295. *Aliphatic Nitro-compounds. Part XVI. Condensation of Hydroxymethyldialkylamines with Nitro-paraffins.*

By A. LAMBERT and J. D. ROSE.

Hydroxymethyl derivatives of secondary amines and nitromethane or nitroethane yield, on heating, only nitro-diamines of type II (R = H or Me). 1-Nitropropane gives chiefly the nitro-amine (III; R = Et) and a little nitro-diamine (I; R = Et). Nitro-amines (III; R = Me) are prepared from nitroethane and hydroxymethyldialkylamine by carrying out the reaction for a short time at ordinary temperature. Reductions of the nitro-diamines and nitro-amines to triamines and diamines respectively are described.

In connection with other synthetic work in progress in these laboratories, amines of the types (II) and (IV) were required, and it appeared probable that the simplest and most direct method of synthesis would be from nitro-paraffins and hydroxymethyl derivatives of secondary amines, followed by hydrogenation of the nitro-amine so formed.

$$\mathrm{R{\cdot}CH_2{\cdot}NO_2 + 2CH_2(OH){\cdot}NR'_2 \longrightarrow \underset{(I.)}{(NR'_2{\cdot}CH_2)_2CR{\cdot}NO_2} \longrightarrow \underset{(II.)}{(NR'_2{\cdot}CH_2)_2CR{\cdot}NH_2}}$$

$$\mathrm{R{\cdot}CH_2{\cdot}NO_2 + CH_2(OH){\cdot}NR'_2 \longrightarrow \underset{(III.)}{NR'_2{\cdot}CH_2{\cdot}CHR{\cdot}NO_2} \longrightarrow \underset{(IV.)}{NR'_2{\cdot}CH_2{\cdot}CHR{\cdot}NH_2}}$$

Substances of type (I) (R = H or Me) were prepared first by Henry (*Bull. Soc. chim.*, 1896, **15**, 1225; *Ber.*, 1905, **38**, 2027) from nitromethane and nitroethane with *N*-hydroxymethylpiperidine. Despite this, de Mauney (*Bull. Soc. chim.*, 1937, **4**, 1451, 1460), as a result of experiments on the condensation of hydroxymethyl secondary amines with nitromethane, 1-nitropropane, 1-nitrobutane, and 1-nitro-octane, stated that the reaction product from primary nitro-paraffin always contained one free α-hydrogen atom, *i.e.*, nitromethane combines with two and other primary nitro-paraffins with only one mol. of hydroxymethylamine. As was shown by Zief and Mason (*J. Org. Chem.*, 1943, **8**, 1), nitroethane is an exception to this rule as it condenses with *N*-hydroxymethylpiperidine (Henry, *loc. cit.*) and with *N*-hydroxymethylmorpholine to give compounds of type (I) (R = Me). Furthermore, although 1-nitropropane reacts with *N*-hydroxymethyldiethylamine to give mainly 2-nitro-1-diethylaminobutane (III; R = R′ = Et), we have also obtained small yields of the bis-condensate, 2-*nitro*-1 : 3-*bis*(*diethylamino*)-2-*ethylpropane*, from this reaction.

The formation of amines of the type (III) (R = Me) from nitroethane is a matter of some difficulty. Attempts to degrade the bis-adducts of type (I) from nitroethane to mono-adducts of type (III) by alkaline reagents were uniformly unsuccessful, although this method is applicable to the degradation of, *e.g.*, tris(hydroxymethyl)nitromethane to 2-nitropropane-1 : 3-diol. Since 2-nitro-2-methylpropane-1 : 3-diol condenses with, *e.g.*, hydroxymethylpiperidine to give the nitro-diamine in good yield, an attempt was made to effect a similar reaction with 2-nitro-*n*-propyl alcohol. Disproportionation occurred, the only product isolated being 2-nitro-1 : 3-dipiperidino-2-methylpropane, formed by fission of the nitro-alcohol to nitroethane and formaldehyde, followed by recombination in the appropriate proportions. Similarly, 2-nitroethyl alcohol and piperidine yielded only 2-nitro-1 : 3-dipiperidinopropane, and 2-nitro*iso*propyl alcohol (from nitromethane and acetaldehyde), on treatment with hydroxymethylpiperidine, gave acetaldehyde and 2-nitro-1 : 3-dipiperidinopropane.

Finally, the nitro-monoamines of type (III) were obtained by allowing equimolecular proportions of the nitro-paraffin and the hydroxymethylamine to interact at room temperature. In this way, 2-*nitro*-1-*diethylaminopropane* was obtained in 70% yield from nitroethane and hydroxymethyldiethylamine, and 2-nitro-1-piperidinopropane was formed from nitroethane and hydroxymethylpiperidine. Although the nitro-amines were unstable and could not be obtained pure, and precipitated nitro-diamine on storage, reduction of the freshly prepared crude products gave the diamines (IV).

EXPERIMENTAL.

Analyses are by Mr. E. S. Morton. All m. ps. are uncorrected.

2-*Nitro*-1 : 3-*dipiperidino-2-methylpropane*.—(*a*) This was prepared from hydroxymethylpiperidine and nitroethane according to Henry (*loc. cit.*); white needles from alcohol, m. p. 102°. Henry (*loc. cit.*) gives m. p. 98—99° (Found : C, 62·3; H, 9·7; N, 15·3. Calc. for $C_{14}H_{27}O_2N_3$: C, 62·8; H, 10·0; N, 15·6%).

(*b*) A mixture of 2-nitro-2-methylpropane-1 : 3-diol (Vanderbilt and Hass, *Ind. Eng. Chem.*, 1940, **32**, 34; 136 g.) and piperidine (170 g.) in alcohol (300 c.c.) was refluxed for 3 hours. After cooling, the crystals were collected, washed with a little alcohol, and dried, and had m. p. 102° alone and in admixture with a sample prepared as (*a*) above. Yield, 172 g.

2-*Nitro*-1 : 3-*bis*(*diethylamino*)-2-*methylpropane*.—Formaldehyde (40%; 75 c.c.) was treated with diethylamine (74 g.) in water (75 c.c.) at 0°, and to the mixture nitroethane (37 g.) was added with stirring at room temperature. After 16 hours' stirring the supernatant oil was isolated with ether, dried (K_2CO_3), and fractionated to give 2-*nitro*-1 : 3-*bis*(*diethylamino*)-2-*methylpropane* as an almost colourless liquid, b. p. 94—96°/0·2 mm. (Found : C, 58·8; H, 10·7; N, 16·6. $C_{12}H_{27}O_2N_3$ requires C, 58·8; H, 11·0; N, 17·1%). This diamine was unchanged by treatment with 1 mol. of sodium methoxide in methyl alcohol at room temperature. Catalytic hydrogenation with Raney nickel and hydrogen caused decomposition to low boiling products among which bis(diethylamino)methane was recognised.

2-*Amino*-1 : 3-*bis*(*diethylamino*)-2-*methylpropane*.—Crude 2-nitro-1 : 3-bis(diethylamino)-2-methylpropane, prepared as above (not distilled; total product after concentration of ethereal solution) from nitroethane (37 g.), was added dropwise with stirring to an ice-cold solution of stannous chloride (327 g.) in concentrated hydrochloric acid (500 c.c.). After 1 hours' stirring, excess of 30% aqueous sodium hydroxide was added and the product isolated with ether, dried (K_2CO_3), and fractionated. The fraction, b. p. 63—67°/0·2 mm., was dried over sodium and redistilled, giving the *amine* as a colourless oil, b. p. 60°/0·1 mm. (Found : N, 19·6. $C_{12}H_{29}N_3$ requires N, 19·5%).

2-*Amino*-1 : 3-*bis*(*diethylamino*)-2-*ethylpropane*.—A solution of diethylamine (73 g.) in water (75 c.c.) was added at 0° to formaldehyde (40%; 75 c.c.) and 1-nitropropane (45 g.) then added and the mixture stirred at room temperature for 20 hours. The upper layer was isolated with ether and distilled, giving chiefly 2-nitro-1-diethylaminobutane, b. p. 70°/0·4 mm. (cf. de Mauney, *loc. cit.*), and crude 2-*nitro*-1 : 3-*bis*(*diethylamino*)-2-*ethylpropane* (18 g.), b. p. 108°/0·2 mm., with slight decomposition (Found : N, 15·3. $C_{13}H_{29}O_2N_3$ requires N, 16·2%). This latter was reduced as described above for the lower homologue, with stannous chloride (60 g.) and hydrochloric acid (100 c.c.) at 0°, giving 2-*amino*-1 : 3-*bis*(*diethylamino*)-2-*ethylpropane* (5 g.) as a colourless oil, b. p. 112—114°/10 mm. (Found : C, 67·7; H, 12·8; N, 17·8. $C_{13}H_{31}N_3$ requires C, 68·1; H, 13·5; N, 18·3%). The *tripicrate* formed yellow prisms from water, m. p. 162° (Found : C, 40·6; H, 4·4; N, 17·8. $C_{13}H_{31}N_3,3C_6H_3O_7N_3$ requires C, 40·6; H, 4·4; N, 18·3%).

2-*Nitro*-1-*diethylaminopropane*.—Formaldehyde (40%; 8·1 c.c.) and diethylamine (7·3 g.) in water (10 c.c.) were mixed at 0° and nitroethane (7·5 g.) was added slowly with cooling. The mixture was kept at room temperature for 4 hours, extracted with ether, and the ethereal extract dried and distilled. 2-*Nitro*-1-*diethylaminopropane* was obtained as a pale yellow oil (11 g.), b. p. 83·5°/11 mm. (Found : C, 52·6; H, 10·1; N, 17·3. $C_7H_{16}O_2N_2$ requires C, 52·5; H, 10·0; N, 17·5%), which decomposed slowly on keeping.

2-*Amino*-1-*diethylaminopropane*.—The nitro-amine (above) was reduced in methyl-alcoholic solution with Raney nickel and hydrogen at 70 atmospheres (initial pressure) and room temperature. Fractionation of the filtered solution gave 2-*amino*-1-*diethylaminopropane*, b. p. 148—149°/772 mm., in 47% yield [Found : equiv. (by titration), 66·9. $C_7H_{18}N_2$ requires equiv., 65].

2-*Amino*-1-*piperidinopropane*.—Formaldehyde (87%; 81 c.c.), piperidine (85 g.), water (85 c.c.), and nitroethane (75 g.) were brought into reaction as described above for the diethylamino-analogue. 2-Nitro-1-piperidinopropane was obtained as an oil (142 g.), b. p. 99—104°/7 mm. (slight decomp.), and could not be obtained analytically pure. On keeping, decomposition occurred and 2-nitro-1 : 3-dipiperidino-2-methylpropane was precipitated. Reduction of the freshly prepared material (128 g.) with Raney nickel and hydrogen at 60 atms. and 40° gave 2-amino-1-piperidinopropane as a colourless oil (54 g.), b. p. 92—93°/15 mm. (Found : equiv. by titration), 71·4. Calc. for $C_8H_{18}N_{20}$: equiv., 71). Wenker (*J. Amer. Chem. Soc.*, 1938, **60**, 158), who prepared this compound by amination of 2-chloro-1-piperidinopropane, gives b. p. 193—194°/760 mm.).

Reaction of 2-*Nitroethyl Alcohol with Piperidine*.—2-Nitroethyl alcohol (10 g.), piperidine (20 c.c.), and dioxan (20 c.c.) were refluxed for 20 minutes and poured into water. The product was mainly 2-nitro-1 : 3-dipiperidinopropane, m. p. 93—94°, undepressed by admixture with an authentic specimen prepared from nitromethane and hydroxymethylpiperidine (Henry, *loc. cit.*).

Reaction of 2-*Nitro*-n-*propyl Alcohol with Piperidine*.—2-Nitro-*n*-propyl alcohol (21 g.) and piperidine (17 g.) were mixed; there was considerable heat evolution and the mixture was warmed on the steam-bath for one hour. On cooling, the dark liquor deposited crystals, which were collected and recrystallised from alcohol, giving 2-nitro-1 : 3-dipiperidino-2-methylpropane, m. p. 104° alone and in admixture with an authentic specimen.

Reaction of 2-*Nitro*iso*propyl Alcohol with Piperidine and Formaldehyde*.—2-Nitro*iso*propyl alcohol (10·5 g.) and piperidine (17·0 g.) were mixed and cooled, and formaldehyde (15 c.c.) was added. A pronounced smell of acetaldehyde became apparent and a crystalline solid separated. Recrystallised from alcohol, this gave 2-nitro-1 : 3-dipiperidinopropane, m. p. 93—94° alone and in admixture with an authentic specimen.

2 : 2′-*Dipiperidino*iso*propylamine*.—2-Nitro-1 : 3-dipiperidinopropane (200 g.) in methyl alcohol (750 c.c.) was reduced with Raney nickel and hydrogen at 130 atms. (initial pressure) and 50°. Distillation of the filtered solution yielded 2 : 2′-*dipiperidino*iso*propylamine*, b. p. 152—154°/11 mm. Yield, 124 g. (70%) (Found : C, 68·6; H, 11·9; N, 18·4. $C_{13}H_{27}N_3$ requires C, 69·3; H, 12·0; N, 18·6%). The *trihydrochloride* formed pearly plates from aqueous alcohol, m. p. 260° (Found : Cl, 31·7. $C_{13}H_{27}N_3,3HCl$ requires Cl, 31·8%).

2 : 2′-*Dipiperidino*iso*propylurea*.—The amine (8 g.), suspended in boiling water (100 c.c.), was treated cautiously with nitrourea; 11 g. (3 mols.) were necessary to give a clear solution. The filtered solution was treated with an excess of 10N-sodium hydroxide; the precipitated oil solidified immediately and was recrystallised from acetone. The *urea* had m. p. 86° (Found : C, 62·3; H, 10·3. $C_{14}H_{28}ON_4$ requires C, 62·6; H, 10·4%). The *dimethiodide*, from aqueous alcohol, had m. p. 257° (decomp.) (Found : N, 9·6; I, 45·7. $C_{16}H_{34}ON_4I_2$ requires N, 10·1; I, 46·0%).

The authors wish to acknowledge the interest and advice of Mr. C. Paine and Dr. H. A. Piggott in this work.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, RESEARCH LABORATORIES,
HEXAGON HOUSE, BLACKLEY, MANCHESTER, 9. [*Received, January 23rd*, 1947.]