(360)
81.....	$-CH_2CH_2CH_2N(CH_3)_2$			(360)
82.....	$-CH_2CH(CH_3)CH_2N(C_4H_9)_2$			(360)
83.....	$-CH(CH_3)CH_2N(CH_3)_2$			(360)
84.....	$-CH_2CH_2CH_2CH_2CH_2CH_2N$ 			(360)
85.....	$-CH_2C(CH_3)_2CH_2N$ 			(360)
86.....	$-CH_2CH_2NHCH_3$			(360)

TABLE 6—*Concluded*

NO.	R	BOILING POINT	MELTING POINT OF SALT (OR BASE)	REFERENCES
		°C.	°C.	
87.....	$-CH_2CH_2CH_2CH_2N(C_2H_5)_2$			(360)
88.....			177 (HCl)	(327)
	FORMULA			
89.....	$(p\text{-}CH_3C_6H_4)_2CHSCH_2CH_2N(C_3H_7)_2$			(360)
90.....	$m\text{-}CH_3OC_6H_4CH(C_6H_5)SCH_2CH_2CH_2CH_2NHC_3H_7(i)$			(360)
91.....	$2,4\text{-}(CH_3)_2C_6H_3CH(C_6H_5)OCH_2CH_2N(CH_3)_2$			(92)

TABLE 6A

Activity of salts of benzhydryl ethers studied by Alles and Redemann (6)

NO.*	ANTIHISTAMINE ACTIVITY†‡	NO.*	ANTIHISTAMINE ACTIVITY†‡
	per cent		*per cent*
6 (Benadryl)	53–88	13	11
7	33	14	46
8	20	15	61 (acid succinate)
12	3	73	10

* The numbers correspond to those in table 6.

† Average reduction of response of guinea-pig ileum to 5×10^{-7} molal histamine.

‡ Hydrochloride unless otherwise stated.

TABLE 7

Haloxanthine salts of benzhydryl ethers (101)

$(C_6H_5)_2CHO(CH_2)_nR$

NO.	*n*	R	SALT	MELTING POINT
				°C.
1	2	$-N(CH_3)_2$	8-Chlorotheophyllinate	104
2	2	$-N(CH_3)_2$	8-Bromotheophyllinate	113
3	2	$-N(CH_3)_2$	8-Iodotheophyllinate	
4	2	$-N(C_2H_5)_2$	8-Chlorotheophyllinate	
5	3	$-N(CH_3)_2$	8-Bromotheophyllinate	
6	2	$-N(CH_3)C_2H_4OH$	8-Chlorotheophyllinate	225–230
	BASE			
7	$(p\text{-}IC_6H_4)_2CHOCH_2CH_2N(CH_3)_2$		8-Chlorotheophyllinate	

TABLE 8

Quaternary ammonium salts of benzhydryl ethers

$$\left[(C_6H_5)_2CHOCH_2CH_2\underset{\displaystyle R}{\overset{+}{N}}(CH_3)_2\right]X^-$$

NO.	R	X	MELTING POINT	REFERENCES
			°C.	
1.	CH_3	Cl	177	(262, 350, 459)
2.	CH_3	Br	194	(211, 350, 459)
3.	CH_3	I	193	(211, 262, 350, 459)
4.	CH_3	CH_3SO_4	153	(352, 459)
5.	CH_3	*p*-Toluenesulfonate	153	(127, 352, 459)
6.	C_2H_5	Br	135	(350, 459)
7.	C_2H_5	Benzenesulfonate	120	(352, 459)
8.	C_2H_5	I	138	(350)
9.	C_2H_5	*p*-Toluenesulfonate	114	(127, 352)
10.	C_3H_7	*p*-Toluenesulfonate	133	(352)
11.	C_4H_9	*p*-Toluenesulfonate	121	(352)

$(C_6H_5)_2CHOCH_2CH_2R^+X^-$

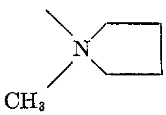
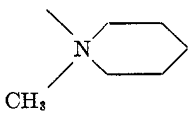
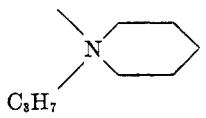
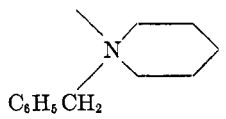
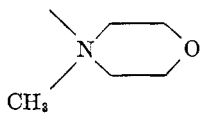
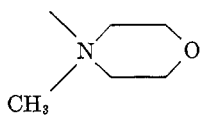
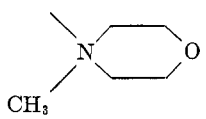
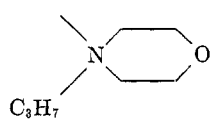
NO.	R^+	X	MELTING POINT	REFERENCES
			°C.	
12.	$-N(C_2H_5)_3$	Br	147	(350)
13.	$-\underset{\displaystyle C_4H_9}{N}(C_2H_5)_2$	Br		(350)
14.	$-\underset{\displaystyle C_3H_7(i)}{N}(n\text{-}C_3H_7)_2$	Br		(350)
15.	$[-N(CH_3)_3]_2$	SO_4		(262)
16.	C_8H_{17}	Br	102	(365)
17.	C_9H_{19}	Br	102	(365)
18.	$C_{10}H_{21}$	Br	97	(365)
19.	$C_{11}H_{23}$	Br		(365)
20.		I	165	(463)
21.		I	182	(350)

TABLE 8—*Continued*

NO.	R^+	X	MELTING POINT	REFERENCES
			°C.	
22.....		I		(350)
23.....		Cl		(357)
24.....		I	206	(350)
25.....		Br	188	(350)
26.....		*p*-Toluene-sulfonate	138	(127, 352)
27.....		I		(350)

$(C_6H_5)_2CHOCH_2CH_2CH_2R^+X^-$

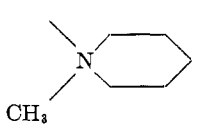
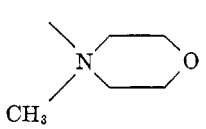
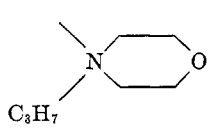
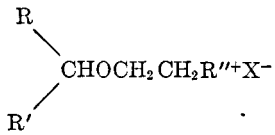
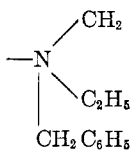
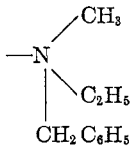
NO.	R^+	X	MELTING POINT	REFERENCES
			°C.	
28.....		Br		(357)
29.....		I		(350)
30.....		I	205	(350)

TABLE 8—*Concluded*



NO.	R	R′	R″+	X	MELTING POINT	REFERENCES
					°C.	
31....	*p*-$CH_3OC_6H_4$—	C_6H_5—	—$N(CH_3)_3$	I	144	(211)
32....	*o*-$CH_3OC_6H_4$—	C_6H_5—		Cl		(350)
33....	*p*-$CH_3OC_6H_4$—	C_6H_5—		Cl		(350)
34....	*p*-$CH_3C_6H_4$—	*p*-$CH_3C_6H_4$—	—$N(n\text{-}C_3H_7)_2$ $C_3H_7(i)$	Br		(350)

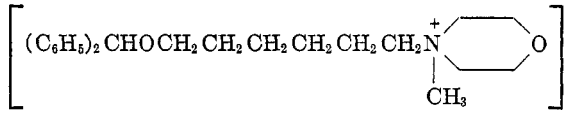
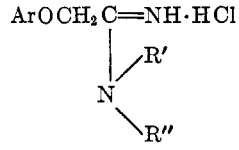
NO.	FORMULA	REFERENCE
35....		(357)

TABLE 9

Aryloxyacetamidine hydrochlorides (113)

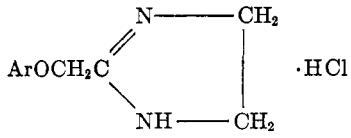


NO.	ArO	R′	R″	MELTING POINT	YIELD	ANTIHISTAMINE ACTIVITY*
				°C.	*per cent*	*γ/ml.*
1....	Phenoxy	H	H	127.5–128.5	72	10
2....	Phenoxy	CH_3	CH_3	187–189	77	0
3....	*o*-Toloxy	H	H	147.5–148.5	86	0
4....	*o*-Toloxy	CH_3	CH_3	177–179	88	0
5....	*m*-Toloxy	H	H	179–180.5	78	10
6....	*m*-Toloxy	CH_3	CH_3	200–202	65	0
7....	*p*-Toloxy	H	H	169.5–170.5	73	0
8....	*p*-Toloxy	CH_3	CH_3	173–174.5	75	0
9....	Thymyloxy	H	H	185–185.5	85	1–10
10....	Thymyloxy	CH_3	CH_3	197–198	80	10
11....	Thymyloxy	C_2H_5	C_2H_5	212–212.5	57	0.5–1
12....	Thymyloxy	*n*-C_3H_7	*n*-C_3H_7	180–182	50	1–10
13....	Thymyloxy	*n*-C_4H_9	*n*-C_4H_9	154–155	61	1
14....	Thymyloxy	$CH_2CH_2C_6H_5$	H	145–147	71	1–10
15....	Carvacryloxy	H	H	183.5–184.5	76	10
16....	Carvacryloxy	CH_3	CH_3	178–180	67	1–10
17....	Carvacryloxy	$CH_2CH_2C_6H_5$	H	158.5–159.5	65	0.1–1
18....	3-Methyl-4-chlorophenoxy	H	H	193–194	87	1
19....	3-Methyl-4-chlorophenoxy	CH_3	CH_3	183.5–185.5	78	10
20....	*o*-Isopropylphenoxy	H	H	147.5–149	83	10
21....	*o*-Isopropylphenoxy	CH_3	CH_3	198–198.5	70	10
22....	2,5-Dimethylphenoxy	H	H	215–217	88	0
23....	2,5-Dimethylphenoxy	CH_3	CH_3	212–214	87	0

*γ of compound per milliliter of bath liquid, capable of neutralizing the contraction of an isolated guinea-pig gut caused by 1 γ/ml. of histamine diphosphate.

TABLE 10

2-(Aryloxymethyl)imidazoline hydrochlorides (113)

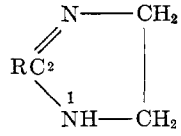


NO.	ArO	MELTING POINT	YIELD	ANTIHISTAMINE ACTIVITY*
		°C.	*per cent*	
24.....	Phenoxy	168–169.5	82	10
25.....	*o*-Toloxy	200–202	71	0
26.....	*m*-Toloxy	225–227	55	0
27.....	*p*-Toloxy	151–153	62	1–10
28.....	Thymyloxy	223.5–225	78	1–10
29.....	Carvacryloxy	175–176	67	0
30.....	3-Methyl-4-chlorophenoxy	221–223	57	10
31.....	*o*-Isopropylphenoxy	173.5–174.5	58	10
32.....	2,5-Dimethylphenoxy	223.5–225.5	67	10

* γ of compound per milliliter of bath liquid, capable of neutralizing the contraction of an isolated guinea-pig gut caused by 1 γ/ml. of histamine diphosphate.

TABLE 11

Aryloxyalkylimidazolines



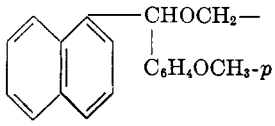
NO.	R	MELTING POINT	MELTING POINT OF SALT	REFERENCES
		°C.	°C.	
1.	$(C_6H_5)_2CHOCH_2$—	102–103	203–205 (HCl) 204 (picrate)	(70, 71, 104, 114, 328)
2.	$(C_6H_5)_2CHOCH_2CH_2CH_2$—		218 (HCl)	(70)
3.	$(C_6H_5)_2CHOCHC_2H_5$		218 (HCl)	(70)
4.	p-$CH_3C_6H_4CHOCH_2$— C_6H_5	99	189 (HCl)	(102)
5.	p-$CH_3OC_6H_4CHOCH_2CH_2$— C_6H_5	87	150 (HCl) 152 (dioxalate) 151 (picrate)	(102)
6.	$C_6H_5CH_2OCH_2$—	58	161 (HCl) 153 (picrate)	(328)
7.	$C_6H_5CH_2CH_2OCH_2$—		128 (HCl) 121 (picrate)	(328)
8.	p-$CH_3OC_6H_4CHOCH_2$— C_6H_5	87	180 (HCl) 145 (dioxalate) 132 (picrate)	(102)
9.	$C_6H_5CH_2CH_2CH_2OCH_2$—		51 (HCl) 168 (picrate)	(328)
10.	$C_6H_5SCH_2$—	85	185 (HCl) 128 (picrate)	(328)
11.	p-$C_6H_5C_6H_4OCH_2$—		225 (HCl)	(70)
12.	o-$C_6H_5C_6H_4OCH_2$—		225 (HCl)	(70)
13.	o-$C_6H_5C_6H_4OCH_2$—		116 (HCl)	(70)
14.			205 (HCl) 126 (dioxalate)	(102)

TABLE 11—*Concluded*

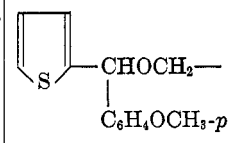
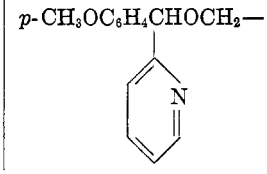
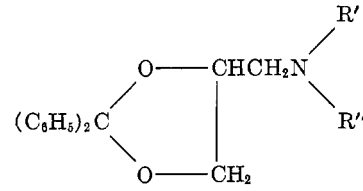
NO.	R	MELTING POINT	MELTING POINT OF SALT	REFERENCES
		°C.	°C.	
15....			156 (dioxalate) 179 (picrate)	(103)
16....			198 (dioxalate)	(103)

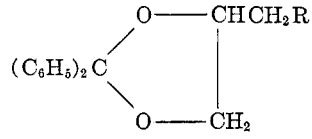
TABLE 12

1,3-*Dioxolanes* (*48*)

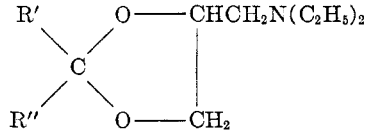


NO.	R′	R″	SALT	ANTIHISTAMINE ACTIVITY*
				μg./ml.
1.....	H	H	HCl	
2.....	H	CH_3	HCl	2
3.....	CH_3	CH_3	HCl	5
4.....	CH_3	CH_3	CH_3Br	5
5.....	CH_3	CH_3	CH_3I	1
6.....	C_2H_5	C_2H_5	HCl	0.5
7.....	H	*i*-C_3H_7	HCl	5
8.....	*n*-C_3H_7	*n*-C_3H_7	HCl	10
9.....	*n*-C_4H_9	*n*-C_4H_9	HBr	720

TABLE 12—*Concluded*



NO.	R	SALT	ANTIHISTAMINE ACTIVITY*
			μg./ml.
10	$-OCH_2CH_2N(C_2H_5)_2$	HCl	0.1
11		HCl	1
12		CH_3I	5
13		HCl	20

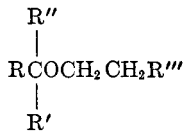


NO.	R′	R″	SALT	ANTIHISTAMINE ACTIVITY*
				μg./ml.
14	Phenyl	α-Thienyl	HCl	
15	α-Thienyl	α-Thienyl	HCl	5
16	*p*-Tolyl	*p*-Tolyl	HCl	5
17	*p*-Tolyl	*p*-Tolyl	CH_3I	10
18	*p*-Chlorophenyl	*p*-Chlorophenyl	HCl	5
19	*p*-Methoxyphenyl	*p*-Methoxyphenyl	HCl	2
20	Diphenylmethyl	Hydrogen	HCl	5
21	Cyclopentamethylene		HCl	>20
22	Cyclopentamethylene		CH_3I	>20
23	*o*-Diphenylene		HBr	10

* Minimum effective concentration to antagonize 0.2 μg./ml. of histamine (isolated guinea-pig intestine) in micrograms per milliliter.

TABLE 13

Miscellaneous cyclic ethers (463)

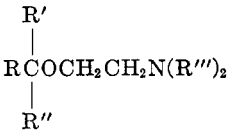


NO.	R	R′	R″	R‴	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY*
					°C.	°C.	
1...	C_6H_5—		H	—$N(CH_3)_2$	133/0.25 mm.	120 (HCl) 177 (CH_3I)	0.4 0.3
2...	C_6H_5—		H		181/0.5 mm.	134 (CH_3I)	0.14–0.25
3...	C_6H_5—		H	—$N(CH_3)_2$	123/0.25 mm.	138 (HCl)	0.06
4...	C_6H_5—		H			153 (HCl)	0.07–0.14
5...	C_6H_5—	$C_6H_5CH_2$—	H	—$N(CH_3)_2$	131/0.35 mm.	133 (HCl)	0.04
6...	C_6H_5—	$C_6H_5CH_2$—	H		196/0.7 mm.	114 (HCl)	0.03
7...	*n*-C_4H_9	*n*-C_4H_9	H		125/2.3 mm.		0.3
8...	*p*-$CH_3OC_6H_4$—	*p*-$CH_3OC_6H_4CH_2$—	H		219/0.35 mm.	144 (HCl)	0.07

* Antihistaminic activity in terms of Benadryl = 1.

TABLE 14

Alkamine ethers (405)



NO.	R	R′	R″	R‴	YIELD	BOILING POINT
					per cent	°C.
1....	2-C_5H_4N—*	C_6H_5—	H	CH_3	82	158–162/1.5 mm.
2....	3-C_5H_4N—	C_6H_5—	H	CH_3	69	149–153/1 mm.
3....	2-C_5H_4N—	*p*-*i*-$C_3H_7C_6H_4$—	H	CH_3	84	165–167/0.5 mm.
4....	2-C_5H_4N—	*p*-$CH_3C_6H_4$—	H	CH_3	88	156–160/1 mm.
5....	2-C_5H_4N—	*m*-$CH_3C_6H_4$—	H	CH_3	72	155–159/0.5 mm.
6....	2-C_5H_4N—	*p*-$CH_3OC_6H_4$—	H	CH_3	86	168–172/0.5 mm.
7....	2-C_5H_4N—	*p*-$(CH_3)_2NC_6H_4$—	H	CH_3	61	168–172/2.5 mm.
8....	2-C_5H_4N—	3,4-(—OCH_2O—)C_6H_3—	H	CH_3	45	176–180/1 mm.
9....	2-C_5H_4N—	*o*-ClC_6H_4—	H	CH_3	28	152–156/2 mm.
10....	2-C_5H_4N—	*p*-ClC_6H_4—	H	CH_3	47	164–167/2 mm.
11....	2-C_5H_4N—	$C_6H_5CH_2$—	H	CH_3	63	138–142/0.5 mm.
12....	2-C_5H_4N—	$C_6H_5CH_2CH_2$—	H	CH_3	56	178–180/0.5 mm.
13....	2-C_5H_4N—	2-C_4H_3S—†	H	CH_3	22	145/1 mm.
14....	2-C_5H_4N—	*n*-C_3H_7	H	CH_3	47	103–105/0.2 mm.
15....	2-C_5H_4N—	C_6H_5—	H	C_2H_5	82	147–150/0.5 mm.
16....	2-C_5H_4N—	*p*-$CH_3C_6H_4$—	H	C_2H_5	50	162–165/1 mm.
17....	2-C_5H_4N—	*p*-$CH_3C_6H_4$—	H	‡	70	143–147/0.5 mm.
18....	3-C_5H_4N—	C_6H_5—	CH_3	CH_3	87	160–161/1.5 mm.
19....	2-C_5H_4N—	C_6H_5—	CH_3	CH_3§	46	137–141/0.5 mm.
20....	2-C_5H_4N—	*p*-ClC_6H_4—	CH_3	CH_3	66	155–159/1 mm.
21....	3-C_5H_4N—	$C_6H_5CH_2$—	CH_3	CH_3	76	170–173/1 mm.

* Pyridyl.

† 2-Thenyl.

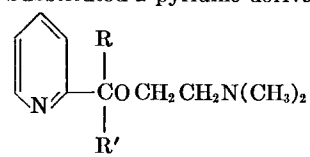
‡ Either $(CH_3)_2NCH_2CH(CH_3)$— or $(CH_3)_2NCH(CH_3)CH_2$— or both.

§ Decapryn.

TABLE 15

Pyridine derivatives (423)

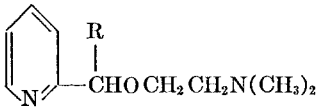
A. Substituted 2-pyridine derivatives



NO.	R	R′	BOILING POINT	YIELD	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY
			°C.	*per cent*	°C.	*γ/ml.*
1....	Phenyl	H	147–151/0.3 mm.	74	103–105 (HCl)	0.05
2....	α-Methylbenzyl	H	148–152/0.2 mm.	7	144–146 (HCl)	1.0
3....	*p*-Cumyl	H	159–163/0.1 mm.	73	122–123 (HCl)	0.5
4....	*o*-Anisyl	H	152–154/0.2 mm.	46	133–135 (HCl)	5.0
5....	3,4-Methylenedioxyphenyl	H	182–185/0.1 mm.	75	147–149 (HCl)	2.0
6....	2-Chlorophenyl	H	174–176/0.15 mm.	43	116–118 (HCl)	1.0
7....	Phenyl	CH_3	145–153/0.4 mm.	75	169–170 (HCl)	0.05
8....	Benzyl	CH_3	146–155/0.3 mm.	75	118–120 (2HBr)	5.0
9....	*p*-Tolyl	CH_3	145–155/0.2 mm.	53	178–179 (HCl)	0.05
10....	*o*-Tolyl	CH_3	160–162/0.1 mm.	31	172–174 (HCl)	5.0
11....	*m*-Tolyl	CH_3	152–156/0.1 mm.	44	134–136 (HCl)	0.5
12....	3,4-Xylyl	CH_3	162–164/0.08 mm.	58	152–154 (HCl)	1.0
13....	Carvacryl	CH_3	160–165/0.15 mm.	42	184–186 (HCl)	5.0
14....	α-Naphthyl	CH_3	185–195/0.3 mm.	56	229–230 (HCl)	5.0
15....	β-Naphthyl	CH_3	185–195/0.2 mm.	50	161–162 (HCl)	5.0
16....	*m*-Anisyl	CH_3	167–173/0.2 mm.	60	130–132 (HCl)	0.05
17....	*p*-Anisyl	CH_3	173–175/0.2 mm.	67	152–153 (HCl)	0.1
18....	3,4-Dimethoxyphenyl	CH_3	175–180/0.2 mm.	52	174–175 (HCl)	20.0
19....	3-Chlorophenyl	CH_3	158–162/0.1 mm.	58	137–138 (HCl)	0.1
20....	4-Chlorophenyl	CH_3	154–156/0.2 mm.	60	162–164 (HCl)	0.1
21....	3-Bromophenyl	CH_3	180–185/0.2 mm.	39	126–128 (HCl)	0.1

NO.	R	R′	BOILING POINT	YIELD	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY
			°C.	*per cent*	°C.	*γ/ml.*
22....	Phenyl	C_2H_5	150–153/0.09 mm.	34	201–202 (HCl)	0.5
23....	Phenyl	*i*-C_3H_7	158–162/0.1 mm.	34	161–163 (HCl)	5.0
24....	Phenyl	—$CH_2CH_2N(CH_3)_2$		70	244–245 (2HBr)	1.0
25....	Phenyl	Phenyl	180–188/0.3 mm.	26	186–187 (HCl)	1.0
26....	Benzyl	Benzyl	175–180/0.25 mm.	40	267–268 (2HCl)	20.0
27....	1-Cyclohexenyl	CH_3	138–142/0.2 mm.	32	136–138 (HCl)	0.1
28....	Cyclohexyl	CH_3	128–132/0.2 mm.	25	164–165 (HCl)	3.0
29....	Cyclopropyl	CH_3	95–102/0.28 mm.	35	95–97 (HCl)	10.0
30....	*n*-Hexyl	CH_3	138–143/0.3 mm.	28	95–96 (HCl)	5.0
31....	$CH(CH_3)_2$	*i*-C_3H_7	95–103/0.3 mm.	19	187–188 (HCl)	10.0
32....	CH_3	—$CH_2CH_2CH_2N(C_2H_5)_2$	155–160/0.23 mm.	41	191–192 (3HCl)	20.0
33....	2-Pyridyl	CH_3		10	154–156 (3HBr)	1.0
34....	2-Thienyl	CH_3	155–158/0.5 mm.	41	119–120 (HCl)	10.0

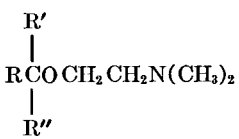
B. Cyclic 2-pyridine derivatives



NO.	R	BOILING POINT	YIELD	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY
		°C.	*per cent*	°C.	*γ/ml.*
35.....	Cyclohexylidene	139–142/1.0 mm.	14	163–164 (2HCl)	20.0
36.....	*dl*-Bornylidene	134–138/0.2 mm.	48	146–148 (2HCl)	5.0
37.....	*dl*-Fenchylidene	135–138/0.2 mm.	61	197–198 (HCl)	1.0
38.....	1-Indanylidene	162–164/0.3 mm.	28	137–139 (HCl)	5.0

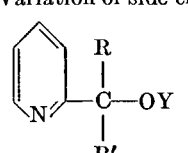
TABLE 15—*Continued*

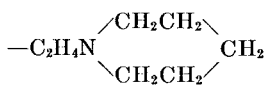
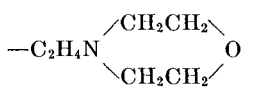
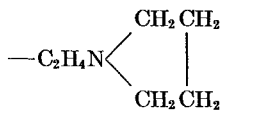
C. 2-, 3-, and 4-Pyridine derivatives



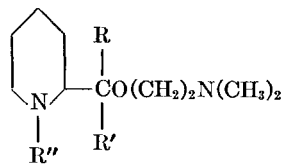
NO.	R	R′	R″	BOILING POINT	YIELD	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY*
				°C.	*per cent*	°C.	γ/*ml.*
39	3-Pyridyl	Phenyl	H	160–165/0.2 mm.	55	79–81 (HBr)	1.0
40	4-Pyridyl	Phenyl	H	145–148/0.2 mm.	32	103–105 (HCl)	0.5
41	4-Pyridyl	Phenyl	CH_3	158–160/0.3 mm.	51	282.5–284.5 (2HCl)	20.0
42	(2-Pyridyl)methyl	Phenyl	H	150–160/0.5 mm.	7	152–154 (2HBr)	5.0
43	2-(4-Picolyl)	Phenyl	CH_3	152–156/0.1 mm.	66	162–164 (HCl)	1.0
44	2-(6-Picolyl)	Phenyl	CH_3	145–150/0.3 mm.	30	153–155 (HCl)	0.1

D. Variation of side chain



NO.	R	R′	Y	BOILING POINT	YIELD	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY*
				°C.	*per cent*	°C.	
45.....	Phenyl	CH_3	$-C_2H_4N(CH_3)_2 \cdot 2CH_3I$		47	143–144 (HCl)	20.0
46.....	Phenyl	CH_3	$-C_2H_4N(CH_3)_2 \cdot HOC_2H_4Cl$		75	73–75 (HCl)	0.5
47.....	Phenyl	CH_3	$-C_2H_4N(C_2H_5)_2$	150–156/0.2 mm.	73	109–111 (HBr)	0.5
48.....	Phenyl	CH_3	$-CH_2CH(CH_3)N(CH_3)_2$	148–151/0.05 mm.	61	147–149 (HCl)	1.0
49.....	Phenyl	CH_3		160–166/0.08 mm.	68	177–179 (HCl)	0.1
50.....	Phenyl	CH_3		168–174/0.1 mm.	61	184–186 (HCl)	1.0
51.....	Phenyl	CH_3		156–162/0.1 mm.	53	145–147 (HCl)	1.0
52.....	*dl*-Fenchyl		$-C_2H_4N(C_2H_5)_2$	150–156/0.2 mm.	65	192–194 (HCl)	5.0

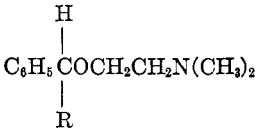
E. Substituted 2-piperidine derivatives

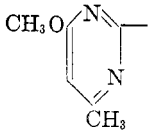
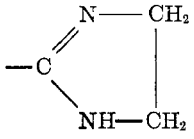


NO.	R	R′	R″	BOILING POINT	YIELD	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY*
				°C.	*per cent*	°C.	*γ/ml.*
53.....	Phenyl	Phenyl	H	150–155/0.2 mm.	40	246–246.5 (2HCl)	5.0
54.....	Phenyl	CH_3	CH_3	133–139/0.1 mm.	30	222–224 (2HCl)	50.0

* Minimum dose of test compound necessary to antagonize 0.1 μg./ml. of histamine diphosphate on isolated intestine of guinea pig. Benadryl = 0.05.

TABLE 16



NO.	R	BOILING POINT	YIELD	MELTING POINT OF SALT	ANTI-HISTAMINE ACTIVITY*	REFERENCES
		°C.	*per cent*	°C.		
1..		135–140/0.2 mm.	30	150 (HCl) 177 (2HCl)	20† 20†	(425)
2..		155–160/0.08 mm.	63	247(2HCl)	20†	(425)
3..		100–101/0.035 mm.	39		30‡	(25)
4..	$C_6H_5CH_2$—	169–171/2–3 mm.		117 (HCl)	1.0§	(327)
	FORMULA					
5..	$C_6H_5CHOCH_2CH_2N(CH_3)_2$ $CH_2C_6H_5$	190–195/3 mm.		124 (HCl)	0.22§	(327)
6..	*p*-$CH_3OC_6H_4CHOCH_2CH_2N$ $CH_2C_6H_5$			144 (CH_3I)		(463)

* Reference 463.

† See table 15.

‡ Average per cent by which a bath concentration of 9.37×10^{-5} μg./ml. of antihistaminic reduced the response of guinea-pig ileum to a histamine base concentration of 0.024 μg./ml. Benadryl = 17.

§ See table 4, Nos. 10 and 11.

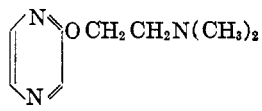
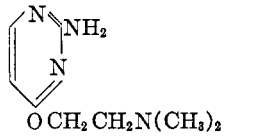
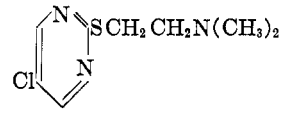
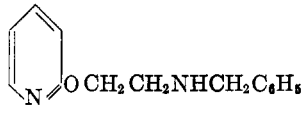
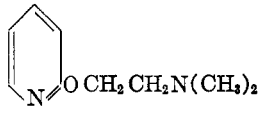
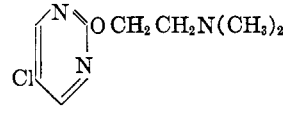
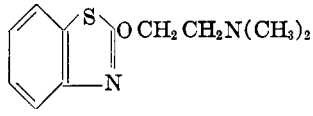
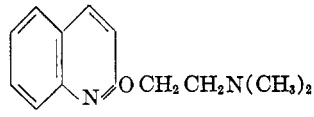
TABLE 17

3-(N,N-Diethylamino)propyl sulfides (31)

NO.	R	BOILING POINT	YIELD	MELTING POINT OF HYDROCHLORIDE
	$RSCH_2CH_2CH_2N(C_2H_5)_2$			
		°C.	*per cent*	°C.
1	o-$ClC_6H_4CH_2$—	190–193/12 mm.	80	84
2	2,4-$Cl_2C_6H_3CH_2$—	165–168/4 mm.	73	117
3	3,4-$Cl_2C_6H_3CH_2$—	169–172/3 mm.	81	76
4	C_6H_5—	141–143/6 mm.	81	62
5	o-$CH_3C_6H_4$—	150–153/5 mm.	71	127
6	m-$CH_3C_6H_4$—	168–173/13 mm.	88	66
7	p-$CH_3C_6H_4$—	155–158/7 mm.	81	98
	$RSCH_2CHOHCH_2N(C_2H_5)_2$			
8	o-$ClC_6H_4CH_2$—	190–195/4 mm.	60	
9	2,4-$Cl_2C_6H_3CH_2$—	210–215/4 mm.	66	
10	3,4-$Cl_2C_6H_3CH_2$—	210–215/4 mm.	69	
11	C_6H_5—	168–171/4 mm.	86	
12	o-$CH_3C_6H_4$—	154–157/1 mm.	65	
13	m-$CH_3C_6H_4$—	168–172/3 mm.	60	
14	p-$CH_3C_6H_4$—	168–172/3 mm.	64	

TABLE 18

Heterocyclic alkamine ethers (415)

NO.	FORMULA	BOILING POINT	MELTING POINT OF SALT
		°C.	°C.
1.....		80–89/5 mm.	138 (picrate)
2.....			111 (HCl)
3.....		110–120/2 mm.	190 (HCl) 179 (picrate)
4.....			175 (HCl)
5.....		80–90/0.3 mm.	155 (dipicrate)
6.....			182 (HCl) 161 (picrate)
7.....		147–155/4 mm.	191 (HCl)
8.....		165–175/2 mm.	156 (2HCl) 153 (picrate)*

* Reference 307.

TABLE 19

Alkamine ethers of benzylphenols (81)

ROR′

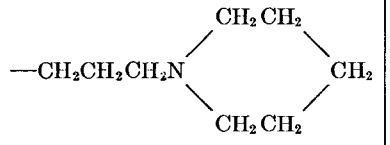
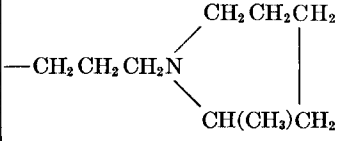
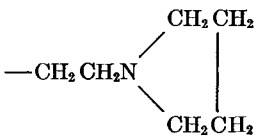
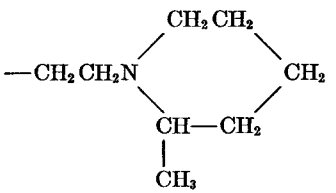
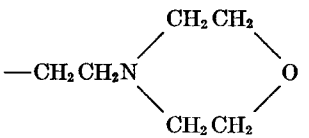
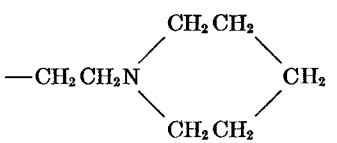
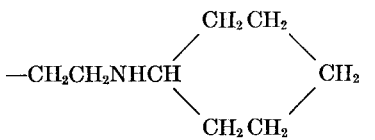
NO.	CODE NO.	R	R′	YIELD	BOILING POINT AT 1 MM. PRESSURE	MELTING POINT OF HYDROCHLORIDE
				per cent	°C.	°C.
1....	C-5581-H	2-Benzylphenyl	$-CH_2CH_2N(CH_3)_2$	94.3	141–144	119–120
2....	338-20	4-Benzylphenyl	$-CH_2CH_2N(CH_3)_2$	64.5	152–153	179–182
3....	338-19A	2-Benzylphenyl	$-CH(CH_3)CH_2N(CH_3)_2$		148–152	75–80
4....	338-19B	2-Benzylphenyl	$-CH_2CH(CH_3)N(CH_3)_2$		152–157	170–171.5
5....	338-22	2-Benzylphenyl	$-CH_2CH_2N(C_2H_5)_2$	76.8	160–164	158–159
6....	546-1	2-Benzylphenyl		68.3	192–198	167–168
7....	546-2	2-Benzylphenyl		66.2	194.5–197	149–150
8....	546-3	2-Benzylphenyl	$-CH_2CH_2CH_2N(CH_3)_2$	86.6	149–153	159–160
9....	546-13	2-Benzylphenyl	$-CH_2CH_2CH_2N(n\text{-}C_4H_9)_2$	98.2	174–176	86–89
10....	546-14	4-Benzylphenyl	$-CH_2CH_2CH_2N(n\text{-}C_4H_9)_2$	75	197–200	96–98

TABLE 19—*Continued*

NO.	CODE NO.	R	R′	YIELD	BOILING POINT AT 1 MM. PRESSURE	MELTING POINT OF HYDROCHLORIDE
				per cent	°C.	°C.
11....	612-9	2-Benzylphenyl		73.5	152–163	140–141.5
12....	612-10	2-Benzylphenyl		75.5	151–167	139.5–142
13....	380-1	2-Benzylphenyl		85.5		184–185
14....	380-3	2-Benzylphenyl		55.3	180–183	139–141
15....	489-27	2,6-Dibenzylphenyl	$-CH_2CH_2N(CH_3)_2$	31.5		143–144.5

16....	489-2	Hexahydro-2-benzylphenyl	$-CH_2CH_2N(CH_3)_2$	25.7		170
17....	489-1	2-Cyclohexylmethylcyclohexyl	$-CH_2CH_2N(CH_3)_2$	38		128.5–129
18....	489-9	2-Benzylphenyl	$-CH_2CH_2NHCH(CH_3)_2$	81.2		174–175
19....	489-10	2-Benzylphenyl	$-CH_2CH_2NHCH_3$	22.3		178.5–179.5
20....	518-14	2-Benzylphenyl		34.8	165–171	182–183.5

Substituted 2-benzylphenyl 2-dimethylaminoethyl ethers (453)

$ROCH_2CH_2N(CH_3)_2$

NO.	CODE NO.	R	YIELD	BOILING POINT	MELTING POINT OF HYDROCHLORIDE
			per cent	°C.	°C.
21.....	446-24	2-Benzyl-4-tolyl	89	168–174/3 mm.	126.5–128.0
22.....	480-6	4-*tert*-Butyl-2-benzylphenyl	87	137–140/1 mm.	162.5–164.0
23.....	446-44	4-Cyclohexyl-2-benzylphenyl	87	186–190/1 mm.	152.5–154.0
24.....	446-15	4-Methoxy-2-benzylphenyl	86	174–177/1mm.	131.0–132.0
25.....	446-28	4-Ethoxy-2-benzylphenyl	79	167–171/1 mm.	136.0–137.0
26.....	446-21	4-Chloro-2-benzylphenyl	82	172–176/1 mm.	173.5–175.5
27.....	551-43	6-Chloro-2-benzylphenyl	76	160–164/1 mm.	93.0–95.0
28.....	480-25	2-(4′-Isopropylbenzyl)phenyl	90	151–152/1 mm.	144.0–145.5
29.....	446-34	2-(4′-Methoxybenzyl)phenyl	89	149–152/1 mm.	123.0–126.0
30.....	480-38	2-(2′,3′-Dimethoxybenzyl)phenyl	90	164–166/ 1mm.	
31.....	518-35	2-(2′-Chlorobenzyl)phenyl	80	155–167/1 mm.	139.5–142.5
32.....	551-13	2-(3′-Chlorobenzyl)phenyl	82	146–152/1 mm.	120.0–121.5
33.....	446-48	2-(4′-Chlorobenzyl)phenyl	81	179–185/3 mm.	152.0–153.0
34.....	570-26	2-(4′-Bromobenzyl)phenyl	92	162–165/1 mm.	158.0–160.5
35.....	518-39	4-Chloro-2-(4′-chlorobenzyl)phenyl	86	177–182/1 mm.	150.0–152.0
36.....	570-31	2-(2′,4′-Dichlorobenzyl)phenyl	91	149–152/1 mm.	139.5–141.0

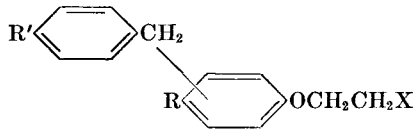
TABLE 19—*Continued*

NO.	CODE NO.	R	YIELD	BOILING POINT	MELTING POINT OF HYDROCHLORIDE
			per cent	°C.	°C.
37	570-35	4,6-Dichloro-2-benzylphenyl	85	159–163/1 mm.	137.5–140.5
38	490-12	2-Benzoylphenyl	95	180–181/1 mm.	144.0–145.5
39	490-15	2-(α-Hydroxybenzyl)phenyl	70		153.0–154.0
40	518-49	2-(α-Methylbenzyl)phenyl	78	142–146/1 mm.	141.0–142.5
41	518-19	2-Benzhydrylphenyl	88	189–192/1 mm.	184.0–186.5

$ROCH_2CH_2N(CH_3)_2$

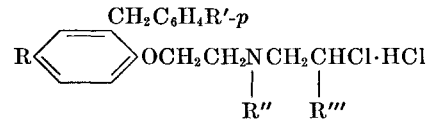
NO.	R	YIELD	BOILING POINT	MELTING POINT OF HYDROCHLORIDE
		per cent	°C.	°C.
42	2-Methoxy-6-benzylphenyl	83	144–148/1 mm.	92.5–94.0
43	4-Bromo-2-benzylphenyl	89	164–167/1.5 mm.	179.5–181.0
44	4-Iodo-2-benzylphenyl	73		167.0–170.0
45	4-Fluoro-2-benzylphenyl	89	131–134/1 mm.	124.5–125.5
46	4-Dimethylamino-2-benzylphenyl	73	171–186/1 mm.	154.0–156.0
47	2-(4′-Fluorobenzyl)phenyl	72	140–146/2 mm.	131.0–132.5
48	2-Cinnamylphenyl	82	137–141/1 mm.	154.0–156.5
49	2-(2′-Thenyl)phenyl	76	159–160/1 mm.	129.0–130.0
50	2-(5′-Chloro-2′-thenyl)phenyl	86	149–150/1 mm.	103.0–106.0
51	1-Benzyl-2-naphthyl	88	184–192/1.5 mm.	178.0–181.0
52	2-Benzyl-1-naphthyl	79	200–207/2 mm.	183.5–185.5
53	1-Allyl-2-naphthyl	87	139–143/1 mm.	151.0–152.5
54	2-Allyl-1-naphthyl	79	136–145/1 mm.	
55	7-Benzyl-8-quinolyl	86	190–197/1 mm.	205.0–207.0

2-(Benzylphenoxy)ethyl halides (456)



NO.	R	R′	X	POSITION OF BENZYL GROUP	YIELD	BOILING POINT	MELTING POINT
					per cent	°C.	°C.
56	H	H	Cl	Ortho	89		65.0–66.0
57	H	H	I	Ortho	88		95.0–98.0
58		H	Cl	Para	94		64.0–65.0
59	H	Cl	Cl	Ortho	91	148/1 mm.	
60	Cl	H	Cl	Ortho	98		46.5–48.5
61	H	F	Cl	Ortho	97	144–147/2 mm.	

2-Chloroethylamines



NO.	R	R′	R″	R‴	YIELD	MELTING POINT OF HYDROCHLORIDE
					per cent	°C.
62	H	H	$-CH_3$	H	78	118
63	H	H	$-C_2H_5$	H	71	163
64	H	H	$-CH(CH_3)_2$	H	78	139
65	H	H	$-CH_2CH_2CH_2CH_3$	H	76	111
66	H	H	$-CH(CH_3)C_2H_5$	H	63	110
67	H	H	$-CH_2CH(CH_3)_2$	H	80	103

TABLE 19—*Concluded*

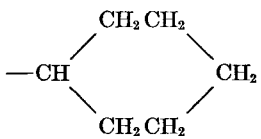
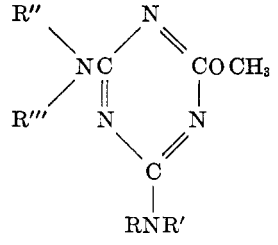
NO.	R	R′	R″	R‴	YIELD	MELTING POINT OF HYDROCHLORIDE
					per cent	°C.
68	H	H	$-CH_2CH(C_2H_5)C_4H_9$	H	72	84
69	H	H	$-CH_2C_6H_5$	H	67	153
70	H	H		H	87	110
71	H	H	$-CH(CH_3)CH_2C_6H_5$	H	73	155
72	H	H	$-CH_2CH_2Cl$	H	54	158
73	H	H	$-CH(CH_3)_2$	CH_3	61	118
74	H	H	$-CH(CH_3)_2$	$-CH=CH_2$	31	102
75	H	H	$-CH(CH_3)_2$	$-C_6H_5$	62	127
76	H	Cl	$-CH(CH_3)_2$	H	69	133
77	Cl	H	$-CH(CH_3)_2$	H	76	147
78	H	F	$-CH(CH_3)_2$	H	83	138
79	H	H	$-CH(CH_3)_2$	H	49	109

TABLE 20

Alkoxy-s-triazines (94)

2-R-4,6-Diamino-s-triazines

NO.	R	MELTING POINT	YIELD	RELATIVE ANTIHISTAMINE ACTIVITY[a]
		°C.	*per cent*	
1....	Methoxy	229–230	81	1
2....	Ethoxy	182	72	2
3....	*n*-Propoxy	182–183	88	4
4....	Isopropoxy	172	78	4
5....	*n*-Butoxy	174–175	75	2
6....	Isobutoxy	186	93	4
7....	*sec*-Butoxy	173–174	50	4
8....	*n*-Pentoxy	147	28	2
9....	*n*-Hexoxy	152	58	3
10....	*n*-Heptoxy	139	63	
11....	*n*-Octoxy	122–124	46	
12....	*n*-Nonoxy	115	41	
13....	*n*-Decoxy	121–123	29	
14....	Allyloxy	181–182	82	2
15....	2-Ethoxyethoxy	155–156	33	1
16....	2-Phenoxyethoxy	184–185	77	
17....	Cyclohexoxy	209	53	4
18....	Benzyloxy	187	65	
19....	2-Dimethylaminoethoxy	122	37	
20....	3-Diethylaminopropoxy	147	38	
21....	2-Morpholinoethoxy	211–212	46	
22....	Isopropylthio	190	68	4
	NAME			
23....	2-Ethoxy-4,6-di(monoisopropanolamino)-*s*-triazine	119–120	49	2
24....	2 Ethoxy-4-monoisopropanolamino-6-amino-*s*-triazine	140–142	83	
25....	2-*N*-Butoxy-4-monoisopropanolamino-6-amino-*s*-triazine	131	87	4

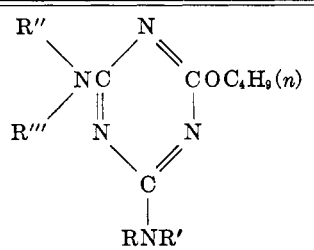


(312)

NO.	R	R′	R″	R‴	MELTING POINT	YIELD	ANTIHISTAMINE ACTIVITY[b]
					°C.	*per cent*	*mg./kg.*
26..	Methyl	H	H	H	155–156	66	50
27..	Ethyl	H	H	H	168–170	24	25
28..	*n*-Propyl	H	H	H	148–150	81	12
29..	*n*-Butyl	H	H	H	125–127	89	>50
30..	*n*-Amyl	H	H	H	[c]	86	12
31..	*n*-Hexyl	H	H	H	104–106	92	12
32..	Allyl	H	H	H	148–150	89	12

TABLE 20—*Continued*

NO.	R	R′	R″	R‴	MELTING POINT	YIELD	ANTIHISTAMINE ACTIVITY[b]
					°C.	*per cent*	*mg./kg.*
33..	Methallyl	H	H	H	129–131	88	>50
34..	Cyclohexyl	H	H	H	170–172	99	12
35..	Methyl	Methyl	H	H	169–171	81	25
36..	Ethyl	Ethyl	H	H	113–115	73	12
37..	Allyl	Allyl	H	H	87–89	83	>50
38..	Methallyl	Methallyl	H	H	101–103	90	50
39..	$HOCH_2CH_2$—	Ethyl	H	H	162–164	87	>50
40..	$HOCH_2CH_2$—	Phenyl	H	H	224–226	91	50
41..	—C_5H_{10}—[d]		H	H	137–139	95	6
42..	—$C_2H_4OC_2H_4$—[e]		H	H	182–184	80	50
43..	Methyl	H	Methyl	H	184–186	76	6
44..	Ethyl	H	Ethyl	H	81–83	46	6
45..	Allyl	H	Allyl	H	84–86	88	25
46..	Methallyl	H	Methallyl	H	112–114	93	12
47..	Methyl	Methyl	Methyl	H	187–188	80	25
48..	Ethyl	Ethyl	Ethyl	H	107–109	99	12
49..	Methyl	Methyl	Methyl	Methyl	90–92	73	25
50..	Ethyl	Ethyl	Ethyl	Ethyl	146–149/1.5 mm.[f]	65	50
51..	Allyl	Allyl	Allyl	Allyl	150–153/1 mm.[f]	93	>50
52..	Methallyl	Methallyl	Methallyl	Methallyl	151–154/1.5 mm.[f]	71	>50
53..	Piperidino		Piperidino		89–91	94	>50
54..	Morpholino		Morpholino		153–155	78	12

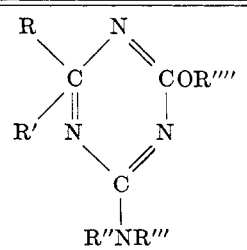


(312)

NO.	R	R′	R″	R‴	MELTING POINT	YIELD	ANTIHISTAMINE ACTIVITY[b]
					°C.	*per cent*	*mg./kg.*
55..	Methyl	H	H	H	173–175	88	6
56..	Ethyl	H	H	H	116–118	86	12
57..	*n*-Propyl	H	H	H	116–118	85	25
58..	*n*-Butyl	H	H	H	103–104	72	
59..	*n*-Amyl	H	H	H	107–109	81	12
60..	*n*-Hexyl	H	H	H	119–121	99	12
61..	Allyl	H	H	H	87–89	75	12

TABLE 20—*Continued*

NO.	R	R′	R″	R‴	MELTING POINT	YIELD	ANTIHISTAMINE ACTIVITY[b]
					°C.	*per cent*	*mg./kg.*
62..	Methallyl	H	H	H	106–108	79	>50
63..	Cyclohexyl	H	H	H	141–143	96	>50
64..	Methyl	Methyl	H	H	103–104	88	12
65..	Ethyl	Ethyl	H	H	73–75	51	50
66..	Allyl	Allyl	H	H	172–175/1 mm.[f]	65	>50
67..	Methallyl	Methallyl	H	H	60–62	87	>50
68..	$HOCH_2CH_2$—	Ethyl	H	H	123–125	64	>25
69..	$HOCH_2CH_2$—	Phenyl	H	H	157–159	61	>50
70..	—C_5H_{10}—[d]		H	H	115–117	87	>50
71..	—$C_2H_4OC_2H_4$—[e]		H	H	108–110	43	12
72..	Methyl	H	Methyl	H	103–104	60	12
73..	Ethyl	H	Ethyl	H	50–52	85	25
74..	Allyl	H	Allyl	H	185–190/1 mm.[f]	51	25
75..	Methallyl	H	Methallyl	H	58–60	70	
76..	Methyl	Methyl	Methyl	H	129–131	87	>25
77..	Ethyl	Ethyl	Ethyl	H	80–82	96	>50
78..	Methyl	Methyl	Methyl	Methyl	155–157/4 mm.[f]	69	>25
79..	Ethyl	Ethyl	Ethyl	Ethyl	164–165/4 mm.[f]	84	>25
80..	Allyl	Allyl	Allyl	Allyl	157–160/1 mm.[f]	93	>50
81..	Methallyl	Methallyl	Methallyl	Methallyl	164–167/1 mm.[f]	82	>25
82..	—C_5H_{10}—[d]		—C_5H_{10}—[d]		182–185/2 mm.[f]	71	>50
83..	—$C_2H_4OC_2H_4$—[e]		—$C_2H_4OC_2H_4$—[e]		117–119	66	>25



(313)

NO.	R, R′	R″, R‴	R‴′	MELTING POINT	YIELD	ANTIHISTAMINE ACTIVITY[b]
				°C.	*per cent*	*mg./kg.*
84....	H, H	H, H	C_5H_{11}[g]	181–183	30	25
85....	H, H	H, H	C_5H_{11}[h]	170–172	30	50
86....	H, H	H, CH_3	C_2H_5	170–171	79	12.5
87....	H, H	H, CH_3	*n*-C_3H_7	175–177	68	12.5
88....	H, H	H, CH_3	*n*-C_6H_{13}	166–168	75	>50

TABLE 20—*Concluded*

NO.	R, R′	R″, R‴	R⁗	MELTING POINT	YIELD	ANTIHISTAMINE ACTIVITY[b]
				°C.	*per cent*	*mg./kg.*
89....	H, H	H, CH_3	*n*-C_6H_{11}	232–234	64	12.5
90....	H, H	H, CH_3	Phenyl	211–213	64	>25
91....	H, CH_3	H, CH_3	C_2H_5	171–173	61	12.5
92....	H, H	$(CH_3)_2$	C_2H_5	156–158	88	25
93....	H, CH_3	$(CH_3)_2$	C_2H_5	173–175	80	25
94....	H, CH_3	$(CH_3)_2$	Cyclo-C_6H_{11}	154	75	>25
95....	H, H	H, C_5H_{11}	C_2H_5	103–105	55	>25
96....	H, H	H, C_5H_{11}	*n*-C_3H_7	92–95	46	
97....	H, C_2H_5	H, C_2H_5	C_2H_5	116–118	44	>25
98....	H, C_2H_5	H, C_2H_5	*n*-C_3H_7	82–84	88	
99....	H, H	C_2H_5O[i], C_6H_5	C_2H_5	194–196	83	50

[a] Antihistamine activity compared to aminophylline = 1.

[b] Dose of compound in milligrams per kilogram intraperitoneally allowing survival of 50 per cent of histamine-shocked guinea pigs. The comparable dose for aminophylline is 50 and for Benadryl is 1.5.

[c] Sinters at 98–104°C.

[d] Piperidino.

[e] Morpholino.

[f] Boiling point.

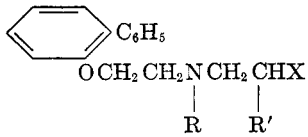
[g] 3-Methylbutyl.

[h] 2-Methylbutyl.

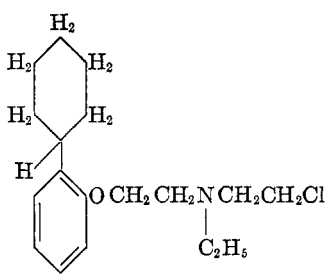
[i] Hydroxyethyl.

TABLE 21

2-(2-Biphenylyloxy)ethyl-2-haloalkylamines (364)



NO.	R	R′	X	MELTING POINT OF HYDROCHLORIDE	ANTIHISTAMINE ACTIVITY*
				°C.	*mg./kg.*
1	C_3H_7	H	Cl	166	12.5
2	CH_3	H	Cl	170	1.5
3	C_2H_5	H	Cl	166	6.0
4	C_2H_5	H	Br		
5	*i*-C_3H_7	H	Cl	133	>12.5
6	CH_2=$CHCH_2$—	H	Cl	127	>12.5
7	C_4H_9	H	Cl	118	>25.0
8	*i*-C_4H_9	H	Cl	156	
9	*i*-C_4H_9	H	Br		
10	*sec*-C_4H_9	H	Cl	158	
11	C_5H_{11}	H	Cl	115	>12.5
12	C_6H_{13}	H	Cl	102	>25.0
13	C_2H_5	CH_3	Cl	160	
14	C_3H_7	CH_3	Br		
15	CH_2=$CHCH_2$—	H	Br		
16	C_2H_5	H	H		

NO.	FORMULA	ANTIHISTAMINE ACTIVITY*
		mg./kg.
17	*m*-$C_6H_5C_6H_4OCH_2CH_2NCH_2CH_2Cl$ (N-C_2H_5)	
18		>25
19	*p*-$C_6H_5C_6H_4OCH_2CH_2CH_2NCH_2CH_2Cl$ (N-C_2H_5)	
20	*o*-$C_6H_5C_6H_4OCH_2CH_2NCH_2CH_2CH_2Cl$ (N-C_2H_5)	12.5

* Diminution of histamine-induced bronchospasm in guinea pigs. Minimum effective dose subcutaneously.

TABLE 22

Fourneau amines (407)

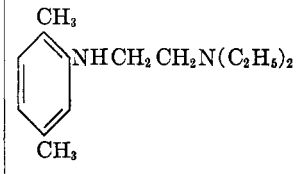
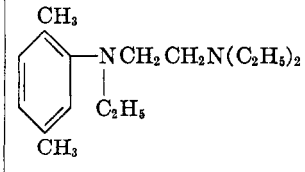
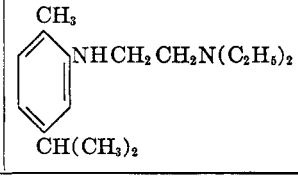
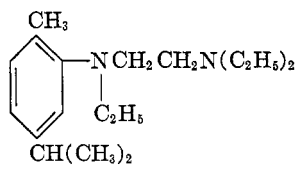
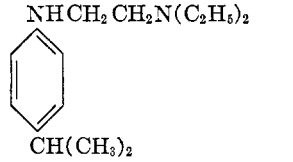
CODE NO.	FORMULA	TOXICITY TO RABBITS		ANTIHISTAMINE INDEX‡
		M.T.D.*	M.L.D.†	
		g./kg.	*g./kg.*	
F 1167....	$C_6H_5NHCH_2CH_2N(C_2H_5)_2$	0.015	0.05	1
F 1332....	o-$CH_3C_6H_4NHCH_2CH_2N(C_2H_5)_2$	0.005	0.03	1
F 1335....	$C_6H_5N(CH_3)CH_2CH_2N(C_2H_5)_2$	0.01	0.04	1.5
F 1540....	$C_6H_5NHCH_2CH_2NH_2$			Inactive
F 1551....	$C_6H_5N(C_2H_5)CH_2CH_2NH_2$	0.02	0.06	1
F 1571....	$C_6H_5N(C_2H_5)CH_2CH_2N(C_2H_5)_2$	0.005	0.02	4
F 1590....	$C_6H_5N(CH_2CH_2NH_2)_2$			Inactive (also with hydroxyl groups in o-, m-, and p-positions)
F 1599....	o-$CH_3C_6H_4N(C_2H_5)CH_2CH_2N(C_2H_5)_2$	0.005	0.02	2
F 1656....		0.005	0.03	2
F 1670....		0.0025	0.02	1.5
F 1691....		0.01	0.02	3

TABLE 22—*Concluded*

CODE. NO	FORMULA	TOXICITY TO RABBITS		ANTIHISTAMINE INDEX‡
		M.T.D.*	M.L.D.†	
		g./kg.	*g./kg.*	
F 1699....		0.0025	0.015	1
F 1709....	$C_6H_5NCH_2CH_2N(C_2H_5)_2$ $C_3H_7(i)$	0.002	0.015	3
F 1718....		0.0025	0.025	1

* Maximum tolerated dose.
† Minimum lethal dose.
‡ Antihistamine index (histamine shock).

TABLE 23

Isocyclic diamines prepared by Fourneau and Lestrange (144)

NO.	R	R′	BOILING POINT	MELTING POINT	MELTING POINT OF SALT
		$RNCH_2CH_2NH_2$ R′			
			°C.	°C.	°C.
1 (F 1540)*	C_6H_5—	H	143–145/15 mm.		205 (HCl) 187 (2HCl)
2	C_6H_5—	CH_3			205 (2HCl)
3 (F 1551)*	C_6H_5—	C_2H_5	134–135/15 mm.		201 (HCl) 237 (2HCl)
4	*p*-$CH_3C_6H_4$—	H	150/15 mm.	110	249 (HCl)
5	*o*-$CH_3C_6H_4$—	H	157–160/15 mm.		200 (HCl)
6	*m*-$CH_3C_6H_4$—	H	168/28 mm.		213 (HCl)
7	2-CH_3-5-*i*-$C_3H_7C_6H_3$—	H	122–128/0.96 mm.		222 (HCl)
8	*p*-$C_6H_5C_6H_4$—	H			284 (HCl)
9	*o*-$C_6H_5C_6H_4$—	H	155–157/1.2 mm.	69.5	225 (HCl)
10	*p*-$CH_3OC_6H_4$—	H		64	228 (HCl) 218 (2HCl) 160 (picrate)
11	*p*-$CH_3OC_6H_4$—	C_2H_5		125	189 d. (2HCl)
12	*o*-$CH_3OC_6H_4$—	H			206 (HCl) 178 (2HCl)
13	*m*-$CH_3OC_6H_4$—	H	188/24 mm.	46	184 (HCl) 163 d. (2HCl) 166 (picrate)
14	3,4-$(CH_3O)_2C_6H_3$—	H	212/24 mm.		172 (HCl) 192 d. (2HCl) 95–100 (picrate)
15	*p*-HOC_6H_4—	H	230/25 mm.	115	181 (HCl) 242 (2HCl)
16	*p*-HOC_6H_4—	—$CH_2CH_2NH_2$			227 (3HCl)
17	*p*-HOC_6H_4—	C_2H_5			194 (2HCl)
18	*o*-HOC_6H_4—	H			165 (2HCl)
19	*m*-HOC_6H_4—	H		131	200 (2HCl) 159 (picrate)
20	3,4-$(HO)_2C_6H_3$—	H			212 (2HCl)
21	*m*-$O_2NC_6H_4$—	H			200 (2HCl)
22	*m*-$H_2NC_6H_4$—	H			242 (3HCl)

TABLE 23—*Continued*

NO.	R	R′	BOILING POINT	MELTING POINT	MELTING POINT OF SALT
			°C.	°C.	°C.
23	2-$C_{10}H_7$—	H			260 (2HCl)
24	*o*-$O_2NC_6H_4$—	H	205/17 mm.		261 (HCl)
25	*o*-$H_2NC_6H_4$—	H			233 (HCl)
					212 (2HCl)
26	*p*-$O_2NC_6H_4$—	H		144	
27	*p*-$H_2NC_6H_4$—	H			195 (HCl)
					269 (3HCl)

$$RNCH_2CH_2CH_2NH_2$$
$$|$$
$$R'$$

NO.	R	R′	BOILING POINT	MELTING POINT	MELTING POINT OF SALT
			°C.	°C.	°C.
28	C_6H_5—	H	158/17 mm.		
29	*p*-HOC_6H_4—	H			250 (2HCl)
30	3,4-$(HO)_2C_6H_3$—	H			240 (2HCl)

$$RNCH_2CH_2N(C_2H_5)_2$$
$$|$$
$$R'$$

NO.	R	R′	BOILING POINT	MELTING POINT OF SALT
			°C.	°C.
31 (F 1167)*	C_6H_5—	H		135 (HCl)
32 (F 1335)*	C_6H_5—	CH_3	190/22 mm.	
33 (F 1571)*	C_6H_5—	C_2H_5	152/14 mm.	114 (HCl)
				166 (2HCl)
			159–161/18 mm.	147 (picrate)
34 (F 1709)*	C_6H_5—	*i*-C_3H_7	147–149/13 mm.	132 (HCl)
35	*p*-$CH_3C_6H_4$—	H	188/20 mm.	
			179/15 mm.	
36	*p*-$CH_3C_6H_4$—	C_2H_5	160–163/15 mm.	111 (HCl)
37 (F 1599)*	*o*-$CH_3C_6H_4$—	C_2H_5	150–155/22 mm.	96 (HCl)
38	*m*-$CH_3C_6H_4$—	C_2H_5	165–166/20 mm.	111 (HCl)
39	3,5-$(CH_3)_2C_6H_3$—	H	171–172/15 mm.	168 (HCl)
40 (F 1670)*	2,5-$(CH_3)_2C_6H_3$—	C_2H_5	147–150/15 mm.	139 (HCl)
41	2,4-$(CH_3)_2C_6H_3$—	C_2H_5	155–160/15 mm.	100 (HCl)
42 (F 1718)*	*p*-*i*-$C_3H_7C_6H_4$—	H	175–180/15 mm.	125 (HCl)
43 (F 1691)*	2-CH_3-5-*i*-$C_3H_7C_6H_3$— (carvacryl)	H	180–190/15 mm.	153 (HCl)
			132–134/1.1 mm.	
44 (F 1699)*	Carvacryl	C_2H_5	167/15 mm.	107 (HCl)
45	Carvacryl	C_4H_9	135–140/1.1 mm.	
46	*p*-$C_6H_5C_6H_4$—	H	190/1.0 mm.	139 (HCl)

TABLE 23—*Concluded*

NO.	R	R′	BOILING POINT	MELTING POINT OF SALT
			°C.	°C.
47	*o*-$C_6H_5C_6H_4$—	H	152–155/0.84 mm.	125 (HCl)
48	*p*-$CH_3OC_6H_4$—	H	186–187/18 mm.	129 (HCl)
49	*p*-$CH_3OC_6H_4$—	C_2H_5	189–190/24 mm.	128 (HCl)
50	*m*-$CH_3OC_6H_4$—	H	198/27 mm.	119 (HCl)
51	2-$C_{10}H_7$—	H	165–167/0.7 mm.	143 (HCl)
52	C_6H_5—	—$CH_2CH_2N(C_2H_5)_2$	151/1.2 mm.	210 (2HCl)
53	Carvacryl	—$CH_2CH_2N(C_2H_5)_2$	150–155/1.1 mm.	173 (2HCl)
54	*p*-HOC_6H_4—	H	200/30 mm.	179 (picrate) Dihydrochloride hygroscopic
55	*p*-HOC_6H_4—	C_2H_5		Dihydrochloride hygroscopic
56	*m*-HOC_6H_4—	C_2H_5	205/30 mm.	Dihydrochloride hygroscopic

$$RNCH(CH_3)CH_2N(C_2H_5)_2$$
$$|$$
$$R$$

NO.	R	R′	BOILING POINT
			°C.
57	C_6H_5—	H	149/14 mm.
58	*p*-$CH_3OC_6H_4$—	H	184/18 mm.
59	*m*-$CH_3OC_6H_4$—	H	188/16 mm.
60	*p*-HOC_6H_4—	H	192–194/14 mm.
61	*m*-HOC_6H_4—	H	195/17 mm.

NO.	FORMULA	BOILING POINT
		°C.
62	$C_6H_5NHCH_2CH_2NHCH_3$	143–145/18 mm.

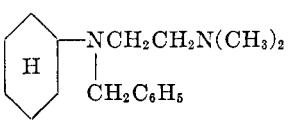
* Fourneau code number.

TABLE 24

Rhône-Poulenc isocyclic amines (200, 443)

$C_6H_5NCH_2CH_2NR'_2$
|
R

Rhône-Poulenc code number	R	R′	Rhône-Poulenc code number	R	R′
RP 2236	H	CH_3	RP 2347	*i*-C_3H_7	CH_3
RP 2315 (F 1571)*	C_2H_5	C_2H_5	RP 2349	$CH_2{=}CHCH_2$—	CH_3
RP 2323	$C_6H_5CH_2$—	C_2H_5	RP 2352	$C_6H_5CH_2CH_2$—	CH_3
RP 2325	C_2H_5	CH_3	RP 2354	*p*-$CH_3OC_6H_4CH_2$—	CH_3
RP 2337	CH_3	CH_3	RP 2355	*p*-$C_2H_5OC_6H_4CH_2$—	CH_3
RP 2338	*n*-C_4H_9	CH_3	RP 2357	C_2H_5	CH_3
RP 2339 (Antergan)	$C_6H_5CH_2$—	CH_3	RP 2358	C_2H_5	C_4H_9
RP 2342	*n*-C_3H_7	CH_3			

Rhône-Poulenc code number	formula
RP 2360	$C_6H_5N(CH_2CH_2CH_2N(CH_3)_2)(CH_2C_6H_5)$
RP 2368	$C_6H_5N[CH_2CH_2N(CH_3)_2]_2$
RP 2378	*p*-$H_2NC_6H_4N(CH_2CH_2N(CH_3)_2)(CH_2C_6H_5)$
RP 2488	$C_6H_5N(CH_2C(CH_3)_2CH_2N(CH_3)_2)(C_4H_9)$
RP 2497	
RP 2503	$C_6H_5CH_2N(CH_2CH_2N(CH_3)_2)(CH_2C_6H_5)$
RP 2504	$C_6H_5N(CH(CH_3)CH_2N(CH_3)_2)(C_2H_5)$
RP 2511	$C_6H_5N(CH(CH_3)CH_2N(CH_3)_2)(C_4H_9)$
RP 2565	$(C_6H_5)_2NCH_2CH_2N(CH_3)_2$

* Fourneau code number.

TABLE 24—*Continued*

RHÔNE-POULENC CODE NUMBER	FORMULA
RP 2612	$C_6H_5N(C_6H_{13}(n))CH_2CH_2N(CH_3)_2$
RP 2614	$C_6H_5N(C_7H_{15}(n))CH_2CH_2N(CH_3)_2$
RP 2621	$C_6H_5N(CH_2CH{=}CHC_6H_5)CH_2CH_2N(CH_3)_2$
RP 2630	$C_6H_5N(CH_2CH_2OCH_2C_6H_5)CH_2CH_2N(CH_3)_2$
RP 2637	$C_6H_5N(CH_2C_6H_4OH\text{-}p)CH_2CH_2N(CH_3)_2$
RP 2639	$p\text{-}CH_3C_6H_4N(CH_2C_6H_5)CH_2CH_2N(CH_3)_2$
RP 2665	$C_6H_5N(C_2H_5)CH_2CH_2CH_2N(CH_3)_2$
RP 2650	$C_6H_5N(C_2H_5)CH_2CH_2NH_2$
RP 2744	$C_6H_5N(C_6H_{11})CH_2CH_2N(CH_3)_2$
RP 2757	$C_6H_5N(C_5H_{11})CH_2CH_2N(CH_3)_2$
RP 2762	$C_6H_5N(CH_2C_6H_5)CH_2CH_2\overset{+}{N}(CH_3)_3\ I^-$
RP 2768	$C_6H_5N(CH_2C_6H_4CH(CH_3)_2\text{-}p)CH_2CH_2N(CH_3)_2$

TABLE 24—*Concluded*

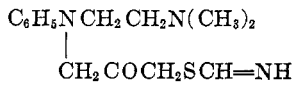
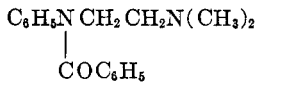
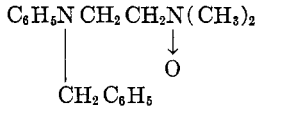
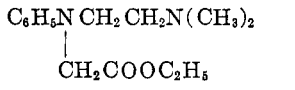
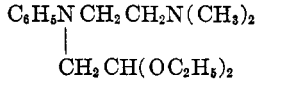
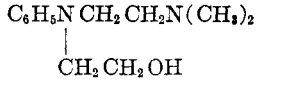
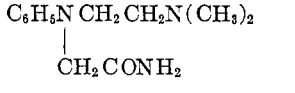
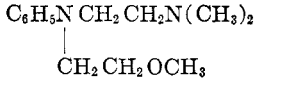
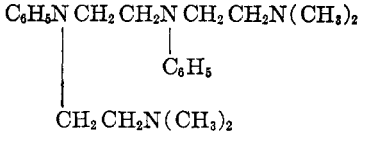
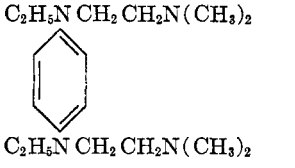
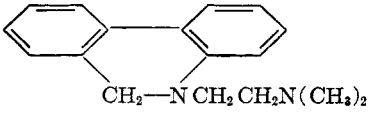
RHÔNE-POULENC CODE NUMBER	FORMULA
RP 2776	
RP 2813	
RP 2835	
RP 2846	
RP 2875	
RP 2881	
RP 2886	
RP 2887	
RP 2889	
RP 2902	
RP 3110	

TABLE 24A

Antihistamine activity of aniline derivatives (443)

NO.	R	ANTIHISTAMINE ACTIVITY	
		Aerosol*	Ileal spasm†
	$C_6H_5N(C_2H_5)CH_2CH_2R$		
		mg.	
1	$-NH_2$	Inactive	0
2 (RP 2325)	$-N(CH_3)_2$	5	1/15
3 (F 1571)	$-N(C_2H_5)_2$	10	1/100
4	$-N(C_4H_9)_2$	200	Inactive
	$C_6H_5N(C_2H_5)R$		
5	$-CH_2CH_2CH_2N(CH_3)_2$	1.5	1/50
6	$-CH_2CH(CH_3)N(CH_3)_2$	100	
7	$-CH_2CH_2CH_2CH_2N(CH_3)_2$	Inactive	
	$C_6H_5N(CH_2C_6H_5)CH_2CH_2R$		
8 (Antergan)	$-N(CH_3)_2$	1	1
9	$-N(C_2H_5)_2$	20	1/6
10	$-\overset{+}{N}(CH_3)OH^-$	10	
11	$-N(CH_3)_2 \rightarrow O$	10	1/50
	$C_6H_5N(CH_2C_6H_5)R$		
12	$-CH_2CH_2CH_2N(CH_3)_2$	20	1/15
13	$-CH_2CH(CH_3)N(CH_3)_2$	25	
	$C_6H_5N(CH_2CH_2N(CH_3)_2)R$		
14	H	Inactive	1/100
15	CH_3	50	1/100
16	*n*-C_3H_7	2.5	1/8
17	*n*-C_4H_9	2.5	1/4
18	*n*-C_5H_{11}	2.5	

TABLE 24A—*Concluded*

NO.	R	ANTIHISTAMINE ACTIVITY	
		Aerosol*	Ileal spasm†
19	n-C_6H_{13}	8	1/10
20	n-C_7H_{15}	50	1/30
21	i-C_3H_7	20	1/50
22	$-CH_2CH{=}CH_2$	15	1/15
23	Cyclo-C_6H_{11}	Inactive	1/100
24	$-CH_2CH_2OH$	Inactive	
25	$-CH_2CH_2OCH_3$	2.5	1/4
26	$-CH_2CH_2OC_2H_5$	2	1
27	$-CH_2CH_2COOC_2H_5$	20	
28	$-CH_2COSCH{=}CH_2$	1.2	1/1.2
29	$-COC_6H_5$	10	
30	$-CH_2CH_2N(CH_3)_2$	0	0
31	$-C_6H_5$	50	
32	$-CH_2CH{=}CHC_6H_5$	20	

* Dose of antihistamine in milligrams to prevent bronchospasm by inhalation of an aerosol of histamine.

† Antihistamine activity on isolated guinea-pig intestine. Antergan = 1.

TABLE 25

Isocyclic alkylenediamines

NO.	R	R′	BOILING POINT	MELTING POINT OF SALT	REFERENCES
		$RNCH_2CH_2N(CH_3)_2$ R			
			°C.	°C.	
1 (RP 2339).....	C_6H_5—	$C_6H_5CH_2$—	157–158/1 mm.	208 (HCl)	(64)
			195–196/0.03 mm.	202 (HCl)	(228, 396)
				178 (2HCl)	(200)
				158 (CH_3I)	(211)
				131 (CH_3Br)	(211)
2 (RP 2503).....	$C_6H_5CH_2$—	$C_6H_5CH_2$—		262 (HCl)	(65)
3 (RP 2565).....	C_6H_5—	C_6H_5—		254 (HCl)	(65)
			160–175/6 mm.		(52, 146)
4 (RP 2349).....	C_6H_5—	CH_2=$CHCH_2$—	138–141/11 mm.	161 (HCl)	(228, 396)
5.....	*o*-$CH_3OC_6H_4$—	$C_6H_5CH_2$—	200–206/11 mm.		(228, 396)
6 (RP 2352).....	C_6H_5—	$C_6H_5CH_2CH_2$—	210–211/12 mm.		(228, 396)
7 (RP 2354).....	C_6H_5—	*p*-$CH_3OC_6H_4CH_2$—	225–227/12 mm.		(228, 396)
				184 (CH_3I)	(211)
8 (RP 2639).....	*o*-$CH_3C_6H_4$—	$C_6H_5CH_2$—	181–184/11 mm.		(228, 396)
9.....	*p*-$CH_3OC_6H_4$—	$C_6H_5CH_2$—	219–221/12 mm.		(228, 396)
			167–169/0.6 mm.	182 (HCl)	(230)

10	2,5-$(CH_3O)_2C_6H_3$—	$C_6H_5CH_2$—	141–143/0.1 mm.		(228, 396)
11	*o*-$C_2H_5OC_6H_4$—	$C_6H_5CH_2$—	200–203/10 mm.		(228, 396)
12	C_6H_5—	*m*-$CH_3OC_6H_4$—	217–218/12 mm.		(228, 396)
13	*o*-$O_2NC_6H_4$—	H	129–135/2 mm.	188 (HCl)	(415)

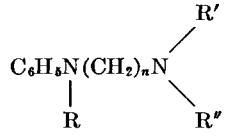
$$RNCH_2CH_2CH_2N(CH_3)_2$$
$$|$$
$$R'$$

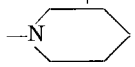
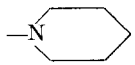
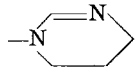
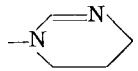
14	*o*-$CH_3OC_6H_4$—	H		153 (HCl)	(396)
15	*o*-$CH_3OC_6H_4$—	$C_6H_5CH_2$—	210/11 mm.	152 (HCl)	(396)
16 (RP 2360)	C_6H_5—	$C_6H_5CH_2$—	170–175/2 mm.	122 (HCl) 127 (picrate) 158 (2HCl)	(64, 200) (200) (200)

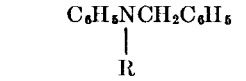
$$RN(CH_2)_nN(C_2H_5)_2$$
$$|$$
$$R'$$

NO.	R	R′	*n*	BOILING POINT	MELTING POINT OF HYDROCHLORIDE	REFERENCES
				°C.	°C.	
17 (F 1167)	C_6H_5—	H	3		123	(396)
18	$C_6H_5CH_2$—	H	3	218–219/10 mm.	132	(396)
19 (F 1571) (RP 2315)	C_6H_5—	C_2H_5	2	149–150/11 mm.		(396)
20 (RP 2323)	C_6H_5—	$C_6H_5CH_2$—	2	209–210/11 mm.	170	(228, 396)

TABLE 25—*Continued*

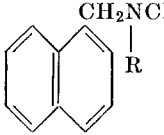


NO.	R	R′	R″	*n*	BOILING POINT	MELTING POINT OF SALT OR BASE	REFERENCES
					°C.	°C.	
21	$C_6H_5CH_2$—	H	CH_3	2	210–212/13 mm.	175 (HCl)	(228, 396)
22	$C_6H_5CH_2$—	H	C_2H_5	2	206–208/14 mm.	194 (HCl)	(396)
23	$C_6H_5CH_2$—			2	201–205/0.1 mm. 235/13 mm.	206 (HCl)	(323, 396) (228)
24	*m*-$CH_3OC_6H_4CH_2$—			2	215–218/0.8 mm.		(228, 396)
25	H			1		190 (HCl)	(396)
26	$C_6H_5CH_2$—			1	143 (base)	143 (base) 214 (HCl)	(396)



NO.	R	BOILING POINT	MELTING POINT OF SALT	REFERENCES
		°C.	°C.	
27	$-CH_2CH_2N(C_6H_5)_2$	173–174/2 mm.	170 (HCl)	(64)
28	$-CH_2CH_2\overset{+}{N}(CH_3)_2[Br^-]$		183 (HCl)	(65)
29 (RP 2762)	$-CH_2CH_2\overset{+}{N}(CH_3)_3[I^-]$		152 (HCl)	(65)
30	Isoamyl	169–171/2–3 mm.	183 (HCl)	(65)
31	$-CH_2CHOHCH_2N(CH_3)_2$			(208)
32	$-CH_2CH(CH_3)N(CH_3)_2$			(209)
33	$-CH_2CH(CH_3)N(C_2H_5)_2$			(209)

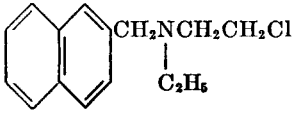
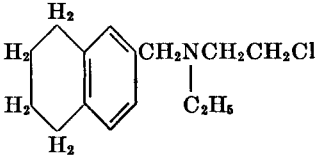
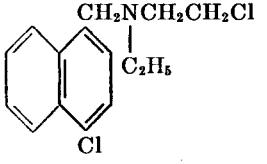
N-(2-Haloalkyl)-1-naphthalenemethylamine derivatives (265)



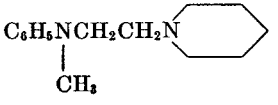
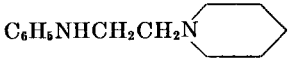
NO.	R	X	ANTIHISTAMINE ACTIVITY*	NO.	R	X	ANTIHISTAMINE ACTIVITY*
			mg./kg.				*mg./kg.*
34	CH_3	Cl	0.05	41	*sec*-C_4H_9	Cl	12.5
35	C_2H_5	Cl	0.025	42	*i*-C_4H_9	Cl	>12.5
36	C_2H_5	Br (HBr)	0.03	43	*n*-C_5H_{11}	Cl	>12.5
37	*n*-C_3H_7	Cl	1.0	44	*n*-C_6H_{13}	Cl	>25.0
38	*i*-C_3H_7	Cl	<3.0	45	$-CH_2CH_2OC_2H_5$	Cl	1.5
39	Allyl	Cl	3.0	46	$-CH_2CH_2Cl$	Cl	25.0
40	*n*-C_4H_9	Cl	12.5	47	C_2H_5	OH	>25.0

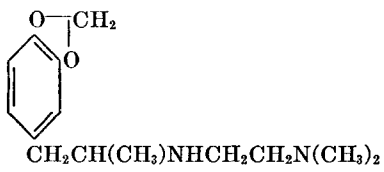
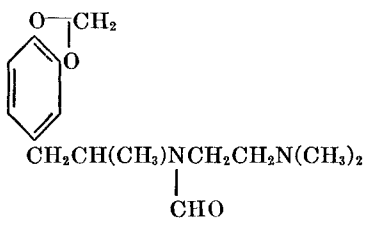
TABLE 25—*Concluded*

N-(Haloalkyl)naphthalenealkylamines

NO.	FORMULA	ANTIHISTAMINE ACTIVITY*
		mg./kg.
48		
49		
50		>12.5

Miscellaneous diamines†

NO.	FORMULA	BOILING POINT	MELTING POINT OF SALT	REFERENCES
		°C.	°C.	
51				(323)
52				(323)

53.....		143–145/5 mm.	208 (2HCl) 196 (picrate)	(307)
54.....		193–195/5 mm.		(307)
55.....	$C_6H_5NCH_2CH_2NH_2$ $\lvert$ $CH_2C_6H_5$	206–208/14 mm.	194 (HCl)	(288)
56.....	$C_6H_5NCH_2CH_2CH_2N(C_2H_5)_2$ $\lvert$ $CH_2C_6H_5$	218–219/10 mm.	132 (HCl)	(288)
57.....	$C_6H_5NCH_2CH(OCH_3)CH_2N(CH_3)_2$ $\lvert$ $CH_2C_6H_5$	208–210/11 mm.	152 (HCl)	(288)
58.....	$C_6H_5NHCH_2CH_2N(C_2H_5)_2$	149–150/11 mm.		(288)

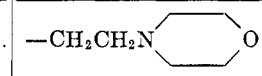
* Minimum effective dose (subcutaneous) for diminution of histamine-induced bronchospasm in guinea pigs.

† Added after the table had been assembled.

TABLE 26

Benzhydrylamines tested by Loew, Kaiser, and Moore (263)

$(C_6H_5)_2CHNHR$

NO.	R	ANTIHISTAMINE ACTIVITY*
1		<2
2	$-CH_2CH_2N(C_2H_5)_2$	<2
3	$-CH_2CH_2CH_2N(C_2H_5)_2$	<1
4	$-CH_2CH_2NHC_2H_5$	<1
	NAME	
5	Benadryl	33

* Efficacy in the prevention of fatal histamine-induced bronchoconstriction in guinea pigs.

TABLE 27

C-Substituted benzhydrylamines (4)

$$\begin{array}{l} RCHNHR'' \\ | \\ R' \end{array}$$

NO.	R	R′	R″
1	C_6H_5-	C_6H_5-	H
2	C_6H_5-	C_6H_5-	C_6H_{13}
3	p-$CH_3C_6H_4-$	C_6H_5-	H
4	p-$CH_3C_6H_4-$	p-$CH_3C_6H_4-$	H
5	p-$CH_3OC_6H_4-$	C_6H_5-	H
6	p-$CH_3OC_6H_4-$	C_6H_5-	$-CH_2CH_2N(C_2H_5)_2$
7	p-$CH_3OC_6H_4-$	C_6H_5-	$-COCH_2CH_2COOH$
8	2,4-$(CH_3O)_2C_6H_3-$	C_6H_5-	H
9	2,5-$(CH_3O)_2C_6H_3-$	C_6H_5-	H
10	3,4-$(CH_3O)_2C_6H_3-$	C_6H_5-	H
11	p-ClC_6H_4-	C_6H_5-	H
12	p-ClC_6H_4-	p-ClC_6H_4-	H
13	p-$HOOCC_6H_4-$	C_6H_5-	H
14	p-$CH_3OC_6H_4-$	C_6H_5-	$-CH_2CH_2OCH_3$
15	p-$CH_3OC_6H_4-$	p-$CH_3OC_6H_4-$	$-CH_2CH_2N(C_2H_5)_2$
16	p-$C_6H_5OC_6H_4-$	C_6H_5-	H
17	p-$C_6H_5OC_6H_4-$	p-$CH_3OC_6H_4-$	H

TABLE 28

N-Substituted benzhydrylamines (98)

$C_6H_5CHC_6H_5$
|
RNR′

NO.	R	R′	MELTING POINT	MELTING POINT OF SALT	YIELD
			°C.	°C.	*per cent*
1.....	CH_3	*p*-$CH_3OC_6H_4CH_2$—	62		83
2.....	CH_3	—CH_2CH_2OH		159 (HCl)	62
3.....	$C_6H_5CH_2$—	—CH_2CH_2OH		179 (HCl)	75
4.....	CH_3	—CH_2CH_2Cl		191 (HCl)	90
5.....	$C_6H_5CH_2$—	—CH_2CH_2Cl		171 (HCl)	63
6.....	CH_3	—$CH_2CH_2N(CH_3)_2$		227 (2HCl)	67
7.....	CH_3	—CH_2CH_2N⟨ ⟩O		237 (2HCl)	70
8*....	$C_6H_5CH_2$—	—$CH_2CH_2N(CH_3)_2$		102 (maleate)	

* Reference 70.

TABLE 29

Benzhydryl-2-haloalkylamines (259, 363)

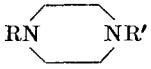
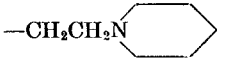
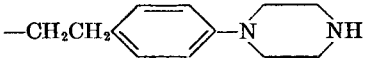
$(C_6H_5)_2CHNCH_2CHX$
| |
R R′

NO.	R	R′	X	MELTING POINT OF HYDROCHLORIDE	ANTIHISTAMINE ACTIVITY*
				°C.	*mg./kg.*
1....	CH_3	H	Cl	192	12.5
2....	C_2H_5	H	Cl	169	12.5
3....	C_2H_5	H	Br		
4....	C_3H_7	H	Cl		25.0
5....	*i*-C_3H_7	H	Cl		25.0
6....	Allyl	H	Cl		
7....	C_6H_{13}	H	Cl		
8....	*n*-C_4H_9	H	Cl		
9....	*sec*-C_4H_9	H	Cl		12.5
10....	CH_3	CH_3	Br		
11....	C_2H_5	CH_3	Cl		
12....	Allyl	CH_3	Cl		
13....	C_3H_7	CH_3	Cl		

* Dose in milligrams per kilogram which failed to diminish histamine-induced bronchospasm in guinea pigs (subcutaneous).

TABLE 30

N-Isocyclic-substituted heterocycles prepared by Cerkovnikov and coworkers (73, 74, 75)

NO.	R	R′	BOILING POINT	MELTING POINT	YIELD	L.D.$_{100}$	ANTIHISTAMINE ACTIVITY*
							
			°C.	°C.	*per cent*	*mg.*	*mg.*
1....	C_6H_5—	*p*-$(C_2H_5)_2NC_6H_4$—		136 234 (3HCl) 185 d. (tripicrate)	48.9	70	>50
2....	C_6H_5—	*p*-$CH_3OC_6H_4$—	192–194/0.4 mm.	165 216 (2HCl)	47.3	30	25–50
3....	C_6H_5—	*p*-HOC_6H_4—		283 d. (2HBr)	100	25	>25
4....	C_6H_5—	—CH_2CH_2OH	172–175/0.5 mm.	83 187 (2HCl)	43.4	30	25–50
5....	C_6H_5—	$C_6H_5COOCH_2CH_2$—		214 (HCl) 197 (2HCl)	100	60	25–50
6....	C_6H_5—	—$CH_2CH_2N(CH_3)_2$	228–230/0.5 mm.	267 (2HCl) 196 d. (dipicrate)	51.8	15	12.5
7....	C_6H_5—		195–200/0.6 mm.	283 (3HCl) 169 d. (tripicrate)	31.2	20	>25
8....	C_6H_5—			173 269 (4HCl) 213 (tetrapicrate)	61.9	10	>25

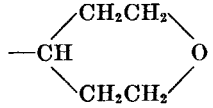
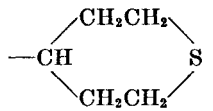
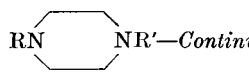
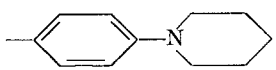
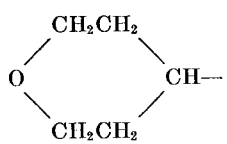
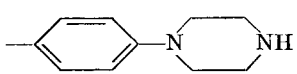
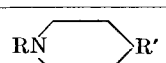
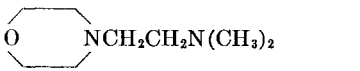
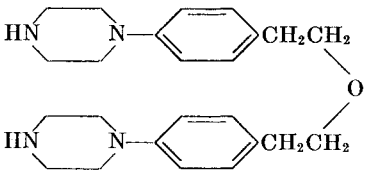
9....	C_6H_5—		228–230/0.4 mm.	122 246 (HCl) 269 (2HBr) 203 (picrate)		15	20–40
10....	C_6H_5—		220–230/0.5 mm.	231 (2HCl) 189 (picrate)	21.3		
11....	C_6H_5—	—$CH_2CH_2NH_2$	175–180	267 (3HCl) 204 d. (picrate)	52.5	25	>25
12....	*p*-HOC_6H_4—	—CH_2CH_2OH	198–200/0.2 mm.	220 (2HCl) 205 (dipicrate)		30	>100
13....	*p*-$CH_3OC_6H_4$—	H				1.5	>20
14....	*p*-$CH_3C_6H_4$—	H				1.5	>20
15....	1-$C_{10}H_7$—	H				1.0	>20
16....	C_6H_5—	—$COCH_3$				4	>20
17....	C_6H_5—	$C_6H_5CH_2$—				25	>40
18....	C_6H_5—	—$CH_2CH_2N(C_2H_5)_2$	235–236/0.4 mm.	185 (2HCl) 183 (dipicrate)	36.4	70	>50
19....	$C_6H_5CH_2$—	—$CH_2CH_2N(CH_3)_2$	190–210/0.4 mm.	237 (2HCl) 223 (dipicrate)	56.4	70	25

TABLE 30—*Concluded*

NO.	R	R′	BOILING POINT	MELTING POINT	YIELD	L.D.$_{100}$	ANTIHISTAMINE ACTIVITY*
		 *Continued*					
			°C.	°C.	*per cent*	*mg.*	*mg.*
20....	C_6H_5—			193 270 (3HCl) 206 (dipicrate)	39.6	30	>50
21....				175 226 (picrate)			
22....	C_6H_5—	—$CH_2CH_2CH_2N(CH_3)_2$		180	63	20	25
23....	C_6H_5—	[—$CH_2CH_2CH_2N(CH_3)_2$]$_2$		241 (4HCl) 197 (tetrapicrate)	59	4	15
							
24....	C_6H_5—	—$N(CH_3)_2$	123–126/0.5 mm.	48 253 (2HCl) 204 (dipicrate)		6	30
25....	CH_3	—$N(CH_3)_2$	174–175	312 (2HCl)	31.6	45	>50
26....	C_6H_5—	—$CH_2N(CH_3)_2$	200–202/20 mm.	125 (picrate) 164 (picrolonate)	45.3	0.75	>2
27....	—$CH_2CH_2N(CH_3)_2$	H	192–194	289 (2HCl)	33.3	25	100

	FORMULA					
28....		93–94/20 mm.	278 (2HCl) 219 (dipicrate) 234 (dipicrolonate)	61	25	>50
29....		265–267	245 (HBr) 192 d. (tetrapicrate)	25.5	2.5	15

* Lethal dose in milligrams to kill mice (mode of administration not stated in *Chemical Abstracts*).

† Milligrams necessary to protect guinea pigs against one lethal dose of histamine.

TABLE 31

Dibenzylpiperazines (243, 284)

NO.	R, R′	MELTING POINT	MELTING POINT OF HYDROCHLORIDE
		°C.	°C.
1.....	H	92	240 d.
2.....	NO_2		
3.....	NH_2		
4.....	OH		

TABLE 32

Unsymmetrically disubstituted piperazines (5, 15)

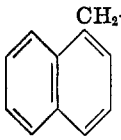
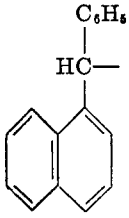
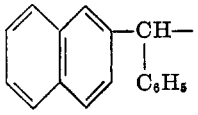
NO.	R	MELTING POINT OF HYDROCHLORIDE OR BASE	YIELD
		°C.	*per cent*
1.....	*o*-$O_2NC_6H_4$—	235 (HCl)	60
2.....	*p*-$O_2NC_6H_4$—	270 (HCl)	90
3.....	*p*-$H_2NC_6H_4$—	274 (HCl)	61
4.....	2,4-$(O_2N)_2C_6H_3$—	234 (HCl)	100
5.....		245 (2HCl)	20
6.....		213 (2HCl)	90
7.....		220 (2HCl)	65

TABLE 32—*Concluded*

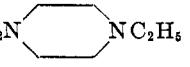
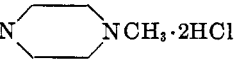
NO.	R	MELTING POINT OF HYDROCHLORIDE OR BASE	YIELD
		°C.	*per cent*
8.....	p-$C_6H_5C_6H_4CH(C_6H_5)$—	220 (2HCl)	85
9.....	p-$C_6H_5OC_6H_4CH(C_6H_5)$—	204 (2HCl) 91 (base)	65
10.....	$C_6H_5COCH(C_6H_5)$—	228 (2HCl)	90
11.....	$C_6H_5CHOHCH(C_6H_5)$—	234 (2HCl)	60
12.....	p-$HOC_6H_4COCH(C_6H_5)$—	216 d. (2HCl)	65
13.....	$C_6H_5CH_2$—	250 d. (2HCl)	
	FORMULA		
14.....		250 d. (2HCl)	

TABLE 33

N-Benzhydryl-N'-methylpiperazines (16)



NO.	BENZHYDRYL SUBSTITUTION	BOILING POINT	MELTING POINT OF SALT OR BASE
		°C.	°C.
1.....	None		>255 d. (2HCl)
2.....	Methochloride hydrochloride		240 d. (2HCl)
3.....	1,2,3,4,5,6-Hexahydro		249 d. (2HCl)
4.....	2-Cl		248 (2HCl)
5.....	3-Cl		252 (2HCl)
6.....	4-Cl	137–145/0.12 mm.	216.5 (2HCl)
7.....	2-Br		252 d. (2HCl) 78 (base)
8.....	4-Br		228 (2HCl)
9.....	4-CH_3-4'-Cl		226 (2HCl)
10.....	2,4-Cl_2		233 (2HCl)
11.....	3,4-Cl_2		238 (2HCl)

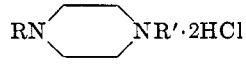
TABLE 33—*Concluded*

NO.	BENZHYDRYL SUBSTITUTION	BOILING POINT	MELTING POINT OF SALT OR BASE
		°C.	°C.
12.....	4,4′-Cl_2		249 (2HCl)
			78 (base)
13.....	4-Cl-4′-Br		243 (2HCl)
			101 (base)
14.....	2,4,4′-Cl_3		258 (HCl)
15.....	2-OCH_3		196 d. (2HCl)
16.....	3-OC_2H_5	140–150/0.04 mm.	228 (2HCl)
			77 (base)
17.....	4-OCH_3		192 (2HCl)
18.....	4′-OCH_3-1,2,3,4,5,6-hexahydro		218 d. (2HCl)
19.....	2-OCH_3-5-Cl		227 (2HCl)
			125 (base)
20.....	4-OCH_3-3-Cl		221 d. (2HCl)
21.....	4-OCH_3-4′-Cl		184 d. (2HCl)
			65 (base)
22.....	4-OCH_3-3-Br		209 (2HCl)
23.....	4-OCH_3-2′-Br		213 d. (2HCl)
24.....	4-OCH_3-2,4′-Cl_2	140*/0.0002–0.0003 mm.	172 (2HCl)
25.....	4-OCH_3-3,4′-Cl_2	140*/0.0002–0.0003 mm.	211 (2HCl)
26.....	4,4′-$(OCH_3)_2$-3,3′-Cl_2		227 (2HCl)
			99 (base)

* Bath temperature.

TABLE 34

Antihistaminic activity of piperazines (68)*



COMPOUND NO.	R	R′	ANTIHISTAMINE ACTIVITY†
46-125.....	$C_6H_5CH_2$—	CH_3	Slight
46-126.....	$C_6H_5CH_2$—	—CH_2CH_2	Very slight
895.....	$C_6H_5CH_2$—	*n*-Lauryl	None
47-83.....	$(C_6H_5)_2CH$—	CH_3	100 per cent
47-282.....	*p*-Cl C_6H_4 $\underset{\displaystyle C_6H_5}{\overset{\displaystyle \vert}{CH}}$—	CH_3	400 per cent

* Compounds prepared at the laboratories of Burroughs Wellcome and Company.

† Antihistamine potency in terms of Benadryl = 100 per cent.

TABLE 35

*Isocyclic-substituted piperazines (183, 184)**

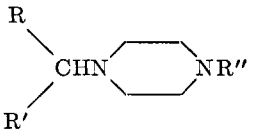
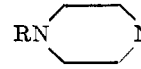
NO.	R	R′	R″	BOILING POINT	MELTING POINT OF SALT OR BASE
					
				°C.	°C.
1...	C_6H_5—	C_6H_5—	CH_3		260 (2HCl) 108 (base)
2...	C_6H_5—	C_6H_5—	—CH_2OH		190 (2HCl)
3...	C_6H_5—	C_6H_5—	C_2H_5		242 (2HCl)
4...	C_6H_5—	C_6H_5—	—CH_2CH_2OH		229 d. (2HCl)
5...	C_6H_5—	C_6H_5—	n-C_4H_9		248 d. (2HCl)
6...	C_6H_5—	C_6H_5—			295 (0.5-H_2SO_4)
7...	C_6H_5—	C_6H_5—	—$CH_2CH_2N(CH_3)_2$	162–164/0.7 mm.	257 (2HCl)
8...	C_6H_5—	p-FC_6H_4—	CH_3	140–141/0.6 mm.	231 (HCl) 64 (base)
9...	C_6H_5—	p-ClC_6H_4—	CH_3	160–161/0.5 mm.	224 (HCl)
10...	C_6H_5—	p-BrC_6H_4—	CH_3	175–176/0.8 mm.	250 (HCl)
11...	C_6H_5—	p-IC_6H_4—	CH_3	180–181/0.5 mm.	261 (HCl)
12...	C_6H_5—	o-ClC_6H_4—	CH_3	179–180/2 mm.	273 (HCl)
13...	C_6H_5—	m-ClC_6H_4—	CH_3	177/1.5 mm.	250 (HCl)
14...	C_6H_5—	p-$CH_3C_6H_4$—	CH_3	159–160/1 mm.	229 (HCl)
15...	C_6H_5—	p-$CH_3OC_6H_4$—	CH_3	168–169/0.7 mm.	195 (2HCl)
16...	Cyclo-C_6H_{11}	p-ClC_6H_4—	CH_3		279 d. (2HCl)
17...	n-C_3H_7	p-ClC_6H_4—	CH_3	142–143/1.7 mm.	177 (2HCl)
18...	p-ClC_6H_4—	p-ClC_6H_4—	CH_3	168/0.3 mm.	246 (2HCl)
19...	C_6H_5—	p-ClC_6H_4—	C_2H_5		228 (2HCl)
20...	C_6H_5—	p-ClC_6H_4—	n-C_4H_9		255 (2HBr)
21...	C_6H_5—	p-ClC_6H_4—	—$CH_2CH_2CH_2$-CH_2OH		212 (2HCl)
22...	C_6H_5—	p-ClC_6H_4—	n-$C_{10}H_{21}$	245–250/0.4 mm.	

TABLE 35—*Continued*



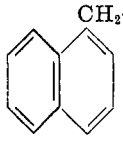
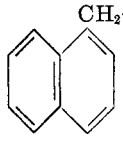
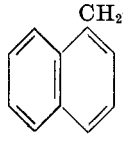
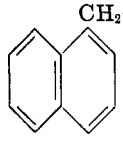
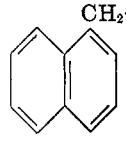
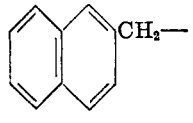
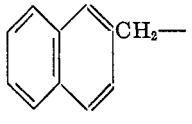
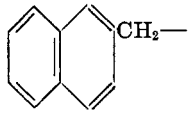
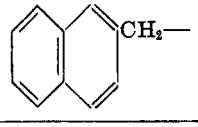
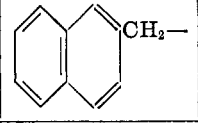
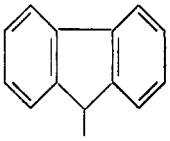
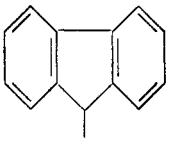
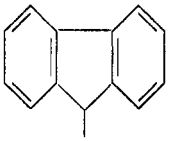
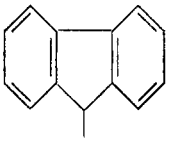
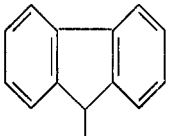
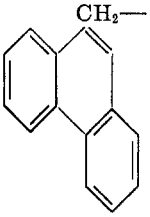
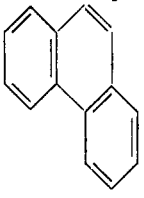
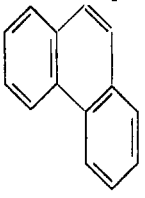
NO.	R	R′	YIELD	BOILING POINT	MELTING POINT OF SALT OR BASE
				°C.	°C.
23.....	*p*-$BrC_6H_4CH_2$—	CH_3	86		294 (2HCl)
24.....	$(C_6H_5)_2CHCH_2$—	CH_3	40		279 (2HCl)
25.....	$(C_6H_5)_2C{=}CHCH_2$—	CH_3	71	165–170/0.9 mm.	140 (HCl)
26.....		H	37	154–156/1 mm.	228 (HCl)
27.....		CH_3	100		241 (2HCl)
28.....		—CH_2CH_2OH	81		206 d. (2HCl)
29.....			27		164 (base)
30.....		H	33	155–160/1 mm.	195 (HCl)
31.....		CH_3	82		281 d. (2HCl)
32.....		—CH_2CH_2OH	33		241 d. (2HCl)
33.....			23		160 (base)

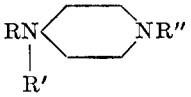
TABLE 35—*Concluded*

NO.	R	R′	YIELD	BOILING POINT	MELTING POINT OF SALT OR BASE
				°C.	°C.
34.....		H	89		285 d. (2HCl)
35.....		CH_3	57		268 d. (2HBr)
36.....		$-CH_2CH_2OH$	68		244 d. (2HCl) 144 (base)
37.....			100		292 d. (base)
38.....	CH_2— 	CH_3	43		255 d. (2HCl)
39.....	CH_2— 	CH_2— 	100		286 (2HCl) 254 (base)

* Compounds prepared at the Abbott Laboratories.

TABLE 36

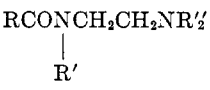
4-Aminopiperidines (340, 342)



NO.	R	R′	R″	BOILING POINT	MELTING POINT OF SALT OR BASE
				°C.	°C.
1...	H	$C_6H_5CH_2$—	CH_3	168–172/17 mm.	227 d. (dipicrate)
2...	H	$C_6H_5CH_2$—	C_2H_5	113–115/0.2 mm.	304 (2HCl) 228 d. (dipicrate)
3...	H	—CH_2CH_2OH	C_2H_5	117–119/17 mm.	219 d. (dipicrate)
4...	H	—$CH_2CH_2N(CH_3)_2$	C_2H_5	136–139/17–18 mm.	239 d. (tripicrate)
5...	$C_6H_5CH_2$—	—$CH_2CH_2N(CH_3)_2$	C_2H_5	185–188/0.7 mm.	100 (base) 195 d. (tripicrate)

TABLE 37

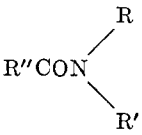
Amides of ethylenediamine (444)



NO.	R	R′	R″	BOILING POINT	YIELD
				°C.	*per cent*
1.....	C_6H_5—	C_6H_5—	CH_3	158–159/1 mm.	80
2.....	C_6H_5—	*p*-$CH_3C_6H_4$—	CH_3	159–162/0.5 mm.	78
3.....	C_6H_5—	2-C_5H_4N—	CH_3	155–158/1 mm.	74
4.....	2-C_5H_4N—*	H	CH_3	113–124/1 mm.	29
5.....	2-C_5H_4N—	C_6H_5—	CH_3	177–178/2 mm.	27
6.....	2-C_5H_4N—	C_6H_5—	CH_3	177–178/2 mm.	13
7.....	2-C_5H_4N—	*p*-$CH_3C_6H_4$—	CH_3	185–190/1 mm.	53
8.....	2-C_5H_4N—	*m*-ClC_6H_4—	CH_3	182–186/2 mm.	69
9.....	2-C_5H_4N—	*p*-ClC_6H_4—	CH_3	185–190/1.5 mm.	33
10.....	2-C_5H_4N—	*o*-$CH_3OC_6H_4$—	CH_3	183–186/1 mm.	28
11.....	2-C_5H_4N—	$C_6H_5CH_2$—	CH_3	196–200/2 mm.	47
12.....	2-C_5H_4N—	2-C_5H_4N—	CH_3	175–179/1 mm.	18
13.....	3-C_5H_4N—	H	CH_3	140–143/1 mm.	32
14.....	3-C_5H_4N—	C_6H_5—	CH_3	187–190/1 mm.	51
15.....	3-C_5H_4N—	C_6H_5—	C_2H_5	187–189/0.5 mm.	62
16.....	3-C_5H_4N—	*p*-$CH_3C_6H_4$—	CH_3	180–189/0.5 mm.	64
17.....	3-C_5H_4N—	*m*-ClC_6H_4—	CH_3	176–185/2 mm.	80
18.....	3-C_5H_4N—	*p*-ClC_6H_4—	CH_3	185–187/1 mm.	74
19.....	3-C_5H_4N—	*o*-$CH_3OC_6H_4$—	CH_3	188–192/1 mm.	80
20.....	3-C_6H_4N—	$C_6H_5CH_2$—	CH_3	193–197/2 mm.	
21.....	3-C_5H_4N—	$C_6H_5CH_2$—	C_2H_5	193–196/1 mm.	81
22.....	2-C_4H_3S—†	$C_6H_5CH_2$—	CH_3	187–193/0.5 mm.	44
23.....	3-C_5H_4N—	2-C_3H_2NS—‡	CH_3	164–169/0.5 mm.	52

TABLE 37—*Concluded*

Other amides

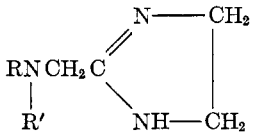


NO.	R	R′	R″	BOILING POINT	MELTING POINT	YIELD
				°C.	°C.	*per cent*
24....	C_6H_5—	2-C_5H_4N—	3-C_5H_4N—		177–178	51
25....	C_6H_5—	2-C_5H_4N—	2-C_5H_4N—		107–108	18
26....	$C_6H_5CHCH_2$— (2-C_5H_4N)	H	3-C_5H_4N—	184–187/0.5 mm.		19
27....	$C_6H_5CHCH_2$— (2-C_5H_4N)	H	2-C_5H_4N—	191–196/2 mm.		32

* Pyridyl. † Thienyl. ‡ Thiazyl.

TABLE 38

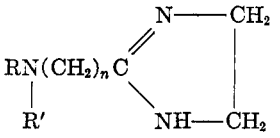
2-Isocyclic imidazolines



NO.	R	R′	MELTING POINT OF SALT OR BASE	REFERENCES
			°C.	
1.....	C_6H_5—	H	182 (HCl)	(398)
2.....	*o*-$CH_3OC_6H_4$—	H	200 (HCl) 87 (base)	(399)
3.....	*p*-HOC_6H_4—	H	225 (HCl)	(287)
4.....	*m*-HOC_6H_4—	H	194 (HCl)	(287)
5.....	*p*-$CH_3OC_6H_4$—	H	181 (HCl) 111 (base)	(287)
6.....	*p*-$CH_3C_6H_4$—	*m*-HOC_6H_4—	240 (HCl) 175 (base)	(188, 282, 287)
7.....	*p*-$CH_3C_6H_4$—	*m*-$CH_3OC_6H_4$—	151 (HCl) 93 (base)	(287)
8 (Antistine)..	C_6H_5—	$C_6H_5CH_2$—	229 (HCl) 121 (base) 159 (picrate)	(82, 83, 86, 207, 285, 396)
9.....	*p*-HOC_6H_4—	$C_6H_5CH_2$—	229 (HCl)	(84, 207, 396)
10.....	*p*-HOC_6H_4—	$C_6H_5CH_2$—	228 (HCl)	(82)
11.....	*o*-$CH_3OC_6H_4$—	$C_6H_5CH_2$—	169 (HCl)	(82, 288, 396)

TABLE 38—*Concluded*

NO.	R	R′	MELTING POINT OF SALT OR BASE	REFERENCES
			°C.	
12.....	*p*-$CH_3OC_6H_4$—	$C_6H_5CH_2$—	208 (HCl)	(82, 207, 285, 288, 396)
13.....	*o*-$C_2H_5OC_6H_4$—	$C_6H_5CH_2$—	188 (HCl)	(82, 207, 285, 288, 396)
14.....	*p*-$C_2H_5OC_6H_4$—	$C_6H_5CH_2$—	218 (HCl)	(207, 285, 288, 396)
15.....	*p*-ClC_6H_4O—	$C_6H_5CH_2$—	244 (HCl)	(82, 84, 207, 396)
16.....	C_6H_5—	*p*-$ClC_6H_4CH_2$—	277 (HCl)	(82, 84, 207)
17.....	C_6H_5—	*p*-$CH_3OC_6H_4CH_2$—	212 (HCl)	(82, 84, 207)
18.....	*p*-ClC_6H_4—	*p*-$ClC_6H_4CH_2$—	264 (HCl)	(82, 84, 207)
19.....	C_6H_5—	$C_6H_5CH_2CH_2$—	222 (HCl)	(82, 85, 207, 285)
20.....	1-$C_{10}H_7$—	$C_6H_5CH_2$—	209 (HCl)	(82, 207, 285, 288, 396)
21.....	2-$C_{10}H_7$—	$C_6H_5CH_2$—	232 (HCl)	(82, 84, 207)
22.....	*p*-$C_6H_5OC_6H_4$—	$C_6H_5CH_2$—	213 (HCl)	(82, 84, 207)



NO.	R	R′	*n*	MELTING POINT OF SALT	REFERENCES
				°C.	
23.....	C_6H_5—	$C_6H_5CH_2$—	2	116 (HCl)	(207, 288, 396)
24.....	*o*-$CH_3OC_6H_4$—	$C_6H_5CH_2$—	2	169 (HCl)	(285)
25.....	C_6H_5—	$C_6H_5CH_2$—	3	195 (HCl)	(82, 207, 285, 288, 396)

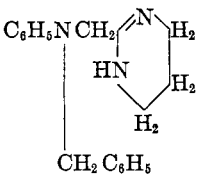
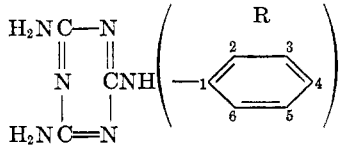
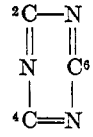
NO.	FORMULA	BOILING POINT	MELTING POINT OF SALT	REFERENCE
		°C.	°C.	
26.....		192–195/2.5 mm.	212 (HCl)	(230)

TABLE 39

Anilino-s-triazines (446)



NO.	R	MELTING POINT	YIELD
		°C.	*per cent*
1	H	284–286	82
2	2-CH_3	211–212	81
3	3-CH_3	229–230	82
4	4-CH_3	265–266	80
5	2,4-$(CH_3)_2$	239–241	92
6	2,5-$(CH_3)_2$	237–239	89
7	2-Cl	205–208	81
8	3-Cl	173–174	98
9	4-Cl	245–249	82
10	2,4-Cl_2	255–257	86
11	2,5-Cl_2	228–230	84
12	3,4-Cl_2	210–211	98
13	2-OH	257–259	87
14	3-OH	241–242	76
15	4-OH	282–283	88
16	2-OC_2H_5	203–205	76
17	3-OC_2H_5	211–212	82
18	2-NO_2	300	
19	3-NO_2	144–145	99
20	4-NO_2	300	
21	2-COOH	Indefinite	42
22	3-COOH	304–306	42
23	4-COOH	300	68
24	4-$COCH_3$		98



NO.	GROUP IN POSITION 2	GROUP IN POSITION 4	GROUP IN POSITION 6	MELTING POINT	YIELD
				°C.	*per cent*
25	$-NH_2$	$-NH_2$	Naphthylamino	>300	75
26	$-NH_2$	$-NH_2$	*N*-Methylanilino	257–259	97
27	$-NH_2$	$-NH_2$	*N*-Ethylanilino	215–217	94
28	$-NH_2$	$-NH_2$	*N*-Benzylanilino	311–314	99
29	$-NH_2$	$-NH_2$	Piperidino	216–217	22
30	$-NH_2$	$-NH_2$	Morpholino	236–240	48
31	$-NH_2$	$-NHCH_3$	Anilino	84–86	48
32	$-NH_2$	$-NHC_2H_5$	Anilino	153–155	49

TABLE 39—*Concluded*

NO.	GROUP IN POSITION 2	GROUP IN POSITION 4	GROUP IN POSITION 6	MELTING POINT	YIELD
				°C.	*per cent*
33..	$-NH_2$	$-NHCH_2C(CH_3)=CH_2$	*p*-Chloroanilino·HCl	237–239	64
34..	$-NH_2$	$-NHCH_2C(CH_3)=CH_2$	*p*-Toluidino	137–139	60
35..	$-NH_2$	$-NHC_2H_4OH$	Anilino	156–158	76
36..	$-NH_2$	$-NHC_2H_4OH$	*m*-Chloroanilino	147–150	43
37..	$-NH_2$	$-NHC_2H_4OH$	*p*-Chloranilino	173–174	40
38..	$-NH_2$	$-NHCH_2CHOHCH_3$	Anilino	138–140	
39..	$-NH_2$	$-N(CH_3)_2$	*o*-Chloroanilino	133–135	50
40..	$-NH_2$	$-N(CH_3)_2$	*p*-Chloroanilino	173–175	50
41..	$-NH_2$	$-N(CH_2CH=CH_2)_2$	*p*-Chloroanilino	137–141	
42..	$-NH_2$	$-N(CH_2CH=CH_2)_2$	*p*-Toluidino	119–121	60
43..	$-NH_2$	$-N[CH_2C(CH_3)=CH_2]_2$	*o*-Chloroanilino	78–81	44
44..	$-NH_2$	$-N[CH_2C(CH_3)=CH_2]_2$	*p*-Chloroanilino	154–157	
45..	$-NHCH_3$	$-NHCH_3$	2,5-Dichloro-anilino	153–155	76
46..	$-NHC_2H_5$	$-NHC_2H_5$	Anilino·2HCl	178–180	70
47..	$-NHC_2H_5$	$-NHC_2H_5$	*m*-Chloroanilino·HCl	165–167	95
48..	$-NHCH_2CH=CH_2$	$-NHCH_2CH=CH_2$	*o*-Chloroanilino	56–59	
49..	$-NHCH_2CH=CH_2$	$-NHCH_2CH=CH_2$	*p*-Chloroanilino	103–106	66
50..	$-NHC_2H_4OH$	$-NHC_2H_4OH$	Anilino	130–132	
51..	$-NHCH_2CHOHCH_3$	$-NHCH_2CHOHCH_3$	Anilino·HCl	150–152	
52..	$-NHCH_2COOH$	$-NHCH_2COOH$	Anilino·$3H_2O$		
53..	$-N(CH_3)_2$	$-N(CH_3)_2$	*o*-Chloroanilino	114–117	43
54..	$-N(C_2H_5)_2$	$-N(C_2H_5)_2$	Anilino	87–89	90
55..	$-N(C_2H_5)_2$	$-N(C_2H_5)_2$	*p*-Chloroanilino	134–135	76
56..	$-NH_2$	$-N(C_6H_5)C_2H_4OH$	$-N(C_6H_5)C_2H_4OH$	158–159	10
57..	$-NH_2$	$-Cl$	4-Carboxy-3-hydroxyanilino	263–266	54

TABLE 40

Rhône-Poulenc N-monoheterocyclic alkylenediamines (443)

Ethylenediamines: $RNCH_2CH_2N(CH_3)_2$ with R′ on the N

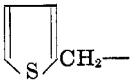
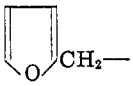
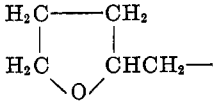
RHÔNE-POULENC CODE NO.	R	R′	ANTIHISTAMINE ACTIVITY	
			Aerosol*	Spasm
			mg./kg.	
RP 2740.....	C_6H_5-		Inactive	
RP 2747.....	C_6H_5-		1	1†
RP 2749.....	C_6H_5-		20	

TABLE 40—*Continued*

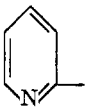
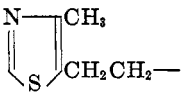
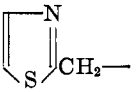
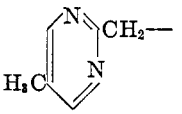
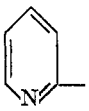
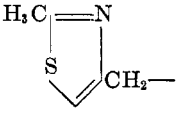
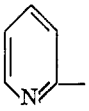
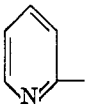
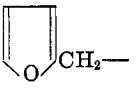
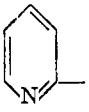
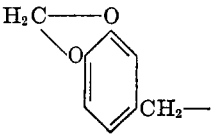
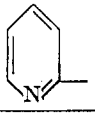
RHÔNE-POULENC CODE NO.	R	R′	ANTIHISTAMINE ACTIVITY	
			Aerosol*	Spasm
			mg./kg.	
RP 2750.....		$C_6H_5CH_2$—	0.5	1.3‡
RP 2758.....	C_6H_5—			
RP 2764.....	C_6H_5—		1	1/1.6†
RP 2765.....	C_6H_5—			
RP 2786.....		p-$CH_3OC_6H_4CH_2$—	0.1	1‡
RP 2788.....	C_6H_5—			
RP 2796.....		—$CH_2CH_2OC_2H_5$		
RP 2803.....			0.5	1/6‡
RP 2833.....			5	1/8‡
RP 2843.....		p-$C_2H_5OC_6H_4CH_2$—	0.5	1‡

TABLE 40—*Continued*

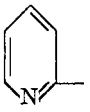
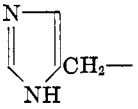
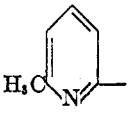
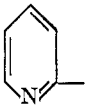
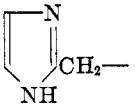
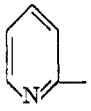
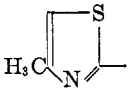
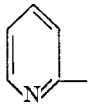
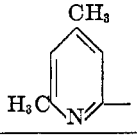
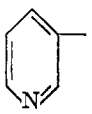
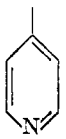
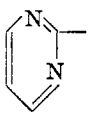
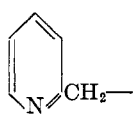
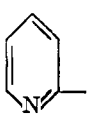
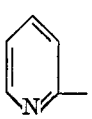
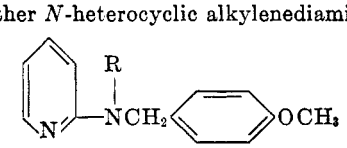
Rhône-Poulenc code no.	R	R′	Antihistamine activity	
			Aerosol*	Spasm
			mg./kg.	
RP 2855.....		*o*-$CH_3OC_6H_4CH_2$—	10	1/20‡
RP 2880.....	C_6H_5—			
RP 2890.....		$C_6H_5CH_2$—		
RP 2892.....		3,4-$(CH_3O)_2C_6H_3CH_2$—	Inactive	1/80‡
RP 2895.....	C_6H_5—			
RP 2909.....		*p*-$CH_3OC_6H_4CH_2$—	10	
RP 2910.....		*p*-$C_2H_5C_6H_4CH_2$—	10	
RP 2914.....		*p*-$CH_3OC_6H_4CH_2$—		
RP 2932.....		*p*-$CH_3C_6H_4CH_2$—	1	
RP 2933.....		*p*-$CH_3OC_6H_4CH_2$—		

TABLE 40—*Concluded*

RHÔNE-POULENC CODE NO.	R	R′	ANTIHISTAMINE ACTIVITY	
			Aerosol*	Spasm
			mg./kg.	
RP 2938.....		*p*-$CH_3OC_6H_4CH_2$—	10	
RP 2958.....		*p*-$CH_3OC_6H_4CH_2$—	50	
RP 2971.....		$C_6H_5CH_2$—	25	
RP 2972.....	C_6H_5—		25	
RP 3325.....		*m*-$CH_3OC_6H_4CH_2$—	Inactive	0‡
RP 3407.....		C_6H_5—		

Other *N*-heterocyclic alkylenediamines



RHÔNE-POULENC CODE NO.	R	ANTIHISTAMINE ACTIVITY	
		Aerosol*	Spasm
		mg./kg.	
RP 2800.....	$-CH_2CH_2CH_2N(CH_3)_2$	2	1/10‡
RP 3420.....	$-CH_2CH(CH_3)N(CH_3)_2$	1	1/4‡
RP 3427.....	$-CH(CH_3)CH_2N(CH_3)_2$		

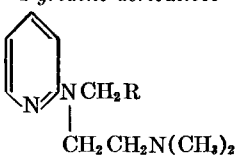
* Antihistamine dose to prevent bronchospasm in guinea pigs by inhalation of an aerosol of histamine (in milligrams per kilogram subcutaneously).

† Antihistamine activity on the isolated intestine of the guinea pig. Antergan = 1.

‡ Antihistamine activity on the isolated intestine of the guinea pig. Neoantergan = 1.

TABLE 41

Pyridine derivatives



NO.	R	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY	TOXICITY L.D.$_{50}$	REFERENCES
		°C.	°C.			
1 (Pyribenzamine)....	C_6H_5—	177–179/0.13 mm.	170 (HBr)			(200)
		167–172/0.1 mm.	195 (picrate)			
		193–205/2.0 mm.				(112)
		138–142/0.01 mm.	193 (HCl)	0.02[a]		(203)
		185–190/1.7 mm.	182 (HCl)			(193, 392)
					62[b]	(256)
2.....	$C_6H_5CH_2$—	195–200/4.0 mm.	143 (HCl)			(193, 392)
		131–141/0.02 mm.	162 (HCl)	>10[a]		(203)
3.....	p-i-$C_3H_7C_6H_4CH_2$—	190–195/1.9 mm.				(193, 392)
4 (Neoantergan).....	p-$CH_3OC_6H_4$—	168–172/0.06 mm.	143 (HCl)	0.02[a]		(203)
		185–190/2.0 mm.	135 (HCl)			(193, 392)
			131 (CH_3I)			(211)
5.....	3,4-$(CH_3O)_2C_6H_4$—	200–205/2 mm.	180 (HCl)			(230)
6.....	p-i-$C_3H_7OC_6H_4$—	194–195/0.20 mm.	152 (HCl)	60[c]	18.5[d]	(25)
7.....	p-FC_6H_4—	130–145/0.25 mm.	53 (base)	3–4[c]		(442)
			170 (HCl)			
8.....	p-ClC_6H_4—	145–170/1.0 mm.	173 (HCl)	2–3[c]		(442)

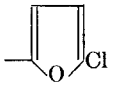
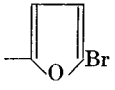
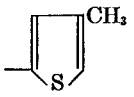
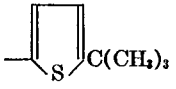
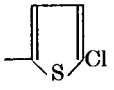
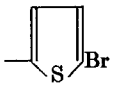
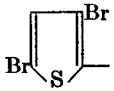
9	*o*-ClC_6H_4—	161–164/1.0 mm.	204 (HCl)	<0.5[e]		(442)
10	*p*-BrC_6H_4—	184–190/0.5–1.0 mm.	186 (HCl)	1[e]		(442)
					160[b]	(256)
11	*m*-BrC_6H_4—	176–178/1.0 mm.	170 (HCl)	<0.5[e]		(442)
12	*p*-IC_6H_4—	194–207/1.0 mm.	195 (HCl)	0.3–0.5[e]		(442)
13	Cyclo-C_6H_{11}—	160–165/13 mm.	226 (HCl)			(230)
14	H	132–138/13 mm.				(112)
15	*n*-C_4H_9	116–121/2 mm.	127 (HCl)			(392)
16	$(CH_3)_2NCH_2$—	103–107/0.04 mm.	225 (3HCl)	>10[a]		(203)
17	*n*-C_6H_{13}	136–146/1 mm.	105 (HCl)	Inactive		(442)
18 (Foralamin)		106–108/0.02 mm.	164 (HCl)	76[c]	19.0[d]	(25)
		117–118/0.2 mm.	119 (HCl)			(229)
		136–137/0.7 mm.	97 (dihydrogen citrate)	100[f]	126[h]	(441)
		108–111/0.2 mm.	142 (fumarate)	106[g]	221[h]	(187)
19		149–152/2.0 mm.	109 (fumarate)	134[g]	232[h]	(187)
20		156–158/0.5 mm.	107 (dihydrogen citrate)	>100[b]	*ca.* 230[h]	(441)
		135–140/0.4 mm.	136 (fumarate)	203[g]	206[h]	(187)
21 (Histadyl, Thenylene)		173–175/3.0 mm.	163 (HCl)	100[g]		(452)
			157 d. (CH_3I)			(452)
		185–186/8.0 mm.	161 (HCl)			(228)
		123–135/0.1 mm.	165 (HCl)	1–10[i]		(90)
		166–168/2.0 mm.	163 (HCl)			(242)

TABLE 41—*Continued*

NO.	R	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY	TOXICITY L.D.$_{50}$	REFERENCES
		°C.	°C.			
22		185–190/2 mm.				(392)
23		185–190/3.5 mm.	146 (HCl)	0.01–0.1[i]		(90)
24 (Chlorothen)		171–173/1.8 mm.	111 (HCl)			(230)
		155–156/1 mm.	108 (HCl)	10–100[i]	230[h]	(88, 90)
			106 (dihydrogen phosphate)	10–100[i]		(90)
			118 (dihydrogen citrate)	10–100[i]		(90)
					112[b]	(256)
25 (Bromothen)		173–175/1 mm.	126 (HCl)	10–100[i]	230[h]	(88, 90)
					130[b]	(256)
26			185 (HCl)	0.1–1.0[i]		(90)
27		150–160/0.001 mm.	209 (HCl)	0.01–0.1[i]		(90)

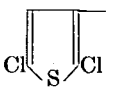
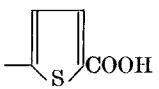
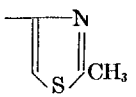
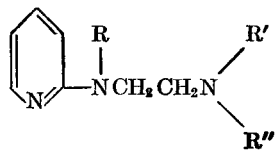
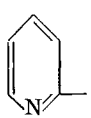
28		174–180/1.0 mm. 179–181/1.0 mm.	170 (HCl)	0.1–1.0[i]		(90) (62)
29 (Thenfadil)		169–172/1.0 mm.	170 (HCl)	8.3[j]	17.5[k]	(62, 235)
30		177–179/1 mm.		7.9[j]	18.0[k]	(62, 235)
31		156–158/1 mm.		7.2[j]	21.0[k]	(62, 235)
32			200 (dipicrate)	0.01–0.1[i]		(90)
33		185–190/2 mm.				(193)
34	1-$C_{10}H_7$—	200/1 mm.	95 (base) 226 (HCl)	Inactive		(442)

TABLE 41—*Continued*



NO.	R	R′	R″	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY	REFERENCES
				°C.	°C.		
35	C_2H_5	CH_3	CH_3	99–104/0.04 mm.	112 (HCl)	1[a]	(203)
36	i-C_3H_7	CH_3	CH_3	120–125/1 mm.	226 (HCl)		(112, 203)
37	n-C_3H_7	C_2H_5	C_2H_5	151–155/13 mm.		>10[a]	(203)
38	$C_2H_5OCH_2CH_2$—	CH_3	CH_3	160–165/1.7 mm.			(393)
39	C_6H_5—	CH_3	CH_3	185–187/14 mm.	217 (HCl)	>5[a]	(203)
40	C_6H_5—	C_2H_5	C_2H_5	135–149/0.08 mm.			(112)
				145–150/0.08 mm.	136 (HCl)	>10[a]	(203)
41	$C_6H_5CH_2$—	H	H		158 (sulfate)		(156)
42	$C_6H_5CH_2$—	CH_3	i-C_3H_7	155–156/0.075 mm.		21[c]	(25)
43	$C_6H_5CH_2$—	C_2H_5	C_2H_5	142–150/0.02 mm.	206 (2HCl)	>5[a]	(203)
44	p-i-$C_3H_7C_6H_4CH_2$—	CH_3	CH_3	194–195/0.20 mm.	152 (HCl)	60[c]	(25)
45	$C_6H_5CH_2CH_2$—	CH_3	CH_3	131–141/0.02 mm.	162 (HCl)	>10[a]	(203)
46	C_6H_5CO—	CH_3	CH_3	150–152/0.01 mm.	154 (HCl)	>5[a]	(203)
47		CH_3	CH_3	126–130/0.01 mm.	181 (2HCl)		(203)
48		C_2H_5	C_2H_5	136–140/0.04 mm.	192 (2HCl)	>10[a]	(203)

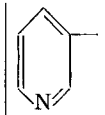
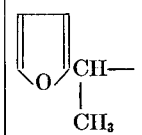
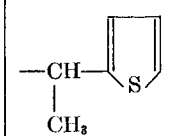
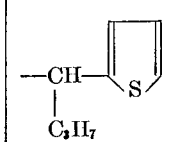
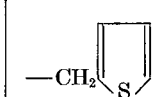
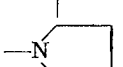
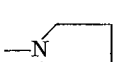
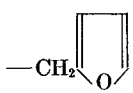
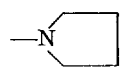
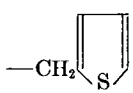
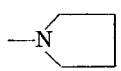
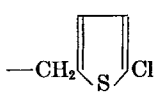
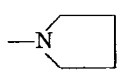
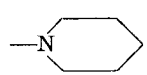
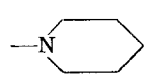
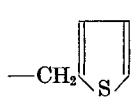
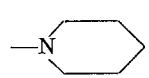
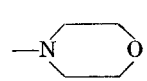
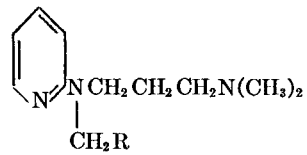
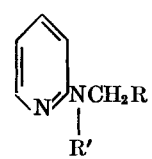
49.....		CH_3	CH_3	138–143/0.03 mm.		>10[a]	(112, 203)
50.....		CH_3	CH_3	121–126/1.0 mm.	136 (fumarate)	2[g]	(187)
51.....		CH_3	CH_3	150–151/1 mm.	173 (HCl)	0.1–1.0[i]	(90)
52.....		CH_3	CH_3	130–135/0.5 mm.		0.1–1.0	(90)
53.....		C_2H_5	C_2H_5	157–160/2 mm.	145 (2HCl)		(228)
54.....	*p*-$CH_3OC_6H_4CH_2$—			193–198/0.2 mm.	171 (2HCl)	1/4[l]	(244)
55.....	—CH_2CH_2 			178–179/0.45 mm.	151 (citrate)	<1/100[l]	(244)

TABLE 41—*Continued*

NO.	R	R′ R″	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY	REFERENCES
			°C.	°C.		
56			149–153/0.25 mm.	138 (citrate) 154 (dipicrate)	1/10[1]	(244)
57			155–165/0.5 mm.	113 (citrate)	1/10[1]	(244)
58			168–172/0.1 mm.	118 (citrate)	1/6[1]	(244)
59	C_2H_5		122–126/0.01 mm.	187 (HCl)		(203)
60	$C_6H_5CH_2$—		170–180/0.02 mm.	176 (HCl)	>2[a]	(203)
61			189–194/1 mm.	136 (HCl)		(242)
62	$C_6H_5CH_2$—		174–180/0.03 mm.	206 (2HCl)		(203)

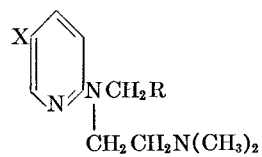


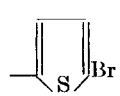
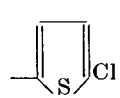
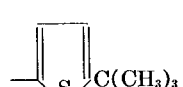
NO.	R	BOILING POINT	MELTING POINT OF SALT	REFERENCES
		°C.	°C.	
63	C_6H_5—	200–205/3 mm.		(193, 392)
64	p-$CH_3OC_6H_4$—	195–200/2.5 mm.		(193, 392)
65		171–174/4 mm.	124 (HCl)	(242)

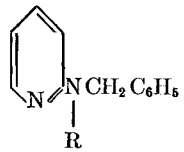


NO.	R	R′	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY	REFERENCES
			°C.	°C.		
66	$(C_4H_9)_3C$—	$(CH_3)_2NCH_2CH_2$—	175–177/2 mm.	185 (2HCl)	0.4[1]	(402)
67	$(C_4H_9)_3C$—	$(C_2H_5)_2NCH_2CH_2$—	190–195/2 mm.	205 (2HCl)	0.04–0.08[1]	(403)
68		$(CH_3)_2NCH(CH_3)CH_2$—	162–169/1.5 mm.	102 (bisuccinate)		(242)
69	C_6H_5—	$(C_2H_5)_2NCH_2C(CH_3)_2CH_2$—				(112)

TABLE 41—*Continued*



NO.	X	R	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY	L.D.$_{50}$	REFERENCES
			°C.	°C.			
70.....	Br	C_6H_5—		182 (HCl)	<0.5[e]		(442)
71.....	Cl	C_6H_5—	145–146/0.02 mm.	180 (HCl)	58[e]	15.0[d]	(25)
			163–185/0.02–0.05 mm.	180 (HCl)	<0.5[e]		(442)
72.....	Br	*m*-BrC_6H_4—		147 (HCl)	<0.5[e]		(442)
73.....	Cl	*p*-$CH_3OC_6H_4$—	180–185/0.05 mm.	142 (HCl)	34[e]	26.0[d]	(25)
74.....	Br		175–185/0.6 mm.	141 (HCl)	0.1–1.0[i]		(90)
75.....	Br		175–190/0.0001 mm.	166 (HCl)	0.01–1.0[i]		(90)
76.....	Br			137 (HCl)	0.1–1.0[i]		(90)
77.....	Br			176 (HCl)	0.01–1.0[i]		(90)



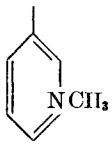
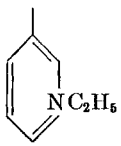
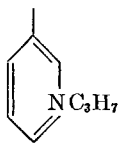
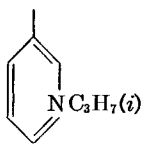
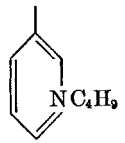
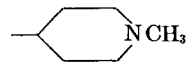
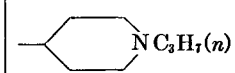
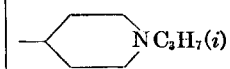
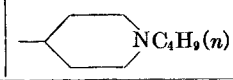
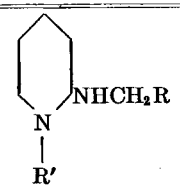
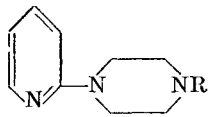
NO.	R	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY	REFERENCES
		°C.	°C.		
78.....	$-CH_2CON(CH_3)_2$		184 (HCl)	Inactive	(442)
79.....	$-CH_2CON(C_2H_5)_2$		148 (HCl)	Inactive	(442)
80.....		163–164/0.1 mm.			(341, 343)
81.....		155–160/0.2 mm.	163 d. (dipicrate)		(341, 343)
82.....					(341)
83.....					(341)

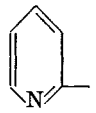
TABLE 41—*Continued*

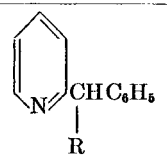
NO.	R	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY	REFERENCES
		°C.	°C.		
84.....					(341)
85.....		188–189/0.5 mm.	260 (3HCl)		(341, 342)
86.....		188–194/0.3–0.6 mm.	225 d. (dipicrate)	0.75[m]	(341, 342)
87.....					(341)
88.....					(341)
89.....					(341)



NO.	R	R′	MELTING POINT OF SALT	REFERENCES
			°C.	
90.....	C_6H_5—	—$CH_2CH_2N(CH_3)_2$	160 (picrate)	(70)
91.....	p-$CH_2OC_6H_4$—	—$CH_2CH_2N(CH_3)_2$	87 (HCl)	(70)
92.....	C_6H_5—	—$CH_2CH_2N(C_2H_5)_2$	110 (HCl)	(70)



NO.	R	BOILING POINT	MELTING POINT OF SALT	REFERENCES
		°C.	°C.	
93	H	114–116/1.4 mm.	276 (2HCl)	(184)
94	CH_3	106–107/2.7 mm.	259 (2HCl)	(184)
95		135–140/1.4 mm.	283 (2HCl)	(184)



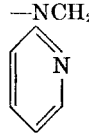
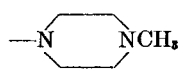
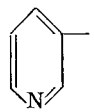
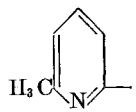
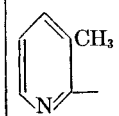
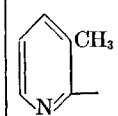
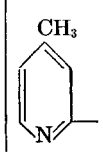
NO.	R	BOILING POINT	MELTING POINT OF SALT OR BASE	ANTIHISTAMINE ACTIVITY	REFERENCES
		°C.	°C.		
96	$-NHCH_2CH_2N(CH_3)_2$	140–143/0.5 mm.	175 (HCl)	5.0[n]	(423)
97	$-N(CH_3)CH_2CH_2N(CH_3)_2$	160–163/1.0 mm.	140 (HCl)	20.0[n]	(423)
98	$-NCH_2CH_2N(CH_3)_2$ 	185–190/0.2 mm.	178 (HCl)	5.0[n]	(423)
99			94 (base)		(183)

TABLE 41—*Continued*

R—N$CH_2CH_2N(CH_3)_2$
|
R′

NO.	R	R′	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY	REFERENCES
			°C.	°C.		
100.....		C_6H_5—	161–165/0.08 mm.	204 (2HCl)	>10[a]	(203)
101.....		$C_6H_5CH_2$—	150–160/0.02 mm.	170 (HCl)	1.0[a]	(203)
102.....		H	125–144/13 mm.			(112)
103.....		$C_6H_5CH_2$—	185–188/14 mm.	241 (2HCl)	2[a]	(112, 203)
104.....		$C_6H_5CH_2$—	156–161/0.18 mm.	176 (HCl)	0.2[a]	(203)

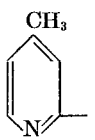
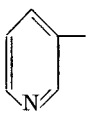
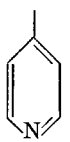
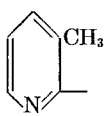
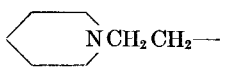
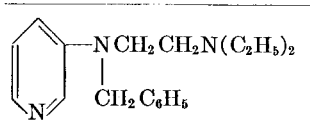
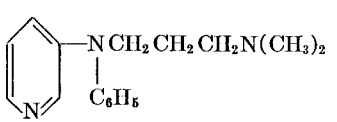
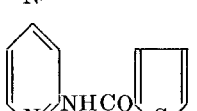
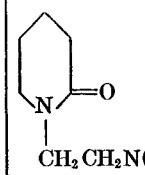
105.....			98–100/0.04 mm.	137 (HCl)	>5.0[a]	(203)
106.....		$C_6H_5CH_2$—				(112)
107.....						(112)
	FORMULA					
108.....			112–113/0.03 mm.		10[a]	(203)
109.....						(112)
110.....			165–170/2 mm.	217 (HCl)	Inactive	(228)

TABLE 41—*Concluded*

NO.	R	R′	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY	REFERENCES
	FORMULA					
111.....			138/7 mm.	131 (picrate) 252 (CH_3I)		(307)

[a] Micrograms of compound per milliliter of bath liquid capable of neutralizing the contraction of an isolated guinea-pig gut caused by 1 γ/ml. of histamine diphosphate.

[b] Intraperitoneally (milligrams per kilogram).

[c] Average per cent by which a bath concentration of 9.375×10^{-5} μg./ml. of antihistaminic reduced the response of guinea-pig ileum to a histamine base concentration of 0.024 μg./ml. Pyribenzamine = 37; Benadryl = 17.

[d] Acute toxicity (milligrams per killgram) to rats (intravenous injection).

[e] Spasmolytic index when tested on the isolated guinea-pig ileum by the method of Litchfield and coworkers (256).

[f] Activity by histamine aerosol technique. Pyribenzamine = 100.

[g] Relative activity on the basis of Pyribenzamine = 100. Based on the amount of drug, on a free-base basis, that on the average produced a 50 per cent relaxation of a maximal histaminic spasm of the isolated strip of guinea-pig ileum.

[h] Acute toxicity, on a free-base basis, for 50 per cent mortality in 24 hr. after oral dosing in male white mice (milligrams per kilogram).

[i] H ratio = micrograms of histamine to produce a given contraction per microgram of compound required to suppress this response. Determined on the isolated guinea-pig gut.

[j] Spasmolytic potency expressed as the log of the effective dilution as determined by Miller, Becker, and Tainter (289). Values represent the concentration of base. Pyribenzamine = 7.4; Thenylene = 7.7.

[k] Intravenously in milligrams of base per kilogram.

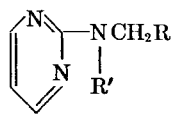
[l] Spasmolytic index compared to Pyribenzamine = 100.

[m] Spasmolytic activity compared to Benadryl = 1.

[n] Minimum dose of compound necessary to antagonize 0.1 γ/ml. of histamine diphosphate on isolated guinea-pig intestine. Pyribenzamine = 0.01.

TABLE 42

Pyrimidine derivatives



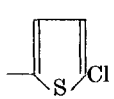
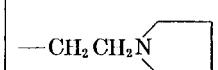
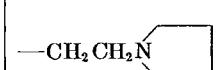
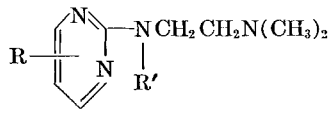
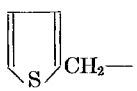
NO.	R	R′	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY	REFERENCES
			°C.	°C.		
1		$-CH_2CH_2N(CH_3)_2$	131–133/0.05 mm.	177 (HCl)	10*	(25)
2			180–181/0.23 mm.	126 (citrate)	1/10–1/30†	(244)
3 (Hetramine)	C_6H_5—	$-CH_2CH_2N(CH_3)_2$	148–155/3.0 mm.	198 (HCl) 212 (HCl)		(193, 392) (150)
4 (Neohetramine)	*p*-$CH_3OC_6H_4$—	$-CH_2CH_2N(CH_3)_2$	185–187/2.2 mm.			(150)
5	*p*-$CH_3OC_6H_4$—	$-CH_2CH_2N(C_2H_5)_2$		113 (HCl)		(112)
6	*p*-$CH_3OC_6H_4$—		203–206/0.6 mm.	136 (HCl)	1/30–1/60†	(244)

TABLE 42—*Concluded*

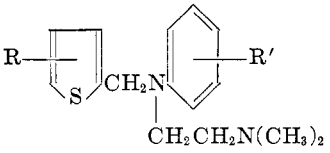
NO.	R	R′	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY	REFERENCES
						
			°C.	°C.		
7	4-CH_3		147–148/1.2 mm.	143 (HCl)		(230)
8	4-CH_3	$C_6H_5CH_2$—	138/1.4 mm.			(150)
9	4-OCH_3	$C_6H_5CH_2$—	141–143/0.04 mm.	166 (HCl)	36*	(25)
10	4,6-$(CH_3)_2$	$C_6H_5CH_2$—	117/1.7 mm.	165 (HCl)		(150, 193, 392)
11	H	2,4-$(CH_3)_2C_6H_3$—				(112)

* Average per cent by which a bath concentration of 9.375×10^{-5} μg./ml. of antihistaminic reduced the response of guinea-pig ileum to a histamine base concentration of 0.024 μg./ml. Pyribenzamine = 37; Benadryl = 17.

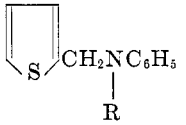
† Spasmolytic index compared to Pyribenzamine = 100.

TABLE 43

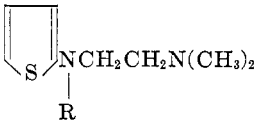
Thiophene derivatives



NO.	R	R′	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY	REFERENCES
			°C.	°C.		
1(Diatrin)	H	H	183–185/7 mm.	187 (HCl)	1*	(131, 242)
			185–186/8 mm.	184 (HCl)	2/3*	(228)
2	H	2-Cl	175–176/3.5 mm.	185 (HCl)	Inactive	(230)
3	H	3-Cl	190–191/3.5 mm.	165 (HCl)	Slight	(230)
4	H	4-Cl	184–186/1.5 mm.	187 (HCl)	1/2*	(230)
5	H	4-OCH_3	175–180/1.5 mm.	148 (HCl)		(230)
6	5-Cl	H	171/2 mm.	164 (HCl)	1.25*	(230)
7	5-Cl	2-Cl	184–186/2 mm.	144 (HCl)		(230)
8	5-Cl	3-Cl	195–197/2 mm.	168 (HCl)		(230)
9	5-Cl	4-Cl	197–200/2 mm.	188 (HCl)		(230)
10	5-Cl	4-OCH_3	178/1.5 mm.	110 (HCl)		(230)

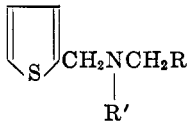


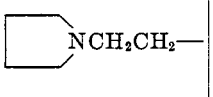
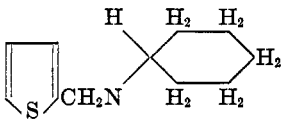
NO.	R	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY	REFERENCES
		°C.	°C.		
11	$-CH_2CH_2N(C_2H_5)_2$	157–160/2 mm.	145 (2HCl)	1/5*	(228)
12	$-CH_2CH(CH_3)N(CH_3)_2$	164–171/3 mm.	100 (bisuccinate)		(242)
13	$-CH_2CH_2N$ 	198–199/1.3 mm.	130 (citrate)	1/10–1/15†	(244)
14	$-CH_2CH_2N$ 	215–218/5 mm.	188 (HCl)		(242)

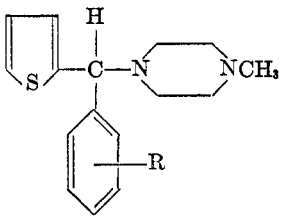


NO.	R	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY	REFERENCES
		°C.	°C.		
15	CH_3	83–92/4 mm.	231 d. (HCl)	Inactive	(230)
16	C_2H_5				(112)

TABLE 43—*Concluded*



NO.	R	R′	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY	REFERENCES
			°C.	°C.		
17..			167–170/0.25 mm.	100 (citrate) 177 (dipicrate)	1/100†	(244)
18..	C_6H_5—	$ClCH_2CH_2$—		178 d. (HCl)	Inactive	(63, 230)
	FORMULA					
19..			153–154/0.2 mm.	97 (citrate)	<1/100†	(244)



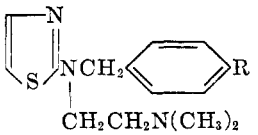
NO.	R	MELTING POINT OF SALT	REFERENCES
		°C.	
20	H	202 d. (2HCl)	(183)
21	4-Cl	216 d. (oxalate)	(183)

* Activity compared to Antergan = 1.

† Spasmolytic index compared to Pyribenzamine = 100.

TABLE 44

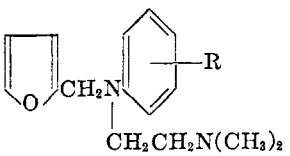
Thiazole derivatives

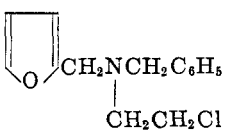


NO.	R	MELTING POINT OF SALT	REFERENCES
		°C.	
1	H	172 (HCl)	(222)
		141 (picrate)	(400)
2	CH_3O	164 (HCl)	(222)
3	Cl	151 (HCl)	(222)

TABLE 45

Furan derivatives



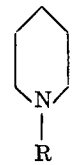
NO.	R	BOILING POINT	MELTING POINT OF HYDROCHLORIDE	ANTIHISTAMINE ACTIVITY	$L.D._{50}$	REFERENCES
		°C.	°C.			
1	H	127–129/0.05 mm.	148	70*	30.0†	(25)
2	4-*i*-C_3H_7	130–131/0.04 mm.	139	29*	9.4†	(25)
3	4-Methoxyl	155–156/0.075 mm.	126	3*	35.0†	(25)
	FORMULA					
4			120 d.			(63)

* Average per cent by which a bath concentration of 9.375×10^{-5} μg./ml. of antihistaminic reduced the response of guinea-pig ileum to a histamine base concentration of 0.024 μg./ml. Pyribenzamine = 37; Benadryl = 17.

† Acute toxicity to rats, intravenously, in milligrams per kilogram.

TABLE 46

Piperidine derivatives



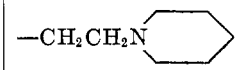
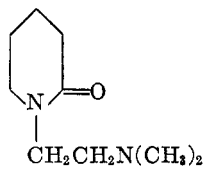
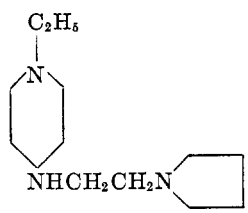
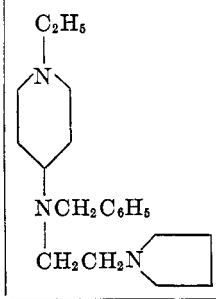
NO.	R	BOILING POINT	MELTING POINT OF SALT	ANTIHISTAMINE ACTIVITY	REFERENCES
		°C.	°C.		
1....	$-CH_2CH_2N(CH_3)_2$		293 (2HCl)	Inactive	(307, 323)
2....	$-CH_2CH_2N(C_2H_5)_2$			Inactive	(323)
3....				Inactive	(323)
	FORMULA				
4....		138/7 mm.	131 (picrate) 252 (CH_3I)		(307)
5....		101–104/0.05 mm.	255 d. (dipicrate)		(342)
6....		167–189/0.8 mm.	200 d. (tripicrate)		(342)

TABLE 47

Pyrrolidone, pyrazine, and pyridazine derivatives

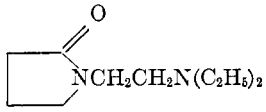
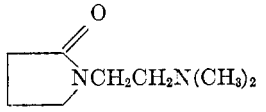
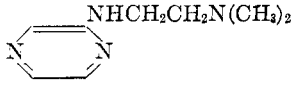
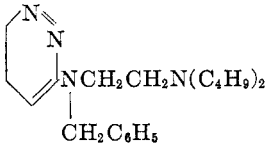
NO.	FORMULA	BOILING POINT	MELTING POINT OF SALT	REFERENCES
		°C.	°C.	
1.....		122/4 mm.	94 (picrate)	(307)
2.....		118–122/20 mm.	156 (HCl) 282 (CH_3I)	(307)
3.....		120–124/4 mm.	159 (picrate)	(112)
4.....				(415)

TABLE 48

4-Alkylimidazoles

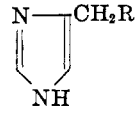
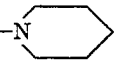
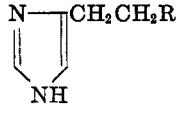
NO.	R	MELTING POINT OF SALT OR BASE	YIELD
	 (432)		
		°C.	*per cent*
1	—OH	91 (HCl)	85
2	—Cl	141 (HCl)	77
3	$-CH_2N(CH_3)_2$	198 (2HCl)	84
4	$-CH_2N(C_2H_5)_2$	193 (2HCl)	69
5		225 (2HCl)	69
6	$-N(CH_3)CH_2C_6H_5$	209 (2HCl)	90
7	$-N(C_2H_5)CH_2C_6H_5$	209 (HCl)	90
8	$-N(CH_2C_6H_5)_2$	149 (base)	84
9	$-N(C_6H_5)CH_2C_6H_5$	148 (base)	
10	$-NHCH_3$	199 (2HCl)	75
11	$-NHC_2H_5$	170 (2HCl)	81
12	$-NHCH_2C_6H_5$	201 (2HCl)	70
13	$-SCH_3$	128 (HCl) 146 (picrate)	
14	$-NH_2$	247 (2HCl)	
	 (196)		
15	$-N(CH_3)_2$	184 (2HCl) 215 (dipicrate)	25
16	$-NHC_2H_5$	163 (2HCl) 185 (dipicrate)	35
17	$-NHC_3H_7$	100 (2HCl) 165 (dipicrate)	50

TABLE 48—*Concluded*

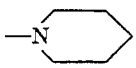
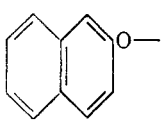
NO.	R	MELTING POINT OF SALT OR BASE	YIELD
		°C.	*per cent*
18	$-NHCH(CH_3)_2$	196 (2HCl) 175 (dipicrate)	35
19	$-N(C_2H_5)_2$	220 (2HCl)	15
20	$-N(C_3H_7)_2$	sirup (2HCl) 190 (dipicrate)	45
21		278 (2HCl) 191 (dipicrate)	55
22		243 (2HCl)	55
23	$-NCH_2C_6H_5$ $\vert$ CH_3	179 (2HBr)	20
24	$-NCH_2C_6H_5$ $\vert$ C_2H_5	83 (2HBr)	5
25	$-N(CH_2C_6H_5)_2$	156 (2HBr)	15
26	$-OC_6H_5$	137 (HCl) 120 (picrate)	40
27		152 (base)	25

TABLE 49

N-Heterocyclic imidazolines and imidazoles

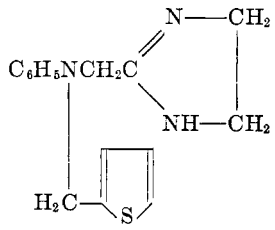
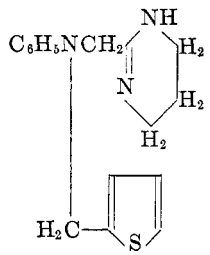
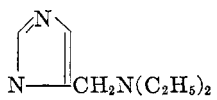
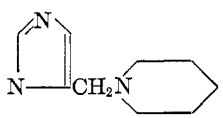
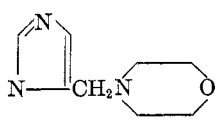
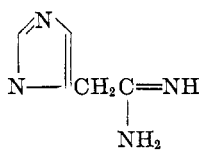
NO.	FORMULA	BOILING POINT	MELTING POINT OF SALT	REFERENCES
		°C.	°C.	
1.....		190–200/0.4 mm.	220 (HCl)	(228)
2.....			223 (HCl)	(230)
3.....			200 (2HCl)	(431)
4.....			227 (2HCl)	(431)
5.....			173 (2HCl)	(431)
6.....			230 (2HCl)	(431)

TABLE 50

N-Polycyclic Rhône-Poulenc diamines (443)

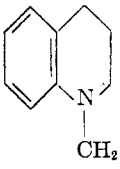
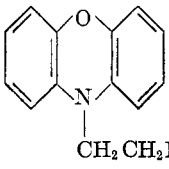
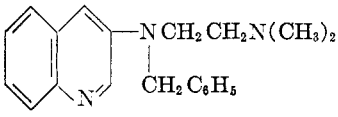
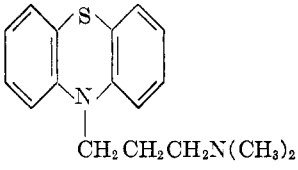
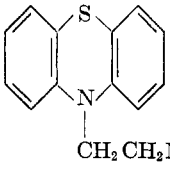
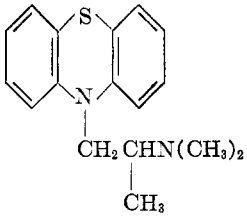
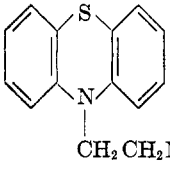
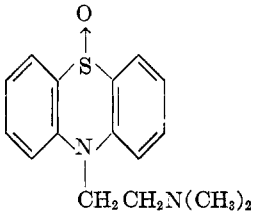
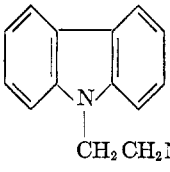
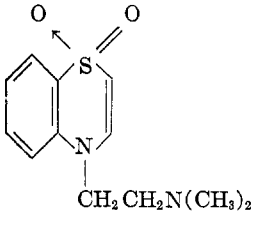
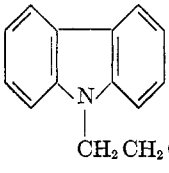
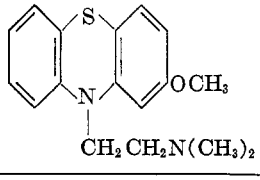
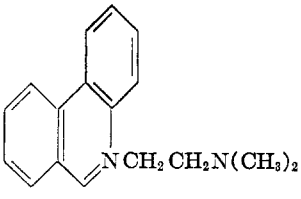
CODE NO.	FORMULA	CODE NO.	FORMULA
RP 2756..		RP 3192..	
RP 2970..		RP 3276..	
RP 2987..		RP 3277..	
RP 3015..		RP 3283..	
RP 3040..		RP 3289..	
RP 3041..		RP 3298..	
RP 3110..			

TABLE 50—*Concluded*

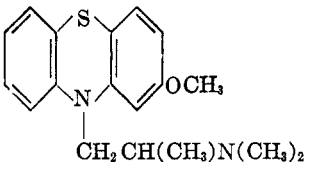
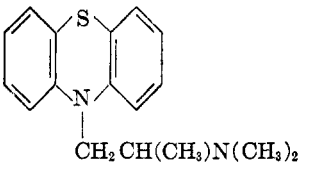
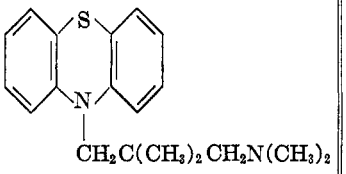
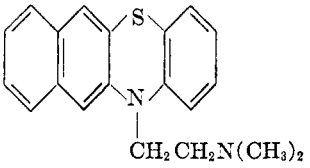
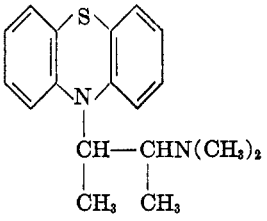
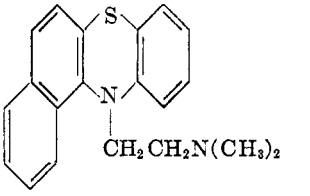
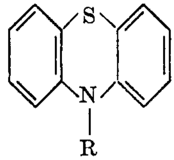
CODE NO.	FORMULA	CODE NO.	FORMULA
RP 3299..		RP 3389..	
RP 3300..		RP 3390..	
RP 3349..		RP 3398..	

TABLE 51

10-Substituted phenothiazines



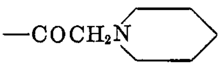
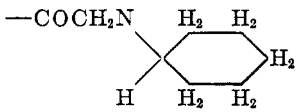
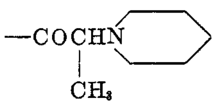
NO.	R	BOILING POINT	MELTING POINT OF SALT OR BASE	REFERENCES
		°C.	°C.	
1..........	$—CH_2CH_2N(CH_3)_2$	183–187/1 mm.	60 (base)	(146)
		190–192/3 mm.	201 (HCl)	(394)
2..........	$—CH_2CH_2CH_2N(CH_3)_2$	208–210/3 mm.	181 (HCl)	(394)
3..........	$—CH_2CH_2N(C_2H_5)_2$	200–205/1.1 mm.	175 (HCl)	(394)
4..........	$—CH_2CH_2CH_2N(C_2H_5)_2$	213–215/1.5 mm.		(394)
5 (Phenergan)...	$—CH_2C(CH_3)N(CH_3)_2$	190–192/3 mm.	204 (HCl)	(394)
			207 (CH_3I)	
			275 (methyl benzenesulfonate)	(77)
6..........	$—CH_2C(CH_3)_2CH_2N(CH_3)_2$	196–199/3 mm.		(394)
7..........	$—CH_2CH_2N(CH_3)CH_2CH_2OH$		186	(99, 170)
			155 (CH_3Br)	
8..........	$—COCH_2N(CH_3)_2$		116 (base)	(126)
9..........	$—COCH_2N(C_2H_5)_2$		59 (base)	(126)
10..........			165 (base)	(126)
11..........			126 (base)	(126)
12..........	$—COCHN(C_2H_5)_2$ CH_3		100 (base)	(126)
13..........			111 (base)	(126)
14..........	$—COCHN(CH_3)_2$ C_2H_5		99 (base)	(126)
15..........	$—COCHN(C_2H_5)_2$ C_2H_5		203 d. (HCl)	(126)

TABLE 51—*Continued*

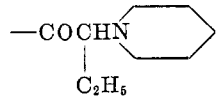
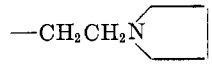
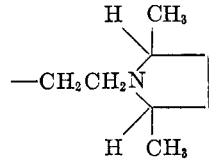
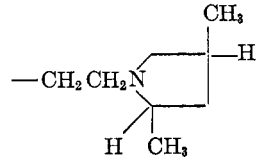
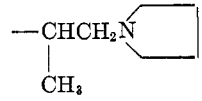
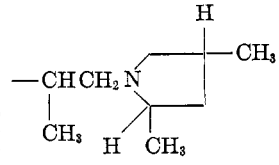
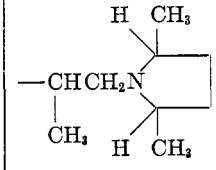
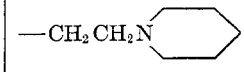
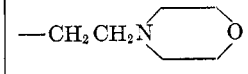
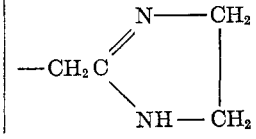
NO.	R	BOILING POINT	MELTING POINT OF SALT OR BASE	REFERENCES
		°C.	°C.	
16.....			216 d. (HCl)	(126)
17 (Pyrrolazote)...			197 (HCl)	(199, 338)
18.....			196 (HCl)	(198, 338)
19.....			162 (HCl)	(198, 338)
20.....			194 (HCl) 181 d. (oxalate)	(198, 338)
21.....			250 (HCl)	(198, 338)
22.....			103 (base)	(198, 338)
23.....		210–212/2 mm.	170 (HCl)	(395)
24.....		229–232/2 mm.	185 (HCl)	(395)
25.....			243 (HCl)	(286)

TABLE 51—*Continued*

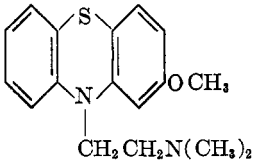
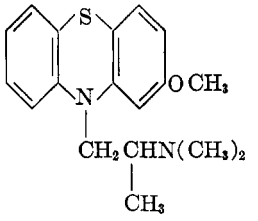
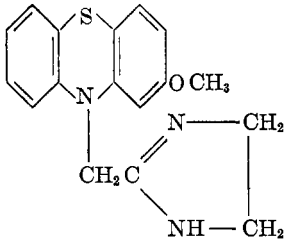
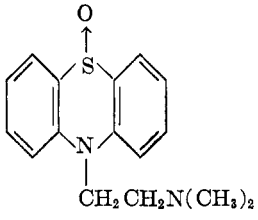
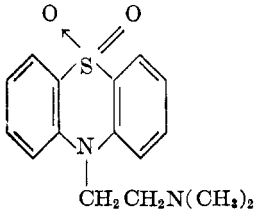
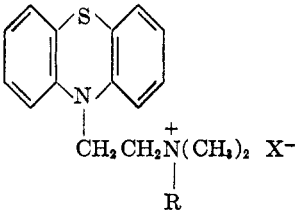
NO.	FORMULA	BOILING POINT	MELTING POINT OF SALT OR BASE	REFERENCES
		°C.	°C.	
26.....		220–223/3 mm.	182 (HCl)	(394)
27.....		218–222/3 mm.		(394)
28.....			213 (HCl)	(286)
29.....				(95, 146)
30.....				(95, 146)

TABLE 51—*Concluded*

Quaternary ammonium bases derived from 10-substituted phenothiazines (78)



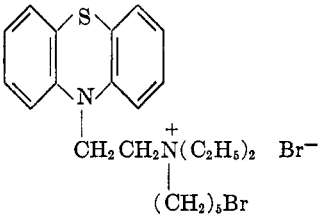
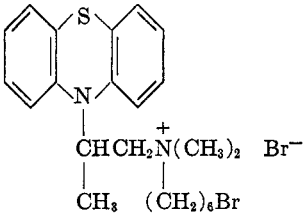
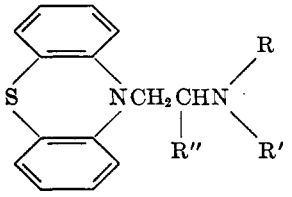
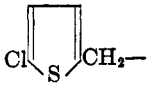
NO.	R	X	MELTING POINT
			°C.
31	$-CH_2CH_2Br$	Br	226
32	$-CH_2CH_2CH_2CH_2Br$	Br	218
33	$-CH_2CH_2CH_2CH_2CH_2Br$	Br	195
34	$-CH_2CH_2CH_2CH_2CH_2CH_2Br$	Br	186
35	$-CH_2CH_2CH_2CH_2CH_2CH_2CH_2Br$	Br	150
36	$-CH_2CH_2CH_2Cl$	Cl	200
37	$-CH_2CH_2CH_2CHBrCH_3$	Br	221
	FORMULA		
38			140
39			290

TABLE 52

N-(Dialkylaminoalkyl)phenothiazines (464)



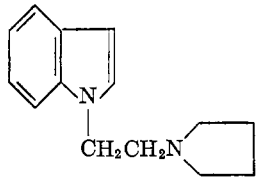
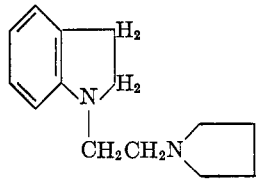
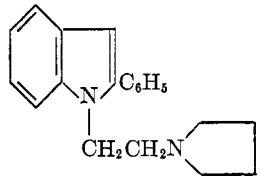
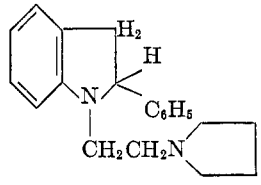
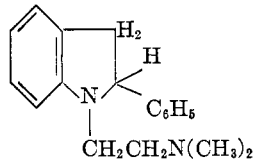
NO.	R	R′	R″	BOILING POINT	MELTING POINT OF SALT OR BASE	ANTIHISTAMINE ACTIVITY*
				°C.	°C.	
1...	CH_3	i-C_3H_7	H		179 (HCl)	3
2...	C_2H_5	i-C_3H_7	H	168–172/0.1 mm.	173 (HCl)	1/2
3...	CH_3	$C_6H_5CH_2$—	H		92 (base)	<1/100
4...	CH_3	n-C_4H_9	H	185–195/0.7 mm.	144 (HCl)	1/3–1/2
5...	CH_3	i-C_4H_9	H	162–164/0.3 mm.	154 (HCl)	1/5
6...	CH_3	CH_2=$CHCH_2$—	H	187–190/1.0 mm.	179 (HCl)	1.5–2
7...	C_2H_5	CH_2=$CHCH_2$—	H	165–185/0.1 mm.	127 (HCl)	1/4
8...	CH_2=$CHCH_2$—	CH_2=$CHCH_2$—	H	220–223/2.6 mm.	126 (HCl)	<1/200
9...	CH_3	i-C_3H_7	CH_3		70 (base)	1
10...	n-C_3H_7	n-C_3H_7	H	204–207/0.5 mm.	172 (HCl)	<1/2, >1/20
11...	n-C_3H_7	i-C_3H_7	H	203–209/0.7 mm.	202 (HCl)	<1/10
12...	n-C_3H_7	CH_2=$CHCH_2$—	H	212–216/0.5 mm.	148 (HCl)	<1/20
13...	i-C_3H_7	i-C_3H_7	H	180–181/0.5 mm.	199 (HCl)	1/10
14...	i-C_3H_7	CH_2=$CHCH_2$—	H	212–213/0.9 mm.	171 (HCl)	<1/2, >1/20
15...	$C_6H_5CH_2$—	$C_6H_5CH_2$—	H		200 (HCl)	
16...		n-C_3H_7	H		148 (HCl)	

* Antihistamine activity determined on isolated strip of guinea-pig ileum. Benadryl = 1; RP 3015 = 3–5; Pyrrolazote = 4–5.

TABLE 53

N-Polycyclic derivatives of ethylenediamine

Derivatives of indole

NO.	FORMULA	BOILING POINT	MELTING POINT OF SALT	REFERENCES
		°C.	°C.	
1...		128–129/0.25 mm.	142 (picrate)	(460)
2...		102–105/0.2 mm.		(460)
3...		187–189/0.9 mm.	78 (base)	(460)
4...		162–165/0.2 mm.	191 (HCl)	(460)
5...		183–184/3.8 mm.	212 (HCl)	(460)

Derivatives of benzimidazole

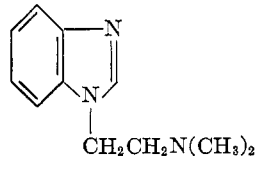
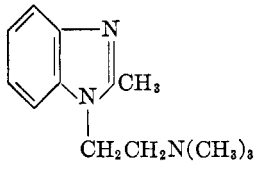
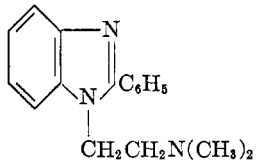
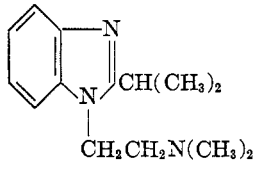
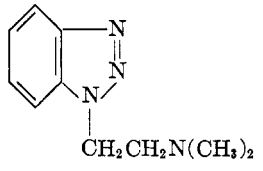
NO.	FORMULA	BOILING POINT	MELTING POINT OF SALT	REFERENCES
		°C.	°C.	
6...		115–120/0.2 mm.	235 (2HCl)	(461)

TABLE 53—*Continued*

NO.	FORMULA	BOILING POINT	MELTING POINT OF SALT	REFERENCES
		°C.	°C.	
7...		117/0.3 mm.	239 (2HCl)	(461)
8...			72 (base) 234 d. (2HCl)	(461)
9...		130–136/1.1 mm.	236 (dipicrate)	(461)

Derivatives of benzotriazole

NO.	FORMULA	BOILING POINT	MELTING POINT OF SALT	REFERENCES
		°C.	°C.	
10...		115–117/0.3 mm.	171 (HCl)	(461, 462)

Derivatives of phthalimidine

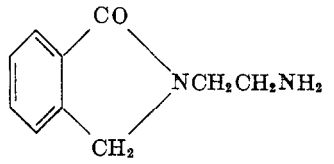
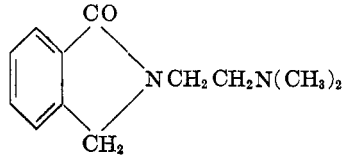
NO.	FORMULA	BOILING POINT	MELTING POINT OF SALT	REFERENCES
		°C.	°C.	
11...			65 (base) 282 (CH_3I)	(307)
12...			70 (base) 282 (CH_3I) 195 (picrate)	(307)

TABLE 53—*Continued*

Derivatives of quinoline

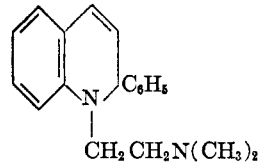
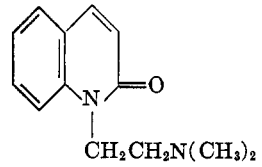
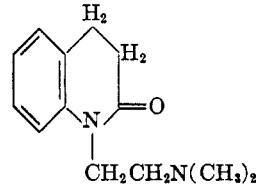
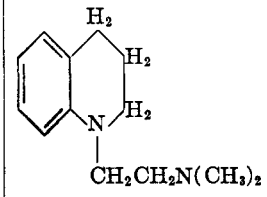
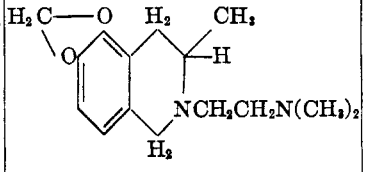
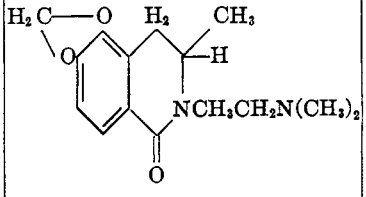
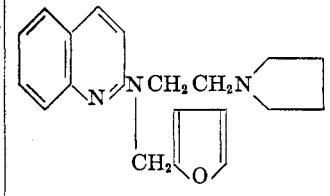
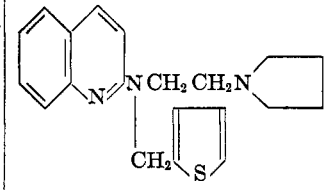
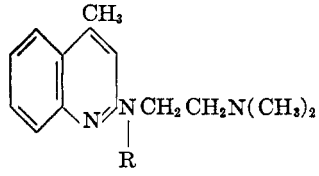
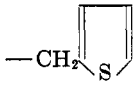
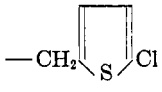
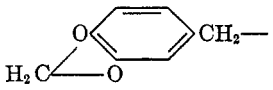
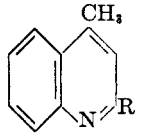
NO.	FORMULA	BOILING POINT	MELTING POINT OF SALT	REFERENCES
		°C.	°C.	
13...		175–178/4–5 mm.	221 (HCl)	(65)
14...		185–188/7 mm.	194 (picrate) 240 (HCl)	(307)
15...			193 (base·$5H_2O$)	(307)
16...		152–153/10 mm.	195 (HCl)	(307)
17...			216 (HI)	(307)
18...		213–215/5 mm.	225 (HCl) 175 (picrate)	(307)
19...		188/1.6 mm.	136 (citrate)	(244)
20...		155–160/0.2 mm.	247 (HCl)	(244)

TABLE 53—*Continued*
Derivatives of lepidyl



NO.	R	BOILING POINT	MELTING POINT OF SALT	REFERENCES
		°C.	°C.	
21...	$C_6H_5CH_2$—	158–165/0.06 mm.		(220)
22...	*o*-$ClC_6H_4CH_2$—	156/0.03 mm.	215 (HCl)	(220)
23...	*p*-$ClC_6H_4CH_2$—	178/0.04 mm.		(220)
24...	2,4-$Cl_2C_6H_3CH_2$—	192/0.05 mm.		(220)
25...	3,4-$Cl_2C_6H_3CH_2$—	183–187/0.03 mm.		(220)
26...		159–172/0.05 mm.		(220)
27...		161–164/0.07 mm.		(220)
28...	*p*-$CH_3OC_6H_4CH_2$—	180/0.07 mm.		(220)
29...	2,3-$(CH_3O)_2C_6H_3CH_2$—	189–191/0.08 mm.		(220)
30...	3,4-$(CH_3O)_2C_6H_3CH_2$—	192–193/0.07 mm.		(220)
31...		189–190/0.06 mm.		(220)



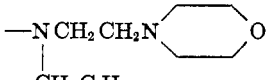
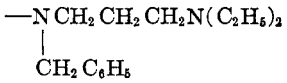
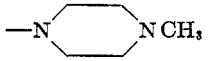
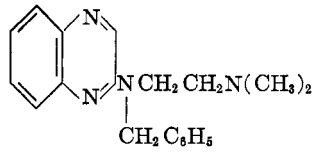
NO.	R	BOILING POINT	MELTING POINT OF SALT	REFERENCES
		°C.	°C.	
32...		196/0.05 mm.		(220)
33...		176–182/0.05 mm.		(220)
34...			295 d. (2HCl)	(5)

TABLE 53—*Continued*

Derivatives of quinoxaline

NO.	FORMULA	MELTING POINT OF SALT	REFERENCES
		°C.	
35.....		218 (HCl)	(156)

Derivatives of carbazole

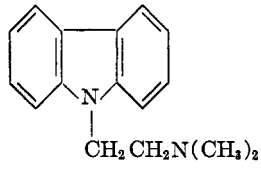
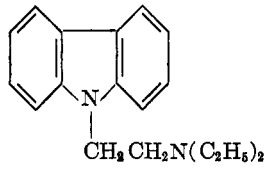
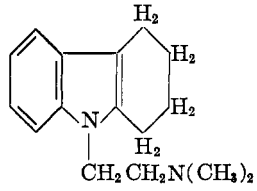
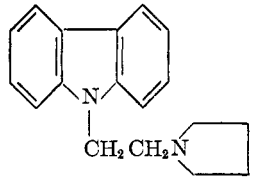
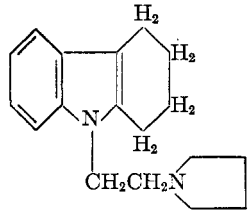
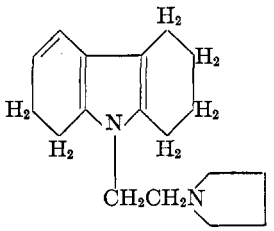
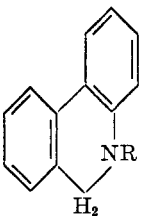
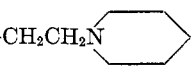
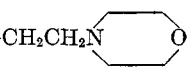
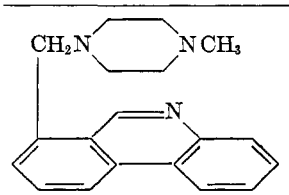
NO.	FORMULA	BOILING POINT	MELTING POINT OF SALT OR BASE	REFERENCES
		°C.	°C.	
36...		190–210/4–6 mm.	242 d. (HCl)	(52, 146)
37...		160/0.9 mm.		(144)
38...			250 (HCl)	(65)
39...			81 (base)	(460)
40...			220 (HCl)	(460)

TABLE 53—*Continued*

NO.	FORMULA	BOILING POINT	MELTING POINT OF SALT OR BASE	REFERENCES
		°C.	°C.	
41...		147–149/0.5 mm.	137 (HCl)	(460)

Derivatives of phenanthridine



NO.	R	MELTING POINT OF SALT	REFERENCES
		°C.	
42.....	$-CH_2CH_2N(CH_3)_2$	179 (dimaleate) 184 (dipicrate)	(202)
43.....	$-CH_2CH_2N(C_2H_5)_2$	159 (dipicrate)	(202)
44.....		238 (2HCl) 158 (dimaleate)	(202)
45.....		191 (HCl) 248 (2HCl)	(202)
	FORMULA		
46.....		223 (2HCl)	(5)

Derivatives of acridine

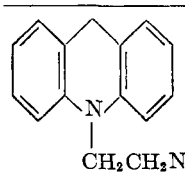
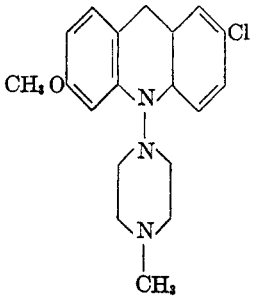
NO.	FORMULA	MELTING POINT OF SALT	REFERENCES
47.....			(146, 290)

TABLE 53—*Concluded*

NO.	FORMULA	MELTING POINT OF SALT	REFERENCES
		°C.	
48.....		293 (2HCl)	(5)

Derivatives of phenoxazine

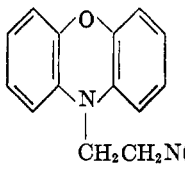
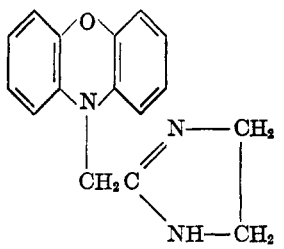
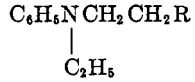
NO.	FORMULA	MELTING POINT OF SALT	REFERENCES
		°C.	
49.....			(146)
50.....		239 (HCl)	(286)

TABLE 54

Correlation of structure and activity in the ethylenediamines (384)



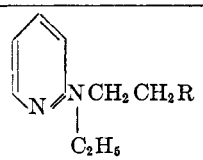
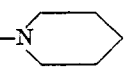
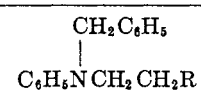
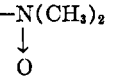
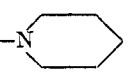
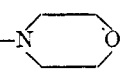
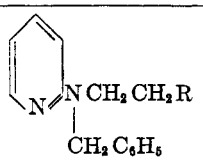
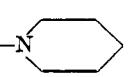
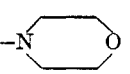
NO.	R	ANTIHISTAMINE ACTIVITY*	
		Intestine†	Asthma‡
1 (F 1571)	$-N(C_2H_5)_2$	<1	5
2 (RP 2325)	$-N(CH_3)_2$	6+	20
3	$-NH_2$		0
			
4	$-N(CH_3)_2$	4+	
5		1+	
			
6	$-N(C_2H_5)_2$	13	5
7 (Antergan)	$-N(CH_3)_2$	100	100
8	$-\overset{+}{N}(CH_3)_3I^-$		0
9		2	10–20
10		1–2	
11		1	
			
12	$-N(C_2H_5)_2$	1–10	
13 (Pyribenzamine)	$-N(CH_3)_2$	200	200
14	$-\overset{+}{N}(CH_3)_3I^-$		
15		4	4–33+
16		0–1+	1+

TABLE 54—*Continued*

$C_6H_5NCH_2CH_2N(CH_3)_2$
|
R

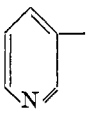
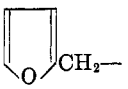
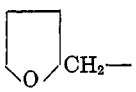
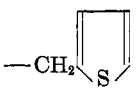
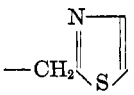
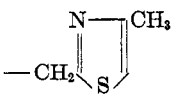
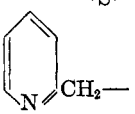
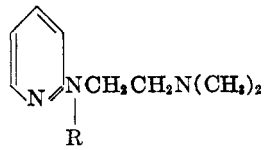
NO.	R	ANTIHISTAMINE ACTIVITY*	
		Intestine†	Asthma‡
17	C_2H_5	6	20
18	n-C_4H_9	26	40
19	CH_2=$CHCH_2$—	6	6
20	$HOCH_2CH_2$—		<1
21	$CH_3OCH_2CH_2$—	140	40
22	$C_2H_5OCH_2CH_2$—	100	50
23	$C_6H_5CH_2$—	100	100
24	p-$CH_3OC_6H_4CH_2$—	33	
25	C_6H_5CH=$CHCH_2$—		5
26	$C_6H_5CH_2OCH_2CH_2$—		
27	C_6H_5CO—		10
28	C_6H_5—	50	0–50
29		0+	
30		100	100
31		5	5
32 (Diatrin)		65	65
33		65	100
34			40
35			4

TABLE 54—*Continued*



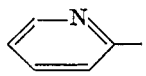
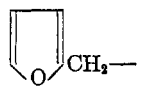
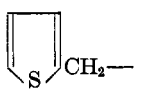
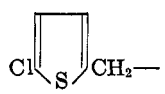
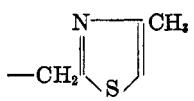
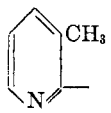
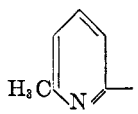
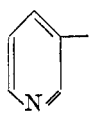
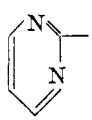
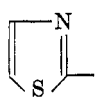
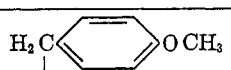
NO.	R	ANTIHISTAMINE ACTIVITY*	
		Intestine†	Asthma‡
36	C_2H_5	4+	
37	*i*-C_3H_7	2+	
38	$(CH_3)_2NCH_2CH_2$—	0+	
39 (Pyribenzamine)	$C_6H_5CH_2$—	200	200
40	$C_6H_5CH_2CH_2$—	1+	
41	*p*-$CH_3C_6H_4CH_2$—		100
42	*p*-$C_2H_5C_6H_4CH_2$—		10
43 (Neoantergan)	*p*-$CH_3OC_6H_4CH_2$—	200–250+	1000
44	*p*-$C_2H_5OC_6H_4CH_2$—	200	200
45	*m*-$CH_3OC_6H_4CH_2$—		0
46	*o*-$CH_3OC_6H_4CH_2$—	4+	10
47	C_6H_5CO—	0–1+	
48	C_6H_5—	3+	10
49		1–2+	
50 (Foralamin)		66	200
51 (Histadyl, Thenylene)		200	200
52 (Bromothen)		400	
53 (Chlorothen)		400	
54			40

TABLE 54—*Continued*

$C_6H_5CH_2NCH_2CH_2N(CH_3)_2$
|
R

NO.	R	ANTIHISTAMINE ACTIVITY	
		Intestine†	Asthma‡
55 (Pyribenzamine)		200	200
56.....		2+	
57.....		4+	
58.....		20+	
59.....		20	
60 (Hetramine)		2–4+	4
61.....		20+	



H_2C (O CH_3)

$RNCH_2CH_2N(CH_3)_2$

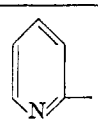
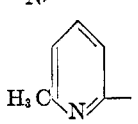
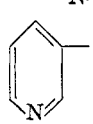
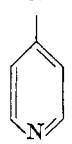
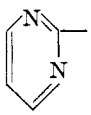
62 (Neoantergan)		200–250+	1000
63.....			20
64.....			10
65.....			2

TABLE 54—*Continued*

NO.	R	ANTIHISTAMINE ACTIVITY	
		Intestine†	Asthma‡
66 (Neohetramine)		2–4	
67 (White 194B)			10

R = $-CH_2CH_2N(CH_3)_2$; R′ = $-CH(CH_3)CH_2CH_2N(CH_3)_2$

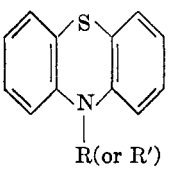
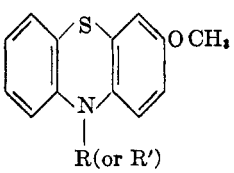
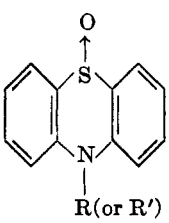
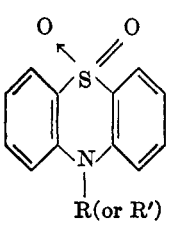
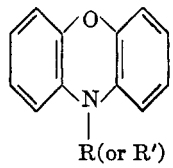
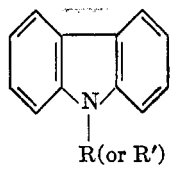
NO.	FORMULA	ANTIHISTAMINE ACTIVITY			
		Intestine		Asthma	
		R	R′	R	R′
68.....		100 (RP 3015)	100 (Phenergan)	100	200
69.....		100	50	100	200
70.....		10			
71.....		50		100	

TABLE 54—*Concluded*

NO.	FORMULA	ANTIHISTAMINE ACTIVITY			
		Intestine		Asthma	
		R	R′	R	R′
72.....				0	
73.....				2–4+	

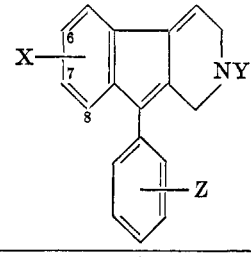
* Antihistaminic activity: Pyribenzamine = 200 (intestine), 200 (asthma).

† Action in relieving spasmolytic action of histamine on isolated guinea-pig intestine.

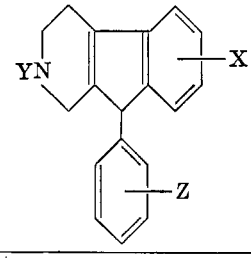
‡ Action in relieving bronchoconstriction in guinea pigs by histamine aerosol.

TABLE 55

1-Pyridindene derivatives (319, 320)

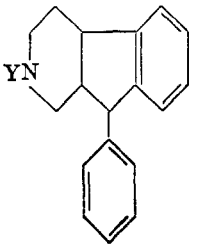


NO.	X	Y	Z	MELTING POINT OF SALT
				°C.
1.....	H	H	H	204 (HBr)
2.....	H	C_2H_5	H	204 (HBr) 162 (SCN)
3.....	H	*i*-C_3H_7	H	245 (HBr)
4.....	H	*n*-C_4H_9	H	195 (HBr)
5.....	7-CH_3	CH_3	H	203 (HBr)
6.....	6(or 8)-OCH_3	CH_3	H	210 (HBr)
7.....	7-CH_3	CH_3	*p*-CH_3	203 (HBr)
8.....	6(or 8)-OCH_3	CH_3	*m*-OCH_3	210 (HBr)



9 (Thephorin)...	H	CH_3	H	154 (HCl) 126 (HBr) 171 (maleate) 160 (tartrate) 161 (salicylate) 189 (thiocyanate) 251 d. (methochloride) 114 (methyl *p*-toluenesulfonate)
10.....	H	C_2H_5	H	162 (thiocyanate)
11.....	H	*i*-C_3H_7	H	184 (oxalate)
12.....	7-CH_3	CH_3	*p*-CH_3	186 (oxalate)

TABLE 55—*Concluded*



NO.	Y	MELTING POINT OF SALT
		°C.
13	CH_3	261 (HCl) 246 (HBr) 293 (CH_3I)
14	C_2H_5	251 (HBr)

TABLE 56

Aminoalkyl esters, propanols, propenes, propanes, and propanones (1)

$RNCH_2CH_2COOC_2H_5$

R	BOILING POINT	MELTING POINT OF SALT	YIELD
	°C.	°C.	*per cent*
Dibutyl			80
Diallyl	108–110/15 mm.		80
d-*N*-Methylamphetamino	165–166/12 mm.	126 (acid oxalate)	78
1-Piperidyl			85
4-Morpholinyl			86
1-Pyrrolidyl	108–110/22 mm.		40

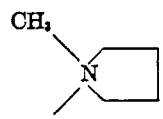
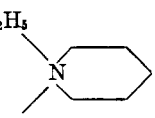
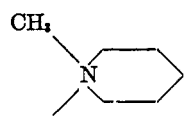
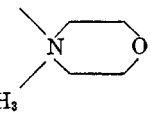
$(C_6H_5)_2C(OH)CH_2CH_2R$

R	BOILING POINT	MELTING POINT	MELTING POINT OF SALT	YIELD
	°C.	°C.	°C.	*per cent*
Amino		143	184 (HCl)	33
Methylamino	148–150/0.2 mm.	146	151 (HCl)	24
Ethylamino		142	177 (HCl)	38
Benzylamino		152	203 (HCl)	16
Dimethylamino		166	205 (HCl)	62
Diethylamino	154/0.2 mm.	53	203 (HCl)	56
Dipropylamino	154/0.1 mm.	53	161 (HCl)	51
Dibutylamino	157–159/0.1 mm.	42	109 (HCl)	54
N-Methylanilino		97	170 d.(HCl)	84
d-*N*-Methylamphetamino		58	208 (HCl)	55
Diallylamino	157–159/0.4 mm.	27	156 (HCl)	60
1-Pyrrolidyl		172	191 (HCl)	63
4-Morpholinyl		106	231 (HCl)	50

$\left[(C_6H_5)_2C(OH)CH_2CH_2{-}\overset{R}{\overset{|}{\overset{+}{N}}}{-}R'\right]I^-$
$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad R''$

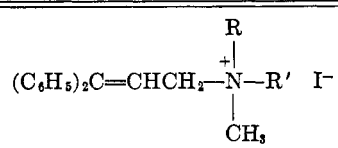
R	R′	R″	MELTING POINT	R	R′	R″	MELTING POINT
			°C.				°C.
CH_3	CH_3	CH_3	243 d.	C_2H_5	C_2H_5	C_2H_5	208
CH_3	CH_3	C_2H_5	201 d.	CH_3	C_3H_7	C_3H_7	183
CH_3	CH_3	Phenyl	176 d.	CH_3	C_4H_9	C_4H_9	196
CH_3	CH_3	2-Phenyl-isopropyl	226 d.	CH_3	Allyl	Allyl	197 d.
				CH_3	CH_3	C_3H_7 (bromide)	233
CH_3	C_2H_5	C_2H_5	199	CH_3	CH_3	C_4H_9 (bromide)	235 d.

TABLE 56—*Continued*

R	MELTING POINT	R	MELTING POINT
	°C.		°C.
	210		205
	215		204 d.

$(C_6H_5)_2C{=}CHCH_2R$

R	BOILING POINT	MELTING POINT	MELTING POINT OF SALT
	°C.	°C.	°C.
Amino	Decomposes at 0.1 mm.		215 d. (HCl)
Ethylamino	116–117/0.15 mm.		179 d. (HCl)
Dimethylamino	192–193/18 mm.		170 (HCl)
Diethylamino	111/0.05 mm.		147 (HCl)
Dipropylamino	146–148/0.4 mm.		129 (HCl)
Dibutylamino	139–142/0.05 mm.		150 (HCl)
N-Methylanilino	200–204/0.5 mm.		
d-*N*-Methylamphetamino	168–170/0.07 mm.		164 (acid oxalate)
Diallylamino	134/0.2 mm.		
1-Pyrrolidyl	125/0.02 mm.		167 (HCl)
1-Piperidyl	138/0.1 mm.		210 (HCl)
4-Morpholinyl		72	219 (HCl)



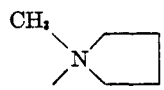
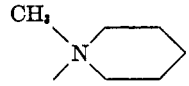
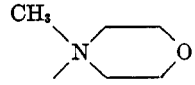
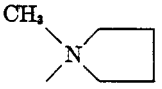
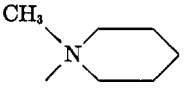
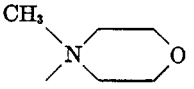
R	R′	MELTING POINT	R, R′	MELTING POINT
		°C.		°C.
CH_3	CH_3	205 d.		154
C_2H_5	C_2H_5	186		
C_3H_7	C_3H_7	158 d.		
C_4H_9	C_4H_9	125		
CH_3	$-CH(CH_3)CH_2C_6H_5$	151 d.		190 d.
Allyl	Allyl	151 d.		
				164

TABLE 56—*Continued*

$(C_6H_5)_2CCH_2CH_2NR$ (OH)

R	BOILING POINT	MELTING POINT	MELTING POINT OF SALT
	°C.	°C.	°C.
Ethyl			164 (HCl)
Dimethyl	183–185/16 mm.	45	170 (HCl)
Dipropyl			115 (HCl)
Dibutyl			114 (HCl)
1-Pyrrolidyl	125/0.02 mm.		136 (HCl)
1-Piperidyl		41	217 (HCl)
4-Morpholinyl			209 (HCl)

$(C_6H_5)_2CHCH_2CH_2\overset{+}{N}(CH_3)R\ I^-$ (R′)

R	R′	MELTING POINT	R, R′	MELTING POINT
		°C.		°C.
CH_3	CH_3	180		157
C_2H_5	C_2H_5	163		
C_3H_7	C_3H_7	145		
C_4H_9	C_4H_9	143		176 d.
				163

$RCOCH_2CH_2NR'R''$

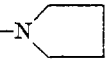
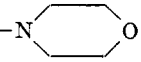
R	NR′R″	MELTING POINT OF SALT OR BASE
		°C.
C_6H_5—	$-N(CH_3)_2$	153 (HCl)
C_6H_5—	$-N(C_2H_5)_2$	112 (HCl)
C_6H_5—		164 (HCl)
C_6H_5—		190 (HCl)
C_6H_5—		182 (HCl)

TABLE 56—*Concluded*

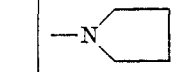
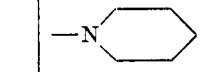
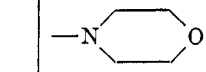
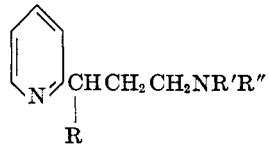
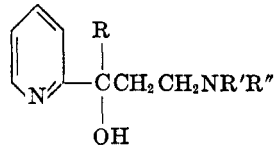
R	NR′R″	MELTING POINT OF SALT OR BASE
		°C.
p-ClC_6H_4—	—$N(CH_3)_2$	175 (HCl) 59 (base)
p-ClC_6H_4—	—$N(C_2H_5)_2$	142 (HCl)
p-ClC_6H_4—		188 (HCl) 73 (base)
p-ClC_6H_4—		191 d. (HCl) 51 (base)
p-ClC_6H_4—		209 d. (HCl) 90 (base)
p-$CH_3OC_6H_4$—	—$N(CH_3)_2$	188 (HCl)
	—$N(CH_3)_2$	179 (HCl)

TABLE 57

3-Tertiary-amino-1-aryl-1-(2-pyridyl) compounds (2)

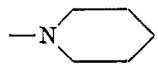
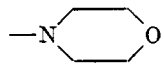


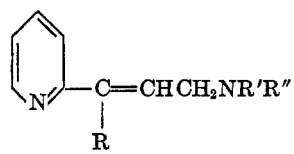
R	NR′R″	BOILING POINT	MELTING POINT OF SALT
		°C.	°C.
C_6H_5— (Trimeton)	—$N(CH_3)_2$	104–106/0.05 mm.	154 (oxalate) 202 (picrate)
C_6H_5—	—N⟨ ⟩	120–122/0.01 mm.	174 d. (oxalate)
p-ClC_6H_4— (Chlortrimeton)	—$N(CH_3)_2$	120–122/0.01 mm.	139 (oxalate)
p-ClC_6H_4—	—$N(C_2H_5)_2$		140 d. (oxalate)
p-ClC_6H_4—	—N⟨ ⟩	155–160/0.01 mm.	149 (oxalate)



R	NR′R″	MELTING POINT OF SALT OR BASE
		°C.
C_6H_5—	—$N(CH_3)_2$	100 (base) 208 d. (2HCl) 153 (oxalate) 173 d. (CH_3I)
C_6H_5—	—$N(C_2H_5)_2$	162 (base) 161 (oxalate)
C_6H_5—	—N⟨ ⟩	94 (base) 177 d. (oxalate)
C_6H_5—	—N⟨ ⟩	85 (base) 205 (oxalate)
C_6H_5—	—$N(CH_3)_2$	90 (base) 159 d. (oxalate)
p-ClC_6H_4—	—$N(C_2H_5)_2$	165 d. (oxalate)
p-ClC_6H_4—	—N⟨ ⟩	131 (base) 128 d. (oxalate)

TABLE 57—*Concluded*

R	NR′R″	MELTING POINT OF SALT OR BASE
		°C.
p-ClC_6H_4—		98 (base) 152 d. (oxalate)
p-ClC_6H_4—		84 (base) 165 d. (oxalate)
p-$CH_3OC_6H_4$—	—$N(CH_3)_2$	90 (base) 209 d. (2HCl)
	—$N(CH_3)_2$	67 (base)



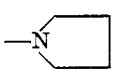
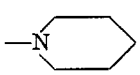
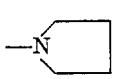
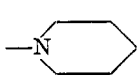
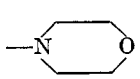
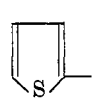
R	NR′R″	BOILING POINT	MELTING POINT OF SALT
		°C.	°C.
C_6H_5—	—$N(CH_3)_2$	108/0.05 mm.	182 (HCl)
C_6H_5—	—$N(C_2H_5)_2$	119–121/0.01 mm.	155 d. (oxalate)
C_6H_5—		128–135/0.01 mm.	167 d. (oxalate) 153 d. (mucate)
C_6H_5—		154–158/0.01 mm.	170 d. (oxalate)
p-ClC_6H_4—	—$N(CH_3)_2$	118–120/0.01 mm.	171 d. (oxalate) 166 d. (maleate)
p-ClC_6H_4—	—$N(C_2H_5)_2$	136–138/0.01 mm.	152 d. (oxalate)
p-ClC_6H_4—		165–169/0.01 mm.	177 d. (oxalate) 149 d. (maleate)
p-ClC_6H_4—		182–184/0.01 mm.	168 d. (oxalate)
p-ClC_6H_4—		186–188/0.01 mm.	181 d. (oxalate)
p-$CH_3OC_6H_4$—	—$N(CH_3)_2$	156–158/0.3 mm.	208 d. (2HCl)
	—$N(CH_3)_2$	116–122/0.5 mm.	162 d. (oxalate)

TABLE 58

Bridged-ring propylamines (95, 146)

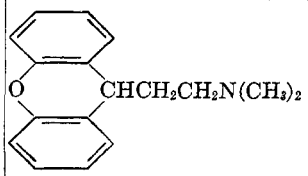
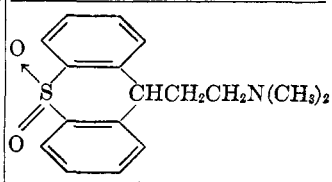
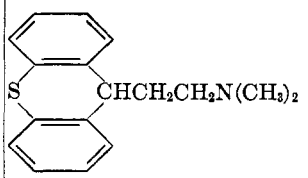
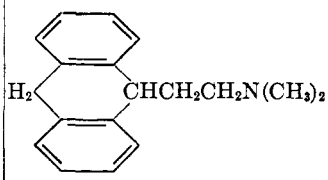
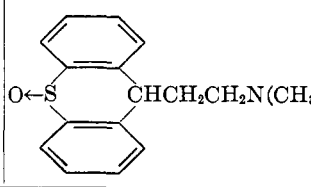
NO.	FORMULA	NO.	FORMULA
1		4	
2		5	
3		6	$(C_6H_5)_2CHCH_2CH_2N(CH_3)_2$
		7 (Aspasan) (28)	$(C_6H_5)_2CHCH_2CH_2N(CH_3)_2$

TABLE 59

Amidines and imidazolines of aminoalkanes

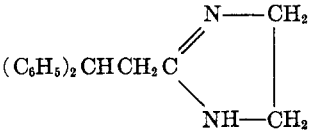
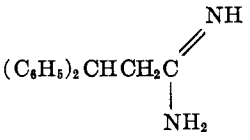
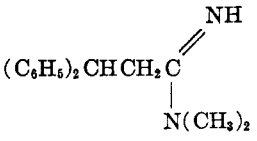
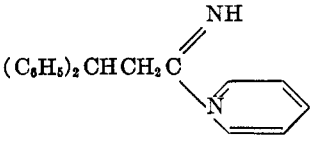
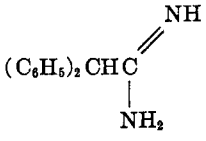
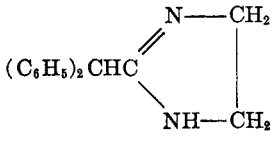
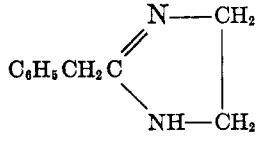
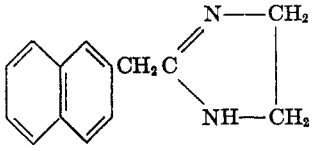
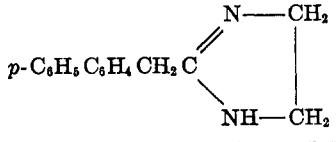
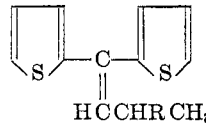
NO.	FORMULA	MELTING POINT OF SALT OR BASE	REFERENCES
		°C.	
1		101 (base) 90 ($HCl \cdot H_2O$) 170 (picrate)	(212)
2		209 (picrate)	(212)
3		249 (HCl)	(212)
4		250 (HCl)	(212)
5		225 (picrate)	(212)
6		135 (base) 182 (HCl) 185 (picrate)	(12, 212)
7		62 (base) 172 (HCl)	(283)
8		120 (base) 253 (HCl)	(283, 397)
9			(70)

TABLE 60

Dithienylbutenes (3)



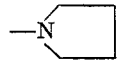
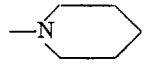
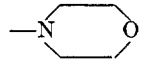
NO.	R	MELTING POINT OF HYDROCHLORIDE
		°C.
1	—$NHCH_3$	170
2	—NHC_2H_5	153
3		169
4		189
5		182

TABLE 61

Amino esters of substituted alicyclic carboxylic acids (424, 440)

2-Diethylaminoethyl esters

NO.	CARBOXYLIC ACID	MELTING POINT OF HYDROCHLORIDE	ANTIHISTAMINE ACTIVITY*
		°C.	
1	1-α-Naphthylcyclohexane	185	20
2	1-Benzylcyclohexane	150	1
3	2-Methyl-1-phenylcyclohexane	128	5
4	1-Phenylcyclohexane	161	10
5	1-Cyclohexylcyclohexane	166	5
6	2-Phenylcyclohexane	76	
7	2-Cyclohexylcyclohexane	109	0.5
8	2-Benzoyl-Δ^4-cyclohexene	133	5
9	2-Benzoylcyclohexane	100	20
10	2-Hexahydrobenzoyl-Δ^4-cyclohexene (diastereoisomers)	122	
11	2-Hexahydrobenzoylcyclohexane (diastereoisomers)	136	5
12	2-Benzylcyclohexane	116	5
13	4-Phenylcyclohexane	162	5
14	4-Cyclohexylcyclohexane	192	10
15	1-α-Naphthylcyclopentane	176	5
16	2-Phenyl-2-indane	162	5
17	1-Benzylcyclopentane	122	1
18	2-Methyl-1-phenylcyclopentane	145	5
19	1-Phenylcyclopentane	144	5
20	2-Methyl-1-cyclohexylcyclopentane	143	1
21	1-Cyclohexylcyclopentane	128	5
22	3-Methyl-1-phenylcyclobutane	139	5
23	1-Phenylcyclobutane	146	
24	1-Cyclohexylcyclobutane	127	10
25	2-Methyl-2-phenylcyclopropane	81	10
26	1-Phenylcyclopropane		

2-Dimethylaminoethyl esters

27	1-Phenylcyclohexane	177	5
28	2-Cyclohexylcyclohexane	142	1
29	2-Methyl-1-phenylcyclopentane	138	5
30	1-Phenylcyclopentane	118	5

1-Phenylcyclohexanecarboxylates

NO.	AMINO ALCOHOL	MELTING POINT OF HYDROCHLORIDE	ANTIHISTAMINE ACTIVITY*
		°C.	
31	2-Dimethylaminoethoxyethyl	130	10
32	3-Piperidino-2-hydroxypropyl	145	10
33	3-Piperidino-2-phenylurethanpropyl	164	50
34	1,3-Bis(diethylamino)-2-propyl	137	5
35	1,2-Divinylene-1,4,5,6-tetrahydro-5-pyrimidyl	188	5
36	2,2-Bis(hydroxymethyl)-2-aminoethyl	214	5

* Minimum dose of test compound necessary to antagonize 0.1 γ/ml. of histamine diphosphate on isolated guinea-pig intestine. Benadryl = 0.02.

TABLE 62

2-Diethylaminoethyl benzilate hydrochlorides (30)

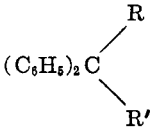
$R(R'C_6H_4)C(OH)COOCH_2CH_2N(C_2H_5)_2 \cdot HCl$

NO.	R	R′	MELTING POINT	ANTIHISTAMINE ACTIVITY*
			°C.	
1.....	H	H		1
2.....	4-$CH_3OC_6H_4$—	H	171	0.2
3.....	4-$C_2H_5OC_6H_4$—	H	174	0.1
4.....	4-*n*-$C_3H_7OC_6H_4$—	H	142	0.5
5.....	4-*i*-$C_3H_7OC_6H_4$—	H	162	0.33
6.....	4-*n*-$C_4H_9OC_6H_4$—	H	148	1
7.....	4-*i*-$C_4H_9OC_6H_4$—	H	142	0.5
8.....	4-*n*-$C_5H_{11}OC_6H_4$—	H	137	1
9.....	4-*i*-$C_5H_{11}OC_6H_4$—	H	135	0.5
10.....	4-*n*-$C_6H_{13}OC_6H_4$—	H	125	1
11.....	4-*n*-$C_7H_{15}OC_6H_4$—	H	132	
12.....	4-*n*-$C_8H_{17}OC_6H_4$—	H	127	
13.....	4-*n*-$C_{10}H_{21}OC_6H_4$—	H	125	
14.....	4-$C_6H_5OC_6H_4$—	H	154	0.5
15.....	4-$C_6H_5CH_2OC_6H_4$—	H	149	0.25
16.....	2,5-$(C_2H_5O)_2C_6H_3$—	H	153	
17.....	3,4-$(C_2H_5O)_2C_6H_3$—	H	140	
18.....	4-*n*-$C_4H_9OCH_2CH_2OC_6H_4$—	H	117	
19.....	4-$C_6H_5OCH_2CH_2OC_6H_4$—	H	130	1
20.....	4-*n*-$C_4H_9OC_6H_4$—	4-*n*-C_4H_9O—	123	

* Activity on isolated guinea-pig gut stimulated by histamine.

TABLE 63

Benzhydryl esters and ketones



NO.	R	R′	BOILING POINT	MELTING POINT OF HYDROCHLORIDE	REFERENCES
			°C.	°C.	
1...	H	—$COOCH_2CH_2N(CH_3)_2$		163	(6)
2...	H	—$COCH_2N(CH_3)_2$	155–175/2 mm.	179 d.	(6)
3...	H	—$COCH_2CH_2N(CH_3)_2$	161–162/1.5 mm.	160	(6)
4..	—$OCH_2CH_2N(CH_3)_2$	—$COOCH_2CH_2N(CH_3)_2$	188–190/0.7 mm.		(294, 295)
5..	—$OCH_2CH_2N(CH_3)_2$	—$COOCH_2N$⬡			(294)

TABLE 64

Alkyl 1-(2-dialkylaminoalkoxy)phenylacetates (429)

$$C_6H_5CHOCH_2CH_2R'$$
$$|$$
$$COOR$$

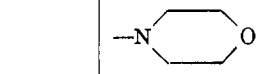
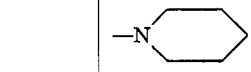
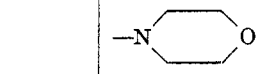
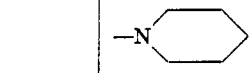
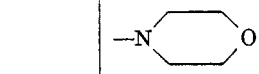
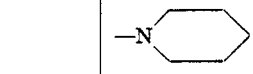
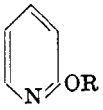
NO.	R	R′	BOILING POINT	MELTING POINT OF HYDROBROMIDE
			°C.	°C.
1.....	CH_3	$-N(CH_3)_2$		201
2.....	CH_3	$-N(C_2H_5)_2$	160–165/4 mm.	
3.....	CH_3		168–170/4 mm.	
4.....	C_2H_5	$-N(CH_3)_2$	145–146/3 mm.	
5.....	C_2H_5	$-N(C_2H_5)_2$	148–150/2 mm.	
6.....	C_2H_5		178–182/2 mm.	
7.....	C_2H_5		177–179/3 mm.	
8.....	*i*-C_3H_7	$-N(CH_3)_2$	129–133/2 mm.	
9.....	*i*-C_3H_7	$-N(C_2H_5)_2$	150–155/3 mm.	
10.....	*i*-C_3H_7		140–144/4 mm.	
11.....	*i*-C_3H_7	$-CH_2N(CH_3)_2$	138–140/2 mm.	
12.....	*i*-C_3H_7	$-N(C_4H_9)_2$	170–173/4 mm.	
13.....	*n*-C_6H_{13}	$-N(CH_3)_2$	140–144/4 mm.	
14.....	*n*-C_6H_{13}	$-N(n\text{-}C_4H_9)_2$	130–135/4 mm.	
15.....	*n*-C_6H_{13}		155–159/3 mm.	
16.....	*n*-C_6H_{13}	$-N(C_2H_5)_2$	160–163/1 mm.	
17.....	*n*-C_6H_{13}	$-CH_2N(C_2H_5)_2$	190–193/7 mm.	
18.....	$C_6H_5CH_2-$	$-N(CH_3)_2$		213
19.....	$C_6H_5CH_2-$			230
20.....	$C_6H_5CH_2-$	$-N(C_2H_5)_2$	195–199/3 mm.	
21.....	$C_6H_5CH_2-$	$-N(n\text{-}C_4H_9)_2$	200–205/3 mm.	

TABLE 65

2-Pyridyl amino esters (190)



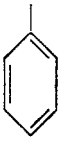
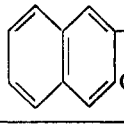
NO.	R	BOILING POINT	MELTING POINT OF SALT
		°C.	°C.
1	 $COOCH_2CH_2N(C_2H_5)_2$	170–171/1 mm.	
2	 $COOCH_2CH_2CH_2N(C_2H_5)_2$	179—180/1 mm.	
3	 $COOCH_2CH_2N(C_2H_5)_2$	169–170/1 mm.	112 (2HCl)
4	 $COOCH_2CH_2CH_2N(C_2H_5)_2$	174–175/1 mm.	130 (2HCl)
5	 $COOCH_2CH_2N(C_2H_5)_2$	184–185/1 mm.	142 (2HCl)
6	 $COOCH_2CH_2CH_2N(C_2H_5)_2$	187–189/1 mm.	164 (2HCl)
7	 $COOCH_2CH_2N(C_2H_5)_2$		140 (2HCl)

TABLE 65—*Concluded*

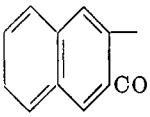
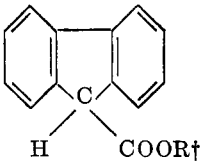
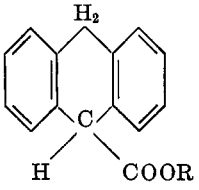
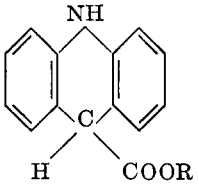
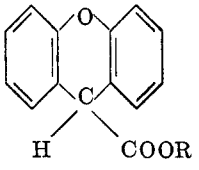
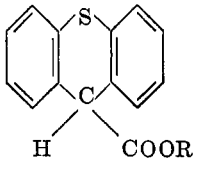
NO.	R	BOILING POINT	MELTING POINT OF SALT
		°C.	°C.
8	 $COOCH_2CH_2CH_2N(C_2H_5)_2$		151 (2HCl)
9	$-CH_2COOCH_2CH_2N(C_2H_5)_2$	103–105/0.14 mm.	96 (HCl)
10	$-CH_2COOCH_2CH_2CH_2N(C_2H_5)_2$	114–115/0.2 mm.	
11	$-CH(CH_3)COOCH_2CH_2N(C_2H_5)_2$	121–123/1 mm.	
12	$-CH(CH_3)COOCH_2CH_2CH_2N(C_2H_5)_2$	122–123/0.4 mm.	
13	$-CH(C_6H_5)COOCH_2CH_2CH_2N(C_2H_5)_2$		112 (2HCl)
14	$-CH(C_6H_5)COOCH_2CH_2CH_2N(C_2H_5)_2$		

TABLE 66

Bridged esters (239, 240)

NO.	FORMULA	ANTIHISTAMINE ACTIVITY*
1		1
2		0.05
3		2
4		0.4
5		0.33

* Antihistamine ratio (papaverine = 1.5). Action on isolated intestine of guinea pig against spasm caused by 2×10^{-6} *M* histamine acid phosphate.

† R is 2-diethylaminoethyl.