Synthesis of Ketoximino-Esters and -Ethers as Antihypertensive Agents

MAN M. KOCHHAR, BYRON B. WILLIAMS, and JEN H. FAN

Abstract □ In a search for new antihypertensives, a series of oximino-esters and -ethers of 4,4′-bis(dimethylamino) benzophenone oxime and 4,4′-bis(diethylamino)benzophenone oxime were prepared. The synthesis of oximino-esters and -ethers was accomplished by esterifications and *o*-alkylations of the above oximes. In the course of this investigation, 12 new compounds were synthesized and evaluated for their antihypertensive activity.

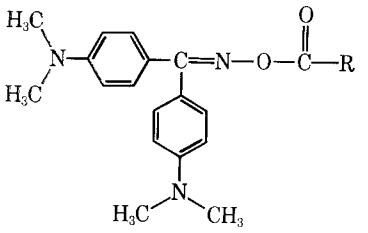
Keyphrases □ Esters, ketoximino—synthesis □ Ethers, ketoximino—synthesis □ Hypotensive activity—ketoximino esters ethers □ IR spectrophotometry—identity

Lyon *et al.* (1) reported the first effective antihypertensive agent. Since that time, a multitude of compounds have been prepared and tested for their hypotensive properties. The chemical structure and mechanism of pharmacological action of these drugs vary, yet the prominent compounds exert similar therapeutic action. Several review articles (2–5) have appeared in the literature. Particular attention has been given to the series of compounds which demonstrate ganglionic blockade action. Reduction of vasoconstrictor impulses by ganglionic blockade at sympathetic ganglionic sites may provide valuable therapeutic assistance in many cases of hypertension.

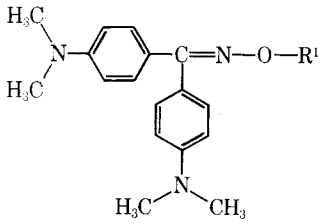
The widely used ganglionic blockers can be classified as monoquaternary ammonium, bis-quaternary ammonium, polyammonium compounds, branched amines, inorganic ions, and nonbasic compounds. Most of these compounds contain at least a tertiary or a quaternary nitrogen atom. In the bis-quaternary series, the greatest activity was found to be induced by compounds containing the quaternary ammonium group. The substituent at quaternary nitrogen or a critical distance between two onium centers has led to highly active compounds. It is known that the physicochemical properties of the compound can influence the biological activities such as accessibility to the site of action, relative distribution of the drug between sites of action and site of loss, nature of bonding at the site of action, rate of excretion, and the ability of penetration through the membrane. 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 and -ethers of 4,4′-bis(dimethylamino)benzophenone and 4,4′-bis(diethylamino)benzophenone and to determine whether they possessed significant antihypertensive action. According to Kochhar (6), the oximino group may undoubtedly alter the partition coefficient of the compound and thus influence its distribution in the body. In addition, the oximino linkage might affect not only the intrinsic reactivity but also the stereochemistry of a given compound as well as its susceptibility toward metabolic degradation. A study of such compounds may contribute to the understanding of hypotensive phenomena from a structure-activity standpoint.

DISCUSSION

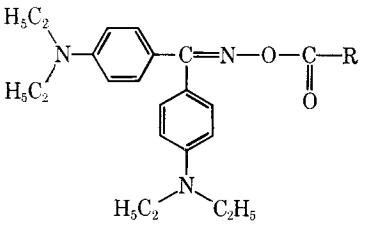
The compounds which were selected for synthesis are the oximino-esters and -ethers of 4,4′-bis(dimethylamino) benzophenone and 4,4′-bis(diethylamino)benzophenone (Types I, II, III, and IV).



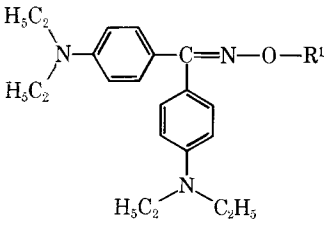
Type I



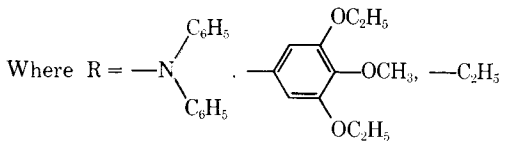
Type II

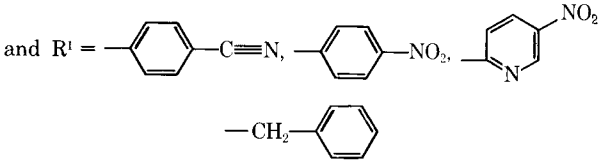


Type III



Type IV





The preparation of 12 new esters and ethers of Types I, II, III, or IV, starting with 4,4′-bis(dimethylamino) benzophenone and 4,4′-bis(diethylamino) benzophenone, was accomplished by modifying the methods described in the literature (7–9). The reaction conditions were very critical in the formation of final products. The oximes can undergo Beckmann rearrangement with greater ease to anilide if reaction conditions are not sufficiently alkaline. Pearson (10), Chapman (11), and Higman (12) had indicated that the rate of rearrangement depends partly on the relative tendency of the migrating group to donate a pair of electrons to the oximino-nitrogen atom. The strong electrophilic influence of dialkylamino groups presumably explains the ease of rearrangement of the above oximes and their esters and ethers. As this is a symmetrical molecule, the end product, amide does not affect *syn-* or *anti-* configuration. Sufficiently strong bases, *e.g.*, sodium hydroxide, sodium hydride, and potassium tertiary butoxide, were applied in oximination, esterification, and *o*-alkylation to prevent Beckmann rearrangement of the oximes to an amide. The use of strong base was also necessary to prevent the formation of 3,4,5-trimethoxybenzoic anhydride in the case of Compounds II and V. It is proposed that 3,4,5-trimethoxybenzoyl chloride is converted to 3,4,5-trimethoxybenzoic acid and that in turn reacts with acyl chloride to yield an anhydride.

A general study of the structural features of the oximino-esters and -ethers tested for their effect on blood pressure of experimental animals led to the following observations. None of the compounds in lower dosage showed any impressive activity. Compounds I and IV, the diphenyl carbamates, at dose level of 100 mg./kg. induced the most impressive decrease in systolic pressure. Compounds III and VI, the propionate derivatives, showed a significant but lesser hypotensive effect at the same dose level. The dimethylamino compounds in each instance were more effective as hypotensives than the corresponding diethylamino compounds. As a general observation the oximino-ester exhibited greater activity than oximino-ethers.

Although proof of ganglioplegic activity as the mechanism for the vascular effects of these experimental compounds has not been provided, certain structural and activity features support the ganglionic site. Affinity for the cholinergic receptor is a characteristic of methyl substituted amines and while there are in most cholinergic stimulants onium groups with methyl substitution, secondary or tertiary amines are capable of binding to the receptor and tertiary amines are potent ganglioplegics (13). Therefore, the dimethylamino compounds could conceivably bind to the cholinergic ganglion receptors of vascular innervations. The response from such binding could be either activation or blockage. According to Sice (14), the blocking effect of methyl substituted ganglionic agents is sometimes preceded by a transient stimulation, and Barlow states that these are among such ganglionic agents, some which stimulate, and some which block (15). It is a recognized characteristic of cholinergic activators that the stimulant effect may be reversed by a sufficient increase in dose. Such an effect was seen with three of the compounds under study here. Compounds III, VIII, and X, at low doses evoked hypertensive effect and at higher doses either caused no significant change in blood pressure or lowered it. The diethylamino compounds evoked no hypertensive effect at either low or high dose levels which is consistent with Ing's suggestion that ethyl substitution tends to convert stimulant compounds into purely blocking agents (16). The greater hypotensive efficacy of the trimethylamino compounds as compared with the triethylamino could have resulted from a reduction in receptor affinity effected by substitution of the larger group.

PHARMACOLOGIC EVALUATION

The synthesized oximino-esters and -ethers were evaluated for blood pressure effect on anesthetized normotensive rats. Pentobarbital solution (50 mg./kg.) was used for anesthesia as a standard. Acacia suspension (1%) of the oximino-esters and -ethers were prepared as test drugs. Blood pressure change was estimated by standard indirect method using the electrosphygmograph[1] which combines a linear core pressure transducer and a preamplifier to provide single-channel recordings of occluding cuff pressure and superimposed arterial pulsations. The rat previously anesthetized with a subcutaneous injection of pentobarbital sodium was placed in a Lucite restrainer box, a tubular occluding cuff slipped over the tail, and a pneumatic pulse sensor placed over the tail distal to the occluding cuff. Both pulse sensor and cuff were connected to the electrosphygmograph to allow simultaneous recording of arterial pulsations and cuff pressure. Pressure level at point of beginning of tail pulsations as occluding pressure dropped was considered to be a reliable estimate of the systolic pressure. The pressure was recorded initially, then the drug was administered subcutaneously and further blood pressure recordings were made at 5-min. intervals during 1 hr. Table I presents the blood pressure data so obtained. Replicates were done for the experiments which indicated significant activity, and values reported are means of the two.

[1] E & M model MK IV.

Table I—*Effects of Oximino-Esters and -Ethers on the Blood Pressure in Normotensive Anesthetized Rats*

Compound	Dose, mg./kg.	Blood Pressure: Origin, mm. Hg	Blood Pressure: Increase, %	Blood Pressure: Decrease, %
I	40	101	—	—
	100	127	—	28.7
II	40	103	—	—
	100	117	—	—
III	40	101	35.6	—
	100	123	—	15.0
IV	40	123	—	—
	100	132	—	15.9
V	40	113	—	—
	100	110	—	—
VI	40	120	—	10.0
	100	123	—	10.6
VII	40	124	—	—
	100	128	—	7.9
VIII	40	100	33	—
	100	110	—	—
IX	40	115	—	6.9
	100	136	—	10.3
X	40	115	20	—
	100	136	—	—
XI	40	120	—	—
	100	133	—	5.9
XII	40	136	—	9.5
	100	106	—	—

EXPERIMENTAL[2]

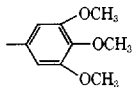
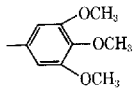
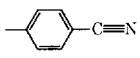
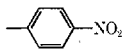
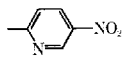
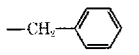
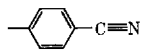
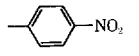
Synthesis of Oximes—*4,4′-Bis(dimethylamino)benzophenone Oxime*—A mixture of 4,4′-bis(dimethylamino) benzophenone (26.8 g., 0.10 mole), hydroxylamine hydrochloride (27.8 g., 1.10 mole), potassium hydroxide (60 g., 1.92 mole), alcohol (600 ml.) and water (50 ml.) was refluxed for 3 hr. After standing overnight at room temperature, the reaction mixture was poured into ice water (1500 ml.). The crude product obtained was recrystallized from a mixture of benzene and ethanol, yielded colorless needles (21 g.; 74% of theory), m.p. 215–216° [lit. (7) m.p. 213-216°].

4,4′-Bis(diethylamino)benzophenone Oxime—The above procedure was adapted to this preparation. A pure sample of this compound melted at 199–201° [lit. (7) m.p. 200–201°] and yielded 16 g. (41% of theory).

Synthesis of Oximino Esters—*4,4′-Bis(dimethylamino)benzophenone Oxime Diphenylcarbamate (I)—Method A*—Sodium hydride (0.5 g., 0.011 mole, 55.6% mineral oil dispersion) was added with stirring to a solution of 4,4′-bis(dimethylamino)benzophenone oxime (2.8 g., 0.01 mole) in tetrahydrofuran (30 ml.) and the mixture stirred for 15 to 20 min. till the evolution of gas ceased. Diphenylcarbamyl chloride (2.3 g., 0.01 mole) was added to the above mixture in small portions and mixture stirred for 2 hr. at room temperature and then diluted with water (300 ml.). The resulting mixture was extracted with ether. The ether layers were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Repeated crystallization from

[2] Reported melting points are uncorrected. A Thomas-Hoover Unimelt apparatus was used for melting point determination. Galbraith Laboratories, Inc., Knoxville, Tenn., conducted the elemental analysis.

Table II—Physical Constants and Analytical Data

Compound	R or R[1]	Method of Prepn.	M.p. °C.	Recrystn. Solvent	Yield, %	Empirical Formula	Anal. % Calcd.	Anal. % Found
				Type I				
I		*A*	209–210	Benzene	62.0	$C_{30}H_{30}N_4O_2$	C, 75.28 H, 6.13	C, 75.13 H, 6.32
II		*B*	131–132	Benzene	35.9	$C_{27}H_{31}N_3O_5$	C, 67.90 H, 6.54	C, 67.70 H, 6.54
III	$-C_2H_5$	*A*	107–108	Benzene	13.3	$C_{20}H_{25}N_3O_2$	C, 70.79 H, 7.42	C, 70.55 H, 7.35
				Type III				
IV		*A*	102–103	Benzene-alcohol	78.0	$C_{34}H_{38}N_4O_2$	C, 76.36 H, 7.16	C, 76.31 H, 7.06
V		*B*	106–107	Benzene-ether	46.9	$C_{31}H_{39}N_3O_5$	C, 69.77 H, 7.36	C, 70.07 H, 7.48
VI	$-C_2H_5$	*A*	100–102	Ethanol	28.7	$C_{24}H_{33}N_3O_2$	C, 72.85 H, 8.40	C, 72.76 H, 8.36
				Type II				
VII		*C*	147–147.5	Benzene	36.4	$C_{24}H_{24}N_4O$	C, 74.97 H, 6.25	C, 75.13 H, 6.42
VIII		*C*	121–122	Ethanol	6.0	$C_{23}H_{24}N_4O_3$	C, 68.31 H, 5.94	C, 68.14 H, 5.82
IX		*C*	160–161	Chloroform	13.8	$C_{22}H_{23}N_5O_3$	C, 65.18 H, 5.68	C, 65.38 H, 5.91
X		*C*	131–132	Benzene	9.7	$C_{24}H_{27}N_3O$	C, 77.21 H, 7.24	C, 77.39 H, 7.30
				Type IV				
XI		*C*	134–135	Ethanol	47.7	$C_{28}H_{32}N_4O$	C, 76.36 H, 7.27	C, 76.49 H, 7.26
XII		*C*	146–147	Chloroform	6.4	$C_{27}H_{32}N_4O_3$	C, 70.43 H, 6.96	C, 70.63 H, 6.78

benzene afforded the pure product, m.p. 209–210°; yield 3.2 g. (62% of theory). Strong bands in the IR at 5.75 and 6.2 μ are indicative of $-\overset{O}{\overset{\|}{C}}-O-$ and $-C{=}N-$, respectively.

4,4′-Bis(dimethylamino)benzophenone Oxime 3,4,5-Trimethoxybenzoate (II)—Method B—Sodium hydroxide (3.0 g., 0.075 mole) in water (10 ml.) was added with stirring to a solution of 4,4′-bis(dimethylamino) benzophenone oxime (2.8 g., 0.01 mole) in acetone (50 ml.) To this mixture was added 3,4,5-trimethoxybenzoyl chloride (2.3., 0.01 mole) in small portions. The mixture stirred at room temperature for 2 hr. and then diluted with water (300 ml.) The above procedure described under the synthesis of Compound I was then followed. The solid residue obtained was crystallized from benzene to give pure sample (1.75 g., 35.9% of theory), m.p. 131–132°.

Synthesis of Oximino-Ethers[2]—*4,4′-Bis(dimethylamino)benzophenone Oxime p-Benzonitrile Ether (VII)—Method* C—Pptassium tertiary butoxide (1.1 g., 0.01 mole) was added with stirring to the solution of 4,4′-bis(dimethylamino) benzophenone oxime (2.8 g., 0.01 mole) in dimethyl sulfoxide (20 ml.), *p*-fluorobenzonitrile (1.2 g., 0.01 mole) in dimethyl sulfoxide (20 ml.) was added dropwise to the above mixture. The mixture was stirred for 2 hr. at room temperature. The resulting mixture was diluted with saturated sodium chloride solution (300 ml.). The crude product thus obtained was recrystallized from benzene which afforded the compound, m.p. 147–147.5°; yield 1.4 g. (36.4% of theory). It showed no absorption in the IR spectrum in the region between 5.5–6 μ.

REFERENCES

(1) R. H. Lyons, G. K. Moe, R. B. Neligh, S. W. Hoobler, K. N. Campbell, R. L. Berry, and B. R. Rennick, *J. Am. Med. Sci.*, **213**, 325(1947).

(2) E. Schlittler, J. Druey, and A. Marxer, *Progr. Drug Res.*, **4**, 295(1962).

(3) E. D. Freis, "Molecular Modification in Drug Design," Am. Chem. Soc., Advances in Chem. Ser. No. 45, Washington, D. C. 1964, p 67.

(4) A. Grollman, "Pharmacology and Therapeutics," 6th ed., Lea & Febiger, Philadelphia, Pa., 1965, pp. 416, 526.

(5) A. Burger, "Medicinal Chemistry," 2nd ed., Interscience, New York, N. Y., 1960, pp. 509, 551.

(6) M. M. Kochhar, R. G. Brown, and J. N. Delgado, *J. Pharm. Sci.*, **54**, 393(1965).

(7) R. D. Morin, J. S. Warner, and R. H. Poirier, *J. Org. Chem.*, **21**, 616(1956).

(8) S. L. Lee, B. B. Williams, and M. M. Kochhar, *J. Pharm. Sci.*, **56**, 1354(1967).

(9) M. M. Kochhar and B. B. Williams, *ibid.*, **54**, 1149(1965).

(10) D. E. Pearson and F. Bull, *J. Org. Chem.*, **14**, 118 (1949).

(11) A. W. Chapman, *J. Chem. Soc.*, **1934**, 1550; **1936**, 448.

(12) B. Higman, *Nature*, **156**, 242(1945).

(13) J. Sice, "General Pharmacology," Saunders, Philadelphia, Pa., 1962, p. 128.

(14) *Ibid.*, p. 111.

(15) R. B. Barlow, "Introduction to Chemical Pharmacology," 2nd ed., Methusen & Co., London, England, 1964, p. 180.

(16) H. R. Ing, in "Hypotensive Drugs," Pergamon Press, London, England, 1957, p. 7.

ACKNOWLEDGMENTS AND ADDRESSES

Received June 4, 1969 from the *School of Pharmacy, Auburn University, Auburn, AL 36830*

Accepted for publication July 28, 1969.

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