321. *The Preparation of Amino-alcohols. Part II.*

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Experiments on the synthesis of amino-alcohols of the adrenaline type by the method recently described (J., 1934, 1988) have been continued. In one more case all the four stages there given (p. 1989) have been carried out, so the method is established as a general one. In three other syntheses the substituted esters, the amides, and the hydroxy-amides have been prepared, but the final reaction in each case has not been studied. As the authors have been obliged to discontinue their joint work, the new amino-alcohol and the various intermediate compounds of the other series are described here.

Ethyl α-benzoyl*iso*valerate, COPh·CHPr$^{\beta}$·CO$_2$Et, prepared from ethyl benzoylacetate, *iso*propyl iodide in large excess, and an alcoholic solution of sodium ethoxide in the usual way (yield, 72%), had b. p. 161—162°/12 mm., gave no colouration with alcoholic ferric chloride, and was not appreciably soluble in dilute sodium hydroxide solution.

Ethyl α-benzoyl-γ-methylvalerate, COPh·CHBu$^{\beta}$·CO$_2$Et, obtained in a similar manner using *iso*butyl iodide in considerable excess (yield, about 72%), boiled at 152—155°/5 mm. When *iso*butyl bromide was used instead of the iodide, the yield fell to about 42%.

Ethyl α-benzoyl-δδ-dimethylvalerate, CH$_2$Pr$^{\beta}$·CH$_2$·CH(COPh)·CO$_2$Et, prepared in 83% yield from ethyl benzoylacetate, *iso*amyl iodide, and an alcoholic solution of sodium ethoxide, boiled at 169—170°/6 mm. (Found : C, 73·1; H, 8·4. $C_{16}H_{22}O_3$ requires C, 73·3; H, 8·4%). It was a pleasant-smelling, rather viscous oil, which gave no distinct colouration with alcoholic ferric chloride and did not form a copper compound as do ethyl benzoylacetate and ethyl α-benzoylpropionate.

Some physical constants of the esters, COPh·CHR·CO$_2$Et, are :

R =	H.	C_2H_5.	C_3H_7.	C_4H_9.	C_5H_{11}.
$n_D^{22°}$	1·526	1·506	1·505	1·500	1·496
$d^{22°}$	1·116	1·070	—	1·036	1·023
$[R_L]_D$	52·8	61·3	—	70·4	74·6

In the preparation of ethyl α-benzoylpropionate (*loc. cit.*) the yield has been increased from about 72 to 90% of the theoretical by treating ethyl benzoylacetate (1 mol.) with ethyl iodide (4 mols.) and an alcoholic solution of sodium ethoxide (1 mol.).

The conversion of the above-described esters into the corresponding amides takes place extremely slowly when the esters are left in contact with aqueous ammonia (*d* 0·88) or dissolved in a saturated alcoholic solution of ammonia; in the latter case it would seem that equilibrium is established, since, although the respective amides are doubtless produced more quickly, they remain in solution and their quantities are relatively small even after the lapse of several weeks. Other methods were being investigated, but have not yet been worked out.

*α-Benzoyl*iso*valeramide* was obtained from a solution of the ester in saturated alcoholic ammonia at the ordinary temperature after some 14 days; it crystallised from alcohol in long colourless plates, m. p. 179—180° (Found : C, 70·5; H, 7·25. $C_{12}H_{15}O_2N$ requires C, 70·2; H, 7·3%). The yield was only about 7%, and when the ester was shaken, discontinuously, and left in contact with saturated aqueous ammonia (10 vols.) during about 7 days it seemed to be entirely unchanged.

α-Benzoyl-γ-methylvaleramide was obtained by shaking the ester, discontinuously, with concentrated aqueous ammonia (15 vols.) during some 24 days; it crystallised from alcohol in compact prisms, m. p. 157—158° (yield, about 30%) (Found : C, 70·9; H, 7·7. $C_{13}H_{17}O_2N$ requires C, 71·2; H, 7·8%).

α-Benzoyl-δδ-dimethylvaleramide, obtained from the corresponding ester in a similar manner, crystallised from alcohol in colourless needles, m. p. 156—157° (Found : C, 72·0; H, 8·1. $C_{14}H_{19}O_2N$ requires C, 72·1; H, 8·2%).

These three amides resemble benzoylpropionamide (*loc. cit.*) in being sparingly soluble in water, chloroform, benzene, and ether, but moderately so in boiling alcohol; they do not give a definite colouration with alcoholic ferric chloride and apparently they do not form imines NH:CPh·CHR·CO·NH$_2$. Preliminary experiments have indicated that the rates of formation of the amide from the corresponding ester and aqueous ammonia are, in descending order : R = Me, Et, Bu$^{\beta}$, CH$_2$Pr$^{\beta}$·CH$_2$, Pr$^{\beta}$.

The reduction of α-benzoyl*iso*valeramide with aluminium amalgam and aqueous alcohol seemed to take place normally, but from the product neither of the diastereoisomerides of which it is probably composed could be isolated in crystals.

β-*Hydroxy*-β-*phenyl*-α-iso*butylpropionamide*, $CHPh(OH)\cdot CHBu^{\beta}\cdot CO\cdot NH_2$, was obtained, together with the corresponding *pinacol*, $[NH_2\cdot CO\cdot CHBu^{\beta}\cdot CPh(OH)\cdot]_2$, by treating the solution of the appropriate amide (9 g.) in aqueous alcohol (160 c.c. of alcohol, 40 c.c. of water) with aluminium amalgam (8 g. of aluminium), the mixture being warmed on the water-bath during about 3 hours. The filtered solution was evaporated to dryness, and the yellowish semi-crystalline residue treated with hot ethyl acetate containing a small proportion of benzene. As the solution cooled, long colourless needles (0·89 g.) were precipitated; the mother-liquor was decanted as soon as hexagonal plates (about 1 g.) began to separate, and later on a further crop of needles was obtained. These two products were separately recrystallised. The first compound (needles) melted at 169°, and below 140° when mixed with the parent ketone. Compared with the amide (below), it was only moderately easily soluble in boiling alcohol, ethyl acetate, and benzene, sparingly so in the cold solvents, and was doubtless the pinacol (Found: C, 70·4; H, 8·3. $C_{26}H_{36}O_4N_2$ requires C, 70·9; H, 8·2%). The second compound, the amide, crystallised from hot ethyl acetate in lustrous hexagonal plates, m. p. 136—137°, and was rather sparingly soluble in boiling water (Found: C, 70·4; H, 8·5; *M*, in camphor, 197. $C_{13}H_{19}O_2N$ requires C, 70·6; H, 8·6%; *M*, 221).

β-*Hydroxy*-β-*phenyl*-α-iso*amylpropionamide* was prepared by reducing the corresponding amide under conditions similar to those just described. The semi-solid product, obtained by evaporating the filtered solution, fractionated from ethyl acetate–light petroleum, gave sparingly soluble needles (m. p. 159°; m. p. with ketone, below 130°), which probably consisted of the pinacol, and transparent hexagonal plates (m. p. 137—138°) of the amide (Found: C, 71·6; H, 8·8; *M*, in camphor, 242. $C_{14}H_{21}O_2N$ requires C, 71·5; H, 8·9%; *M*, 235).

β-*Amino*-α-*phenylbutyl alcohol*, $CHPh(OH)\cdot CHEt\cdot NH_2$, was prepared by gradually adding a suspension of β-hydroxy-β-phenyl-α-ethylpropionamide (*loc. cit.*) (1·5 g.) in water (12 c.c.) in the course of 15 minutes to 10 c.c. of sodium hypobromite solution (bromine 9·0 g.; sodium hydroxide 18·0 g. in 100 c.c. of solution). The mixture was maintained at 0° during 2 hours; excess of sodium hydroxide was then added and the turbid solution was warmed on the water-bath during a further 2 hours. The biscuit-coloured semi-solid product which then separated was extracted from the cooled solution with chloroform, and the extract was shaken with dilute (1 : 1) hydrochloric acid; from the acid solution the liberated base was again extracted with chloroform and dry hydrogen chloride was passed into the dried chloroform solution. The hydrochloride was then precipitated in lustrous colourless prisms, only moderately soluble in chloroform, but readily soluble in water, and alcohol. The yield of pure product (m. p. 195—196°) was 0·5 g. or 32% of the theoretical. A small proportion of a yellow non-basic substance was also obtained. The platinichloride crystallised in yellow lustrous plates, only moderately soluble in water. The free base, obtained from the hydrochloride, melted at 79—80°, was fairly soluble in chloroform and benzene, sparingly soluble in light petroleum, and readily soluble in alcohol. It crystallised from benzene–light petroleum in thick shining colourless plates (Found: C, 72·8; H, 9·1. $C_{10}H_{15}ON$ requires C, 72·7; H, 9·1%). The base was reconverted into its hydrochloride by the evaporation of an alcoholic hydrochloric acid solution: the crystalline product again melted at 195—196°. The base, therefore, does not seem to be identical with that described by Hartung *et al.* (*J. Amer. Chem. Soc.*, 1930, **52**, 3317) and may be the diastereoisomeride.

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