[CONTRIBUTION FROM THE BURROUGHS WELLCOME & CO. U. S. A. EXPERIMENTAL RESEARCH LABORATORIES]

Esters of Secondary Hydroxyaralkylalkylamines[1]

BY JOHANNES S. BUCK AND RICHARD BALTZLY

The preparation of esters of phenolic secondary amines of the type of 4-hydroxyphenethylmethylamine, wherein the amino group is not also acylated, presents difficulties. No compounds of this type have been found in the literature. The sensitiveness of phenolic esters precludes their use as starting materials for building up the amine, and the reactivity of the amino group of the hydroxyamines prevents preferential acylation of the hydroxy groups.[2] Furthermore, it is not possible to remove only the N-acyl group from the completely acylated hydroxy amine.[3] Protection by the carbobenzoxy group was not found to be feasible as the group did not survive the reactions used.

By extending the method previously described[4] for preparing secondary amines, the authors have succeeded in obtaining the desired O-acyl compounds by a series of smooth reactions of general applicability. In the cases described below, a methoxy- or dimethoxyphenethylbenzylmethylamine was O-demethylated, the phenolic group or groups acylated, and the protecting benzyl group then removed by catalytic hydrogenation. From homoanisylamine were prepared 4-acetoxy-, 4-benzoyloxy- and 4-ethylcarbonatophenethylmethylamines. Similarly N-methylhomoveratrylamine was converted into 3,4-diacetoxy-, 3,4-dibenzoyloxy- and 3,4-diethylcarbonatophenethylmethylamines.

The compounds in question, being stabilized or protected forms of pressors and the like, are of considerable pharmacological interest, and they are being investigated from this point of view.

Experimental

4-Methoxyphenethylbenzylmethylamine Hydrochloride.—4-Methoxyphenethylbenzylamine[5] was methylated by the Eschweiler–Clarke[6] method, using 1.1 mol of formaldehyde and 5 mols of absolute formic acid, and the product was isolated as the hydrochloride. The yield approached the theoretical.

3,4-Dimethoxyphenethylbenzylmethylamine Hydrochloride.—Attempts to prepare this compound from benzylhomoveratrylamine[7] by the foregoing method, gave unsatisfactory results, probably owing to partial cyclization.[8] It was therefore prepared as follows: one mol of 3,4-dimethoxyphenethylmethylamine[9] dissolved in three volumes of ethanol, was treated with one mol of benzyl chloride. After three days the alcohol was evaporated off, water added, and the whole made acid; 0.8 mol of sodium nitrite, in solution, was added, and the whole extracted with ether. The aqueous layer, after making alkaline, was extracted with ether. After evaporation of the ether, the residue was converted into the hydrochloride; the yield was mediocre (30%).

4-Hydroxy- and 3,4-Dihydroxyphenethylbenzylmethylamines.—The corresponding 4-methoxy and 3,4-dimethoxyphenethylbenzylmethylamine hydrochlorides were demethylated with concentrated hydrochloric acid, in a carbon dioxide atmosphere, for two hours at 170°. The colorless solutions were evaporated to dryness *in vacuo*. The yields approached the theoretical.

Acylation of the Phenolic Amines.—Acetylation was accomplished by refluxing the amine hydrochlorides in a mixture of acetic anhydride and acetyl chloride, in which they gradually dissolved. After about two hours, the solvent was removed in an air stream. The residues were ground with acetone and filtered off prior to recrystallization. Use of alcohols in crystallizing the acetoxy derivatives is inadvisable. With the benzoyloxy and ethylcarbonato compounds alcohols are probably permissible but were avoided.[10]

Benzoylation of the phenolic amines was carried out by the Schotten–Baumann method. The oils resulting from the reaction were taken into ether and dried over potassium carbonate before being converted to the hydrochlorides.

The carbethoxylations required a modified Schotten–Baumann technique of which the following is an example. One mol of 4-hydroxyphenethylbenzylmethylamine hydrochloride was dissolved in water and stirred in an atmosphere of nitrogen, with ice-cooling. A solution of sodium hydroxide (3 mols), was run in slowly, 2 mols of ethyl chlorocarbonate being admitted simultaneously, keeping the alkali a little ahead of the chlorocarbonate (any considerable excess of chlorocarbonate could be detected in the stream of escaping nitrogen). The resulting oil was extracted with ether, dried over anhydrous potassium carbonate and the hydrochloride precipitated by gaseous hydrogen chloride.

In the preparation of 3,4-diethylcarbonatophenethylbenzylmethylamine hydrochloride an additional mol of sodium hydroxide and of ethyl chlorocarbonate was used. This compound, however, was not obtained crystalline,

(1) This work is part of a joint research started in collaboration with a pharmacological group then under Dr. A. M. Hjort, at the above laboratories.

(2) *Cf.* Barger, *J. Chem. Soc.*, **95**, 1128 (1909).

(3) *Cf.* Tutin, Caton and Hann, *ibid.*, **95**, 2123 (1909).

(4) Buck and Baltzly, THIS JOURNAL, **63**, 1964 (1941).

(5) By reduction of benzylidene homoanisylamine, method of ref. 7.

(6) Clarke, Gillespie and Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

(7) Buck, *ibid.*, **53**, 2192 (1931).

(8) *Cf.* Buck, *ibid.*, **56**, 1769 (1934).

(9) Buck, *ibid.*, **52**, 4119 (1930).

(10) *Cf.* Baltzly and Buck, *ibid.*, **63**, 2022 (1941).

TABLE I

DERIVATIVES OF PHENETHYLBENZYLMETHYLAMINE HYDROCHLORIDE, 4-R($C_{16}H_{19}NCl$) AND 3,4-R_2($C_{16}H_{18}NCl$)

4-R or 3,4-R_2	Recrystn. solvent + ether	Crystal form	M. p., °C.	Formula	Percentages Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
CH_3O	E. Al.,[c] E. Ac.[c]	Needles	170	$C_{17}H_{22}ONCl$	69.96	69.95	7.61	7.82
$(CH_3O)_2$	E. Al., E. Ac.	Leaves	205	$C_{18}H_{24}O_2NCl$	67.17	67.34	7.52	7.70
OH	M. Al.,[c] E. Ac.	Prisms	198	$C_{16}H_{20}ONCl$	69.16	69.26	7.26	7.48
$(OH)_2$	E. Al., E. Ac.[a]	Prisms	153	$C_{16}H_{20}O_2NCl$	65.40	65.50	6.87	7.05
CH_3COO	E. Al., H_2O	Spindles	211	$C_{18}H_{22}O_2NCl$	67.59	67.73	6.94	7.07
$(CH_3COO)_2$	Ac.,[a] E. Ac.	Needle prisms	174–5	$C_{20}H_{24}O_4NCl$	63.55	63.58	6.41	6.64
C_6H_5COO	Ac.[b]	Prisms	191	$C_{23}H_{24}O_2NCl$	72.33	72.37	6.34	6.67
$(C_6H_5COO)_2$	Ac.	Prisms	131–2	$C_{30}H_{28}O_4NCl$	71.76	71.93	5.62	5.87
$C_2H_5CO_3$	Ac.	Prisms	128–9	$C_{19}H_{24}O_3NCl$	65.20	65.20	6.92	7.23
DERIVATIVES OF PHENETHYLMETHYLAMINE HYDROCHLORIDE, 4-R($C_9H_{13}NCl$) AND 3,4-R_2($C_9H_{12}NCl$)								
CH_3COO	Ac.,[b] E. Ac.	Leaves	194	$C_{11}H_{16}O_2NCl$	57.49	57.71	7.02	7.20
$(CH_3COO)_2$	Ac., E. Ac.	Leaves	142–3	$C_{13}H_{18}O_4NCl$	54.24	54.16	6.31	6.64
C_6H_5COO	Ac.[b]	Leaves	198	$C_{16}H_{18}O_2NCl$	65.84	65.80	6.22	6.30
$(C_6H_5COO)_2$	Ac.[b]	Needles	163–4	$C_{23}H_{22}O_4NCl$	67.05	66.87	5.39	5.55
$C_2H_5CO_3$	Ac.	Leaves	138.5–139	$C_{12}H_{18}O_3NCl$	55.47	55.65	6.99	7.06
$(C_2H_5CO_3)_2$	Ac., E. Ac.	Leaves	115	$C_{15}H_{22}O_6NCl$	51.78	51.99	6.38	6.68

[a] No ether. [b] Moist acetone. [c] Ac. = acetone, E. Al. = ethyl alcohol, M. Al. = methyl alcohol and E. Ac. = ethy acetate.

and was debenzylated directly. The yields of both substances are improved somewhat by using greater excesses of alkali and of acylating agent.

Debenzylations.—These were performed by catalytic hydrogenation of the hydrochlorides in 80% acetic acid solution, using a Burgess–Parr apparatus, at room temperature and three atmospheres pressure. Palladized charcoal (from 1.2 g. of palladium chloride and 6 g. of Darco G60) was used as catalyst. The theoretical amount of hydrogen was taken up in two to three hours (from 10 g. of starting material). The solutions were filtered and evaporated to dryness *in vacuo* before recrystallization. The yields were excellent. The secondary amine hydrochlorides are colorless solids, soluble in water and alcohol, moderately soluble in acetone, sparingly soluble in ethyl acetate and insoluble in ether and non-polar solvents.

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Descriptive and analytical data are presented in the table.

Summary

A method has been developed for preparing phenolic esters wherein an unacylated secondary amino group is required on a side chain. The method involves N-debenzylation.

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Poly-condensation of α-Amino Acid Esters. I. Poly-condensation of Glycine Esters[1]

BY MAX FRANKEL AND EPHRAIM KATCHALSKI

This paper deals with the poly-condensation of methyl, ethyl and isobutyl esters of glycine and with the further condensation of isolated primary reaction products.

Curtius[2] has shown that under certain conditions glycine ethyl ester yields, besides glycine anhydride, a tetraglycine ethyl ester, the so-called "Biuret Base." This tetrapeptide ester is the highest condensation product which hitherto has been obtained directly from the glycine ethyl ester. No clear results are reported in the literature concerning the formation of the corresponding tetrapeptide ester from glycine methyl ester.[3] In any case it is clear that the tetrapeptide esters were regarded as the highest peptide esters formed by condensation from the glycine ester. Nothing definite seems to be known about the condensation to chains of glycine esters other than those of methanol and ethanol.

(1) Certain minor errors in the manuscript as originally submitted were noted by the Editorial Board. Ordinarily these would have been brought to the attention of the authors prior to publication. International conditions at present are such that it appears impossible to follow this procedure except at the risk of indefinite postponement. The Editor has therefore taken the responsibility to make any corrections which appeared to be unquestionably required.—THE EDITOR.

(2) Curtius, *Ber.*, **37**, 1284 (1904).

(3) Curtius and Goebel, *J. prakt. Chem.*, [2] **37**, 159 (1888).