Aminoalkylation of Metal Derivatives of Indole. Part II.[1] Coupling of Indolylmagnesium Iodides with Halogenoalkylamines

By **C. R. Ganellin, D. R. Hollyman,** and **H. F. Ridley,** Smith Kline and French Research Institute, Welwyn Garden City, Hertfordshire

The coupling between indole Grignard reagents and halogenoalkylamines provides a general synthesis of 3-aminoalkylindoles. The reaction of indolylmagnesium iodide with 2-chloro-1-dimethylaminopropane furnishes a mixture of four isomeric amines which have been identified by alternative syntheses. The results indicate that although an aziridinium ion participates in this reaction it is not the main electrophilic agent.

We have reported a synthesis of substituted tryptamines which involves coupling of indole Grignard reagents with 1-chloro-2-dimethylaminoethane.[1] This reaction has been further examined and in this Paper we exemplify its scope and describe some of its limitations as a general synthesis for aminoalkylindoles. The possibility of coupling indole Grignard reagents with halogenoalkylamines has previously been considered [2-4] but, because of a poor choice of conditions, the reaction has not been successful, *e.g.*, with 1-chloro-2-dimethylaminopropane,[3] 1-chloro-2-diethylaminoethane,[4] or 1-chloro-2-di-isopropylaminoethane.[4] Earlier we reported [1] that this reaction, which is unusually sensitive to experimental conditions, requires the use of indolylmagnesium iodide in anisole at −5°. Under these conditions we have obtained tryptamine derivatives from 2-chloro-1-dimethylaminopropane and 1-chloro-2-diethylaminoethane, in approximately 20% yield. A discussion of the factors which affect the coupling reaction, together with a mechanistic interpretation, will be published separately.

Further examples of the coupling reaction are given in the Table. The identities of new compounds were confirmed by alternative syntheses. The tryptamines (II; $R^1 = PhCH_2$, $R^2 = H$; and $R^1 = Ph$, $R^2 = OMe$) were prepared, by way of the glyoxylamides (I), by the procedure of Speeter and Anthony.[5] The tryptamine homologue (IIIc) was prepared by reduction of the Mannich base (IIIb), obtained from 3-acetyl-2-phenylindole (IIIa). The latter was conveniently synthesised from 2-phenylindolylmagnesium iodide and acetyl chloride.

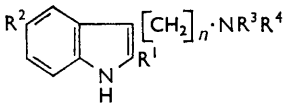
Extension of the coupling reaction to the synthesis of 3*H*-indoles from 3-methyl- or phenyl-indoles was unsuccessful. 3-Methylindolylmagnesium iodide, with 1-chloro-2-dimethylaminoethane, underwent *N*-substitution to afford a small quantity of 1-(2-dimethylaminoethyl)-3-methylindole, identified by comparison with material prepared from the alkylation of 3-methylindolylsodium.

The synthesis of 3-(4-dimethylaminobutyl)indole from *NN*-dimethylpyrrolidinium iodide or 1-bromo-4-di-

[1] C. R. Ganellin and H. F. Ridley, *Chem. and Ind.*, 1964, 1388, is considered as Part I.
[2] J. Klarer and F. Mietzsch, U.S.P., 1,793,176/1931.
[3] K. Eiter and O. Svierak, *Monatsh.*, 1952, **83**, 1453.
[4] A. Kalir and S. Szara, *J. Medicin. Chem.*, 1966, **9**, 341.
[5] M. E. Speeter and W. C. Anthony, *J. Amer. Chem. Soc.*, 1954, **76**, 6208.

methylaminobutane (as free amine or hydrobromide) was also investigated. The use of similar reagents for the alkylation of alkali metal derivatives of phthalimide [6] and diethylmalonate [7] has been reported. In the present study, however, neither reagent coupled with indolylmagnesium iodide in anisole.

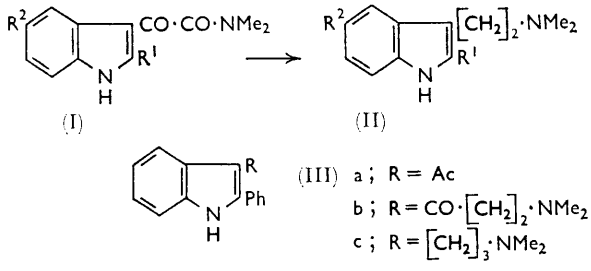
3-Aminoalkylindoles



R^1	R^2	n	R^3	R^4	Halogenoalkylamine reagent	Yield [a] (%)	M. p.[b]
H	H	2	H	H	Cl·$[CH_2]_2$·NH_2	10	247—249° [c]
					Br·$[CH_2]_2$·NH_2	4	
H	H	2	H	Me	Cl·$[CH_2]_2$·NHMe	14	178—179 [d]
H	H	2	Me	Me	Cl·$[CH_2]_2$·NMe_2,HCl	7 [e]	
					Cl·$[CH_2]_2$·NMe_2	25 [f]	
H	H	2	Et	Et	Cl·$[CH_2]_2$·NEt_2	19	89—90 [g]
Ph	OMe	2	Me	Me	Cl·$[CH_2]_2$·NMe_2	5	120—122 [h]
$PhCH_2$	H	2	Me	Me	Cl·$[CH_2]_2$·NMe_2	15	96—98 [h]
Ph	H	3	Me	Me	Cl·$[CH_2]_3$·NMe_2	39	101—103 [h]

[a] Calc. from the weight of amine isolated before crystallisation. [b] After crystallisation. [c] Hydrochloride (from propan-2-ol); lit., m. p. 248° (R. H. F. Manske, *J. Amer. Chem. Soc.*, 1929, **51**, 1202). [d] Hydrochloride (from ethanol–ether); lit., m. p. 180° (R. H. F. Manske, *Canad. J. Res.*, 1931, **5**, 592). [e] Together with 1-(2-dimethylaminoethyl)indole (3%). Yields determined by g.l.c. analysis. [f] See ref. 1. [g] Lit., m. p. 85—88° (ref. 17). [h] Mixed m. p. undepressed; for synthesis of material for comparison see Experimental section.

The reported [8] participation of iminium ions in the reactions of halogenoalkylamines with nucleophiles suggested the possibility of their involvement in the



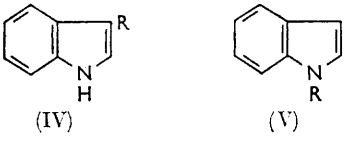
(I) (II)

(III) a; R = Ac
b; R = CO·$[CH_2]_2$·NMe_2
c; R = $[CH_2]_3$·NMe_2

above coupling reaction. The coupling between indolylmagnesium iodide and 2-chloro-1-dimethylaminopropane was selected for study since the latter forms an aziridinium ion which, with nucleophiles, may open in either of two ways to furnish isomeric products. Thus the composition of the product mixture indicates whether the aziridinium ion is involved at some stage of the reaction. The experiment was conducted in duplicate and the mixture of amines which resulted was analysed by g.l.c. and t.l.c. The four compounds detected were identified as the isomers (IVa), (IVb) (ratio 3 : 1), (Va) (trace), and (Vb) (trace) by chromatographic comparison with materials synthesised by alternative procedures.

3-(1-Dimethylamino-2-propyl)indole (IVa), the main product, isolated pure from the mixture, was identical with material prepared by reduction of the amide (IVc) obtained from indolylmagnesium iodide and 2-chloro-*NN*-dimethylpropionamide.

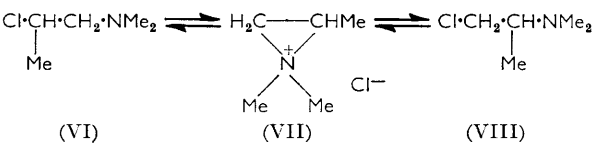
3-(2-Dimethylaminopropyl)indole (IVb), which has since been described,[4] was prepared by hydride reduction of the amino-ketone (IVe) in tetrahydrofuran. When the reduction was conducted in diethyl ether, only the carbinol (IVf) was obtained. The amino-ketone (IVe) was derived from 3-(2-chloropropionyl)indole (IVd); the latter was synthesised from indolylmagnesium iodide



(IV) (V)

a; R = CHMe·CH_2·NMe_2
b; R = CH_2·CHMe·NMe_2
c; R = CHMe·CO·NMe_2

d; R = CO·CHMe·Cl
e; R = CO·CHMe·NMe_2
f; R = CHOH·CHMe·NMe_2



(VI) (VII) (VIII)

and 2-chloropropionyl chloride in anisole [in contrast to the reported [4] formation of 1,3-bis-(2-chloropropionyl)-indole in diethyl ether–toluene].

1-(1-Dimethylamino-2-propyl)indole (Va) was synthesised by reduction of the amide (Vc) prepared from indolylsodium and 2-chloro-*NN*-dimethylpropionamide. 1-(2-Dimethylaminopropyl)indole (Vb) was obtained, together with the isomer (Va) [the ratio (Vb) : (Va) from duplicate experiments assessed by g.l.c. was *ca.* 5 : 1], from indolylsodium and 2-chloro-1-dimethylaminopropane and was readily isolated as its hydrochloride. Its structure was confirmed by the ^1H n.m.r. spectrum, which indicated the presence of indolic 2- and 3-protons, and the $ABCX_3$ system of the secondary *C*-methyl and CH_2·CH protons. Additional evidence was provided by comparing the ^1H n.m.r. spectra of the base and hydrochloride, since, when the side-chain nitrogen atom was protonated, the secondary methyl signal moved downfield by 23 cycles measured at infinite dilution in deuteriochloroform (see reference 9 for an interpretation of this effect in similarly constituted benzimidazole derivatives).

The formation of the products (Va) and (Vb) from the alkylation of indolylsodium indicates that the aziridinium ion (VII) participates in this reaction, but does not prove that it is the electrophilic agent. Since the ion (VII) may serve as an intermediate in an equilibrium between the secondary (VI) and primary (VIII) chlorides, this study does not show whether nucleophilic attack by the indole anion occurs on the ion

[6] M. S. Kharasch and C. F. Fuchs, *J. Org. Chem.*, 1944, **9**, 359.
[7] C. S. Marvel, W. H. Zartman, and O. D. Bluthardt, *J. Amer. Chem. Soc.*, 1927, **49**, 2299.
[8] E. M. Schultz and J. M. Sprague, *J. Amer. Chem. Soc.*, 1948, **70**, 48; J. F. Kerwin, G. E. Ullyot, R. C. Fuson, and C. L. Zirkle, *ibid.*, 1947, **69**, 2961 and references cited therein.
[9] A. F. Casy and J. Wright, *J. Chem. Soc.* (*C*), 1966, 1167.

(VII) or on the chlorides (VI) and (VIII).[10] The preponderance of the product (Vb), however, suggests that, in either case, the steric and inductive effects of the methyl group have favoured attack by the nucleophile at CH_2, rather than at CHMe, and is comparable with the results reported [9] for the alkylation of 2-benzylbenzimidazolylsodium. Alkylation of indolyl-lithium with 1-chloro-2-dimethylaminopropane has been reported [3] to yield compound (Vb), which was characterised as a picrate melting at 158°. This was probably a mixture of the isomers (Va and b), since our picrate of (Vb) has a higher melting point.

Participation of the aziridinium ion in the coupling reaction of the indole Grignard reagent is also indicated by the formation of isomeric products (IVa and b). In this instance, however, attack at the CHMe centre predominates [to yield (IVa)], which suggests that at least part of the product (IVa) arises from reaction with the secondary chloride (VI). That chloroalkanes would couple with the indole Grignard reagent under these conditions was confirmed by the formation of 3-n-butylindole from 1-chlorobutane. These results, together with the lack of reactivity of *NN*-dimethylpyrrolidinium iodide (a homologous iminium ion) towards the Grignard reagent, imply that there is insufficient evidence for iminium ions as the reactive species in this coupling reaction.

EXPERIMENTAL

Melting points were taken with an Electrothermal apparatus. Microanalyses are by M. J. Graham of these laboratories. Ultraviolet absorption spectra (ethanol) were recorded with a Beckman DK2 spectrophotometer. Infrared spectra were recorded with a Unicam SP 200 spectrometer, and ^1H n.m.r. spectra with a Varian A60A spectrometer. Sodium hydride refers to a 53·8% dispersion of sodium hydride in paraffin oil.

Gas chromatographic (g.l.c.) data were obtained with an F and M 720 instrument fitted with a katharometer detector and columns (2 m. × 5 mm.) of 10% Carbowax 20M, or 10% Silicone gum rubber SE 30, on 60/80 diatoport W. Helium was the carrier gas (60 ml. per min.) and column temperatures were programmed to increase from 100° at a fixed rate of 5 or 10° per min.

Thin-layer chromatography (t.l.c.) was carried out with layers of fluorescent silica gel (300 μ) type HF 254 (Merck AG).

Indole and 2-methyl-, 3-methyl-, and 2-phenyl-indole were obtained commercially. 2-Benzyl-,[11] 3-phenyl-,[12] and 5-methoxy-2-phenyl-indole [13] were prepared according to published procedures.

1-Amino-2-bromoethane hydrobromide, *NN*-dimethylpyrrolidinium iodide, and the hydrochlorides of 1-amino-2-chloroethane, 1-chloro-2-dimethylaminoethane, 2-chloro-1-dimethylaminopropane (dimethylaminoisopropyl chloride), and 1-chloro-3-dimethylaminopropane were obtained from commercial sources.

1-Chloro-2-methylaminoethane hydrochloride, prepared from 2-methylaminoethanol and thionyl chloride in benzene, had m. p. 88—90° (from propan-2-ol) (lit.,[14] 89—90°).

1-*Bromo*-4-*dimethylaminobutane Hydrobromide*.—1-Dimethylamino-4-phenoxybutane [15] (63 g, 0·33 mole) was heated in 47% aqueous hydrobromic acid (100 ml.) with continuous removal of phenol by distillation through a Vigreux fractionating column (16 × 1 in.). The distillation required 7 hr.; during this period more hydrobromic acid (225 ml.) was added to maintain the original volume of the reaction mixture. The residue was then diluted with water (100 ml.), boiled (charcoal), filtered, and evaporated. The residue gave the *hydrobromide* (53·6 g., 63%) as needles, m. p. 113—114° (from ethanol–ether) (Found: C, 27·9; H, 5·7; Br, 61·3; N, 5·3. $C_6H_{15}Br_2N$ requires C, 27·6; H, 5·8; Br, 61·2; N, 5·4%).

Liberation of Halogenoalkylamines.—The halogenoalkylamine salts were finely ground and suspended in benzene. Sufficient 40% sodium hydroxide was added, at 0° with stirring, to make the mixture alkaline (pH 8—9). Anhydrous potassium carbonate was then added until the aqueous layer of the mixture became semi-solid, and the benzene was decanted off. The residue was extracted four times with benzene, and the benzene solutions were combined and dried (KOH). The total volume of benzene used was *ca.* 40 ml. per 0·1 mole of amine salt and the drying time never exceeded 1 hr. Assay of the benzene solution by titration against standard 0·1N-perchloric acid in acetic acid (Oracet Blue) [16] showed that this procedure afforded at least 95% of the free amine.

Coupling of Indolylmagnesium Iodides with Halogenoalkylamines.—The compounds in the Table were prepared by carefully controlled procedure, exemplified by the method for 3-(2-diethylaminoethyl)indole.

Ethylmagnesium iodide [from ethyl iodide (31·2 g., 0·2 mole) and magnesium turnings (5·28 g., 0·2 mole)] was prepared in 100 ml. of dry anisole and the mixture was heated for 1 hr. at 50—60° in an atmosphere of nitrogen. It was then cooled to 10°, and indole (11·7 g., 0·1 mole) in dry anisole (50 ml.) was added; the temperature was maintained below 25°. The mixture was then heated at 50° for 45 min. (The yield of indole Grignard reagent was assessed from the volume of ethane evolved; it was generally 93—97%.) The resulting solution was cooled to −5° in a thermostatically controlled cold bath, and a freshly prepared solution of 1-chloro-2-diethylaminoethane (0·2 mole) in 85 ml. of dry benzene was added during 1 hr. with the temperature at −5° ± 1° throughout. The mixture was then stirred for 3 hr. at −5° (after this time efficient stirring was prevented by the precipitation of a sticky solid) and set aside at −5° for a further 5 hr. It then warmed to 20—25° during 8 hr.

The precipitate was broken up and the mixture was poured on to saturated aqueous ammonium chloride (500 ml.) and stirred for 30 min. The organic layer was separated, and the aqueous layer was extracted with ether. The organic solutions were combined and extracted three times with 10% hydrochloric acid. The extracts were

[10] J. Hine, 'Physical Organic Chemistry,' McGraw-Hill, 2nd edn., 1962, p. 146.
[11] G. R. Clemo and J. C. Seaton, *J. Chem. Soc.*, 1954, 2582.
[12] H. Dyrsting, B.P., 959,203/1964.
[13] C. Mentzer, D. Molho, and Y. Berguer, *Bull. Soc. chim. France*, 1950, 555.
[14] A. F. Nikolaev, M. E. Rozenberg, N. V. Daniel, and G. P. Tereshchenko, *Zhur. obshchei Khim.*, 1963, **33**, 391.
[15] E. R. Littmann and C. S. Marvel, *J. Amer. Chem. Soc.*, 1930, **52**, 287.
[16] A. H. Beckett and E. H. Tinley, 'Titration in Non-Aqueous Sovents,' British Drug Houses, Poole, Dorset, 1958, p. 19.

washed with ether, cooled to 0°, made alkaline with 40% sodium hydroxide, and extracted three times with ether. These extracts were dried ($CaSO_4$) and evaporated to afford 3-(2-diethylaminoethyl)indole as an oil (97% pure by g.l.c.) which solidified when seeded (4·2 g., 19%) and gave prisms, m. p. 89—90° [from light petroleum (b. p. 40—60°)] (lit.,[17] 85—88°) (Found: C, 78·0; H, 9·4; N, 12·9. Calc. for $C_{14}H_{20}N_2$: C, 77·7; H, 9·3; N, 12·95%).

2-Benzyl-3-(2-dimethylaminoethyl)indole (II; R^1 = $PhCH_2$, R^2 = H).—Oxalyl chloride (6·1 g., 0·048 mole) in dry ether (40 ml.) was added to a solution of 2-benzylindole (10 g., 0·048 mole) in ether (500 ml.) and the mixture was stirred at 20° for 2 hr. Dimethylamine (13·1 g., 0·29 mole) in ether (100 ml.) was then added and, after the mixture had been stirred for 2 hr., water (200 ml.) was added. The mixture was stirred for 1 hr., then filtered, and the solid residue gave *(2-benzylindol-3-yl)-NN-dimethylglyoxylamide* (8·1 g., 55%) as needles, m. p. 191—192° (from ethanol) (Found: C, 74·5; H, 5·8; N, 9·1. $C_{19}H_{18}N_2O_2$ requires C, 74·5; H, 5·9; N, 9·15%).

A suspension of the amide (8·0 g., 0·026 mole) in dry tetrahydrofuran (200 ml.) was added dropwise to lithium aluminium hydride (3·0 g., 0·079 mole) in tetrahydrofuran (200 ml.) and the mixture was heated under reflux for 3 hr., cooled, and poured carefully on to crushed ice. The organic layer was extracted with 5N-hydrochloric acid and the extract was basified with 40% sodium hydroxide. The product was isolated by extraction into ether and gave *2-benzyl-3-(2-dimethylaminoethyl)indole* (5·2 g., 71%) as needles, m. p. 98—99° [from light petroleum (b. p. 60—80°)] (Found: C, 82·2; H, 8·1; N, 10·0. $C_{19}H_{22}N_2$ requires C, 82·0; H, 8·0; N, 10·1%).

3-(2-Dimethylaminoethyl)-5-methoxy-2-phenylindole (II; R^1 = Ph, R^2 = OMe).—5-Methoxy-2-phenylindole (11·2 g., 0·05 mole) was converted by the same procedure into *(5-methoxy-2-phenylindole-3-yl)-NN-dimethylglyoxylamide*, (13·5 g., 83%) obtained as prisms, m. p. 258—260° [from dimethylformamide–ethanol (3 : 2)] (Found: C, 71·0; H, 5·6; N, 8·7. $C_{19}H_{18}N_2O_3$ requires C, 70·8; H, 5·6; N, 8·7%).

Reduction of the amide with lithium aluminium hydride in ether afforded *3-(2-dimethylaminoethyl)-5-methoxy-2-phenylindole* (6·3 g., 53%) as needles, m. p. 124—125° [from light petroleum (b. p. 80—100°) containing a few ml. of benzene] (Found: C, 77·7; H, 7·6; N, 9·6. $C_{19}H_{22}N_2O$ requires C, 77·5; H, 7·5; N, 9·5%).

3-(3-Dimethylaminopropyl)-2-phenylindole (IIIc).—Acetyl chloride (17·3 g., 0·22 mole) in dry benzene (80 ml.) was added to a solution of 2-phenylindolylmagnesium iodide [prepared from ethylmagnesium iodide (0·4 mole) and 2-phenylindole (0·2 mole)] in dry anisole (300 ml.) at −10° in an atmosphere of nitrogen. The mixture was stirred at −5° for 45 min., warmed to 20° overnight, and then poured on to saturated aqueous ammonium chloride. The precipitate was collected and extracted with hot methanol. The cooled methanolic solution deposited 3-acetyl-2-phenylindole (29·4 g., 62%) as needles, m. p. 220—221° (from methanol) (lit.,[18] 220—221°) (Found: C, 81·4; H, 5·5; N, 6·0. Calc. for $C_{16}H_{13}NO$: C, 81·7; H, 5·6; N, 5·95%), $\nu_{max.}$ (Nujol) 1610 (C=O) and 3200b (NH) $cm.^{-1}$. A similar preparative method has since been published.[19]

3-Acetyl-2-phenylindole (23·6 g., 0·1 mole), paraformaldehyde (4·5 g., 0·15 mole), and dimethylamine hydrochloride (8·15 g., 0·1 mole) were heated together in boiling ethanol (200 ml.) for 24 hr. The solvent was then evaporated off, water was added to the residue, and the mixture was filtered from unchanged 3-acetyl-2-phenylindole (8 g.). The aqueous filtrate was washed with ether and made alkaline at 0° with 40% sodium hydroxide. The precipitated *3-(2-dimethylaminopropionyl)-2-phenylindole* was collected and gave needles (10·8 g., 37%), m. p. 157—158° (from ethanol) (Found: C, 78·3; H, 6·9; N, 9·5. $C_{19}H_{20}N_2O$ requires C, 78·1; H, 6·9; N, 9·6%), $\nu_{max.}$ (Nujol) 1620 (C=O) $cm.^{-1}$; $\lambda_{max.}$ (EtOH) 252 and 304 mμ (log ε 4·31 and 4·13).

This amine (1·9 g., 0·0065 mole) in dry tetrahydrofuran (25 ml.) was added to lithium aluminium hydride (0·57 g., 0·015 mole) in tetrahydrofuran (25 ml.) and the mixture was heated under reflux for 3 hr., cooled, poured on to saturated aqueous ammonium chloride, and extracted with ether. The organic layer was dried ($MgSO_4$) and concentrated to afford *3-(3-dimethylaminopropyl)-2-phenylindole*, obtained as prisms (1·5 g., 83%), m. p. 103—105° (from methanol) (Found: C, 81·7; H, 7·8; N, 10·3. $C_{19}H_{22}N_2$ requires C, 82·0; H, 8·0; N, 10·1%); $\lambda_{max.}$ (EtOH) 306 mμ (log ε 4·29). This compound has since been described,[20] m. p. 104°.

Reaction of 3-Methylindolylmagnesium Iodide with 1-Chloro-2-dimethylaminoethane.— 3-Methylindolylmagnesium iodide (0·1 mole) reacted with 1-chloro-2-dimethylaminoethane (0·2 mole) according to the general procedure for coupling reactions. The described method for the isolation of amine-containing products afforded a viscous oil (3·4 g.) which was extracted with benzene. The extract was evaporated and the resulting oil (2·1 g.) was converted into an oxalate obtained as needles (0·9 g., 3%), m. p. 209—210° (decomp.) (from ethanol), identified as *1-(2-dimethylaminoethyl)-3-methylindole hydrogen oxalate* by comparison with an authentic sample (mixed m. p.) synthesised as follows. 3-Methylindole (13 g., 0·1 mole) and sodium hydride (4·5 g., 0·1 mole) were stirred in dry dimethylformamide (150 ml.) at 60° for 3 hr. 1-Chloro-2-dimethylaminoethane (0·2 mole) in benzene (90 ml.) was added and the mixture was stirred for 5 hr. at 80°, cooled, and diluted with water (100 ml.). The aqueous layer was separated and extracted with ether. The ethereal extracts and the benzene solution were combined and extracted with 2N-hydrochloric acid. The acidic extracts were made alkaline and the oily amine (14·6 g.) which precipitated was extracted into ether and then converted into the hydrogen oxalate (13·7 g., 47%), m. p. 213—215° (decomp.) (from ethanol) (Found: C, 61·8; H, 7·0; N, 9·5. $C_{15}H_{20}N_2O_4$ requires C, 61·6; H, 6·9; N, 9·6%). The free amines liberated from the two oxalate samples had identical infrared spectra.

The reaction between 3-phenylindolylmagnesium iodide (0·05 mole) and 1-chloro-2-dimethylaminoethane, conducted in a similar manner, afforded 0·5 g. of the amine-containing products as a viscous oil. The latter yielded an impure oxalate which, on examination by t.l.c., appeared to contain five components (detected by Dragendorff's reagent).

Reaction of Indolylmagnesium Iodide with 2-Chloro-1-dimethylaminopropane.—The hydrochloride of 2-chloro-1-dimethylaminopropane had m. p. 186—187° (lit.,[8]

[17] T. Nogradi, *Monatsh.*, 1957, **88**, 768.
[18] A. K. Kiang and F. G. Mann, *J. Chem. Soc.*, 1953, 594.
[19] G. Buchmann and D. Rossner, *J. prakt. Chem.*, 1964, (**4**) **25**, 117.
[20] M. Julia, R. Melamed, and R. Gombert, *Ann. Inst. Pasteur*, 1965, **109**, 343.

185—186°); its structure was confirmed by its ^{1}H n.m.r. spectrum (D_2O): τ 8·43 (doublet, C–CH_3), 7·02 [singlet, N(CH_3)$_2$], 6·6—6·4 (complex, CH_2N), and 5·8—5·2 (complex, C*H*Cl). The free amine in benzene, obtained from the hydrochloride by the procedure described, was homogeneous (g.l.c.). A portion was reconverted into the hydrochloride, m. p. 186—187°. A portion was also converted into the picrate, m. p. 99—101° (lit.,[8] 101—103°).

Indolylmagnesium iodide (0·1 mole) reacted with 2-chloro-1-dimethylaminopropane (0·2 mole) according to the general procedure described. The solid amine-containing product (4·6 g., 23%) contained four components, retention temperatures 229, 222, 210, and 199° (*ca.* 25 : 75 : <1 : <1), identified as (IVb), (IVa), (Vb), and (Va). The identification was confirmed by t.l.c. (methanol–silica gel); potassium iodoplatinate detected four spots, R_F 0—0·15, 0·15—0·25, 0·3, and 0·45 corresponding to compounds (IVb), (IVa), (Vb), and (Va), respectively.

Crystallisation of the amine mixture from light petroleum (b. p. 60—80°) afforded needles which, after three recrystallisations, furnished 0·4 g. of pure (t.l.c. and g.l.c.) material, m. p. 107—109°, identified as 3-(1-*dimethylamino*-2-*propyl*)*indole* (IVa) (Found: C, 77·0; H, 9·1; N, 14·0. $C_{13}H_{18}N_2$ requires C, 77·2; H, 9·0; N, 13·85%).

Confirmation of Identification of (IVa), (IVb), (Va), *and* (Vb). — 3-(1-*Dimethylamino*-2-*propyl*)*indole* (IVa). 2-Chloro-*NN*-dimethylpropionamide (15 g., 0·11 mole) in dry ether (50 ml.) was added to indolylmagnesium iodide (0·1 mole) in ether (200 ml.) at 20° and the ether was then distilled off. The residue was heated at 80—90° for 3 hr., cooled, and then stirred vigorously for 1 hr. with 5% acetic acid (200 ml.) and ether (200 ml.). The ethereal layer was washed successively with 10% aqueous sodium carbonate and water, dried ($MgSO_4$), and concentrated to afford 2-*indol*-3-*yl*-NN-*dimethylpropionamide* (IVc) (10·4 g., 48%), obtained as needles, m. p. 124—125° (from ethyl acetate) (Found: C, 72·0; H, 7·6; N, 12·7. $C_{13}H_{16}N_2O$ requires C, 72·2; H, 7·5; N, 12·95%).

The amide (IVc) (3·24 g., 0·015 mole) was added as a suspension in dry ether (50 ml.) to lithium aluminium hydride (0·39 g., 0·01 mole) in ether (30 ml.) and the mixture was heated under reflux for 4 hr., then cooled, and poured on to saturated aqueous ammonium chloride. The ethereal layer was separated and extracted with dilute hydrochloric acid. The acidic extract was made alkaline and the oily amine (1·9 g.) which precipitated was isolated by extraction in ether. Crystallisation of the amine from light petroleum (b. p. 60—80°) afforded 3-(1-dimethylamino-2-propyl)-indole (1 g., 33%), m. p. and mixed m. p. with the material obtained from the Grignard reaction 107—109°.

3-(2-*Dimethylaminopropyl*)*indole* (IVb). 2-Chloropropionyl chloride (27·2 g., 0·22 mole) in dry anisole (25 ml.) was added during 40 min. to indolylmagnesium iodide (0·2 mole) in anisole (200 ml.) at 0—5°; the reaction rate was controlled by cooling. The mixture warmed to 20° overnight and was then poured on to aqueous ammonium chloride. The organic layer was separated, dried ($MgSO_4$), and concentrated to afford 3-(2-*chloropropionyl*)*indole* (IVd), obtained as needles (5·7 g., 14%), m. p. 192—193° (from propan-2-ol). Recrystallisation from ethyl methyl ketone increased the m. p. to 194—195° (Found: C, 63·5; H, 4·7; N, 6·5. $C_{11}H_{10}ClNO$ requires C, 63·6; H, 4·85; N, 6·7%); $\nu_{max.}$ (Nujol) 1635 (C=O) and 3220 (NH) cm.$^{-1}$.

3-(2-Chloropropionyl)indole (2·4 g.) and dimethylamine (2 ml. of a 33% ethanolic solution) were stirred together for 6 hr. at 25° and the mixture was then diluted with water. The precipitate of 3-(2-dimethylaminopropionyl)indole (IVe) was collected and gave prisms (1·6 g., 67%), m. p. 186—188° (from propan-2-ol) (lit.,[4] 192—193°) (Found: C, 72·2; H, 7·5; N, 12·8. Calc. for $C_{13}H_{16}N_2O$: C, 72·2; H, 7·5; N, 12·95%), $\nu_{max.}$ (Nujol) 1645 (C=O) and 3160 (NH) cm.$^{-1}$.

The amino-ketone (IVe) (1·3 g., 0·006 mole) was added as a suspension in tetrahydrofuran (20 ml.) to lithium aluminium hydride (0·76 g., 0·02 mole) in tetrahydrofuran (20 ml.) and the mixture was heated under reflux for 2·5 hr., cooled, poured into aqueous ammonium chloride, and extracted with ether. The organic layer was dried ($MgSO_4$) and concentrated, and the oily residue was chromatographed on a column of alumina [elution with benzene–light petroleum (2 : 1)]. The product gave 3-(2-*dimethylaminopropyl*)*indole* (0·35 g., 20%) as prisms, m. p. 58—60° (from pentane at −5°) (Found: C, 76·9; H, 9·0; N, 13·65. $C_{13}H_{18}N_2$ requires C, 77·2; H, 9·0; N, 13·85%).

When this reduction was conducted in diethyl ether, the sole product was 3-(2-*dimethylamino*-1-*hydroxypropyl*)-*indole* (IVf) (91%), obtained as needles, m. p. 110—111° (from benzene–light petroleum) (Found: C, 71·2; H, 8·3; N, 12·7. $C_{13}H_{18}N_2O$ requires C, 71·5; H, 8·3; N, 12·8%).

1-(1-*Dimethylamino*-2-*propyl*)*indole* (Va).—2-Chloro-*NN*-dimethylpropionamide (15 g., 0·11 mole) in dry dimethylformamide (50 ml.) was added, during 10 min., to indolylsodium (0·1 mole, from indole and sodium hydride) in dimethylformamide (200 ml.) at 20° in an atmosphere of nitrogen. The mixture was stirred for 3·5 hr. at 50—60°, cooled, diluted with 2% hydrochloric acid (200 ml.), and extracted with ether. The ether extract was dried ($MgSO_4$) and concentrated, and the residue was heated *in vacuo* to remove unchanged indole (1·2 g., b. p. 65—68°/0·1 mm.). The remaining oil (17 g.), 2-*indol*-1-*yl*-NN-*dimethylpropionamide* (Vc), could not be distilled and was used without further purification. It was characterised as a 1,3,5-*trinitrobenzene adduct*, yellow needles, m. p. 107—109° (from ethanol) (Found: C, 53·3; H, 4·6; N, 16·0. $C_{19}H_{19}N_5O_7$ requires C, 53·1; H, 4·5; N, 16·3%).

The amide (Vc) (2·1 g.) was heated with lithium aluminium hydride (0·26 g.) in refluxing ether (50 ml.) for 4 hr. 1-(1-*Dimethylamino*-2-*propyl*)*indole* was isolated from the reaction mixture by extraction into hydrochloric acid and neutralisation of the extract. It was obtained as a mobile pale yellow oil (1·3 g., 65%) and characterised as the *hydrogen oxalate*, needles from propan-2-ol, m. p. 133—135° (Found: C, 61·6; H, 7·0; N, 9·4. $C_{15}H_{20}N_2O_4$ requires C, 61·6; H, 6·9; N, 9·6%). The amine hydrochloride was obtained as an oil which could not be induced to solidify.

1-(2-*Dimethylaminopropyl*)*indole* (Vb).—Indole (17·5 g., 0·15 mole) and sodium hydride (6·6 g., 0·15 mole) were stirred for 2 hr. in dry anisole (225 ml.) at 50° in an atmosphere of nitrogen. The mixture, which contained indolylsodium as a solid suspension, was cooled to 10° and 2-chloro-1-dimethylaminopropane (0·3 mole) in dry benzene (110 ml.) was added. The mixture was then stirred for 4 hr. at 80°, cooled, and extracted with dilute hydrochloric acid (3 × 50 ml.). The combined acidic extracts, were washed with ether, made alkaline, and extracted with ether. The dried ($MgSO_4$) ethereal extract was concentrated and the resulting oil (22·3 g.) was distilled *in vacuo* to afford a mixture of the isomeric amines (Va) and (Vb) (16 g., 53%), b. p. 100—102°/0·2 mm., as a mobile oil (Found: C, 77·3; H, 9·1; N, 13·6. Calc for $C_{13}H_{18}N_2$: C, 77·2; H, 9·0; N, 13·85%). The latter formed a mixture of picrates,

m. p. 152—153°. The amine mixture contained only two components (g.l.c. or t.l.c.) in the ratio 5 : 1 (g.l.c.); the minor constituent was identified as the amine (Va) by comparison of retention temperatures with that of authentic material. The identification was confirmed by separation of a small portion of the mixture into its constituents by preparative g.l.c., and comparison of the infrared spectra with the spectrum of the authentic material.

A portion of the amine mixture in ethyl acetate was treated with hydrogen chloride in propan-2-ol; 1-(2-*dimethylaminopropyl*)*indole hydrochloride*, which precipitated as a solid, was collected and gave prisms, m. p. 186—188° (from ethanol) (Found: C, 65·5; H, 8·0; Cl, 14·6; N, 11·8. $C_{13}H_{19}ClN_2$ requires C, 65·4; H, 8·0; Cl, 14·85; N, 11·7%), τ ($CDCl_3$) 8·75 (doublet, J = 7 c./sec., C–CH_3), 7·26 [singlet, N(CH_3)$_2$], 6·6—6·1 (complex, CH), 5·95—4·75 (octet, CH_2), 3·47 (doublet, J = 3·3 c./sec., indolic 3-proton), 2·92 (doublet, J = 3·3 c./sec., indolic 2-proton), and 2·85—2·25 (multiplet, aromatic H). Integration agreed with the assigned numbers of protons.

The free amine, liberated from the hydrochloride, was pure (g.l.c.) and was identified (g.l.c. and infrared spectrum) as the major component of the amine mixture; τ ($CDCl_3$) corresponding to the assignments of the hydrochloride, 9·12, 7·69, 7·25—6·65, 6·35—5·5, 3·51, 2·92, and 2·83—2·25. The signal from the indolic 3-proton appeared as a quartet due to coupling with the 2- and 7-protons [21] ($J_{2,3}$ = 3·3, $J_{3,7}$ = 0·7 c./sec.).

The picrate, prepared from the amine, was obtained as yellow needles, m. p. 166—167° (from ethanol) (lit.,[3] 158°) (Found: C, 50·7; H, 5·1; N, 15·8. $C_{19}H_{21}N_5O_7,H_2O$ requires C, 50·8; H, 5·2; N, 15·6%).

Reaction of Indolylmagnesium Iodide with 1-*Chlorobutane*. —Indolylmagnesium iodide (0·1 mole) reacted with 1-chlorobutane (18·4 g., 0·2 mole, in 85 ml. of dry benzene) according to the general procedure described. The reaction mixture was poured on to saturated ammonium chloride solution and stirred for 10 min. The organic layer was separated off and the aqueous layer was extracted with ether. The combined organic solutions were dried ($MgSO_4$) and distilled to give indole (6·5 g.), b. p. 82—90°/0·5 mm., and 3-n-butylindole (7·3 g., 42%), b. p. 120°/0·3 mm. (Found: C, 83·1; H, 8·7; N, 8·0. Calc. for $C_{12}H_{15}N$: C, 83·2; H, 8·7; N, 8·1%), $\nu_{max.}$ (liquid) 3450 (NH) cm.$^{-1}$, τ ($CDCl_3$) 9·09 (complex triplet, CH_3), 8·9—8·0 (complex, CH_2·CH_2), 7·28 (triplet, :C–CH_2), 3·34 (multiplet, indolic 2-proton), 3·1—2·2 (complex, aromatic H) and no evidence of a signal from an indolic 3-proton. The picrate had m. p. 112—114° (from ethanol) (lit.,[22] 114°).

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