Synthesis of Phenolic Alkamine Ethers of Adrenaline and Some Related Compounds

JAAKKO HUKKI and ERKKI HONKANEN

Lääketehdas Orion Oy, Helsinki, Finland

Both of the possible isomers of the phenolic dimethylaminoethyl monoethers of adrenaline (III and IX) were synthesized. The corresponding ethers of meta and para-synephrine (XIIa and XIIb) were also prepared.

In the hope of obtaining adrenaline-like substances possessing antihistamine activity the synthesis of phenolic dimethylaminoethyl ethers of adrenaline was attempted. Compounds of this type are not reported in the literature.

In the case of adrenaline, there are two possible isomeric phenolic monoothers (III and IX). To obtain each of these, the preferential reactivity of the hydroxyl group in the 4-position in 3,4-dihydroxyacetophenones was made use of. N-Benzyladrenalone (I), when allowed to react with one equivalent of dimethylaminoethylchloride in dry acetone in the presence of anhydrous potassium carbonate, was converted to the 4-dimethylaminoethyl ether (II). This, after subjection to simultaneous catalytic hydrogenation and hydrogenolysis, afforded the desired 4-dimethylaminoethyl ether of adrenaline (III).

In order to prepare the other isomer, an attempt was made to protect the hydroxyl group in the 4-position in N-benzyladrenalone by benzylation, after which the hydroxyl group in the 3-position would be amenable to selective etherification with dimethylaminoethylchloride. Unfortunately, the reaction of N-benzyladrenalone with benzyl chloride resulted in the formation of a dark resin, from which no individual compound could be isolated. Thus, a more complicated method of synthesis had to be devised:

From the reaction of 3,4-dihydroxyacetophenone (IV) with one equivalent of benzylchloride the 4-benzyl ether (V) was obtained. To confirm the position of the benzyl group this compound was methylated with diazomethane. A methyl ether was obtained which proved identical with one prepared by benzylation of acetovanillone (3-methoxy-4-hydroxyacetophenone). 3-Hydroxy-4-benzylxacetophenone was brominated to give the ω-bromoderivative (VI), which on condensation with methylenamine formed the very compound (VII), which could not be obtained from N-benzyladrenalone by the direct
HUKKI AND HONKANEN

\[
\begin{align*}
\text{III} & \quad \text{IV} \quad \text{V} \quad \text{VI} \quad \text{VII} \\
\text{IX} & \quad \text{X} \quad \text{XI} \quad \text{XII}
\end{align*}
\]

\[\text{Xa, XIa and XIIa are metacompounds} \quad \text{Xb, XIb and XIIb are para} \]

ADRENALINE MONOETHERS

procedure described above. Etherification of the 4-benzyl ether (VII) with dimethylaminoethylchloride and hydrogenation and hydrogenolysis of the resulting compound (VIII) afforded the desired 3-dimethylaminoethyl ether of adrenalone (IX). The above mode of synthesis being unequivocal at every step, the constitution of the final product (IX) is established. Hence the other monoether prepared earlier, being distinctly different, must have the alternative constitution III.

For comparative pharmacologic evaluation, the corresponding phenolic alkamine ethers of meta- and para-synephrine (XII) were also prepared. The principle in both syntheses was the same: m- or p-hydroxy-ω-methylbenzylaminocetophenone (X) was etherified with dimethylaminoethylchloride and the resulting alkamine ether ketone (XI) subjected to simultaneous catalytic hydrogenation and hydrogenolysis.

As salts, these dimethylaminoethyl ethers of adrenalone, m- and p-synephrine, are stable, colorless, crystalline compounds, readily soluble in water.

EXPERIMENTAL

All melting points are uncorrected. Microanalyses were performed by the Microanalytisches Laboratorium im Max-Planck-Institut für Kohlenforschung, Mülheim, Germany.

N-Benzyladrenalone (I). This was prepared from 3,4-dihydroxy-ω-chloroacetophenone and methylbenzylamine according to Dalglish. It was isolated as the monoethanolate.

3-Hydroxy-4-dimethylaminoethoxy-ω-methylbenzylaminocetophenone (II). A mixture of 15.9 g (0.05 mole) of N-benzyladrenalone monoethanolate, 7.3 g (0.05 mole) of dimethylaminoethylchloride hydrochloride and 18.0 g (0.13 mole) of anhydrous potassium carbonate in 150 ml of dry acetone was refluxed for 24 h. The inorganic salts were filtered off and the solvent evaporated. The residue, upon admixture of ether saturated with hydrogen chloride, afforded the desired product as the dihydrochloride. The yield was 5.0 g (24 %), m. p. 235—236° (decomp.) (from dilute ethanol). (Found: C 57.48; H 6.95; N 6.51; Cl 16.74. Calc. for C_{16}H_{16}O_{3}NCl: C 57.80; H 6.78; N 6.74; Cl 17.08.)

a-(3-Hydroxy-4-dimethylaminoethylphenyl)-β-methylaminoethylhydrochloride (III). A solution of 1.04 g (0.0025 mole) of 3-hydroxy-4-dimethylaminoethoxy-ω-methylbenzylaminocetophenone dihydrochloride in 20 ml of water was hydrogenated with 0.5 g of 10 % palladium-on-carbon catalyst at room temperature and atmospheric pressure. Two molar equivalents of hydrogen were absorbed in about 2 h. After removal of the catalyst by filtration, the solvent was evaporated under reduced pressure. The residue, after crystallization from acetone-methanol, afforded the dihydrochloride of the 4-dimethylaminoethyl ether of adrenalone, m. p. 225—226°. (Found: C 47.89; H 7.63; N 8.31; Cl 21.66. Calc. for C_{15}H_{15}O_{3}N_{2}Cl: C 47.75; H 7.40; N 8.57; Cl 21.69.)

3,4-Dihydroxycetophenone (IV). This was prepared from catechol diacetate by the method of Rosenmund and Lohfert.

3-Hydroxy-4-benzoylacetoephene (V). To a boiling solution of 15.2 g (0.1 mole) of 3,4-dihydroxycetophenone and 12.7 g (0.1 mole) of benzylchloride in 250 ml of absolute ethanol, 2.3 g (0.1 mole) of sodium in 100 ml of absolute ethanol was added gradually during 1 h, after which time boiling was continued for a further 4 h. After filtration the solvent was evaporated. The residue was dissolved in 80 ml of 2 N sodium hydroxide solution and extracted with chloroform to remove the dibenzyl ether formed (about 7.5 g). Upon neutralization of the aqueous layer with carbon dioxide, 3-hydroxy-4-benzylxycetophenone was precipitated. The yield, after crystallization from ethanol, was 12.7 g (52.5 %), m. p. 119—120°. (Found: C 74.10; H 5.94. Calc. for C_{15}H_{16}O: C 74.36; H 5.83.)

From the above compound the following derivatives were prepared:

The benzene, m. p. 76—77°. (Found: C 76.59; H 5.42. Calc. for C_{22}H_{19}O_{4}: C 76.28; H 5.24.)

The methyl ether, m. p. 83—84° (from methanol), was obtained with diazomethane. (Found: C 74.38; H 6.25. Calc. for C_{22}H_{19}O_{4}: C 74.98; H 6.29.) It was shown by mixed melting point determination to be identical with 3-methoxy-4-benzoyloxyacetophenone.

This was prepared by benzylation of acetovanillone obtained from veratrole by the method of Pratt and Robinson 4.

3-Hydroxy-4-benzoyloxy-α-bromoacetophenone (VI). A solution of 12.1 g (0.05 mole) of 3-hydroxy-4-benzoyloxyacetophenone in 250 ml of glacial acetic acid (99—100 %) was cooled below +10°. To this solution 8.0 g (0.08 mole) of bromine in 50 ml of glacial acetic acid was added in the course of half an hour with stirring. The solvent was evaporated under reduced pressure. The residue, upon trituration with water, deposited crystals, which were recrystallized first from benzene, then from methanol. The yield was 8.0 g (50 %), m. p. 143—144°. (Found: C 55.84; H 4.13; Br 25.09. Calc. for C_{24}H_{23}O_{5}Br: C 56.09; H 4.08; Br 24.90.)

From the above compound the benzene, m. p. 104—106°, was also prepared.

3-Hydroxy-4-benzoyloxy-α-methylbenzylaminooacetoaphenone (VII). A mixture of 3.21 g (0.01 mole) of 3-hydroxy-4-benzoyloxy-α-bromoacetophenone and 2.42 g (0.02 mole) of methylbenzylamine in 50 ml of benzene was shaken for 4 h and allowed to stand at room temperature overnight. The separated methylbenzylamine hydrochloride (1.55 g = 95 %) was filtered off and the solvent evaporated. The residue was a reddish brown oil, which did not crystallize. It was used without further purification for the following reaction.

3-Dimethylaminooxy-4-benzoyloxy-α-methylbenzylaminooacetoaphenone dihydrochloride (VIII). A mixture of 3.6 g (0.01 mole) of the crude 3-hydroxy-4-benzoyloxy-α-methylbenzylaminooacetoaphenone, 2.16 g (0.015 mole) of dimethylaminooxychloride hydrochloride and 5.6 g (0.04 mole) of anhydrous potassium carbonate in 100 ml of acetone was refluxed for 48 h. After filtration the solvent was evaporated. The residue, upon addition of absolute ethanol and ether saturated with hydrogen chloride, afforded the desired product as the dihydrochloride. The overall yield from 3-hydroxy-4-benzoyloxy-α-bromoacetophenone (VI → VIII), after recrystallization from acetone-methanol, was 2.0 g (46 %), m. p. 202—204°. (Found: N 5.86; Cl 14.77. Calc. for C_{28}H_{27}O_{2}N_{2}·2HCl: N 5.53; Cl 14.10.)

α-(3-Dimethylaminooxy-4-hydroxyphenyl)-β-methylaminooxydihydrochloride (IX). A solution of 1.0 g (0.002 mole) of 3-dimethylaminooxy-4-benzoyloxy-α-methylbenzylaminooacetoaphenone dihydrochloride in 20 ml of water was hydrogenated at room temperature and atmospheric pressure in the presence of 0.5 g of 10 % palladium-on-carbon catalyst. Three molar equivalents of hydrogen were absorbed in 2 h. After filtration, the solvent was evaporated under diminished pressure. The residue, upon trituration with acetone-methanol, yielded the desired product as the crystalline dihydrochloride, m. p. 248—249° (decomp.). (Found: C 47.56; H 7.46; N 8.59; Cl 21.92. Calc. for C_{30}H_{30}O_{2}N_{2}·2HCl: C 47.75; H 7.40; N 8.57; Cl 21.92.)

3-Hydroxy-α-methylbenzylaminooacetoaphenone hydrochloride (X). The synthesis of this compound was carried out by the sequence of reactions devised by Sergeyevskaya and Ravdel 4. The starting material, 3-hydroxyacetophenone (a product of Winthrop Products Co.), was brominated after protection of the phenolic hydroxy group by benzylation, to give 3-benzoyloxy-α-bromoacetophenone. This, by condensation with methylbenzylamine and subsequent debenzylation, afforded 3-hydroxy-α-methylbenzylaminooacetoaphenone hydrochloride, m. p. 202—203°, in 46 % overall yield (based on 3-hydroxyacetophenone).

3-Dimethylaminooxy-α-methylbenzylaminooacetoaphenone hydrochloride (XIa). A mixture of 2.95 g (0.01 mole) of 3-hydroxy-α-methylbenzylaminooacetoaphenone hydrochloride, 2.16 g (0.015 mole) of dimethylaminooxychloride hydrochloride and 6.9 g (0.05 mole) of anhydrous potassium carbonate in 100 ml of dry acetone was refluxed for 48 h. After filtration the solvent was evaporated under reduced pressure. The residue was dissolved in ethanol. This solution, upon addition of ether saturated with hydrogen chloride, deposited crystals of dihydrochloride, which were recrystallized from acetone-methanol. The yield was 3.5 g (88 %), m. p. 198—200°. (Found: C 59.58; H 7.46; N 6.88; Cl 17.87. Calc. for C_{30}H_{30}O_{2}N_{2}·2HCl: C 60.00; H 7.07; N 7.02; Cl 17.77.)

α-(3-Dimethylaminoethoxyphenyl)-β-methylaminoethanol dioxalate (XIIa). A solution of 2.00 g (0.005 mole) of 3-dimethylaminoethoxy-α-methylbenzylaminoacetophenone dihydrochloride in 30 ml of water was hydrogenated with 0.5 g of 10% palladium-on-carbon catalyst at room temperature and atmospheric pressure. Two molar equivalents of hydrogen were absorbed in 2 h. After removal of the catalyst and evaporation of the solvent under reduced pressure, the remainder, a viscous, colorless, non-crystallizable oil, was dissolved in 5 ml of 2 N aqueous sodium hydroxide solution and extracted with ether. The ether layer was dried over anhydrous sodium sulfate. After evaporation of the solvent the residue was dissolved in methanol. This solution, after addition of 0.9 g (0.01 mole) of anhydrous oxalic acid, was heated to boiling. On cooling, the dioxalate of the desired amine was obtained as colorless crystals, m.p. 156–158°. (Found: C 48.40; H 6.31; N 6.59. Calc. for C₉H₁₈O₂N₂, 2(COOH): C 48.79; H 6.27; N 6.70.)

4-Hydroxy-α-methylbenzylaminoacetophenone monohydrate (Xb). A mixture of 3.41 g (0.02 mole) of 4-hydroxy-α-chloroacetophenone (prepared by the method of Tutin et al.) and 4.84 g (0.04 mole) of methylbenzylamine in 20 ml of benzene was shaken for 4 h and allowed to stand overnight at room temperature. After removal of the methylbenzylamine hydrochloride formed and evaporation of the solvent, the residue was crystallized from dilute ethanol. The yield was 6.2 g (95 %) and m.p. 106–109°. This same compound has been prepared previously by Asscher from phenol and methylbenzylaminoacetoniitrile. The yield and melting point recorded by this author are 16.5 % and 102–110°, respectively.

4-Dimethylaminoethoxy-α-methylbenzylaminoacetophenone dioxalate (XIIb). A mixture of 2.73 g (0.01 mole) of 4-hydroxy-α-methylbenzylaminoacetophenone monohydrate and 2.16 g (0.015 mole) of dimethylaminomethylchloride hydrochloride and 5.60 g (0.04 mole) of anhydrous potassium carbonate in 100 ml of acetone was refluxed for 48 h. The inorganic salts were filtered off, the solvent evaporated and the residue dissolved in ethanol. After addition of 1.80 g (0.02 mole) of anhydrous oxalic acid, the amine ether separated as the dioxalate. The yield was 2.7 g (52 %), m.p., after recrystallization from ethanol, 148–150°. (Found: N 5.42. Calc. for C₁₅H₂₆O₂N₂, 2(COOH): N 5.54.)

α-(4-Dimethylaminoethoxy)-β-methylaminoethanol dihydrochloride (XIIb). A solution of 2.53 g (0.005 mole) of 4-dimethylaminoethoxy-α-methylbenzylaminoacetophenone dioxalate in 30 ml of water was hydrogenated at room temperature and atmospheric pressure in the presence of 0.5 g of 10% palladium-on-carbon catalyst. Two molar equivalents of hydrogen were consumed in 2 h. After removal of the catalyst and evaporation of the solvent the hydrogenation product was obtained as crystalline dioxalate, m.p. 153–154°. By treatment with ether saturated with hydrogen chloride, this was converted to the corresponding dihydrochloride, m.p., after recrystallization from acetonemethanol, 200–201°. (Found: C 50.02; H 7.86; N 9.04; Cl 22.49. Calc. for C₁₅H₂₆O₂N₂, 2HCl: C 50.16; H 7.78; N 9.04; Cl 22.78.)

REFERENCES

2. Rosenmund, K. and Lohiert, H. Ber. 61 (1928) 2691.

Received November 22, 1958.

Acta Chem. Scand. 13 (1959) No. 2