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THE SYNTHESIS OF SOME ACETYLAMINO-PHENOXYETHYLAMINES[1]

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Acetophenetidine has long been used as a mild analgesic and antipyretic agent and numerous efforts have been made to enhance its effectiveness by structural modifications. The local anesthetic properties associated with many *tertiary* aryloxyethylamines suggested the possibility that the analgesic properties of acetophenetidine might be enhanced by introduction of a *tertiary*-amino group in the ethoxyl portion of the molecule. With this in mind the synthesis of a few *tertiary* *p*-acetylaminophenoxyethylamines was undertaken.

A number of methods for the synthesis of aryloxyethylamines were considered in a previous communication (1). Since the objective was the modification of the ethoxyl group with a variety of substituted amino residues, *p*-acetylaminophenyl 2-chloroethyl ether appeared to be the most convenient intermediate. Several methods for the preparation of this compound were investigated. Clemo and Perkin (2) had prepared the chloroethyl ether by interaction of 2-chloroethyl *p*-toluenesulfonate and *p*-acetylaminophenol in alkaline aqueous medium. We have found it equally convenient to use 2-chloroethyl benzenesulfonate which was prepared by a modification of Földi's procedure (1, 3).

$$C_6H_5SO_2Cl + HOCH_2CH_2Cl \xrightarrow{(NaOH)} C_6H_5SO_3CH_2CH_2Cl + HCl$$

$$C_6H_5SO_3CH_2CH_2Cl + p\text{-}CH_3CONHC_6H_4OH \xrightarrow{(NaOH)} p\text{-}CH_3CONHC_6H_4OCH_2CH_2Cl + C_6H_5SO_3H$$

Better over-all yields of the chloroethyl ether were obtained by way of *p*-acetylaminophenyl 2-hydroxyethyl ether which could be prepared in excellent yield by interaction of ethylene chlorohydrin and *p*-acetylaminophenol in aqueous alkaline medium. Preparation of the hydroxyethyl ether from *p*-acetylaminophenol by interaction with ethylene oxide at 150° or with ethylene chlorohydrin in boiling aqueous alcoholic potassium hydroxide has been described (4); its pharmacological properties have been studied by Cow (5). Treatment of the hydroxyethyl ether with thionyl chloride in chloroform, a procedure recommended by Fuson and Koehneke (6) for certain hydroxyalkyl phenyl sulfides, gave *p*-acetylaminophenyl 2-chloroethyl ether in almost quantitative yield. It should be noted that treatment of the hydroxyethyl ether with thionyl chloride in the presence of pyridine usually gave a dark product that could be

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purified only with difficulty and in appreciably lower yield. Diluents such as 1,4-dioxane minimized the formation of dark by-products somewhat.

$$p\text{-}CH_3CONHC_6H_4OH + ClCH_2CH_2OH \xrightarrow{(NaOH)} p\text{-}CH_3CONHC_6H_4OCH_2CH_2OH \xrightarrow{SOCl_2}$$

$$p\text{-}CH_3CONHC_6H_4OCH_2CH_2Cl \xrightarrow{HNR_2} p\text{-}CH_3CHNHC_6H_4OCH_2CH_2NR_2$$

The *tertiary* amines were prepared by interaction of the chloroethyl ether with an excess of different secondary amines either in boiling toluene at atmospheric pressure or in a sealed tube depending upon the volatility of the secondary amine. When dimethylamine was employed, it was found advantageous to use a concentrated aqueous solution of the amine and a 1,4-dioxane solution of the chloroethyl ether to provide a homogeneous medium for the reaction. The *tertiary* amines were isolated as hydrochlorides and characterized both in this form and as free bases. Only the free base of *p*-acetylaminophenyl 2-diethylaminoethyl ether failed to crystallize. Acid hydrolysis of the acetyl compounds gave the corresponding diamines which were characterized as free bases and as dihydrochlorides. Acetylation of the diamines gave the original acetylamino compounds again.

Only very slight local anesthetic action was apparent when the *tertiary* amine hydrochlorides were placed on the tip of the tongue. Pharmacological activity of the compounds is being studied by the Parke-Davis Research Laboratories through whose courtesy the following observations are available. The analgesic action of four *tertiary* *p*-acetylaminophenoxyethylamines was studied. *p*-Acetylaminophenyl piperidylethyl ether exhibited the highest potency. It was followed in decreasing order of potency by the diethylaminoethyl ether, the morpholinylethyl ether, and the dimethylaminoethyl ether. The analgesic action of *p*-acetylaminophenyl piperidylethyl ether was comparable to that of aspirin. In each instance the analgesic action was complicated by stimulatory effects apparently of central nervous origin.

EXPERIMENTAL

2-Chloroethyl benzenesulfonate was prepared from ethylene chlorohydrin and benzenesulfonyl chloride as previously described (1).

p-Acetyl-aminophenyl 2-hydroxyethyl ether. From individual separatory-funnels 160 g. (2 moles) of ethylene chlorohydrin and a solution of 80 g. (2 moles) of sodium hydroxide in 175 ml. of water were added dropwise at comparable rates and with continuous stirring to 151 g. (1 mole) of *p*-acetyl-aminophenol in a 1-liter 3-necked flask. The reaction mixture was cooled externally until addition of the reagents was complete after which it was warmed gently and maintained at 40° for 1.5 hours. At first a homogeneous solution was formed from which the product separated as a thick crystalline sludge. The product was filtered, washed with water, and recrystallized from 1,4-dioxane, yield 171 g. (88%), m.p. 119–120° (4, 5).

p-Acetyl-aminophenyl 2-chloroethyl ether. Method A. A mixture of 100 g. (0.66 mole) of *p*-acetyl-aminophenol and 30 g. (0.75 mole) of sodium hydroxide in 60 ml. of water was heated on a boiling-water bath while 148 g. (0.66 mole) of 2-chloroethyl benzenesulfonate

was added dropwise with continuous stirring. Heating and stirring were continued for an hour after complete addition of the chloroethyl ester after which the mixture was poured onto ice. The product solidified, and was filtered and washed, first with dilute sodium hydroxide solution and then with water. The product was recrystallized from benzene, yield 103 g. (71%), m.p. 126–127° (2).

Method B. To a solution of 97 g. (0.49 mole) of *p*-acetyl-aminophenyl 2-hydroxyethyl ether in 200 ml. of chloroform, 67 g. (0.56 mole) of thionyl chloride in 50 ml. of chloroform was added dropwise with stirring and cooling. The reaction mixture was stirred for several hours at room temperature after which the solvent and excess thionyl chloride were removed by distillation under diminished pressure. The residue was recrystallized from benzene, yield 100 g. (94%), m.p. 126–127°.

A similar preparation was carried out in 1,4-dioxane in the presence of pyridine. From 39 g. of *p*-acetyl-aminophenyl 2-hydroxyethyl ether dissolved in 75 ml. of 1,4-dioxane and 24 g. of pyridine, after treatment with 35 g. of thionyl chloride, 42.6 g. (75%) of the chloroethyl ether could be isolated.

Tertiary AMINES

Analytical data for all of the tertiary amines and related products are recorded in Tables I and II.

TABLE I

p-ACETYLAMINOPHENYL 2-DIALKYLAMINOETHYL ETHERS AND THEIR HYDROCHLORIDES

p-$CH_3CONHC_6H_4OCH_2CH_2R$

R	BASES			HYDROCHLORIDES		
	Formula	N		Formula	N	
		Calc'd	Found		Calc'd	Found
Dimethylamino	$C_{12}H_{18}N_2O_2$	12.6	12.8	$C_{12}H_{19}ClN_2O_2$	10.8	10.7
Diethylamino	$C_{14}H_{22}N_2O_2$	—	—	$C_{14}H_{23}ClN_2O_2$	9.7	9.6
1-Piperidyl	$C_{15}H_{22}N_2O_2$	10.7	10.6	$C_{15}H_{23}ClN_2O_2$	9.3	9.2
4-Morpholinyl	$C_{14}H_{20}N_2O_3$	10.6	10.4	$C_{14}H_{21}ClN_2O_3$	9.2	9.1

TABLE II

p-AMINOPHENYL 2-DIALKYLAMINOETHYL ETHERS AND THEIR DIHYDROCHLORIDES

p-$NH_2C_6H_4OCH_2CH_2R$

R	BASES			DIHYDROCHLORIDES				
	Formula	N		Formula	Analyses			
		Calc'd	Found		Calc'd		Found	
					Cl	N	Cl	N
Dimethylamino	$C_{10}H_{16}N_2O$	15.5	15.4	$C_{10}H_{18}Cl_2N_2O$	28.0	11.1	28.1	11.3
Diethylamino	$C_{12}H_{20}N_2O$	—	—	$C_{12}H_{22}Cl_2N_2O$	25.2	9.9	25.3	9.8
1-Piperidyl	$C_{13}H_{20}N_2O$	12.7	12.5	$C_{13}H_{22}Cl_2N_2O$	24.2	9.6	24.1	9.4
4-Morpholinyl	$C_{12}H_{18}N_2O_2$	12.6	12.5	$C_{12}H_{20}Cl_2N_2O_2$	24.0	9.5	24.2	9.3

p-Acetyl-aminophenyl 2-dimethylaminoethyl ether. To a solution of 6.5 g. (0.03 mole) of *p*-acetyl-aminophenyl 2-chloroethyl ether in 50 ml. of 1,4-dioxane in a Pyrex tube, 20 ml. of 25% aqueous dimethylamine solution was added. The tube was sealed and heated

for 24 hours at 150°. After completion of the reaction the contents of four such tubes were combined, diluted with 400 ml. of water, and treated with enough sodium carbonate to liberate the bases. Solvents and excess secondary amine were removed by evaporation under diminished pressure. The residual material was taken up in dilute aqueous hydrochloric acid, the clear solution made just alkaline with sodium carbonate, and the *tertiary* amine extracted with benzene and the benzene solution dried over potassium carbonate. After evaporation of the benzene under diminished pressure, the residual *tertiary* amine was taken up in a small volume of absolute ethanol and treated with dry hydrogen chloride. The *hydrochloride* crystallized from the concentrated alcoholic solution, m.p. 223–224°, yield 23.9 g. (77%).

The *base* was obtained upon addition of sodium carbonate to an aqueous solution of the hydrochloride. On recrystallization from ligroin it separated as colorless needles, m.p. 105–107°.

After hydrolysis of the acetyl compound by boiling with 20% hydrochloric acid, the diamine was isolated on neutralization of the hydrolysate. On recrystallization from "Skellysolve B" the *diamine* separated as a faintly pink solid, m.p. 53–54.5°. The *dihydrochloride* crystallized from methanol-ether mixture, m.p. 230–232° with decomposition.

p-Acetyl-aminophenyl 2-diethylaminoethyl ether. A mixture of 6.5 g. (0.03 mole) of *p*-acetyl-aminophenyl 2-chloroethyl ether, 10 ml. (0.09 mole) of diethylamine, and 40 ml. of toluene was heated in a sealed tube at 150° as described in the preceding example. The products from four tubes were combined and the *tertiary* amine hydrochloride was isolated as in the foregoing example excepting that absolute isopropyl alcohol was used for the crystallization of the *hydrochloride*. Yield 29 g. (83%); m.p. 214–215°.

The *free base* was obtained as a viscous liquid that could not be induced to crystallize nor could it be distilled under reduced pressure without decomposition.

The *diamine* was obtained by hydrolysis of the acetyl derivative but could be crystallized only in the form of its *dihydrochloride*, m.p. 196–198° with decomposition; recrystallized from methanol-ether mixture.

p-Acetyl-aminophenyl 2-(1-piperidyl)ethyl ether. A solution of 23.3 g. (0.1 mole) of *p*-acetyl-aminophenyl 2-chloroethyl ether and 25 g. (0.3 mole) of piperidine in 100 ml. of toluene was boiled under reflux for eight hours. The *tertiary* amine was separated and converted into its hydrochloride in absolute isopropyl alcohol solution as described in the preceding example. The yield of *hydrochloride* was 28 g. (87%), m.p. 255–256° with decomposition.

The *free base* crystallized from ligroin, m.p. 100–101°.

Hydrolysis of the acetyl compound with 20% hydrochloric acid led to the *diamine*, m.p. 65–66.5° after recrystallization from "Skellysolve B"; the *dihydrochloride*, m.p. 216–217° with decomposition, crystallized from a methanol-ether mixture.

p-Acetyl-aminophenyl 2-(4-morpholinyl)ethyl ether. A solution of 26 g. (0.12 mole) of *p*-acetyl-aminophenyl 2-chloroethyl ether and 31 g. (0.36 mole) of morpholine in 50 ml. of toluene was boiled under reflux for eight hours. The *tertiary* amine was isolated and converted into its hydrochloride in absolute isopropyl alcohol solution as described in the previous examples. Yield of *hydrochloride* 31.2 g. (85%); m.p. 229–230° with decomposition.

The *free base* crystallized from ligroin as colorless needles, m.p. 111.5–113°.

The *diamine* was isolated after hydrolysis of the acetyl compound with 20% hydrochloric acid. It separated from cyclohexane as faintly pink needles, m.p. 69.5–70.5°. The *dihydrochloride*, m.p. 201–202° with decomposition, crystallized from a methanol-ether mixture.

SUMMARY

1. A group of four *p*-acetylaminophenyl *tertiary* aminoethyl ethers has been prepared and characterized.

2. The corresponding diamines were obtained by acid hydrolysis of the acetyl derivatives and characterized as bases and dihydrochlorides.

3. A brief statement of some of the pharmacological properties of the compounds is given.

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