361. *Attempts to find New Spasmolytics. Part VIII. The Synthesis of* 6 : 7-*Diethoxy*-3-*alkyl- and* 6 : 7-*Diethoxy*-3-*phenyl*-isoquinolines.

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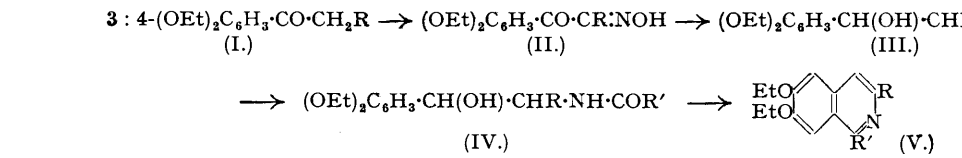
A number of 1-substituted 6 : 7-diethoxy-3-ethyl-, -3-propyl-, and -3-phenyl-*iso*quinolines has been synthesized. Except for the 1 : 3-diphenyl compound, all exert similar spasmolytic activity and are more active than papaverine, but none is an appreciable improvement on the 1-phenyl-3-methyl compound.

In previous communications (for references see Part VII, *J.*, 1948, 885) we recorded the synthesis of some 1-substituted 3-methyl*iso*quinolines. 3-Methyl*iso*quinolines are effective spasmolytics of low toxicity (Kreitmair, *Arch. exp. Path. Pharm.*, 1932, **164**, 509; cf. B.P. 488,423). Recently a number of 6 : 7-diethoxy-3-methyl*iso*quinolines was prepared (Part VII, *loc. cit.*) and some of these, *e.g.*, the 1-phenyl derivative, were of therapeutic value (Polgár and Zelenka, *Magyar Nógyóyászok Lapja*, 1948, **7**, 1). The methyl group at position 3 of the heterocyclic ring and the two ethoxy-groups in the benzene ring seem to play an important part in the activity and in the low toxicity of these compounds.

In view of these results it was of interest to synthesize 6 : 7-diethoxy-3-ethyl-, -3-propyl-, and -3-phenyl-*iso*quinoline as potentially more effective spasmolytics. We also prepared 6 : 7-diethoxy-3-phenyl-1-methyl*iso*quinoline, to investigate whether an interchange of the methyl and the phenyl radical exerted any influence on the activity.

The route followed was that described in our recent work (*loc. cit.*) :



Experimental.

Ketones (I).—The ketones (I), prepared as described for 3 : 4-diethoxypropiophenone (Part VII, *loc. cit.*), were purified by distillation in a vacuum, and sometimes by recrystallisation from ethanol. M. p.s quoted are those of the recrystallised samples.

3 : 4-*Diethoxybutyrophenone* (I; R = Et). *o*-Diethoxybenzene (33·4 g.), butyryl chloride (21·2 g.), and anhydrous aluminium chloride (28 g.) in nitrobenzene (130 g.) gave the *propyl ketone* (34·5 g., 73%), b. p. 170—175°/5 mm., m. p. 49—49·5° (Found : C, 71·0; H, 8·3. $C_{14}H_{20}O_3$ requires C, 71·2; H, 8·5%).

3 : 4-*Diethoxyvalerophenone* (I; R = Pr^n). *o*-Diethoxybenzene (27·6 g.), valeryl chloride (20 g.), and anhydrous aluminium chloride (23·2 g.) in nitrobenzene (107·7 g.) gave the *butyl ketone* (36 g., 87%), b. p. 170—173°/4 mm., m. p. 45—46° (needles) (Found : C, 72·3; H, 8·9. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·9%).

3 : 4-*Diethoxy*-ω-*phenylacetophenone* (I; R = Ph). *o*-Diethoxybenzene (16·6 g.), phenylacetyl chloride (20 g.), and anhydrous aluminium chloride (13·9 g.) in nitrobenzene (64·8 g.) gave the *benzyl ketone* (21 g., 74%), b. p. 206—215°/4—5 mm., m. p. 90—91° (needles) (Found : C, 75·9; H, 7·3. $C_{18}H_{20}O_3$ requires C, 76·0; H, 7·1%).

Oximino-ketones (II).—The ketones were dissolved in dry benzene, and 20% hydrogen chloride in anhydrous ether was added, followed by *iso*butyl nitrite dropwise during 40—65 minutes at 0°. The solution was then stirred at 0° for 90—100 minutes, the crystals were filtered off, and the filtrate was concentrated in a vacuum. A further crop was obtained by washing the residue with light petroleum or benzene. Recrystallisation was from 50—80% alcohol in all cases. Total yields are recorded.

α-*Oximino*-3 : 4-*diethoxybutyrophenone* (II; R = Et). (I; R = Et) (11·8 g.) in benzene (60 ml.), ethereal hydrogen chloride (20%; 10 g.), and *iso*butyl nitrite (6 g.) gave the *oximino*-compound (11·5 g., 87%) as needles, m. p. 102—103° (Found : C, 63·2; H, 7·3. $C_{14}H_{19}O_4N$ requires C, 63·4; H, 7·2%).

α-*Oximino*-3 : 4-*diethoxyvalerophenone* (II; R = Pr^n). The ketone (I; R = Pr^n) (12·5 g.) in benzene (100 ml.), ethereal hydrogen chloride (9·1 g.), and *iso*butyl nitrite (5·6 g.) gave the *oxime* (10·5 g., 75%) as yellow needles, m. p. 95—96° (Found : C, 64·8; H, 7·4. $C_{15}H_{21}O_4N$ requires C, 64·5; H, 7·6%).

ω-*Oximino*-3 : 4-*diethoxy*-ω-*phenylacetophenone* (II; R = Ph). The ketone (I; R = Ph) (14·2 g.) in benzene (60 ml.), ethereal hydrogen chloride (8·9 g.), and *iso*butyl nitrite (5·5 g.) gave the *oximino-ketone* (12 g., 77%) as yellow needles, m. p. 146° (Found : C, 68·9; H, 6·2. $C_{18}H_{19}O_4N$ requires C, 69·0; H, 6·1%).

Amino-alcohols (III).—These were prepared by Hartung's general method (*J. Amer. Chem. Soc.*, 1931, **53**, 4149; cf. Part VII, *loc. cit.*), involving catalytic reduction of the oximino-ketones in absolute ethanol in the presence of palladised charcoal and hydrogen chloride to the amino-ketone hydrochloride. The excess of hydrogen chloride was then neutralised, and the catalyst and a part of the solvent removed. The amino-ketone salt was further hydrogenated in dilute alcohol with Adams's catalyst to the amino-alcohol hydrochloride which, after removal of water by evaporation, could be crystallised from ethyl

acetate. The period of hydrogenation given is the total for both stages; the yields of amino-alcohols are based on the oximino-ketones reduced.

2-*Amino*-1-3′ : 4′-*diethoxyphenylbutanol hydrochloride* (III; R = Et). Reduction of the oximino-ketone (II; R = Et) (10·7 g.) in alcohol (350 ml.) and alcoholic hydrogen chloride (8·9 ml.) in the presence of palladised charcoal (6 g.) and then in 50% alcohol (160 ml.) in the presence of Adams's catalyst (0·7 g.) gave, after 24 hours, the *amino-alcohol hydrochloride* (5·5 g., 47%), m. p. 181—182° (Found: C, 57·7; H, 8·3. $C_{14}H_{22}O_3N$,HCl requires C, 58·0; H, 8·4%).

2-*Amino*-1-3′ : 4′-*diethoxyphenylpentanol hydrochloride* (III; R = Pr^n). Reduction of (II; R = Pr^n) (17 g.) in alcohol (200 ml.) and 5N-alcoholic hydrogen chloride (30 ml.) in the presence of palladised charcoal (5 g.) and then in 60% alcohol (260 ml.) in the presence of Adams's catalyst (1 g.) gave the *pentanol* (3·7 g., 20%) as needles, m. p. 192—193° (Found: C, 58·1; H, 8·7. $C_{15}H_{25}O_3N$,HCl,$C_4H_8O_2$ requires C, 58·2; H, 8·7%), containing solvent of crystallisation.

2-*Amino*-2-*phenyl*-1-3′ : 4′-*diethoxyphenylethanol hydrochloride* (III; R = Ph). The ketone (II; R = Ph) was reduced in ethanol (200 ml.) and 5N-alcoholic hydrogen chloride (8 ml.) in the presence of palladised charcoal and then in 80% alcohol (135 ml.) in the presence of Adams's catalyst (0·7 g.). The salt (III; R = Ph) (4 g., 59%) had m. p. 186—187°. The *base*, m. p. 142—143°, was crystallised from benzene (Found: N, 4·8. $C_{18}H_{23}O_3N$ requires N, 4·65%).

Acylamides (IV).—These were prepared as described in Part VII (*loc. cit.*) and recrystallised from dilute alcohol.

Derivatives of (III; R = Et). The amino-alcohol (III; R = Et) (0·5 g.) in water (12 ml.) and benzoyl chloride (0·7 g.) in benzene (6 ml.) gave 2-*benzamido*-1-3′ : 4′-*diethoxyphenylbutanol* (IV; R = Et, R′ = Ph) (0·6 g., 97%), m. p. 158—159° (Found: C, 70·4; H, 8·1. $C_{21}H_{27}O_4N$ requires C, 70·6; H, 7·7%). The *phenylacetamide* (IV; R = Et, R′ = CH_2Ph) (1·2 g., 97%), m. p. 143—145°, was prepared from (III; R = Et) (1 g.) in water (18 ml.) and phenylacetyl chloride (0·7 g.) in benzene (7 ml.) (Found: C, 70·9; H, 7·9. $C_{22}H_{29}O_4N$ requires C, 71·1; H, 7·9%). The 3″ : 4″-*dimethoxybenzoyl* derivative [IV; R = Et, R′ = 3 : 4-$C_6H_3(OMe)_2$] was obtained from (III; R = Et) (1 g.) in water (10 ml.) and 3 : 4-dimethoxybenzoyl chloride (0·8 g.) in benzene (8 ml.); yield, 1·3 g. (90%); m. p. 154—155° (Found: C, 65·2; H, 8·2. $C_{23}H_{31}O_6N$ requires C, 66·1; H, 7·5%).

Derivatives of (III; R = Pr^n). 2-*Benzamido*-1-3′ : 4′-*diethoxyphenylpentanol* (IV; R = Pr^n R′ = Ph), m. p. 162—163°, was prepared from (III; R = Pr^n) (0·8 g.) in water (30 ml.) and benzoyl chloride (0·15 ml.) in benzene (5 ml.) (Found: C, 71·0; H, 8·0. $C_{22}H_{29}O_4N$ requires C, 71·1; H, 7·8%). The ON-*bisphenylacetyl* derivative (IV; R = Pr^n, R′ = CH_2Ph) was made from (III; R = Pr^n) (0·8 g.) in water (30 ml.) and phenylacetyl chloride (0·8 g.) in benzene (6 ml.); yield, 71% (0·94 g.); m. p. 140—141° (Found: C, 73·3; H, 7·5. $C_{31}H_{37}O_5N$ requires C, 73·9; H, 7·4%). The 3″ : 4″-*dimethoxybenzoyl* derivative [IV; R = Pr^n, R′ = 3 : 4-$C_6H_3(OMe)_2$] was obtained from (III; R = Pr^n) (0·8 g.) in water (30 ml.) and 3 : 4-dimethoxybenzoyl chloride (0·8 g.) in benzene (6 ml.); yield, 1·12 g. (98%); m. p. 164—165° (Found: C, 68·0; H, 7·8. $C_{24}H_{33}O_6N$ requires C, 68·8; H, 7·7%).

Derivatives of (III; R = Ph). 2-*Benzamido*-2-*phenyl*-1-3′ : 4′-*diethoxyphenylethanol* (IV; R = R′ = Ph) was prepared from (III; R = Ph) (1·5 g.) in water (60 ml.) and benzoyl chloride (2 ml.) in benzene (6 ml.); yield, 1·5 g. (85%); m. p. 214—215° (Found: C, 73·7; H, 6·8. $C_{25}H_{27}O_4N$ requires C, 74·1; H, 6·7%). The *acetyl* derivative (IV; R = Ph, R′ = Me) was prepared from the alcohol (1 g.) in dry pyridine (20 ml.) and acetic anhydride (0·6 ml.) at 20°; yield, 1 g. (90%); m. p. 171—172° (Found: C, 69·7; H, 7·5. $C_{20}H_{25}O_4N$ requires C, 69·9; H, 7·3%).

iso*Quinolines* (V).—The following *iso*quinolines were obtained by boiling the acylamides in toluene with an excess of phosphoryl chloride for an hour (Part VII, *loc. cit.*). The yields quoted refer to the free bases, which were recrystallised from 50% alcohol. 6 : 7-*Diethoxy*-1-*phenyl*-3-*methyl*iso*quinoline* (75·5% yield), m. p. 100—101°, from (IV; R = Et, R′ = Ph) (Found: C, 78·7; H, 7·1. $C_{21}H_{23}O_2N$ requires C, 78·5; H, 7·2%); 6 : 7-*diethoxy*-1-*benzyl*-3-*ethyl*iso*quinoline* (44% yield), m. p. 88—89°, from (IV; R = Et, R′ = CH_2Ph) (Found: C, 78·0; H, 7·7. $C_{22}H_{25}O_2N$ requires C, 78·8; H, 7·5%); 6 : 7-*diethoxy*-1-3′ : 4′-*dimethoxyphenyl*-3-*ethyl*iso*quinoline* (66% yield), m. p. 98—99°, from [IV; R = Et, R′ = 3 : 4-$C_6H_3(OMe)_2$] (Found: C, 69·0; H, 7·2. $C_{23}H_{27}O_4N$,H_2O requires C, 69·2; H, 7·3%); 6 : 7-*diethoxyphenyl*-3-*propyl*iso*quinoline* (52% yield), m. p. 94—95°, from (IV; R = Pr^n, R′ = Ph) (Found: N, 4·2. $C_{22}H_{25}O_2N$ requires N, 4·3%); 6 : 7-*diethoxy*-1-*benzyl*-3-*propyl*iso*quinoline* (48% yield), m. p. 107—108°, from (IV; R = Pr^n, R′ = CH_2Ph) (Found: C, 78·9; H, 8·3. $C_{23}H_{27}O_2N$ requires C, 79·1; H, 7·8%); 6 : 7-*diethoxy*-1-3′ : 4′-*dimethoxyphenyl*-3-*propyl*iso*quinoline* (48·5% yield), m. p. 90—91°, from [IV; R = Pr^n, R′ = 3 : 4-$C_6H_3(OMe)_2$] (Found: N, 3·9. $C_{24}H_{29}O_4N$ requires N, 3·5%); 6 : 7-*diethoxy*-1 : 3-*diphenyl*iso*quinoline* (44% yield), m. p. 173—174°, from (IV; R = R′ = Ph) (Found: C, 80·9; H, 7·8. $C_{25}H_{23}O_2N$ requires C, 81·3; H, 7·3%); and 6 : 7-*diethoxy*-3-*phenyl*-1-*methyl*iso*quinoline* (50% yield), m. p. 137—138°, from (IV; R = Ph, R′ = Me) (Found: C, 78·1; H, 6·8. $C_{20}H_{21}O_2N$ requires C, 78·3; H, 6·9%).

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