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Derivatives of 2-Aminotetralin

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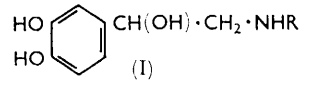
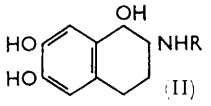
Some 2-amino-6,7-dimethoxytetralins have been prepared for pharmacological test. Certain differences in reactivity of 2-amino-1-tetralol and 2-amino-1-indanol compared with the analogues containing methoxyl *para* to the benzylic group are noted.

AMONG the manifold physiological effects shown by compounds of the adrenaline series (I) is that of dilatation of the bronchioles,[1] and certain members, for example isoprenaline (I; R = Pr^i), find use in the treatment of asthmatic attacks. Several bicyclic systems[2] also


(I)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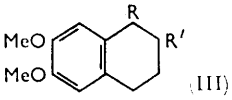
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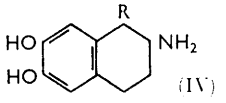
(IV)

cause bronchodilation, and in order to extend this knowledge a series of substituted 2-aminotetralins was prepared. The amine (II) can be regarded as a derivative of adrenaline (I; R = Me) in which the side-chain is "cyclised" through the addition of two methylene groups, and the synthesis of similar structures was undertaken.

Veratrole and succinic anhydride were converted by standard procedures into 6,7-dimethoxy-1-tetralone (III; R = :O, R′ = H) which, with butyl nitrite in ethereal potassium t-butoxide, gave the hydroxyimino-ketone (III; R = :O, R′ = :N·OH). Reduction with zinc in acetic acid–acetic anhydride yielded the useful acetamido-compound (III; R = :O, R′ = NHAc) from which a series of derivatives was prepared. The Decker–Becker method[3] for the preparation of *N*-mono-

[1] W. H. Hartung, *Chem. Rev.*, 1931, **9**, 389; D. M. Aviado, *J. Pharm. Sci.*, 1962, **51**, 191; D. S. Dittmer and R. M. Grebe, "Handbook of Respiration," Saunders, London, 1958; H. D. Moed, J. van Dijk, and H. Niewind, *Rec. Trav. chim.*, 1958, **77**, 273.

[2] (*a*) R. V. Heinzelmann, B. D. Aspergen, and J. H. Hunter, *J. Org. Chem.*, 1949, **14**, 907; (*b*) N. Levin, B. E. Graham, and H. G. Kolloff, *ibid.*, 1944, **9**, 380; (*c*) R. V. Heinzelmann, H. G. Kolloff, and J. H. Hunter, *J. Amer. Chem. Soc.*, 1948, **70**, 1386; (*d*) R. Tiffeneau and M. C. Beauvallet, *Compt. rend. Soc. Biol.*, 1945, **139**, 944; D. E. Jackson, *J. Pharm. Exper. Ther.*, 1914, **5**, 479; J. Knoll, K. Nàdor, B. Knoll, J. Heidt, and J. G. Nievel, *Magyar Tudomànyos Akadèmia Biològiai ès Orvosi Tudomànyok Osztàlyànak Közlemènyei*, 1960, **2**, 329; (*e*) D. W. Fassett and A. M. Hjort, *J. Pharm. Exper. Ther.*, 1938, **63**, 253; (*f*) P. F. Wiley, *J. Amer. Chem. Soc.*, 1952, **74**, 4329; U.S.P. 2,803,627/1957; G. W. Miller and F. L. Rose, *J. Chem. Soc.*, 1963, 5642; N. K. Basu and F. L. Rose, *ibid.*, p. 5660.

[3] "Chemistry of Carbon Compounds," ed. E. H. Rodd, Elsevier, 1951, vol. **1***A*, p. 387.

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methyl derivatives [*e.g.*, (III; R = OH, R′ = NHMe)] was unsatisfactory, and reduction of the urethane of the amino-alcohol or -ketone with lithium aluminium hydride (as used on the demethoxy-compound [4]) produced mixtures, possibly owing to partial loss of the benzylic hydroxyl under the activation of the methoxyl groups.[5] When the acetamido-tetralone (III; R = :O, R′ = NHAc) was *N*-methylated by the action of sodium hydride followed by methyl iodide, concomitant *C*-methylation occurred. The nicely crystalline dimethyl compound so formed (III; R = :O, R′ = Me, NAcMe) furnished the amine (III; R = :O, R′ = Me, NHMe) on hydrolysis.

The other 2-alkylamino-derivatives (described in the experimental section) were prepared by standard methods, and the 1-alkylamines (III; R = NHBu^n, R′ = H; R = NMeBu^n, R′ = H; R = NHMe, R′ = H) were obtained by reductive amination of the tetralone (III; R = :O, R′ = H).

Compounds lacking a benzylic hydroxyl were demethylated [*e.g.* to (IV; R = H or :O)] with boiling hydrobromic acid, but the 2-amino-1-tetralols were unstable to even dilute acids or boron trifluoride,[6] owing to facile elimination of the amino group and formation of 6,7-dimethoxy-2-tetralone (III; R = H, R′ = :O) and ammonium salts. This effect was rationalised by loss of the hydroxyl through protonation, rearrangement of the carbonium ion so formed, and hydrolysis of the resultant enamine, and has also been noted recently by other workers.[7] A mechanism of this type explains the formation of phenylacetone from ephedrine hydrochloride.[8]

The effect produced by a *p*-methoxyl group on the heterolysis [9] of the benzylic oxygen was interesting; whereas 2-amino-1-tetralol and 2-amino-1-indanol produced β-ketones in 8—15% yield after 2 days' treatment at 20° with concentrated hydrochloric acid, the *p*-methoxy-compounds gave yields of the ketone in the region of 60—80%.

Owing to elimination of the amino-group, it was not possible to hydrolyse the acetamido-alcohol (III; R = OH, R′ = NHAc) to the amino-alcohol (III; R = OH, R′ = NH_2) with acid, although this product was easily produced by basic hydrolysis. But, in the case of the parent amido-tetralols and -indanols with the activating methoxyl absent, acid hydrolysis was successful. However, acid (but not basic) hydrolysis of these *trans*-amido-alcohols was accompanied by inversion.* This inversion, which does not occur on acid hydrolysis of the *cis*-amides, results from participation of a cyclic intermediate [11] and can provide a useful guide in assigning configurations. For example, two 2-amino-1-indanols are described in the literature,[2b] and it was found that either could be formed from the same 2-acetamido-1-indanol according to whether the reagent was acid or alkaline. The amide thus has the *trans* configuration and the amino-alcohols *cis* and *trans* configurations, respectively. The *cis*-amino-indanol was the stronger base.

A selection of the compounds described was tested for bronchodilatory activity, measured as the degree to which the compounds would antagonise the broncho-constrictor effect of acetylcholine on the guinea-pig lung. Compared with isoprenaline (I; R = Pr^i), for example, all the compounds were appreciably less active, and the substituents in the 6,7-positions apparently had little effect in improving activity.

EXPERIMENTAL

The grating spectra were determined on a Unicam S.P. 700 spectrophotometer.

γ-3,4-Dimethoxyphenylbutyric Acid.—β-(3,4-Dimethoxybenzoyl)propionic acid was prepared essentially by the method of Fieser and Hershberg [12] and on a 4-molar scale, by stirring at 0° for 9 hr. and then at 22° for 18 hr., yields were improved up to 80%. The keto-acid, after treatment of a solution of its sodium salt with charcoal, formed fine granules, m. p. 161—162° (lit.,[13] 160—161°, and [14] 163°). Its spectrum showed a lactone structure in the solid state,[15] and the keto-acid structure in solution ($CHCl_3$); $\nu_{max.}$ (KBr disc) 3350, 1745, 1667 cm.$^{-1}$, etc., $\nu_{max.}$ (Nujol) 3295, 1740, 1659 cm.$^{-1}$, etc., $\nu_{max.}$ ($CHCl_3$) 3496vw, 1740sh, 1709 cm.$^{-1}$, etc. The following procedure worked better than Clemmensen reduction.[13] The keto-acid (200 g.) in acetic acid (1·5 l.) containing perchloric acid [16] (34 ml.) and 10% palladised charcoal (6 g.) was hydrogenated at 30—40°/15 atm. for 12 hr. The filtered solution was concentrated to 700 ml., diluted with water (800 ml.), and extracted with benzene. The combined extracts were filtered, washed, dried, and concentrated to small bulk. Dilution with light petroleum (b. p. 80—100°) gave the product (85—90%) as needles, m. p. 61—62° (lit.,[17] 58—59° and [14] 61°).

6,7-Dimethoxy-1-tetralone † (III; R = :O, R′ = H).—Cyclisation of the foregoing acid by polyphosphoric acid

* Failure to appreciate this has led to the incorrect configuration for 2-acetamido-1-tetralol,[10] and similar cases in the literature should be treated with caution.

† The shorter route used for 1-tetralone [18] caused demethylation.

[4] R. Lukeš, J. Pitha, J. Kovář, and K. Bláha, *Coll. Czech. Chem. Comm.*, 1960, **25**, 492.

[5] Cf. "Reduction with Complex Metal Hydrides," N. G. Gaylord, Interscience, London, 1956, ch. 16.

[6] R. D. Youssefyeh and Y. Mazur, *Chem. and Ind.*, 1963, 609; J. F. W. McOmie and M. L. Watts, *ibid.*, p. 1658.

[7] T. Chiemprasert, H. J. Rimek, and F. Zymalkowski, *Annalen*, 1965, **685**, 141.

[8] K. Bodendorf and K. Dettke, *Chem. Ber.*, 1956, **89**, 114.

[9] A. G. Davis and J. Kenyon, *Quart. Rev.*, 1955, **9**, 225; R. J. Gillespie and J. A. Leisten, *ibid.*, 1954, **8**, 49.

[10] F. Zymalkowski and H. J. Rimek, *Arch. Pharm.*, 1961, **294**, 581.

[11] M. S. Newman, ed., "Steric Effects in Organic Chemistry," Chapman and Hall, London, 1956, p. 290 *et seq.*; J. Sicher and M. Pánková, *Coll. Czech. Chem. Comm.*, 1955, **20**, 1409, and references cited therein; see also ref. 7.

[12] L. F. Fieser and E. B. Hershberg, *J. Amer. Chem. Soc.*, 1936, **58**, 2314.

[13] R. D. Haworth and C. R. Mavin, *J. Chem. Soc.*, 1932, 1485.

[14] P. C. Mitter and Shyamakanta De, *J. Indian Chem. Soc.*, 1935, **12**, 747.

[15] L. J. Bellamy, "Infra-red Spectra of Complex Molecules," Methuen, London, 2nd edn., p. 169.

[16] R. H. Baker and W. W. Jenkins, *J. Amer. Chem. Soc.*, 1946, **68**, 2102.

[17] G. Rosh and Sir R. Robinson, *J. Chem. Soc.*, 1944, 506.

[18] C. E. Olson and R. Bader, *Org. Synth.*, **35**, 95.

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was more satisfactory than the method using sulphuric acid.[13] Under Snyder and Werber's conditions for tetralone,[19] and by using a powerful centrifugal stirrer, yields of 80—90% were obtained on 60—90 g. batches. The product, m. p. 99—100° (lit.,[13] 98—99°, and [14] 99—100°), from petroleum (b. p. 100—120°), gave no colour in the "Tetralone-Blue" test;[20] $\nu_{max.}$ (Nujol) 1655 cm.$^{-1}$. Its oxime had m. p. 161° (lit.,[13] 157—158°).

6,7-*Dimethoxy*-1-*methylaminotetralin* (III; R = NHMe; R′ = H).—6,7-Dimethoxy-1-tetralone (2 g.) in ethanol (10 ml.) was hydrogenated in the presence of 10% palladised charcoal (0·4 g.) and methylamine (20 ml. of 40% aqueous solution). At the theoretical uptake, the solution was filtered and evaporated to dryness under reduced pressure. The residual amber oil, on addition of acetic acid (1 ml.), gave the *amine* (III; R = NHMe, R′ = H) *acetate* as needles (60%), m. p. 132° (from ethyl acetate) (Found: C, 63·9; H, 8·2; N, 5·1. $C_{15}H_{23}NO_4$ requires C, 64·0; H, 8·2; N, 5·0%).

1-*Butylmethylamino*-6,7-*dimethoxytetralin* (III; R = NMeBu^n, R′ = H).—The tetralone (III; R = :O, R′ = H) (11 g.) was refluxed for 0·5 hr. in absolute ethanol with butylamine (11 g.). The solution was cooled, hydrogenated to theoretical uptake on palladised charcoal, filtered, and evaporated *in vacuo*. A solution of the residual gum in 1N-hydrochloric acid (20 ml.) was treated with charcoal and evaporated, to give 1-*butylamino*-6,7-*dimethoxytetralin* (III; R = NHBu^n, R′ = H) *hydrochloride* as granules (50%), m. p. 176° (from propan-2-ol–di-isopropyl ether) (Found: C, 63·7; H, 8·6; Cl, 12·2. $C_{16}H_{26}ClNO_2$ requires C, 64·1; H, 8·7; Cl, 11·8%). The compound (1·5 g.) was hydrogenated in ethanol (30 ml.) in the presence of formalin (3·6 ml. of 40%) and platinised charcoal (0·8 g.). At the theoretical uptake, the solution was filtered and evaporated, and the residue was purified through extraction into dilute acid. The free *amine* (III; R = NMeBu^n, R′ = H) was obtained as a mobile oil, and its infrared spectrum showed an absence of NH (Found: C, 73·5; H, 9·7; N, 5·2. $C_{17}H_{27}NO_2$ requires C, 73·6; H, 9·8; N, 5·05%).

2-*Dimethylaminomethyl*-6,7-*dimethoxy*-1-*tetralone* (III; R = :O, R′ = CH_2NMe_2) *Hydrochloride*.—6,7-Dimethoxy-1-tetralone (2 g.), paraformaldehyde (0·3 g.), and dimethylamine hydrochloride (1 g.) were refluxed together in absolute ethanol (10 ml.) for 6 hr., and on cooling the *product* crystallised, microcrystals (1·7 g.) (from ethanol), m. p. 185—186° (Found: C, 60·3; H, 7·1; N, 4·5. $C_{15}H_{22}ClNO_3$ requires C, 60·1; H, 7·4; N, 4·7%).

Introduction of a nitrogen atom into the 2-position [in (III; R = :O, R′ = H)] was unsatisfactory by the Neber reaction or reaction of the 2-bromo-ketone with amines. Oximation using hydrogen chloride catalysis (cf. ref. 21) gave a chlorinated product, an effect also observed with tetralone itself.

2-*Hydroxyimino*-6,7-*dimethoxy*-1-*tetralone* (III; R = :O, R′ = :N·OH).—The reaction was conducted anhydrous, under nitrogen, with continuous stirring. Potassium chips (14 g.) were boiled in ether (1·6 l.) and anhydrous t-butyl alcohol (120 ml.) until dissolved (*ca.* 4 hr.). Powdered 6,7-dimethoxy-1-tetralone (72 g.) was added and, immediately this dissolved, fresh butyl nitrite [22] (48 ml.) was run in at a rate sufficient to keep the mixture boiling without external heating. Afterwards, the mixture was refluxed for 3 hr. The potassium salt, which was precipitated as a buff powder, was washed with ether and stirred into 1N-hydrochloric acid (600 ml.), dried, and ground with ether, to give the product (85%), m. p. 184° (decomp.). Recrystallisation from dioxan gave buff needles, m. p. 190° (decomp.) (lit.,[7] 191—192°) but this caused appreciable decomposition losses; $\nu_{max.}$ (Nujol) 3260, 1695, 1605 cm.$^{-1}$, etc. (Found: C, 61·1; H, 5·8; N, 5·5. Calc. for $C_{12}H_{13}NO_4$: C, 61·3; H, 5·6; N, 5·95%). When the above method was applied to the oximation of tetralone itself, yields about 20% higher than those of Straus and Ekhard [23] were obtained.

2-*Amino*-6,7-*dimethoxy*-1-*tetralone* (III; R = :O, R′ = NH_2).—After a saturated solution of the hydroxyimino-ketone in acetic acid–acetic anhydride mixture was warmed slightly, 2-*hydroxyimino*-6,7-*dimethoxy*-1-*tetralone acetate ester* (III; R = :O, R′ = :NOAc) (90%) crystallised on cooling, orange needles, m. p. 186—187° (decomp.), $\nu_{max.}$ (Nujol) 1775, 1655, 1590, 1570 cm.$^{-1}$ etc., and no peaks between 3000 and 5000 cm.$^{-1}$ (Found: C, 60·8; H, 5·6; N, 4·8. $C_{14}H_{15}NO_5$ requires C, 60·6; H, 5·45; N, 5·05%). Reduction of this ester with zinc and acetic acid at 40° gave the required amino-ketone (III; R = :O, R′ = NH_2), but a more convenient route, which avoided purifying the hydroxyimino-ketone, was as follows. Portions of zinc dust were sprinkled on to a stirred solution of the crude oximation product (40 g.), m. p. 185°, in acetic acid (400 ml.) and acetic anhydride (300 ml.) until the exothermic reaction ceased. The mixture was kept at *ca.* 30° during the addition and for 1 hr. thereafter. Evaporation of the filtered solution *in vacuo* gave 2-acetamido-6,7-dimethoxy-1-tetralone (III; R = :O, R′ = NHAc) (20 g.), needles (from ethyl acetate), m. p. 166° (lit.,[7] 167°), which was somewhat water-soluble; $\nu_{max.}$ (Nujol) 3300, 1660, 1630 cm.$^{-1}$, etc. (Found: C, 64·0; H, 6·6; N, 5·6. Calc. for $C_{14}H_{17}NO_4$: C, 63·9; H, 6·5; N, 5·3%). Its *oxime* formed cream granules or needles, m. p. 227° (decomp.) (from ethanol) (Found: C, 60·1; H, 6·6; N, 9·8. $C_{14}H_{18}N_2O_4$ requires C, 60·4; H, 6·5; N, 10·1%). The amide was hydrolysed in refluxing 4N-hydrochloric acid during 4 hr. The solution was treated with charcoal, filtered, and evaporated *in vacuo*, to yield the product (III; R = :O, R′ = NH_2) hydrochloride which ormed needles (94%) (from aqueous propanol), m. p. 243—245° (lit.,[7] 236—237°) (Found: C, 56·2; H, 6·2; Cl, 13·9; N, 5·6%; Equiv., 252. Calc. for $C_{12}H_{16}ClNO_3$: C, 55·9; H, 6·3; Cl, 13·8; N, 5·4%; *M*, 257·7).

2-*Ethylamino*-6,7-*dimethoxy*-1-*tetralol* (III; R = OH, R′ = NHEt).—The acetamido-ketone (III; R = :O, R′ = NHAc) and lithium aluminium hydride were stirred in refluxing tetrahydrofuran for 5 hr. On cooling, wet ether was added, followed by 12N-sodium hydroxide. After stirring for 1 hr., the ether layer was worked up, to yield *prisms* (70%), m. p. 115—116° [from benzene–light petroleum (b. p. 60—80°)]; the infrared spectrum showed no carbonyl band (Found: C, 67·2; H, 8·5; N, 5·45%; Equiv., 250. $C_{14}H_{21}NO_3$ requires C, 66·9; H, 8·4; N, 5·6%; *M*, 251), pK_a (50% EtOH) = 8·8.

trans-2-*Amino*-6,7-*dimethoxy*-1-*tetralol* (III; R = OH, R′ = NH_2).—Hydrogenation of the acetamido-ketone (III; R = :O, R′ = NHAc) with Adams platinum catalyst was

[19] H. R. Snyder and F. X. Werber, *Org. Synth.*, 1955, Coll. Vol. III, p. 798.
[20] J. H. Burckhalter and J. R. Campbell, *J. Org. Chem.*, 1961, **26**, 4232.
[21] G.P. 952,441; cf. W. H. Perkin and R. Robinson, *J. Chem. Soc.*, 1907, **91**, 1073.
[22] W. A. Noyes, *Org. Synth.*, coll. vol. **2**, 108.
[23] F. Straus and W. Ekhard, *Annalen*, 1925, **444**, 146.

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less satisfactory than borohydride reduction which caused 2-acetamido-6,7-dimethoxy-1-tetralol (III; R = OH, R′ = NHAc) to crystallise from the solution on standing overnight at 20° as prisms (90%), m. p. 215° (lit.,[7] 215°), $\nu_{max.}$ (Nujol) 3440, 3390, 1640 cm.$^{-1}$. Hydrolysis under the conditions used for the acetamido-ketone (III; R = :O, R′ = NHAc) gave 90% yield of ammonium chloride and crude 6,7-dimethoxy-2-tetralone. Hydrolysis proceeded normally when the amide (10 g.) was boiled in methanol (170 ml.) and 10N-sodium hydroxide (100 ml.) under nitrogen for 3 hr. The methanol was distilled off, an excess of dilute acetic acid added, and coloured impurities were removed by solvent extraction. Basification of the aqueous solution and extraction with methylene chloride gave the product (III; R = OH, R′ = NH_2), needles (90%), m. p. 164—165° (lit.,[7] 166—167°) (from ethyl acetate), $\nu_{max.}$ (Nujol) 3380, 3290, 3190, 1605 cm.$^{-1}$, etc., pK_a (50% EtOH) = 8·5. On treatment with acetic anhydride, the starting amide (m. p. and mixed m. p. 213°) was re-formed. When the amino-ketone (III; R = :O, R′ = NH_2) hydrochloride was reduced with borohydride, the alcohol so formed (80%) was identical (spectrum and mixed m. p.) with that (III; R = OH, R′ = NH_2) obtained above.

Treatment of the Foregoing and Related Amino-alcohols with Concentrated Hydrochloric Acid.—The general method was as follows. The amino-alcohol (1 g.), dissolved in concentrated hydrochloric acid (40 ml.), was stirred with benzene (150 ml.) at 20° for several hours. The benzene was decanted, washed, dried, and evaporated, leaving the ketone as a residue. The yields below are based on the crude products.

(*a*) 2-Amino-6,7-dimethoxy-1-tetralol (III; R = OH, R′ = NH_2) gave 6,7-dimethoxy-2-tetralone (III; R = H, R′ = :O) (70%) after 50 hr., and 90% yield after prolonged treatment. On recrystallisation (charcoal) from light petroleum (b. p. 60—80°), pale yellow plates, m. p. 86°, were obtained (lit.,[7] 87—88°). Addition of sodium hydroxide solution to an ethanolic solution of this ketone gave a blue-green colour which turned pink of acidification ("Tetralone-Blue" test [20]); $\nu_{max.}$ (Nujol) 1704 cm.$^{-1}$ (no NH or OH absorption) (Found: C, 70·0; H, 6·9; N, 0·0. Calc. for $C_{12}H_{14}O_3$: C, 69·9; H, 6·8%). The structure was confirmed by Clemmensen reduction to the tetralin (III; R = H, R′ = H). The product, eluted from alumina with benzene–cyclohexane, formed needles (95%), m. p. 55—57°, identical with those obtained by similar reduction of the ketone (III; R = :O, R′ = H) (Found: C, 75·2; H, 8·5. Calc. for $C_{12}H_{16}O_2$: C, 75·0; H, 8·4%).

(*b*) *trans*-2-Amino-1-tetralol (see below) gave 2-tetralone (15%) after 50 hr., identified by comparison of its spectrum with that of an authentic sample (Aldrich Chemical Co.).

(*c*) *cis*-2-Amino-1-tetralol (see below) gave 2-tetralone (8%) after 50 hr., and 16% yield after prolonged treatment.

(*d*) 2-Amino-5-methoxy-1-indanol hydrochloride,[2c] m. p. *ca.* 160° (decomp.), gave 5-methoxy-2-indanone (62%) after 50 hr. This ketone formed prisms, m. p. 78° (lit.,[24] 75—80°), on sublimation at 50°/0·1 mm., $\nu_{max.}$ (Nujol) 1730 cm.$^{-1}$ (no NH or OH absorption) (Found: C, 73·7; H, 6·7. Calc. for $C_{10}H_{10}O_2$: C, 74·05; H, 6·2%).

(*e*) 2-Amino-1-indanol hydrochloride gave 2-indanone (9%), m. p. 52—55°, after 50 hr., and 17% yield after prolonged treatment. It formed prisms, m. p. 55—57°, on sublimation (lit.,[2b] 56—57°), $\nu_{max.}$ (Nujol) 1740 cm.$^{-1}$ (C=O).

2-*Benzylideneamino*-6,7-*dimethoxy*-1-*tetralone* (III; R = :O, R′ = N:CHPh).—2-Amino-6,7-dimethoxy-1-tetralone (III; R = :O, R′ = NH_2) hydrochloride (0·4 g.), benzaldehyde (0·3 g.), and anhydrous sodium acetate (0·3 g.) were stirred together in ethanol under nitrogen for 1·5 hr. When the mixture was diluted with ice–water the *Schiffs base* was precipitated as a lemon powder, m. p. 114° (Found: C, 73·8; H, 6·3; N, 4·6. $C_{19}H_{19}NO_3$ requires C, 73·8; H, 6·2; N, 4·5%).

6,7-*Dimethoxy*-2-*methyl*-2-*methylamino*-1-*tetralone* (III; R = :O, R′ = Me, NHMe).—2-Acetamido-6,7-dimethoxy-1-tetralone (III; R = :O, R′ = NHAc) was refluxed in dry dioxan under nitrogen for 0·5 hr. with sodium hydride (excess). On cooling, methyl iodide (excess) was added and the mixture was boiled for 4 hr. more. Unchanged sodium hydride was decomposed with methanol, the solution was neutralised, and, through extraction into chloroform, 6,7-*dimethoxy*-2-*methyl*-2-(N-*methylacetamido*)-1-*tetralone* (III; R = :O, R′ = Me, NMeAc) was obtained as prisms, m. p. 155° [from benzene–light petroleum (b. p. 80—100°)], $\nu_{max.}$ (Nujol) 1665 (ring C=O), 1625 cm.$^{-1}$ (amide C=O), etc. No NH band. The n.m.r. spectrum confirmed the structure (Found: C, 65·8; H, 7·2; N, 5·0. $C_{16}H_{21}NO_4$ requires C, 65·95; H, 7·3; N, 4·8%). This material was boiled for 4 hr. in 3·5N-hydrochloric acid; the solution was treated with charcoal and evaporated, and the residue gave the *product* (III; R = :O, R′ = Me, NHMe) *hydrochloride* as fine prisms, m. p. 280° (decomp.) (from methanol) (Found: C, 58·8; H, 7·0; N, 5·2. $C_{14}H_{20}ClNO_3$ requires C, 58·8; H, 7·05; N, 4·9%), pK_a (50% EtOH) = 8·1.

2-*Amino*-6,7-*dihydroxy*-1-*tetralone* (IV; R = :O).—2-Acetamido-6,7-dimethoxy-1-tetralone (III; R = :O, R′ = NHAc) (1 g.) was heated at 150° in 48% hydrobromic acid (20 ml.) for 5 hr. The solution was diluted with water, filtered (charcoal), and evaporated *in vacuo*. The residue gave the *product hydrobromide* as irregular granules (84%), m. p. 262—265° (decomp.) (from propan-2-ol) (Found: C, 43·95; H, 4·4; Br, 29·4; N, 5·1. $C_{10}H_{12}BrNO_3$ requires C, 43·8; H, 4·4; Br, 29·2; N, 5·1%). The *picrate*, needles (from water), had m. p. 245—250° (decomp.) (Found: C, 45·4; H, 3·4; N, 13·5. $C_{16}H_{14}N_4O_{10}$ requires C, 45·5; H, 3·3; N, 13·3%).

The foregoing hydrobromide was hydrogenated with prereduced Adams catalyst in ethanol. Afterwards, the solution was filtered rapidly and evaporated at 20° *in vacuo*. The residue was dissolved in propan-2-ol, and on adding di-isopropyl ether an unstable white powder was precipitated. With sodium picrate this gave 2-*amino*-6,7-*dihydroxy*-1-*tetralol* (IV; R = OH) *picrate*, needles, m. p. 155° (from water) (Found: C, 45·4; H, 3·9; N, 13·5. $C_{16}H_{16}N_4O_{10}$ requires C, 45·3; H, 3·8; N, 13·2%).

2-*Amino*-6,7-*dimethoxytetralin* (III; R = H, R′ = NH_2).—2-Acetamido-6,7-dimethoxy-1-tetralone (6 g.) in acetic acid (60 ml.) was hydrogenated at 3 atm. with 5% palladised charcoal (2 g.) and perchloric acid (1 ml.). The solution was then filtered, made basic, and extracted with chloroform. The extracts yielded N-(1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-*naphthyl*)*acetamide* (III; R = H, R′ = NHAc) as fine needles (83%), m. p. 153° (from butyl acetate) (Found: C, 67·35; H, 8·0; N, 5·8. $C_{14}H_{19}NO_3$ requires C, 67·4; H, 7·7; N, 5·6%). This amide was hydrolysed with boiling 4N-hydrochloric acid, and the solution was evaporated. The residue crystallised from propan-2-ol to give the *product hydrochloride* as fine irregular prisms (95%), m. p.

[24] A. Chatterjee, R. C. Chatterjee, and B. K. Bhattacharyya, *J. Indian Chem. Soc.*, 1958, **35**, 391.

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220—221° (decomp.) (Found: C, 59·1; H, 7·6; Cl, 14·9; N, 5·6. $C_{12}H_{18}ClNO_2$ requires C, 59·1; H, 7·4; Cl, 14·55; N, 5·7%).

2-*Amino*-6,7-*dihydroxytetralin* (IV; R = H).—Demethylation of the aforementioned salt, under the conditions used to prepare the ketone (IV; R = :O), gave the *product hydrobromide* as granules (84%), m. p. 270—271° (decomp.) (from propan-2-ol and di-isopropyl ether) (Found: C, 46·35; H, 5·5; Br, 31·0; N, 5·3. $C_{10}H_{14}BrNO_2$ requires C, 46·2; H, 5·4; Br, 30·7; N, 5·4%).

2-*Butylamino*-6,7-*dimethoxy*-1-*tetralol* (III; R = OH, R′ = NHBu^n).—When 2-amino-6,7-dimethoxy-1-tetralol (1·7 g.) and butyric anhydride (2·4 g.) were stirred overnight in methanol (24 ml.), 2-*butyramido*-6,7-*dimethoxy*-1-*tetralol* (III; R = OH, R′ = NH·COPr^n) (1·8 g.) crystallised on adding ether (70 ml.), as needles, m. p. 152°. The infrared spectrum showed no ester C=O (Found: C, 65·2; H, 7·9; N, 4·8. $C_{16}H_{23}NO_4$ requires C, 65·5; H, 7·9; N, 4·8%). This amide was reduced with lithium aluminium hydride in boiling tetrahydrofuran during 4 hr. by the method used for the preparation of the ethyl analogue (III; R = OH, R′ = NHEt). The *butylamino-tetralol* (III; R = OH, R′ = NHBu^n) so formed gave microcrystals (61%), m. p. 137° (from ethyl acetate). The infrared spectrum showed an absence of carbonyl (Found: C, 68·5; H, 8·7; N, 5·0. $C_{16}H_{25}NO_3$ requires C, 68·8; H, 9·0; N, 5·0%), pK_a (50% EtOH) = 8·6.

Ethyl (1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-1-*oxo*-2-*naphthyl*)-*carbamate* (III; R = :O, R′ = NH·CO_2Et).—A solution of sodium hydrogen carbonate (1·5 g.) in water (15 ml.) was added slowly to a stirred mixture of redistilled ethyl chloroformate (1·5 ml.) and the amino-ketone (III; R = :O, R′ = NH_2) hydrochloride (1·1 g.) in water (15 ml.). The product crystallised during 30 min. and furnished needles (65%), m. p. 123° [from benzene–light petroleum (b. p. 60—80°)], $\nu_{max.}$ (CCl_4) 3350, 1724, 1671 (ring C=O) (Found: C, 61·3; H, 6·4; N, 5·0. $C_{15}H_{19}NO_5$ requires C, 61·4; H, 6·5; N, 4·8%).

trans-2-*Amino*-1-*tetralol*.—2-Acetamido-1-tetralone, obtained in 80% yield by reductive acetylation of 2-hydroxyimino-1-tetralone by the technique used in the preparation of the dimethoxy-analogue (III; R = :O, R′ = NHAc), had m. p. 124—126° (from water) (lit.,[10] 125—125·5°), solubility (H_2O, 24°) = 0·56% (u.v. method), $\lambda_{max.}$ (H_2O) 205, 252, 296 mμ (ε 25,800, 12,750, 2060). Reduction with sodium borohydride by the method used on the dimethoxy-analogue (III; R = :O, R′ = NHAc) gave trans-2-*acetamido*-1-*tetralol* as needles (70%), m. p. 175—176° (from ethyl acetate). This compound was also obtained by hydrogenation of the starting material in acetic acid with 10% palladised charcoal. Solubility (H_2O, 24°) = 0·47%, $\lambda_{max.}$ (H_2O) 265, 271 (ε 448, 410), $\nu_{max.}$ (CCl_4) (grating) 3595, 3448, 3360 cm.$^{-1}$ (Found: C, 70·1; H, 7·5; N, 6·9. $C_{12}H_{15}NO_2$ requires C, 70·2; H, 7·4; N, 6·8%). A solution of the acetamido-alcohol (3 g.) in ethanol (30 ml.) and 10N-sodium hydroxide (7 ml.) was refluxed for 4 hr. under nitrogen. Water (15 ml.) was added and the methanol was evaporated. Addition of concentrated hydrochloric acid (8 ml.) gave a solution which was treated with charcoal, basified, and extracted with methylene chloride. The extracts were dried ($MgSO_4$), and, on evaporation, yielded the product as needles, m. p. 91—92° [from ethyl acetate–light petroleum (b. p. 60—80°)] [or from benzene (charcoal)] (lit.,[10] 89—90°), $\nu_{max.}$ (CCl_4) (grating) 3594, 3538, 3395 {$\Delta\nu_{OH}$ [*i.e.*, ν(OH)(free) − ν(OH)(bonded)] = 56 cm.$^{-1}$}. Compare the results of Pitha *et al.*,[25] where the determination was made in tetrachloroethylene (Found: C, 73·3; H, 8·0; N, 8·7. Calc. for $C_{10}H_{13}NO$: C, 73·6; H, 8·0; N, 8·6%). When a portion of this amine was acetylated (Ac_2O in warm MeOH), the derivative produced was identical with the foregoing *trans*-acetamido-alcohol.

cis-2-*Acetamido*-1-*tetralol*.—*trans*-2-Acetamido-1-tetralol (7 g.) was refluxed for 12 hr. with 0·3N-hydrochloric acid (310 ml.). The filtered solution was washed with ethyl acetate, basified, and extracted with methylene chloride. The combined extracts afforded *cis*-2-amino-1-tetralol, obtained from ethyl acetate–light petroleum (b. p. 60—80°) as clusters of prisms (75%), m. p. 101—103° (lit.,[10] 100—102°) (mixed m. p. with the *trans*-isomer, 70°), $\nu_{max.}$ (CCl_4) (grating spectrophotometer) 3620, 3468, 3407, cm.$^{-1}$ {Δν(OH) 152 cm.$^{-1}$ [lit.,[25] (C_2Cl_4) 147 cm.$^{-1}$]}. The *cis*-amino-alcohol (4 g.) was acetylated (Ac_2O in warm MeOH), and evaporation of the solution gave the *product* which formed long prisms, m. p. 151° (from benzene); mixed m. p. with the *trans*-isomer, 127—130°. Solubility (H_2O, 24°) = 0·73%, $\lambda_{max.}$ (H_2O) 265, 272 mμ (ε 393, 379), $\nu_{max.}$ (CCl_4) (grating) 3617, 3448 cm.$^{-1}$ (Found: C, 70·1; H, 7·3; N, 6·7. $C_{12}H_{15}NO_2$ requires C, 70·2; H, 7·4; N, 6·8%). By acid or base hydrolysis, under the conditions used for the *trans*-amide, the *cis*-amino-alcohol was reformed.

2-*Acetamido*-1-*indanone*.—(*a*) 2-Hydroxyimino-1-indanone[26] (16 g., 0·1 mole) was hydrogenated in ethanol on 10% palladised charcoal (7 g.). After an uptake of 0·2 mole, acetic anhydride (20 ml.) was added. The solution was set aside overnight, filtered, and evaporated, to give the product * (65% after recrystallisation). (*b*) By dissolving 2-amino-1-indanone hydrochloride[26] in acetic acid–acetic anhydride and adding sodium acetate. (*c*) By slowly sprinkling, during 1 hr., an intimate mixture of zinc powder (10 g.) and the hydroxyimino-ketone (2 g.) on to a stirred mixture of acetic acid (50 ml.) and acetic anhydride (50 ml.) maintained at 20°. When the very exothermic reaction ceased, the solution was filtered and evaporated (yield *ca.* 40%). The *product* gave prisms (from EtAc, H_2O, or CCl_4–$CHCl_3$), m. p. 166° (Found: C, 69·9; H, 5·6; N, 7·5. $C_{11}H_{11}NO_2$ requires C, 69·8; H, 5·9; N, 7·4%).

trans-2-*Acetamido*-1-*indanol*.—Sodium borohydride (4 g.) in water (25 ml.) was added to the foregoing amide (6 g.) in methanol (70 ml.). The *product* crystallised overnight and formed stout prisms (70%), m. p. 191° (from ethyl acetate) (Found: C, 69·3; H, 6·9; N, 7·3. $C_{11}H_{13}NO_2$ requires C, 69·1; H, 6·85; N, 7·3%).

trans-2-*Amino*-1-*indanol*.—(*a*) By hydrogenation of 2-hydroxyimino-1-indanone (8 g.) in ethanol (500 ml.) with 10% palladised charcoal (4 g.). Addition of concentrated hydrochloric acid (10 ml.) and evaporation gave the hydrochloride (65%). (*b*) By cautious treatment of 2-amino-1-indanone hydrochloride (1 g.) in methanol (5 ml.) at 0° with sodium borohydride (0·9 g.) in water (5 ml.) and stirring afterwards at 20° for several hours. (*c*) By basic hydrolysis

* Although reduction of the ketone normally does not occur,[26] it did in fact take place with some of the more active commercial catalysts which, for example, would ignite ethanol. Reduction with stannous chloride[26b] satisfactorily avoided this.

[25] J. Pitha, M. Horák, J. Kovář, and K. Bláha, *Coll. Czech. Chem. Comm.*, 1960, **25**, 2733.

[26] (*a*) T. Kurihara and H. Takeda, *Tohoku Yakka Daigaku Kenkyu Nempo*, 1963, **10**, 57; (*b*) S. Gabriel and R. Stelzner, *Ber.*, 1896, **29**, III, 2603.

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of *trans*-2-acetamido-1-indanol by the method used for the tetralin analogue. The product had m. p. 105—106° [from benzene–light petroleum (b. p. 60—80°)]. The *hydrochloride* had m.p. 216—217° (decomp.) (from propan-2-ol) and showed absorption characteristic of this isomer at $\nu_{max.}$ (Nujol) 1620m, 1110s, and 740s cm.$^{-1}$ (Found: C, 58·0; H, 6·6; N, 7·4. $C_9H_{12}ClNO$ requires C, 58·2; H, 6·5; N, 7·55%), pK_a (50% EtOH) = 8·1. The reductions (*a*) and (*b*) in some runs gave material contaminated with the *cis*-isomer, which may explain the appreciably lower m. p. for this hydrochloride as reported in the literature.[27]

cis-2-*Amino*-1-*indanol*.—*trans*-2-Acetamido-1-indanol (2·3 g.) was refluxed in 0·25N-hydrochloric acid for 20 hr. Evaporation *in vacuo* gave the *product hydrochloride*, m. p. 206° (from alcohol–ether), which showed absorption characteristic of this isomer at $\nu_{max.}$ (Nujol) 1580s, 1015, 760s, and 735s cm.$^{-1}$ (Found: C, 58·1; H, 6·6; N, 7·5%), pK_a = 8·4. This material depressed the m. p. of the *trans*-hydrochloride.

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[27] W. E. Rosen and M. J. Green, *J. Org. Chem.*, 1963, **28**, 2797.

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