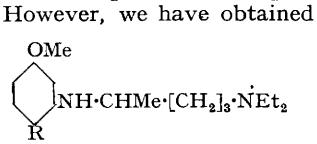
73. *Some Basically Substituted Derivatives of Benziminazole and Lupinane.*

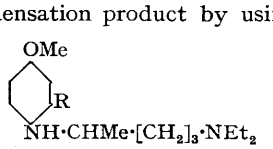
By G. R. CLEMO and G. A. SWAN.

The preparation of 1-(ε-diethylamino-β-pentyl)benziminazole derivatives carrying a methoxyl group in the 5- or 6-position, with or without a methyl group in the 2-position of the nucleus, is recorded. 11-(ε-Diethylamino-β-pentyl)aminolupinane has also been prepared.

THE preparation of 4-nitro-3-(ε-diethylamino-β-pentyl)aminoanisole (I) by condensation of δ-amino-α-diethylaminopentane with 3 : 4-dinitroanisole is described by Topeijev (*Compt. rend. Acad. Sci. U.R.S.S.*, 1935, **4**, 201), although the evidence put forward to prove that replacement occurs in the 3- rather than the 4- position is not conclusive. However, we have obtained the same condensation product by using 3-bromo-4-nitro-



(I), R = NO_2. (II), R = NH_2.

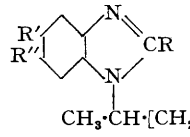


(III), R = NO_2. (IV), R = NH_2.

instead of 3 : 4-dinitro-anisole; but from the preparative point of view, Topeijev's method is superior. Reduction of (I) gives the corresponding derivative of 3-aminoanisole (II). We have also carried out the condens-

ation with 4-bromo-3-nitroanisole, and obtained 3-*nitro*-4-(ε-*diethylamino*-β-*pentyl*)*aminoanisole* (III), which, on reduction, gave the corresponding 3-*amino*-compound (IV).

By condensing (II) and (IV) with anhydrous formic acid or acetic anhydride, the benziminazole *derivatives* (V)—(VIII) were obtained. The compounds (I)—(VIII) are all oils but whereas (I)—(IV) fail to give



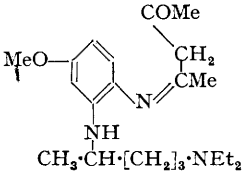
(V), R, R′ = H; R″ = OMe. (VI), R = Me; R′ = H; R″ = OMe.

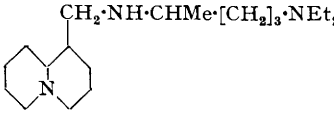
(VII), R, R″ = H; R′ = OMe. (VIII), R = Me; R′ = OMe; R″ = H.

crystalline picrates or picrolonates, the benziminazole compounds (V)—(VIII) give highly crystalline derivatives of sharp melting point. By making use of the latter, we have definitely established the identity of the products of the reaction of δ-amino-α-diethylaminopentane with 3 : 4-dinitro- and with 3-bromo-4-nitroanisole.

Attempts to condense (II) with acetylacetone, with a view to obtain a plasmoquin-like compound with methyl groups substituted in the 2- and the 4-position of the quinoline nucleus, gave only an oil which appears to be the Schiff's base (IX)

(IX.)





(X.)

Condensation of δ-amino-α-diethylaminopentane with 11-bromolupinane gave 11-(ε-diethylamino-β-pentyl)aminolupinane (X). Biological tests show that these compounds are without action on avian malaria.

Experimental.

Preparation of 4-*Nitro*-3-(ε-*diethylamino*-β-*pentyl*)*aminoanisole* (I).—Method I. 3-Bromo-4-nitroanisole was prepared as follows. 3-Bromo-4-nitrophenol (11 g.) (Hodgson and Crook, J., 1936, 1677) was dissolved in dry xylene (200 c.c.); sodium bicarbonate (40 g.) and freshly purified methyl sulphate (19 c.c.) were added, the mixture stirred at 120° for 6 hours and cooled, and water added. The xylene layer was separated, washed (dilute sodium hydroxide solution), dried (sodium sulphate), the xylene removed in a vacuum, and the residue crystallised from light petroleum; yield, 11·3 g.; m. p. 45°.

This compound (4 g.), δ-amino-α-diethylaminopentane (7·2 c.c.), and a trace of copper powder were heated together in a sealed tube for 10 hours in the water-bath. Dilute sodium carbonate solution was then added, the excess of pentane base removed by steam-distillation, and the alkaline solution extracted with ether. The extract was shaken with dilute hydrochloric acid, the base reprecipitated from the acid extract by addition of sodium hydroxide solution, taken up in ether, dried with potassium carbonate, and distilled (2·5 g., b. p. 200—205°/1·5 mm.).

Method II. 3 : 4-Dinitroanisole was prepared from 3-nitro-*p*-anisidine by Topeijev's method (*loc. cit.*) (yield, 65%). This compound (3·5 g.) was mixed with δ-amino-α-diethylaminopentane (5 c.c.) and gradually heated under reflux in an oil-bath. When the temperature reached 80°, a violent reaction suddenly began; after this had subsided, the mixture was heated at 145° for 8 hours, cooled, sodium carbonate solution added, and the product worked up as in method (I), giving 4 g., b. p. 205°/2 mm.

The reduction to 4-amino-3-(ε-diethylamino-β-pentyl)aminoanisole (II) was carried out by Topeijev's method (*loc. cit.*).

3-*Nitro*-4-(ε-*diethylamino*-β-*pentyl*)*aminoanisole* (III).—4-Bromo-3-nitroanisole (11·5 g.) (Hodgson, J., 1935, 947), δ-amino-α-diethylaminopentane (20 c.c.), and a trace of copper powder were heated together in a sealed tube for 9 hours at 140°. Sodium carbonate solution was added to the product, and the excess of pentane base removed by steam-distillation. After cooling, the non-volatile oil was taken up in ether, the basic material extracted from the ether with dilute acetic acid, the acid extract basified (sodium hydroxide solution), and extracted with ether. After drying (potassium carbonate), the ether was removed, and the residue distilled, giving the *base* as a red, viscous oil (2·8 g., b. p. 195—200°/2 mm.) (Found : C, 62·8; H, 8·75. $C_{16}H_{27}O_3N_3$ requires C, 62·1; H, 8·75%).

The above steam-distillate was acidified (hydrochloric acid), evaporated on the water-bath to a thick gum, and basified (40% sodium hydroxide solution), and the pentane base separated, dried, and distilled, giving 10 g. of pure compound.

3-*Amino*-4-(ε-*diethylamino*-β-*pentyl*)*aminoanisole* (IV).—To a cooled solution of the above nitro-compound (2·7 g.) in concentrated hydrochloric acid (7 c.c.), stannous chloride (7 g. of dihydrate) in concentrated hydrochloric acid (10 c.c.) was gradually added with shaking. After standing overnight, excess of sodium hydroxide solution was added, the product extracted with ether, the extract dried (potassium carbonate), the ether removed, and the residue distilled, giving the *base* (IV) as a pale yellow, viscous oil (1·55 g., b. p. 180—185°/2 mm.) (Found : C, 68·6; H, 10·45. $C_{16}H_{29}ON_3$ requires C, 68·8; H, 10·4%).

1-(ε-*Diethylamino*-β-*pentyl*)-6-*methoxybenziminazole* (V).—4-Amino-3-(ε-diethylamino-β-pentyl)aminoanisole (1·9 g.) was heated with anhydrous formic acid (2 c.c.) for 2 hours at 165°. After cooling, the product was dissolved in water, basified (sodium hydroxide), extracted with ether, the extract dried with potassium carbonate, the ether removed, and the residue distilled in a vacuum (yield 0·91 g.). A solution of this base in methanol was added to a hot, saturated solution of picrolonic acid (2 mols.) in the same solvent; on cooling, crystals of the *dipicrolonate* (1·8 g., m. p. 193°) separated. Recrystallisation from acetone–methanol raised the m. p. to 197° (Found C, 54·0; H, 4·9. $C_{17}H_{27}ON_3,2C_{10}H_8O_5N_4$ requires C, 54·35; H, 5·25%). The picrolonate (1 g.) was ground with warm, concentrated hydrochloric acid, the precipitated picrolonic acid filtered off, and the filtrate basified (sodium hydroxide), and extracted with ether. The extract was dried with potassium carbonate, the ether removed, and the residue distilled, giving the *base* (V) as a pale yellow oil (0·29 g., b. p. 190°/1·5 mm.) (Found : C, 70·1; H, 9·55. $C_{17}H_{27}ON_3$ requires C, 70·55; H, 9·35%). The picrate, recrystallised from methanol, had m. p. 135°.

1-(ε-*Diethylamino-β-pentyl*)-6-*methoxy*-2-*methylbenziminazole* (VI).—4-Amino-3 (ε-diethylamino-β-pentyl)aminoanisole (1·1 g.) was heated with acetic anhydride (2 c.c.) for 5 hours at 165°, and the product (1 g.) worked up as before. This crude base gave 1·8 g. of *dipicrolonate*, m. p. 230° (Found, on material crystallised from acetone–methanol: C, 55·0; H, 5·5. $C_{18}H_{29}ON_3,2C_{10}H_8O_5N_4$ requires C, 54·9; H, 5·4%). The free *base* (0·3 g., b. p. 190°/1·5 mm.) recovered from the pure picrolonate (0·95 g.) was a pale yellow, viscous liquid (Found: C, 71·25; H, 9·8. $C_{18}H_{29}ON_3$ requires C, 71·3; H, 9·6%). The picrate had m. p. 192°.

This preparation was carried out with specimens of the starting material prepared from 3-bromo-4-nitroanisole by method (I) and from 3 : 4-dinitroanisole by method (II). The picrate and picrolonate prepared from each product were indistinguishable, and no depression of m. p. was observed on admixture. Depression of m. p. was, however, observed on admixture with the corresponding derivatives of 4-bromo-3-nitroanisole.

1-(ε-*Diethylamino-β-pentyl*)-5-*methoxybenziminazole* (VII).—3-Amino-4-(ε-diethylamino-β-pentyl)aminoanisole (1·5 g.) was heated with anhydrous formic acid (3 c.c.) for 3 hours at 165°, and the product (1·1 g.) worked up as before. Its solution in methanol was added to a hot solution of picric acid (2 mols.) in methanol. After cooling, the crude *picrate* (m. p. 150° approx.) was filtered off and recrystallised from acetone–methanol (1·55 g.; m. p. 161°) (Found: C, 46·4; H, 4·55. $C_{17}H_{27}ON_3,2C_6H_3O_7N_3$ requires C, 46·6; H, 4·4%). The free *base* (0·43 g.; b. p. 195°/2 mm.), recovered from the pure picrate (1·5 g.) as described for the decomposition of the picrolonates, was a pale yellow, viscous liquid (Found: C, 70·7; H, 9·55. $C_{17}H_{27}ON_3$ requires C, 70·55; H, 9·35%).

1-(ε-*Diethylamino-β-pentyl*)-5-*methoxy*-2-*methylbenziminazole* (VIII).—3-Amino-4-(ε-diethylamino-β-pentyl)aminoanisole (1·55 g.) was heated with acetic anhydride (2·7 c.c.) for 5 hours at 165°, and the product (1·34 g.) worked up as before. This crude base gave 2 g. of *dipicrate*, which by recrystallisation from acetone–methanol gave 1·2 g., m. p. 198° (Found: C, 46·9; H, 4·65. $C_{18}H_{29}ON_3,2C_6H_3O_7N_3$ requires C, 47·3; H, 4·6%). On decomposition, this pure picrate gave the *base* (0·3 g.; b. p. 195°/2 mm.) as a viscous liquid (Found: C, 70·6; H, 9·65. $C_{18}H_{29}ON_3$ requires C, 71·3; H, 9·55%). The picrolonate had m. p. 229°.

11-(ε-*Diethylamino-β-pentyl*)*aminolupinane* (X).—11-Bromolupinane (1·3 g.) (Clemo, Raper, and Tenniswood; J., 1931, 433), δ-amino-*a*-diethylaminopentane (1·7 c.c.), and a trace of copper powder were heated together in a sealed tube for 20 hours in the water-bath. After the addition of sodium carbonate solution, the excess of pentane base was removed by steam-distillation, the non-volatile base extracted with ether, the extract dried with potassium carbonate, the ether removed, and the product distilled (yield 1·02 g., b. p. 165—167°/2 mm.). When this base was mixed with picrolonic acid (3 mols.) in warm, dilute methanol, and the mixed solution allowed to cool slowly, the *tripicrolonate* (m. p. 166—172° approx.) separated slowly (Found: C, 53·1; H, 6·25; N, 19·25. $C_{19}H_{39}N_3,3C_{10}H_8O_5N_4$ requires C, 53·4; H, 5·7; N, 19·05%). On decomposition in the usual way, this gave the free *base*, as an almost colourless liquid (b. p. 165—167°/2 mm.) (Found: C, 73·75; H, 12·9. $C_{19}H_{39}N_3$ requires C, 73·8; H, 12·6%).

Condensation of 4-*Amino*-3-(ε-*diethylamino-β-pentyl*)*aminoanisole with Acetylacetone*.—The base (0·8 g.) and acetylacetone (0·3 g.) were mixed and gently warmed, and the mixture kept for 14 hours at room temperature. Sulphuric acid (4 c.c., *d* 1·8) was then added, the mixture heated for one hour on the water-bath, cooled, and poured into ice-water. After basification (sodium hydroxide), the product was extracted with ether, the extract dried with potassium carbonate, the ether removed, and the residue distilled, affording 0·4 g. of the *base* as a yellow, viscous oil, b. p. 175°/1·5 mm. (Found: C, 69·3; H, 9·75. $C_{21}H_{35}O_2N_3$ requires C, 69·8; H, 9·7%)

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