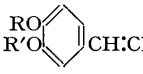
174. *Synthesis of* 6 : 7-*Diethoxy*-3-*methyl*isoquinolines.

By V. Bruckner, G. Fodor, J. Kiss, and J. Kovács.

The preparation of 1-substituted 6 : 7-diethoxy-3-methyl*iso*quinolines by two alternative routes is described: (A) The ψ-nitrosite (II*g*) of 3 : 4-diethoxypropenylbenzene (I*g*) was converted into 2-nitro-1-3′ : 4′-diethoxyphenylpropyl acetate (III*g*) and thence through the amino-ester (IV*g*), the acetamido-alcohol (V*g*, R″ = Ac), and the acylamidopropanols (V*g*, R″ = acyl) into the required compounds (VI; R = R′ = Et). (B) 3 : 4-Diethoxypropiophenone afforded compounds of the type (V) *via* its *iso*nitroso-derivative (VII) and 2-amino-1-3′ : 4′-diethoxyphenylpropanol (V*g*, R″ = H).

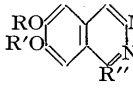
The aminopropanols and their acyl derivatives obtained by both routes were stereoisomers. The instant migration of the acyl group from N to O was only observed in case of some compounds prepared according to route (A). Both series of acylamides yielded on ring closure the same 3-methyl*iso*quinolines. The latter, *e.g.*, the 1-phenyl derivative, have a higher spasmolytic activity and a lower toxicity than papaverine.

In previous communications (Parts I—VI; Bruckner and Krámli, *J. pr Chem.*, 1936, **145**, 293; Bruckner and Fodor, *Ber.*, 1938, **71**, 541; Bruckner and Bodnár, *Magy. Biol. Kut. Munk.*, 1943, **15**, 404; Fodor, *Ber.*, 1943, **76**, 1216; Kovács, *Acta Chem. et Phys. Univ. Szeged*, 1943, I, 109; Bruckner and Kovács, *Ber.*, 1944, **77**, 610) the synthesis of some 3-methyl*iso*quinolines was described: ψ-nitrosites (II) of propenylphenyl ethers (I) were converted by an acetylating decomposition into 2-nitro-1-arylpropyl acetates (III), these were electrolytically reduced in acid medium to salts of the 2-amino-1-arylpropyl acetates (IV), and on addition of alkali migration of the acetyl group afforded 2-acetamido-1-arylpropanols (V, R″ = Ac). These can be easily hydrolysed by means of dilute sulphuric acid, as the acetyl group migrates to the oxygen, and the amino-propanols are formed. These were then acylated, and the acylamides obtained condensed to the corresponding 1-substituted 3-methyl*iso*quinolines (VI). This cyclisation leads (see Bruckner and Kovács, *loc. cit.*) in all cases to 6 : 7-disubstituted *iso*quinolines; the suggested formation of 7 : 8-disubstituted isomers (cf. Pfeiffer, Breitbach, and Scholl, *J. pr. Chem.*, 1940, **154**, 157) could not be detected.

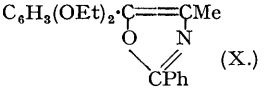

(I.) $C_6H_3(OR)(OR')\cdot CH(NO)\cdot CHMe\cdot NO_2$ (II.)

$C_6H_3(OR)(OR')\cdot CH(OAc)\cdot CHMe\cdot NO_2$ (III.)
$C_6H_3(OR)(OR')\cdot CH(OAc)\cdot CHMe\cdot NH_2$ (IV.)
$C_6H_3(OR)(OR')\cdot CH(OH)\cdot CHMe\cdot NHR''$ (V.)

(*a*: R = R′ = Me; *b*: R, R′ = CH_2; *c*: R = Me, R′O = H; *d*: R = CH_2Ph, R′ = Me; *e*: R = CH_2Ph, R′ = CH_2Ph; *f*: R = Me, R′ = Et; *g*: R = R′ = Et; *h*: R = H, R′ = $CH_2\cdot OMe$; *i*: R = $CH_2\cdot OMe$, R′ = H.)


(VI.)

$C_6H_3(OEt)_2\cdot CO\cdot CMe{:}N\cdot OH$ (VII.)
$C_6H_3(OEt)_2\cdot CO\cdot CHMe\cdot NHR$ (VIII.)


(X.)

$C_6H_3(OEt)_2\cdot CH(OH)\cdot CHMe\cdot NH_2$ (IX.)

The *iso*quinolines already described (Part I—VI) were prepared by this route from propenylphenyl ethers (I, *a*—*f*). The synthesis of 6 : 7-diethoxy-1-aryl- or -1-aralkyl-3-methyl-*iso*quinolines (VI) from 3 : 4-diethoxypropenylbenzene (I*g*) is of pharmacological interest.

Investigations on the relationship between chemical structure and spasmolytic activity of *iso*quinolines show that tetraethoxypapaveroline is the most active of this series; moreover, 3-methyl*iso*quinolines have lower toxicity than the 3-unsubstituted analogues (Sugasawa and Sugimito, *J. Pharm. Soc. Japan*, 1941, **61**, 62).

3 : 4-Diethoxypropenylbenzene (I*g*) was prepared from safrole by four different methods (cf. Part V). The cleavage of safrole with methanolic potash to a mixture of methoxy*iso*eugenol (I*h*) and methoxy*iso*chavibetol (I*i*) (cf. Bruckner and Fodor, *Ber.*, 1943, **76**, 466), followed by hydrolysis of each and subsequent ethylation without isolation of the intermediate 3 : 4-dihydroxypropenylbenzene to (I*g*), was found to be the best way of preparation. (I*g*) was converted by the route described above (II*g* ⟶ III*g* ⟶ IV*g* ⟶ V*g*, R″ = Ac) into the acetamido-propanol (V*g*; R″ = Ac). Migration of the acetyl group and deacetylation, followed by Schotten–Baumann acylation of 2-amino-1-3′ : 4′-diethoxyphenylpropanol, gave the *acylamides* (V*g*; R″ = acyl), and cyclisation of these by means of phosphorus oxychloride gave good yields of the *iso*quinolines (VI; R = R′ = Et).

As safrole was not available during the war, the same *iso*quinolines had been also prepared by another route starting from *o*-diethoxybenzene *via iso*nitroso-3 : 4-diethoxypropiophenone (VII). This novel route was also an attempt to synthesise the isomeric aminopropanols related to ephedrine, as reduction of *iso*nitrosopropiophenone yielded norephedrine. Starting from the ψ-nitrosites, on the contrary, always leads to the corresponding ψ-ephedrine derivatives. It was further of interest to effect the ring closure of acylamides of different steric configurations, as the direction of this condensation (*m*,*p* or *o*,*m*) of some acylnor-ψ-ephedrines was questioned by Pfeiffer (*loc. cit.*).

o-Diethoxybenzene was converted very smoothly into 3 : 4-diethoxypropiophenone, which was also obtained on ethylation of the already known 3 : 4-dihydroxypropiophenone. Diethoxypropiophenone reacts with *iso*butyl nitrite in benzene or methanolic solution to give in a nearly quantitative yield α-*iso*nitroso-3 : 4-diethoxypropiophenone (VII). This was easily reduced in alcoholic solution in the presence of Adams's catalyst and of alcoholic hydrogen chloride to 2-amino-1-3′ : 4′-diethoxyphenylpropanol (V; R = R′ = Et, R″ = H). It is not necessary to isolate the intermediate amino-ketone (VIII, R = H).

The amino-propanol was acylated to give the acetamido-derivative (V*g*, R″ = Ac); the physical properties of this amino-propanol and of its derivatives are evidently different from these of the amino-propanol obtained from the ψ-nitrosite (II*g*) (see table), indicating a difference in steric configuration. By analogy, the compounds obtained from the *iso*nitroso-ketone may be regarded as norephedrine derivatives (cf. Hartung *et al.*, *J. Amer. Chem. Soc.*, 1931, **53**, 4149; Rabe, *Ber.*, 1912, **45**, 2166), and those from the ψ-nitrosites as ψ-norephedrines (cf. Bruckner and Fodor, *Ber.*, 1943, **76**, 472). The acylamides obtained from the *iso*nitroso-ketone yielded on ring closure, which eliminates the molecular asymmetry, the same *iso*quinolines as the acylamides (see table). The steric configuration therefore has no influence upon the direction of the ring closure.

	From ψ-nitrosites.		From *iso*nitroso-ketone.		
V; R″ =	(V*g*), m. p.	(VI; R=R′=Et), m. p.	(V*g*), m. p.	(VI; R=R′=Et), m. p.	Mixed m. p.†
COMe	128°	96—97°	124—125°	96—97°	96°
COPh	128·5—129	125—126	168	125—126	125—126
$CO{\cdot}CH_2Ph$	132 *	85—86	135	85—86	85—86
$CO{\cdot}C_6H_3(OMe)_2$	149—151	111—112	110	110—112	110—112
$CO{\cdot}C_6H_3(OEt)_2$	158·5	96—97	123—124	96—97	96—97
$CO{\cdot}C_6H_3(OEt)_2{\cdot}CH_2$ ...	98—99	117—118	112—113	113—114	114

* Diacylated product (cf. Experimental).
† From the *iso*quinolines obtained in different ways.

The two series of acylamides show a difference in one respect. The ψ-acylamides will undergo instant migration of the acyl group from N to O on addition of 1 mol. of alcoholic hydrogen chloride; whereas the *N*-acylamides related to the norephedrine remain unchanged under the same conditions. The different chemical behaviour is probably due to the different steric relationship of the hydroxy- and the amino-group in the acylnorephedrine and the acylnor-ψ-ephedrine molecules. Further investigations on the acyl migration of ephedrine and ψ-ephedrine derivatives will be reported elsewhere.

If the reduction of α-*iso*nitroso-3 : 4-diethoxypropiophenone is interrupted after the uptake of 2 mols. of hydrogen, α-amino-3 : 4-diethoxypropiophenone hydrochloride (VIII,

R = H) is obtained. This was benzoylated under Schotten–Baumann conditions to give (VIII; R = Bz). Attempts to cyclise the latter by means of phosphorus oxychloride to the corresponding *iso*quinol-4-one failed because of the formation of the oxazole (X). The structure of the latter was confirmed by its formation from the benzamido-ketone at room temperature with thionyl chloride. Preparation of oxazoles by a similar treatment had already been reported (Robinson, *J.*, **1909**, **95**, 2167; cf. Campbell, Haworth, and Perkin, *J.*, 1926, 32). The hydrochloride of (X) was converted by water into the free base, which could be distilled unchanged even under atmospheric pressure.

Prof. B. Issekutz, junr., has assayed the spasmolytic effect of all these *iso*quinolines and found all except the 1-methyl derivative to be more active than papaverine. It is surprising that the 1-phenyl derivative possesses the same activity as tetraethylpapaveroline and as the alkoxyphenyl and the alkoxybenzyl derivatives of 6 : 7-diethoxy-3-methyl*iso*quinoline. It is not toxic and could be used medicinally.

Experimental.

(A) *Synthesis of* ψ-2-*Amino*-1-3′ : 4′-*diethoxyphenylpropanol*.—3 : 4-*Diethoxypropenylbenzene* (cf. Hiraidzumi, *J. Soc. Chem. Ind. Japan* 1931, **34**, 208B, 12B). The mixture (b. p. 120—138°) of 300 g. of (I*h*) and (I*i*) obtained by alkaline cleavage of safrole was dissolved in anhydrous ethanol (700 c.c.) and heated to the b. p. in a stream of carbon dioxide, oxygen being excluded. Then 12 drops of concentrated sulphuric acid dissolved in anhydrous ethanol (25 c.c.) were added, and the mixture refluxed for a further 45 mins.; it was then cooled, ethyl iodide (600 g.) and anhydrous potassium carbonate (420 g.) were rapidly added, and the whole heated under reflux for 16 hrs. (interrupted overnight). The yellowish alcoholic solution was filtered from inorganic salts, these were extracted several times with anhydrous alcohol, and the united extract evaporated in vacuum. The residual yellow oil was dissolved in ether, and the solution shaken with 20% sodium hydroxide to remove phenolic compounds, washed with water, dried (Na_2SO_4), and the solvent evaporated. The residual oil crystallised on cooling. It distilled (b. p. 126—128°/3—4 mm.) as a colourless liquid, which crystallised (270 g.); yield 85%. The product could be recrystallised from dilute alcohol, m. p. 54°. This is sufficiently pure for the preparation of the ψ-nitrosite; however, it contains a small amount of 3-methoxymethoxy-4-ethoxypropenylbenzene, which can be eliminated as follows: the distillate (270 g.) is dissolved in anhydrous ethanol (500 c.c.), and the solution refluxed for 45 mins. after addition of sulphuric acid (10 drops) in ethanol (25 c.c.); then anhydrous potassium carbonate is added, and the whole evaporated in a vacuum to dryness, the resulting oil taken up in ether, the ethereal solution washed with alkali and water as above, and evaporated, and the residue distilled in vacuum. The loss is 3—5% (Found: C, 75·45; H, 8·7. Calc. for $C_{13}H_{18}O_2$: C, 75·7; H, 8·8%).

ψ-*Nitrosite* (II*g*) (cf. Kovács, Inaug. Diss., Szeged, 1943). Freshly distilled diethoxypropenylbenzene (110 g.) was dissolved in ether and converted into the ψ-nitrosite in the usual manner (Bruckner, *Annalen*, 1935, **518**, 226); it is necessary to add the 20% sulphuric acid (300 c.c.) during 1 hour to the sodium nitrite (150 g.). The crystalline crude product (80 g., 53%) was washed and dried as described (*loc. cit.*), and can be used for the following decomposition without recrystallisation. The ψ-*nitrosite* is soluble in chloroform and benzene, insoluble in ether; m. p. 124·5—125·5° (decomp.) (Found: C, 55·1; H, 6·1. $C_{13}H_{18}O_5N_2$ requires C, 55·3; R, 6·4%).

2-*Nitro*-1-3′ : 4′-*diethoxyphenylpropyl acetate* (III*g*). The foregoing ψ-nitrosite (80 g.) was powdered and suspended in acetic anhydride (240 c.c.), then a mixture of acetic anhydride and concentrated sulphuric acid (4 drops) was added dropwise with ice-cooling and vigorous stirring. The ψ-nitrosite dissolved with evolution of nitrous gases, the reddish-brown solution was poured into mechanically stirred ice–water, and stirring was continued until the separated oil crystallised. Recrystallised from methanol, the *acetate* formed colourless prisms (52 g., 59%), m. p. 75° (Found: C, 58·0; H, 6·9. $C_{15}H_{21}O_6N$ requires C, 57·8; H, 6·8%).

ψ-2-*Acetamido*-1-3′ : 4′-*diethoxyphenylpropanol* (V*g*, R″ = Ac).—The above acetate (30 g.) was dissolved in a mixture of ethanol (170 c.c.) and glacial acetic acid (80 c.c.), concentrated hydrochloric acid (26 c.c.) added, and the solution reduced electrolytically in a mercury electrode apparatus (cf. Bruckner and Fodor, *Ber.*, 1943, **76**, 474). As anolyte, 20% sulphuric acid solution was used; c.d., 0·07 amp./cm.^{2}; temperature, not above 60°. After passage of double the theoretical quantity of current, the catholyte solution was treated with a saturated aqueous solution of sodium acetate (25 g.) and evaporated to dryness in a vacuum at 50° (bath temp.). The residue was diluted with water, and solid sodium bicarbonate added in excess; the *acetamido*-compound which separated was filtered off, washed with water, dried, and washed with ether; snow-white crystals (18·5 g., 65·8%) resulted, which could be recrystallised from toluene, ethyl acetate, or chloroform–ether; m. p. 128—131° (Found: C, 63·9; H, 8·1. $C_{15}H_{23}O_4N$ requires C, 64·0; H, 8·2%).

ψ-2-*Amino*-1-3′ : 4′-*diethoxyphenylpropyl acetate hydrochloride* (as IV*g*) : *migration of acetyl group*. The compound (V*g*, R″ = Ac) (3 g.) was dissolved in anhydrous methanol (10 c.c.), methanolic 32·1% hydrogen chloride (1·26 c.c.) added, and the solution evaporated to dryness in a desiccator (over $CaCl_2$ and KOH). The resulting crystalline *hydrochloride* was recrystallised by dissolving it in chloroform (10 c.c.) and adding ether (10 c.c.); colourless needles, m. p. 162°, very soluble in water, alcohol, and chloroform (Found: C, 56·4; H, 7·9. $C_{15}H_{24}O_4NCl$ requires C, 56·7; H, 7·6%). An aqueous solution of this hydrochloride (1 g.) was dissolved in water and made alkaline with sodium carbonate; the separated crystals showed the same m. p. and mixed m. p. as the *N*-acetamido-compound (V*g*, R″ = Ac), above.

ψ-2-*Amino*-1-3′ : 4′-*diethoxyphenylpropanol* (IX). The acetamido-compound (V*g*, R″ = Ac) (3·6 g.) was dissolved by heating it with 10% sulphuric acid (38 c.c.) on a steam-bath, and the resulting solution

was treated with charcoal, filtered, the filtrate cooled, and made alkaline with 10% sodium hydroxide. The precipitated base was filtered off, washed with water, dried, and washed with ether. A white solid (2 g.) was obtained, easily soluble in dilute hydrochloric acid. Recrystallised from benzene or ethyl acetate, it formed plates or needles, respectively, m. p. 116—117°. On dissolving the amine (0·5 g.) in the theoretical amount of 10% hydrochloric acid and adding acetone (10 c.c.) and ether (10 c.c.), the *hydrochloride* separated on standing; m. p. 176—177° (Found: C, 56·4; H, 8·4. $C_{13}H_{22}O_3NCl$ requires C, 56·6; H, 8·05%).

(B) *Acyl Derivatives* (Vg, R'' = acyl) *of* ψ-2-*Amino*-1-3' : 4'-*diethoxyphenylpropanol*.—For the preparation of the ψ-*N*-acylamides it is not necessary to isolate the above amine, for it can be acylated after neutralisation with 2N-sodium hydroxide by adding simultaneously a 25% benzene solution of the appropriate acid chloride, and the equivalent amount of sodium hydroxide, so as to keep the solution slightly alkaline. Stirring was continued for an hour, and the water was then decanted from the pasty solid product and the latter treated with water until crystalline. Generally, after 1—2 hours in the ice-box, the acylamide was filtered off, washed with water (sometimes with methanol) and, after drying, with ether. All these amides were recrystallised from dilute alcohol; the m. p.s are those of the recrystallised substances and are uncorrected. *Benzoyl* derivative, from amine (3 g.) and benzoyl chloride (1·6 g.), colourless needles (3·2 g., 81%), m. p. 129° (Found: C, 70·0; H, 7·6. $C_{20}H_{25}O_4N$ requires C, 69·9; H, 7·3%); *veratroyl* derivative, from amine (4 g.) and veratroyl chloride (3 g.), crystals (5 g., 87%), m. p. 149—151° (Found: C, 65·2; H, 7·4. $C_{22}H_{29}O_6N$ requires C, 65·5; H, 7·25%); 3'' : 4''-*diethoxybenzamido*-compound, from base (9 g.) and acyl chloride (7·2 g.), colourless delicate needles (11·3 g., 81·8%), m. p. 158·5° (Found: C, 66·85; H, 7·85. $C_{24}H_{33}O_5N$ requires C, 66·8; H, 7·7%); 3'' : 4''-*diethoxyphenylacetamido*-compound, from amine (4·2 g.) and acyl chloride (3·8 g.; crude oil obtained from the acid with thionyl chloride), delicate needles (3 g., 41%), m. p. 98—99° (Found: C, 66·7; H, 7·8. $C_{25}H_{35}O_6N$ requires C, 67·4; H, 7·9%); *phenylacetamido*-compound, from amine (2·5 g.) and phenylacetyl chloride (1·5 g.), crystals (1·5 g., 60%), m. p. 132° (Found: C, 73·4; H, 7·2. $C_{29}H_{33}O_5N$ requires C, 73·2; H, 7·0%).

(C) *Preparation of* 2-*Amino*-1-3' : 4'-*diethoxyphenylpropanol from* α-iso*Nitroso*-3 : 4-*diethoxypropiophenone*.—3 : 4-*Diethoxypropiophenone*. (*a*) From *o*-diethoxybenzene. Anydrous aluminium chloride (147 g.) was dissolved in nitrobenzene (650 g.), *o*-diethoxybenzene (174 g.) added, and the solution cooled to − 5°. Propionyl chloride (110 g.) was added during 30 mins., the mixture kept for 2 hrs. between 0° and − 5°, then poured into ice (750 g.) acidified with concentrated hydrochloric acid (12·5 c.c.). The nitrobenzene layer was diluted with ether (1000 c.c.), washed with water, and three times with 10% sodium hydroxide (3 × 200 c.c.), then once more with water, and dried ($CaCl_2$). The solvents were removed, and the residue distilled in a vacuum (b. p. 181—184°/32 mm.). The solidified distillate (170 g., 73·1%) was recrystallised for analysis from light petroleum; pale yellow needles, m. p. 38—39° (Found: C, 70·0; H, 7·75. $C_{13}H_{18}O_3$ requires C, 70·2; H, 8·2%).

(*b*) From dihydroxypropiophenone. 3 : 4-Dihydroxypropiophenone (41·5 g.; Miller, Hartung, *et al.*, *J. Amer. Chem. Soc.*, 1931, **53**, 4149) was dissolved in alcohol (200 c.c.), the solution mixed with ethyl bromide (60 g.), 25% alcoholic solution (80 c.c.) of potassium hydroxide (28 g.) added dropwise with stirring, and the whole boiled for 5 mins. The mixture was then heated under reflux for 3 hrs., more ethyl bromide (10 g.) added, and refluxing continued for 6 hrs. After 12 hrs.' standing in an ice-box, the potassium bromide was filtered off, the filtrate evaporated, and the residue extracted with hot benzene. This extract was washed three times with 20% sodium hydroxide solution, dried ($CaCl_2$), the benzene removed, and the oily residue distilled; b. p. 181°/30 mm. The resulting crystals (30 g., 54%) melted alone and in admixture with the specimen obtained above at 38—39°. Acidification of the alkaline extracts afforded the monoethylated ketone (18·5 g.), which could be ethylated to the diethoxy-ketone.

α-iso*Nitroso*-3 : 4-*diethoxypropiophenone* (VII). To a solution of 3 : 4-diethoxypropiophenone (44·4 g.) in anhydrous methanol (200 c.c.), 20% ethereal hydrogen chloride (37·6 g.) was added, followed by freshly distilled *iso*butyl nitrite (23·7 g.) dropwise during 30—45 mins. The mixture was kept for 12 hrs. at room temperature, then neutralised with calcium carbonate, filtered, and the filtrate evaporated to dryness in a vacuum. The residue became crystalline, and was filtered off and washed with cold dilute alcohol to furnish pale yellow needles (45 g., 90%), m. p. 121°, after recrystallisation from 50% alcohol. When the condensation was carried out in benzene solution, the iso*nitroso-ketone* crystallised from the reaction mixture on standing (Found: C, 62·4; H, 7·0. $C_{13}H_{17}O_4N$ requires C, 62·1; H, 6·8%).

α-*Amino*-3 : 4-*diethoxypropiophenone* (VIII, R = H). An alcoholic (50 c.c.) suspension of Adams's catalyst (2 g.) was saturated with hydrogen, and the *iso*nitroso-ketone (16·5 g.) in anhydrous alcohol (200 c.c.) added, followed by 4N-hydrogen chloride in anhydrous alcohol (49·5 c.c.). During about 8 hrs.' shaking under hydrogen at room temperature 2 mols. of hydrogen per mol. of ketone were absorbed; the mixture was treated with 5N-sodium hydroxide (26 c.c.) and 5 c.c. of the solution were evaporated to isolate the *amino-ketone*, the greater part being hydrogenated as below to the amino-alcohol. The crystalline residue of the aliquot part recrystallised from alcoholic hydrogen chloride as glistening needles, m. p. 203° (Found: C, 57·4; H, 6·8. $C_{13}H_{19}O_3N,HCl$ requires C, 57·0; H, 7·0%).

2-*Amino*-1-3' : 4'-*diethoxyphenylpropanol* (IX).—The major part of the solution obtained in the foregoing experiment was treated with platinum oxide (0·2 g.) after neutralisation of the excess of hydrochloric acid, and hydrogenated for 4 hours until a further 1 mol. of hydrogen was absorbed, the solution then no longer reducing Fehling's solution; it was evaporated, and the resulting crystalline *hydrochloride* (18 g.) crystallised from ethyl acetate as colourless needles, m. p. 199° (Found: C, 57·1; H, 8·3. $C_{13}H_{21}O_3N,HCl$ requires C, 56·6; H, 8·05%). The free *base* was obtained as colourless crystals, m. p. 146—147° (Found: C, 65·05; H, 9·0. $C_{13}H_{21}O_3N$ requires C, 65·2; H, 8·85%), on decomposition of the hydrochloride with 50% sodium hydroxide.

(D) N-*Acyl Derivatives* (Vg, R'' = acyl) *of* 2-*Amino*-1-3' : 4'-*diethoxyphenylpropanol*.—All acylamines except the acetyl derivative (obtained by acetylation with acetic anhydride in pyridine) were

prepared as follows. The crude hydrochloride, obtained from the *iso*nitroso-ketone, was dissolved in 15—20 times its weight of water at 40°, and a 50% benzene solution of 1·2—1·5 mols. of the acid chloride and 50% sodium hydroxide were added dropwise and simultaneously with vigorous stirring, the reaction mixture being kept slightly alkaline during this process. The mixture was stirred until the separated oil crystallised. The product was filtered off, and washed with water then with dilute hydrochloric acid. All acylamines, except the *N*-acetyl derivative, were recrystallised from dilute alcohol; the m. p.s are uncorrected and relate to the purified compounds.

Acetamido-compound (Vg, R″ = Ac). The amino-derivative (IX) (3·8 g., m. p. 146°), dissolved in anhydrous pyridine (60 c.c.), was treated with acetic anhydride (1·6 g.) under shaking and cooling with ice-water. After standing for 24 hours the solution was evaporated to dryness in a vacuum and the resulting yellow oil crystallised on standing. Recrystallised from benzene, it formed colourless needles (3·5 g., 78·3%), m. p. 124—125°, mixed m. p. with ψ-analogue 108° (Found : C, 64·3; H, 8·5. $C_{15}H_{23}O_4N$ requires C, 64·0; H, 8·2%). The *compound* was insoluble in dilute aqueous hydrochloric acid and unaffected by treatment with an equivalent of alcoholic hydrochloric acid. On condensation with phosphoryl chloride, it afforded 1 : 3-dimethyl*iso*quinoline.

The ON-*diacetyl* compound was obtained by dissolving the hydrochloride of the amino-alcohol (m. p. 146°) in anhydrous pyridine (10 c.c.) and acetylating it as described above but with a further 1·5 g. of acetic anhydride. The crude product was washed with a small amount of acetone and recrystallised from toluene, yielding colourless micro-crystals (0·6 g., 64%), m. p. 134—135° (Found : C, 63·3; H, 8·0. $C_{17}H_{25}O_5N$ requires C, 63·1; H, 7·8%).

The *benzamido*-compound, from the aminopropanol hydrochloride (8 g.) and benzoyl chloride (5·4 g.), formed long needles (8·8 g., 84%), m. p. 168° (Found : C, 70·2; H, 7·5. $C_{20}H_{25}O_4N$ requires C, 69·9; H, 7·3%); the *veratroyl* derivative, from the hydrochloride (2·75 g.) and veratroyl chloride (2 g.), formed colourless prisms (3·1 g., 79·4%), m. p. 110° (Found : C, 65·9; H, 7·4. $C_{22}H_{29}O_6N$ requires C, 65·5; H, 7·25%); the *diethoxybenzamido*-compound, from the aminopropanol (2·75 g.) and the acyl chloride (2·3 g.), when purified was obtained as colourless needles (3 g., 69·7%), m. p. 124° (Found : C, 66·8; H, 7·7. $C_{24}H_{33}O_6N$ requires C, 66·8; H, 7·7%); the 3′ : 4′-*diethoxyphenylacetamido*-compound, from hydrochloride (1·37 g.) and acyl chloride (1·75 g.), was obtained in 58·4% yield (1·3 g.) when recrystallised; m. p. 112—113° (Found : C, 67·8; H, 7·65. $C_{25}H_{35}O_6N$ requires C, 67·4; H, 7·9%); and the *phenylacetamido*-compound, from hydrochloride (2·75 g.) and phenylacetyl chloride (1·7 g.), formed delicate needles (2·7 g., 75·4%), m. p. 135° (Found : C, 70·5; H, 7·5. $C_{21}H_{27}O_4N$ requires C, 70·5; H, 7·6%).

(E) *Ring Closure of the Stereoisomeric Acylamides to* iso*Quinolines* (VI).—The intramolecular condensation of the acylamides was effected in chloroform or in toluene (for preparation of toluene for this reaction see Part II, p. 547) solution by means of phosphoryl chloride as follows : the acylamide (1 g.) was dissolved in chloroform or toluene (5—30 c.c.), phosphoryl chloride (1·5—2 g.) added, and the mixture refluxed for 40—120 mins., the *iso*quinoline salt being precipitated. The reaction mixture was allowed to cool, then extracted repeatedly with warm water, and the yellowish-green extract cleared with charcoal; on cooling, the hydrochloride separated as greenish-yellow crystals, which could be recrystallised from 2N-hydrochloric acid. When the aqueous solution or the mother-liquor was made alkaline, the free base crystallised. It could be recrystallised from dilute alcohol. The ring closure of the ψ-acylamides is described under (*a*), that of acylamides under (*b*).

6 : 7-*Diethoxy*-1 : 3-*dimethyl*iso*quinoline* (VI, R = R′ = Et, R″ = Me). (*a*) Treatment of the ψ-*N*-acetylamine (Vg, 2 g.) in chloroform (20 c.c.) with phosphoryl chloride (3 c.c.) yielded the free *base* (1·3 g., 74%), m. p. 96—97°. (*b*) The stereoisomeric acetylamine (0·5 g.) dissolved in chloroform (8 c.c.), similarly yielded the free base (0·4 g., 92·3%), m. p. alone and mixed with the *iso*quinoline from (*a*) 96° (Found : C, 72·8; H, 8·1. $C_{15}H_{19}O_2N$ requires C, 73·4; H, 7·8%).

6 : 7-*Diethoxy*-1-*phenyl*-3-*methyl*iso*quinoline* (VI; R = R′ = Et, R″ = Ph). (*a*) From the ψ-benzamido-compound (1·5 g.) in toluene (30 c.c.) with phosphoryl chloride (2 c.c.), the *base* (0·3 g.), m. p. 125—126°, and *hydrochloride* (0·9 g.), m. p. 230°, were obtained. (*b*) From the isomeric benzamide (7·5 g.) in toluene (160 c.c.) with phosphoryl chloride (10 c.c.) the base (4·8 g., 72%) was obtained, m. p. 126° (Found : C, 78·0; H, 7·0. $C_{20}H_{21}O_2N$ requires C, 78·1; H, 6·9%); hydrochloride, m. p. 230° (Found : C, 69·5; H, 6·8. $C_{20}H_{21}O_2N$,HCl requires C, 69·8; H, 6·45%).

6 : 7-*Diethoxy*-1-3′ : 4′-*dimethoxyphenyl*-3-*methyl*iso*quinoline*. (*a*) From the ψ-compound (2 g.) in toluene (40 c.c.) and phosphoryl chloride (3 c.c.) the *iso*quinoline *hydrochloride* (1·8 g., 80%) was obtained, m. p. 236·5—237°; the *base* formed needles, m. p. 111—112°. (*b*) From the *N*-veratroylamide (1 g.) in toluene (25 c.c.) and phosphoryl chloride (1·5 c.c.), the hydrochloride was obtained (0·65 g., 65%), m. p. 236—237° (Found : C, 64·6; H, 6·85. $C_{22}H_{25}O_4N$,HCl requires C, 64·9; H, 6·5%); base (Found : C, 71·75; H, 7·2. $C_{22}H_{25}O_4N$ requires C, 71·9; H, 6·9%).

3′ : 4′ : 6 : 7-*Tetraethoxy*-1-*phenyl*-3-*methyl*iso*quinoline*. (*a*) The ψ-amide (10 g.) in toluene (50 c.c.) and phosphoryl chloride (15 c.c.) yielded the *iso*quinoline *hydrochloride* (5 g., 50%), m. p. 222°; the base formed delicate needles, m. p. 96—97°. (*b*) The *N*-acylamide (1 g.) in toluene (25 c.c.) and phosphoryl chloride (1·5 c.c.) yielded the same hydrochloride (0·63 g., 63%) (Found : C, 66·5; H, 6·9. $C_{24}H_{29}O_4N$,HCl requires C, 66·7; H, 7·0%) and base.

6 : 7-*Diethoxy*-1-*benzyl*-3-*methyl*iso*quinoline*. (*a*) The ψ-amide (1 g.) with toluene (25 c.c.) and phosphoryl chloride (1·5 c.c.) yielded the free *base*, m. p. 86°, forming colourless octahedra; hydrochloride, m. p. 213—215° (decomp.). (*b*) The *N*-phenylacetamide (1 g.), toluene (25 c.c.), and phosphoryl chloride (1·5 c.c.) yielded the same *iso*quinoline (0·65 g., 73%), m. p. 85—86° (Found : C, 70·1; H, 6·8. $C_{21}H_{23}O_2N$ requires C, 70·45; H, 6·5%).

3′ : 4′ : 6 : 7-*Tetraethoxy*-1-*benzyl*-3-*methyl*iso*quinoline*. (*a*) The ψ-amide (1·2 g.), toluene (40 c.c.), and phosphoryl chloride (2 c.c.) yielded the *iso*quinoline hydrochloride (0·96 g., 80%) as needles, m. p. 201—202°. The *base* formed needles, m. p. 117—118°. (*b*) The isomeric amide (0·5 g.), toluene (15 c.c.), and phosphoryl chloride (1 c.c.) gave the same *iso*quinoline (0·3 g.) and hydrochloride (0·12 g.) (Found : C, 73·0; H, 7·8. $C_{25}H_{31}O_4N$ requires C, 73·3; H, 7·6%).

(F) *Derivatives of α-Amino-3 : 4-diethoxypropiophenone* (VIII, R = H).—*Benzoyl derivatives.* The amino-ketone hydrochloride (3 g.) was dissolved in water (50 c.c.) at 40—50°, benzoyl chloride (1·5 g.) dissolved in benzene (4·5 c.c.) was added, and the mixture basified with 50% sodium hydroxide, with continuous stirring. In a few minutes, yellowish crystals separated; these were filtered off, washed with water, and the resulting *benzoyl* compound (3 g., 80%) recrystallised from dilute alcohol, forming colourless needles, m. p. 124·5° (Found : C, 70·4; H, 7·1. $C_{20}H_{23}O_4N$ requires C, 70·3; H, 6·8%).

2-Phenyl-5-3′ : 4′-diethoxyphenyl-4-methyloxazole. (*a*) The amide (VIII; R = Bz) (2 g.), dissolved in toluene (50 c.c.), was refluxed for 4 hours with phosphoryl chloride (4 c.c.), the solution evaporated to 10 c.c., and cooled; pale yellow crystals separated, which were recrystallised from 65% alcohol; m. p. 114—114·5°. The solution showed a bluish-violet fluorescence. (*b*) The amide (VIII; R = Bz) (1 g.) was dissolved in pure cold thionyl chloride (3·5 g.), and the yellowish-brown solution kept for 30 mins. at room temperature. On addition of anhydrous ether (40 c.c.) a delicate crystal powder (0·25 g.) separated, and removal of the solvent in a vacuum afforded a further crop of the same crystals (0·2 g.), m. p. 166—167°, consisting of the hydrochloride of the oxazole. When these were dissolved in hot 33% alcohol, hydrolysis took place and the free *base*, m. p. 114°, crystallised (Found : C, 74·5; H, 6·8. $C_{20}H_{21}O_3N$ requires C, 74·4; H, 6·55%).

UNIVERSITY, SZEGED, HUNGARY.

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