New Compounds

Some 3,4,5-Trimethoxphenyl Analogs of Antihistamines[1]

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The 3,4,5-trimethoxyphenyl group frequently occurs in compounds which have as one of their pharmacological actions a pronounced effect upon the central nervous system. Since many of these compounds are otherwise unrelated chemically, the 3,4,5-trimethoxyphenyl group may play an important part in the activity of some tranquilizers and hallucinogens.

Several antihistamines are also known to have a distinct effect upon the central nervous system. In this communication, the synthesis of several 3,4,5-trimethoxyphenyl-containing antihistamine analogs is reported.

Experimental Section

3,4,5-Trimethoxybenzhydrol.—A mixture of 10.0 g (0.037 mole) of 3,4,5-trimethoxybenzophenone,[3] 10.0 g of technical grade zinc dust, 10.0 g of NaOH pellets, and 100 ml of 95% ethanol was stirred for 3 hr. The mixture, which had warmed spontaneously, was filtered and the clear filtrate was poured into 500 ml of ice water, previously acidified with 25 ml of concentrated HCl. The crystalline product which separated was recrystallized from ethanol; yield 9.4 g (94%), mp 113–113.5°.[4,5]

2-(3,4,5-Trimethoxybenzhydryloxy)-N,N-dimethylethylamine.—A mixture of 11.5 g (0.042 mole) of 3,4,5-trimethoxybenzhydrol, 1.65 g of (0.042 g-atom) of potassium, and 200 ml of anhydrous toluene was refluxed and stirred for 8 hr. An excess (6 ml) of β-dimethylaminoethyl chloride in 25 ml of toluene was added and the resulting mixture was then refluxed and stirred for 3 hr. The mixture was cooled, washed with water, then extracted with 5% HCl. The oil which separated after neutralization with NaOH was distilled at reduced pressure and the fraction distilling at 179–190° (1.25 mm) was collected; yield 11.3 g (77.9%). A cyclamate derivative melting at 278.5–280° and a hydrochloride melting at 54–55° were prepared.

Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.36; H, 7.71;[6] N, 3.92.[7] Calcd for $C_{20}H_{28}ClNO_4$ (hydrochloride): N, 3.67. Found: N, 3.58.[7]

α-(β-Dimethylaminoethyl)-3,4,5-trimethoxyphenylacetonitrile.—3,4,5-Trimethoxybenzyl cyanide was prepared in a manner similar to that described by Silverman.[8] Acetone was used as the solvent for the reaction between 3,4,5-trimethoxybenzyl chloride[8] and NaCN. Increased yields were obtained by extending the reaction time to 10 days. A suspension of 15.0 g (0.072 mole) of 3,4,5-trimethoxybenzyl cyanide, 3.1 g (0.080 mole) of powdered sodamide, and 35 ml of anhydrous benzene was refluxed and stirred for 3 hr. A solution of 7.8 g (0.072 mole) of β-dimethylaminoethyl chloride in 15 ml of benzene was added and the resulting mixture was refluxed and stirred for an additional 12 hr. The mixture was cooled, washed with water, and extracted with 5% HCl. The oil which separated after neutralization with NH_4OH was distilled at reduced pressure and the fraction boiling at 165–174° (0.45 mm) was collected; yield 13.6 g (67.9%).

Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.72; H, 7.97. Found: C, 64.41; H, 7.82.

α-(2-Pyridyl)-3,4,5-trimethoxyphenylacetonitrile.—To a solution of 3.9 g (0.17 g-atom) of sodium in 150 ml of liquid NH_3 was added slowly, with stirring, 16.7 g (0.087 mole) of 3,4,5-trimethoxybenzyl cyanide suspended in 50 ml of anhydrous ether. This mixture was stirred for 30 min before 12.8 g (0.081 mole) of 2-bromopyridine dissolved in 50 ml of ether was added slowly. Stirring was continued for 1 hr before the ammonia was allowed to evaporate. Heat was gently applied until reflux temperature was reached. The mixture was refluxed and stirred for 15 hr, then cooled. Water (25 ml) was slowly added and the layers were separated. The ether layer was extracted with 10% HCl and the acid extracts neutralized with NaOH. The oily base was extracted with ether, washed with water, and dried ($MgSO_4$). After filtration, the solution was distilled yielding 8.8 g (38.4%) of product, 179–184° (0.25 mm).

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.44; H, 5.73; N, 9.85.

α-(β-Dimethylaminoethyl)-α-(2-pyridyl)-3,4,5-trimethoxyphenylacetonitrile.—To a solution of 0.85 g (0.035 g-atom) of sodium in 150 ml of liquid NH_3 was added slowly, with stirring, a solution of 8.8 g (0.031 mole) of α-(2-pyridyl)-3,4,5-trimethoxyphenylacetonitrile in 50 ml of anhydrous ether. This mixture was stirred for 30 min before 3.34 g (0.031 mole) of β-dimethylaminoethyl chloride dissolved in 100 ml of ether was added. The ammonia was slowly evaporated and the mixture was refluxed and stirred for 10 hr. Water (25 ml) was added to the cooled solution, and the layers were separated. The ether layer was dried ($MgSO_4$), filtered, and distilled at reduced pressure. The fraction distilling at 191–196° (0.25 mm) was collected; yield 6.2 g (59.5%). A picrate had mp 137–138°.

Anal. Calcd for $C_{20}H_{25}N_3O_3$: C, 67.50; H, 7.08; N, 11.82. Found: C, 67.07; H, 6.44; N, 11.61.[7]

1-(2-Pyridyl)-1-(3,4,5-trimethoxyphenyl)-3-dimethylaminopropane.—A suspension consisting of 1.15 g (0.050 mole) of $LiNH_2$, 8.8 g (0.025 mole) of α-(β-dimethylaminoethyl)-α-(2-pyridyl)-3,4,5-trimethoxyphenylacetonitrile, and 50 ml of anhydrous xylene was refluxed and stirred for 32 hr. This mixture was cooled before 25 ml of water was added. The xylene layer was dried ($MgSO_4$) and filtered. Evaporation of the solvent yielded 8.1 g (89.9%) of crude product which was purified by fractional crystallization of the cyclamate derivative, mp 185–186.5° dec.

Anal. Calcd for $C_{19}H_{26}N_2O_3$: C, 69.06; H, 7.93; N, 8.48. Found: C, 69.04; H, 7.70; N, 8.58.[7] Calcd for $C_{25}H_{39}N_3O_6$: N, 8.25. Found: N, 8.63.[7]

2-(3,4,5-Trimethoxybenzyl)aminopyridine.—A mixture of 19.9 g (0.10 mole) of 3,4,5-trimethoxybenzyl alcohol, 8.8 g (0.094 mole) of 2-aminopyridine, 10 g of KOH, and 25 ml of toluene was refluxed and stirred for 14 hr. Extraction with 10% HCl, followed by neutralization with KOH yielded a viscous yellow oil which was extracted with ether, dried ($MgSO_4$), filtered, and distilled at reduced pressure. The fraction distilling at 179–187° (0.4 mm) was collected; yield 12.0 g (53.2%). A picrate had mp 186–187°.

Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.56; H, 6.49; N, 10.09.

N,N-Dimethyl-N′-(2-pyridyl)-N′-(3,4,5-trimethoxybenzyl)-ethylenediamine.—A suspension of 1.4 g (0.061 mole) of $LiNH_2$, 13.7 g (0.050 mole) of 2-(3,4,5-trimethoxybenzyl)aminopyridine, and 75 ml of anhydrous benzene was refluxed and stirred for 3 hr. A solution of 6.5 g (0.060 mole) of β-dimethylaminoethyl chloride in 15 ml of benzene was then added slowly with stirring and the resulting mixture was refluxed and stirred for 12 hr. The mixture was then cooled, filtered, and dried ($MgSO_4$). After evaporation of the solvent, the oily residue was distilled

(1) (a) A portion of this paper was presented at the Walter H. Hartung Memorial Symposium of the Division of Medicinal Chemistry at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 2, 1963. (b) This paper is taken in part from the thesis of Louis T. DiFazio, submitted to the University of Rhode Island, Kingston, R. I., in partial fulfillment of the requirements for the Ph.D. degree. (c) This investigation was supported by research grant (MH-04132) from the National Institute of Mental Health, U. S. Public Health Service.

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(3) C. F. Koelsch and R. H. Flesch, *J. Org. Chem.*, **20**, 1276 (1955).

(4) Melting points were determined with a Koffler melting point apparatus and are corrected.

(5) This compound was prepared by a different method by R. B. Moffett, A. R. Hause, and P. H. Seay, *J. Med. Chem.*, **7**, 184 (1964).

(6) Microanalyses were performed by Micro-Analysis, Inc. Wilmington, Del., unless otherwise indicated.

(7) Semimicro Kjeldahl method for nitrogen by the author.

(8) B. Silverman, Ph.D. Thesis, University of Florida, 1961.

TABLE I
SUBSTITUTED 3,4,5-TRIMETHOXYBENZYLETHYLENEDIAMINES

No.	R	Bp, °C (mm)	Yield, %	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
1	$N(C_2H_5)_2$	170–181 (0.35)	59.8	$C_{21}H_{39}N_3O_3$	67.53	67.90	8.37	8.35	11.15	11.86
2	Pyrolidino	146–160 (0.27)	39.7	$C_{21}H_{29}N_3O_3$	67.90	68.16	7.84	8.34	11.31	11.16
3	Piperidino	205–215 (0.35)	56.2	$C_{22}H_{31}N_3O_3$	68.54	68.35	8.11	8.04	10.90	10.80[a]
4	Morpholino	180–195 (0.35)	27.2	$C_{21}H_{29}N_3O_4$	65.09	65.12	7.54	7.55	10.85	60.65

at reduced pressure. The fraction distilling at 163–171° (0.40 mm) was collected; yield 12.3 g (71.6%). A disuccinate derivative had mp 136.5°.

Anal. Calcd for $C_{19}H_{27}N_3O_3$: C, 66.02; H, 7.88; N, 12.16. Found: C, 65.72; H, 7.52; N, 11.93. Calcd for $C_{27}H_{39}N_3O_7$ (disuccinate): N, 7.23. Found: N, 7.12.[3]

The physical constants, yields, and analyses of additional 3,4,5-trimethoxybenzylethylenediamines, prepared in a manner similar to that described above, are given in Table I.

O-Diethyl Phosphoryl Esters of Quaternary and Tertiary Aminophenols[1]

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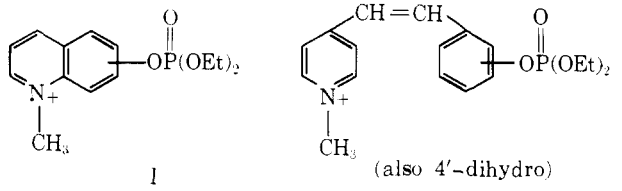
Tertiary esters of phosphoric acid which contain a rather acidic alcohol or phenol residue are inhibitors of acetylcholinesterase and other hydrolytic enzymes. Acetylcholinesterase in its reactions with other types of compounds reacts much more rapidly with compounds containing a quaternary ammonium or substituted ammonium function in the leaving group than it reacts with similar compounds lacking this structure.

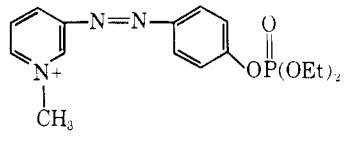
It would seem then that O-diethyl phosphoryl esters of aminophenols might be interesting compounds for this field of study. Although this principle is widely recognized, only a few compounds of this type have been previously prepared,[2-4] and we have therefore undertaken the preparation of a number of new ones. The compounds are of the types I, II, III, and some bisquaternary compounds containing a dimethylene ether bridge, $-CH_2OCH_2-$, between the two ring nitrogens (see Table I).



I

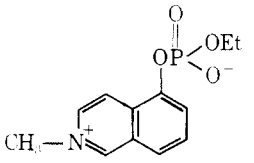
(also 4′-dihydro)

II



III

The general procedure was to diethylphosphorylate the aminophenol and then to quaternize the amine with methyl *p*-toluenesulfonate. The product is not obtained with methyl iodide, and Andrews[2] suggested that the resulting product might be the following betaine.



Our results support this view. It is therefore necessary to avoid heating these compounds in the presence of a nucleophilic agent such as I^- but it is safe to heat in the presence of anions such as picrate and *p*-toluenesulfonate.

Experimental Section

Quinolinols and 5-isoquinolinol were commercial products. Stilbazoles were prepared according to the method of Papa, *et al.*[5] The 4,3′ derivative, not previously prepared was also obtained by this method; yield 74%, mp 225°.

Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 78.93; H, 5.53; N, 7.13.

The 4,4′-hydroxystilbazole was reduced to the dihydrostilbazole with sodium amalgam at reflux temperature for 6 hr in methanol containing sodium methoxide using the one-half amount of NaHg; yield 70%.

4-(3-Pyridylazo)phenol was prepared by coupling 3-pyridinediazonium chloride with phenol in aqueous alkali. The product was precipitated by neutralization with acid; yield 81%; recrystallized from methanol, mp 219°.

Anal. Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.10. Found: C, 65.87, H, 4.35, N, 20.58.

Diethyl Phosphorylation.—The procedure using diethyl phosphoryl chloride was slightly modified after Andrews, *et al.*[2] Sodium methoxide was used instead of sodium ethoxide and the reaction mixture was not heated. After 1 hr at room temperature the reaction mixture was diluted with H_2O and the product was extracted with ether. After washing (NaOH, H_2O) the ether layer was dried (Na_2SO_4) in the presence of charcoal. The ether was evaporated and the crude product was sufficiently pure to be used for subsequent preparations without distillation. Yields varied from 25 to 60%. Picrates were prepared for identification.

Quaternization.—The N-methyl quaternary salts were prepared by heating the diethyl phosphate ester with 50% excess methyl *p*-toluenesulfonate in dimethylformamide (DMF) on a steam bath. The crude product was precipitated with ether. If the product was relatively high melting, it was recrystallized from acetone. If it was an oil, or oily, it was transformed into the picrate by dissolving in hot water or methanol and adding hot aqueous sodium picrate. The picrates separated on cooling. The picrates were recrystallized from methanol. The yields ranged from 50 to 75%.

To check Andrews' hypothesis that methyl iodide might yield the betaine, the diethyl phosphoryl ester of 5-isoquinolinol was heated for 1 hr on a steam bath with excess methyl iodide in DMF. The solution was cooled and a lemon-colored precipitate, mp 238°, insoluble in acetone, was obtained with ether. The compound was very soluble in water and gave a negative iodide test with $AgNO_3$. The analysis agrees with the betaine hydrate.

Anal. Calcd for $C_{12}H_{14}NO_4 \cdot H_2O$: C, 50.52; H, 5.66; N, 4.91; P, 10.86. Found: C, 50.07; H, 6.13; N, 4.93; P, 10.91.

Bisquaternary Compounds Containing an N,N′-Dimethylene Ether Bridge.—Bis(chloromethyl) ether was transformed to the iodide with excess NaI in acetone. NaCl was filtered off and the O-diethyl phosphorylated tertiary amine in acetone solution was added. A dilute aqueous solution of sodium picrate was

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