Tetrahedron, 1958, Vol. 4, pp. 205–212. Pergamon Press Ltd., London

EXTENSION OF BISCHLER–NAPIERALSKI REACTION—I

SYNTHESIS OF *ISO*QUINOLINE DERIVATIVES: A SYNTHESIS OF *RAC.*-APOMORPHINE DIMETHYL ETHER

SHIGEHIKO SUGASAWA and RYUJI TACHIKAWA
Pharmaceutical Institute, University of Tokyo, Tokyo, Japan

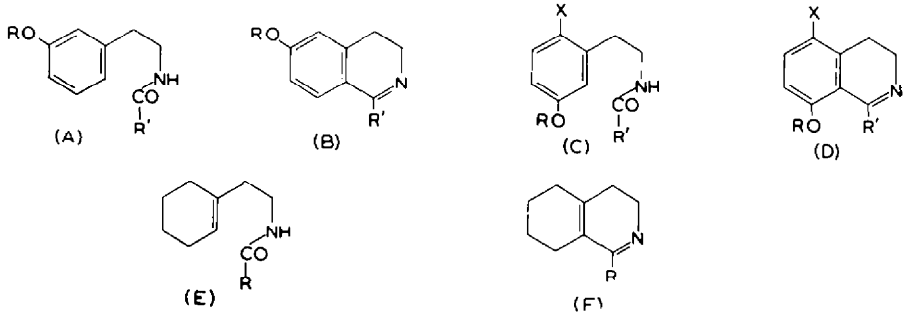
(*Received* 28 *March* 1958)

Abstract—The scope of Bischler–Napieralski reaction has now been extended to include acyl *cyclo*hexa-1:4-dienylethylamide types, which cyclise smoothly to yield various *iso*quinolines after dehydrogenation. 1-(2-Nitro-3:4-dimethoxybenzyl)-3:4-dihydro*iso*quinoline, hitherto difficultly accessible, could be prepared and converted to *rac.*-apomorphine dimethyl ether.

THE Bischler–Napieralksi reaction[1] in modified forms has been extensively used for the cyclisation of 3-alkoxyphenethylamides (A) to furnish 6-alkoxy*iso*quinolines (B). When the *para*position to the alkoxy group in (A) is occupied, as in (C), the cyclisation occurs at the *ortho*position to form 8-alkoxy*iso*quinoline derivatives (D).[2]

The cyclisation of simple phenethylamides having no activating group takes place with difficulty to give poor yields of the products. Thus the synthesis of apomorphine dimethyl ether has been the subject of long dispute by various workers, to which the recent communication by Hey and Palluel,[3] which appeared during our present work, seems to have offered a solution.

In their paper published in 1950, Schnider and Hellerbach[4] reported an improved synthesis of 1-substituted 3:4:5:6:7:8-hexahydro*iso*quinoline derivatives (F), useful intermediates for the preparation of morphinans from acyl *cyclo*hexen-1-ylethylamides (E) by treating with phosphoryl chloride in boiling benzene.



This would seem to suggest that the Bischler–Napieralski reaction takes place toward a carbon-to-carbon double bond, provided the double bond is suitably located with regard to the acyl amido-group. This was verified by synthesising 1-methyl- and

[1] W. M. Whaley and T. R. Govindachari, *Organic Reactions* (Ed.-in-Chief Roger Adams) Vol. VI, p. 74. Wiley, New York (1951).
[2] S. Sugasawa and H. Shigehara, *Ber. Dtsch. Chem. Ges.* **74**, 459 (1941).
[3] D. H. Hey and A. L. Palluel, *Proc. Chem. Soc.* 7 (1957).
[4] O. Schnider and J. Hellerbach, *Helv. Chim. Acta* **33**, 1437 (1950).

1-benzyl-*iso*quinolines (Va) and (Vb) from aceto- and phenylaceto-*cyclo*hexa-1:4-dienlyethylamides (IIa) and (IIb) by refluxing with phosphoryl chloride in benzene solution followed by dehydrogenation.

Thus phenethylamine was reduced according to Birch as modified by Wilds and Nelson[5] to furnish *β-cyclo*hexa-1:4-dienylethylamine (I), which was then acylated to the corresponding amides (IIa) and (IIb). The absence of aromatic contamination in both (I) and (II) was confirmed by their ultra-violet spectra (Fig. 1). When (IIa) was

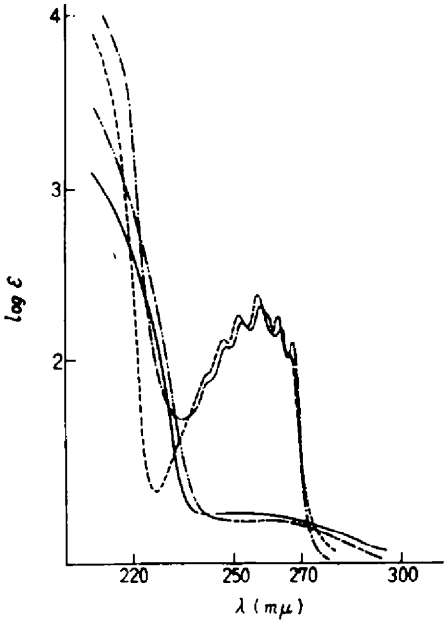


FIG. 1. Ultra-violet spectra of amines and their acetyl derivatives.
- - - - - - - - - -Phenethylamine
———————— Amine (I)
— · — · — · Acetophenethylamide
·· — ·· — ·· Amide (IIa).

refluxed with phosphoryl chloride in benzene, cyclisation proceeded smoothly to yield a viscous syrup b.p. 95–96°/4·5 mm, but the product was not the expected (IIIa). The picrate melted over a range 178–187°, which was raised to 190–191° and this was not depressed when admixed with the picrate of 1-methyl-3:4-dihydro*iso*quinoline (IVa) m.p. 191–193°, prepared by cyclising acetophenethylamide. The methiodide of the above-mentioned syrup separated first as a glass, which crystallised and melted at 193–195°. (IVa) gave at once a crystalline methiodide, which melted at 193–195° alone or admixed with the above sample.

These facts would seem to show that the cyclised product, b.p. 95–96°/4·5 mm, is impure 1-methyl-3:4-dihydro*iso*quinoline (IVa), rather than the crude 1-methyl-3:4:5:8-tetrahydro*iso*quinoline (IIIa),* which probably owed its formation to the latter through disproportionation during the cyclisation reaction or air-oxidation during working-up.

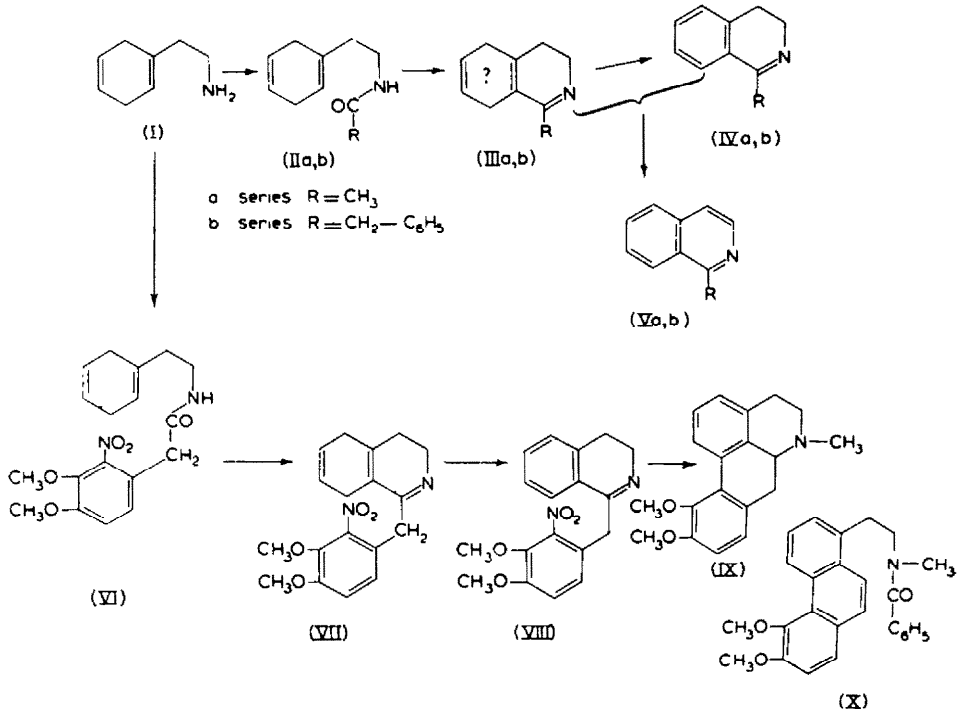
* Fig. 2 shows the ultra-violet absorption curves of the pure (IVa) and the oil of b.p. 95–96°/4·5 mm. The somewhat lower intensity at λ_{max} 248 mμ of the latter compound is probably due to the presence of non-aromatic contamination.

[5] A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.* **75**, 5630 (1953).

The oil, b.p. 95–96°/4·5 mm, was treated with palladium–carbon in boiling *p*-cymene, when 1-methyl*iso*quinoline (Va) was obtained, which was identified by comparison with an authentic specimen.

1-Benzyl*iso*quinoline (Vb) was also prepared from phenylaceto*cyclo*hexa-1:4-dienylethylamide (IIb).

This method was now successfully extended to synthesise *rac.*-apomorphine dimethyl ether (IX).



The amine (I) was acylated with the chloride of 2-nitro-3:4-dimethoxyphenylacetic acid, prepared according to Pschorr and Sumuleanu[6] and Kay and Pictet[7] to give a crystalline amide (VI), m.p. 90–91·5°. The cyclisation of the latter was effected with phosphoryl chloride in boiling benzene to give an uncharacterised intermediate (VII) in about 70 per cent yield. The dehydrogenation of this compound to 1-(2-nitro-3:4-dimethoxybenzyl)-3:4-dihydro*iso*quinoline (VIII) was achieved by boiling with palladium–carbon in xylene, which melted at 127–128° alone or admixed with an authentic specimen of (VIII).† The conversion of (VIII) to *rac.*-apomorphine dimethyl ether (IX) gave a faint-yellow viscous syrup, b.p. 186–190°/0·01 mm (cf. Figs. 3 and 4). For further characterisation this was benzoylated according to Späth and Hromatoka,[8]

† Prepared according to Späth in small yield by cyclising 2-nitro-3:4-dimethoxyphenylacetophenethylamide with phosphorous pentoxide in boiling xylene. A large quantity of the neutral product of m.p. 124–125° (cf. Hey and Palluel[9]) was recovered.

[6] R. Pschorr and C. Sumuleanu, *Ber. Dtsch. Chem. Ges.* **32**, 3405 (1899).
[7] F. W. Kay and A. Pictet, *J. Chem. Soc.* **103**, 947 (1913).
[8] E. Späth and O. Hromatoka, *Ber. Dtsch. Chem. Ges.* **62**, 326 (1929).

when 5:6-dimethoxy-1-(benzamethylamidoethyl)phenathrene (X), m.p. 163–164·5°, was obtained.

On the other hand *l*-apomorphine was methylated with diazomethane as usual and the resulting dimethyl ether was benzoylated as above to yield (X), which was proved to be identical with the above obtained product.

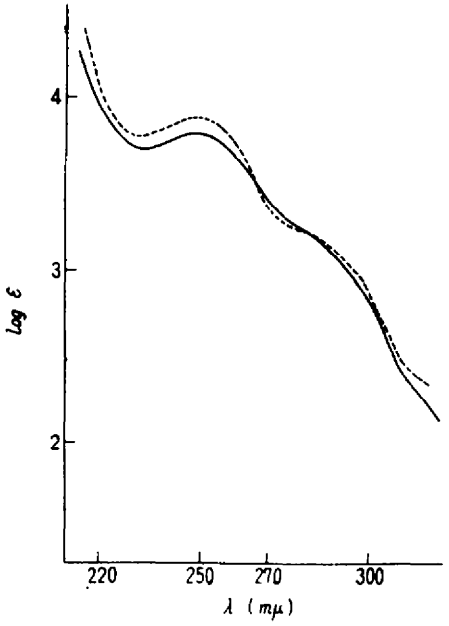


FIG. 2. Ultra-violet spectra of pure (IVa) and the oil of b.p. 95–96°/4·5 mm.
---------Pure (IVa)
———— Oil of b.p. 95–96°/4·5 mm.

The work will be extended to include other $\gamma\delta$-unsaturated acyl amides for preparing various nitrogen heterocyclic compounds.

EXPERIMENTAL

β-cyclo*Hexa*-1:4-*dienylethylamine* (I). Liquid ammonia (150 ml) was added to phenethylamine (12 g) in absolute ethanol (45·6 g), cooled in a solid carbon dioxide–ethanol bath. Metallic lithium (7 g) was now added to this mixture in small portions with stirring. The added metal was rapidly consumed and the mixture developed a blue colour after 30 min. The addition of lithium was now regulated to maintain the blue colour. After all the metal had been added (2 hr) the stirring was continued for 30–40 min until decolorisation occurred. Ammonia was now evaporated and the residue was treated with cold water (300 ml) with cooling, and an oily layer separated, which was taken up in ether and dried, and the solvent was evaporated in an atmosphere of nitrogen. The product was obtained as a colourless oil, b.p. 61–62°/4·5 mm, and is a strong base absorbing carbon dioxide to form a salt. The yield of distilled product was 10·8 g (88·5 per cent).

Aceto-(β-cyclohexa-1:4-dienyl)ethylamide (IIa). The base (I) (3·5 g) in benzene (30 ml) was acylated with acetyl chloride (2·4 g) in sodium hydroxide solution. The

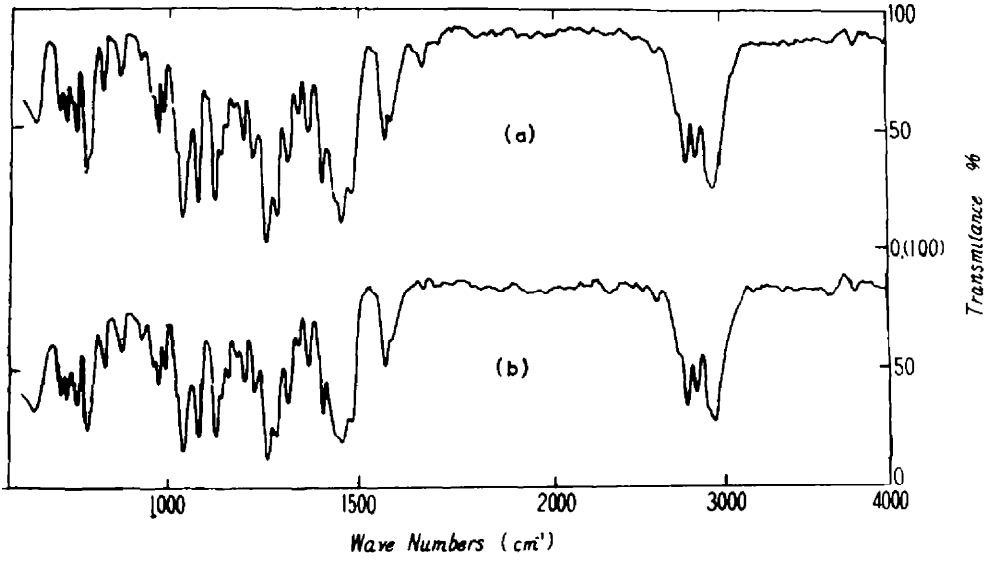


FIG. 3. Infra-red spectra of *rac.*-apomorphine dimethyl ether (a) and L-apomorphine dimethyl ether (b).

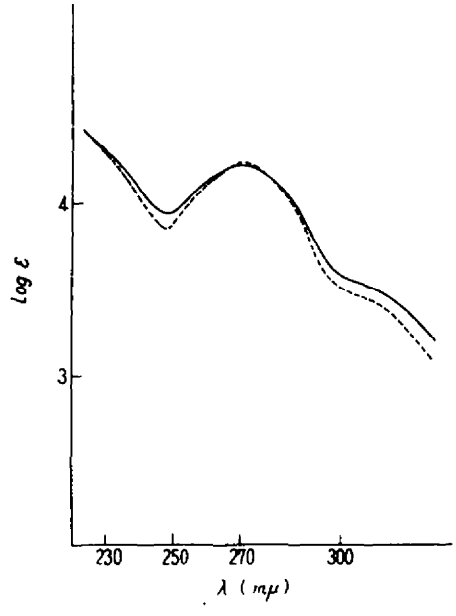


FIG. 4. Ultra-violet spectra of *rac.*- and L-apomorphine dimethyl ether.
——— *rac.*-compound
- - - - - - - L-compound.

crude amide (4·7 g, 94·8 per cent) was obtained as a glass, which solidified on standing, and, when purified from *n*-hexane, formed colourless needles, m.p. 46·5–47·5° (Found: C, 72·6; H, 8·9; N, 8·5. $C_{10}H_{15}ON$ requires C, 72·7; H, 9·1; N, 8·5 per cent).

Cyclisation of (IIa). The amide (2 g) in pure benzene (20 ml) was mixed with freshly purified phosphoryl chloride (3 ml) and refluxed on a steam-bath. A copious evolution of hydrogen chloride was observed, which ceased after 30 min. On cooling sufficient light petroleum was added to cause a reddish brown layer to separate, and the supernatant layer was discarded. The residue was dissolved in dilute hydrochloric acid and the solution shaken once with benzene to remove non-basic contaminants. The acid layer was now treated with sodium carbonate solution, and the oily layer which separated was collected in benzene, washed and dried, and the solvent was removed by distillation in an atmosphere of nitrogen. The residue distilled at 95–96° under 4·5 mm, as a clear colourless oil, which gradually became brown on exposure to air. The yield of the distilled product was 1·51 g (85·7 per cent). The picrate separated as yellow crystals, m.p. 178–187°, which was raised to 190–191° on being purified by repeated crystallisation from acetone, when yellow prisms were obtained. The m.p. of the prisms was not depressed on admixture with an authentic picrate of 1-methyl-3:4- dihydro*iso*quinoline (IVa).

1-*Methyl*iso*quinoline* (Va). The foregoing cyclised product (0·2 g) in *p*-cymene (5 ml) was refluxed with 30% Pd–C (0·1 g) in an oil-bath for 2 hr. On cooling, the catalyst was filtered off and the filtrate was repeatedly extracted with dilute hydrochloric acid. The combined acid extracts were then made alkaline with sodium hydroxide solution and the base was collected in benzene, washed and dried, and the solvent was evaporated to leave a faint-yellow oily base, which amounted to 0·17 g, or 86·3 per cent. This was characterised as the picrate, which formed yellow needles, m.p. 210–212°, from acetone and was identified with an authentic picrate of 1-methyl*iso*quinoline.

The hydrochloride was also prepared, which crystallised in colourless needles, m.p. 185–187°, from acetone–ethanol and was proved to be identical with 1-methyl-*iso*quinoline hydrochloride.

*Phenylaceto-β-*cyclo*hexa*-1:4-*dienyl*)*ethylamide* (IIb). This was prepared as (IIa). The crude product was obtained as a white solid (95·2 per cent), and when purified from benzene–light petroleum formed colourless plates, m.p. 94–95° (Found C: 79·2; H, 7·7; N, 6·0. $C_{16}H_{19}ON$ requires C, 79·7; H, 7·9; N, 5·8 per cent). The cyclisation of this amide and working-up of the product were carried out as described above, to give a brown oil, which distilled at 145–148°/0·1 mm; the yield was 79 per cent. The picrate separated as a yellow solid, m.p. 164–168°, which was raised to 173–175° on purification from acetone, when yellow plates were obtained, and the m.p. was not depressed on admixture with the picrate of 1-benzyl-3:4-dihydro*iso*-quinoline.

1-*Benzyl*iso*quinoline* (Vb). The foregoing base, b.p. 145–148°/0·1 mm, (0·3 g) in *p*-cymene (10 ml) was refluxed with 30 per cent Pd–C (0·1 g) in an atmosphere of nitrogen for 2 hr and then worked up as described above. The crude product was obtained as a brown syrup (0·21 g, 70·6 per cent), which distilled at 164–166°/0·1 mm to give a faint yellow viscous oil, which solidified on being agitated and was purified from *n*-hexane, to give colourless prisms, m.p. 51–52°, which were identified by direct comparison with 1-benzyl*iso*quinoline.

The picrate formed yellow prisms, m.p. 181–183°, from ethanol and the hydrochloride separated in colourless needles, m.p. 170–172°, from acetone–ethanol. The two compounds were also identified with the corresponding authentic specimens from 1-benzyl*iso*quinoline.

2-*Nitro*-3:4-*dimethoxyphenylaceto*-(β-cyclo*hexa*-1:4-*dienyl*)*ethylamide* (VI). The base (I) (1·3 g) in pure benzene (30 ml), mixed with 5 per cent sodium hydrogen carbonate solution (50 ml), was acylated with 2-nitro-3:4-dimethoxyphenylacetyl chloride* (2·6 g) dissolved in 30 ml of pure benzene with stirring and cooling at 5°. After stirring for an additional 2 hr, the supernatant benzene layer was washed successively with dilute hydrochloric acid, sodium hydrogen carbonate solution and water and then dried, and the solvent was removed *in vacuo*. The residual viscous brown syrup was dissolved in a small amount of benzene and filtered through a short alumina column. A faint yellow glass thus obtained amounted to 3·4 g (92·9 per cent), which solidified. When purified from benzene–light petroleum, colourless needles were obtained, m.p. 90–91·5° (Found: C, 62·2; H, 6·3; N, 7·9. $C_{18}H_{22}O_5N_2$ requires C, 62·4; H, 6·4; N, 8·1 per cent).

Cyclisation of the amide (VI). A mixture of the foregoing amide (2 g), absolute benzene (50 ml) and phosphoryl chloride (2 ml) was refluxed on a steam-bath. A copious evolution of hydrogen chloride occurred and ceased after about 30 min, to give a dark-brown solution. Benzene and excess of phosphoryl chloride were removed in a hydrogen atmosphere under reduced pressure, and the resulting dark-coloured residue was dissolved in 10 per cent hydrochloric acid, leaving some undissolved material, which was removed by shaking with benzene. The clear acid solution was treated with decolorising charcoal and then basified with sodium carbonate solution, and the free base that separated was dissolved in benzene, washed and dried, and the solvent was removed in an atmosphere of hydrogen under reduced pressure. A brown syrup thus obtained weighed 1·45 g (76·5 per cent), which was again dissolved in benzene and filtered through an alumina column. The product was now obtained as a solid and was purified from light petroleum to give yellow prisms 1·27 g, or 66·9 per cent, m.p. 112–113°. Though the m.p. of this compound was sharp, it did not give satisfactory analyses for (VIII) (Found: C, 65·5; 65·5; H, 5·2; 5·1; N, 8·5. $C_{18}H_{20}O_4N_2$ requires C, 65·8; H, 6·1; N, 8·5 per cent).

1-(2-*Nitro*-3:4-*dimethoxybenzyl*)-3:4-*dihydroisoquinoline* (VIII). For the partial dehydrogenation of (VII) the following procedure was found to be satisfactory. The base (1·2 g), m.p. 112–113°, in xylene (30 ml) was refluxed with 30 per cent Pd–C (0·2 g) in an atmosphere of nitrogen for 3 hr. On cooling, the filtrate from the catalyst was evaporated *in vacuo* to leave a yellow viscous syrup, which was again dissolved in pure benzene and purified through an alumina column. From the filtrate a yellow solid was recovered (1·05 g, 88 per cent), which separated from acetone in pale-yellow prisms, m.p. 127–128° (Found: C, 66·5; H, 5·3; N, 8·3. $C_{18}H_{18}O_4N_2$ requires C, 66·3; H, 5·5; N, 8·6 per cent). The methiodide was obtained as yellow needles from methanol, m.p. 201–203° (dec.).

rac.-*Apomorphine dimethyl ether* (IX). This was prepared by the usual method and was obtained as a very viscous pale-yellow syrup, b.p. 186–190°/0·01. The yield of

* 2-Nitro-3:4-dimethoxybenzyl alcohol, the intermediate for this chloride, was prepared from the corresponding aldehyde by the crossed Cannizarro method.

the distilled product was 49·6 per cent based on 1-(2-nitro-3:4-dimethoxybenzyl)-2-methyl-1:2:3:4-tetrahydro*iso*quinoline.

5:6-*Dimethoxy*-1-(*benzamethylamidoethyl*)*phenanthrene* (X). *rac.*-Apomorphine dimethyl ether was boiled with benzoyl chloride for 1 hr according to the method of Späth. The benzoyl derivative (X) formed pale-yellow minute needles from *n*-hexane. The m.p. 164–165° was not depressed on admixture with an authentic specimen of the same m.p. prepared from L-apomorphine dimethyl ether (Found: C, 77·9; H, 6·4; N, 3·8. $C_{26}H_{25}O_3N$ requires C, 78·2; H, 6·3; N, 3·5 per cent).