dehydrogenation of dihydrodiols to catechols was observed previously (14–16). The formation of the methylated catechol from 3,4-catechol may be due to the enzyme, catechol O-methyltransferase, since other catechols are known to be methylated *via* this enzyme (8, 17, 18).

In conclusion, it was demonstrated that the catechol metabolite in humans, reported by Borga *et al.* (9), is a mixture of the catechol Metabolite II and the methylated catechol Metabolite III. These metabolites are also formed in minor amounts in other species such as the monkey and dog.

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ACKNOWLEDGMENTS AND ADDRESSES

Received November 29, 1976, from the *Drug Research Laboratories, Health and Welfare Canada, Ottawa, Ontario, Canada, and the ‡College of Pharmacy, University of Saskatchewan, Saskatoon, Saskatchewan, Canada.

Accepted for publication February 11, 1977.

The authors express their appreciation to Dr. T. Chang for supplying the synthetic metabolites, Dr. A. By and Mr. J.-C. Ethier for running the mass spectra, and Mr. A. Trottier for drafting. Appreciation is extended to the University of Saskatchewan (Saskatoon) for a study leave to K. W. Hindmarsh. Dr. J. W. Hubbard, University of Manitoba, Winnipeg, Manitoba, Canada, is gratefully acknowledged for his helpful discussions.

ˣ To whom inquiries should be directed.

Synthesis and Structure–Activity Relationships of Selected Isomeric Oxime *O*-Ethers as Anticholinergic Agents

WILLIAM G. HANEY, ROBERT G. BROWN, EUGENE I. ISAACSON *, and JAIME N. DELGADO ˣ

Abstract □ A series of isomeric (*Z*)- and (*E*)-oxime *O*-β-dimethylaminoethyl ether methylhalide derivatives was synthesized, and their (*Z*)- and (*E*)-assignments were made on the basis of chemical and spectral data. The respective (*Z*)- and (*E*)-isomers were evaluated as anticholinergic agents on the rat ileum. The antimuscarinic potencies of the respective (*Z*)- and (*E*)-isomers were compared to determine the effect upon potency of this type of geometric isomerism. Three general structure–activity relationships are discernible among the synthesized compounds: (*a*) among oxime *O*-ethers derived from aromatic aldehydes, the higher potency consistently resides in the isomer where the aryl substituent is (*E*) to the ammonium ether substituent; (*b*) among oxime *O*-ethers derived from diaryl ketones, the (*Z*)- and (*E*)-isomers are approximately equipotent; and (*c*) oxime *O*-ethers derived from diaryl ketones are the most potent of the synthesized compounds.

Keyphrases □ Oxime *O*-ethers, various—isomers synthesized, anticholinergic activity of methylhalide salts evaluated on rat ileum □ *O*-Dimethylaminoethyl oxime ethers, various—isomers synthesized, anticholinergic activity of methylhalide salts evaluated on rat ileum □ Anticholinergic activity—evaluated on rat ileum for isomers of various oxime *O*-dimethylaminoethyl ethers □ Structure–activity relationships—isomers of various oxime *O*-dimethylaminoethyl ethers evaluated for anticholinergic activity on rat ileum

The parasympathetic postganglionic cholinergic receptor site is of considerable interest. In particular, among anticholinergics the muscarinic receptor exhibits stereospecificity toward optical isomers, and this stereospecificity contributes to a knowledge of the receptor (1). The relationship between anticholinergic potency and geometric isomerism also may be informative, but it has not been investigated extensively. Therefore, such an investigation was undertaken to determine whether or not the receptor was stereospecific toward geometric isomers and to yield further information about the receptor.

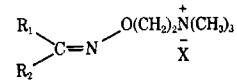
Oxime *O*-ethers were selected for study since they possess anticholinergic activity (2, 3) and the oxyimino moiety allows the preparation of geometric isomers.

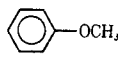
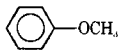
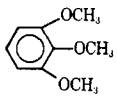
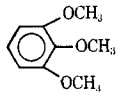
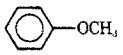
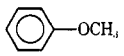
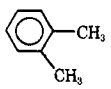
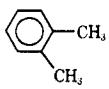
DISCUSSION

The ketone oximes were prepared by the method of Lachman and Noller (4) (Table I). The method involves the generation of hydroxylamine from the hydrochloride salt with excess base in the presence of the ketone, with water as the solvent for low molecular weight ketones and with alcohol for higher molecular weight ketones. The isomer ratios produced are easily predicted qualitatively based on the general rule that the more nearly equal they are in bulk the more nearly equal will be the isomer ratio (5). Thus, the ratio is 89:11 (*E*)–(*Z*) for acetophenone oxime. As can be expected for the diaryl compounds, the isomer ratio is not great.

Separation by fractional crystallization was successful for only one of the 3,4-dimethylbenzophenone oxime isomers. Differences in chelating

Table I—Elemental Analysis for the Synthesized Compounds



Compound[a]	R_1	R_2	Recrystallization Solvent	Melting Point	Analysis, % Calc.	Found
I*a*	H		Ethanol	180–182°	C 50.1 H 6.6	50.26 6.89
I*b*		H	2-Propanol	212–214°	C 43.32 H 5.78	43.47 5.83
II*a*	H		2-Propanol	146–147°	C 42.86 H 5.76	42.72 5.70
II*b*		H	2-Propanol	239–240°	C 42.86 H 5.76	43.14 5.87
III*a*	H		Ethanol	185–186°	C 42.48 H 5.89	42.66 6.04
III*b*		H	2-Propanol	199–200°	C 42.48 H 5.89	42.63 6.00
IV*a*	H		2-Propanol	164–166°	C 35.27 H 5.00	35.20 4.94
IV*b*		H	2-Propanol	258–259°	C 35.27 H 5.00	35.14 4.96
V*a*	CH_3		2-Propanol	182–183°	C 44.83 H 6.10	44.57 6.09
V*b*		CH_3	2-Propanol–ethanol	182–183°	C 44.83 H 6.10	45.03 6.18
VI*a*	CH_3		2-Propanol	185–186°	C 42.48 H 5.89	42.63 6.00
VI*b*		CH_3	2-Propanol	199–200°	C 42.48 H 5.89	42.66 6.04
VII*a*			2-Propanol	189–190°	C 56.00 H 6.04	55.96 5.94
VII*b*			2-Propanol–ethanol	196–198°	C 56.00 H 6.04	55.98 6.16
VIII*a*			Hexane–2-propanol	165–166°	C 53.70 H 6.35	53.76 6.45
VIII*b*			Isopropyl ether–2-propanol	184–186°	C 53.70 H 6.35	53.20 6.20

[a] The methiodide derivative of the ether was characterized, with the exception of I*a*, VII*a*, and VII*b*, in which the methobromide derivative was characterized. [b] NMR analysis revealed about 10% of the opposite isomer.

ability of the phenyl-2-pyridyl isomers were used to effect a separation. The other oximes were etherified as mixtures, and the isomeric ethers were separated *via* fractional distillation.

For the aldehyde oximes, the same method (4) was employed for (*Z*)-isomers. Because the rule for the production of isomers applies, the method is not applicable for the (*E*)-isomers. Initially, an adaption of Vogel's method (6) was employed, *e.g.*, passing hydrogen bromide gas through a refluxing methylene chloride solution of the oxime and neutralizing the resulting hydrobromide salt at low temperatures. The method was not highly successful, and the more stable isomer was usually obtained. An adaptation of the Schoenewaldt *et al.* method (7), which employs a higher boiling solvent (benzene), gave better yields and was used thereafter.

The oximes were converted to the corresponding ethers by treatment of their anions with 2-dimethylaminoethyl chloride. Acetophenone and *p*-methoxyacetophenone oximes were etherified as a mixture, and the ethers were separated *via* fractional distillation. The (*E*)- and (*Z*)-3,4-dimethylbenzophenone oximes were etherified as a mixture, but only the (*E*)-isomer was obtained on multiple distillation. The pure (*Z*)-oxime isomer was used to obtain the (*Z*)-oxime ether.

Alkylation of the (*Z*)-aldehyde oximes proceeded satisfactorily with the cited method. With the (*E*)-oximes, 50–70% etherification occurred. However, isomerization occurred, and the yield of the (*E*)-oxime ether fell in the range of 8–14% based on the aldehyde. The isomerization appeared to be unidirectional since no (*E*)-oxime derivative was obtained from procedures beginning with the (*Z*)-oxime. This result might be expected from a consideration of the relative stability of the two oximes. Because isomerization occurred during etherification, it was necessary to separate the oxime ethers derived from the (*E*)-oximes. This separation was done by vacuum distillation and, for the (*E*)-*p*-methoxybenzaldehyde and (*E*)-3,4,5-trimethoxybenzaldehyde *O*-oxime ethers, by chromatography on silica.

Isomeric identity of the oxime *O*-ethers was established primarily on the basis of magnetic resonance values of protons of the *O*-alkyl substituent. The isomeric differences in the resonance values depend on the position of the substituent relative to the aromatic ring of the ether. In the benzaldehyde oxime ethers, for example, the OCH_2 resonance occurs at τ 5.8 ppm in the (*e*)-isomer and at τ 6.0 ppm in the (*Z*)-isomer. The NCH_2 absorption occurs at τ 7.4 ppm in the latter. Since diamagnetic anisotropic effects decrease rapidly with distance, the anisotropic effects are strongest in the (*Z*)-isomer.

The diamagnetic field of the aromatic substituent, which may shield or deshield proximate protons depending on their position relative to the field (8), shields the OCH_2 protons. However, since the preferred con-

formation of protons of the aromatic substituent is skew (9), the NCH_2 protons are deshielded because the field of the aromatic substituent is different in this area. This rationalization is supported by the fact that the OCH_2 absorption is more strongly affected, indicating that the effect is strongly distance dependent.

For aryl aldehyde oxime derivatives, the NMR isomeric assignments were supported by UV spectral data. Assignments were based on the convention (10) that the isomer with the highest λ_{max} and molar absorptivity is the (*E*)-isomer.

Structural assignments based upon the Beckmann rearrangement were used only for oximes (VIII*a* and VIII*b*) with similar substituents since isomerization may precede rearrangement where the migratory propensity of the two substituents is greatly different. The rearrangement was conducted with the oxime prior to etherification, and subsequent spectral data confirmed that isomerization had not taken place in the ether derivative.

EXPERIMENTAL[1]

Synthesis of Oximes—*Method 1* (*4*): (Z)-*Benzaldehyde Oxime*—Freshly distilled benzaldehyde (106 g, 1.0 mole) was mixed with a solution of sodium hydroxide (95 g) in water (175 ml) and cooled to room temperature. Hydroxylamine hydrochloride (146 g, 2.0 moles) was added in one portion to the reaction mixture, and the clear solution was heated to boiling. The solution was cooled to room temperature and acidified by means of a carbon dioxide generator. The separated oil was extracted with ether (two 100-ml portions), and the combined extracts were dried over sodium sulfate. The solvent was removed under reduced pressure, and the remaining mass was recrystallized from benzene. The yield was 96 g (80%), mp 28–29°. NMR analysis (11) showed the presence of only one oxime.

Method 2 (*6*): (E)-*Benzaldehyde Oxime*—The (*Z*)-oxime was dissolved in methylene chloride (300 ml), and hydrogen bromide gas was passed through the system. Following partial solvent evaporation, the resulting precipitate was neutralized with aqueous sodium hydroxide solution (10%). The product was recrystallized from hexane, and the yield was 5 g (44%), mp 127–129° [lit. (6) mp 130°].

Method 3 (*7*): (E)-*Benzaldehyde Oxime*—(*Z*)-Benzaldehyde oxime (40 g, 0.32 mole) was placed in dry benzene (600 ml), and the solution was heated to boiling. While the solution was heated and vigorously stirred, hydrogen bromide gas was forced through the system. This treatment was maintained until the temperature dropped to 50°. Then the solution was cooled to room temperature, and the oxime salt was removed by filtration. An aqueous solution of sodium hydroxide (80 g in 150 ml) was cooled to 10°. The salt was dropped into the solution, and the mixture was stirred until complete dissolution occurred. Excess ammonium chloride was dropped into the mixture, and the mixture then was extracted with ether (two 100-ml portions). The combined ether extracts were dried over sodium sulfate, and the ether was removed under reduced pressure. The yield was 36 g (88%), mp 124–126°.

Synthesis of Oxime Precursors Using Method 1—Method 1 also was used for the synthesis of the oxime precursors of II*a*, III*a*, IV*a*, IV*b*, V*a*, V*b*, VI*a*, VI*b*, VII*a*, VII*b*, VIII*a*, and VIII*b*. The yields were never lower than 44%. No separation was made of the oxime precursors of IV*a* and IV*b*, V*a* and V*b*, and VI*a* and VI*b*. Separation of the (*E*)- and (*Z*)-isomers was made after etherification. The isomeric oxime precursors of VII were separated and identified on the basis of their chelating ability (adopted from Ref. 12).

The mixture of oxime isomers was used for the synthesis of the ether VIII*a*. Both ethers probably were formed, but fractional distillations were repeated until only pure VIII*a* was isolated. The oxime precursor to VIII*b* was obtained *via* repeated fractional crystallizations of the mixture of oxime isomers and used for the synthesis of that ether. Since VIII*b* was deduced from Beckmann rearrangement data to be the (*Z*)-isomer, it may be considered that VIII*a* is the (*E*)-isomer.

Synthesis of Other Oximes—The following summarizes the results of Method 1 applied to oximes other than (*Z*)-benzaldehyde oxime.

(Z)-p-*Methoxybenzaldehyde Oxime*—Freshly redistilled *p*-methoxybenzaldehyde (68.07 g, 0.5 mole) gave, after refluxing for 2 hr and recrystallizing from heptane, 65 g (87%) of the oxime precursor to II*a*, mp 62–64°.

(Z)-*3,4,5-Trimethoxybenzaldehyde Oxime*—3,4,5-Trimethoxybenzaldehyde (25 g, 0.125 mole) dissolved in ethanol (200 ml) was treated according to Method 1 with potassium hydroxide replacing sodium hydroxide (reflux time of 2 hr). The oxime precursor to III*a* crystallized from the reaction mixture in a yield of 21.3 g (85%), mp 99–101°.

(E)- *and* (Z)-*2-Thienylaldehyde Oximes*—Freshly distilled 2-thienylaldehyde (reflux time of 0.5 hr) gave 24.6 g (75%) of the (*E*)- and (*Z*)-oxime precursors to IV*a* and IV*b*.

(E)- *and* (Z)-*Acetophenone Oximes*—Acetophenone (20 g, 0.166 mole) was treated according to Method 1 (reflux time of 2 hr). The oxime precursors to VI*a* and VI*b* were recrystallized from heptane, 18.5 g (82%), mp 52–55°.

(E)- *and* (Z)-*2-Pyridophenone Oximes*—An adaptation of the procedure of Huntress and Walter (12) gave the isomeric oximes. The ketone (110 g, 0.6 mole), dissolved in ethanol (180 ml) and treated according to Method 1, gave the oximes, 121 g (100%), mp 117–131°. This mixture was placed in dry chloroform (210 ml) and refluxed 20 min. Then the solution was cooled to room temperature and filtered. The residue was washed with dry chloroform (30 ml) and recrystallized (ethanol), giving 54 g (90%) of the (*E*)-isomer, mp 150–152°.

The combined filtrates and washings from recrystallization were evaporated under reduced pressure, and the residue (24 g) was solubilized with aqueous hydrochloric acid (20%, 80 ml). Copper sulfate solution (20 g in 100 ml of water) was added, and the mixture was allowed to stand overnight. The mixture was filtered, washed with water (30 ml), and dried. The combined filtrate and washings were purged with hydrogen sulfide. After removal of the black precipitate, the solution was titrated to pH 3.8 with 1 *N* ammonium hydroxide. The precipitate that formed was removed, and titration was continued to neutrality. The yield was 8.5 g (14%) of the (*Z*)-oxime, mp 165–167°.

(E)- *and* (Z)-*3,4-Dimethylbenzophenone Oximes*—The oxime precursors to VII*a* and VII*b* were obtained from the ketone (21 g, 0.1 mole) dissolved in ethanol (250 ml) and treated according to Method 1 (reflux time of 0.5 hr). The yield was 22 g (88%), mp 124–127°. A portion of the mixture was subsequently used in the etherification procedure. Repeated distillation thereafter gave only the amino ether which, in turn, gave the salt VIII*a*. Additionally, a portion of the mixture was recrystallized repeatedly from 2-propanol–water to give one oxime isomer, mp 154–155°, in a 6% yield. Beckmann rearrangement data on this oxime, described under the structural determination of isomer set VIII*a* and VIII*b*, indicated this compound to be the (*Z*)-oxime.

Synthesis of Oxime Precursors Using Method 3—Since Method 3 gave better yields than Method 2, it was used exclusively for the conversion of (*Z*)- to (*E*)-forms. The (*E*)-forms resulting from Method 3 were used for the synthesis of I*b*, II*b*, and III*b*. The following summarizes the results of Method 3 as used for the synthesis of the oxime precursors to II*b* and III*b*.

(E)-p-*Methoxybenzaldehyde Oxime*—(*Z*)-*p*-Methoxybenzaldehyde oxime (50 g, 0.311 mole) was dissolved in anhydrous benzene (700 ml). The solution was heated to boiling with stirring, and 60 ml of the solution was distilled. External heating was discontinued, and hydrogen chloride gas was passed through the solution, the heat of reaction maintaining the solution at reflux. Passage was continued until the temperature fell to 50°, and the mixture was cooled to 10° and filtered. The oxime hydrochloride was dissolved in a solution of sodium hydroxide (50 g) in water (250 ml). Excess ammonium chloride was added, and the resulting precipitate was extracted with ether (two 100-ml portions). The ether extracts were dried, and the ether was removed under reduced pressure to give the (*E*)-oxime, 46.5 g (93%), mp 131–133°.

(E)-*3,4,5-Trimethoxybenzaldehyde Oxime*—The compound, mp 157–158°, was obtained in a yield of 8.8 g (82%) from 12.0 g (0.057 mole) of the (*Z*)-oxime dissolved in dry benzene (750 ml). The solution was brought to reflux, and 100 ml of benzene was distilled out. Treatment thereafter was as described previously, except that the (*E*)-oxime was precipitated by the addition of ammonium phosphate, removed by filtration, and dried at 75° overnight.

Synthesis of Oxime *O*-Ethers—(Z)-*Benzaldehyde Oxime* O-*Dimethylaminoethyl Ether and Methobromide* (*Ia*)—The oxime (20 g, 0.16 mole) was dissolved in ethanol (200 ml). Sodium hydride (24 g of a 51.2% mineral oil dispersion, 0.48 mole) was added with caution to the stirred solution. 2-Dimethylaminoethyl chloride hydrochloride (23 g, 0.16 mole) was dissolved in ethanol (150 ml) and dropped into the reaction mixture over 30 min. The stirred reaction mixture was maintained at reflux for 24 hr. Then the solvent was evaporated under reduced pressure, the residue was dissolved in isopropyl ether, and the solids were filtered off.

[1] Melting points were determined on a Thomas–Hoover Mel-Temp apparatus and are uncorrected. IR spectra for all final compounds and intermediates were determined on a Beckman IR-8 and are in accord with the assigned structures. NMR data were obtained for all compounds in a Varian A-60 and are in accordance with the assigned structures. Noteworthy NMR data used to distinguish between isomers are given in Table II. UV data were obtained on a Beckman DB with ethanol as solvent. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N.Y.

Table II—Physical Constants of the Amines Synthesized

Amino Precursor to Compound	Yield, %	Boiling Point and Pressure (mm Hg) of Amine	NMR Data[a], ppm			UV Data	
			OCH_2	NCH_2	$N(CH_3)_2$	λ_{max}, nm	ξ_{max}
I*a*	51.3	62–70°/0.1–0.05	5.70	7.36	7.75	246	19,770
I*b*	18.2	112°/1.25	6.07	7.20	7.83	236	17,500
II*a*	92.0	88–90°/0.015	5.82	7.42	7.78	248	19,900
II*b*[b]	32.5	69–70°/0.05	6.16	7.21	7.86	237	17,700
III*a*	76.6	126–130°/0.02	5.94	7.56	7.85	256	24,600
III*b*[b,c]	14.2		6.38	7.30	7.92	247	19,750
IV*a*	22.9	84–86°/0.015	5.80	7.42	7.80		
IV*b*	40.0	118–20°/0.01	5.92	7.09	7.70		
V*a*	78.7	82.5–85°/0.20	5.70	7.38	7.79		
V*b*	7.5	104–106°/0.20	6.17	7.20	7.92		
VI*a*	83.0	110–113°/0.05	5.78	7.38	7.79		
VI*b*[b]	4.4	134–137°/0.05	6.18	7.10	7.96		
VII*a*	24.3	147–154°/0.09	5.73	7.43	7.82		
VII*b*	19.0	143–144°/0.40	5.81	7.36	7.86		
VIII*a*	16.4	139–141°/0.05	5.84	7.56	7.91		
VIII*b*[b]	12.2		5.70	7.48	7.96		

[a] Values were obtained on a Varian A-60 [25% (v/v) $DCCl_3$] and are expressed as τ. [b] Chromatographed on silica. [c] NMR analysis indicated about 10% of the (*Z*)-isomer.

The rest of the solvent was removed under reduced pressure, and the remaining liquid was distilled.

The major distillation fraction (bp 65–69°/0.08 mm, 13.83 g, 45%) was subjected to NMR and UV analysis and found to be the (*Z*)-oxime ether. The yield and physical constants are summarized in Table II. The methobromide (I*a*) was prepared by dissolving the amine in isopropyl ether and treating with excess methyl bromide. The analytically pure methobromide was obtained after repeated recrystallization. The recrystallization solvent, melting piont, and analytical data are given in Table I.

The described procedure was applied to the synthesis of the following compounds with exceptions and variations in quantities of reactants as noted. Yields and physical constants for the amino ethers are given in Table II. Recrystallization solvents, melting points, and elemental analytical data for the quaternary derivatives are given in Table I.

(E)-*Benzaldehyde Oxime* O-*Dimethylaminoethyl Ether*—The (*E*)-oxime (20 g, 0.16 mole) was dissolved in ethanol (500 ml), and sodium hydride–mineral oil dispersion (16 g, 0.27 mole) was added. 2-Dimethylaminoethyl chloride hydrochloride (23 g, 0.16 mole) in ethanol (400 ml) then was added over 1 hr. The methiodide (I*b*) was prepared in hexane.

(Z)-p-*Methoxybenzaldehyde Oxime* O-*Dimethylaminoethyl Ether*—The oxime (8.8 g, 0.06 mole) was dissolved in ethanol (250 ml). The sodium hydride dispersion (6.2 g, 0.13 mole) and then the alkylating agent (9.1 g, 0.06 mole) in ethanol (100 ml) were added.

(E)-p-*Methoxybenzaldehyde Oxime* O-*Dimethylaminoethyl Ether*—To the oxime (10 g, 0.066 mole) in ethanol (200 ml) was added the sodium hydride dispersion (6.2 g, 0.13 mole). The alkylating agent (10.1 g, 0.07 mole) in ethanol (150 ml) then was added. The reflux time was 18 hr. Workup gave an oil which was distilled. Data for the first fraction are given in Table II. NMR revealed a contaminant with triplets at τ 7.4 and 6.3 ppm. A short column was packed with silica gel in a slurry form with pentane. The oil was dissolved in the minimum amount of isopropyl ether. The column was developed with pentane–ether mixtures (1:0, 1:25, 1:0.5, 1:1, 0.5:1, and 0:1). Eluates were reduced in volume and treated with iodomethane to determine the presence of the (*E*)-amino ether. The methiodide (II*b*) was prepared in heptane.

A second fraction (bp 101–103°/0.05 mm Hg, 2.4 g, 17%) was shown by NMR analysis to be the (*Z*)-ether.

(Z)-*3,4,5-Trimethoxybenzaldehyde Oxime* O-*Dimethylaminoethyl Ether*—The oxime (6.4 g, 0.03 mole) was added to the sodium hydride dispersion (4 g, 0.08 mole) in ethanol (175 ml). 2-Dimethylaminoethyl chloride hydrochloride (7.2 g, 0.05 mole) then was added slowly to the solution. The methiodide (III*a*) also was prepared.

(E)-*3,4,5-Trimethoxybenzaldehyde Oxime* O-*Dimethylaminoethyl Ether*—The oxime (6.4 g, 0.03 mole) was dissolved in ethanol (200 ml). The sodium hydride dispersion (3.8 g, 0.08 mole) was added, and then the alkylating agent (7.2 g, 0.05 mole) was added slowly. After an attempted distillation, the oil was placed on a silica gel column packed with a hexane slurry. Isopropyl ether was passed through the column until all colored material was eluted; then the column was eluted with ethanol. Evaporation of the ethanol gave a colorless oil. NMR analysis indicated that the oil was the (*E*)-isomer with about 10% of the (*Z*)-isomer. The methiodide (III*b*) also was prepared.

(Z)- *and* (E)-*2-Thienylaldehyde Oxime* O-*Dimethylaminoethyl Ethers*—The oxime mixture (8.6 g, 0.07 mole) was dissolved in ethanol (200 ml), and the sodium hydride dispersion (7.2 g, 0.15 mole) was added. Then the alkylating agent (11.52 g, 0.08 mole) was added. The reflux time was 48 hr. Workup and fractional distillation gave the (*E*)- and (*Z*)-ethers. The methiodides (IV*a* and IV*b*) were prepared in heptane.

(Z)- *and* (E)-*Acetophenone Oxime* O-*Dimethylaminoethyl Ethers*—The oxime mixture (13.5 g, 0.1 mole) was dissolved in ethanol (200 ml). The sodium hydride dispersion (9.6 g, 0.2 mole) and then the alkylating agent (14.4 g, 0.1 mole) were added. The reflux time was 48 hr. Workup and fractional distillation gave the (*E*)- and (*Z*)-isomers. The methiodes (V*a* and V*b*) were prepared in heptane.

(Z)- *and* (E)-p-*Methoxyacetophenone Oxime* O-*Dimethylaminoethyl Ethers*—To the oxime mixture (11.0 g, 0.07 mole) in ethanol was added the sodium hydride dispersion (7.2 g, 0.15 mole) and then the alkylating agent (11.52 g, 0.08 mole). The reflux time was 27 hr. Workup and fractional distillation gave the two compounds. The methiodides (VI*a* and VI*b*) also were prepared.

(E)-*2-Pyridophenone Oxime* O-*Dimethylaminoethyl Ether*—The (*E*)-oxime (11 g, 0.56 mole) was dissolved in ethanol (200 ml). The sodium hydride dispersion (7.2 g, 0.15 mole) and then the alkylating agent (14.4 g, 0.1 mole) in ethanol (110 ml) were added. The methiodide (VII*a*) also was prepared.

(Z)-*2-Pyridophenone Oxime* O-*Dimethylaminoethyl Ether*—The oxime (11 g, 0.056 mole) was mixed with a solution of the sodium hydride dispersion (9.0 g, 0.18 mole) in ethanol (200 ml), and the alkylating agent (14.4 g, 0.1 mole) was added. The reflux time was 16 hr. The methobromide (VII*b*) also was prepared.

(E)-*3,4-Dimethylbenzophenone Oxime* O-*Dimethylaminoethyl Ether*—The oxime mixture (11.2 g, 0.1 mole) was added to the sodium hydride dispersion (4.8 g, 0.1 mole) in ethanol (200 ml), and then the alkylating agent (7.2 g, 0.1 mole) in ethanol (150 ml) was added. The reflux time was 36 hr. Workup and distillation gave a fraction (bp 134–138°/0.05 mm Hg, 9.4 g) which, on NMR analysis, proved to be a mixture of the (*E*)- and (*Z*)-ethers. A second distillation gave a fraction (bp 135–137°/0.05 mm Hg, 8.0 g) which had an increased concentration of the (*E*)-isomer according to NMR analysis. A third distillation gave the pure isomer. The methiodide (VIII*a*) was prepared in hexane.

(Z)-*3,4-Dimethylbenzophenone Oxime* O-*Dimethylaminoethyl Ether*—To the oxime (0.50 g, 0.0024 mole) in ethanol (50 ml) was added the sodium hydride dispersion (0.3 g, 0.006 mole) and the alkylating agent (0.43 g, 0.003 mole). Workup gave an oil, which was chromatographed on silica in the manner described for the amine precursor to III*b*. The methiodide (VIII*b*) was prepared in hexane.

Structural determination for the isomer set VIII*a* and VIII*b* was accomplished in the following manner. The recrystallized oxime (0.225 g, 0.0011 mole) was dissolved in chloroform (10 ml), and the solution was heated to reflux. Excess phosphorus pentachloride was added to the mixture, and an exothermic reaction occurred. Following a period of standing, the solvent was evaporated under reduced pressure. The remaining yellow semisolid was dissolved in concentrated hydrochloric acid (30 ml) and stirred at reflux for 3 hr.

The resultant mixture was cooled to 10° and extracted with two 50-ml portions of ether. The extracts were dried, and the solvent was removed

under reduced pressure. The yield was 0.147 g of the acid, mp 140–143°. NMR data confirmed that only 3,4-dimethylbenzoic acid was present. Subsequent etherification of the oxime derivable from recrystallization gave a product whose NMR spectrum was superimposable on the spectrum of the isomer that disappeared during multiple distillation.

Pharmacology—The anticholinergic potency of these compounds was determined by the classic Magnus method with quantitative procedures devised by Ariens (13). The method involves the measurement of spasmogen-induced intestinal contractions in the presence of the spasmolytic agent. The test tissue consisted of smooth muscle from the rat ileum. The dose–effect curves for spasmogens were determined alone, in the presence of the test compound, and in the presence of the standard spasmolytic agent.

The dose of the spasmogen required to contract the muscle to a maximal level was determined, and the data were plotted using percent response on a probability scale *versus* dose of spasmogen (log millimolar). In this manner, it was possible to determine the dose of spasmogen necessary to induce 50% contraction in the test tissue under the various conditions. This estimation then allowed the comparison of the relative activity of the compounds.

Test samples of the methylhalide derivatives in water were prepared. The spasmogen (bethanechol chloride) was prepared in aqueous solution in dilutions of greatly different concentrations. Since the solutions were potentially susceptible to degradation, no solution was utilized more than 2 hr after preparation.

A glass cylinder of 80-ml capacity, with an inlet for the introduction of the bathing solution and for drainage, was assembled in a constant-temperature bath. A mechanism was devised for the constant aeration of the muscle in the chamber. The bathing solution was composed of 9 g of sodium chloride, 0.4 g of potassium chloride, 0.12 g of calcium chloride, and 0.3 g of sodium bicarbonate in 1 liter of distilled water.

Strips of ileum of uniform length were taken from an unanesthetized male albino rat which had been recently sacrificed. The strip was suspended in the muscle bath chamber, and the bathing solution was added to constant volume (70 ml). The temperature was held constant at 37°. Records of the muscle contractions were recorded using a physiograph with a myograph attachment.

The method for determining dose–response curves uses successive geometric additions of the spasmogen without washing between dose increments. The spasmogen was added to the aerated bath at regular intervals until maximum response was obtained. This constituted the control curve for the spasmogen. The muscle bath was then rinsed repeatedly with the bathing solution (previously heated to 37°). After the muscle resumed spontaneous contractions, the unknown drug was added to the muscle bath. Again, the spasmogen was added in increasing amounts until maximum response was obtained. The muscle was repeatedly washed, then the opposite isomer was added to the bath, and a similar sequence of treatments was used. Following repeated washing, the initial spasmogen–response curve was duplicated to ensure the muscle's responsiveness. The data are summarized in Table III.

Table III—Summary of the Pharmacological Data

Compound	Dose of Test Compound, m*M*/70 ml	Dose of Spasmogen, m*M*/70 ml at 50% Contraction	Ratio *a*/*b*[a]
I*a*	3.0×10^{-2}	$29.33 (\pm 1.40) \times 10^{-2}$	3.25
I*b*	3.0×10^{-2}	$9.03 (\pm 0.73) \times 10^{-2}$	
II*a*	1.09×10^{-2}	$19.4 (\pm 0.09) \times 10^{-2}$	2.66
II*b*	1.09×10^{-2}	$7.3 (\pm 0.34) \times 10^{-2}$	
III*a*	1.17×10^{-2}	$26.00 (\pm 0.27) \times 10^{-2}$	4.40
III*b*	1.17×10^{-2}	$5.90 (\pm 0.18) \times 10^{-2}$	
IV*a*	6.17×10^{-3}	$17.8 (\pm 0.43) \times 10^{-2}$	3.17
IV*b*	6.17×10^{-3}	$5.6 (\pm 0.31) \times 10^{-2}$	3.17
V*a*	5.70×10^{-3}	$28.05 (\pm 0.46) \times 10^{-2}$	4.75
V*b*	5.70×10^{-3}	$6.00 (\pm 0.42) \times 10^{-2}$	
VI*a*	7.33×10^{-3}	$32.68 (\pm 0.79) \times 10^{-2}$	4.39
VI*b*	7.33×10^{-3}	$7.44 (\pm 0.32) \times 10^{-2}$	
VII*a*	1.0×10^{-5}	$22.0 (\pm 0.26) \times 10^{-2}$	1.01
VII*b*	1.0×10^{-5}	$21.45 (\pm 0.30) \times 10^{-2}$	
VIII*a*	1.8×10^{-5}	$17.33 (\pm 0.36) \times 10^{-2}$	0.98
VIII*b*	1.8×10^{-5}	$17.50 (\pm 0.40) \times 10^{-2}$	

[a] Values are the means of at least six separate determinations. The differences between the ED_{50}'s for I–VI are significant at the 0.01 level.

RESULTS

Certain general activity patterns emerge. Compounds I*a*, II*a*, III*a*, IV*a*, V*a*, and VI*a* were uniformly more active than their (*Z*)-counterparts. It is apparent that the muscarinic receptor is stereospecific toward this series of geometric isomers. From this finding, it might be conjectured that the receptor is most nonpolar in the portion complementary to the (*E*)-aryl group.

A second activity pattern is that the isomers are approximately equipotent among the diaryl oxime ethers (VII*a*, VII*b*, VIII*a*, and VIII*b*). A third general activity pattern is that the diaryl compounds are all more active than the monoaryl compounds. The higher activity of the diaryl compounds is in accord with the general structure–activity relationships among anticholinergics. The higher activity of diaryl compounds and the equipotency between diaryl isomers may be explained if the nonpolar portion in this area of the receptor is fairly extensive. Also, the auxiliary polar group often noted for the muscarinic receptor, which may be in this portion of the receptor, is possibly very small and would not interfere with the binding of a second aryl group.

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ACKNOWLEDGMENTS AND ADDRESSES

Received February 19, 1976, from the *College of Pharmacy, University of Texas at Austin, Austin, TX 78712.*

Accepted for publication February 7, 1977.

The authors thank Dr. James F. Stubbins for helpful comments and suggestions.

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