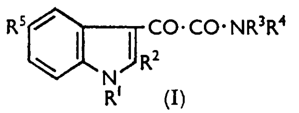
685. *The Synthesis of Some Indolylalkylamines.*

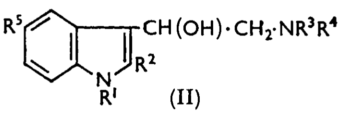
By (Mrs.) A. F. Ames, D. E. Ames, C. R. Coyne, T. F. Grey, I. M. Lockhart, and R. S. Ralph.

A series of 3-indolylalkylamines and a number of their derivatives have been prepared for pharmacological study. Most of these compounds were obtained by reduction of intermediates prepared by the action of oxalyl chloride and then secondary amines on indoles by addition of nitrostyrenes to indoles, or by reactions of substituted gramines. Grignard reagents with *NN*-dialkyl-3-indolylglyoxylamides give high yields of α-substituted glycollamides. The methylation of some 3-indolylalkylamine derivatives with formic acid–formaldehyde and with methyl iodide–sodamide has been examined.

This paper describes the synthesis of a number of substituted 3-indolylalkylamines and related compounds for pharmacological study.

It has been shown [1,2,3] that oxalyl chloride condenses readily with indoles to give 3-indolylglyoxylyl chlorides which can be converted into the corresponding amides. This method has been used to prepare a number of 1,2-disubstituted 3-indolylglyoxylamides (I) (Table 1, p. 3393) which have been reduced with lithium aluminium hydride to the hydroxy-amines (II) (Table 2, p. 3394) by Speeter and Anthony's method.[2,4] The primary amine (II; R^1 = Me, R^2 = Ph, R^3 = R^4 = R^5 = H) could not be obtained satisfactorily in this manner but was prepared from the dibenzylamine (II; R^1 = Me, R^2 = Ph, R^3 = R^4 = CH_2Ph, R^5 = H) by catalytic debenzylation. Oxidation of hydroxy-amine (II; R^1 = R^3 = R^4 = Me, R^2 = Ph, R^5 = H) with perbenzoic acid gave the *N*-oxide (III).


(I)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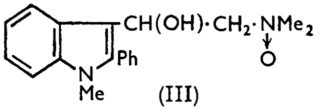
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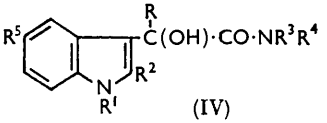
(IV)

It was found that the α-keto-amides (I) with Grignard reagents gave the hydroxy-amides (IV) in good yield. Attempts to use phenyl-lithium in this reaction were unsuccessful although phenylmagnesium bromide gave a product of type (IV). The amides (IV) were also reduced with lithium aluminium hydride, to the corresponding hydroxy-amines (V).

The keto-amide (I; R^1 = R^3 = R^4 = Me, R^2 = Ph, R^5 = H) was reduced with potassium borohydride to *NN*-dimethyl-α-(1-methyl-2-phenyl-3-indolyl)glycollamide (VI), but attempts to convert this into the α-chloro-amide, which it was hoped to reduce to amine (IX; R = Me), were unsuccessful. As an alternative route to (IX; R = Me), 1-methyl-2-phenylindole was formylated, by the phosphorus oxychloride–dimethylformamide method;[5] condensing the resulting aldehyde (VII) with nitromethane[6] gave

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[1] Kharasch, Kane, and Brown, *J. Amer. Chem. Soc.*, 1940, **62**, 2242.

[2] Speeter and Anthony, *ibid.*, 1954, **76**, 6208; Speeter, U.S.P. 2,825,734; Speeter and the Upjohn Co., B.P. 797,258.

[3] Shaw, McMillan, Gudmondson, and Armstrong, *J. Org. Chem.*, 1958, **23**, 1171.

[4] The Upjohn Co., B.P. 778,823 and 797,258.

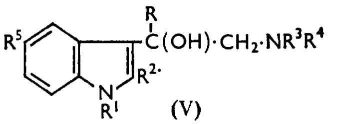
[5] Smith, *J.*, 1954, 3842; Silverstein, Ryskiewicz, and Chaikin, *J. Amer. Chem. Soc.*, 1954, **76**, 4485.

[6] Burger, Stein, and Clements, *J. Org. Chem.*, 1957, **22**, 143; cf. Young, *J.*, 1958, 3493; Ash and Wragg, *J.*, 1958, 3887.

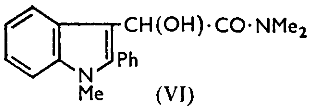
the nitro-compound (VIII) which was reduced with lithium aluminium hydride to 1-methyl-2-phenyl-3-indolylethylamine (IX; R = H). Methylation by catalytic hydrogenation in the presence of formaldehyde gave the tertiary amine (IX; R = Me). Addition of ethylene oxide to amine (IX; R = H) yielded *NN*-di-2′-hydroxyethyl-2-(1-methyl-2-phenyl-3-indolyl)ethylamine (IX; R = $CH_2{\cdot}CH_2{\cdot}OH$).

For the synthesis of the homologous amine (XI), the aldehyde (VII) was condensed with ethyl cyanoacetate,[7] the resulting cyano-ester was hydrogenated and hydrolysed to β-(1-methyl-2-phenyl-3-indolyl)propionic acid (X), the dimethylamide of which was reduced by lithium aluminium hydride.

Synthesis of keto-amines (XII; R = NMe_2) was next examined. 1-Methyl-2-phenylindole-3-carboxylic acid was prepared from the oxime of aldehyde (VII) by dehydration with acetic anhydride followed by vigorous alkaline hydrolysis of the resulting nitrile. An attempt to convert this acid through the acid chloride into a chloro-ketone (XII; R′ = Me, R = Cl) by treatment with diazomethane and hydrogen chloride failed. In view of reports [8] that 1-methylpyrrole can be acylated by using a Grignard reagent and an acyl halide, it was hoped that 1-methyl-2-phenylindole might give the chloride (XII; R′ = Me, R = Cl) on treatment with ethylmagnesium bromide and chloroacetyl chloride, but none could be isolated. When 2-phenylindole was used in these reactions, however, some chloro-ketone (XII; R′ = H, R = Cl) was formed since the action of dimethylamine on the crude product furnished some keto-amine (XII; R′ = H, R = NMe_2).



(V)



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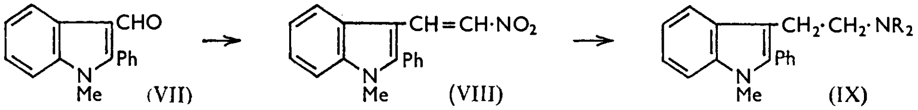
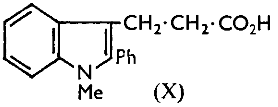
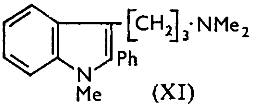


(VII) (VIII) (IX)



(X)



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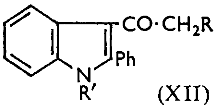

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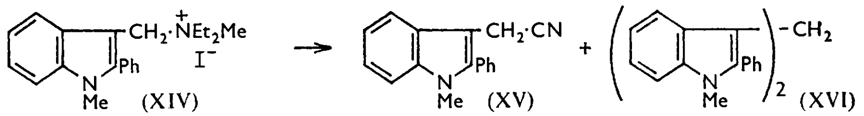
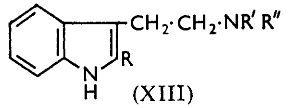
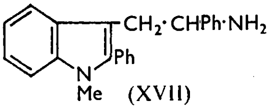


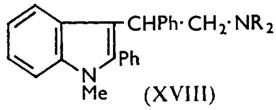
(XIV) (XV) (XVI)



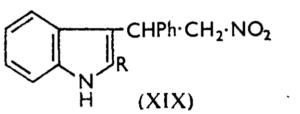
(XIII)



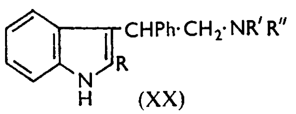
(XVII)



(XVIII)



(XIX)



(XX)

A series of compounds of type (XIII) (Table 3, p. 3394) was prepared from 2-substituted indoles by condensation with oxalyl chloride and reduction of the derived amides with lithium aluminium hydride.[2,9] As with the amides (I), the primary amine (XIII; R = Ph,

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[7] Blume and Lindwall, *J. Org. Chem.*, 1946, **11**, 185.

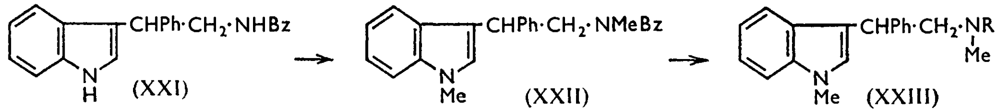
[8] Herz, *ibid.*, 1957, **22**, 1260.

[9] The Upjohn Co., B.P. 781,390.

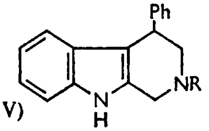
R′ = R″ = H) could not be obtained satisfactorily in this way but was more conveniently prepared by catalytic debenzylation of the tertiary amine (XIII; R = Ph, R′ = R″ = CH_2Ph). When *NN*-diphenyl-α-(2-phenyl-3-indolyl)glyoxylamide (I; $R^1 = R^5 = H$, $R^2 = R^3 = R^4 = Ph$) was reduced with lithium aluminium hydride, the amine was not formed but cleavage of the amide group occurred. The crude products were acetylated and distilled, to give 3-2′-acetoxyethyl-2-phenylindole.

Attention was next turned to the synthesis of compounds with an aryl substituent in the 3-aminoethyl side-chain. The Mannich reaction on 1-methyl-2-phenylindole, followed by treatment with methyl iodide, gave the quaternary salt (XIV) which with potassium silver cyanide[10] yielded mainly the di-indolylmethane (XVI) and only a small yield of nitrile (XV). However, when the salt (XIV) was treated with sodium cyanide in dimethylformamide,[11] the nitrile (XV) was formed in good yield. When this nitrile was allowed to react with phenylmagnesium bromide and then lithium aluminium hydride, 2-(1-methyl-2-phenyl-3-indolyl)-1-phenylethylamine (XVII) was produced in small yield.

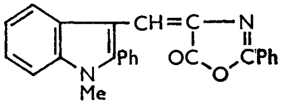
For the synthesis of the related amines (XVIII), the addition of nitrostyrene to indoles appeared to provide a convenient approach. Noland and his collaborators[12] have shown that indole and 2-phenylindole with nitrostyrene give adducts (XIX). The nitro-compound (XIX; R = Ph) was catalytically hydrogenated to amine (XX; R = Ph, R′ = R″ = H) which was converted into the corresponding dimethylamine (XX; R = Ph, R′ = R″ = Me) and other derivatives. Similar reactions starting from 2-*p*-chlorophenylindole and 4-chloro-ω-nitrostyrene were also carried out but attempts to condense ω-nitrostyrene with 1-methyl-2-phenylindole were unsuccessful. *N*-Methylation of amines of type (XX) was therefore examined, experiments being made first with β-3-indolylphenethylamine (XX; R = R′ = R″ = H). The benzoyl derivative (XXI) of this amine was treated with sodamide and methyl iodide in liquid ammonia; the product was shown by the absence of NH bands in the infrared spectrum and by *N*-methyl analysis to be the dimethylated amide (XXII). Reduction by lithium aluminium hydride then yielded the benzylamine (XXIII; R = CH_2Ph) which was catalytically debenzylated to give *N*-methyl-β-(1-methyl-3-indolyl)phenethylamine (XXIII; R = H). Further methylation of this amine by catalytic hydrogenation in the presence of formaldehyde gave the tertiary amine (XXIII; R = Me).



(XXI) (XXII) (XXIII)



(XXIV)



(XXV)

NN-Dimethyl-β-(1-methyl-2-phenyl-3-indolyl)phenethylamine (XVIII; R = Me) was prepared by a similar sequence of reactions from ω-nitrostyrene and 2-phenylindole.

When the primary amine (XX; R = R′ = R″ = H) was treated with formic acid and formaldehyde, a high-melting crystalline product was obtained. This was formulated as (XXIV; R = CHO) since the infrared spectrum showed the presence of an amide group (intense band at 1657 cm.$^{-1}$ in chloroform). Bader and Oroshnik[13] have discussed the

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[10] Snyder, Smith, and Stewart, *J. Amer. Chem. Soc.*, 1944, **66**, 200.

[11] Woodward, Cava, Ollis, Hunger, Daeniker, and Schenker, *ibid.*, 1954, **76**, 4749.

[12] Noland, Christensen, Sauer, and Dutton, *ibid.*, 1955, **77**, 456; Noland and Lange, *ibid.*, 1959, **81**, 1203.

[13] Bader and Oroshnik, *ibid.*, 1957, **79**, 5685.

factors controlling the competition between *N*-methylation and Pictet–Spengler cyclisation of 3-indolylethylamines to tetrahydro-β-carbolines. The isolation of the *N*-formyl compound (XXIV; R = CHO) rather than the *N*-methylamine (XXIV; R = Me) is, however, unexpected. Reduction of the formyl compound with lithium aluminium hydride did give 1,2,3,4-tetrahydro-2-methyl-4-phenyl-β-carboline (XXIV; R = Me).

Finally 1-methyl-2-phenyltryptophan was prepared from the quaternary salt (XIV) and ethyl acetamidomalonate (cf. the synthesis of tryptophan by Snyder and Smith[14]). In an alternative method, 3-formyl-1-methyl-2-phenylindole (VII) was condensed with hippuric acid to give the oxazolone (XXV) but this could not be hydrolysed satisfactorily.

EXPERIMENTAL

2-o-*Chlorophenylindole*.—2-Chloroacetophenone (104 g.), phenylhydrazine (72 g.), and glacial acetic acid (1 c.c.) in ethanol (660 c.c.) were heated under reflux for 8 hr. No crystalline phenylhydrazone could be obtained on cooling; the mixture was evaporated *in vacuo*, the residue was dissolved in toluene (500 c.c.), and the solution evaporated similarly. Zinc chloride (800 g.) was added and the mixture was heated at 180° for 10 min., then poured into 0·3N-hydrochloric acid (3 l.). The mixture was heated on the steam-bath and stirred for 1 hr., cooled to 0°, and filtered, the dark solid being extracted repeatedly with boiling light petroleum (b. p. 80—100°). The *indole* (43 g.) separated as plates, m. p. 86—87° (Found: C, 74·0; H, 4·5; Cl, 15·6. $C_{14}H_{20}NCl$ requires C, 73·8; H, 4·4; Cl, 15·6%).

2-p-*Hydroxyphenylindole*.—4-Hydroxyacetophenone phenylhydrazone (47 g.) was fused with zinc chloride (250 g.), and the product isolated as in the previous example. The crude material was passed in methanol–ether (1 : 20) through a column of aluminium oxide (250 g.). Evaporation of the eluate gave the indole (17 g.) which formed plates, m. p. 227—229°, from benzene (Found: C, 80·6; H, 5·3; N, 6·6. Calc. for $C_{14}H_{11}ON$: C, 80·4; H, 5·3; N, 6·7%). The m. p. (70°) given by Korczynski and Kierzek[15] appears to be erroneous.

2-p-*Methoxyphenylindole*.—Sodium (4·2 g.) in ethanol (650 c.c.) was treated with 2-*p*-hydroxyphenylindole (32·5 g.) and methyl iodide (16·5 c.c.) successively, refluxed for 3 hr., cooled, and filtered; the solid was washed with water and recrystallised from benzene, to give 2-*p*-methoxyphenylindole (21 g.), m. p. 227—228° depressed to 190—195° by the hydroxy-compound (Found: C, 80·9; H, 6·1; N, 6·1. Calc. for $C_{15}H_{13}ON$: C, 80·7; H, 5·9; N, 6·3%). Korczynski and Kierzek[15] give m. p. 228—229°.

2-p-*Benzyloxyphenylindole*.—The hydroxy-compound (37 g.) and benzyl chloride (22 c.c.) were added to sodium ethoxide solution [from sodium (4·6 g.) in ethanol (300 c.c.)], and the mixture was stirred at 90° (bath) for 3 hr., allowed to cool, and filtered. The crude product was washed with water and methanol, then recrystallised from ethyl methyl ketone to give needles of 2-p-*benzyloxyphenylindole* (20 g.), m. p. 243—245° (Found: C, 84·6; H, 5·9; N, 5·0. $C_{21}H_{17}ON$ requires C, 84·3; H, 5·7; N, 4·7%).

2-*Phenethylindole*.—A solution of diazomethane in ether (5 l.) was prepared from methylnitrosourea (300 g.) and cooled below 2° while β-phenylpropionyl chloride (95 g.) in ether (1 l.) was added gradually. After the mixture had been kept for 40 hr., it was cooled below 10° while hydrogen chloride was passed in until 20 min. after evolution of nitrogen had ceased. The ethereal solution was washed with sodium hydrogen carbonate solution and evaporated; the residual chloro-ketone was treated with aniline (150 c.c.) and heated at 120° for 30 min. and then at 180° for 1 hr. The mixture was decomposed with water and ether, and the ethereal layer was washed with 3N-hydrochloric acid (three times) and water, dried ($CaSO_4$–charcoal), filtered, and distilled. 2-*Phenethylindole*, b. p. 160—170°/0·1 mm., solidified rapidly and separated from ethanol as colourless plates, m. p. 123—124° (30 g.) (Found: C, 86·3; H, 6·8; N, 6·4. $C_{16}H_{15}N$ requires C, 86·8; H, 6·8; N, 6·3%).

β-4′-*Benzyloxyphenethylindole*.—By the same procedure as in the previous paragraph, β-*p*-benzyloxyphenylpropionyl chloride[16] (55 g.) was converted into the *indole*, obtained as a

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[14] Snyder and Smith, *J. Amer. Chem. Soc.*, 1944, **66**, 350.

[15] Korczynski and Kierzek, *Gazzetta*, 1925, **55**, 361.

[16] Doherty, *J. Amer. Chem. Soc.*, 1955, **77**, 4891.

solid on evaporation of the ethereal solution. Recrystallisation from methanol–ethyl acetate gave plates (11·2 g.), m. p. 163—164° (Found: C, 84·4; H, 6·5; N, 4·3. $C_{23}H_{21}ON$ requires C, 84·4; H, 6·5; N, 4·3%).

1-*Methyl*-2-*phenylindole*.—A solution of sodamide was prepared from sodium (20 g.) and liquid ammonia (*ca.* 900 c.c.). 2-Phenylindole (75 g.) was added gradually; the mixture was stirred for 30 min., then treated gradually with methyl iodide (150 g.). After the ammonia had evaporated overnight, water (1·5 l.) was added and the solid was collected, washed with more water, and dried. It was dissolved in benzene (400 c.c.) and light petroleum (1200 c.c.; b. p. 60—80°) was added; the filtered solution was passed through a column of alumina (500 g.). The alumina was washed with the same solvent mixture (1 l.) (2-phenylindole remained strongly adsorbed). Evaporation of the effluent and recrystallisation of the residue from light petroleum (b. p. 80—100°) gave 1-methyl-2-phenylindole (64 g.), m. p. 98—100°. Kissman, Farnsworth, and Witkop [17] give m. p. 100—101°.

The following 1-alkyl-2-arylindoles were prepared similarly: 2-o-*chlorophenyl*-1-*methylindole*, prisms, m. p. 107—108°, from light petroleum (b. p. 60—80°) (Found: C, 74·9; H, 5·0; Cl, 14·8. $C_{15}H_{12}NCl$ requires C, 74·5; H, 5·0; Cl, 14·7%); 2-p-*benzyloxyphenyl*-1-*methylindole*, prisms, m. p. 124—126°, from benzene (Found: C, 83·9; H, 6·1; N, 4·2. $C_{22}H_{19}ON$ requires C, 84·3; H, 6·1; N, 4·5%); 2-*phenyl*-1-*propylindole*, b. p. 175—176°/2·5 mm., n_D^{20} 1·6320 (Found: C, 86·6; H, 7·3; N, 5·8. $C_{17}H_{17}N$ requires C, 86·8; H, 7·3; N, 6·0%); and 5-*methoxy*-1-*methyl*-2-*phenylindole* (from 5-methoxy-2-phenylindole [18]), needles, m. p. 128—129°, from light petroleum (b. p. 60—80°) (Found: C, 81·3; H, 6·2; N, 6·3. $C_{16}H_{15}ON$ requires C, 81·0; H, 6·4; N, 5·9%).

5-*Hydroxy*-1-*methyl*-2-*phenylindole*.—5-Methoxy-1-methyl-2-phenylindole (13 g.) was refluxed for 2·5 hr. with 48% hydrobromic acid (200 c.c.). The mixture was cooled, poured into water (650 c.c.), and filtered; recrystallisation of the solid from aqueous ethanol gave the *hydroxy-indole* (13 g.) as plates, m. p. 150—152° (Found: C, 80·3; H, 5·7; N, 6·4. $C_{15}H_{13}ON$ requires C, 80·7; H, 5·9; N, 6·3%).

5-*Benzyloxy*-1-*methyl*-2-*phenylindole*.—The foregoing hydroxy-indole (16 g.) and benzyl chloride (8·5 c.c.) were added successively to sodium ethoxide solution [from sodium (1·8 g.) and ethanol (110 c.c.)], and the mixture was refluxed for 3·5 hr., poured into water (500 c.c.), and filtered. The solid was washed with water and ether and recrystallised from 2-methoxyethanol to give the *benzyloxyindole* (10 g.), m. p. 159—160° (Found: C, 84·1; H, 6·4; N, 4·5. $C_{22}H_{19}ON$ requires C, 84·3; H, 6·1; N, 4·5%).

3-*Indolylglyoxylamides*.—A solution of oxalyl chloride (0·13 mol.) in ether (100 c.c.) was cooled in ice-water and stirred while the indole (0·10 mol.) in ether (500 c.c.) was added gradually. After the mixture had been stirred for 1 hr., dimethylamine was passed in until the mixture was alkaline. Stirring was continued for 1 hr. and then water (500 c.c.) was added. The crude product was filtered off and recrystallised (cf. Speeter and Anthony [2]). The *products* are listed in Table I.

2-*Amino*-1-3′-*indolylethanols*.—The amide (0·075 mole) in boiling benzene (500 c.c.) was added as rapidly as possible to a stirred suspension of lithium aluminium hydride (10 g.) in ether (500 c.c.). The mixture was refluxed for 3 hr., then treated successively with ethyl acetate (50 c.c.) and 5N-sodium hydroxide solution (15 c.c.). After being refluxed for 1 hr., the solid was filtered off and washed with hot ethyl acetate (500 c.c.), and the combined filtrate and washings were evaporated *in vacuo* to give the crude product which was then recrystallised. For the *products* see Table 2.

When the amide was insoluble in hot benzene, the reduction was carried out in 1,2-dimethoxyethane.

O- and *N*-Benzyl groups in the products were removed by catalytic hydrogenation in ethanol with 5% palladised charcoal.

2-*Dimethylamino*-1-(1-*methyl*-2-*phenyl*-3-*indolyl*)*ethanol* N-*Oxide*.—Perbenzoic acid in chloroform (60 c.c.; 0·315M) was added in portions to the amine (5 g.) in chloroform (50 c.c.) at −20° and the mixture set aside for 15 min. The solution was washed with water (300 c.c.), sodium carbonate solution (5 × 40 c.c.), and water (50 c.c.), dried (Na_2SO_4), and evaporated *in vacuo*. Recrystallisation of the residue from benzene–light petroleum (b. p. 60—80°) furnished the

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[17] Kissman, Farnsworth, and Witkop, *J. Amer. Chem. Soc.*, 1952, **74**, 3948.

[18] Terent'ev and Preobrazhenskaya, *Doklady Akad. Nauk S.S.S.R.*, 1957, **114**, 560; *Chem. Abs.*, 1958, **52**, 356.

TABLE 1. 3-*Indolylglyoxylamides* (I).

R^1	R^2	R^3	R^4	R^5	M. p.	Recryst. from	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
Me	Me	Me	Me	H	127—128°	*a*	$C_{14}H_{16}O_2N_2$	69·3	7·0	11·4	68·8	6·6	11·5
Me	Ph	Me	Me	H	198—200	*b*	$C_{19}H_{18}O_2N_2$	75·0	5·9	9·1	74·5	5·9	9·2
Me	*p*-MeC_6H_4	Me	Me	H	186—187	*b*	$C_{20}H_{20}O_2N_2$	75·1	6·3	8·6	75·0	6·3	8·7
Me	*o*-ClC_6H_4	Me	Me	H	189—191	*b*	$C_{19}H_{17}O_2N_2Cl$	67·4	5·2	7·6	67·0	5·0	8·2
Me	*p*-ClC_6H_4	Me	Me	H	215—217	*b*	”	66·5	5·0	7·8	”	”	”
Me	*p*-Ph·CH_2·O·C_6H_4	Me	Me	H	175—177	*c*	$C_{26}H_{24}O_3N_2$	76·1	5·8	6·7	75·7	5·9	6·8
Me	Ph	Me	Me	Me	218—220	*b*	$C_{20}H_{20}O_2N_2$	75·0	6·4	8·8	75·0	6·3	8·7
Me	Ph	Me	Me	Cl	214—216	*b*	$C_{19}H_{17}O_2N_2Cl$	67·3	5·1	8·0	67·0	5·0	8·2
Me	Ph	Me	Me	OMe	162—164	*b*	$C_{20}H_{20}O_3N_2$	71·8	5·8	8·7	71·4	6·0	8·3
Me	Ph	Me	Me	O·CH_2Ph	173—175	*b*	$C_{26}H_{24}O_3N_2$	75·5	5·8	7·0	75·7	5·9	6·8
Me	Ph	Et	Et	H	141—143	*a*	$C_{21}H_{22}O_2N_2$	75·0	6·3	8·7	75·4	6·6	8·4
Me	*p*-ClC_6H_4	Et	Et	H	147—148	*b*	$C_{21}H_{21}O_2N_2Cl$	68·9	5·3	7·5	68·4	5·7	7·6
Me	Ph	Et	Pr^n	H	133—135	*b*	$C_{22}H_{24}O_2N_2$	75·9	7·1	8·0	75·8	6·9	8·0
Me	Ph	Et	CH_2Ph	H	153—154	*b*	$C_{26}H_{24}O_2N_2$	78·4	6·4	7·1	78·8	6·1	7·1
Me	Ph	Pr^n	Pr^n	H	117—119	*b*	$C_{23}H_{26}O_2N_2$	76·7	7·3	8·0	76·2	7·2	7·7
Me	Ph	CH_2Ph	CH_2Ph	H	170—171	*d*	$C_{31}H_{26}O_2N_2$	81·0	5·6	6·1	81·2	5·7	6·1
Et	Ph	Me	Me	H	151—153	*b*	$C_{20}H_{20}O_2N_2$	75·1	6·3	9·0	75·0	6·3	8·7
Pr^n	Ph	Me	Me	H	156—157	*b*	$C_{21}H_{22}O_2N_2$	75·8	6·6	8·5	75·4	6·6	8·4
Ph	H	Me	Me	H	95—96	*e*	$C_{18}H_{16}O_2N_2$	73·9	5·7	9·2	74·0	5·5	9·6
Ph	Ph	Me	Me	H	177—179	*b*	$C_{24}H_{20}O_2N_2$	78·0	5·3	8·0	78·2	5·5	7·6
H	Ph	Me	Me	H	213—215	*b*	$C_{18}H_{16}O_2N_2$	73·7	5·7	9·4	74·0	5·5	9·6
H	Ph	Me	CH_2Ph	H	173—175	*d*	$C_{24}H_{20}O_2N_2$	77·9	5·5	7·5	78·2	5·5	7·6
H	Ph	$-[CH_2]_5-$		H	182—184	*c*	$C_{21}H_{20}O_2N_2$	76·4	5·7	8·2	75·9	6·1	8·4
H	Ph	$-[CH_2]_2$·O·$[CH_2]_2-$		H	173—175	*c*	$C_{20}H_{18}O_3N_2$	71·3	5·3	8·4	71·8	5·4	8·4
H	*p*-Ph·CH_2·O·C_6H_4	Me	Me	H	177—178	*b*	$C_{25}H_{22}O_3N_2$	75·2	5·6	6·8	75·4	5·6	7·0
H	*p*-MeO·C_6H_4	Me	Me	H	198—200	*b*	$C_{19}H_{18}O_3N_2$	70·9	5·7	8·7	70·8	5·6	8·7
H	*p*-Ph·CH_2·O·C_6H_4	$-[CH_2]_2$·O·$[CH_2]_2-$		H	93—94	*f*	$C_{27}H_{24}O_4N_2$ [h]	72·5	5·6	6·1	72·1	5·6	6·2
H	Ph·CH_2·CH_2	Me	Me	H	123—125	*g*	$C_{20}H_{20}O_2N_2$	74·5	6·2	8·8	75·0	6·3	8·7
H	Ph·CH_2·CH_2	CH_2Ph	CH_2Ph	H	160—161	*b*	$C_{32}H_{28}O_2N_2$	80·9	5·8	6·1	81·3	6·0	5·9

[a] Benzene–light petroleum (b. p. 60—80°). [b] Ethanol. [c] Benzene. [d] Chloroform–methanol. Light petroleum (b. p. 80—100°). [f] Methanol. [g] Ether. [h] 0·5H_2O.

TABLE 2. 2-*Amino*-1-3′-*indolylethanols* (II).

R^1	R^2	R^3	R^4	R^5	M. p.	Recryst. from	Formula	Found (%) C	H	N	Required (%) C	H	N
Me	Me	Me	Me	H	110—112°	*a*	$C_{14}H_{20}ON_2$	72·8	8·8	12·0	72·4	8·7	12·1
Me	Ph	Me	Me	H	110—122	*a*	$C_{19}H_{22}ON_2$	77·4	7·6	9·8	77·5	7·5	9·5
Me	*p*-Me·C_6H_4	Me	Me	H	118—119	*a*	$C_{20}H_{24}ON_2$	77·7	7·7	9·1	77·9	7·8	9·1
Me	*o*-ClC_6H_4	Me	Me	H	117—118	*a*	$C_{19}H_{21}ON_2Cl$	69·9	6·4	8·0	69·4	6·4	8·5
Me	*p*-ClC_6H_4	Me	Me	H	157—158	*a*	,,	69·4	6·3	8·0	,,	,,	,,
Me	*p*-Ph·CH_2·O·C_6H_4	Me	Me	H	137—139	*b*	$C_{26}H_{28}O_2N_2$	78·2	7·1	7·3	78·0	7·1	7·0
Me	*p*-HO·C_6H_4	Me	Me	H	171—172	*c, e*	$C_{19}H_{22}O_2N_2$	73·1	7·2	8·8	73·5	7·1	9·0
Me	*p*-MeO·C_6H_4	Me	Me	H	131—133	*d, f*	$C_{20}H_{24}O_2N_2$	74·3	7·5	8·3	74·0	7·5	8·6
Me	Ph	Me	Me	Me	101—102	*a*	$C_{20}H_{24}ON_2$	78·3	7·8	9·2	77·9	7·8	9·1
Me	Ph	Me	Me	Cl	119—121	*a*	$C_{19}H_{21}ON_2Cl$	69·6	6·3	8·8	69·4	6·4	8·5
Me	Ph	Me	Me	OMe	101—103	*a*	$C_{20}H_{24}O_2N_2$	74·7	7·4	8·9	74·0	7·5	8·6
Me	Ph	Me	Me	O·CH_2Ph	121—123	*b*	$C_{26}H_{28}O_2N_2$	77·9	6·9	6·8	78·0	7·1	7·0
Me	Ph	Me	Me	OH	153—155	*d, e*	$C_{19}H_{22}O_2N_2$	73·6	7·3	8·7	73·5	7·1	9·0
Me	Ph	Et	Et	H	85—87	*a*	$C_{21}H_{16}ON_2$	78·2	8·1	8·9	78·2	8·1	8·7
Me	*p*-ClC_6H_4	Et	Et	H	131—132	*d*	$C_{21}H_{25}ON_2Cl$	70·8	7·0	7·4	70·7	7·1	7·9
Me	Ph	Et	Pr^n	H	64—65	*a*	$C_{22}H_{28}ON_2$	78·9	8·9	8·2	78·5	8·4	8·3
Me	Ph	Et	CH_2Ph	H	78—79	*a*	$C_{26}H_{28}ON_2$	80·9	7·7	7·2	81·2	7·3	7·3
Me	Ph	Et	H	H	89—91	*a, e*	$C_{19}H_{22}ON_2$	77·6	7·6	9·3	77·5	7·5	9·5
Me	Ph	Pr^n	Pr^n	H	67—69	*a*	$C_{23}H_{30}ON_2$	79·1	8·7	8·3	78·8	8·6	8·0
Me	Ph	CH_2Ph	CH_2Ph	H	96—98	*d*	$C_{31}H_{30}ON_2$	82·8	6·6	6·2	83·4	6·8	6·3
Me	Ph	H	H	H	130—132	*a, e*	$C_{17}H_{18}ON_2$	76·4	6·4	10·2	76·7	6·8	10·5
Et	Ph	Me	Me	H	118—120	*a*	$C_{20}H_{24}ON_2$	77·6	7·7	8·9	77·9	7·8	9·1
Pr^n	Ph	Me	Me	H	86—87	*a*	$C_{21}H_{26}ON_2$	78·6	8·2	8·5	78·2	8·1	8·7
Ph	H	Me	Me	H	104—105	*a*	$C_{18}H_{20}ON_2$	76·9	7·3	10·1	77·1	7·2	10·0
Ph	Ph	Me	Me	H	148—149	*a*	$C_{24}H_{24}ON_2$	80·9	6·7	8·4	80·9	6·8	7·9

[a] Ethanol. [b] Methanol. [c] Butan-2-one. [d] Aqueous ethanol. [e] Obtained by debenzylation of the preceding compound. [f] Obtained by action of diazomethane on the preceding compound.

TABLE 3. 2-3′-*Indolylethylamines* (XIII).

R	R^1	R^2	M. p.	Recryst. from	Formula	Found (%) C	H	N	Required (%) C	H	N
Ph	Me	Me	124—126°	*a*	$C_{18}H_{20}N_2$	81·6	8·1	10·4	81·8	7·6	10·6
Ph	Me	CH_2Ph	83—85	*b*	$C_{24}H_{24}N_2$	84·3	7·0	8·1	84·7	7·1	8·2
Ph	–$[CH_2]_5$–		128—130	*a*	$C_{21}H_{24}N_2$	81·9	7·9	8·7	82·9	8·0	9·2
Ph	–$[CH_2]_2$·O·$[CH_2]_2$–		153—156	*a*	$C_{20}H_{22}ON_2$	78·8	7·4	9·3	78·4	7·2	9·1
p-Ph·CH_2O·C_6H_4	Me	Me	142—143	*c*	$C_{25}H_{26}ON_2$	81·4	7·0	7·7	81·0	7·1	7·6
p-HO·C_6H_4	Me	Me	216—217	*d, f*	$C_{18}H_{20}ON_2$	76·7	7·5	9·6	77·1	7·2	10·0
p-MeO·C_6H_4	Me	Me	173—175	*c*	$C_{19}H_{22}ON_2$	77·9	7·7	9·5	77·5	7·5	9·5
p-Ph·CH_2·O·C_6H_4	–$[CH_2]_2$·O·$[CH_2]_2$–		159—160	*c*	$C_{27}H_{28}O_2N_2$	78·5	6·7	6·6	78·6	6·8	6·8
p-HO·C_6H_4	–$[CH_2]_2$·O·$[CH_2]_2$–		218—220	*c*	$C_{20}H_{22}O_2N_2$	74·7	6·7	8·6	74·5	6·9	8·7
Ph·CH_2·CH_2	Me	Me	Gum	*g*	—	—	—	—	—	—	—
Ph·CH_2·CH_2	CH_2Ph	CH_2Ph	88—89	*c*	$C_{32}H_{32}N_2$	86·4	7·1	—	86·4	7·3	—
Ph·CH_2·CH_2	H	H	Gum	*h*	$C_{18}H_{20}N_2$	81·4	7·5	—	81·8	7·6	—
p-HO·C_6H_4·CH_2·CH_2	Me	Me	168—169	*i*	$C_{20}H_{24}ON_2$	78·1	7·8	8·4	77·9	7·8	9·1

Ethyl acetate. [b] Benzene–light petroleum (b. p. 60—80°). [c] Methanol. [d] Ethanol. [e] Benzene–acetone. [f] Obtained by debenzylation of the preceding benzyloxy-compound. [g] The *hydrochloride* separated from ether–ethanol; m. p. 162—164° (Found: C, 72·3; H, 7·8; N, 8·2; Cl, 10·8. $C_{20}H_{25}N_2Cl$ requires C, 73·0; H, 7·7; N, 8·5; Cl, 10·8%); *methiodide*, cubes, m. p. 246—248°, from 2-methoxyethanol (Found: C, 58·4; H, 6·4; N, 6·5; I, 29·0. $C_{21}H_{27}N_2I$ requires C, 58·1; H, 6·3; N, 6·5; I, 29·2%). [h] Obtained by debenzylation of the preceding dibenzylamino-compound. [i] Obtained by debenzylation of the oily *O*-benzyl compound which was not isolated.

oxide (3·3 g.) as plates, m. p. 182—184° (Found: C, 73·6; H, 7·2; N, 8·9. $C_{19}H_{22}O_2N_2$ requires C, 73·5; H, 7·1; N, 9·0%).

NN-*Diethyl-α-(1-methyl-2-phenyl-3-indolyl)lactamide*.—A solution of *NN*-diethyl-1-methyl-2-phenyl-3-indolylglyoxylamide (19 g.) in benzene (300 c.c.) was added very rapidly to methylmagnesium iodide solution [from magnesium (2.2 g.) and methyl iodide (7 c.c.) in ether (50 c.c.)]. Ether was removed by distillation and the clear yellow solution was then refluxed for 2 hr. (bath 110°). After addition of ammonium chloride solution, the separated aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, dried ($MgSO_4$), and evaporated. Trituration of the residual gum with benzene–light petroleum (b. p. 60—80°) gave material, m. p. 126—128° depressed to *ca.* 100° by the starting material. Recrystallisation from benzene–light petroleum (b. p. 80—100°) yielded the *amide* (16·2 g.) as prisms, m. p. 127—129° (Found: C, 75·3; H, 7·7; N, 8·3. $C_{22}H_{26}O_2N_2$ requires C, 75·4; H, 7·5; N, 8·0%).

The following compounds were prepared similarly: NN-*dimethyl-α-(1-methyl-2-phenyl-3-indolyl)lactamide*, m. p. 140—142° (from aqueous methanol) (Found: C, 74·9; H, 7·1; N, 8·6. $C_{20}H_{22}O_2N_2$ requires C, 74·5; H, 6·9; N, 8·7%); NN-*diethyl-α-(1-methyl-2-*p-*chlorophenyl-3-indolyl)lactamide*, m. p. 165—166° [from benzene–light petroleum (b. p. 80—100°)] (Found: C, 69·1; H, 6·6; Cl, 9·2. $C_{22}H_{25}O_2N_2Cl$ requires C, 68·7; H, 6·5; Cl, 9·2%). Phenylmagnesium bromide was used similarly to prepare NN-*dimethyl-(1-methyl-2-phenyl-3-indolyl)phenylglycollamide* which formed prisms (from methanol), m. p. 156—158° (Found: C, 78·4; H, 6·3; N, 7·4. $C_{25}H_{24}O_2N_2$ requires C, 78·1; H, 6·3; N, 7·3%).

NN-*Diethyl*-N-*[2-hydroxy-2-(1-methyl-2-phenyl-3-indolyl)propyl]amine*.—Reduction of the foregoing lactic amide by the procedure described above gave the *hydroxy-amine* (75%) as prisms, m. p. 59—60° (from aqueous ethanol) (Found: C, 78·7; H, 8·4; N, 8·5. $C_{22}H_{28}ON_2$ requires C, 78·5; H, 8·4; N, 8·3%).

The following hydroxyamines were prepared similarly: *2-hydroxy-2-(1-methyl-2-phenyl-3-indolyl)propyldimethylamine*, prisms, m. p. 66—67°, from ethanol (Found: C, 78·3; H, 8·3; N, 9·2. $C_{20}H_{24}ON_2$ requires C, 77·9; H, 7·8; N, 9·1%); NN-*diethyl-2-hydroxy-2-(2-*p-*chlorophenyl-1-methyl-3-indolyl)propylamine*, prisms, m. p. 92—93°, from aqueous ethanol (Found: C, 71·4; H, 7·4; Cl, 9·6. $C_{22}H_{27}ON_2Cl$ requires C, 71·2; H, 7·3; Cl, 9·6%). β-Hydroxy-β-(1-methyl-2-phenyl-3-indolyl)phenethyldimethylamine, also prepared similarly, was an oil which could not be crystallised. Shaking it with ethyl acetate and 2N-sulphuric acid gave needles of the *hydrogen sulphate hydrate*, m. p. 90° (decomp.) (Found: C, 61·1; H, 6·2; N, 5·5; S, 6·7. $C_{25}H_{26}ON_2,H_2SO_4,H_2O$ requires C, 61·7; H, 6·2; N, 5·8; S, 6·6%).

NN-*Dimethyl-(1-methyl-2-phenyl-3-indolyl)glycollamide*.—*NN*-Dimethyl-(1-methyl-2-phenyl-3-indolyl)glyoxylamide (9·7 g.) was suspended in ethanol (200 c.c.) and treated with potassium borohydride (5 g.) in water (50 c.c.); the mixture was warmed at 45—50° for 3 hr., diluted with water (200 c.c.), and acidified with 2N-hydrochloric acid (75 c.c.). Repeated recrystallisation of the solid, which separated on cooling, from ethanol, gave the *hydroxy-amide* as prisms, m. p. 137—139° (Found: C, 74·0; H, 6·9; N, 9·1. $C_{19}H_{20}O_2N_2$ requires C, 74·0; H, 6·5; N, 9·1%.)

3-Formyl-1-methyl-2-phenylindole.—Phosphorus oxychloride (20 c.c.) was added gradually to dimethylformamide (64 c.c.) at 10° and 1-methyl-2-phenylindole (41 g.) in warm dimethylformamide (100 c.c.) was added gradually at 15—20°. The solution was warmed at 35° for 45 min., poured into ice-water (1·5 l.), and stirred until crystallisation occurred (*ca.* 15 min.). 5N-Sodium hydroxide was added until the mixture was neutral to Methyl Red and then more alkali (200 c.c. in all) was added immediately. The mixture was heated to the b. p. and then cooled rapidly. The aldehyde formed plates, m. p. 124—126°, from ethanol (yield, 42 g.); Blume and Lindwall [19] give m. p. 122·5—124°.

1-(1-Methyl-2-phenyl-3-indolyl)-2-nitroethylene.—The foregoing aldehyde (7·05 g.) and nitromethane (1·83 g.) were heated with butylamine (0·2 g.) on a steam-bath for 2½ hr. The product, which crystallised on cooling, was triturated with light petroleum (b. p. 60—80°) and recrystallised twice from ethyl acetate to give the *nitro-compound* (4 g.) as prisms, m. p. 149—151° (Found: C, 73·1; H, 5·0; N, 10·5. $C_{17}H_{14}O_2N_2$ requires C, 73·4; H, 5·0; N, 10·1%).

2-(1-Methyl-2-phenyl-3-indolyl)ethylamine.—1-(1-Methyl-2-phenylindol-3-yl)-2-nitroethylene (9 g.) in 1,2-dimethoxyethane (500 c.c.) was refluxed for 12 hr. with lithium aluminium hydride (10 g.). Ether (1 l.), ethyl acetate (50 c.c.), and 5N-sodium hydroxide (25 c.c.) were added successively. The mixture was refluxed for 1 hr. and filtered, the solid being washed with

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[19] Blume and Lindwall, *J. Org. Chem.*, 1945, **10**, 255.

ethyl acetate. The amine, obtained by evaporation, did not crystallise but gave the *picrate*, m. p. 215—217°, as prisms from ethanol–acetone (Found: C, 58·0; H, 4·8; N, 14·6. $C_{23}H_{21}O_7N_5$ requires C, 57·6; H, 4·4; N, 14·6%).

In another experiment, the crude amine in ethanol (150 c.c.) was hydrogenated with 40% aqueous formaldehyde (15 c.c.) over 10% palladised charcoal (6 g.). The filtered solution was evaporated and the residual amine treated with ethereal picric acid. Recrystallisation from ethanol gave NN-*dimethyl*-2-(1-*methyl*-2-*phenyl*-3-*indolyl*)*ethylamine picrate* (7·0 g.) as prismatic needles, m. p. 152—154° (Found: C, 59·5; H, 5·4; N, 13·7. $C_{25}H_{25}O_7N_5$ requires C, 59·2; H, 5·0; N, 13·8%). The *amine*, liberated from the picrate by sodium hydroxide solution and isolated with ether, was a yellow syrup (Found: C, 81·4; H, 8·0; N, 9·9. $C_{19}H_{22}N_2$ requires C, 82·0; H, 8·0; N, 10·1%).

NN-*Di*-(2-*hydroxyethyl*)-2-(1-*methyl*-2-*phenyl*-3-*indolyl*)*ethylamine*.—Another portion (10 g.) of the foregoing nitro-compound was reduced similarly and the crude amine was dissolved in methanol (100 c.c.). Ethylene oxide (40 g.) was slowly bubbled through the solution which was then left overnight. Evaporation furnished a gum which was converted into the *picrate*, m. p. 160—163° (Found: C, 57·1; H, 5·2; N, 12·3. $C_{27}H_{29}O_9N_5$ requires C, 57·1; H, 5·2; N, 12·3%). The *dihydroxy-amine*, liberated as in the previous example, crystallised from ethanol and had m. p. 91—92° (Found: C, 74·6; H, 7·5; N, 8·3. $C_{21}H_{26}O_2N_2$ requires C, 74·5; H, 7·7; N, 8·3%).

Ethyl α-*Cyano*-β-(1-*methyl*-2-*phenyl*-3-*indolyl*)*acrylate*.—A mixture of 3-formyl-1-methyl-2-phenylindole (18 g.), pyridine (22·5 c.c.), piperidine (3·25 c.c.), ethyl cyanoacetate (11·25 c.c.), and propan-2-ol (45 c.c.) was refluxed for 20 min. (cf. Blume and Lindwall[7]). When ethanol–water (100 c.c.; 7 : 3) was added to the cooled mixture, yellow needles separated. Recrystallisation from ethanol gave the *ester* (21 g.), m. p. 142° (Found: C, 76·5; H, 5·3; N, 8·4. $C_{21}H_{18}O_2N_2$ requires C, 76·3; H, 5·4; N, 8·5%).

(1-*Methyl*-2-*phenyl*-3-*indolylmethyl*)*malonic Acid*.—The foregoing ester (5·0 g.) in ethanol (60 c.c.) was hydrogenated in the presence of 10% palladised charcoal (0·5 g.) and 10% palladised strontium carbonate (0·5 g.) until 400 c.c. of hydrogen had been absorbed. Evaporation of the filtered solution gave a glass which was refluxed for 80 hr. with potassium hydroxide (3·5 g.) in water (50 c.c.) and ethanol (50 c.c.). The filtered solution was acidified and extracted with ethyl acetate, and the extracts were washed with water and dried (Na_2SO_4). On trituration of the oily residue with ethylene dichloride it crystallised, and recrystallisation of the solid from aqueous ethanol furnished the *diacid* (2·75 g.) as prisms, m. p. 172° (Found: C, 71·1; H, 5·5; N, 4·5. $C_{19}H_{17}O_4N$ requires C, 70·6; H, 5·3; N, 4·3%).

β-(1-*Methyl*-2-*phenyl*-3-*indolyl*)*propionic Acid*.—After the diacid (2·8 g.) had been heated at 180° until decarboxylation ceased (2·5 hr.), the residual gum was triturated with aqueous ethanol to give the acid which was recrystallised from aqueous ethanol and then from light petroleum (b. p. 80—100°). It formed prisms (2·25 g.), m. p. 106—108° (Found: C, 77·1; H, 6·2; N, 5·0. Calc. for $C_{18}H_{17}O_2N$: C, 77·4; H, 6·1; N, 5·0%). Harley-Mason[20] gave m. p. 114—116°.

A suspension of the acid (3·8 g.) in benzene (75 c.c.) was stirred with oxalyl chloride (5 g.) for 3·5 hr., and excess of dimethylamine was passed into the resulting solution. The mixture was washed with water and evaporated, the resulting *dimethylamide* (3·5 g.), m. p. 99—100°, being isolated by recrystallisation from benzene–light petroleum (b. p. 60—80°) (Found: C, 78·1; H, 7·0; N, 9·4. $C_{20}H_{22}ON_2$ requires C, 78·4; H, 7·2; N, 9·1%).

NN-*Dimethyl*-3-(1-*methyl*-2-*phenyl*-3-*indolyl*)*propylamine*.—Reduction of the dimethylamide (3·3 g.) with lithium aluminium hydride (3 g.) in ether–benzene according to the general procedure yielded the *amine* (1·65 g.), prisms, m. p. 47—49° [from light petroleum (b. p. 40—60°)] (Found: C, 81·8; H, 8·3; N, 9·4. $C_{20}H_{24}N_2$ requires C, 82·1; H, 8·3; N, 9·6%).

3-*Cyano*-1-*methyl*-2-*phenylindole*.—3-Formyl-1-methyl-2-phenylindole oxime[19] (5·0 g.) and acetic anhydride (50 c.c.) were heated under reflux for 2 hr. and then evaporated *in vacuo*. The solid residue was recrystallised from ethanol to give 3-*cyano*-1-*methyl*-2-*phenylindole* (2 g.) as needles, m. p. 117—119° (Found: C, 82·7; H, 5·1; N, 12·3. $C_{16}H_{12}N_2$ requires C, 82·7; H, 5·2; N, 12·1%).

1-*Methyl*-2-*phenylindole*-3-*carboxylic Acid*.—The cyano-indole (7 g.) and potassium hydroxide (20 g.) in water (20 c.c.) and ethylene glycol (100 c.c.) were refluxed together for 72 hr. Water (100 c.c.) was added and the hot solution was filtered and acidified with acetic acid (50 c.c.).

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[20] Harley-Mason, *J.*, 1952, 2433.

The acid was collected and recrystallised from benzene to give tablets (5·2 g.), m. p. 200—201°. Borsche and Klein [21] report m. p. 201—202°.

3-*Dimethylaminoacetyl*-2-*phenylindole*.—Ethylmagnesium iodide solution (from 4·5 g. of magnesium) in ether (100 c.c.) was stirred and cooled (ice-bath) while 2-phenylindole (26 g.) in ether (300 c.c.) was added rapidly. After 5 min. chloroacetyl chloride (20 g.) in ether (50 c.c.) was added. The mixture was stirred and cooled for 15 min., then treated with ammonium chloride solution and extracted with benzene. The combined organic layers were washed with water, sodium hydrogen carbonate solution, and water, dried (Na_2SO_4), and concentrated to small volume. 2-Phenylindole, which gradually separated, was filtered off; evaporation of the filtrate gave a gum which was refluxed (bath 120°) with 2-methoxyethanol (50 c.c.) and 30% ethanolic dimethylamine (50 c.c.) for 5 hr. The residue obtained by evaporation under reduced pressure was dissolved in ethyl acetate, washed with sodium carbonate solution and water, and extracted with 2N-sulphuric acid (2 × 75 c.c.). Basification of the acid extracts followed by isolation with ethyl acetate and evaporation yielded a gum which crystallised on trituration with a little ethyl acetate. Recrystallisation from ethyl acetate gave prisms of the *keto-amine*, m. p. 188—190° (Found: C, 77·5; H, 6·3; N, 9·8. $C_{18}H_{18}ON_2$ requires C, 77·7; H, 6·5; N, 10·1%).

Reduction of N,N,2-*Triphenyl*-3-*indolylglyoxylamide by Lithium Aluminium Hydride*.—The *amide* was prepared by the general procedure except that diphenylamine (50 g.) in pyridine (150 c.c.) was added to the acid chloride from 2-phenylindole (35 g.). It formed cream-coloured needles, m. p. 263—265°, from 2-methoxyethanol (Found: C, 81·0; H, 5·0; N, 6·5. $C_{28}H_{20}O_2N_2$ requires C, 80·7; H, 4·8; N, 6·7%).

Reduction of the amide (8 g.) with lithium aluminium hydride (5 g.) in 1,2-dimethoxyethane was carried out according to the general procedure. The resulting gum was refluxed for 8 hr. with acetic anhydride and then distilled to give the product, b. p. 180—200°/0·2 mm. Redistillation gave 3-(2-*acetoxyethyl*)-2-*phenylindole*, b. p. 180—184°/0·2 mm., n_D^{20} 1·6374 (Found: C, 77·6; H, 6·2; N, 5·4. $C_{18}H_{17}O_2N$ requires C, 77·4; H, 6·1; N, 5·0%).

1-*Methyl*-2-*phenyl*-3-*indolylacetonitrile*.—A mixture of acetic acid (70 c.c.), diethylamine (6·0 g.), 40% formaldehyde solution (5·9 c.c.), and 1-methyl-2-phenylindole (16·1 g.) was stirred and cooled in ice-water for 6 hr. Water (1 l.) was added and the filtered solution was basified with aqueous ammonia and extracted with ether–ethyl acetate (1 : 1), the extracts being washed with water, dried (Na_2SO_4), and evaporated *in vacuo* (bath 40°). The residue was taken up in ethanol (100 c.c.), ether (50 c.c.) and methyl iodide (10 c.c.) and left overnight. NN-*Diethyl*-(1-*methyl*-2-*phenyl*-3-*indolylmethyl*)*amine methiodide* (21 g.) was collected and washed with ether; it decomposed at *ca.* 150° (Found: C, 58·4; H, 6·5; N, 6·2; I, 28·9. $C_{21}H_{27}N_2I$ requires C, 58·1; H, 6·3; N, 6·5; I, 29·2%). When dimethylamine was used similarly in place of diethylamine, a large amount of precipitate was obtained on addition of water to the reaction mixture. Recrystallisation from butan-2-one gave *di*-(1-*methyl*-2-*phenyl*-3-*indolyl*)*methane*, plates, m. p. 177—179° (Found: C, 87·3; H, 6·1; N, 7·2. $C_{31}H_{26}N_2$ requires C, 87·3; H, 6·1; N, 6·6%).

The foregoing methiodide (21 g.), sodium cyanide (11 g.), and dimethylformamide (100 c.c.) were refluxed for 20 hr. (cf. Woodward *et al.*[11]). Water (800 c.c.) was added and the oily product was isolated with ethyl acetate. Evaporation furnished the *nitrile* (10·9 g.), which formed prisms, m. p. 101—102°, from methanol (Found: C, 82·5; H, 6·0; N, 11·6. $C_{17}H_{14}N_2$ requires C, 82·9; H, 5·7; N, 11·4%).

1-*Methyl*-2-*phenyl*-3-*indolylacetic Acid*.—The crude nitrile (from methiodide, 14 g.) was refluxed with 2-methoxyethanol (50 c.c.) and potassium hydroxide (20 g.) in water (50 c.c.) for 20 hr. After addition of water (100 c.c.), the hot solution was filtered to remove some gum and poured into ice-cold dilute hydrochloric acid. The *acid* which separated was recrystallised from benzene–light petroleum (b. p. 60—80°) to give prisms (7·2 g.), m. p. 147—149° (Found: C, 77·3; H, 5·7; N, 5·5. $C_{17}H_{15}O_2N$ requires C, 77·0; H, 5·7; N, 5·3%).

The derived N-*methylamide* (obtained by successive treatment with oxalyl chloride in ether and dimethylamine) formed plates, m. p. 177—179°, from ethanol (Found: C, 77·7; H, 6·9; N, 10·0. $C_{18}H_{18}ON_2$ requires C, 77·7; H, 6·5; N, 10·1%).

2-(1-*Methyl*-2-*phenyl*-3-*indolyl*)-1-*phenylethylamine Picrate*.—A solution of phenylmagnesium bromide [from bromobenzene (9·4 g.) and magnesium (1·3 g.) in ether (100 c.c.)] was refluxed while 1-methyl-2-phenyl-3-indolylacetonitrile (10·5 g.) was added rapidly. After the mixture had been refluxed for 1 hr., a slurry of lithium aluminium hydride (5 g.) in ether

(400 c.c.) was added. The mixture was refluxed for 3 hr., then worked up by the general procedure, but the gummy product did not crystallise. It was taken up in ether (100 c.c.) and added to picric acid (12 g.) in ether (1 l.). The precipitated oil which gradually crystallised was recrystallised from methanol to give the *picrate* (10·5 g.) as dark red needles, m. p. 198—199° (decomp.) (Found: C, 62·2; H, 5·1; N, 12·1. $C_{29}H_{25}O_5N_7$ requires C, 62·7; H, 4·5; N, 12·6%).

NN-*Dimethyl-2-(1-methyl-2-phenyl-3-indolyl)-1-phenylethylamine*.—The foregoing picrate (10 g.) was shaken with 0·5N-sodium hydroxide (1 l.) and ether (500 c.c.) until all the solid had been decomposed. The organic layer was washed with 0·5N-sodium hydroxide (2 × 50 c.c.) and water (2 × 50 c.c.), dried (Na_2SO_4), and evaporated; the residual amine was hydrogenated with 40% aqueous formaldehyde (10 c.c.) in ethanol (70 c.c.) in the presence of 10% palladised charcoal (3 g.) until absorption ceased. Evaporation of the filtered solution gave a gum which was dissolved in ether and stirred with 2N-sulphuric acid (200 c.c.). The colourless plates of hydrated *amine hydrogen sulphate* (4·5 g.) were collected, washed with ether and 2N-sulphuric acid, and dried *in vacuo* at room temperature; the salt decomposed rapidly above 120° and darkened slowly at room temperature (Found: C, 62·1; H, 6·2; N, 5·7; S, 7·0. $C_{25}H_{26}N_2,H_2SO_4,2H_2O$ requires C, 61·5; H, 6·6; N, 5·7; S, 6·6%).

A portion of the salt (1·5 g.) was decomposed with sodium hydroxide solution, and the amine was isolated by means of ethyl acetate, and treated with ethereal picric acid. Deep red crystals, m. p. 130° (decomp.), of the *dipicrate* slowly separated (Found: C, 54·8; H, 4·4; N, 13·7. $C_{37}H_{32}O_{14}N_8$ requires C, 54·7; H, 4·0; N, 13·8%).

NN-*Dimethyl-β-(2-phenyl-3-indolyl)phenethylamine*.—2-Nitro-1-phenyl-1-(2-phenyl-3-indolyl)-ethane[12] (5 g.) in ethanol (70 c.c.) was hydrogenated with 10% palladised charcoal until absorption ceased; 36% aqueous formaldehyde (10 c.c.) and 10% palladised charcoal (2 g.) were added and hydrogenation was resumed until absorption ceased. Evaporation of the filtered solution gave NN-*dimethyl-β-(2-phenyl-3-indolyl)phenethylamine* (3·3 g.), prisms, m. p. 180—182°, from ethanol (Found: C, 84·3; H, 6·9; N, 8·3. $C_{24}H_{24}N_2$ requires C, 84·6; H, 7·1; N, 8·2%).

β-(2-Phenyl-3-indolyl)phenethylurea.—The foregoing primary amine (4 g.) was boiled with 0·15N-hydrochloric acid (85 c.c.); the solution was cooled and filtered and treated with potassium cyanate (1 g.). After 1·5 hr., the precipitate was collected and boiled with water (200 c.c.); decantation of the aqueous solution left an oil which crystallised on trituration with ethanol. Recrystallisation from ethanol afforded the *urea* (1·4 g.) as needles, m. p. 153—155° (Found: C, 77·2; H, 6·4; N, 11·6. $C_{23}H_{21}ON_3$ requires C, 77·7; H, 6·0; N, 11·8%).

N-*Ethoxycarbonyl-β-(2-phenyl-3-indolyl)phenethylamine*.—Ethyl chloroformate (0·9 c.c.) was added to an ice-cold solution of β-(2-phenyl-3-indolyl)phenethylamine (3 g.) in pyridine (50 c.c.) and the mixture was left overnight. After addition of water (200 c.c.), the *urethane* (1·5 g.) was isolated with ether; recrystallised from ethanol, it had m. p. 138—139° (Found: C, 76·3; H, 6·7; N, 7·1. $C_{25}H_{24}O_2N_2,0{\cdot}5H_2O$ requires C, 76·4; H, 6·3; N, 7·1%).

NN-*Di-(2-hydroxyethyl)-β-(2-phenyl-3-indolyl)phenethylamine*.—Ethylene oxide was bubbled through a solution of the indolylethylamine (5 g.) in methanol (200 c.c.) for 2 hr. The solution was left at room temperature for 20 hr., then concentrated to small volume. The *amine* (2·7 g.) which separated on cooling recrystallised from methanol as prisms, m. p. 178—179° (Found: C, 78·4; H, 7·5; N, 7·4. $C_{26}H_{28}O_2N_2$ requires C, 78·0; H, 7·1; N, 7·0%).

*2-Nitro-1-phenyl-1-(2-*p*-chlorophenyl-3-indolyl)ethane*.—A mixture of 2-*p*-chlorophenylindole (50 g.), β-nitrostyrene (40 g.), and 2-butoxyethanol (500 c.c.) was refluxed for 14 hr. and then evaporated under reduced pressure. Recrystallisation of the residue from ethanol gave the *nitro-compound* (51 g.), m. p. 164—165° (Found: C, 70·3; H, 5·0; N, 7·2. $C_{22}H_{17}O_2N_2Cl$ requires C, 70·1; H, 4·6; N, 7·4%). When the solvent was omitted a much lower yield was obtained.

*β-(2-*p*-Chlorophenyl-3-indolyl)phenethylamine*.—The foregoing nitro-compound (8 g.) in methanol (100 c.c.) was hydrogenated in the presence of 1 g. of platinised charcoal.[22] After an induction period of about 1 hr., hydrogenation proceeded slowly and was complete in 30 hr. The filtered solution was evaporated and the residue recrystallised from ethanol to give the *amine* (2 g.), m. p. 182—184° (Found: C, 76·1; H, 5·9; N, 8·1. $C_{22}H_{19}N_2Cl$ requires C, 76·2; H, 5·5; N, 8·1%).

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[21] Borsche and Klein, *Annalen*, 1941, **584**, 64.

[22] Baltzly, *J. Amer. Chem. Soc.*, 1952, **74**, 4586.

β-p-*Chlorophenyl*-β-(2-*phenyl*-3-*indolyl*)*phenethylamine.*—2-Phenylindole (20 g.) and 4-chloronitrostyrene [23] (19 g.) were fused together (bath 130°) for 6 hr. A solution of the mass in hot ethanol was filtered (charcoal) and cooled to give 1-p-*chlorophenyl*-2-*nitro*-1-(2-*phenyl*-3-*indolyl*)-*ethane* (27 g.) which formed yellow prisms, m. p. 147—148°, on recrystallisation from ethanol (Found: C, 69·7; H, 4·8; N, 7·7%).

Hydrogenation of the nitro-compound (10 g.) in the presence of platinised charcoal as in the previous example gave the *amine* (4·4 g.) as needles, m. p. 188—190° (Found: C, 76·2; H, 5·4; N, 7·7%).

N-*Benzoyl*-β-3-*indolylphenethylamine.*—Benzoylation (benzoyl chloride–pyridine overnight at room temperature) of β-3-indolylphenethylamine [12] gave the *benzoyl derivative*, needles, m. p. 188° (from ethanol) (Found: C, 80·4; H, 5·8; N, 8·0. $C_{23}H_{20}ON_2$ requires C, 81·1; H, 5·9; N, 8·2%).

N-*Benzoyl*-N-*methyl*-β-(1-*methyl*-3-*indolyl*)*phenethylamine.*—The foregoing benzoyl derivative (8·5 g.) was added to a solution of sodamide (from sodium, 3 g.) in liquid ammonia (250 c.c.). After 45 min., methyl iodide (9 c.c.) was added and the solvent was allowed to evaporate. The solid obtained on addition of water (200 c.c.) recrystallised from ethanol to give needles of the *amide*, m. p. 139—141° (Found: C, 81·8; H, 6·5; N, 7·7; *N*-Me, 9·9. $C_{25}H_{24}ON_2$ requires C, 81·5; H, 6·6; N, 7·6; *N*-Me, 8·2%).

N-*Methyl*-β-(1-*methyl*-3-*indolyl*)*phenethylamine.*—Reduction of the amide (6·2 g.) with lithium aluminium hydride (5 g.) in ether (150 c.c.) and benzene (150 c.c.) by the general procedure furnished the *N*-benzylamine as a yellow oil. A small portion was catalytically hydrogenated and then treated with ethereal picric acid, to give the *amine picrate*, dark red prisms, m. p. 181° (from ethanol) (Found: C, 57·9; H, 4·8; N, 13·9. $C_{24}H_{23}O_7N_5$ requires C, 58·4; H, 4·7 N, 14·2%).

NN-*Dimethyl*-β-(1-*methyl*-3-*indolyl*)*phenethylamine.*—The foregoing crude benzylamine (1·9 g.) in ethanol (50 c.c.) was hydrogenated in the presence of 10% palladised charcoal (0·5 g.). When 1 mol. of hydrogen had been absorbed (3·5 hr.), 40% aqueous formaldehyde (0·9 c.c.) and more catalyst (1 g.) were added and hydrogenation was resumed until absorption ceased. Evaporation of the filtered solution gave an oil which with ethereal citric acid gave the *amine citrate dihydrate* (1·45 g.) as prisms, m. p. 69° (decomp.) (Found: C, 59·7; H, 7·1; N, 5·1; *N*-Me, 8·3. $C_{25}H_{30}O_7N_2,2H_2O$ requires C, 59·3; H, 6·8; N, 5·5; *N*-Me, 8·9%).

In another experiment, the crude amine was treated with ethereal picric acid to give the orange *picrate*, m. p. 199° (Found: C, 58·8; H, 5·3; N, 13·4. $C_{25}H_{25}O_7N_5$ requires C, 59·2; H, 5·0; N, 13·8%).

2-*Formyl*-1,2,3,4-*tetrahydro*-4-*phenyl*-β-*carboline.*—β-3-Indolylphenethylamine (4·7 g.), 40% formaldehyde (1·8 c.c.), and water (4 c.c.) were added successively to 90% formic acid (2·6 c.c.) in ice-water. The mixture was refluxed for 16 hr., poured into N-sodium hydroxide, and extracted repeatedly with benzene. A solid, which separated on concentration of the extracts to small volume, recrystallised from benzene–cyclohexane to give the *amide* (2·0 g.), prisms, m. p. 235—236° (Found: C, 78·7; H, 5·9; N, 9·8. $C_{18}H_{16}ON_2$ requires C, 78·2; H, 5·8; N, 10·1%).

1,2,3,4-*Tetrahydro*-2-*methyl*-4-*phenyl*-β-*carboline.*—The foregoing amide (2 g.) was reduced with lithium aluminium hydride (2 g.) in ether–benzene according to the general procedure. The resulting *amine* separated from benzene as needles (1·5 g.), m. p. 216—218° (Found: C, 82·2; H, 7·1; N, 10·1; *N*-Me, 4·8. $C_{18}H_{18}N_2$ requires C, 82·4; H, 6·9; N, 10·7; *N*-Me, 5·7%).

N-*Benzoyl*-β-(2-*phenyl*-3-*indolyl*)*phenethylamine.*—β-(2-Phenyl-3-indolyl)phenethylamine (11·2 g.) was benzoylated (benzoyl chloride–pyridine at room temperature) to give the *amide* (7·5 g.) as prisms, m. p. 188—189° (from ethanol) (Found: C, 83·7; H, 5·5; N, 6·9. $C_{29}H_{24}ON_2$ requires C, 83·6; H, 5·8; N, 6·7%).

N-*Benzoyl*-N-*methyl*-β-(1-*methyl*-2-*phenyl*-3-*indolyl*)*phenethylamine.*—The foregoing amide (2 g.) and methyl iodide (3·4 g.) were added successively to sodamide (from sodium, 0·5 g.) in liquid ammonia (40 c.c.). After the ammonia had evaporated, the residue was washed with water and recrystallised from ethanol to furnish the *product* (1·0 g.), needles, m. p. 168—169° (Found: C, 83·8; H, 6·4; N, 6·2; *N*-Me, 5·8. $C_{31}H_{28}ON_2$ requires C, 83·8; H, 6·4; N, 6·3; *N*-Me, 6·8%).

N-*Benzyl*-N-*methyl*-β-(1-*methyl*-2-*phenyl*-3-*indolyl*)*phenethylamine.*—The methylation product (14 g.) was reduced with lithium aluminium hydride (10 g.) in ether–benzene (each 300 c.c.) by

[23] Campbell, Anderson, and Gilmore, *J.*, 1940, 446.

the general procedure. The *amine* (8·5 g.) separated from ethanol as prisms, m. p. 83—85° (Found: C, 86·2; H, 7·1; N, 6·5; *N*-Me, 7·1. $C_{31}H_{30}N_2$ requires C, 86·5; H, 7·0; N, 6·5; *N*-Me, 7·0%). It gave the *picrate* as orange prisms, m. p. 148—150° (Found: C, 67·5; H, 5·1; N, 10·5. $C_{37}H_{33}O_7N_5$ requires C, 67·4; H, 5·0; N, 10·6%).

NN-*Dimethyl*-β-(1-*methyl*-2-*phenyl*-3-*indolyl*)*phenethylamine*.—A suspension of the foregoing benzylamine (2·5 g.) in ethanol (50 c.c.) was hydrogenated in the presence of 10% palladised charcoal (0·5 g.) and 10% palladised strontium carbonate (0·5 g.). After hydrogen (1 mol.) had been absorbed in 6 hr., 40% aqueous formaldehyde (0·9 c.c.) and more palladised charcoal (1 g.) were added and hydrogenation was continued until absorption ceased. Evaporation of the filtered solution afforded the *amine* (1·3 g.), prisms, m. p. 122—124° (from ethanol) (Found: C, 84·5; H, 7·2; N, 7·9. $C_{25}H_{26}N_2$ requires C, 84·7; H, 7·4; N, 7·9%).

4-(1-*Methyl*-2-*phenyl*-3-*indolylmethylene*)-2-*phenyloxazol*-5-*one*.—Hippuric acid (3·6 g.), anhydrous sodium acetate (1·64 g.), and 3-formyl-1-methyl-2-phenylindole (4·7 g.) were ground together and then treated with acetic anhydride (10 c.c.); the mixture was heated on a steam-bath for 20 min., cooled, and shaken with water (50 c.c.). The solid was collected and recrystallised from acetic acid (charcoal) and then from 2-methoxyethanol to give the *oxazolone* (2·7 g.), yellow plates, m. p. 240—242° (Found: C, 79·2; H, 5·0; N, 7·1. $C_{25}H_{18}O_2N_2$ requires C, 79·4; H, 4·8; N, 7·4%).

1-*Methyl*-2-*phenyltryptophan*.—Sodium (1·5 g.) was dissolved in dry ethanol (50 c.c.), and the solution evaporated to small volume; a foam of sodium ethoxide was then obtained by sudden reduction of pressure. After the foam had been dried *in vacuo* for 5 min., dioxan (150 c.c.; redistilled from sodium) and ethyl acetamidomalonate (13·4 g.) were added successively. The mixture was refluxed (bath 140°) for 1·5 hr. and cooled; *NN*-diethyl-(1-methyl-2-phenyl-3-indolylmethyl)amine methiodide (28 g.; finely powdered) was added and the mixture was refluxed (bath 120°) for 30 hr., then poured into water (500 c.c.). The oily product was isolated with ether and hydrolysed for 3 hr. with potassium hydroxide (30 g.) in boiling ethanol (100 c.c.) and water (100 c.c.) (bath 130°). After addition of water (100 c.c.), ethanol was removed by distillation; the cooled solution was filtered and treated with excess of ice and then concentrated hydrochloric acid (50 c.c.). The precipitate was boiled with water (200 c.c.) for 2·5 hr.; N-*acetyl*-1-*methyl*-2-*phenyltryptophan* (15 g.) was collected by filtration of the cooled mixture and was recrystallised from ethanol; it formed needles, m. p. 230—232° (decomp.) (Found: C, 71·8; H, 6·2; N, 8·2. $C_{20}H_{20}O_3N_2$ requires C, 71·4; H, 6·0; N, 8·3%).

A solution of the acetamido-acid (14 g.) in 3N-potassium hydroxide was refluxed for 24 hr., cooled, and acidified with acetic acid. The precipitate was collected and recrystallised from aqueous ethanol, to give 1-*methyl*-2-*phenyltryptophan*, m. p. 200—202° (decomp.) (Found: C, 73·0; H, 6·3; N, 9·3. $C_{18}H_{18}O_2N_2$ requires C, 73·5; H, 6·2; N, 9·5%)

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