U. S. Patent 2,898,339 (1959); *Chem. Abstr.*, **54**, 58/c (1960).
(7) R. P. Mull, British Patent 1,142,030 (1969); *Chem. Abstr.*, **70**, 68186 (1969).
(8) D. L. Wheeler, Ph.D. Thesis, University of Aston in Birmingham (1971).
(9) A. F. Casy, *Progr. Med. Chem.*, **7**, 229 (1970).
(10) W. J. Welstead, G. C. Helsley, R. L. Duncan, A. D. Cale, C. R. Taylor, J. P. Davanzo, B. V. Franko, and C. D. Lunsford, *J. Med. Chem.*, **12**, 435 (1969).

1-(4-Dimethylaminoethoxy-3-methoxyphenyl)-2-aminoalkanes†

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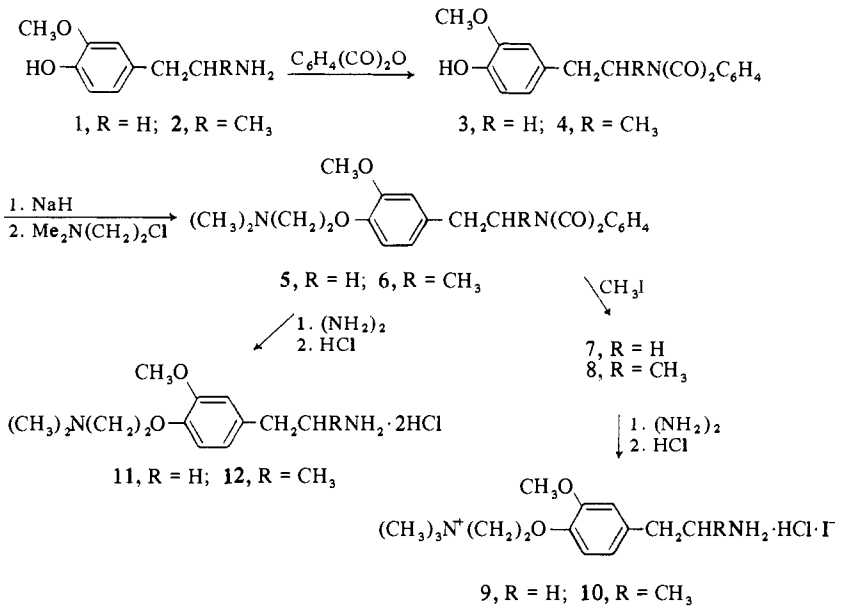
Compounds which contain both β-aminoalkyl ("adrenergic") and choline ether groups attached to the same aromatic ring have not been reported previously. We are describing here the synthesis of 4-dimethylaminoethoxy-3-methoxyphenethylamine and 1-(4-dimethylaminoethoxy-3-methoxyphenyl)-2-aminopropane and their trimethylammonium ions, derived from the tertiary amine functions. Since the effects of divergent pharmacophores in the same molecule are usually not complementary, it was not too surprising to find that none of these compounds exhibited any noteworthy activities in mouse dose-range tests.



Experimental Section

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Elemental analyses, performed by Galbraith Laboratories, Knoxville, Tenn., gave values within 0.25% of those calcd. Ir spectra (Perkin-Elmer spectrophotometer Model 337) were detd in KBr pellets for solids, and NaCl disks for liquids (neat); nmr spectra were measured on a Hitachi-Perkin-Elmer spectrometer, Model R-20 [Me_4Si or 2,2-dimethyl-2-silapentane-5-sulfonate (D_2O)]. Mass spectra of amines were detd on a Model RMU-6E mass spectrometer; all spectra were as expected. Removal of solvents was carried out using a Rinco rotary evaporator.

4-Hydroxy-3-methoxyphenethylamine·HCl (1). Modifying the procedure of Ramirez and Burger,[1] a mixt of 27.5 g (0.14 mole) of 1-(4-hydroxy-3-methoxyphenyl)-2-nitroethene and 400 ml of dry THF was added dropwise to a stirred refluxing mixt of 26.5 g (0.7 mole) of LAH in 1 l. of abs Et_2O over 3.5 hr. After an addl 60 hr of good stirring and refluxing the mixt was cooled to 5°, excess LAH was decompd with pieces of ice followed by 1.5 l. of 1.5 *N* H_2SO_4 at 0°. The aqueous layer was sepd, Li_2CO_3 was added to pH 6, and the mixt was filtered while hot. To this hot soln 35 g (0.15 mole) of picric acid was added, and after *ca.* 16 hr 45 g (*ca.* 80%) of orange cryst picrate, mp 195–198°, was filtered off. The crystals were placed in 1.2 l. of boiling H_2O and 210 ml of 37% HCl was added. Upon cooling, picric acid was collected, the filtrate was extd twice with $PhNO_2$ (150 ml) and 3 times with Et_2O. The aqueous layer was evapd. The residual beige crystals weighed 20.9 g (73.6%), mp 212–213° dec.

1-(4-Hydroxy-3-methoxyphenyl)-2-aminopropane·HCl (2) was obtd similarly from 1-(4-hydroxy-3-methoxyphenyl)-2-nitro-1-propene in 58.6% yield as almost colorless crystals, mp 258–259° dec (lit.[2] mp 251° dec).

1-(4-Hydroxy-3-methoxyphenyl)-2-phthalimidoethane (3). Toluene (125 ml) was added to a mixt of 10.2 g (0.05 mole) of 1, 7.5 g (0.05 mole) of phthalic anhydride, and 9 ml of Et_3N. The mixt was refluxed under a Dean–Stark trap for 2 hr and then stirred overnight. A yellow solid settled out. It was filtered and washed with 3 × 17 ml of H_2O; yield 16.7 g, mp 145–148°. Recrystn from 300 ml of EtOH produced iridescent greenish yellow crystals, mp 148.5–150°. Addl material from the H_2O–PhMe filtrate gave a total of 12.05 g (81.1%). *Anal.* ($C_{17}H_{15}NO_4$) C, H, N; *m/e* 297 (M^+).

1-(4-Hydroxy-3-methoxyphenyl)-2-phthalimidopropane (4) was prepd similarly from **2**. It took 8 hr to form the calcd amt of H_2O. The crude material was dark brown, yield of pure **4**, 77.1%, mp 153–154°. *Anal.* ($C_{18}H_{17}NO_4$) C, H, N.

1-(4-Dimethylaminoethoxy-3-methoxyphenyl)-2-phthalimidoethane·HCl (5). NAH [50% in mineral oil, 1.5 g (33 mmoles)] was added to a soln of 8.91 g (30 mmoles) of 3 in 35 ml of dry PhMe. The mixt was refluxed under N_2 for 8 hr and cooled, and 33 mmoles of dimethylaminoethyl chloride was added. After refluxing overnight, another 16 mmoles of $Me_2N(CH_2)_2Cl$ was added, and refluxing contd for 5 hr. The milky brownish mixt was treated with ice, acidified (HCl), and extd with 3 × 35 ml of Et_2O. A white ppt forming in the aqueous layer was salted out with NaCl, filtered off, and recrystd from abs EtOH and a little acetone, yield 11.1 g (91.4%), mp 175–175.5°. *Anal.* ($C_{21}H_{25}ClN_2O_4 \cdot H_2O$) C, H, N.

1-(4-Dimethylaminoethoxy-3-methoxyphenyl)-2-phthalimidopropane (6) was prepd analogously from **4**. The hygroscopic HCl salt could not be crystd but the base, liberated at pH 12 at 0°, was triturated with dry Et_2O and crystd after several days. Recrystn from abs EtOH afforded colorless crystals (8.2 g, 65.2%), mp 64–65°. *Anal.* ($C_{22}H_{26}N_2O_4$) C, H, N; *m/e* 382 (M^+).

1-(3-Methoxy-4-trimethylammoniumethoxyphenyl)-2-phthal-

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imidoethane Iodide (7). To 7.3 g (1.98 mmoles) of **5** in 150 ml of abs EtOH was added gradually MeI (3.76 g, 26.5 mmoles) and the mixt was refluxed for 1 hr. On standing, 7 pptd; some more 7 pptd on addn of dry Et_2O. The light-sensitive salt was filtered, washed (Et_2O), and dried at 0°, yield 9.2 g (91.1%), mp 186–187°. *Anal.* ($C_{22}H_{27}IN_2O_4$) C, H, N; *m/e* 368 ($M^+ - CH_3I$).

The homologous salt (**8**) prepd from **6** was obtd in 99% yield, mp 152–153°. *Anal.* ($C_{23}H_{29}IN_2O_4$) C, H, N.

Hydrazinolysis of Methiodides 7 and 8. To a suspension of **8** or **7** (2.4–2.55 g, 4.5–5 mmoles) in 25 ml of 95% EtOH was added 0.7–0.75 g (*ca.* 14.5 mmoles) of 64% hydrazine hydrate. The mixt turned pale yellow and the solid went into soln on heating. After 2 hr of reflux and cooling overnight, a white ppt had formed. HCl (37%) was added dropwise to Congo Red, and the yellowish ppt was filtered off and washed with EtOH and then H_2O, and the filtrate was evapd. Recrystn of the pale yellow residue from EtOH and from hexane gave 1.28 g (61.5%) of **3-methoxy-4-trimethylammoniumethoxyphenethylamine·HCl·I⁻ (9)**, mp 181–182° dec [*Anal.* ($C_{14}H_{26}ClIN_2O_2$) C, H], and **1-(3-methoxy-4-trimethylammoniumethoxyphenyl)-2-aminopropane·HCl·I⁻ (10)** (1.4 g, 71%), mp 177–179° dec [*Anal.* ($C_{15}H_{28}ClIN_2O_2$) C, H, N], respectively.

Hydrazinolysis of 5 and 6. To an iced aqueous soln of salts **5** (or **6**) (0.01 mole) was added NaOH (0.01 mole) and the liberated amine was extd with Et_2O (3 × 50 ml). The solvent was evapd, and the residue dissolved in 25 ml of EtOH and a 10% excess of 64% hydrazine hydrate. The warm mixt was refluxed for 45 min, then 6 *N* HCl (2 ml) was added dropwise. Phthalhydrazide was filtered off and washed (EtOH, H_2O), the filtrate was concd, and a white ppt was filtered off. The yellow residue from the evapd filtrate was recrystd from abs EtOH: **4-dimethylaminoethoxy-3-methoxyphenethylamine·2HCl (11)**, mp 198–200° dec, yield 36% [*Anal.* ($C_{13}H_{24}Cl_2N_2O_2·H_2O$) C, H, N]; **1-(4-dimethylaminoethoxy-3-methoxyphenyl)-2-aminopropane·2HCl (12)**, mp 209–211°, yield 54% [*Anal.* ($C_{14}H_{26}Cl_2N_2O_2$) C, H, N; *m/e* 252 (M^+)].

References

(1) F. A. Ramirez and A. Burger, *J. Amer. Chem. Soc.*, **72**, 2781 (1950).

(2) G. R. Clemo and J. H. Turnbull, *J. Chem. Soc.*, 534 (1945).

1,4-Disubstituted Piperazines. 3. Piperazinylbenzothiazoles†

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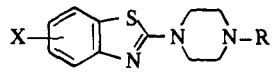
In the course of synthesis of 1,4-disubstituted piperazines,[1] 4-(2-benzothiazolyl)-*N,N*-diethyl-1-piperazinecarboxamide (**2**) was prepared and appeared to exhibit activity against coccidiosis in chickens. Since 2-(1-piperazinyl)-benzothiazole was new to the literature, the synthesis and biological studies of this parent and its derivatives I, reported in this paper, were undertaken. Retesting of **2**, however, failed to sustain coccidiostatic activity; nor was this activity shown by any of the type I compounds. Of interest, though, was the antifungal action and CNS effects shown by some of these piperazinylbenzothiazoles.

Biological Data.‡ Compds **1**, **5**, and **6** were marginal psychomotor stimulants in mice at 300 mg/kg po. Compd **1** also showed antihypertensive activity in rats (approx ED_{50} = 6 mg/kg sc). Compds **8** and **14** produced decreased locomotor activity in mice at 16 mg/kg po, and 64 mg/kg po, respectively. Mice were hyperactive at 256 mg/kg po with **20**, **21**, **22**, and **23**. They showed ataxia at 256 mg/kg po with **24**. In spot tests against *Trichophton mentagrophytes*, *Asperigillus niger*, and *Candida albicans*, **21**, **22**, **23**, and **24** were active. Compd **9** showed marginal *in vitro* activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Proteus vulgaris*, but was inactive against staphylococcal infections in mice. Many of these compounds were also tested for possible anthelmintic, amebi-



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asis, antimalarial, schistosomiasis, antiviral, and antiinflammatory activities.

Experimental Section §

All microanalyses were performed at the Sterling-Winthrop Research Institute. The chemicals were either purchased from Eastman, K and K, or Aldrich, including 1-methylpiperazine and 2-(1-piperazinyl)ethanol. The following monosubstituted piperazines were prepd by literature methods: 1-(*N,N*-diethylcarbamoyl)piperazine,[2] 1-formylpiperazine,[3] 1-diphenylmethylpiperazine,[4] 1-(2-*N,N*-dimethylaminoethyl)piperazine,[5] 1-benzylpiperazine,[6] and 1-*p*-chlorophenylpiperazine.[7]

Also prepd as intermediates were: 2-bromo-4-chlorobenzothiazole,[8] 2-chloro-6-methoxybenzothiazole,[9] 2-chloro-6-nitrobenzothiazole,[10] and 1-chloroacetyl-3-methylurea.[11] 2-Chloro-6-ethoxybenzothiazole was prepd according to the procedure used in making 2-chloro-6-methoxybenzothiazole, but was not analyzed: mp 63–67° from hexane.

1,4-Disubstituted Piperazines (Table I). Procedure A. One equiv of the alkyl halide was slowly added to a vigorously agitated mixt of 2 equiv of piperazine in 80% alcohol plus excess $NaHCO_3$ heated at reflux. After filtration, the solvent was removed under reduced pressure. Addn of concd HCl resulted in pptn of the corresponding salt for **1**. For **15**, in addn to many other compds here described, dil HCl dissolved the residue, which was then washed with Et_2O or EtOAc and repptd by addn of NaOH. The products were recrystd from the solvents shown in Table I.

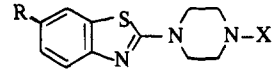
Procedure B. Two equiv of the appropriate monosubstituted piperazine was used to 1 equiv of the alkyl halide in PhH.

Procedure C. A 10% molar excess of the appropriate alkyl halide plus 2-(1-piperazinyl)benzothiazole·HCl in an excess of $NaHCO_3$ and EtOH–H_2O represented the reaction mixt.

Procedure D. Two equiv of the appropriate monosubstituted piperazine to 1 equiv of the alkyl halide in EtOH was used.

Procedure E. A 10% molar excess of the alkyl halide to the appropriate monosubstituted piperazine in excess $NaHCO_3$ plus EtOH–H_2O was used.

Procedure F. Here the mixt consisted of an EtOH soln of a 20% excess of the corresponding C=O compd plus 2-(4-amino-1-piperazinyl)benzothiazole.#



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§Where analyses are indicated only by symbols of the elements or functions, analytical results obtained were within ±0.4% of the theoretical values.

#This compd was prepd impure from **9** according to Conroy's[12] method of reduction of 1-(*p*-chlorophenyl)-4-nitrosopiperazine; mp 78–85° from petr ether (90–120°), followed by washing with ether.