the alcohol content in a sample for analysis as suggested by Jaselskis and Warriner, or the equation:

$$y = c + mx$$

may be solved; where c is the y-intercept, m is the slope, y is the millimoles of xenon trioxide, and x is the millimoles of alcohol in the sample. This technique was applied to the alcohol samples listed in the first column of Table II. The alcohol concentrations found by substituting in the above equation are listed in the second column. Per cent recovery was better than 97% in most cases.

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Synthesis of Ketoximino Esters as Antihistaminics

By S. L. LEE, B. B. WILLIAMS, and M. M. KOCHHAR*

In a search for new antihistamines, a series of oximino esters of 2-, 3-, and 4-benzoylpyridine oxime and 2-benzoylthiophene oxime was prepared. The respective ketones were oximinated in pyridine with hydroxylamine hydrochloride. The esterification was conducted in benzene with equimolar quantities of acetyl chloride, oxime, and a basic reagent. Twelve new oximino esters were synthesized and evaluated for their antihistaminic activity. All synthesized compounds exhibited antihistaminic activity with almost no anticholinergic action. The propionyl analogs showed the most significant antihistaminic effectiveness.

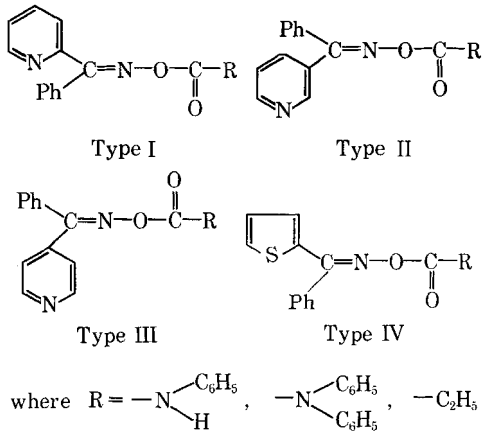
BOVET (1) issued preliminary reports concerning the first effective synthetic antihistaminic drugs. Since that time, a multitude of compounds have been prepared and tested for antihistaminic activity. The chemical structures of these antihistaminic drugs vary, yet the prominent compounds exert similar pharmacological and therapeutic action. Several review articles (2–5) have appeared in the literature. Some of the many useful antihistaminic agents differ sufficiently to hold out hope of attaining drugs which would be more specific for a given allergic manifestation.

Most commonly used drugs can be classified as derivatives of ethanolamine, ethylenediamine, aminopropane, phenothiazine, or piperazine (6). Almost all of these compounds contain a terminal tertiary nitrogen, generally having dimethyl substitution or part of the heterocyclic structure. In the ethanolamine series, the most effective group attached to the oxygen atom has been found to be the benzhydryl radical (7); whereas in the ethylenediamine series, several different radicals on the second nitrogen of the chain have led to active compounds. Several physical properties of antihistaminics have been studied in an effort to relate them to activity of the various drugs (8), but no direct relationship can be made between physical properties and antihistaminic activity.

These observations prompted the investigations reported in this paper. The object of the present work was to prepare and examine some of the oximino esters of benzoylpyridines and benzoylthiophene and to determine whether they possessed significant antihistaminic action.

DISCUSSION

The compounds which were selected for synthesis are the oximino esters of benzoylpyridines and benzoylthiophenes (types I, II, III, and IV).



The preparation of 12 new esters of type I, II, III, or IV, starting with respective benzoylpyridines and 2-benzoylthiophene, was accomplished by modifying the methods described in the literature (9, 10).

The oximes selected in this study included representatives of both syn- (types I and III) and anti- (types II and IV) configuration. The esters were not geometrically confirmed since it was assumed that esterification did not alter configuration. The purpose of including compounds of both configurations was to allow some comparison of antihistaminic effect of the isomers. Pharmacological screening provided no evidence of effect of geometric configuration on intensity of antihistaminic action.

The basic unit for all effective agents contains the ethylamine skeleton in one form or another. It is interesting that the ethylamine skeleton also corresponds to the side chain of the histamine molecule and to part of the imidazole ring. With this in mind the authors attempted replacement of the

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ethylamine side chain with oximino linkage to see its effect on antihistamine activity. The terminal nitrogen is an amide nitrogen having one or two phenyl substituents (compounds I, II, IV, V, VII, VIII, X, and XI). These compounds exhibited antihistaminic activity ranging from 0.5 to 0.1 of diphenhydramine. This very clearly indicates that the ethylamine side chain is not an essential feature. The authors feel that a region of high electron density in that neighborhood is essential for the binding of drug to the receptor. This is further substantiated by synthesis of the propionyl derivatives (III, VI, IX, and XII) in which the carbonyl oxygen exhibits a higher electron density. These exhibited higher antihistaminic activity, 0.5 to 0.2 of diphenhydramine. This also indicates that the terminal nitrogen is not absolutely essential for biological activity. The oximino group should certainly alter the partition coefficient of the compound and thus affect its distribution in the body. Additionally, the oximino linkage should affect the intrinsic reactivity and stereochemistry of a given compound as well as its susceptibility toward metabolic degradation.

Most of the antihistaminic drugs have a minimum of two aryl or aralkyl groups or their equivalent in a polycyclic ring system or one aryl and one heterocyclic ring system. The authors' experimental compounds have benzoylpyridines or 2-benzoylthiophene. This moiety of the drug is the flat portion and this might occupy the flat area on the receptor.

Another very striking similarity among some of the known antihistaminics is the interatomic distances.[1] The interatomic distances between the terminal nitrogen atom of histamine and the 1 and 3 nitrogens of the imidazole ring are 6.12 and 4.52 Å., respectively. The interatomic distance between the pyridine nitrogen and the dimethylamino nitrogen of mepyramine, 2-[(2-dimethylaminoethyl) (*p*-methoxybenzyl) amino] pyridine, is 6.12 Å. The distance between the methoxy oxygen and the terminal nitrogen of mepyramine is 4.52 Å. In methapyrilene,2-[(2-dimethylaminoethyl)-2-thenylamino]-pyridine, the distance between pyridine *N* and terminal nitrogen is 6.12 Å. The distances in some of the more potent antihistaminics are very close to the above-mentioned compounds. The interatomic distances in the synthesized compounds are very comparable to histamine, mepyramine, methapyrilene, diphenhydramine, *etc.* In 2-diphenylcarbamyloximino benzoylpyridine (II) and 2-phenylcarbamyloximino benzoylpyridine (I), the interatomic distances between the pyridine nitrogen and the carbamyl nitrogen and between the pyridine nitrogen and the ether oxygen are 6.16 Å. and 4.2 Å., respectively. Similarly the interatomic distances in compounds IV, V, VII, VIII, X, and XI are very comparable with some of the known antihistaminics.

Studies of spatial dispositions, bond angles, and other physicochemical properties might possibly reveal correlations.

PHARMACOLOGIC EVALUATION

Antihistaminic potency was estimated by use of isolated strips of guinea pig ileum. The lowest concentration which blocked the spasmogenic effect of histamine was determined for the 12 test compounds and for diphenhydramine according to the procedure of Zielenski (11). A Phipps and Bird isolated tissue apparatus was used which provided for temperature maintenance of reservoirs of physiological solution and provided also for upward draining and replacement of physiological solution in the tissue chamber. Contractions were recorded with an E and M myograph photoelectric force transducer and physiograph recording system. Histamine phosphate (0.2 ml. of a 0.055% solution) was added to give a concentration of 5.5×10^{-6} in the tissue chamber. The test compound in water or aqueous propylene glycol was added followed in 1 min. by histamine in the same quantity as the first addition. Failure of needle deflection on addition of the challenge dose of histamine was considered the end point. Strips of ileum were washed after presentation of each concentration of test drug and replaced after two tests or in event of failure of a strip to respond to histamine after washing. For most of the end point concentrations at least one replication was done. Table I presents data from the antihistaminic activity tests.

TABLE I—ANTIHISTAMINIC ACTIVITY OF KETOXIMINO ESTERS ON EXCISED ILEUM SEGMENTS OF THE GUINEA PIG

Compd.	Lowest Histamine Blocking Concn., Gm./ml.
I	3.12×10^{-5}
II	6.25×10^{-5}
III	1.56×10^{-5}
IV	3.12×10^{-5}
V	1.25×10^{-4}
VI	6.25×10^{-6}
VII	7.81×10^{-6}
VIII	3.12×10^{-5}
IX	1.56×10^{-5}
X	3.12×10^{-5}
XI	3.12×10^{-5}
XII	7.81×10^{-6}
Diphenhydramine	3.91×10^{-6}

EXPERIMENTAL[2]

Synthesis of Oximes

2-Benzoylpyridine Oxime—2-Benzoylpyridine (5.49 Gm., 0.03 mole), hydroxylamine hydrochloride (3.5 Gm., 0.05 mole), and pyridine (20 ml.) in ethanol were refluxed for 12 hr. The bulk of the ethanol was removed under reduced pressure and the mixture was poured into cold water. The crude product thus obtained was recrystallized from ethanol which afforded the oxime, m.p. 151–152.5°. [Lit. (12) m.p. 150.5–152.5°.]

3-Benzoylpyridine Oxime—The above procedure was adapted to this preparation. A pure sample of this compound melted at 160.5°. [Lit. (13) m.p. 161°.]

4-Benzoylpyridine Oxime—The method of Kochhar *et al.* (10) was adapted to this oxime. The oxime

[1] Interatomic distances were estimated from Dreiding

[2] Reported melting points are uncorrected. A Thomas-Hoover Unimelt apparatus was used for melting point determination. Schwarzkopf Microanalytical Laboratory, Woodside, N.Y., conducted the elemental analyses.

TABLE II—PHYSICAL CONSTANTS AND ANALYTICAL DATA

Compd.	R	Method of Prepn.	M.p.	Recrystn. Solvent	% Yield (Crude)	Empirical Formula	Anal., % Calcd.	Anal., % Found.
				Type I				
I	$-N(C_6H_5)H$	*A*	167–168° dec.	Ethanol	95	$C_{19}H_{15}N_3O_2$	C, 71.90 H, 4.76	C, 72.22 H, 4.76
II	$-N(C_6H_5)_2$	*B*	165° dec.	Benzene	74	$C_{25}H_{19}N_3O_2$	C, 76.31 H, 4.86	C, 76.20 H, 4.91
III	$-C_2H_5$	*C*	67°	Methanol	82	$C_{15}H_{14}N_2O_2$	C, 70.84 H, 5.55	C, 71.01 H, 5.71
				Type II				
IV	$-N(C_6H_5)H$	*A*	153–154°	Benzene	79	$C_{19}H_{15}N_3O_2$	C, 71.90 H, 4.76	C, 72.22 H, 4.93
V	$-N(C_6H_5)_2$	*B*	193° dec.	Ethanol–methanol	52	$C_{25}H_{19}N_3O_2$	C, 76.31 H, 4.86	C, 76.34 H, 4.97
VI	$-C_2H_5$	*C*	82–83.5°	Ethanol	42	$C_{15}H_{14}N_2O_2$	C, 70.84 H, 5.55	C, 70.60 H, 5.42
				Type III				
VII	$-N(C_6H_5)H$	*A*	198–199° dec.	Benzene	91	$C_{19}H_{15}N_3O_2$	C, 71.90 H, 4.76	C, 71.90 H, 4.76
VIII	$-N(C_6H_5)_2$	*B*	173° dec.	Ethanol	64	$C_{25}H_{19}N_3O_2$	C, 76.31 H, 4.86	C, 76.13 H, 4.83
IX	$-C_2H_5$	*C*	100–101°	Propanol–methanol	74	$C_{15}H_{14}N_2O_2$	C, 70.84 H, 5.55	C, 71.12 H, 5.62
				Type IV				
X	$-N(C_6H_5)H$	*A*	128°	Ethanol	51	$C_{18}H_{14}N_2O_2S$	C, 67.03 H, 4.37	C, 66.90 H, 4.28
XI	$-N(C_6H_5)_2$	*B*	211–212° dec.	Ethanol–methanol	48	$C_{24}H_{18}N_2O_2S$	C, 72.33 H, 4.55	C, 71.93 H, 4.44
XII	$-C_2H_5$	*C*	112–113°	Methanol	38	$C_{14}H_{13}NO_2S$	C, 64.83 H, 5.05	C, 64.94 H, 4.98

exhibited m.p. of 153°. [Lit. (14) m.p. 152–155°.]

2-Benzoylthiophene Oxime—The procedure mentioned under 2-benzoylpyridine oxime was followed. The pure sample gave a m.p. of 113°. [Lit. (14) m.p. 113–114°.]

Synthesis of Oximino Esters[3]

2-Phenylcarbamyloximino Benzoylpyridine (I)—*Method A*—2-Benzoylpyridine oxime (1.98 Gm., 0.01 mole), pyridine (1 Gm. 0.0126 mole), and phenylisocyanate (2.38 Gm., 0.02 mole) were refluxed for 1 hr. A brownish solid residue was obtained on cooling the mixture. The solid residue was washed with distilled water until there was no pyridine odor. Three repeated recrystallizations from ethanol afforded a pure analytical sample, m.p. 167–168° dec. Strong bands in the I.R. at 5.8 μ ($-\overset{\overset{O}{\|}}{C}-O-$) and 6.2 μ ($-C=N-$) are indicative of $-C-O-$ and $-C=N$, respectively; yield was 95% of theory.

3-Diphenylcarbamyloximino Benzoylpyridine (V)—*Method B*—In a three-neck flask, fitted with a stirrer, condenser, and dropping funnel, were placed 3-benzoylpyridine (1.98 Gm., 0.01 mole), pyridine (25 ml., the minimum amount which will dissolve the oxime), and benzene (100 ml.). The mixture was stirred and diphenylcarbamylchloride (2.31 Gm., 0.01 mole) in benzene (100 ml.) was added dropwise. After the completion of addition, the mixture was refluxed for 12 hr. with stirring. The mixture was cooled, washed with 10% potassium bicarbonate (5 times), and then washed with water (4 times), and the benzene phase was dried over anhydrous magnesium sulfate. On evaporation of benzene under reduced pressure a solid residue was obtained which on recrystallization from a mixture of ethanol–methanol afforded a pure sample, m.p. 193° dec. The I.R. gave a sharp band at 5.75 μ indicative of ester linkage. Yield was 52% of theory.

2-Propionyloximino Benzoylthiophene (XII)—*Method C*—2-Benzoylthiophene oxime (2.03 Gm., 0.01 mole) dissolved in the minimum quantity of pyridine was placed in a round-bottom flask. The mixture was diluted with benzene (200 ml.). On addition of propionylchloride (1.15 Gm., 0.016 mole) dropwise while stirring, a white suspension formed. This mixture was stirred for 4 hr. at room temperature, refluxed for 12 hr., cooled, and benzene washed with 10% potassium bicarbonate and water successively, and dried as in method *B*. On evaporation of benzene, under reduced pressure, an oily residue was obtained which on repeated washing

[3] See Table II for physical constants and analytical data.

with cold water gave a solid residue. The crude mixture was recrystallized from methanol, and yielded a pure sample, m.p. 112–113°. The I.R. gave a sharp peak at 5.70 μ indicative of ester. Yield was 38% of theory.

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New Compounds: Synthesis of Some Phosphorus–Nitrogen Compounds for Pharmacological Study I

By A. ABOU-MOUSTAFA, M. KHALIFA, and H. EL MANGOWRI

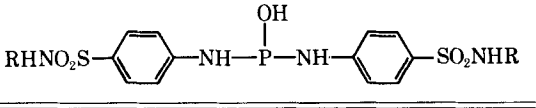
The synthesis of some phosphorus–nitrogen compounds *via* the condensation of phosphorus trichloride with a number of sulfa drugs is described. With sulfacetamide, sulfathiazole, and sulfadimidine three molecules of the sulfa compound condensed with one molecule of the acid (sulfamethazine) chloride although the molecular ratio of the reactants was 2 of the former to 1 of the latter. On the other hand, with sulfanilamide and sulfapyridine the condensation took place according to the ratio mentioned earlier.

THE INTEREST in the synthesis of phosphorus–nitrogen compounds arises from the fact that some of these compounds are of potential medicinal value. Cates *et al.* in a series of publications (1–5) reported the synthesis of nearly 60 such compounds and those containing substituted *p*-toluidine and 2-aminopyridine moieties were prepared for evaluation as antineoplastic agents. Likewise, it has been reported that the *N*-arylsulfonylphosphinimide derivatives synthesized by Oyamada have tumor inhibiting activity against mammary carcinoma (6).

The present investigation, however, is concerned with the synthesis of some phosphorus compounds *via* the condensation of phosphorus trichloride with a number of sulfonamides since these latter drugs are of considerable therapeutic value.[1]

Several attempts were made to condense sulfanilamide with phosphorus trichloride. Condensation in reagent dioxane according to the method of Cates (1, 4) proved to be unsatisfactory due to the immediate formation of an insoluble addition complex which did not dissolve even when the reflux was continued for several hours. The addition product afforded the starting sulfa compound after being worked up. The use of other nonpolar solvents such as carbon tetrachloride (6–8), absolute ether (2–4, 9), and dry benzene (2, 9) which were used by other investigators proved unsuitable because sulfanilamide itself is insoluble in these solvents and it was recovered unchanged from the reaction mixture. Accordingly, attention was directed to the use of polar solvents. Audrieth and

TABLE I—*N*-SUBSTITUTED DERIVATIVES OF PHOSPHORODIAMIDOUS ACID



R	Solvent of Crystallization[a]	M.p.,[b] °C.	Formula	Anal.,[c] % N Calcd.	N Found	S Calcd.	S Found	P Calcd.	P Found
H	A	178–180 230 dec.	$C_{12}H_{15}N_4O_5PS_2$	14.35	13.90	16.42	16.50	7.93	7.94
2-Pyridyl	B	195–200 250 dec.	$C_{22}H_{21}N_6O_5PS_2$	15.44	15.07	11.78	11.35	...	...

[a] A, aqueous alcohol; B, absolute alcohol. [b] Liquid crystal. Melting points were performed by the capillary tube method and are uncorrected. [c] Analyses performed by Janssen Pharmaceutica, Beerse, Belgium.

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[1] The products at present are under preliminary screening for possible antineoplastic action or any useful pharmacological activity.