Aust. J. Chem., 1984, **37**, 1931–7

Synthesis of Dihydroisotryptamines

Emery Gellert and Onn-Choon Wong

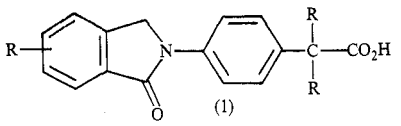
Department of Chemistry, University of Wollongong,
P.O. Box 1144, Wollongong, N.S.W. 2500.

Abstract

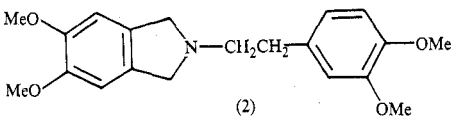
To enable exploration of the physiological activity of isotryptamine derivatives, a number of 1,3-dihydroisotryptamines, isomers of known tryptamine derivatives possessing significant physiological activity, were synthesized for the first time. Ring-substituted 1-nitrosonaphthalen-2-ols on tosylation and alkaline treatment gave the appropriate (*Z*)-3-(2′-cyanophenyl)propenoic acids, and by hydration, cyclization and ring-opening these acids were converted into (3′-oxo-1′,3′-dihydroisoindol-1′-yl)-acetic acids. Fusion of these products with ureas yielded the corresponding (3′-oxodihydroisoindol-1′-yl)acetamides, which, on simultaneous reduction of the amide and lactam functions by diborane, yielded 1,3-dihydroisotryptamines. Some features of their n.m.r. spectra are also discussed.

Introduction

The very significant physiological activity of indole derivatives (e.g., reserpine, lysergic acid diethylamide, psylocine) and dihydroindole derivatives (e.g., vinblastine, physostigmine) has been extensively reported and discussed in the literature. However, hardly any research has been carried out concerning the synthesis and physiological activity of their structural isomers, the isoindoles and dihyroisoindoles. Of the few compounds investigated, [4-(1′-oxo-1′,3′-dihydroisoindol-2′-yl)phenyl]acetic acid derivatives[1] (1) were shown to possess both analgesic and antiinflammatory activities, while (5,6-dimethoxydihydroisoindolyl)alkenes or their aryl-substituted alkane derivatives,[2] e.g., (2), exhibited α-adrenergic blocking activity.



(1)



(2)

[1] Nannini, G., Giraldi, P. N., Molgora, G., Biasoli, G., Spinnelli, F., Logemann, W., Dradi, E., Zanni, G., Buttinoni, A., and Tommasini, R., *Arzneim.-Forsch.*, 1973, **23**, 1090.
[2] Casagrande, C., Galli, A., Ferrini, R., and Miragoli, G., *Farmaco*, 1972, **27**, 445.

0004-9425/84/091931$02.00

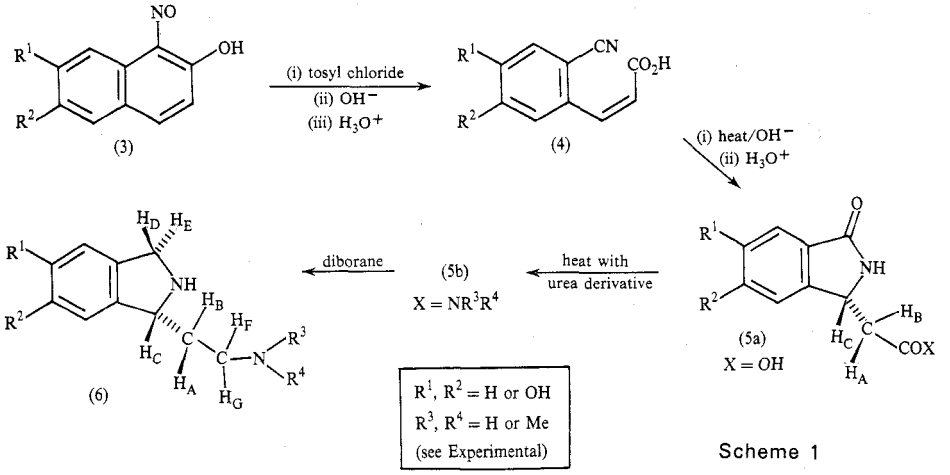
A limited number of dihydroisoindoles and phthalimidines showed no thymoleptic activity,[3] whereas the physiological activity of isoindolobenzazepine derivatives[4] has not yet been explored. Dihydroisoindole itself was first synthesized from reaction of 2-bromomethylbenzyl bromide with *p*-toluenesulfonamide.[5,6] Its more readily available 1-oxo derivatives were easily prepared either from phthalides[7] by condensation with primary amines, or from phthalimides[8] predominantly by electrolytic reduction. 1-Oxodihydroisoindoles can be prepared either by reduction with zinc and hydrochloric acid of phthalimidines (which can also be prepared from phthalazones),[9] or by cyclodehydration of the reaction product formed between *o*-carboxybenzophenone derivatives and ammonium cyanide,[10] or by hydrolysis and simultaneous ring closure of substituted *o*-cyanobenzylamines.[11] 1,1-Disubstituted 3-iminodihydroisoindoles, which can be hydrolysed to the corresponding 1,1-disubstituted 3-oxo derivatives, were prepared by treating phthalonitriles with suitable Grignard reagents.[12] The method used for the first substituted 3-oxodihydroisoindole derivatives[13,14] was considerably improved by changing the starting material first to sodium *o*-carboxycinamate[15] to *o*-cyanocinnamate.[16,17] This change allows not only for an easier introduction of substituents into specified positions of the benzene ring, but also for the preparation of larger ring systems.

Discussion

As most of the physiologically active indole alkaloids contain the tryptamine skeleton in their molecules, this work deals with the synthesis of compounds which possess, instead of the tryptamine, the corresponding isotryptamine moiety in their molecules. The biological activities of the compounds synthesized here will be reported elsewhere at a later date. The method (Scheme 1) employed in this investigation converts, by the action of alkali in acetone or in ethanol/acetone solution, substituted 1-nitroso-2-tosyloxynaphthalene derivatives (prepared by Bridge's classical method[18]) into substituted (*Z*)-3-(2′-cyanophenyl)propenoic acids through Beckmann fragmentation.[19,20] This reaction follows the general mechanism described by Ferris *et al.*,[21]

[3] Petersen, P. V., Lassen, N., Hansen, V., Huld, T., Hjortkjaer, J., Holmblad, J., Nielsen, I. M., Nymark, M., Pedersen, V., Jorgensen, A., and Hougs, W., *Acta Pharmacol. Toxicol.*, 1966, **24**, 121.
[4] Scartoni, V., Fiaschi, R., Catalano, S., Morelli, I., and Marsili, A., *J. Chem. Soc., Perkin Trans. 1*, 1979, 1547.
[5] Fenton, G. W., and Ingold, C. K., *J. Chem. Soc.*, 1928, 3295.
[6] Bornstein, J., Lashua, S., and Boisselle, A. P., *J. Org. Chem.*, 1957, 1255.
[7] Graebe, C., *Justus Liebigs Ann. Chem.*, 1888, **247**, 288.
[8] Sakurai, B., *Bull. Chem. Soc. Jpn*, 1934, **7**, 127.
[9] Darapsky, A., and Henricks, P., *J. Prakt. Chem.*, 1936, **146**, 307.
[10] Pfeiffer, P., and Jaensch, E., *J. Prakt. Chem.*, 1941, **159**, 241.
[11] Racine, S., *Justus Liebigs Ann. Chem.*, 1887, **239**, 78.
[12] Weiss, R., and Freund, E., *Monatsh. Chem.*, 1924, **45**, 105.
[13] Barrett, P. A., Linstead, R. P., and Tuey, G. A. P., *J. Chem. Soc.*, 1939, 1807.
[14] Fisher, O., and Wolter, H., *J. Prakt. Chem.*, 1909, **80**, 102.
[15] Rodionov, V. M., and Chukhina, E. I., *J. Gen. Chem. USSR*, 1944, **14**, 325.
[16] Rowe, F. M., Haig, A. S., and Peters, A. T., *J. Chem. Soc.*, 1936, 1098.
[17] Gabriel, S., *Ber. Dtsch. Chem. Ges.*, 1885, **18**, 2433.
[18] Bridge, J. L., *Justus Liebigs Ann. Chem.*, 1893, **277**, 85.
[19] Edwards, G. A., *J. Chem. Soc.*, 1926, 813.
[20] Werner, A., and Piquet, A., *Ber. Dtsch. Chem. Ges.*, 1904, **37**, 4295.
[21] Ferris, A. F., Johnson, G. S., and Gould, F. E., *J. Org. Chem.*, 1960, **25**, 1813.

otherwise the concerted mechanism proposed by Freeman[22] will be followed. Refluxing (*Z*)-3-(2-cyanophenyl)propenoic acid derivatives in alkali, followed by acidification, yields (3′-oxo-1′,3′-dihydroisoindol-1′-yl)acetic acid derivatives. (3′-Oxo-1′,3′-dihydroisoindol-1′-yl)acetic acids were converted into (3′-oxo-1′,3′-dihydroisoindol-1′-yl)acetamides by high-temperature fusion with urea. Both the amide and lactam carbonyl groups can simultaneously be reduced by diborane to the diamine, in good yields, by employing the method of Brown and Heim.[23,24]



Scheme 1

Some features of the n.m.r. spectra obtained require explanation. The methylene protons (H_A and H_B) of (3′-oxo-1′,3′-dihydroisoindol-1′-yl)acetic acid derivatives [cf. (5)] are made magnetically non-equivalent by the presence of an asymmetric centre, as discussed by Silverstein and Bassler,[25] even up to seven bonds away. Therefore, these signals appear as doublets of doublets with $J_{AC} \approx 5{\cdot}8$, $J_{BC} \approx 8{\cdot}3$ and $J_{AB} \approx 15$ Hz, centring at δ 2·8, H_A; 2·4, H_B; and 5·0, H_C. The same argument can be used for the magnetic non-equivalence of the methylene protons (H_F and H_G) between the above methylene groups and the nitrogen atom of 1,3-dihydroisotryptamine derivatives [cf. (6)]. These signals, however, are broader than those recorded for H_A and H_B. This is due to partly unresolved long-range coupling with the benzylic protons of the molecule. The benzylic protons (H_D and H_E) in (6), formed by reduction of the lactam carbonyl group in (5), consist of two doublets which appear as an unequal quartet[26] centring at δ 4·6 ($J \approx 14{\cdot}6$ Hz) as established by, e.g., Fitzgerald,[27] Hamlow[28] and Johns *et al.*[29] for quinolizidine derivatives, and by Chauncy and Gellert[30] for indolizidine derivatives.

[22] Freeman, J. P., *J. Org. Chem.*, 1961, **26**, 3507.
[23] Brown, H. C., and Heim, P., *J. Org. Chem.*, 1973, **38**, 912.
[24] Brown, H. C., Heim, P., and Yoon, N. M., *J. Am. Chem. Soc.*, 1970, **92**, 1637.
[25] Silverstein, R. M., and Bassler, G. C., 'Spectrometric Identification of Organic Compounds' p. 129 (John Wiley: New York 1968).
[26] Parikh, V. M., 'Absorption Spectroscopy of Organic Molecules' p. 119 (Addison-Wesley: New York 1974).
[27] Fitzgerald, J. S., Johns, S. R., Lamberton, J. A., and Redcliffe, A. H., *Aust. J. Chem.*, 1966, **19**, 151.
[28] Hamlow, H. P., Okuda, S., and Nakagawa, N., *Tetrahedron Lett.*, 1964, 2553.
[29] Johns, S. R., Lamberton, J. A., Sioumis, A. A., and Willing, R. I., *Aust. J. Chem.*, 1970, **23**, 353.
[30] Chauncy, B., and Gellert, E., *Aust. J. Chem.*, 1970, **23**, 2503.

Experimental

Melting points were determined on an electrically heated Reichert melting point apparatus and are uncorrected. Microanalyses were carried out by the Amdel Microanalytical Laboratory, Melbourne. ^{1}H n.m.r. spectra were recorded by the Australian N.M.R. National Service Centre at the Australian National University, Canberra. Mass spectra were recorded on a Dupont 21-419B spectrometer.

(*a*) *Cinnamic Acid Derivatives* (*4*)

(i) Nitrosation[31] of naphthalen-2-ol gave 1-nitrosonaphthalen-2-ol which was converted, via its *p*-toluenesulfonate intermediate in alkaline solution, into (*Z*)-3-(2′-cyanophenyl)propenoic acid, $C_{10}H_7NO_2$, m.p. 137° (lit. 137°).[16]

(ii) Nitrosation of naphthalene-2,6-diol gave 1-nitrosonaphthalene-2,6-diol.[32] Conversion of this (11·0 g, 58·2 mmol), as above, in aqueous alkaline solution with *p*-toluenesulfonyl chloride (24·3 g, 128 mmol) dissolved in acetone/tetrahydrofuran (250 ml), gave on acidification (*Z*)-*3-(2′-cyano-5′-hydroxyphenyl)propenoic acid.* Recrystallization from aqueous methanol gave the pure acid (0·8 g, 7·3%), m.p. 176° (Found: C, 63·2; H, 3·8; N, 7·2. $C_{10}H_7NO_3$ requires C, 63·5; H, 3·7; N, 7·4%). N.m.r. spectrum (CD_3–CO–CD_3) δ 7·7, d, *J c.* 9 Hz, H3′; 7·2, s, H6′; 7·1, d, H4′ (obscured); 7·0, d, *J c.* 12 Hz, (*Z*) **CH**–CHCO$_2$H; 6·1, d, *J c.* 12 Hz, (*Z*) CH=**CH**CO$_2$H. Mass spectrum (c.i.) *m/z* 190 (MH), 172 (MH − H_2O).

(iii) Nitrosation, as above, of naphthalene-2,7-diol gave 1-nitrosonaphthalene-2,7-diol.[33] Conversion of this (5·0 g, 26·5 mmol), as above, in aqueous alkaline solution with *p*-toluenesulfonyl chloride (12·8 g, 64·3 mmol) dissolved in acetone/tetrahydrofuran (125 ml), gave (*Z*)-*3-(2′-cyano-4′-hydroxyphenyl)propenoic acid* on acidification. Recrystallization from water gave the pure acid (2·3 g, 42·5%), m.p. 180° (Found: C, 63·3; H, 3·9; N, 7·5. $C_{10}H_7NO_3$ requires C, 63·5; H, 3·7; N, 7·4%). N.m.r. spectrum (CD_3–CO–CD_3) δ 7·7, d, *J c.* 9 Hz, H6′; 7·1, s, H3′; 7·1, d, H5′ (obscured); 7·0, d, *J c.* 12 Hz, (*Z*) **CH**=CHCO$_2$H; 6·1, d, *J c.* 12 Hz, (*Z*) CH=**CH**CO$_2$H. Mass spectrum (c.i.) *m/z* 190 (MH), 172 (MH − H_2O).

(*b*) *(3′-Oxo-1′,3′-dihydroisoindol-1′-yl)acetic Acids* (*5a*)

(i) Refluxing (*Z*)-3-(2′-cyanophenyl)propenoic acid (7·0 g, 40·5 mmol) in 2 N sodium hydroxide (50 ml) for 2½ h gave, after acidification and standing at room temperature overnight, (3′-oxo-1′,3′-dihydroisoindol-1′-yl)acetic acid (6·9 g, 89·0%), $C_{11}H_9NO_4$, m.p. 180–182° (lit. 182°).[16] N.m.r. spectrum (CD_3OD) δ 7·79, dd, H4′, $J_{4',5'}$ 7·5, $J_{4',6'}$ 1·1 Hz; 7·76–7·45, m, H7′, H6′, H5′; 5·0, dd, H1′ (obscured); 2·95, dd, **HCHCO$_2$H**, J_{AB} 16·7, J_{AC} 5·1 Hz, 2·58, dd, **HCHCO$_2$H**, J_{AB} 16·7, J_{AC} 8·4 Hz. Mass spectrum (c.i.) *m/z* 192 (MH).

(ii) Refluxing (*Z*)-3-(2′-cyano-4′-hydroxyphenyl)propenoic acid (8·0 g, 42·3 mmol) for 5 h in 2 N sodium hydroxide (75 ml), under the conditions described in (i), gave *(5′-hydroxy-3′-oxo-1′,3′-dihydroisoindol-1′-yl)acetic acid* which was recrystallized (charcoal) from aqueous methanol (yield 5·7 g, 71%), m.p. 250–253° (Found: C, 58·5; H, 4·4; N, 6·6. $C_{10}H_9NO_4$ requires C, 58·0; H, 4·3; N, 6·8%). N.m.r. spectrum (CD_3OD) δ 7·4, d, $J_{6',7'}$ 8·3 Hz, H7′; 7·13, d, $J_{4',6'}$ 2·4 Hz, H4′; 7·03, dd, $J_{6',7'}$ 8·3, $J_{4',6'}$ 2·4 Hz, H6′; 4·9, dd (obscured), H1′; 2·84, dd, **HCHCO$_2$H**, J_{AB} 16·5, J_{AC} 5·4 Hz; 2·52, dd, HCHCO$_2$H, J_{AB} 16·5, J_{BC} 8·2 Hz. Mass spectrum (c.i.) *m/z* 208 (MH), 190 (MH − H_2O).

(iii) Refluxing (*Z*)-3-(2′-cyano-5′-hydroxyphenyl)propenoic acid (8·0 g, 42·3 mmol) for 5 h in sodium hydroxide (130 ml), under the conditions described in (i), gave, after acidification, *(6′-hydroxy-3′-oxo-1′,3′-dihydroisoindol-1′-yl)acetic acid* which was recrystallized from water (yield 3·8 g, 47%), m.p. 246° (Found: C, 57·8; H, 4·3; N, 6·6. $C_{10}H_9NO_4$ requires C, 58·0; H, 4·3; N, 6·8%). N.m.r. spectrum (CD_3OD) δ 7·59, d, $J_{4',5'}$ 8·4 Hz, H4′; 6·96, d, $J_{5',7'}$ 2·2 Hz, H7′; 6·9, dd, $J_{4',5'}$ 8·4, $J_{5',7'}$ 2·2 Hz, H5′; 4·9, dd (obscured), H1′; 2·86, dd, **HCHCO$_2$H**, J_{AB} 16·7, J_{AC} 5·4 Hz; 2·57, dd, HCHCO$_2$H, J_{AB} 16·7, J_{BC} 8·3 Hz. Mass spectrum (c.i.) *m/z* 208 (MH), 190 (MH − H_2O).

[31] Marvel, C. S., and Porter, P. K., *Org. Synth.*, 1944, Coll. Vol. I, 411.
[32] Thorpe, J. F., and Whiteley, M. A., 'Thorpe's Dictionary of Applied Science' 4th Edn, Vol. 8, p. 365 (Longmans: New York 1949).
[33] Fisher, O., and Hammerschmidt, U., *J. Prakt. Chem.*, 1916, **94**, 24.

(*c*) *Primary Amides* (*5b*; $R^3 = R^4 = H$)

(i) Heating a mixture of (3-oxo-1′,3′-dihydroisoindol-1′-yl)acetic acid (6·0 g, 31·4 mmol) and urea (2·8 g, 47·1 mmol) for 3 h at 170–180°, and for an additional 15 min at 200°, gave, after cooling overnight, crude crystals of *2-(3′-oxo-1′,3′-dihydroisoindol-1′-yl)acetamide* which were recrystallized (charcoal) from water (yield 3·6 g, 60%), m.p. 218° (Found: C, 63·1; H, 5·4; N, 15·0. $C_{10}H_{10}N_2O_2$ requires C, 63·2; H, 5·3; N, 14·7%). N.m.r. spectrum (CD_3OD) δ 7·77, dd, $J_{4',5'}$ 7·6, $J_{4',6'}$ 1·1 Hz, H4′; 7·63–7·57, m, H5′, H6′; 7·50, dd, $J_{6',7'}$ 7·6, $J_{5',7'}$ 1·8 Hz, H7; 5·0, dd, J_{BC} 8·3, J_{AC} 5·8 Hz, H1′; 2·77, dd, HCHCON, J_{AB} 15·1, J_{AC} 5·8 Hz; 2·52, dd, HCHCON, J_{AB} 15·1, J_{BC} 8·3 Hz. Mass spectrum (c.i.) *m/z* 191 (MH), 173 (MH−H_2O).

(ii) Heating a mixture of (5-hydroxy-3′-oxo-1′,3′-dihydroisoindol-1′-yl)acetic acid (10·0 g, 48·3 mmol) and urea (5·8 g, 96·6 mmol) for 1 h at 160°, then for another 2 h at 190° and finally for 15 min at 200°, gave, after cooling overnight, crude crystals of *2-(5′-hydroxy-3′-oxo-1′,3′-dihydroisoindol-1′-yl)acetamide* which was recrystallized (charcoal) from water (yield 2·7 g, 46·0%), m.p. 225–226° (Found: C, 58·5; H, 4·7; N, 13·8. $C_{10}H_{10}N_2O_3$ requires C, 58·3; H, 4·9; N, 13·6%). N.m.r. spectrum (CD_3OD) δ 7·38, d, $J_{6',7'}$ 8·3 Hz, H7′; 7·14, d, $J_{4',6'}$ 2·3 Hz, H4′; 7·05, dd, $J_{6',7'}$ 8·3, $J_{4',6'}$ 2·3 Hz, H6′; 4·9, dd (obscured), H1′; 2·70, dd, HCHCON, J_{AB} 15·0, J_{AC} 5·9 Hz; 2·48, dd, HCHCON, J_{AB} 15·0, J_{BC} 8·3 Hz. Mass spectrum (c.i.) *m/z* 207 (MH), 191 (MH−NH_2), 189 (MH−H_2O).

(iii) Heating a mixture of (6′-hydroxy-3′-oxo-1′,3′-dihydroisoindol-1′-yl)acetic acid (5·0 g, 24·2 mmol) and urea (2·9 g, 48·3 mmol), as in (ii), gave *2-(6′-hydroxy-3′-oxo-1′,3′-dihydroisoindol-1′-yl)acetamide* (5·5 g, 55·6%), m.p. 238–239° (Found: C, 58·2; H, 4·9; N, 13·8. $C_{10}H_{10}N_2O_3$ requires C, 58·3; H, 4·9; N, 13·6%). N.m.r. spectrum (CD_3OD) δ 7·57, d, $J_{4',5'}$ 8·4 Hz, H4′; 6·96, d, $J_{5',7'}$ 2·2 Hz, H7′; 6·90, dd, $J_{4',5'}$ 8·4, $J_{5',7'}$ 2·2 Hz, H5′; 4·9, dd (obscured), H1′: 2·70, dd, HCHCON, J_{AB} 15·0, J_{AC} 5·9 Hz; 2·45, dd, HCHCON, J_{AB} 15·0, J_{BC} 8·3 Hz. Mass spectrum (c.i.) *m/z* 207 (MH).

(*d*) *Secondary Amides* (*5b*; $R^3 = H$, $R^4 = Me$)

(i) (3′-Oxo-1′,3′-dihydroisoindol-1′-yl)acetic acid (10 g, 52·4 mmol) and excess 1,3-dimethylurea (13·8 g, 157·1 mmol) were mixed and heated at 170–180° for 2 h. The temperature was raised to 200° for 15 min to give N-*methyl-2-(3′-oxo-1′,3′-dihydroisoindol-1′-yl)acetamide* (4·3 g, 40%) which was recrystallized (charcoal) from water, m.p. 190° (Found: C, 64·7; H, 5·9; N, 13·7. $C_{11}H_{12}N_2O_2$ requires C, 64·7; H, 5·9; N, 13·7%). N.m.r. spectrum (CD_3OD) δ 7·76, dd, $J_{4',5'}$ 7·4, $J_{4',6'}$ 11·1 Hz, H4′; 7·7–7·5, m, H5′, H6′; 7·48, dd, $J_{6',7'}$ 7·0, $J_{5',7'}$ 1·1 Hz, H7′; 5·01, dd, J_{BC} 8·3, J_{AC} 5·8 Hz, H1′; 2·77, s, NCH_3; 2·72, dd, HCHCON, J_{AB} 14·6, J_{AC} 5·8 Hz; 2·47, dd, HCHCON, J_{AB} 14·6, J_{BC} 8·3 Hz. Mass spectrum (c.i.) *m/z* 205 (MH).

(ii) (5′-Hydroxy-3′-oxo-1′,3′-dihydroisoindol-1′yl)acetic acid (6·0 g, 29·0 mmol) and excess 1,3-dimethylurea (7·7 g, 87·0 mmol) were mixed and allowed to react as in (i). The product was recrystallized (charcoal) from water to give *2-(5′-hydroxy-3′-oxo-1′,3′-dihydroisoindol-1′-yl)*-N-*methylacetamide* (2·6 g, 39·0%), m.p. 223–226° (Found: C, 59·7; H, 5·4; N, 12·7. $C_{11}H_{12}N_2O_3$ requires C, 60·0; H, 5·5; N, 12·7%). N.m.r. spectrum (CD_3OD) δ 7·32, d, $J_{6',7'}$ 8·3 Hz, H7′; 7·13, d, $J_{4',6'}$ 2·4 Hz, H4′; 7·03, dd, $J_{6',7'}$ 8·3, $J_{4',6'}$ 2·4 Hz, H6′; 4·9, dd (obscured), H1′; 2·77, s, NCH_3; 2·64, dd, HCHCON, J_{AB} 14·6, J_{AC} 6·0 Hz; 2·42, dd, HCHCON, J_{AB} 14·6, J_{BC} 8·3 Hz. Mass spectrum (c.i.) *m/z* 221 (MH), 205 (MH−CH_3−H).

(*e*) *Tertiary Amides* (*5b*; $R^3 = R^4 = Me$)

(i) A mixture of (3′-oxo-1′,3′-dihydroisoindol-1′-yl)acetic acid (10·0 g, 52·4 mmol) and 1,1-dimethylurea (4·6 g, 52·4 mmol) was heated for 1½ h at 170–190°, then for another hour at 190° and finally for 15 min at 200°. The reaction mixture was worked up (charcoal) as in the earlier experiment to give N,N-*dimethyl-2-(3′-oxo-1′,3′-dihydroisoindol-1′-yl)acetamide*. Recrystallized from water (yield 4·5 g, 42·0%), it melted at 103° (Found: C, 66·3; H, 6·4; N, 12·5. $C_{12}H_{14}N_2O_2$ requires C, 66·0; H, 6·5; N, 12·8%). N.m.r. spectrum (CD_3OD) δ 7·77, dd, $J_{4',5'}$ 7·4, $J_{4',6'}$ 1·1 Hz, H4′; 7·6–7·5, m, H5′, H6′; 7·5, dd, $J_{6',7'}$ 7·0, $J_{5',7'}$ 1·1 Hz, H7′; 5·04, dd, J_{BC} 8·9, J_{AC} 4·8 Hz, H1′; 3·06, dd, HCHCON, J_{AB} 16·3, J_{AC} 4·8 Hz; 3·00, s, NCH_3; 2·99, s, NCH_3; 2·62, dd, HCHCON, J_{AB} 16·3, J_{BC} 8·9 Hz. Mass spectrum (c.i.) *m/z* 219 (MH).

(ii) A mixture of (5′-hydroxy-3′-oxo-1′,3′-dihydroisoindol-1′-yl)acetic acid (5·0 g, 24·1 mmol) and 1,1-dimethylurea (4·25 g, 48·3 mmol) was heated at 160° for 1 h, then for another 2 h at 180°

and finally for 15 min at 200°. The reaction product was purified (charcoal) and recrystallized from water to yield *2-(5′-hydroxy-3′-oxo-1′,3′-dihydroisoindol-1′-yl)*-N,N-*dimethylacetamide* (2·4 g, 42%), m.p. 94° (Found: C, 61·7; H, 5·8; N, 12·3. $C_{12}H_{14}N_2O_3$ requires C, 61·5; H, 6·0; N, 12·0%). N.m.r. spectrum (CD_3OD) δ 7·4, d, $J_{6',7'}$ 8·2 Hz, H7′; 7·15, d, $J_{4',6'}$ 2·3 Hz, H4′; 7·05, dd, $J_{6',7'}$ 8·2, $J_{4',6'}$ 2·3 Hz, H6′; 4·93, dd, J_{BC} 9·0, J_{AC} 4·6 Hz, H1′; 3·0, dd, HCHCON (obscured); 3·0, s, NCH_3; 2·98, s, NCH_3; 2·55, dd, HCHCON, J_{AB} 16·5, J_{BC} 9·0 Hz. Mass spectrum (c.i.) *m/z* 235 (MH).

(f) Primary Amines (6; $R^3 = R^4 = H$) from Primary Amides

(i) 2-(3′-Oxo-1′,3′-dihydroisoindol-1′-yl)acetamide (2·8 g, 14·7 mmol) was dissolved in freshly distilled boron trifluoride/tetrahydrofuran (34·7 ml/100 ml), and stirred under nitrogen for 24 h while sodium borohydride (5·7 g, 149 mmol), suspended in diglyme (75 ml), was added dropwise. The mixture was stirred for another 3 days at 30° to complete the reduction of both amide groups. The excess diborane was destroyed by slow addition of ethanol, and the solution was evaporated under vacuum below 30°. The amine/borane complex was hydrolysed by standing in 0·5 N methanolic hydrochloric acid (30 ml) overnight. Any borate which separated was filtered off, and the filtrate evaporated to dryness under vacuum. Any free amide which remained in the mixture was extracted with methylene chloride. The basified solution was then repeatedly extracted with chloroform. The chloroform solution was dried, evaporated under nitrogen, and then chromatographed on a silica column. Elution with methanol/chloroform/ammonium hydroxide (6 N) (2 : 3 : 6) gave *1,3-dihydroisotryptamine* [2-(1′,3′-dihydroisoindol-1′-yl)ethylamine] (1·7 g, 70·7%) as a viscous oil. Its *hydrochloride salt* had m.p. 264–266° (Found: C, 51·0; H, 6·7; N, 12·0. $C_{10}H_{16}Cl_2N_2$ requires C, 51·1; H, 6·9; N, 11·9%). N.m.r. spectrum (CD_3OD) of the base: δ 7·47, s, H4′, H5′, H6′, H7′; 5·1, dd, J_{BC} 8·7, J_{AC} 4·7 Hz, H1′; 4·7, d, J_{DE} 14 Hz, H3′; 4·6, d, J_{DE} 14 Hz, H3′; 3·3, m, br, $HCHNH_2$; 3·2, m, br, $HCHNH_2$; 2·5, m, $HCHCH_2NH_2$; 2·4, m, $HCHCH_2NH_2$. Mass spectrum (c.i.) *m/z* 163 (MH).

(ii) 2-(5′-Hydroxy-3′-oxo-1′,3′-dihydroisoindol-1′-yl)acetamide (3·0 g, 14·5 mmol) was reduced as described for the preparation of the unsubstituted dihydroisotryptamine to yield *5-hydroxy-1,3-dihydroisotryptamine** (1·4 g, 55%) as a viscous oil (Found: C, 67·3; H, 7·7; N, 15·5. $C_{10}H_{14}N_2O$ requires C, 67·4; H, 7·9; N, 15·7%). N.m.r. spectrum (CD_3OD) δ 7·25, d, $J_{6',7'}$ 13·2 Hz, H7′; 6·83, s, H4′; 6·82, d (unresolved), $J_{6',7'}$ 13 Hz, H6′; 5·0, dd (obscured), H1′; 4·6, d, J_{DE} 12 Hz, H3′; 4·5, d, J_{DE} 12 Hz, H3′; 3·4, m, br, $HCHNH_2$; 3·2, m, br, $HCHNH_2$; 2·4, m, br, $HCHCH_2NH_2$; 2·3, m, br, $HCHCH_2NH_2$. Mass spectrum (c.i.) *m/z* 179 (MH).

(iii) 2-(6′-Hydroxy-3′-oxo-1′,3′-dihydroisoindol-1′-yl)acetamide (2·8 g, 145 mmol) was reduced as above to yield *6-hydroxy-1,3-dihydroisotryptamine* (1·7 g, 70·7%) as a viscous oil (Found: C, 67·1; H, 7·9; N, 15·9. $C_{10}H_{14}N_2O_2$ requires C, 67·4; H, 7·9; N, 15·7%). N.m.r. spectrum (CD_3OD) δ 7·3, d, $J_{4',5'}$ 6·8 Hz, H4′; 6·8, s, H7′; 6·8, d (unresolved), H5′; 5·0, dd (obscured), H1′; 4·6, d, J_{DE} 12 Hz, H3′; 4·5, d, J_{DE} 12 Hz, H3′; 3·6, m, br, $HCHNH_2$; 3·4, m, br, $HCHNH_2$; 2·5, m, br, $HCHCH_2NH_2$; 2·3, m, br, $HCHCH_2NH_2$. Mass spectrum (c.i.) *m/z* 179 (MH).

(g) Secondary Amines (6; $R^3 = H$, $R^4 = Me$) from Secondary Amides

N-Methyl-2-(3′-oxo-1′,3′-dihydroisoindol-1′-yl)acetamide (1 g, 4·9 mmol) was reduced, as described for the corresponding primary amide, to a viscous oil, *1,3-dihydro*-N-*methylisotryptamine* (0·5 g, 58%) (Found: C, 75·3; H, 9·2; N, 15·9. $C_{11}H_{16}N_2$ requires C, 75·0; H, 9·2; N, 15·9%). N.m.r. spectrum (D_2O) δ 7·5–7·4, m, H4′, H5′, H6′, H7′; 5·15, dd, J_{BC} 7·8, J_{AC} 5·5 Hz, H1′; 4·7, d (obscured), H3′; 4·6, d, J_{DE} 14 Hz, H3′; 3·3, m, br, HCHN; 3·2, m, br, HCHN; 2·7, s, $NHCH_3$; 2·5, m, br, $HCHCH_2N$; 2·4, m, br, $HCHCH_2N$. Mass spectrum (c.i.) *m/z* 193 (MH).

(h) Tertiary Amines (6; $R^3 = R^4 = Me$) from Tertiary Amides

(i) *N,N*-Dimethyl-2-(3′-oxo-1′,3′-dihydroisoindol-1′-yl)acetamide (1 g, 4·6 mmol) was reduced, as described for the corresponding primary amide, to a viscous oil, *1,3-dihydro*-N,N-*dimethylisotryptamine* (0·6 g, 70%) (Found: C, 75·9; H, 9·2; N, 14·8. $C_{12}H_{18}N_2$ requires C, 75·7; H, 9·5;

* Systematic name: 1-(2′-aminoethyl)-1,3-dihydroisoindol-5-ol. By application of IUPAC rules, similar names may be derived for the other hydroxydihydroisotryptamines described in this paper; for example, 6-hydroxy-1,3-dihydroisotryptamine becomes 3-(2′-aminoethyl)-1,3-dihydroisoindol-5-ol.

N, 14·7%). N.m.r. spectrum (D_2O) δ 7·4, m, H4′, H5′, H6′, H7′; 5·1, dd (unresolved), H1′; 4·7, d (unresolved), H3′; 3·4, m, br, **H**CHN; 3·3, m, br, HC**H**N; 2·96, s, NCH_3; 2·6, m, br, **H**CHCH$_2$N; 2·5, m, br, HC**H**CH$_2$N. Mass spectrum (c.i.) *m/z* 191 (MH).

(ii) 2-(5′-Hydroxy-3′-oxo-1′,3′-dihydroisoindol-1′-yl)-*N,N*-dimethylacetamide (1 g, 4·3 mmol) was reduced, as described for the corresponding primary amide, to yield *5-hydroxy-1,3-dihydro-N,N-dimethylisotryptamine* (0·75 g, 85%) as a viscous oil (Found: C, 70·0; H, 8·6; N, 13·9. $C_{12}H_{18}N_2O$ requires C, 69·9; H, 8·8; N, 13·6%). N.m.r. spectrum (CD_3OD) δ 7·3, d, $J_{6',7'}$ 8·6 Hz, H7′; 6·85, d, $J_{6',7'}$ 8·6 Hz, H6′; 6·83, s, H4′; 5·0, dd (obscured), H1′; 4·6, d (partly obscured), H3′; 4·5, d (partly obscured); 3·9, m, br, **H**CHN; 3·3, m, br, HC**H**N; 2·95, s, NCH_3; 2·90, s, NCH_3; 2·5, m, br, **H**CHCH$_2$N; 2·4, m, br, HC**H**CH$_2$N. Mass spectrum (c.i.) *m/z* 207 (MH).

Acknowledgments

The authors thank Dr A. J. Jones, Australian National University, Canberra, for recording the n.m.r. spectra. One of us (O.-C.W.) gratefully acknowledges the support provided by the Ampol Postgraduate Award.

Manuscript received 17 May 1983