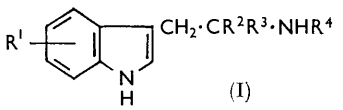
1322. *Studies in the Indole Series. Part II.*[1] *Indolylalkylhydroxylamines*

By A. Cohen and B. Heath-Brown

A series of indolylalkylhydroxylamines (II) has been prepared by suitable reduction of nitroalkylindoles. Some cases of hydrogenation of such nitro-compounds are discussed, in which the indole nucleus is reduced with retention of the nitro-group.

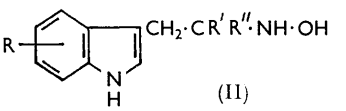
Our studies[1] of the synthesis and pharmacological properties of the indolylalkylamines (I) have been extended to the indolylalkylhydroxylamines (II) which form the subject of this communication; these compounds have been investigated in the search for novel analogues of indolylalkylamines with pharmacological properties of potential clinical use.

In recent years, interest in 5-hydroxytryptamine (serotonin), monoamineoxidase inhibitors, and antidepressant drugs has stimulated much work on substituted tryptamines, and this has been reported extensively in the chemical, biochemical, and pharmacological literature. By constrast, no studies of the corresponding *N*-substituted hydroxylamine derivatives had been published until quite recently, the nearest approach to this series of compounds being represented by a hydroxyamino-ester (II; R = H, R′ = R″ = CO_2Et).[2,3]



(I)

R^1 = H, Me, Cl, MeO, etc;
R^2, R^3, R^4 = H or alkyl



(II)

R = H, Me, Cl, or MeO;
R′, R″ = H or alkyl.

A recent Paper,[4a] which appeared after the completion of our work, reports the preparation of 1-(indol-3-yl)-2-hydroxyaminopropane, isolated as an acid oxalate, m. p. 180—181°, but the analytical data are not concordant. Salts of this hydroxylamine derivative (Table, compound 2) are described in the Experimental section of the present Paper.

In the benzene series, hydroxyamino-analogues of the substituted 2-phenylethylamines have also received some attention. Thus, reduction of 1-(2,4-dichlorophenyl)-2-nitropropene with lithium aluminium hydride yielded *N*-(α-methyl-2,4-dichlorophenethyl)-hydroxylamine, a compound with marked anorectic but little stimulant effect,[5] and the comparative central and autonomic effects of 2-phenylisopropylhydroxylamine, its *O*-methyl ether, and the parent amine, amphetamine, have been examined.[4b]

Some of the indolylalkylhydroxylamines now described for the first time have been examined by our colleagues, Drs. Lessin, Long, and Parkes, who will report elsewhere on the metabolic conversion of these compounds into the corresponding amines, which they resemble closely in pharmacological effects.

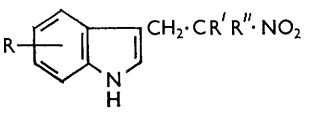
Of several methods previously reported for making *N*-alkylhydroxylamines, only three appear to be of general application. These are (a) reduction of oximes catalytically[6,7] or by diborane,[8] (b) reduction of nitro-olefins by the reversed lithium aluminium hydride

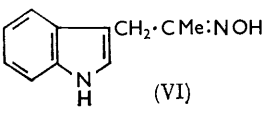
[1] Part I, B. Heath-Brown and P. G. Philpott, preceding Paper.
[2] D. I. Weissblat and D. A. Lyttle, *J. Amer. Chem. Soc.*, 1949, **71**, 3079.
[3] M. Masui and C. Yijima, *J.*, 1963, 1101.
[4] F. Benington, R. D. Morin, and L. C. Clark, (*a*) *J. Medicin. Chem.*, 1965, **8**, 100; (*b*) *Nature*, 1964, **202**, 813.
[5] M. W. Goldberg and M. Müller, U.S.P. 3,118,933/1964.
[6] G. Vavon and Krajcinovic, *Bull. Soc. chim. France*, 1928, [4], **43**, 231; E. Müller, D. Fries, and H. Metzger, *Chem. Ber.*, 1955, **88**, 1891.
[7] R. T. Gilsdorf and F. F. Nord, *J. Amer. Chem. Soc.*, 1952, **74**, 1837.
[8] H. Feuer and B. F. Vincent, *J. Amer. Chem. Soc.*, 1962, **84**, 3771.

procedure,[7] (c) reduction of nitro-compounds by electrochemical methods,[3,9] and (d) reduction of nitro-compounds with zinc and ammonium chloride.[10]

The wide applicability of the last method rendered it very suitable for the synthesis of the compounds in which we were interested. The precursor nitro-compounds were readily available by reaction of the appropriate gramine derivatives with nitroalkanes,[1] and reduction of each of the three types (III), (IV), and (V) (R = H, Me, Cl, or MeO) gave the corresponding hydroxylamines, with yields up to 76% in some cases. The particular value of this

(III) $R' = R'' = H$
(IV) $R' = H, R'' = Me$
(V) $R' = R'' = Me$





(VI)

method is especially seen in the synthesis of compounds possessing a fully substituted carbon atom adjacent to the hydroxyamino-group which cannot be prepared by methods (a) or (b) (cf. II; R′ = R″ = Me). Method (a) was used in one case only when partial

Indolylalkylhydroxylamines (II)*

No.	R	R′	R″	M. p.	Solvent	Yield (%)
1	H	H	H	113—115°	C_6H_6	46 (*a*)
2	H	H	Me	68	,,	(i) 74·5 (*b*) (*c*) (ii) 49·5 (*d*)
3	H	H	Et	76—78	BuOH–pet. (1 : 8)	76 (*e*)
4	H	Me	Me	124—126	C_6H_6	76 (*f*) (*g*)
5	H	$-[CH_2]_5-$		164—165	,,	10 (*h*) (*i*)
6	6-Me	Me	Me	167—169	EtOH	58
7	6-MeO	H	Me	—	— (*j*)	57
8	5-MeO	Me	Me	162—163	EtOH	68
9	5-Cl	H	Me	119—120	C_6H_6	68
10	5-Cl	Me	Me	139—140	,,	65

	Found (%)				Required (%)		
No.	C	H	N	Formula	C	H	N
1	68·4	7·2	—	$C_{10}H_{12}N_2O$	68·2	6·9	—
2	76·1	7·5	10·3	$C_{11}H_{14}N_2O,C_6H_6$	76·0	7·5	10·4
3	70·9	7·7	13·6	$C_{12}H_{16}N_2O$	70·6	7·9	13·7
4	70·7	8·1	—	$C_{12}H_{16}N_2O$	70·6	7·9	—
5	74·0	8·3	—	$C_{15}H_{20}N_2O$	73·7	8·3	—
6	71·9	8·5	12·9	$C_{13}H_{18}N_2O$	71·5	8·3	12·8
7	65·6	7·2	12·2	$C_{12}H_{16}N_2O_2$	65·4	7·3	12·7
8	66·3	7·6	11·7	$C_{13}H_{18}N_2O_2$	66·6	7·8	12·0
9	58·6	6·0	12·3	$C_{11}H_{13}ClN_2O$	58·8	5·8	12·5
10	60·4	6·6	11·7	$C_{12}H_{15}ClN_2O$	60·4	6·3	11·7

* The hydroxylamines were prepared by the general method described; a slightly higher proportion of alcohol was used occasionally to achieve solution. Compound 2 was also made by hydrogenation of the oxime (VI). (*a*) A neutral by-product was indol-3-ylacetaldoxime (VI), m. p. 149—150·5° (from benzene), Ahmed, Eelnurme, and Spenser, *Canad. J. Chem.*, 1960, **38**, 2523, give 140—141°; Coker, Kohlhase, Martens, Rogers, and Allan, *J. Org. Chem.*, 1962, **27**, 3201, report 140—142° (Found: N, 16·6. Calc. for $C_{10}H_{10}N_2O$: N, 16·1%). (*b*) Yield from nitro-compound. The product contained benzene of crystallisation. (*c*) For salts of this base see Experimental section. (*d*) Yield from oxime. (*e*) The *maleate* formed yellowish crystals from ethanol, m. p. 133—134° (Found: C, 60·0; H, 6·3; N, 8·6. $C_{16}H_{20}N_2O_5$ requires C, 60·0; H, 6·3; N, 8·7%). (*f*) The *maleate* formed yellowish crystals from ethanol, m. p. 137—138° (Found: C, 59·8; H, 6·7; N, 8·8%). (*g*) The *hydrochloride* formed pinkish crystals from 2N-hydrochloric acid, m. p. 170—172° (Found: Cl, 14·8; N, 11·6; O, 6·8. $C_{12}H_{16}N_2O$,HCl requires Cl, 14·7; N, 11·6; O, 6·7%). (*h*) The low yield was due to the insolubility of the starting material, over 50% of which was recovered. A clear solution could not be obtained under the general conditions despite considerable dilution with ethanol. (*i*) The *methanesulphonate* crystallised from ethanol–ether, m. p. 202—203° (Found: C, 56·8; H, 7·0. $C_{16}H_{24}N_2O_4S$ requires C, 56·5; H, 7·1%). (*j*) This material could not be crystallised. It distilled at 150° (air-bath)/10^{-3} mm. as a viscous syrup.

[9] M. W. Leeds and G. B. L. Smith, *J. Electrochem. Soc.*, 1951, **98**, 129; A. I. Ryer and G. B. L. Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 5675.
[10] M. Lesbre, " Traité de Chimie Organique," Masson, Paris, 1948, vol. 15, p. 600.

catalytic reduction of the oxime (VI) gave the hydroxylamine (II; R = R′ = H, R″ = Me), identical with that made by method (d).

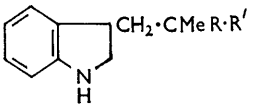
The indolylalkylhydroxylamines (Table) were generally stable crystalline solids; exceptions were compound 7 which was a distillable gum, and compound 2 which was crystalline only when combined with one mole of benzene. All the hydroxylamines were moderately strong bases soluble in 2N-acetic acid, and, characteristically, they reduced cold alkaline silver nitrate instantaneously. Catalytic reduction resulted in the absorption of two equivalents of hydrogen and formation of the primary amine.

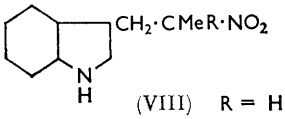
Interesting results were obtained in attempts to make the indolylalkylhydroxylamines by partial catalytic reduction of the nitroalkylindoles. Thus, when 3-2′-nitropropylindole (IV; R = H) was hydrogenated in methanolic hydrochloric acid in presence of platinum, the product was not the expected hydroxylamine, although the calculated uptake of hydrogen was observed. Instead, two new bases, A and B, were isolated in both of which the nitro-group was still present, as shown by analysis and by the strong infrared band near 1550 cm.$^{-1}$.

Confirmation of the presence of the nitro-group in base A was obtained by a zinc–ammonium chloride reduction, which yielded a hydroxylamine (IX), the infrared spectrum of which no longer showed the band at 1550 cm.$^{-1}$. More vigorous reduction with Raney nickel and hydrogen yielded the strongly basic amine (XI), a dihydro-derivative of α-methyltryptamine.

Base A was soluble in 2N-hydrochloric acid, but insoluble in acetic acid; it had appreciable absorption in the ultraviolet, but this was quite different from that of the starting material, and was more like that reported for 2-methylindoline.[11] In aqueous acid the absorption was changed significantly, the main bands at 243·5 and 296 mμ being replaced by several bands of low intensity in the 254—266 mμ region. Further investigation showed that the absorption was almost identical with that of indoline itself, both in neutral and in acid solutions. It was therefore concluded that base A was 3-2′-nitropropylindoline (VII). It readily formed a crystalline hydrochloride in good yield, indicating the probable formation of a single racemate. For the purposes of this comparison, indole was hydrogenated in methanolic hydrogen chloride in presence of platinum; indoline was obtained in 52% yield.

(VII) R = H, R′ = NO_2
(IX) R = H, R′ = NH·OH
(XI) R = H, R′ = NH_2
(XII) R = Me, R′ = NO_2





(VIII) R = H
(X) R = Me

Base B was soluble in 2N-acetic acid. Its ultraviolet spectrum showed practically no absorption above 206 mμ, and the infrared spectrum showed almost complete absence of aromatic bands. The microanalysis corresponded to $C_{11}H_{20}N_2O_2$, in agreement with that of a 3-2′-nitropropyloctahydroindole (VIII). Since it gave no solid derivatives, it seems likely that it was a mixture of racemates.

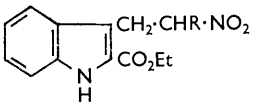
Similar results were obtained in reducing the homologue (V; R = H). No hydroxylamine derivative was formed but the reaction yielded two bases, C and D, whose properties were analogous to those of bases A and B. Base C was evidently 3-(2-methyl-2-nitropropyl)indoline (XII), while base D was a mixture of the racemates of 3-(2-methyl-2-nitropropyl)octahydroindole (X).

When the above hydrogenations were continued for a prolonged period there was still no reduction of the nitro-group, but the proportion of octahydroindole derivative was increased.

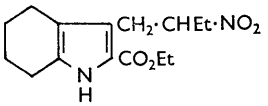
The survival of a nitro-group in catalytic reductions of this kind is not unprecedented.

[11] H. Kondo and H. Katsura, *Ber.*, 1940, **73**, 1426.

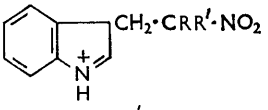
Ethyl 3-2′-nitrobutylindole-2-carboxylate (XIII) was hydrogenated by Young and Snyder [12] who found that, in acetic acid in presence of palladium–charcoal, reduction of the aromatic ring occurred while the nitro-group remained intact. The product was shown to have the structure (XIV). The failure to reduce the nitro-group was thought to be due to a steric effect since similar reduction of the lower homologue (XV) proceeded normally.



(XIII) R = Et
(XV) R = Me



(XIV)



(XVI) R,R′ = H or Me

A steric effect similar to that suggested by Young and Snyder cannot be advanced in the present case as a cause for the non-reduction of the nitro-group. The formation of the indolines may possibly occur through the readily reducible indoleninium ion (XVI) which could be produced in small quantity in the presence of the methanolic hydrogen chloride.

Experimental

Solvents were as in Part I.[1] Spectra were determined with the same instruments as in Part I.[1] Ultraviolet spectra are for ethanol solutions, and infrared spectra for liquid films.

Thin-layer chromatograms with alkaline Silicagel G (Merck) were run at 20° in tanks containing a mixture of 85% benzene and 15% methanol, and sprayed with 0·2% permanganate followed, if necessary, by exposure to iodine vapour. Hydroxylamines could also be detected by spraying with ammoniacal silver nitrate solution.

Indol-3-ylacetone Oxime.—Indol-3-ylacetone (17·3 g., 0·1 mole), hydroxylamine hydrochloride (6·9 g., 0·1 mole), and dry pyridine (100 ml.) were stirred for 16 hr. in a nitrogen atmosphere. The solution was evaporated *in vacuo* at 50°, and an ether extract of the residue was washed with 2N-hydrochloric acid, aqueous sodium hydrogen carbonate solution, and water. The dried ether yielded a gum (20 g.) which gave the *oxime* (9·3 g., 49·4%), m. p. 110—113° (from benzene). A recrystallised sample had m. p. 115—116°; the mixed m. p. with indol-3-ylacetone was 85—90° (Found: C, 70·4; H, 6·4; N, 14·6. $C_{11}H_{12}N_2O$ requires C, 70·2; H, 6·4; N, 14·9%).

3-(2-*Hydroxyaminopropyl*)*indole.*—(a) *General method.* 3-2′-Nitropropylindole (173·5 g., 0·85 mole) was stirred in ethanol (1200 ml.) and water (600 ml.), to give a clear solution, and ammonium chloride (52·2 g., 1·15 × 0·85 mole) was added. With continued stirring at 40° ± 5°, 80% zinc dust (139 g., 2 × 0·85 mole) was added in small portions during 45—60 min. with cooling as necessary. Stirring was continued for a further 1 hr. at 40°. The cooled mixture was filtered, the inorganic material was washed repeatedly with ethanol, and the combined filtrates were evaporated *in vacuo*. The residue was shaken with ether and water, and the ether layer was extracted several times with 2N-hydrochloric acid. The acid layer was then made alkaline with ammonia and extracted with ether, and the ether was washed with water, dried, and evaporated, giving the crude base (150 g.). Recrystallisation from benzene (300 ml.) yielded crystals of the pure *hydroxylamine*, m. p. *ca.* 68°. The product was washed with a little benzene followed by light petroleum, and dried *in vacuo* at 20°. The crystals (170 g., 74·5%) contained one mole of benzene of crystallisation [Found (after drying for ½ hr. at 20°/0·1 mm.): C, 76·1; H, 7·5; N, 10·3%; Equiv., 269·5. $C_{11}H_{14}N_2O,C_6H_6$ requires C, 76·0; H, 7·5; N, 10·4%; Equiv., 268·2].

The crystals were moderately stable in a closed container, but developed a slight smell of benzene after a few days. In an open vessel most of the benzene was lost and the crystals became amorphous. The crystalline form was immediately restored by recrystallisation from fresh solvent. The base could not be recrystallised from any other solvent. An alcoholic solution reduced ammoniacal silver nitrate instantaneously at 20°.

(*b*) Indol-3-ylacetone oxime (8·2 g., 0·0435 mole) in ethanol (150 ml.) containing one equivalent of hydrogen chloride was added to prereduced platinum oxide (0·4 g.) suspended in ethanol

[12] D. V. Young and H. R. Snyder, *J. Amer. Chem. Soc.*, 1961, **83**, 3160.

(30 ml.). The mixture was shaken with hydrogen until two equivalents had been absorbed (1040 ml. in 8 hr. at 20°). The green solution was filtered and evaporated *in vacuo*, and the residue was treated with water and ether, after which the ether layer was extracted with 2N-hydrochloric acid. The combined aqueous layers were made alkaline with aqueous sodium hydrogen carbonate solution and extracted with ether. The dried ether yielded a residue (7·0 g.) which was distilled (4·1 g., b. p. 115°/10^{-5} mm.) (49·5%) and recrystallised from benzene, giving a product, m. p. about 68°, identical with that made by method (*a*). The *oxalate* formed crystals, m. p. 182—183° (from very concentrated ethanolic solution) (Found: C, 55·6; H, 5·9. $C_{13}H_{16}N_2O_5$ requires C, 55·7; H, 5·75%). The *maleate*, made similarly, formed yellowish crystals, m. p. 122—124° (Found: C, 58·7; H, 5·7. $C_{15}H_{18}N_2O_5$ requires C, 58·8; H, 5·9%).

Hydrogenations of 3-2′-*Nitropropylindole.*—(*a*) A solution of the nitro-compound (15·3 g., 0·075 mole) in methanol (150 ml.) and concentrated hydrochloric acid (6·3 ml., 1 equiv.) was added to prereduced platinum oxide (500 mg.) in methanol (20 ml.). The mixture was then shaken in a hydrogen atmosphere (1 atm./20°) until 3·6 l. (4 equiv.) had been absorbed, which took 42 hr. The catalyst was filtered off, the filtrate evaporated *in vacuo*, and the residue shaken with excess ammonia and ether. The ether was extracted successively with 2N-acetic acid (5 times), 2N-hydrochloric acid (5 times), sodium hydrogen carbonate solution, and water. After drying, it yielded starting material (2·6 g., 17%).

The acetic acid extract was treated with ammonia and ether, and yielded a strong base, b. p. 84°/10^{-5} mm., 106—107°/0·15 mm., n_D^{20} 1·5023 (1·84 g., 12%). It formed a colourless oil which was easily soluble in 2N-acetic acid and reacted exothermically with acetic anhydride; it did not reduce silver nitrate solution. $\nu_{max.}$ 3300 (NH, low intensity), 1550 cm.$^{-1}$ (NO_2), practically no aromatic bands, $\lambda_{max.}$ 203·8, 283·3, $\lambda_{min.}$ 271·7 (inflexion) 290·3 mμ (log ε 3·73, 1·81, 1·79, and 1·79). This product was 3-2′-*nitropropyloctahydroindole* (Found: C, 62·2; H, 9·5; N, 13·1. $C_{11}H_{20}N_2O_2$ requires C, 62·2; H, 9·5; N, 13·2%).

The hydrochloric acid extract similarly yielded a weaker base, b. p. 100°/10^{-5} mm., n_D^{20} 1·5598 (6·0 g., 39%). This formed a yellowish oil, insoluble in 2N-acetic acid but soluble in stronger acids; it became hot on mixing with acetic anhydride. $\nu_{max.}$ 3420 (NH), 1550 (NO_2), 745 cm.$^{-1}$ (1,2-substituted benzene) [for the starting material, $\nu_{max.}$ 3440 (NH), 1545 (NO_2), 735 cm.$^{-1}$ (1,2-substituted benzene)], $\lambda_{max.}$ 206, 243·5, 296, $\lambda_{min.}$ 225, 271 mμ (log ε 4·41, 3·84, 3·39, 3·60, and 2·98). This product was 3-2′-*nitropropylindoline* (Found: C, 63·6; H, 6·8. $C_{11}H_{14}N_2O_2$ requires C, 64·1; H, 6·8%).

The *hydrochloride* formed crystals, m. p. 165—166° (88%) (Found: C, 54·6; H, 6·5; Cl, 15·1; N, 11·4. $C_{11}H_{14}N_2O_2$,HCl requires C, 54·4; H, 6·2; Cl, 14·6; N, 11·5%), $\lambda_{max.}$ (in N/100-HCl) 204, 254·5, 260, 266·5, $\lambda_{min.}$ 241·5, 256·5, 264 mμ (log ε 4·11, 2·60, 2·72, 2·72, 2·37, 2·59, and 2·45).

(*b*) The above hydrogenation was repeated using 3-2′-nitropropylindole (13·5 g., 0·066 mole), but the time was increased to 5 days, after which 7 l. of hydrogen had been absorbed (Calc. for 8 equiv.: 6·5 l.). The mixture was worked up as before, and yielded starting material (1·7 g., 12%), 3-2′-nitropropylindoline (0·4 g., 3%), and 3-2′-nitropropyloctahydroindole (3·8 g., 27%). When indole was hydrogenated under similar conditions, two equivalents of hydrogen were absorbed in 7 hr. Indoline (52%) was obtained, b. p. 107—109°/14 mm., n_D^{20} 1·5927, $\lambda_{max.}$ 207, 242, 292·5, $\lambda_{min.}$ 222·5, 271 mμ (log ε 4·31, 3·82, 3·35, 3·50, and 2·99), $\lambda_{max.}$ (in N/100-HCl) 205·5, 255·5, 261, 267·5, $\lambda_{min.}$ 230·5, 257, 265 mμ (log ε 3·90, 2·65, 2·81, 2·82, 1·58, 2·64, and 2·49).

3-(2-*Hydroxyaminopropyl*)*indoline.*—3-2′-Nitropropylindoline hydrochloride (1·48 g., 0·006 mole), in ethanol (9 ml.) and water (4·5 ml.), was treated with a solution of sodium (0·14 g., 0·006 mole) in ethanol (2—3 ml.), and the solution was reduced with ammonium chloride (0·37 g.) and zinc dust (1 g.) as already described. The filtered solution was evaporated *in vacuo*, and the residue digested with 2N-acetic acid and ether. Evaporation of the ether yielded the starting base (0·4 g.). The acetic acid was treated with ammonia and ether, and yielded a gum (0·2 g.) which was considerably more basic than the starting material. The *hydroxylamine* crystallised in sticky nodules from benzene–light petroleum, and melted below 50° (unsharp). It dissolved easily in 2N-acetic acid and reduced ammoniacal silver nitrate solution immediately at 20°. The infrared spectrum (film) showed complete absence of the band at 1550 cm.$^{-1}$ due to the NO_2 group (Found: C, 69·0; H, 8·4; N, 14·5. $C_{11}H_{16}N_2O$ requires C, 68·7; H, 8·4; N, 14·6%).

3-2′-*Aminopropylindoline.*—3-2′-Nitropropylindoline (3·6 g., 0·0174 mole) in 2N-ethanolic ammonia (43·5 ml., 5 equiv.) was hydrogenated at 50°/50 atm. for 5 hr. in the presence of

Raney nickel (1 g.). The solution was filtered and evaporated, and the residue shaken with ether and 2N-acetic acid. The acetic acid was treated with excess alkali and extracted with ether, the extract yielding the *base*, b. p. 100°/10^{-5} mm., n_D^{20} 1·576 (Found: C, 74·75; H, 9·1; N, 16·2. $C_{11}H_{16}N_2$ requires C, 74·9; H, 9·1; N, 15·9%).

Thin-layer Chromatograms.—R_F values were as follows: 3-2′-nitropropylindole, 0·83; 3-2′-nitropropylindoline, 0·88; 3-2′-nitropropyloctahydroindole, 0·16; 3-(2-hydroxyaminopropyl)indole, 0·39; 3-(2-hydroxyaminopropyl)indoline, 0·5; 3-2′-aminopropylindole, 0·15; 3-2′-aminopropylindoline, 0·14. The octahydroindole reacted slowly with the permanganate spray in comparison with the other compounds.

Hydrogenation of 3-(2-*Methyl*-2-*nitropropyl*)*indole.*—A solution of the nitro-compound (3·58 g., 0·0164 mole) in methanol (36 ml.) and concentrated hydrochloric acid (1·4 ml., 1 equiv.) was hydrogenated at 20°/1 atm. in presence of prereduced platinum oxide (160 mg.). The reaction was stopped when 790 ml. (4 equiv.) had been absorbed, in 28 hr. The catalyst was filtered off and the filtrate evaporated *in vacuo* and treated with 2N-ammonia and ether. The ether was extracted successively with 2N-acetic acid and then with 2N-hydrochloric acid, as above. The residual ether contained starting material (0·82 g.). The acetic acid, on treatment with ammonia and ether, gave a strong base (1·2 g.) which distilled at 90—95°/10^{-5} mm. It formed a colourless oil, n_D^{20} 1·4993, soluble in acetic acid and reacting exothermically with acetic anhydride; it did not reduce silver nitrate solution. $\nu_{max.}$ 3300 (NH) (very low intensity), 1535 cm.$^{-1}$ (NO_2), no aromatic bands, $\lambda_{max.}$ 206 (inflexion), 280, and 288 mμ (log ε 3·62, 1·84, and 1·81). The base was evidently 3-(2-*methyl*-2-*nitropropyl*)*octahydroindole* (Found: C, 63·0; H, 9·7; N, 12·6. $C_{12}H_{22}N_2O_2$ requires C, 63·7; H, 9·8; N, 12·4%). The hydrochloric acid with ammonia and ether yielded a weaker base which boiled at 106°/10^{-5} mm. (0·6 g.) and formed a pale yellow oil, n_D^{20} 1·5573. It was 3-(2-*methyl*-2-*nitropropyl*)*indoline* (Found: C, 65·7; H, 7·4; N, 12·6. $C_{12}H_{16}N_2O_2$ requires C, 65·4; H, 7·3; N, 12·7%), $\lambda_{max.}$ 206, 243, 294·5, $\lambda_{min.}$ 225, 271 mμ (log ε 4·40, 3·83, 3·41, 3·64, and 3·02), $\nu_{max.}$ 3420 (NH), 1535 (NO_2), 740 cm.$^{-1}$ (1,2-disubstituted benzene).

The *hydrochloride* crystallised in platelets, m. p. 164—166° (from ethanol–ether) (Found: C, 56·0; H, 6·8; Cl, 13·8; N, 11·1. $C_{12}H_{16}N_2O_2$,HCl requires C, 56·1; H, 6·7; Cl, 13·8; N, 10·9%).

Thin-layer Chromatograms.—R_F values were as follows: 3-(2-methyl-2-nitropropyl)indole, 0·87; 3-(2-methyl-2-nitropropyl)indoline, 0·9; 3-(2-methyl-2-nitropropyl)octahydroindole, 0·2; 3-(2-hydroxyamino-2-methylpropyl)indole, 0·40; 3-(2-amino-2-methylpropyl)indole, 0·17. The octahydroindole reacted very slowly with the permanganate spray.

Hydrogenation of 3-(2-*Hydroxyamino*-2-*methylpropyl*)*indole.*—The hydroxylamine (1·02 g., 0·005 mole) in methanol (20 ml.) was hydrogenated at 20°/1 atm. in the presence of 5% palladium–charcoal (0·2 g.). Two equivalents of hydrogen (130 ml.) were absorbed in 6 hr. The solution was filtered and evaporated *in vacuo*, and the residue recrystallised from benzene. The crystals (0·78 g., 83%) had m. p. 130—131°, and a mixed m. p. with authentic 3-(2-amino-2-methylpropyl)indole showed no depression. The thin-layer chromatogram showed no residual hydroxylamine.

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