catalyzes the degradation of benzyl penicillinic acid, while acetate ion has no effect.

There is a positive primary salt effect in neutral solution (phosphate buffer, pH 6.80) and in weakly alkaline solution (borate buffer, pH 8.75) but no primary salt effect in weakly acid solution (acetate buffer, pH 4.50).

In buffer-free solutions, pH 4–9, at least three separate reactions take place: (*a*) noncatalyzed cleavage of undissociated benzyl penicillinic acid, (*b*) noncatalyzed cleavage of benzyl penicillinate ion, and (*c*) hydroxyl ion catalyzed cleavage of benzyl penicillinate ion. Reaction *a* is about 5000 times faster than reaction *b*.

REFERENCES

(1) Benedict, R. G., *et al.*, *J. Bacteriol.*, **49**, 85(1945).
(2) Brodersen, R., *Acta Pharmacol. Toxicol.*, **3**, 345(1947).
(3) Pratt, R., THIS JOURNAL, **36**, 69(1947).
(4) Clapham, P. C. H. V., *Pharm. J.*, **165**, 126(1950).
(5) Macek, T. J., Hanus, E. J., and Feller, B. A., THIS JOURNAL, **37**, 322(1948).
(6) Hahn, L., *Biochim. Biophys. Acta*, **2**, 113(1948).
(7) Kaern, M., *Dansk Tidsskr. Farm.*, **29**, 93(1955).
(8) Fujiwara, H., *J. Pharm. Soc. Japan*, **75**, 681(1955).
(9) Swintosky, J. V., *et al.*, THIS JOURNAL, **45**, 34(1956).
(10) Schwartz, M. A., Granatek, A. P., and Buckwalter, F. H., *ibid.*, **51**, 523(1962).
(11) Brodersen, R., *Kgl. Danske Videnskab. Selskab Mat. Fys. Medd.*, **24** (No. 14), (1948).
(12) Örtenblad, B., *Acta Chem. Scand.*, **4**, 518(1950).
(13) Alicino, J. F., *Ind. Eng. Chem. Anal. Ed.*, **18**, 619 (1946).
(14) Harned, H. S., and Hamer, W. J., *J. Am. Chem. Soc.*, **55**, 2194(1933).

Anticholinergic Heterocyclic Ketoximino-Ethers and -Esters

By MAN M. KOCHHAR*, ROBERT G. BROWN, and JAIME N. DELGADO

The synthesis of a series of oximino-ethers and -esters was accomplished by *O*-alkylations and esterifications of 1-methyl-4-oximinopiperidine and 3-oximinotropane. In the course of this investigation, 13 new compounds were synthesized and evaluated for their anticholinergic activity.

ALTHOUGH MANY of the anticholinergic compounds are esters, it is known that the ester group is not absolutely essential for this bioaction (1, 2). Consequently, the medicinal chemist has studied how other groups affect the distribution characteristics and the intrinsic reactivity of compounds possessing the anticholinergic pharmacophores (3). The oximino group should certainly alter the partition (lipid-water) 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. In accordance with these considerations, it became of interest to study such structure-activity relationships by synthesizing oximino-esters and -ethers possessing the anticholinergic pharmacophores. Structure-activity studies of anticholinergic agents have led to the postulation of three pharmacophoric groups, *i.e.*, (*a*) a potential or actual cationic-nitrogen function to interact with the anionic region of the acetylcholine-receptor site, (*b*) a polar and/or polarizable group to interact with the esteratic region on this receptor site, (*c*) a large aryl or aralkyl moiety to provide the umbrellalike effect that appears to be necessary for effective blockade of the receptor surface (4, 5). The spatial relations among these groups appear to be critical factors that affect the activity. Accordingly, this work entails a study of structure-activity relationships among certain oximino-esters and oximino-ethers derivable from tropinone and 1-methyl-4-piperidone.

The oximes, starting materials for the synthesis of oximino-ethers and -esters, were prepared according to the method of Dickerman and Lindwall (6), with slight modification of reaction period. In the oximino-ethers, this work demonstrated that 1-methyl-4-oximinopiperidine and 3-oximinotropane can be alkylated to give *O*-alkyl ethers. The *O*-alkylation was effected by allowing a dialkylsulfate or an alkyl halide to react with the salt of the oxime, according to the method of Waters and Hartung (7) and French and Harrison (8). The use of a weak base (*e.g.*, tri-*n*-propylamine, pyridine, etc.) did not promote the reac-

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tion in the forward direction. The purity of these oximino-ethers was confirmed by vapor phase chromatography and infrared spectrophotometry.

The synthesis of the oximino-esters, 1-methyl-4-(benzoyloximino)piperidine and 3-(benzoyloximino)tropane, was accomplished by the method of Gass and Bope (9). This is a simple esterification in which the acylating reagent is an acyl chloride. Other workers (10, 11) have used basic reagents, *e.g.*, pyridine, sodium ethoxide, dilute solution of sodium hydroxide, etc., to promote the reaction with varying degrees of success. All the esterification reactions were conducted in benzene since it was found to be more satisfactory than other solvents. Gass and Bope (9) reported that the acylation of oximes in the presence of pyridine led to the formation of pyridinium chloride and transformation of the syn-oxime *via* the antiform into the respective nitrile when the reaction mixture was allowed to stand in the solvent. However, these reactions were noted to proceed well in the presence of bases such as tri-*n*-propylamine or sodium hydride in ethanol, and improved yields were recorded. The basic reagent proved to be necessary in promoting the desired oxime esterification, *e.g.*, the synthesis of 1-methyl-4-(3,4,5-trimethoxybenzoyloximino)piperidine. In the absence of a base, the product obtained was 3,4,5-trimethoxybenzoic anhydride.

The method of Counsell and Soine (12) with modification was adapted to the preparation of 1-methyl-4-(phenylcarbamyloximino)piperidine. This method involves the treatment of the oxime with phenyl isocyanate.

EXPERIMENTAL[1]

Synthesis of Oximes

1-Methyl-4-oximinopiperidine.—This compound was prepared from 1-methyl-4-piperidone (2.24 Gm., 0.02 mole), hydroxylamine hydrochloride (1.1 Gm., 0.014 mole), sodium bicarbonate (1.32 Gm., 0.014 mole), and water (24 ml.) according to the method of Dickerman and Lindwall (6). The pure sample exhibited a m.p. of 128.5–129°; reported m.p. 129–130° (6). The yield was 2.5 Gm. (95% of theory). The infrared spectrum showed the characteristic bands for —C(=N)— and =N—OH.

3-Oximinotropane.—The above procedure was adapted to this preparation. A pure sample of this compound melted at 110–111°; reported 111–112° (13). Yield was 3.0 Gm. (98% of theory).

[1] Reported melting points are uncorrected. A Thomas-Hoover Uni-melt apparatus was used for melting point determinations. The Alfred Bernhardt Mikroanalytisches Laboratorium, Germany; Dr. K. W. Zimmerman, University of Melbourne, Melbourne, Australia; and Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., conducted the elemental analyses.

Synthesis of Oximino-Ethers[2]

Method A.—1-Methyl-4-(methyloximino)piperidine.—In a 500-ml. three-necked flask, equipped with a stirrer and two burets, a mixture of 1-methyl-4-oximinopiperidine (2.56 Gm., 0.02 mole) and sodium hydroxide solution (20 ml. of 5% solution) was placed. One buret was filled with sodium hydroxide solution (16.5 Gm. in 20 ml. of water), and the second was filled with dimethylsulfate (17.64 Gm., 0.014 mole). Sodium hydroxide solution and dimethylsulfate were added to the reaction mixture while stirring. The rate of addition was regulated so that 1 drop of alkali was added per drop of dimethylsulfate; during this time, the temperature of the bath was increased to approximately 70°. The mixture was then refluxed for 1.5 hr. on a steam bath. It was cooled to room temperature and extracted with ether. The ether extracts were combined, dried over anhydrous sodium sulfate, and concentrated by distillation under reduced pressure (water pump). The residual material was dissolved in anhydrous ether and treated with methyl iodide (excess). The crude methyl iodide salt was purified by repeated recrystallizations from anhydrous isopropanol. The pure sample melted at 208–208.5°; yield was 3.6 Gm. (65% of theory). The infrared spectrum showed an ether group, and no absorption was observed for a carbonyl group.

Method B.—1-Methyl-4-(benzyloximino)piperidine.—The benzyl chloride (2.5 Gm., 0.02 mole) in anhydrous ethanol (10 ml.) was added dropwise to a stirring mixture of 1-methyl-4-oximinopiperidine (2.5 Gm., 0.02 mole), anhydrous ethanol (20 ml.), and sodium hydride (1.5 Gm. of a 51.6% dispersion in mineral oil, 0.03 mole). The mixture was refluxed for 5 hr. on a steam bath. The reaction mixture was filtered, and the filtrate was concentrated by distillation under reduced pressure. The methyl bromide salt was prepared by the conventional method and purified by repeated crystallization. A pure sample melted at 216.5–217°; yield was 3.2 Gm. (52% of theory). It showed no absorption in the infrared spectrum in the region between 5.5–6 μ.

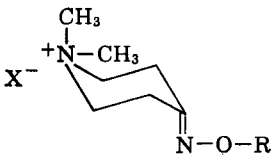
Synthesis of Oximino-Esters[3]

Method A.—1-Methyl-4-(benzoyloximino)piperidine.—This compound was prepared from 1-methyl-4-oximinopiperidine (1.28 Gm., 0.01 mole) and benzoyl chloride (1.4 Gm., 0.01 mole) in anhydrous ether according to the procedure of Gass and Bope (9). The esterification procedure was improved somewhat by increasing the reaction period and using anhydrous benzene as the reaction medium. The solid residue obtained was characterized and identified as the hydrochloride salt on repeated crystallization with anhydrous ethanol, m.p. 169–169.5°. The compound was shown to be an ester by examination of its infrared spectrum. A strong band appearing at 6.1 μ and 5.7 μ is indicative of —C(=N)— and —C(=O)—O—, respectively; yield was 1.3 Gm. (50% of theory).

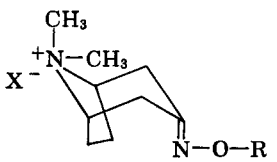
[2] See Table I for physical constants and analytical data.

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

TABLE I.—PHYSICAL CONSTANTS AND ANALYTICAL DATA



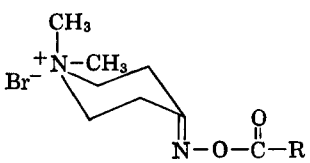
R	X	Compd. No.	Method of Prepn.	M.p., °C.	% Yield	Empirical Formulas	Anal., % Calcd.	Found
CH_3—	I	*1*	*A*, *B*[a]	208–208.5 dec.	68.0	$C_8H_{17}IN_2O$	C, 33.82 H, 6.03	34.58 6.30
C_6H_5—CH_2—	Br	*2*	*B*[b]	216–217 dec.	52.0	$C_{14}H_{21}BrN_2O$	C, 53.67 H, 6.76	53.90 6.76
H_3C—$\overset{\overset{CH_3}{\vert}}{\overset{+}{N}}$—$CH_2CH_2CH_2$— ($CH_3$)	Br	*3*	*B*[b]	217–218 dec.	65.0	$C_{13}H_{29}Br_2N_3O$	C, 38.71 H, 7.25	38.26 7.35

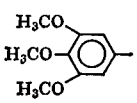
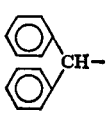
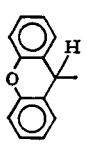
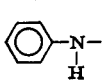


C_6H_5—CH_2—	Br	*4*	*B*[b]	209–210 dec.	94	$C_{16}H_{23}BrN_2O$	C, 56.64 H, 6.83	57.40 7.01

[a] Recrystallized from isopropanol. [b] Recrystallized from ethanol.

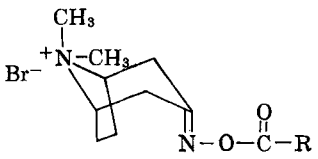
TABLE II.—PHYSICAL CONSTANTS AND ANALYTICAL DATA

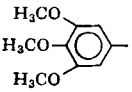
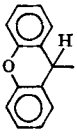
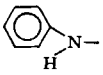


R	Compd. No.	Method of Prepn.	M.p., °C.	% Yield	Empirical Formulas	Anal., % Calcd.	Found
	*5*	*A*[a]	169.0–169.5 dec.	50	$C_{13}H_{17}ClN_2O_2$	C, 58.09 H, 6.37	58.16 6.27
	*6*	*B*, *C*[a]	182.5–183.0 dec.	34	$C_{17}H_{25}BrN_2O_5$	C, 48.91 H, 6.04	48.45 6.35
	*7*	*D*[a]	195.5–196.0 dec.	98	$C_{21}H_{25}BrN_2O_2$	C, 60.43 H, 6.04	60.21 6.41
	*8*	*D*[b]	159.0 dec.	92	$C_{21}H_{23}BrN_2O_3$	C, 58.47 H, 5.37	57.87 5.54
	*9*	*E*[a]	186.0–186.5 dec.	68	$C_{14}H_{20}BrN_3O_2$	C, 49.42 H, 5.89	49.68 6.23

[a] Recrystallized from anhydrous ethanol. [b] Recrystallized from anhydrous isopropanol.

TABLE III.—PHYSICAL CONSTANTS AND ANALYTICAL DATA



	Compd. No.	Method of Prepn.	M.p., °C.	% Yield	Empirical Formulas	Anal., % Calcd.	Found
	*10*	*A*[a]	163.5–164.5 dec.	75	$C_{15}H_{19}ClN_2O_2$	C, 61.10 H, 6.49	60.77 6.67
	*11*	*B, C*[a]	146.0–147.0 dec.	30	$C_{19}H_{27}BrN_2O_5$	C, 51.48 H, 6.14	52.12 6.31
	*12*	*D*[a]	137.0–138.0 dec.	91	$C_{23}H_{25}BrN_2O_3$	C, 60.39 H, 5.50	60.62 5.28
	*13*	*E*[a]	193.5–194.0 dec.	80	$C_{16}H_{23}BrN_3O_2$	C, 52.15 H, 6.01	51.72 5.96

[a] Recrystallized from anhydrous ethanol.

TABLE IV.—SPASMOLYTIC ACTIVITY OF KETOXIMINO-ETHERS AND -ESTERS ON EXCISED ILEUM SEGMENTS OF THE GUINEA PIG

Drug	Dose, mg./70 ml.	Response: No. Positive / No. Tried (All-or-None)	Response: % Decrease in Spasm	Slope Function	ED_{50}, mg.	Relative Potency (Ratio of ED_{50} Compared with Atropine Sulfate)
12	0.006	10/12	83.3	4.11	0.0016	6.375
	0.002	7/12	58.3			
4	1.0	11/12	91.7	2.77	0.242	0.033
	0.3	7/12	58.3			
1	1.0	7/10	70.0	9.15	0.288	0.019
	0.3	7/12	58.3			
2	1.0	11/13	84.6	2.00	0.490	0.016
	0.3	4/17	23.5			
10a[a]	1.0	8/12	66.6	4.05	0.550	0.015
	0.3	4/14	33.3			
8	1.0	9/12	75.0	1.74	0.680	0.015
	0.3	1/14	7.1			
7	1.0	10/12	83.3	1.64	0.600	0.013
	0.3	1/12	8.3			
5[b]	1.0	10/16	62.5	2.66	0.720	0.011
	0.3	3/16	18.7			
5a[a]	1.0	8/12	66.6	2.08	0.722	0.011
	0.3	1/9	11.1			
10[b]	1.0	10/15	66.6	1.93	0.750	0.010
	0.3	1/12	8.3			
13	1.0	7/14	50.0	9.14	1.000	0.006
	0.3	3/10	30.0			
3	1.0	7/12	58.3	3.15	0.780	0.002
	0.3	2/10	20.0			
6	1.0	4/13	30.8	4.65	2.200	0.0009
	0.3	1/10	10.0			

[a] Methyl bromide. [b] Hydrochloride.

Method B.—1-Methyl-4-(3,4,5-trimethoxybenzoyloximino)piperidine.—A mixture of 1-methyl-4-oximinopiperidine (1.28 Gm., 0.01 mole), anhydrous benzene (20 ml.), sodium hydride (1.5 Gm., 51.6% mineral oil dispersion, 0.03 mole), and anhydrous ethanol (1 ml.) was placed in a three-necked flask and the mixture stirred throughout the reaction period. After 15 min., the 3,4,5-trimethoxybenzoyl chloride (2.3 Gm., 0.01 mole) in anhydrous benzene (20 ml.) was added dropwise. The mixture was refluxed for 7 hr. The reaction mixture was allowed to cool to room temperature, filtered, washed successively with 10% potassium carbonate (five 20-ml. portions) and cold water (four 50-ml. portions), dried over anhydrous sodium sulfate, and concentrated by distillation under reduced pressure. An oily residue was obtained. The methyl bromide salt was prepared by the usual method. Fractional crystallization from anhydrous ethanol resulted in two fractions. One was 3,4,5-trimethoxybenzoic anhydride, m.p. 159–160° [reported m.p. 160–161° (12)]; the other fraction was the desired product with m.p. 182–183° dec.; yield was 1.4 Gm. (34% of theory). The infrared spectrum showed an absorption at 11.6 μ, which is indicative of 3,4,5-trisubstituted benzene besides the normal absorption for an ester and oximino link.

Method C.—3-(Xanthene-9-acyloximino)tropane.—Method *B* described above was followed with slight modifications. The base used was tri-*n*-propylamine, and the reaction was conducted for 15 hr. The crude product obtained was crystallized from ethanol to yield a pure sample, m.p. 137–138° dec.

Method D.—The xanthene-9-acylchloride (2.4 Gm., 0.01 mole), prepared from xanthene-9-carboxylic acid (4.5 Gm., 0.02 mole) and thionyl chloride (20 Gm., 0.02 mole), was dissolved in anhydrous benzene (20 ml.). The resulting solution was added slowly with stirring to a mixture of the oxime (1.28 Gm., 0.01 mole) and anhydrous benzene (50 ml.). During the addition of the acyl chloride, the mixture was maintained below room temperature with the aid of an ice-bath. The mixture was allowed to assume room temperature and stirred for 4 hr. under a stream of nitrogen gas. The reaction mixture was washed with a solution of 10% potassium carbonate (four 20-ml. portions). The benzene layer was dried over anhydrous sodium sulfate and concentrated by distillation under reduced pressure (water pump). The residue was treated with methyl bromide to form the quaternary salt by the conventional method. The crude crystals were purified by repeated recrystallizations from anhydrous isopropanol to yield an analytically pure sample, m.p. 159° dec. The infrared spectrum proved the identity of the functional groups.

Method E.—1-Methyl-4-(phenylcarbamyloximino)piperidine.—1-Methyl-4-oximinopiperidine (1.28 Gm., 0.01 mole) and phenyl isocyanate (1.25 Gm., 0.01 mole) were placed in a conical flask provided with a condenser and a drying tube. The reaction mixture was heated on a steam bath for 25 min. An oily residue was obtained which on washing with anhydrous ether yielded a solid material. The methyl bromide salt was prepared by the conventional method. The crude material was recrystallized from anhydrous ethanol to yield a pure sample, m.p. 186–186.5° dec.; the yield was 2.3 Gm. (68% of theory). The compound was identified as a carbamate by examination of its infrared spectrum.

PHARMACOLOGIC EVALUATION

The synthesized compounds were evaluated quantitatively for their spasmolytic activity against the spasm induced by fixed doses of acetylcholine on smooth muscle of excised guinea pig ileum. The method of Miller *et al.* (14) was used for this study. This method involves comparing each compound with a known standard (atropine sulfate) under reproducible conditions. The results are given in Table IV.

The data, so obtained in the above experiment, were treated on an all-or-none basis according to Litchfield and Wilcoxon (15). An appropriate level of relaxation was selected in each experiment so that activities could be compared with that of the standard in the same tissue. A response was deemed positive if the level of contraction was returned to 70% or above for compounds *8* and *12;* 33% or above for compounds *3*, *5*, and *6;* 50% or above for compounds *1* and *13;* and 60% or above for all of the remaining compounds. The percentage response was calculated as (number positive/number tried) × 100.

The potency of the synthesized compounds, relative to atropine, was determined directly from the ED_{50}'s. The compounds are ranked in order of potency in the table. The most potent compound *12* is a methyl bromide.

Subsequent comparison of compound *12* with atropine methylbromide at an 80% spasmolysis level revealed a close relationship for relative potency (atropine sulfate, 1; atropine methylbromide, 4.9; and compound *12*, 4.3).

It also is noteworthy that the oximes, which served as synthetic intermediates, did not exhibit discernible anticholinergic activity. Compound *9* proved to be cholinergic.

STRUCTURE-ACTIVITY RELATIONSHIPS

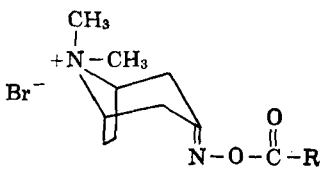
The pharmacologic evaluation reveals that the oximes (1-methyl-4-oximinopiperidine and 3-oximinotropane) do not exhibit discernible anticholinergic activity, whereas their ester and ether derivatives described above do possess this biologic property. Structural considerations indicate that the polarity and polarizability of the oximes is greater than that of its derivatives (esters and ethers) due to the presence of the free oximino group. These oximes are highly water soluble and ionizable—hence must possess different distribution characteristics and intrinsic reactivity when compared with the active derivatives. Second, a relatively large acyl or aralkyl group to provide the umbrellalike effect, which appears to be necessary for effective blockade of the acetylcholine receptor site, is absent in these oximes. Accordingly, it can be concluded that this lack of bioactivity is in agreement with theoretical predictions.

Structure-activity studies indicate that an ester grouping is not essential for anticholinergic activity; *e.g.*, the anticholinergic activity of benztropine (3-diphenylmethoxy tropane) approximates that of atropine (2). Among the oxime derivatives

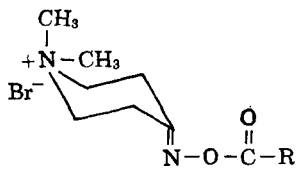
herein described, the anticholinergic activity of the ethers is comparable to the related esters. Hence, this investigation reveals an interesting analogy among these oxime derivatives.

The 3-oximinotropane ethers and esters showed greater activity compared to 1-methyl-4-oximinopiperidine analogs. This higher activity may be due to the greater umbrellalike effect of the tropane moiety. These oximino-ethers and -esters were studied in the quaternized form. In this form, they possess a cationic moiety to complement the anionic region on the acetylcholine receptor site. The effect of quaternization is demonstrated by the higher activity exhibited by quaternary compounds, compared with respective tertiary amine congeners. Compound *10* methyl bromide showed a higher degree of activity when compared with its hydrochloride salt.

Structural considerations of the synthesized compounds reveal that a 4-atom chain intervenes between the quaternary nitrogen and the oxygen function; whereas in many known compounds, a 2-carbon chain is present. However, the rigid ring structure possibly orients the *N*-methyl and the oximino oxygen into more nearly the 2- or 3-carbon chain interprosthetic distance, which appears to be optimal for this activity. The above explanation can be seen clearly by the interatomic distance in VIII or IX. This distance between the quaternary nitrogen and the carbonyl oxygen atom is 5.6 Å. in VIII and 5.7 Å. in IX, which compares favorably with the distance between the carbonyl oxygen and *N*-methyl of atropine (5.4 Å.) (Dreiding stereomodels).



VIII



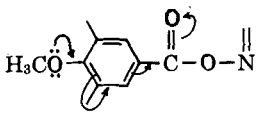
IX

The interpharmacophoric distance between the two nitrogen atoms in IX and in VIII is about 3.7 Å.; such distances approximate that between the *N*-methyl and ether oxygen in atropine (3.7 Å.). Accordingly, these oxime derivatives possess anticholinergic properties because of their general stereoelectronic similarity to the prototype atropine.

Among these oxime-esters and -ethers, the size of the acyl or aralkyl group has marked effect on the anticholinergic activity—the bulkier the group, the greater the activity. The new oximino-ester, 3-(xanthene-9-acyloximino)tropane, was found to be six times more active than atropine. The activity of the xanthene-9-carboxylate of the piperidine analog was found to be 1/60 that of atropine. This difference in activity may be due to the greater umbrellalike effect of the tropane moiety. The activity of 1-methyl-4-(diphenylacetyloximino)-piperidine was slightly less than the xanthene-9-carboxylate.

It was predicted that piperidine analogs would not be so active as tropane analogs. The entire structure of IX would not be so rigid as that of VIII, and the rigidity of tropane ring system *versus* the piperidine ring seems to be of importance in the field of anticholinergics (16). The greater activity of the tropane series can also be attributed to greater umbrellalike effect of the tropane molecule, which may help in the effective blockade of the receptor sites. The pharmacologic data appeared to bear out this prediction.

The substituted acyl derivative (compound *6*) showed weak anticholinergic activity. This might be because the electron distribution of the ester function is affected by the presence of three methoxy groups *e.g.*,



The partition coefficient (lipid-water solubility balance) also should be affected by the polar groups in the molecule. The low activity of the phenylcarbamates (compounds *9* and *13*) might be explained analogously on the basis of electron density principles.

REFERENCES

(1) Barlow, R. B., "Introduction to Chemical Pharmacology," John Wiley & Sons, Inc., New York, N. Y., 1955, p. 154.
(2) Funcke, A. B. H., *et al.*, *J. Med. Pharm. Chem.*, **4**, 215(1961).
(3) Burger, A., "Medicinal Chemistry," Interscience Publishers, Inc., New York, N. Y., 1960, pp. 466–469.
(4) Gyermek, L., and Nador, K., *J. Pharm. Pharmacol.*, **9**, 217(1957).
(5) Long, J. P., *et al.*, *J. Pharmacol.*, **117**, 29(1956).
(6) Dickerman, S. C., and Lindwall, H. G., *J. Org. Chem.*, **14**, 530(1949).
(7) Waters, K. L., and Hartung, W. H., *ibid.*, **12**, 469 (1947).
(8) French, C. M., and Harrison, D., *J. Chem. Soc.*, **1955**, 3513.
(9) Gass, L., and Bope, F. W., THIS JOURNAL, **48**, 186 (1959).
(10) Vermillion, G., *et al.*, *J. Org. Chem.*, **5**, 75(1940).
(11) Exner, O., *Coll. Czech. Chem. Commun.*, **20**, 207 (1955).
(12) Counsell, R. E., and Soine, T. O., THIS JOURNAL, **49**, 289(1960).
(13) Stoll, A., *et al.*, *Helv. Chem. Acta*, **38**, 559(1955).
(14) Miller, L. C., Becker, T. J., and Tainter, M. L., *J. Pharmacol. Exptl. Therap.*, **92**, 260(1948).
(15) Litchfield, J. F., and Wilcoxon, F., *ibid.*, **96**, 99 (1949).
(16) Cusic, J. W., and Robinson, R. A., *J. Org. Chem.*, **16**, 1921(1951).