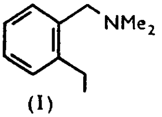
406. *The Hofmann Degradation of* 1 : 2 : 3 : 4-*Tetrahydro*-1 : 2-*dimethyl*iso*quinoline.*

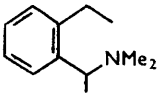
By G. Childs and E. J. Forbes.

Syntheses of 1- and 2-*o*-ethylphenylethyldimethylamine are described. The former amine is shown to be the dihydromethine of the Hofmann degradation product of 1 : 2 : 3 : 4-tetrahydro-1 : 2-dimethyl*iso*quinoline; the latter is shown to be the product of reduction of this *iso*quinoline with sodium and liquid ammonia.

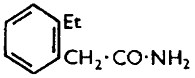
Elsner, Strauss, and Forbes [1] prepared a number of pure *o*-dialkylated benzenes by various routes. One route to *o*-diethylbenzene used *iso*quinoline as the starting material, the intermediate 1 : 2 : 3 : 4-tetrahydro-1 : 2-dimethyl*iso*quinoline being subjected to Hofmann degradation and the resulting styrene reduced. The resulting further intermediate would eventually give *o*-diethylbenzene whether it had structure (I) or (II). It has now been shown, by unequivocal syntheses of the amines (I) and (II), that the dihydromethine is in fact 1-*o*-ethylphenylethyldimethylamine (II).



(I)



(II)



(III)

(IV) : R = CHO
(V) : R = H

2-Ethylphenethyldimethylamine (I) was synthesised as follows. *o*-Ethylaniline was converted by the Sandmeyer reaction into the nitrile, which was hydrolysed to *o*-ethylbenzoic acid. Hydrolysis of *ortho*-substituted benzonitriles is known to be difficult [2] and require drastic conditions. *o*-Ethylbenzonitrile was little affected by strong acids, and alkali (under the usual conditions) gave only the amide. The amide proved resistant to acid-hydrolysis, and even nitrous acid, but prolonged heating with concentrated alkali afforded good yields of the acid. These results confirm previous work [3] that for sterically hindered nitriles hydrolysis to the amide is easier than hydrolysis of the amide to the acid.

o-Ethylbenzoic acid was converted into *o*-ethylphenylacetamide (III) by the Arndt–Eistert procedure, without isolation of the intermediate diazoketone. Reduction of the amide (III) to 2-ethylphenethylamine with lithium aluminium hydride proceeded smoothly, as also did methylation of the primary amine with formaldehyde and formic acid [4] (when

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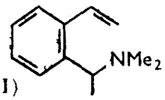
[1] Elsner, Strauss, and Forbes, *J.*, 1957, 578.
[2] Pfeiffer, Engelhardt, and Alfuss, *Annalen*, 1928, **467**, 158.
[3] Sperber, Papa, and Schwenk, *J. Amer. Chem. Soc.*, 1948, **70**, 3091.
[4] Clarke, Gillespie, and Weisshaus, *ibid.*, 1933, **55**, 4571.

applied to phenethylamines this methylation procedure often yields the tetrahydro-1-methyl*iso*quinoline;[5] none of this was obtained from the present reaction). The methiodide of the amine (I) was not identical with that obtained by Elsner *et al.*[1]

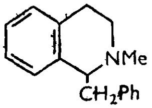
Analyses on rigorously dried specimens indicated that the methiodide of the amine (I) retained most tenaciously half a molecule of water of crystallisation whose presence was clear in the infrared spectrum (band at 3560 cm.$^{-1}$). The same hydrate was obtained when 1 : 2 : 3 : 4-tetrahydro-1 : 2-dimethyl*iso*quinoline methiodide was treated with sodium and liquid ammonia and the product converted into its methiodide. This reaction has been shown[6] to give the same product as Emde reduction[7] (with sodium amalgam or catalytically) and results in the cleavage of the 1 : 2-carbon–nitrogen bond. Thus the amine (I) is the expected product in the present case.

For the preparation of the amine (II), *o*-ethylbenzonitrile was converted into *o*-ethylacetophenone, by an improvement of the known method[8] using methyl-lithium in place of the Grignard reagent. The intermediate ketimine was fairly stable to hydrolysis, a fact which has been previously noted for compounds obtained from sterically hindered nitriles:[9] boiling with dilute acid was necessary for complete hydrolysis.

2-Ethylacetophenone was converted into 1-*o*-ethylphenylethylamine (V; R = H) by the Leuckart procedure.[10] The intermediate *N*-formyl derivative (IV; R = CHO) was not isolated but was hydrolysed to the free base, which was methylated to give 1-*o*-ethylphenylethyldimethylamine (II). The methiodide of the base (II) was identical with that prepared by Elsner, Strauss, and Forbes.[1]



(VI)



(VII)

Thus the styrene (VI) is the product of Hofmann degradation of 1 : 2 : 3 : 4-tetrahydro-1 : 2-dimethyl*iso*quinoline. This result could not have been predicted by the Hofmann rule (formation of the least substituted olefin) since both possible products would be monosubstituted. In general, however, the reaction proceeds in the direction which utilises the most acidic hydrogen β to the quaternary centre, unless the attacking base is so large that steric considerations become important.[11] On this basis the production of the styrene (VI) is understandable since it involves an acidic benzyl-hydrogen atom. That α-phenyl groups may also influence the course of Hofmann pyrolysis[12] is well illustrated in the benzyl*iso*quinoline series (*e.g.*, VII), where the stilbene is formed almost to the exclusion of the styrene.[13]

EXPERIMENTAL

o-Ethylbenzoic Acid.—A solution of *o*-ethylbenzonitrile[14] (5 g.) in ethanol (10 c.c.) was heated with potassium hydroxide (5 g.) in water (5 c.c.) and ethanol (30 c.c.) for 24 hr. Potassium hydroxide (5 g.) was then added and heating continued for a further 24 hr. (ammonia was then no longer being evolved). Removal of the alcohol, followed by the addition of dilute hydrochloric acid to the residue, gave *o*-ethylbenzoic acid (4·08 g.), which afforded plates, m. p. 63—64°, from light petroleum.

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[5] Forbes, *J.*, 1955, 3926; Osgerby and Pauson, *Chem. and Ind.*, 1958, 1144.

[6] Clayson, *J.*, 1949, 2016.

[7] Emde, *Annalen*, 1912, **391**, 88; Emde and Kull, *Arch. Pharm.*, 1936, **274**, 173.

[8] Birch, Dean, Fidler, and Lowry, *J. Amer. Chem. Soc.*, 1949, **71**, 1362.

[9] Ramart-Lucas and Salmon-Legagneur, *Compt. rend.*, 1927, **184**, 102.

[10] Ingersoll, Brown, Kim, Beauchamp, and Jennings, *J. Amer. Chem. Soc.*, 1936, **58**, 1808.

[11] Brown, *J.*, 1956, 1248.

[12] Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953, p. 447.

[13] Decker and Galatty, *Ber.*, 1909, **42**, 1179.

[14] Clarke and Read, *Org. Synth.*, Coll. Vol. I, 2nd edn., p. 514.

Heating the mixture for only 16 hr. gave *o*-ethylbenzamide, m. p. 147—148° (lit.,[15] 153°), in almost quantitative yield.

o-*Ethylphenylacetamide.*—*o*-Ethylbenzoic acid (17 g.) was heated under reflux with thionyl chloride (15 c.c.) for 3 hr. Distillation then gave *o*-ethylbenzoyl chloride (16 g.), b. p. 118°/15 mm. A solution of this in dry ether (20 c.c.) was added dropwise to a solution of diazomethane (from 60 g. of methylnitrosourea) in ether (500 c.c.) at 0°. After being kept overnight, the solution was evaporated, and the residual diazoketone was dissolved in dioxan (100 c.c.). To this solution was added ammonia (150 c.c.; *d* 0·880) and 10% aqueous silver nitrate (30 c.c.). The mixture was kept at 80° for 2 hr., then boiled for 1 hr. Working up in the usual manner gave o-*ethylphenylacetamide* (12 g.), needles, (from water), m. p. 136° (Found: C, 73·5; H, 8·0; N, 8·4. $C_{10}H_{13}ON$ requires C, 73·2; H, 7·9; N, 8·5%).

2-*Ethylphenethylamine.* A solution of *o*-ethylphenylacetamide (7·5 g.) in anhydrous tetrahydrofuran (100 c.c.) was added slowly with stirring to a suspension of lithium aluminium hydride (2·2 g.) in tetrahydrofuran (30 c.c.). The mixture was then heated under reflux for 4—5 hr. After replacement of the tetrahydrofuran by ether, the mixture was decomposed with water and treated with alkali. The aqueous layer was extracted overnight with ether. The combined ethereal layers yielded 2-ethylphenethylamine (4·6 g.), b. p. 142—143°/1 mm. The *picrate* crystallised from water in needles, m. p. 171° (Found: C, 50·5; H, 4·7; N, 14·5. $C_{16}H_{18}O_7N_4$ requires C, 50·8; H, 4·8; N, 14·8%).

2-*Ethylphenethyldimethylamine* (I).—2-Ethylphenethylamine (2·5 g.) in 90% formic acid (5·6 g.) and 40% aqueous formaldehyde (1·8 g.) was heated on a steam-bath overnight. Concentrated hydrochloric acid was added to the cooled mixture, which was next evaporated under reduced pressure. A solution of the residue in water was rendered alkaline and extracted with ether (3 × 20 c.c.). The combined extracts were dried and filtered. To a portion of the filtrate was added methyl iodide, affording 2-*ethylphenethyltrimethylammonium iodide*, plates (from ethyl acetate–ethanol), m. p. 194—195° (Found: C, 47·7; H, 6·7; N, 4·3; I, 38·4. $C_{13}H_{22}NI,\frac{1}{2}H_2O$ requires C, 47·6; H, 7·0; N, 4·3; I, 38·7%), ν 3560 cm.$^{-1}$.

The *picrate*, obtained from an ethereal solution of the base, crystallised from water in needles, m. p. 118—118·5° (Found: C, 53·0; H, 5·5; N, 14·0. $C_{18}H_{22}O_7N_4$ requires C, 53·2; H, 5·4; N, 13·8%).

Reduction of 1 : 2 : 3 : 4-*Tetrahydro*-1 : 2 : 2-*trimethyl*iso*quinoline Iodide with Sodium in Liquid Ammonia.*—To a solution of the methiodide (4 g.) in liquid ammonia (100 c.c.) at −70° was added sodium in small pieces until the blue colour remained permanently. After 1 hr., a crystal of ferric nitrate and then solid ammonium chloride were added to the solution. When the ammonia had evaporated, the residue was extracted with ether (2 × 50 c.c.). The extracts were dried and distilled to give 2-ethylphenethyldimethylamine, b. p. 128—129°/12 mm. Its methiodide gave m. p. 195—195·5°, undepressed on admixture with the specimen obtained as above (Found: C, 47·7; H, 7·0%). The picrate had m. p. and mixed m. p. 119°.

2-*Ethylacetophenone.*—A solution of methyl-lithium [from lithium (3·0 g.)] in ether (40 c.c.) was added dropwise under nitrogen to a solution of *o*-ethylbenzonitrile (14 g.) in ether (30 c.c.) with stirring. After 0·5 hr., the mixture was treated with water, followed by 4N-hydrochloric acid (20 c.c.). The ether layer was removed and the aqueous layer extracted with ether. The combined ethereal extracts were dried, filtered, and evaporated to an oil, which was heated under reflux with dilute hydrochloric acid (30 c.c.) for 45 min. Working up in the usual manner gave 2-ethylacetophenone (10·2 g., 65%), b. p. 120—122°/13 mm. The semicarbazone crystallised from methanol in needles, m. p. 180—181° (Found: N, 21·0. Calc. for $C_{11}H_{15}ON_3$: N, 20·5%); Baddeley[16] cites m. p. 182°. The 2 : 4-*dinitrophenylhydrazone* crystallised from aqueous methanol in orange needles, m. p. 118—119° (Found: C, 58·7; H, 5·3; N, 17·0. $C_{16}H_{16}O_4N_4$ requires C, 58·5; H, 4·9; N, 17·1%).

1-o-*Ethylphenylethylamine.*—2-Ethylacetophenone (5·9 g.) was heated for 10 hr. at *ca.* 180° with ammonium formate prepared from ammonium carbonate (8·6 g.) and 90% formic acid (9 g.). The cooled mixture was triturated with water (50 c.c.), and the aqueous layer discarded. The organic layer was heated under reflux with concentrated hydrochloric acid (40 c.c.) for 1·5 hr. On cooling, the solution was extracted with benzene, then basified. The precipitated oil was extracted with ether. Treating the dried ethereal extract with dry hydrogen chloride gave 1-o-*ethylphenylethylamine hydrochloride* (3·8 g.), which crystallised from ethyl

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[15] Willard and Maresh, *J. Amer. Chem. Soc.*, 1940, **62**, 1253.

[16] Baddeley, *J.*, 1944, 232.

acetate–ethanol in needles, m. p. 175° (Found: C, 64·2; H, 8·6; N, 7·7. $C_{10}H_{16}NCl$ requires C, 64·7; H, 8·6; N, 7·6%). The *picrate* crystallised from water in needles, m. p. 195—196° (Found: C, 50·8; H, 4·8; N, 14·8. $C_{16}H_{18}O_7N_4$ requires C, 50·8; H, 4·6; N, 14·8%).

1-o-*Ethylphenylethyldimethylamine* (II).—1-*o*-Ethylphenylethylamine (2·5 g.), 40% aqueous formaldehyde (1·8 g.), and 90% formic acid (5·6 g.) were heated on a steam-bath overnight. On cooling, the mixture was acidified and extracted with ether. Basification of the aqueous layer gave an oil, which was taken up in ether. When methyl iodide was added to the dried ethereal extract 1-o-*ethylphenylethyltrimethylammonium iodide* was obtained as a solid, which crystallised from ethyl acetate–ethanol in plates, m. p. 173°, undepressed on admixture with "*x*-(*o*-ethylphenyl)ethyltrimethylammonium iodide" prepared by Elsner *et al.*[1] (Found: N, 4·1; I, 39·8. $C_{13}H_{22}NI$ required N, 4·4; I, 39·8%).

The *hydrochloride* crystallised from ethyl acetate–ethanol in needles, m. p. 196° (Found: C, 67·5; H, 9·3; N, 6·7. $C_{12}H_{20}NCl$ requires C, 67·5; H, 9·4; N, 6·6%). The *picrate* crystallised from water in needles, m. p. 183° (Found: C, 53·4; H, 5·4; N, 14·1. $C_{18}H_{22}O_7N_4$ requires C, 53·2; H, 5·4; N, 13·8%).

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