70. *Synthetic Analgesics. Part III. The Action of Hydrogen Halides on Ethers of αα-Bis-(β′-hydroxyethyl)phenylacetonitrile.**

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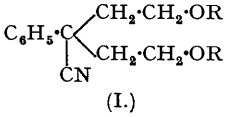
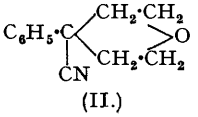
The action of hydrogen halides on various diethers of αα-bis-(β′-hydroxyethyl)phenylacetonitrile and on 4-phenyl-4-pentamethylene oxide-4-nitrile, and the resulting products are described. According to the strength and kind of hydrogen halide α-(*β′-hydroxyethyl*)-α-*phenylbutyrolactone*, α-(*β′-bromoethyl*)-α-*phenylbutyrolactone*, or *αα-bis-(β′-bromoethyl)phenylacetic acid* was formed. The ethyl ester of the last compound when condensed with methylamine gave ethyl 4-phenyl-1-methylpiperidine-4-carboxylate (pethidine).

In Part II (preceding paper) we described the selective hydrolysis of vinyl and alkoxymethyl ethers of αα-bis-(β′-hydroxyethyl)phenylacetonitrile (I, R = H) to the free di-alcohol, the nitrile group not being affected. We have now examined the products of acid hydrolysis of these ethers under more vigorous conditions and have included alkyl ethers and the cyclic ether 4-phenylpentamethylene oxide-4-nitrile (II), first prepared by Eisleb (cf. *Ber.*, **1941**, **74**, **1433**; U.S.P. 2,242,575). He stated that it may be converted into the corresponding piperidinecarboxylic acid, by hydrolysing the nitrile group with potassium hydroxide, then splitting the ether linkage with concentrated solutions of hydrogen halides to give dihalogenated acids which were then condensed with primary amines. No experimental details of these reactions are given, and the dihalogenated acids are described as oils.


(I.)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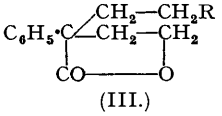
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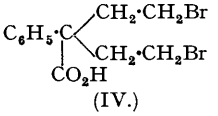
(IV.)

* Pend. Pat. Appl. 17 897, 1942.

αα-Bis-(β′-ethoxyethyl)phenylacetonitrile (I, R = Et), not hitherto described, was prepared by the condensation of phenylacetonitrile with 2 mols. of β-bromoethyl ethyl ether in presence of sodamide.

We did not attempt to hydrolyse the nitrile group in the above compounds with caustic alkali before treatment with hydrogen halide acids, for we had previously noticed that a similar hydrolysis (cf. Part II) proceeded smoothly under acid conditions.

On boiling with dilute hydrochloric acid, (I, R = $CH{:}CH_2$) and (I, R = $CH_2{\cdot}O{\cdot}CH_3$) yielded α-(β′-*hydroxyethyl*)-α-*phenylbutyrolactone* (III, R = OH). When treated with aqueous hydrogen bromide saturated at 0°, and heated in a sealed tube at 100—130°, (I, R = Et) gave as main product α-(β′-*bromoethyl*)-α-*phenylbutyrolactone* (III, R = Br) : (I, R = OH), (I, R = $CH{:}CH_2$), and (I, R = $CH_2{\cdot}O{\cdot}CH_3$) would probably give the same product. In the case of (II), in order to prevent lactone formation, the crude hydrolysis product was not distilled but esterified with ethyl alcohol and then condensed with methylamine. No pethidine, however, could be isolated, which indicated that the original hydrolysis product consisted mainly of the bromolactone (III, R = Br).

We prepared *αα-bis-(β′-bromoethyl)phenylacetic acid* (IV) from all the above ethers and also from the dialcohol by heating with aqueous hydrogen bromide (saturated at −10°) in a sealed vessel at 120—130°. Contrary to Eisleb's findings (*loc. cit.*), this acid is a solid, m. p. 115—118°, which is rather unstable, turning oily on prolonged standing or heating, probably due to partial formation of (III, R = Br). Treatment with aqueous hydrogen chloride saturated at −20° under similar conditions yielded only traces of αα-bis-(β′-chloroethyl)acetic acid and gave mainly α-(β′-chloroethyl)-α-phenylbutyrolactone (III, R = Cl).

Esterification of (IV) with ethyl-alcoholic hydrogen chloride, followed by condensation with methylamine, yielded ethyl 4-phenyl-1-methylpiperidine-4-carboxylate (pethidine).

When α-(β′-bromoethyl)-α-phenylbutyrolactone was condensed with piperidine it yielded α-(β′-*piperidinoethyl*)-α-*phenylbutyrolactone* (III, R = $C_5H_{10}N$).

Experimental.

αα-Bis-(β′-ethoxyethyl)phenylacetonitrile (I, R = Et).—Powdered sodamide (24 g.) was added in several portions with stirring to a solution of phenylacetonitrile (24 g.) and β-bromoethyl ethyl ether (92 g.) in dry toluene (150 c.c.), the temperature of the mixture being kept at 40—50°. The product was washed with water, the toluene distilled off under reduced pressure, and the product distilled in a high vacuum, to give the *nitrile*, b. p. 120—123°/0·05 mm., as a yellowish oil (29 g.) (Found : N, 5·8; OEt, 34·0. $C_{16}H_{23}O_2N$ requires N, 5·3; OEt, 34·5%).

α-(β′-Hydroxyethyl)-α-phenylbutyrolactone (III, R = OH).—A suspension of αα-bis-(β′-vinyloxyethyl)phenylacetonitrile (9·8 g.) in N-hydrochloric acid (75 c.c.) was heated on the water-bath with frequent shaking for one hour, and finally boiled for a few minutes. The oil was taken up in ether, which was washed with water and dried over anhydrous sodium sulphate. After removal of the solvent, the residue on distillation yielded (*β′-hydroxyethyl*)-α-*phenylbutyrolactone* as a slightly yellow, thick oil (5·1 g.), b. p. 172°/0·1 mm. (Found : C, 69·8; H, 7·2. $C_{12}H_{14}O_3$ requires C, 70·0; H, 6·8%).

α-(β′-Bromoethyl)-α-phenylbutyrolactone (III, R = Br).—αα-Bis-(β′-ethoxyethyl)phenylacetonitrile (10 g.) was heated for 2 hours in a sealed tube with an aqueous solution of hydrogen bromide (40 c.c.) saturated at 0°. The reaction product on being worked up as in the previous experiment yielded the *lactone* (III; R = Br) as a yellowish oil (7·3 g.), b. p. 140—142°/0·2 mm. (Found : C, 54·3; H, 5·1; Br, 30·2. $C_{12}H_{13}O_2Br$ requires C, 53·6; H, 4·8; Br, 29·8%).

α-(β′-Chloroethyl)-α-phenylbutyrolactone (III, R = Cl).—αα-Bis-(β′-hydroxyethyl)phenylacetonitrile (3·0 g.) was heated at 130° for 3 hours in a sealed tube with an aqueous solution of hydrogen chloride (25 c.c.) saturated at −20°. The product, worked up as above, gave the *lactone* (III; R = Cl) as a golden-yellow oil (Found : Cl, 15·5. $C_{12}H_{13}O_2Cl$ requires Cl, 15·6%).

α-(β′-Piperidinoethyl)-α-phenylbutyrolactone (III, R = $C_5H_{10}N$).—The bromo-lactone (III; R = Br) (4·0 g.) was dissolved in dry ether (5 c.c.), and piperidine (2·5 g.) in ether (3 c.c.) added slowly with stirring. After the mixture had stood at room temperature overnight, ether (10 c.c.) was added, and the mixture refluxed for 6 hours. The piperidine hydrobromide which separated was filtered off, and the ethereal solution extracted with dilute hydrochloric acid. *α-(β′-Piperidinoethyl)-α-phenylbutyrolactone*, precipitated from this solution by neutralisation with sodium hydroxide solution, distilled at 154°/0·1 mm. as a faintly yellow, viscous oil (2·5 g.) (Found : C, 74·7; H, 8·3; N, 5·2. $C_{17}H_{23}O_2N$ requires C, 74·7; H, 8·4; N, 5·1%). Its *hydrochloride*, a white crystalline solid, after recrystallisation from alcohol melted at 216—217° (Found : C, 65·9; H, 7·8; N, 4·7. $C_{17}H_{24}O_2NCl$ requires C, 66·0; H, 7·8; N, 4·5%).

αα-Bis-(β′-bromoethyl)phenylacetic Acid (IV).—(*a*) 4-Phenylpentamethylene oxide-4-nitrile (5·0 g.) in an aqueous solution of hydrogen bromide (30 c.c.) saturated at −10° was heated in a sealed tube at 120—130° for 2 hours. After cooling, the excess hydrobromic acid was decanted from the solid, which was taken up in ether. After being washed with ice-water, the ethereal extract was concentrated, and benzene added. After further evaporation of solvents and cooling, the *dibromo-acid* (IV) was obtained as a crystalline, white solid (7·7 g.), m. p. 118° (Found : Br, 46·1. $C_{12}H_{14}O_2Br_2$ requires Br, 45·7%). It was prepared in an analogous manner from both αα-bis-(β′-hydroxyethyl)- and -(β′-ethoxyethyl)-phenylacetonitrile (I, R = H and R = Et).

(*b*) αα-Bis-(β′-vinyloxyethyl)phenylacetonitrile (10·0 g.) was suspended in water (30 c.c.), and hydrogen bromide passed through the mixture until the oil dissolved. The solution was then cooled to −10° and saturated with hydrogen bromide. It was heated in a sealed tube at 100—120° for 2 hours, and the product worked up as in the previous experiment. After purification with charcoal and recrystallisation from benzene–light petroleum (b. p. 60—80°), the acid was obtained as a grey-white powder, m. p. 115—118°. It was obtained in the same manner from αα-bis-(β′-methoxymethyloxyethyl)phenylacetonitrile.

Ethyl 4-Phenyl-1-methylpiperidine-4-carboxylate.—αα-Bis-(β′-bromoethyl)phenylacetic acid (8·0 g.) was dissolved in ethanol (50 c.c.), and the solution saturated with dry hydrogen chloride with external cooling. After standing for 5 days at room temperature, the mixture was poured on ice, and the ester extracted with ether. The extract was washed with water and dried over anhydrous sodium sulphate. After evaporation of the ether, a yellow oil (7 g.) remained, which was used without further purification for the condensation with methylamine. It was dissolved in alcohol (20 c.c.), and a 33% alcoholic solution of methylamine (15 c.c.) added to it. The mixture was then gradually heated during 2 hours to 110° in a sealed tube. After cooling, the solvents were evaporated under reduced pressure, and the residue dissolved in dilute hydrochloric acid. Non-basic material was removed by ether extraction. The aqueous part was then

made alkaline, and the liberated base extracted with ether. After being washed, and dried over anhydrous potassium carbonate, the ethereal extract was evaporated, and the residue distilled, giving ethyl 4-phenyl-1-methylpiperidine-4-carboxylate (pethidine) as a mobile, colourless oil (b. p. 115°/0·2 mm.). Recrystallised from alcohol–ether, the hydrochloride melted at 187—189° alone and when mixed with an authentic specimen. It was also obtained in very small yield by treating crude ethyl αα-bis-(β′-chloroethyl)phenylacetate with methylamine in a similar manner to that described in the above experiment.

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