A New Sympatholytic Agent

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Compounds with the structure $RR'NCH_2CH_2Cl$ frequently exhibit adrenolytic or sympatholytic activity. An example is N-(2-chloroethyl)dibenzylamine hydrochloride (Dibenamine®). Theoretical considerations suggested that interesting activity would be found in a compound where R is a large aralkyl radical and to check this, 9-(2-chloroethylethylaminomethyl)anthracene was prepared and tested biologically. A detailed account of the pharmacological activity has been published elsewhere.[4] The compound was found to reverse the pressor effect of epinephrine in barbitalized dogs. The sympatholytic activity is considerably greater than that of N-(2-chloroethyl)dibenzylamine and the effect is prolonged, being evident in dogs for more than 24 hours after oral administration.

The desired compound was prepared by two different routes. In the first method 9-anthraldehyde was converted into 9-hydroxymethylanthracene and this in turn into 9-chloromethylanthracene. Treatment with N-ethylethanolamine gave 9-(ethyl - 2 - hydroxyethylaminomethyl)anthracene, from which the hydrochloride was prepared. On treatment with thionyl chloride the desired product was obtained as the hydrochloride.

The second and shorter method consisted of reacting 9-anthraldehyde with N-ethylethanolamine to give 2-anthranyl-3-ethyloxazolidine. This was readily hydrogenated to 9-(ethyl-2-hydroxyethylaminomethyl)anthracene, which, as before, on treatment with thionyl chloride gave the required 9 - (2 - chloroethylethylaminomethyl)anthracene as hydrochloride.

EXPERIMENTAL[5]

9-Hydroxymethylanthracene. 9-Anthraldehyde[6] (103.5 g., 0.5 mole) and 150 g. (0.74 mole) of aluminum isopropoxide in 3 l. of isopropyl alcohol was refluxed for 12 hours and the solvent then was removed under reduced pressure. The residue was stirred with 1500 ml. of 2 *N* hydrochloric acid and 1500 ml. of chloroform until solution was complete. The mixture was filtered, separated, and the aqueous layer was exhaustively extracted with chloroform. The combined extracts were washed with dilute sodium hydroxide, dried over sodium sulfate and the chloroform was removed under reduced pressure. The residue was recrystallized from 5 l. of benzene and 85 g. (82% yield) of bright yellow needles, melting at 162–164° was obtained.[7]

9-Chloromethylanthracene. 9-Hydroxymethylanthracene (85 g., 0.4 mole) and 48.7 g. (0.4 mole) of thionyl chloride were dissolved in 600 ml. of dioxane and the solution was refluxed for five hours and then concentrated under reduced pressure. The pasty residue was filtered off and washed with hexane. The crude yield was 95%. Recrystallization from a hexane–benzene mixture gave long yellow needles, m.p. 141–142.5°.

Anal. Calc'd for $C_{15}H_{11}Cl$: C, 79.47; H, 4.89; Cl, 15.64. Found: C, 79.85; H, 5.28; Cl, 15.50.

9 - (Ethyl - 2 - hydroxyethylaminomethyl)anthracene hydrochloride. 9-Chloromethylanthracene (15.0 g., 0.07 mole) and 20 g. (0.22 mole) of N-ethylethanolamine, dissolved in 300 ml. of dioxane, were refluxed for 24 hours, after which time the dioxane was removed under reduced pressure. The oily residue was triturated with water until solid. After filtering off the solid, it was dried in a desiccator and recrystallized from hexane. Thus 15 g. (81% yield) of yellow needles was obtained, melting at 73–75°. From this the *hydrochloride* was prepared by means of alcoholic hydrogen chloride. After recrystallization from ethanol it formed a light yellow solid melting at 208.1–210.7° (corr.).

Anal. Calc'd for $C_{19}H_{22}ClNO$: C, 72.25; H, 7.02; Cl, 11.23. Found: C, 72.57; H, 7.19; Cl, 11.12.

9-(2-Chloroethylethylaminomethyl)anthracene hydrochloride. 9-(Ethyl-2-hydroxyethylaminomethyl)anthracene (101 g., 0.32 mole) and 600 ml. of thionyl chloride, dissolved in 800 ml. of chloroform were refluxed for 150 minutes and the solvent and excess thionyl chloride then were removed under reduced pressure. The residue was dissolved in absolute ethanol and the solution was charcoaled, filtered, and treated with absolute ether to incipient turbidity. After chilling, the product was filtered off and washed with a 1:3 ethanol-ether mixture; 78 g. of a yellow powder, m.p. 179–180° (dec.) was obtained. On concentrating the mother liquors, a further 10.5-g. quantity was isolated, m.p. 179–181° (dec.). The total yield was 88.5 g. (83%). This product was dissolved in boiling ethanol, charcoaled and diluted with ether, to give a light yellow crystalline product which had a melting point of 178.0–178.5°C. (dec.) (corr.).

Anal. Calc'd for $C_{19}H_{21}Cl_2N$: C, 68.26; H, 6.33; Cl, 21.21; Cl^-, 10.61. Found: C, 68.05; H, 6.54; Cl, 21.05; Cl^-, 10.87.

2-Anthranyl-3-ethyloxazolidine. A mixture of 20.6 g. (0.1 mole) of anthraldehyde and 8.9 g. (0.1 mole) of N-ethylethanolamine was heated on a steam-bath for 40 minutes, the water formed being removed under reduced pressure. The residue was dissolved in isopropyl alcohol and alcoholic hydrogen chloride was added. The yellow crystalline product was filtered off, washed with isopropyl alcohol and recrystallized from methanol, bright yellow crystals melting at 208.4–211.4° (corr.) being formed.

Anal. Calc'd for $C_{19}H_{20}ClNO$: C, 72.80; H, 6.43; Cl^-, 11.30. Found: C, 73.09; H, 6.51, Cl^-, 11.13.

Ordinarily the crude oxazolidine, before conversion into the hydrochloride, was reduced directly in absolute ethanol solution at room temperature and 40 lbs. pressure by hydrogen and a platinum oxide catalyst. After filtration, the solution was treated with absolute alcoholic hydrogen chloride and ether and the product was recrystallized from absolute ethanol and ether. The compound proved to be identical with that obtained by the first method.

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(4) H. Minatoya and F. P. Luduena, *Arch. intern. pharmacodyniamie*, **108**, 102 (1956).
(5) Melting points are uncorrected unless otherwise noted.
(6) *Org. Syntheses*, **Coll. Vol. 3**, 98 (1955).
(7) Kleiderer and Kornfeld, *J. Org. Chem.*, **13**, 455 (1948) report 10% yield, by another method.