[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF NORTHWESTERN UNIVERSITY DENTAL SCHOOL]

Chloro and Fluoro Compounds Related to Adrenalone

BY HAROLD L. HANSEN

The influence of nuclear chlorine and bromine on the chemical and pharmacological properties of amines of the pressor type has engaged the attention of several investigators. Zeynek¹ prepared both 3,5-dichloro- and 3,5-dibromotyramine. Glynn and Linnell² prepared ω -amino-3,4-dichloroacetophenone as well as 3,4-dichlorophenyl- β -aminoethanol and reported for the latter substance a pressor effect much smaller than that of epinephrine but also a correspondingly lower toxicity. While the present investigation was in progress Edkins and Linnell³ published a report on the preparation of 3-chloro-4-hydroxy- ω aminoacetophenone and several derivatives of ω aminoacetophenone bearing nuclear chlorine or bromine.

Aside from the work of Schiemann and Winkelmüller⁴ on 3-fluoro-4-hydroxyphenylethylamine and 3-fluorophenylethylamine no reference was found in the literature to pressor compounds containing nuclear fluorine.

The purpose of this investigation was to prepare and to make a preliminary pharmacological study of 3-chloro-4-hydroxy- ω -methylaminoacetophenone and of the corresponding fluorine compound, 3 - fluoro - 4 - hydroxy - ω - methylaminoacetophenone. Both of these are closely related chemically to adrenalone and it was hoped they might be of some value in a study of the comparative influence of chlorine and fluorine on substances of the vaso pressor type.

The synthetic methods employed in this investigation are well known and may be summarized as follows



Various attempts to reduce the amino ketones to the secondary alcohols, including the use of

(1) Zeynek, Z. biol. Chem., 114, 275 (1921).

(2) Glynn and Linnell, Quart. J. Pharm. Pharmacol., 5, 480 (1932).

(3) Edkins and Linnell, ibid., 9, 75 (1936).

(4) Schiemann and Winkelmüller, J. prakt. Chem., 135, 101 (1932).

hydrogen with a platinum catalyst, sodium amalgam in acid solution and aluminum amalgam, either failed to give the desired products or produced small amounts of compounds which it has not yet been possible to identify. Apparently both removal of halogen and splitting of the carbon-nitrogen bond were involved in these reduction reactions. Edkins and Linnell³ were unable to obtain the secondary alcohol from 3chloro-4-hydroxy- ω -aminoacetophenone by reduction.

The structures of both derivatives of adrenalone reported here were established by conversion of these compounds to the corresponding halogenated methoxybenzoic acids, the constitution and physical properties of which have been previously reported.

Preliminary pharmacological work shows that both 3-fluoro-4-hydroxy- ω -methylaminoacetophenone and the corresponding chloro compound possess vaso pressor properties weaker than that of adrenalone. Intravenous injections into anesthetized dogs produced a blood pressure rise of 2 to 4 mm. of mercury with doses of 1.3 mg./kg. The work also indicates that the fluoro compound is somewhat less active than the chloro.

Experimental Part

o-Chlorophenyl Chloroacetate.—This was prepared from 119 g. of thionyl chloride, 94.5 g. of chloroacetic acid and 128.5 g. of o-chlorophenol according to the procedure used by Hartung, Munch, Miller and Crossley⁵ in the synthesis of phenyl propionate. The yield of oily product, b. p. 123-125° at 6 mm., was 154 g. or 75%. After two distillations under reduced pressure the product had the following properties: d^{25} , 1.3589, n^{26} D 1.5335; *MR*D found 46.86; calcd. 46.33.

Anal. Calcd. for C₈H₆OCl₂: Cl, 34.60. Found: Cl, 34.44.

3 - Chloro - 4 - hydroxy - ω - chloroacetophenone.— σ -Chlorophenyl chloroacetate, 102 g. was dissolved in about 100 cc. of carbon disulfide and treated with 53 g. of anhydrous aluminum chloride according to the directions of Hartung, *et al.*⁵ At the end of the reaction the hard black mass was pulverized and added in small portions with brisk stirring to a mixture of concentrated hydrochloric acid and ice. The black precipitate was removed by suction filtration, dissolved in ether and the ether solution dried over sodium sulfate. The solid remaining after removal of the

(5) Hartung, Munch, Miller and Crossley, THIS JOURNAL, 53, 4149 (1931).

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Compound	B. p., °C. Yield, % (4 mm.) M. p., °C. Solvent				Formula	Analysi Caled.	es, % Found
o-Fluorophenyl chloroacetate	73	90-94	36-38		$C_8H_6O_2FC1$	Cl, 18.81	18.88
3-Fluoro-4-hydroxy-ω-chloroacetophe- none ^α	27-40		101-102	Tol-hept.	C ₈ H ₆ O ₂ FCl	Cl, 18-81	18.59
3-Fluoro-4-hydroxy-ω-methylaminoace- tophenone ^δ	21-31						
3-Fluoro-4-hydroxy-ω-methylaminoace- tophenone HCl	Soft, d	ark 228°	235–236 dec.	Abs. EtOH	C ₉ H ₁₁ O ₂ CIFN	N, 6.38	6.46
^a Strong irritant and lachrymator.	^b Gray powder, fairly soluble in water.						

TABLE I ANALYTICAL AND OTHER DATA FOR THE FLUORO COMPOUNDS

ether was twice crystallized from dry toluene. The yield varied from 40 to 60 g., or 39 to 59%. Evaporation of the toluene mother liquor gave a few grams of very impure, low melting product which was not studied further. The chloro ketone was further purified by crystallization from dry, crude heptane from which it was obtained as yellow crystals, m. p. 141–142°. This substance is extremely irritating to mucous membrane and is a powerful lachrymator.

Anal. Calcd. for $C_8H_6OCl_2$: Cl, 34.60. Found: Cl, 34.80.

An attempt to prepare this compound by action of phosphorus oxychloride on o-chlorophenyl chloroacetate in benzene solution according to the method used by Ott⁶ in preparation of adrenalone resulted in failure. The starting material was recovered unchanged.

3 - Chloro - 4 - hydroxy - ω - methylaminoacetophenone. -This compound was prepared according to the directions of Stolz⁷ for adrenalone. Fifty grams of finely powdered 3-chloro-4-hydroxy-w-chloroacetophenone and 25 cc. of absolute ethanol were cooled in an ice-salt bath. To the chloro ketone was added with stirring 100 cc. of a 40%methylamine solution. The reaction mixture was then allowed to stand at room temperature for two days. At the end of this time it was reduced to about one-half its original volume under diminished pressure, thoroughly chilled and filtered by suction. The precipitate was washed with cold water, dissolved in dilute hydrochloric acid and reprecipitated with ammonium hydroxide. The yield of pale yellow crystalline product was about 20 g. or 41%. The hydrochloride of this substance was isolated by evaporation of its aqueous solution on the steam-bath. Crystallization from absolute alcohol gave a faint yellow, water soluble, crystalline material. The substance shrivels at 180°, starts to melt at 210-211° and decomposes at 217°.

Anal. Calcd. for $C_9H_{11}O_2Cl_2N$: N, 5.93. Found: N, 5.99.

Proof of Structure for 3-Chloro-4-hydroxy- ω -methylaminoacetophenone.—The compound obtained above was converted to the methyl ether with methyl sulfate and the resulting ether was oxidized with potassium permanganate. The acid thus obtained was crystallized once from dilute acetic acid, from which it was obtained as small white crystals, m. p. 211–212°. This is in good agreement with the properties listed for 3-chloro-4-methoxybenzoic acid.⁸ The benzoic acid derivative obtained above was further converted to the methyl ester which, after one crystallization from dilute ethanol, melted at $94-95^{\circ}$. This corresponds with the properties of methyl 3-chloro-4-methoxybenzo-ate.³

o-Fluorophenol.—This was prepared from o-anisidine according to the directions of Schiemann.⁹

Since the procedures employed in the preparation of the fluoro compounds are identical with those previously mentioned, the analytical and other data have been summarized in Table I.

Proof of Structure of 3-Fluoro-4-hydroxy-ω-methylaminoacetophenone.-The phenol was methylated with methyl sulfate and the resulting ether oxidized with potassium permanganate. The acid thus obtained after crystallizing from dilute ethanol melted at 208-210°. 3-Fluoro-4-methoxybenzoic acid¹⁰ has been found to melt at 204°. The 3-fluoro-4-methoxybenzoic acid was further prepared as follows: p-cresol was nitrated to produce 3-nitro-4-hydroxytoluene according to the directions of Lucas and Liu.11 The phenolic compound was converted to the methyl ether with methyl sulfate and the nitro group was reduced to the amine with hydrogen in the presence of a platinum catalyst. The 3-amino-4-methoxytoluene was converted to the fluoro compound which was found to be identical with the 3-fluoro-4-methoxytoluene described by Schiemann.¹² Oxidation with potassium permanganate gave a product with m. p. 208-210°. A mixed melting point determination showed that this substance is identical with the 3-fluoro-4-methoxybenzoic acid obtained from 3fluoro-4-hydroxy-ω-methylaminoacetophenone.

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Summary

1. The 3-chloro and the 3-fluoro derivatives of adrenalone have been prepared.

2. Both substances possess weak vaso pressor properties.

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⁽⁶⁾ Ott, Ber., 59, 1068 (1926).

⁽⁷⁾ Stoiz, ibid., 37, 4149 (1904).

⁽⁸⁾ Beilstein, 4th ed., Vol. X, p. 176.

⁽⁹⁾ Schiemann, J. prakt. Chem., 140, 97 (1934); 143, 18 (1935).

⁽¹⁰⁾ Beilstein, 4th ed., Vol. X, p. 175.

⁽¹¹⁾ Lucas and Liu, THIS JOURNAL, 55, 1271 (1933).

⁽¹²⁾ Schiemann, Z. physik. Chem., A156, 415 (1931).