paramagnetic regions of the phenyl ring, respectively.[18] The possibility that this is a non-specific shift, resulting from a change in the diamagnetic anisotropy of the solute, is excluded both by the fact that the shift appears relative to other ribose protons and by the fact that the bulk susceptibility correction for the puromycin solutions, as compared to other nucleoside and nucleotide solutions, is of the order of 0–5 c.p.s. This is seen from a comparison of the position of the acetone resonance (0.5% used as an internal standard) in a 0.1 *M* solution of puromycin at +260.4 c.p.s. to that in a 0.1 *M* solution of adenosine at +256.0 c.p.s. The fact that the shifts of the acetone and ribose resonances are relatively insensitive to changes in hydrogen ion concentration has been established previously.[7] Taken in conjunction with the short relaxation times of the phenylalanine moiety (<0.2 sec.), this suggests that the ribose and the phenylalanine rings remain in a relatively fixed orientation with respect to each other.

An examination of molecular models reveals that the number of possible conformations of the puromycin molecule which are consistent with the observed spectrum is quite limited. An assignment of a precise conformation for the entire molecule is of course not possible, but the C'_5-proton shift requires that the mutual orientation of the ribose and the phenyl ring be of the general type shown in Fig. 3. The possibility that part of this shift is due to a shielding by the purine ring cannot be excluded. However, attributing the *entire* shift to a displacement of the C'_5H_2 group into the diamagnetic region of the latter is not consistent with the restriction of rotation in either the ribose or the phenylalanine moiety. If, for example, the molecule would be maximally stretched out, the rotation of the phenyl group would be expected to be as unrestricted as it is in the case of the free amino acid. With the main rotation occurring about the C_2–C_3 bond of the alanine residue, one could expect: (1) a coupling constant for the $-CH-\beta-CH_2$ protons of the order of 6 c.p.s., (2) sharp resonance lines for the entire amino acid spectrum, and (3) additional shielding of the C'_2 and C'_3- protons of ribose, none of which are found. The more compact conformation shown in Fig. 3 (allowing for some variation in position) is also more consistent with the distortion of angles in the ribose as compared to those of the similarity substituted 3′-adenosine monophosphate (AMP), although a plausible alternative explanation is the larger size of the substituent group.

(18) C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

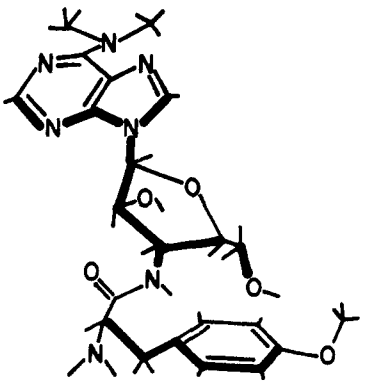


Fig. 3.—Puromycin in a folded conformation.

The reasons for this type of conformation in the case of puromycin are not immediately apparent. The C'_3-endo type of pucker is consistent with the notion that a bulky substituent on a carbon atom will tend to force this atom out of the plane of the ring, as appears to be the case for 2′-AMP. On the other hand, there is no obvious compelling reason for the folding of the molecule and a restriction of rotation in the phenylalanine side chain. The steric relationships are favorable to the formation of a hydrogen bond between the C'_5-hydroxyl and the π-electron system of the phenyl ring. The occurrence of such hydrogen bonds in aromatic solvents has been suggested, *e.g.*,[19] but the bonds are relatively weak (1–4 kcal./mole) and thus far there seems to be no evidence for their existence in strongly hydrogen-bonded solvents, such as water or D_2O. In contrast, hydrogen bonding to the methoxy group is not feasible, while hydrogen bonding to the carbonyl group would not account for the selective shielding of the C'_5 protons. It is conceivable that the molecule (which is positively charged in this *p*H range) is held in this configuration by reasonably stable water bridges, but additional evidence is clearly necessary to elucidate this point.

3. Experimental

The n.m.r. spectra were obtained on a Varian Associates V4300 B 60 Mc. high resolution spectrometer. The procedures were the same as described previously.[7,9] Puromycin was obtained as the dihydrochloride from the Lederle Division of the American Cyanamid Co. The D_2O (99.8% isotopic purity) was purchased from the Bio-Rad Corp., Richmond, Calif.

(19) A. W. Baker and A. T. Shulgin, *J. Am. Chem. Soc.*, **80**, 5358 (1958).

[CONTRIBUTION FROM THE PSYCHIATRIC RESEARCH UNIT, UNIVERSITY HOSPITAL, SASKATOON, SASKATCHEWAN, CAN., AND THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, BETHESDA 14, MD.]

Chemistry of Catecholamines: Revised Structures for the Iodoaminochromes

BY R. A. HEACOCK, O. HUTZINGER, B. D. SCOTT, J. W. DALY AND B. WITKOP

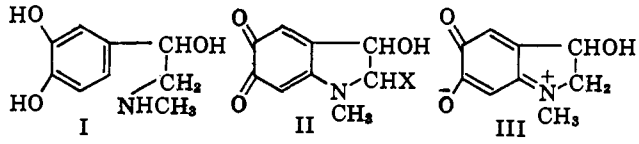
RECEIVED JANUARY 24, 1963

The n.m.r. spectra of 22 indole compounds derived from the oxidation of noradrenaline, adrenaline, 3,4-dihydroxynorephedrine and isoproterenol have been determined. Their evaluation provided unambiguous proof for the position of the halogen in iodo- and bromoaminochromes. The halogen occupies position 7 and not 2 as presumed previously. Independent total syntheses of 5,6-dimethoxy-7-iodoindole (X) and of 5,6-dimethoxy-7-iodo-2-methylindole (XII) confirmed this assignment.

Introduction

Oxidation of adrenaline (I) with potassium iodate gives a deep red-violet solution,[1,2] from which in 1937 Richter and Blaschko[3] isolated deep red prisms of what they considered to be 3-hydroxy-2-iodo-1-methyl-2,3-dihydroindole-5,6-quinone (II, X = I).[3] In the same year Green and Richter[4] reported the isolation of an analogous

(1) S. Frankel and R. Allers, *Biochem. Z.*, **18**, 40 (1909).
(2) L. Kraus, *ibid.*, **22**, 131 (1909).
(3) D. Richter and H. Blaschko, *J. Chem. Soc.*, 601 (1937).
(4) D. E. Green and D. Richter, *Biochem. J.*, **31**, 596 (1937).



I II III

bromo derivative II (X = Br) from the oxidation of adrenaline with bromine. The importance of the zwitterionic contribution III for the parent adrenochrome[5,6] will likewise hold for iodo- and bromoadrenochrome. Substitution by halogen in position 2 of the aminochrome II has been accepted by subsequent investigators,[7-11] although Heacock[7] emphasized the absence of any proof for this assumption.

This missing proof has now been obtained by the application of n.m.r. spectroscopy to a series of aminochrome derivatives. The data presented in Table I established that iodine or bromine were not in the 2- but in the 7-position of the indole nucleus. Confirmation of the spectroscopic evidence was then obtained by the unambiguous synthesis of 5,6-dimethoxy-7-iodoindole (X) and 5,6-dimethoxy-7-iodo-2-methylindole (XII).

Results and Discussion

The results of the n.m.r. studies are presented in Table I. The δ-values obtained refer to single peaks corresponding to the correct number of hydrogens unless otherwise noted. Acetoxy hydrogens in compounds 1, 5, 14, 16 and 20 (see Table I) showed identical absorption at $\sim$2.28 δ units while they were separated in the iodo derivatives, the singlet at lower field probably corresponding to the acetoxy group adjacent to the iodine.[12] Assignment for the 2-methyl peak has been possible in all compounds except numbers 12 and 13 where the number of methyl peaks in this region of the spectrum made a rigorous assignment difficult. In some of the 2-methylindoles, 1,3-interactions as described by Hinman and Shull[13] led to slight splitting of the methyl signal with a coupling constant at <1 c.p.s. The N-alkyl substituents appear at 3.5–6 δ and exhibit a striking dependence on iodine or bromine substitution, the peaks of N-alkyl hydrogens of the halogenoindoles appearing at from 30–90 c.p.s. lower field than in their parent compounds. This effect would be expected as a result of substitution in the 7- but not in the 4-position. The effect is greatest in the N-isopropylindoles in which the tertiary hydrogen is likely to be kept in close juxtaposition to the iodo-substituent because of steric factors.

The signals from the 2- and 3-hydrogens are easily assigned because of their doublet or triplet character.[14] In the case of compounds 5–11 the 3-hydrogen signal is broad due to 1,3-interactions with small coupling constants. The only compounds in which assignments for the 2- or 3-hydrogen peaks were difficult were compounds 20–22. They showed 3 singlets in the aromatic region, which by comparison to the analogous compounds 14–17 were given the assignments shown in the table. In all of the other halogen-free compounds, two sharp aromatic peaks were present which correspond to the 4- and 7-hydrogens. The peak found at higher field has been assigned to the 7-proton since it should be shielded to a greater extent by adjacent oxygen as well as nitrogen atoms than the 4-proton with its single *o*-oxygen atom.[15] Substitution of iodine or bromine results in the disappearance of the 7-hydrogen peak. The 4-hydrogen peak then appears at slightly higher field in keeping with the reported shielding effect of *p*-iodo substitution.[15] Compounds 1 $\rightarrow$ 2, 7 $\rightarrow$ 9 and 12 $\rightarrow$ 13, however, show anomalous shifts (8–11 c.p.s.) to lower field strengths. The n.m.r. data definitely establish the 7-position as the location of the halogen and exclude rigorously any other position.

In addition, the 5,6-dihydroxy compounds (10, 11, 18, 19 of Table I) were measured in deuteriomethanol in which they exchanged not only hydrogen bound to nitrogen in the case of 10, 11 but also hydrogen in the 3-position as indicated in the table by the low intensity of the 3-hydrogen peak. This exchange occurred even with the 5,6-dihydroxy-N-methylindoles (18, 19). In the case of compound 18 the deuterium exchange was slow enough to be measurable: The resonance peak due to the 3-hydrogen diminished in intensity from that of 0.6 hydrogen to 0.2 hydrogen in the course of 1 hour while the resonance peak of the 2-hydrogen concomitantly changed from a doublet to a singlet. Koizumi, *et al.*,[16] have noticed the slow exchange of 3-hydrogen with deuterium under mildly acidic conditions while Hinman, *et al.*,[17,18] have reported 3-protonation under strongly acidic conditions. This rapid exchange in a neutral solvent as observed with 10, 11, 18 and 19 (Table I) is exceptional. It was not found with the 5,6-diacetoxy (5, Table I) or 5,6-dimethoxy (7, Table I) compounds and merits further investigation.

Attempts to investigate the (iodo) aminochromes and their methyl ether semicarbazone derivatives by n.m.r. were unsuccessful because of their limited solubility in D_2O, CD_3OD, deuteriopyridine, deuteriodimethyl sulfoxide and deuteriochloroform.

In order to confirm the assignment of the 7-position to the halogen of the aminochrome derivatives, 5,6-dimethoxy-7-iodoindole (X) and 5,6-dimethoxy-7-iodo-2-methylindole (XII) were prepared by an unambiguous independent route (steps IV $\rightarrow$ X, IV $\rightarrow$ XII).

5-Iodoveratraldehyde (IV) or its nitro derivative VI was condensed with nitromethane or nitroethane to give 3,4-dimethoxy-5-iodo-β-nitrostyrene (V), 3,4-dimethoxy-5-iodo-β-methyl-β-nitrostyrene (VII) or the nitrostyrenes (VIII) and (IX), respectively. Nitration of V and VII gave 3,4-dimethoxy-5-iodo-β,6-dinitrostyrene (VIII) and 3,4-dimethoxy-5-iodo-β-methyl-β,6-dinitrostyrene (IX), respectively. 5-Iodo-6-nitroveratraldehyde (VI) was obtained by the nitration of 5-iodoveratraldehyde[19] (IV) and by the controlled oxidation of the β,6-dinitrostyrenes (VIII) and (IX), further evidence for the position of the nitro group in the latter compounds.

Reductive cyclization with hydrogen and 10% palladium–charcoal catalyst of chromatographically

(5) J. Harley-Mason, *Experientia*, **4**, 307 (1948).
(6) J. Harley-Mason, *J. Chem. Soc.*, 1276 (1950).
(7) R. A. Heacock, *Chem. Rev.*, **59**, 181 (1959).
(8) H. Sobotka, N. Barsel and J. D. Chanley, *Fortschr. Chem. org. Naturstoffe*, **14**, 217 (1957).
(9) R. A. Heacock and B. D. Scott, *Can. J. Chem.*, **38**, 508 (1960).
(10) R. A. Heacock and B. D. Scott, *ibid.*, **38**, 516 (1960).
(11) R. A. Heacock, M. E. Mahon and B. D. Scott, *ibid.*, **39**, 231 (1961).
(12) The infrared spectrum of 5,6-diacetoxy-7-iodo-2-methylindole (XXII, R = CH_3) shows two carbonyl peaks at 1775 and 1751 cm.$^{-1}$, whereas 5,6-diacetoxy-2-methylindole (XXI, R = CH_3) shows essentially a single peak at 1745 cm.$^{-1}$ (with a shoulder at 1755 cm.$^{-1}$), the influence of the *o*-iodine atom having caused a shift in the frequency of the 6-acetoxy carbonyl group. Similarly, 5,6-dihydroxy-7-iodo-2-methylindole (XVIII, R = CH_3) shows three peaks in the OH/NH stretching region at 3500, 3410 and 3355 cm.$^{-1}$, while 5,6-dihydroxy-2-methylindole (XXIII, R = CH_3) shows only two peaks at 3430 and 3385 cm.$^{-1}$.
(13) R. L. Hinman and E. R. Shull, *J. Org. Chem.*, **26**, 2339 (1961).
(14) L. A. Cohen, J. W. Daly, H. Kny and B. Witkop, *J. Am. Chem. Soc.*, **82**, 2184 (1960).
(15) P. L. Corio and B. P. Dailey, *ibid.*, **78**, 3043 (1956).
(16) M. Koizumi and T. Titani, *Bull. Chem. Soc. Japan*, **13**, 307 (1938); M. Koizumi, Y. Komaki and T. Titani, *ibid.*, **13**, 643 (1938); M. Koizumi, *ibid.*, **14**, 453 (1939).
(17) R. L. Hinman and J. Lang, *Tetrahedron Letters*, **21**, 12 (1960).
(18) R. L. Hinman and E. B. Whipple, *J. Am. Chem. Soc.*, **84**, 2534 (1962).
(19) R. A. Heacock and O. Hutzinger, unpublished results.

TABLE I

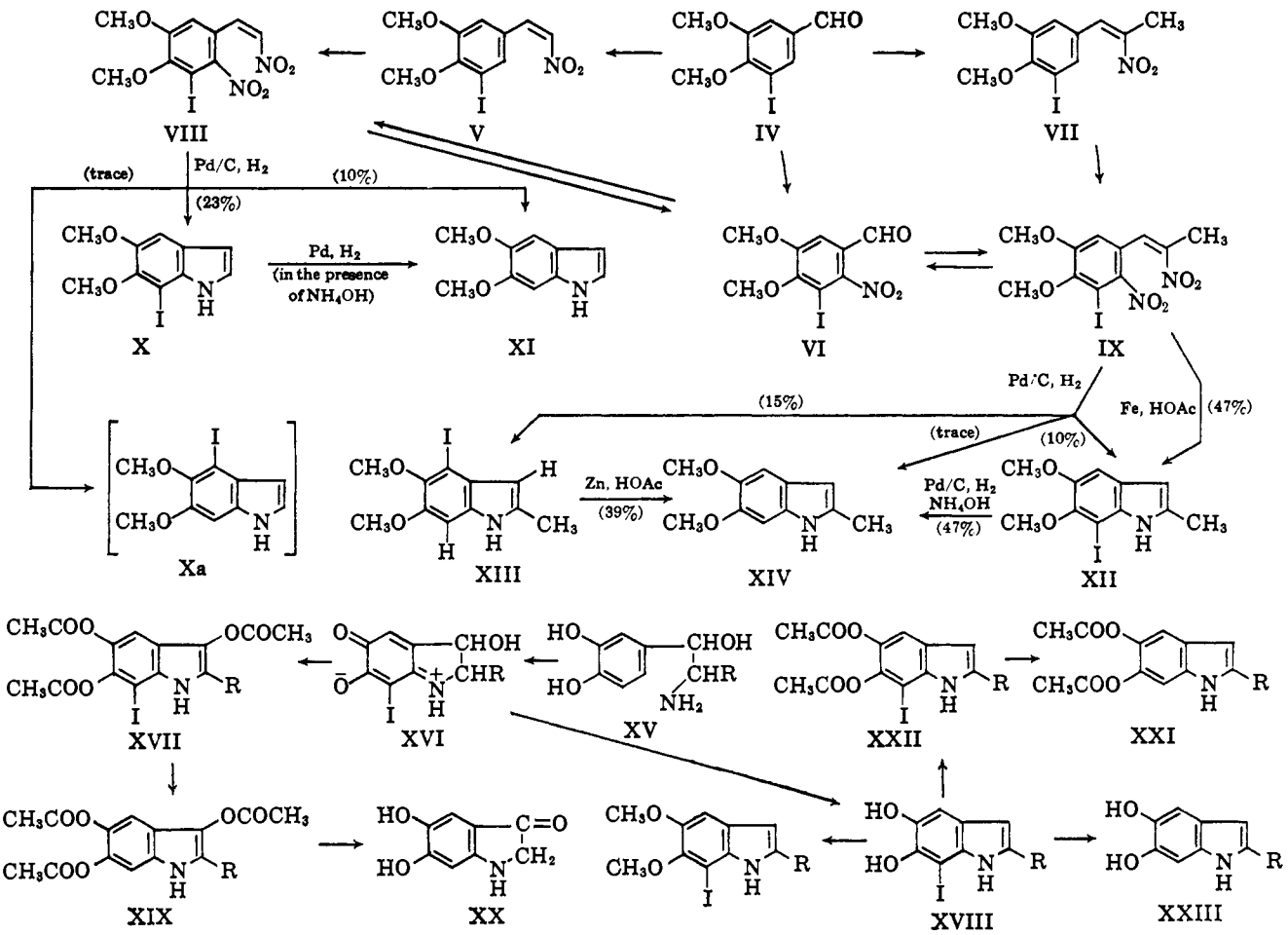
NUCLEAR MAGNETIC RESONANCE SPECTRAL DATA[a]

	Compound, indole	N–H	4-H	7-H	2-H	3-H	N–R	–OCH₃	2-CH₃	–O–C–CH₃ (O ‖ C)
1	5,6-Diacetoxy-[11] (XXI, R = H)	8.44	7.26	6.97	6.88 (triplet)	6.29 (triplet)	..	..	..	2.30
2	5,6-Diacetoxy-7-iodo-[11] (XXII, R = H)	8.46	7.34	..	7.11 (triplet)	6.57 (triplet)	..	..	..	2.29 2.37
3	5,6-Dimethoxy- (XI)	8.16	7.11	6.85	7.07 (triplet)	6.44 (triplet)	..	3.88 3.92	..	..
4	5,6-Dimethoxy-7-iodo-[b] (X)	8.20	7.09	..	7.15 (triplet)	6.60 (triplet)	..	3.90	..	..
5	5,6-Diacetoxy-2-methyl- (XXI, R = CH_3)	8.02	7.18	7.06	..	6.09 (broad)	..	..	2.36	2.28
6	5,6-Diacetoxy-7-iodo-2-methyl- (XXI, R = CH_3)	7.90	7.14	..	..	6.06 (broad)	..	..	2.35	2.29 2.35
7	5,6-Dimethoxy-2-methyl- (XIV)	7.75	7.02	6.75	..	6.14 (broad)	..	3.85 3.92	2.37	..
8	5,6-Dimethoxy-7-iodo-2-methyl-[b] (XII)	7.81	6.97	.	..	6.27 (broad)	..	3.88 3.91	2.42	..
9	5,6-Dimethoxy-4-iodo-2-methyl- (XIII)	7.58	..	6.85	..	5.85 (broad)	..	3.81 3.85	2.36	..
10	5,6-Dihydroxy-2-methyl-[c] (XXIII, R = CH_3)	..	6.91	6.80	..	5.92 (0.2 H) (broad)	..	..	2.25	..
11	5,6-Dihydroxy-7-iodo-2-methyl-[c] (XVIII, R = CH_3)	..	6.85	..	..	6.08 (0.4 H) (broad)	..	..	2.26	..
12	2-Methyl-3,5,6-triacetoxy- (XIX, R = CH_3)	8.03	7.05	6.91	..	..	..	..	2.08 2.28 (6 H) 2.31	
13	7-Iodo-2-methyl-3,5,6-triacetoxy- (XVII, R = CH_3)	7.95	7.16	..	..	..	..	..	2.23 2.27 2.34 2.37	
14	5,6-Diacetoxy-N-methyl-[11]	..	7.33	7.08	6.95 (doublet)	6.37 (doublet)	3.59	..	..	2.28
15	5,6-Diacetoxy-7-iodo-N-methyl-[9]	..	7.33	..	6.96 (doublet)	6.37 (doublet)	4.07	..	..	2.29 2.38
16	5,6-Diacetoxy-N-isopropyl-[11]	..	7.36	7.17	7.20 (doublet)	6.45 (doublet)	4.51 (septet) 1.44 (doublet)	..	..	2.28
17	5,6-Diacetoxy-7-iodo-N-isopropyl-[10]	..	7.36	..	7.33 (doublet)	6.43 (doublet)	5.99 (septet) 1.48 (doublet)	..	..	2.29 2.39
18	5,6-Dihydroxy-N-methyl-[c,11]	..	6.98	6.77	6.82 (doublet-singlet)	6.18 (0.6 H–0.2 H) (doublet)	3.53	..	..	..
19	5,6-Dihydroxy-7-iodo-N-methyl-[c,9]	..	6.93	..	6.86 (singlet)	6.17 (0.1 H) (doublet)	4.07	..	..	..
20	N-Methyl-3,5,6-triacetoxy-[6,22]	..	7.32	7.07	7.22	..	3.57	..	..	2.29
21	7-Iodo-N-methyl-3,5,6-triacetoxy-[6,22]	..	7.32	..	7.25	..	4.10	..	..	2.29 2.32 2.39
22	7-Bromo-N-methyl-3,5,6-triacetoxy-	..	7.32	..	7.27	..	4.09	..	..	2.29 2.32 2.38

[a] The n.m.r. data were obtained on a Varian A-60 instrument by Mr. Robert Bradley, NIAMD. The values are expressed in δ units (p.p.m.) and were relative to an internal standard of tetramethylsilane (0.0 δ). [b] Prepared by unambiguous synthesis. [c] Solvent deuteriomethanol, all other spectra deuteriochloroform.

pure 3,4-dimethoxy-5-iodo-β,6-dinitrostyrene (VIII), gave, invariably, a mixture of 5,6-dimethoxy-7-iodoindole (X), 5,6-dimethoxyindole (XI) and possibly 5,6-dimethoxy-4-iodoindole (Xa) as shown by paper chromatography. No identifiable products were obtained when the dinitrostyrene VIII was reduced with iron in alcoholic acetic acid. Deiodination of 5,6-dimethoxy-7-iodoindole (X) yielded 5,6-dimethoxyindole (XI).

Catalytic hydrogenation of chromatographically pure 3,4-dimethoxy-5-iodo-β-methyl-β,6-dinitrostyrene (IX) gave 5,6-dimethoxy-7-iodo-2-methylindole (XII), an isomeric iodoindole which is probably 5,6-dimethoxy-4-iodo-2-methylindole (XIII) on the basis of its analysis



and n.m.r. spectrum (9, Table I). Formation of the deiodination product, 5,6-dimethoxy-2-methylindole (XIV), was suggested by paper chromatography. This remarkable formation of 4-iodo derivatives merits further investigation. The loss of halogen during reductive cyclization has been previously reported.[20] Both XII and XIII were dehalogenated to 5,6-dimethoxy-2-methylindole (XIV). Reductive cyclization of 3,4-dimethoxy-5-iodo-β-methyl-β,6-dinitrostyrene (IX) could be effected with iron in acetic acid, giving only 5,6-dimethoxy-7-iodo-2-methylindole (XII) in a yield of 47%. Chromatographic and ultraviolet spectroscopic data for many of these indoles are given in Table II.

The 5,6-dihydroxy-7-iodo-2-methylindole (XVIII, R = CH_3) obtained on reduction of the 7-iodo-2-methylnoradrenochrome (XVI, R = CH_3) gave, on methylation, an iodo-5,6-dimethoxy-2-methylindole identical in all respects with 5,6-dimethoxy-7-iodo-2-methylindole (XII). This identity confirms the n.m.r. evidence and furnishes independent proof that substitution of the aminochrome by halogen occurs in the 7-position. Analogously, the 5,6-dihydroxy-7-iodoindole (XVIII, R = H) that was derived by the reduction of iodonoradrenochrome (XV, R = H) gave, on methylation, an iodo-5,6-dimethoxyindole identical, in all respects, with 5,6-dimethoxy-7-iodoindole (X).

Both XVIII, R = H and R = CH_3, proved extremely difficult to methylate, and either prolonged reaction with diazomethane or treatment of the dry sodium derivative of the dihydroxyindole with anhydrous dimethyl sulfate in boiling benzene was necessary to bring about methylation of the hydroxy groups.

(20) F. Benington, D. Morin and L. C. Clark, Jr., *J. Org. Chem.*, **25**, 1545 (1960).

In a preliminary communication[21] the original formulation of an N,O,O,O-tetraacetyliodonoradrenolutin[22] for the rearrangement product of iodonoradrenochrome with acetic anhydride in pyridine was questioned. Now, in line with the n.m.r. data of Table I, iodonoradrenochrome must be formulated as XVI (R = H), and its rearrangement product as 7-iodo-3,5,6-triacetoxyindole (XVII, R = H), which on deiodination yields 3,5,6-triacetoxyindole (XIX, R = H). Alkaline hydrolysis of 3,5,6-triacetoxyindole (XIX, R = H) in the presence of an antioxidant such as sodium hydrosulfite affords 5,6-dihydroxyindoxyl (noradrenolutin, XX).[21] Likewise, reduction of 7-iodoadrenochrome (XVI, R = H) yields 5,6-dihydroxy-7-iodoindole (XVIII, R = H) which may be acetylated to 5,6-diacetoxy-7-iodoindole (XXII). On deiodination of XVIII (R = H) or XXII (R = H) the known compounds 5,6-dihydroxyindole (XXIII, R = H)[23,24] and 5,6-diacetoxyindole (XXI, R = H),[23] respectively, are obtained.

The analogous transformations are shown by 7-iodo-2-methylnoradrenochrome (XVI, R = CH_3)[22] and probably by other iodo-aminochromes.[25]

Experimental

I. Compounds Derived from the Oxidation of 3,4-Dihydroxynorephedrine. 7-Iodo-2-methylnoradrenochrome (XVI, R = CH_3). (A.) Monohydrate.—Potassium iodate (0.8 g.) was added to a solution of 3,4-dihydroxynorephedrine hydrochloride (0.5 g.) in water (150 ml.), and the resulting purple solution was stirred at 30° until crystals began to separate out (usually 1.5

(21) R. A. Heacock and B. D. Scott, *Experientia*, **17**, 347 (1961).

(22) J. Bu'Lock and J. Harley-Mason, *J. Chem. Soc.*, 712 (1951).

(23) R. J. S. Bear, K. Clarke, H. G. Khorana and A. Robertson, *ibid.*, 2223 (1948).

(24) J. Harley-Mason, *ibid.*, 200 (1953).

(25) J. Bu'Lock and J. Harley-Mason, *ibid.*, 2248 (1951).

TABLE II

CHROMATOGRAPHIC AND ULTRAVIOLET ABSORPTION SPECTRAL DATA OF SEVERAL INDOLE DERIVATIVES

Compound	Radial chromatography[a] A	B	C	Thin-layer chromatography[b]	Paper chromatography[c]	λ_{max}, mμ[d]
VII		0.84				
VIII		.21				
IX		.49				
X	0.78				0.31	
Xa	.08					
XI	.21				.42	271, 294, 299, (305)
XII	.86			0.80	.25	224, 277, (295), 308[e]
XIII	.22			.20	.34	222, (275), 283, (300)[e]
XIV	.34			.38	.40	270, 300, 304[e]
XVII, R = H						225, 291 (298)
XVII, R = CH_3			0.50			231, 290, (297)
XVIII, R = H						275, 301, (310)
XVIII, R = CH_3						274, 304, (310)
XIX, R = H						224, 286, (293)
XIX, R = CH_3			.22			226, 289, (295)
XXI, R = H						221, (274), 282, (287), 292
XXI, R = CH_3			.47			224, (276), 290, (294)
XXII, R = H						224, (275), 287, (296)
XXII, R = CH_3			.72			228, (279), 288, (296)
XXIII, R = H						274, (299), 303, (309)
XXIII, R = CH_3						274, (301), 306, (311)

[a] Formamide-treated paper; solvents: A, dichloromethane–petroleum ether (b.p. 60–80°) (1:2); B, petroleum ether (b.p. 80–100°); C, benzene–petroleum ether (b.p. 60–80°) (2:1). [b] Silica Gel-G; solvent, chloroform–carbon tetrachloride (1:1). [c] Whatman No. 1; solvent, 2% aqueous acetic acid. [d] Solvent, methanol; shoulders shown in parentheses. [e] Solvent, ethanol.

to 2.5 hours). The reaction mixture was allowed to stand at 4° overnight and 7-iodo-2-methylnoradrenochrome monohydrate (0.44 g.) (previously described as the 2-iodo derivative[22]) was obtained as a brownish violet crystalline solid (decomposition point *ca.* 130°).

Anal. Calcd. for $C_9H_8INO_3 \cdot H_2O$: C, 33.46; H, 3.12; N, 4.34; I, 39.28. Found: C, 33.43; H, 3.17; N, 4.53; I, 39.95.

(B) **Anhydrous Form.**—In some experiments, crystals did not appear before 4 to 5 hours. This violet-brown crystalline solid was anhydrous 7-iodo-2-methylnoradrenochrome.

Anal. Calcd. for $C_9H_8INO_3$: C, 35.45; H, 2.64; N, 4.59; I, 41.60. Found: C, 35.34; H, 2.72; N, 4.50; I, 41.96.

7-Iodo-2-methyl-3,5,6-triacetoxyindole (XVII, R = CH_3).—7-Iodo-2-methylnoradrenochrome monohydrate (1 g.) was dissolved in a 1:1 mixture of acetic anhydride and dry pyridine (40 ml.) and the solution was allowed to stand at room temperature for 3 hours. The reaction mixture was then added dropwise to a stirred ice–water mixture. The aqueous reaction mixture was extracted with peroxide-free ether; the combined ether extracts were washed with aqueous sodium bicarbonate (until free of acetic acid) and finally with water. Removal of the ether from the dried (Na_2SO_4) extracts *in vacuo* gave a yellowish residue, which on recrystallization from benzene–petroleum ether (b.p. 80–100°) afforded colorless prisms of 7-iodo-2-methyl-3,5,6-triacetoxyindole (m.p. 203°, 0.51 g.). It was demonstrated paper chromatographically that this material was contaminated with some 7-iodo-5,6-diacetoxy-2-methylindole. The crude product was purified chromatographically on silica gel (L. Light & Co., 200–300 mesh). After elution of the column with benzene and recrystallization from benzene–petroleum ether (b.p. 80–100°), colorless needles (0.03 g.) were obtained, m.p. 165°, undepressed on admixture with an authentic sample of 7-iodo-5,6-diacetoxy-2-methylindole. Further elution of the column with benzene–ethyl acetate (97:3) and (95:5) gave solid products which, after recrystallization from benzene–petroleum ether (b.p. 60–80°), afforded colorless prisms (slowly turning yellow on storage) of 7-iodo-2-methyl-3,5,6-triacetoxyindole (0.26 g.), m.p. 205°. (The literature reports[22] m.p. 199–200° for an incorrectly assigned structure.)

Anal. Calcd. for $C_{15}H_{14}INO_6$: C, 41.77; H, 3.25; N, 3.25; I, 29.47; *o*-acetyl, 29.94; mol. wt., 431. Found: C, 41.90; H, 3.18; N, 3.35; I, 29.64; *o*-acetyl, 29.50; mol. wt., 420.

2-Methyl-3,5,6-triacetoxyindole (XIX, R = CH_3). (A) By Deiodination of XVII (R = CH_3) with Zinc Powder.—Zinc powder (2.5 g.) was added cautiously, with vigorous stirring, to a solution of 7-iodo-2-methyl-3,5,6-triacetoxyindole (0.275 g.) in boiling glacial acetic acid (5 ml.). The reaction mixture was then refluxed for 5 minutes and filtered into an ice–water mixture; the residual zinc was washed with acetic acid (3 × 1 ml.) and the washings were added to the filtrate. The pale yellow solution was extracted with peroxide-free ether (3 × 50 ml.) and the combined ether extracts were washed with saturated aqueous sodium bicarbonate (until free of acetic acid) and finally with water. The residue obtained on concentration *in vacuo* under N_2 of the dried (Na_2SO_4) extract was dissolved in benzene (5 ml.) and purified on silica gel. Elution of the column with benzene–ethyl acetate (97.5:2.5) gave a small quantity of a solid product, probably 2-methyl-5,6-diacetoxyindole (shown paper chromatographically). Further elution of the column with benzene–ethyl acetate (95:5) gave, after evaporation of the eluent and recrystallization from benzene–petroleum ether (b.p. 80–100°), colorless prisms (turning pink on storage) of 2-methyl-3,5,6-triacetoxyindole (0.47 g.), m.p. 194–195°. (The literature reports[22] m.p. 185–187° for an incorrectly assigned structure.)

Anal. Calcd. for $C_{15}H_{15}NO_6$: C, 59.01; H, 4.95; N, 4.59; *o*-acetyl, 42.3. Found: C, 59.05; H, 4.96; N, 4.54; *o*-acetyl, 41.59.

(B) **By Oxidation and Acetylation of Dihydroxynorephedrine.**—3,4-Dihydroxynorephedrine hydrochloride (5 g.) was suspended in dry acetonitrile (120 ml.). Silver oxide (18 g.) was added and the suspension was vigorously stirred at room temperature for 35 minutes. The reaction mixture was filtered through anhydrous sodium sulfate and the filtrate added to a 1:1 mixture of acetic anhydride and dry pyridine (30 ml.). The acetonitrile was then removed *in vacuo* at room temperature. After being allowed to stand at room temperature for 24 hours the reaction mixture was added dropwise to a stirred ice–water mixture. The aqueous reaction mixture was extracted with ether (4 × 250 ml.). The combined ether extracts were washed with 5% aqueous sodium bicarbonate (2 × 75 ml.) and water (100 ml.). The dried (Na_2SO_4) ether extracts were evaporated *in vacuo*. A yellow oil was obtained which was extracted successively with benzene and with 5%, 10% and 25% ethyl acetate in benzene. The solids obtained on concentration of these extracts were recrystallized individually from benzene–petroleum ether (b.p. 80–100°). The product obtained from the 5% ethyl acetate in benzene extract was not identified; those obtained with the 10% and 25% ethyl acetate in benzene extracts gave pale yellow crystalline solids, m.p. 187–188° and m.p. 178–180°, respectively, which did not depress the m.p. of 2-methyl-3,5,6-triacetoxyindole prepared by the method described under A.

5,6-Dihydroxy-7-iodo-2-methylindole (XVIII, R = CH_3).—3,4-Dihydroxynorephedrine hydrochloride (2.0 g.) was dissolved in water (600 ml.) and potassium iodate (3.2 g.) was added. After agitation at room temperature for 2 hours, an excess of sodium hydrosulfite (ascorbic acid or sodium borohydride may also be used) was added to the dark purple solution. The color was rapidly discharged and the resulting solution was extracted with ether (5 × 100 ml.). Dry benzene (100 ml.) was added to the dried (Na_2SO_4) ether extracts and the ether was removed *in vacuo*, under nitrogen, below 30°. The solution of the crude product in benzene–petroleum ether (b.p. 80–100°) (2:1) was chromatographed on silica gel and eluted with the same solvent. White needles of 5,6-dihydroxy-7-iodo-2-methylindole (0.9 g.), m.p. 128° dec., were obtained on concentration of the eluent.

Anal. Calcd. for $C_9H_8INO_2$: C, 37.53; H, 2.80; N, 4.86; I, 44.06. Found: C, 37.48; H, 2.83; N, 4.84; I, 44.31.

5,6-Dihydroxy-2-methylindole (XXIII, R = CH_3).—The deiodination of 5,6-dihydroxy-7-iodo-2-methylindole (0.3 g.) was carried out as described above for XVII (R = CH_3) using zinc (2 g.) and glacial acetic acid (4 ml.). Dry benzene (300 ml.) was added to the dried (Na_2SO_4) ether extract and the ether was removed *in vacuo* under nitrogen at *ca.* 30°. The crude product in benzene solution was purified on silica gel and eluted with benzene. The product was then recrystallized from petroleum ether (b.p. 80–100°) and sublimed under high vacuum (187° (0.1 mm.)) to yield colorless plates, m.p. 172–174°. No melting point depression was found on admixture with authentic 5,6-dihydroxy-2-methylindole.[24]

Anal. Calcd. for $C_9H_9NO_2$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.01; H, 5.75; N, 8.87.

5,6-Diacetoxy-7-iodo-2-methylindole (XXII, R = CH_3).—Two grams of 3,4-dihydroxynorephedrine was oxidized with potassium iodate as described above and the product was then reduced by the addition of excess sodium borohydride (ascorbic acid or sodium hydrosulfite may also be used). After cautious addition of 2 *N* H_2SO_4 to decompose the excess borohydride the solution was extracted with peroxide-free ether (5 × 100 ml.). A 1:1 mixture of acetic anhydride and dry pyridine (15 ml.) was added to the combined, dried (Na_2SO_4) ether extracts and the ether was removed *in vacuo* under nitrogen at *ca.* 30°. The acetylation mixture was allowed to stand at room temperature overnight and was then added dropwise to a stirred ice–water mixture. The yellow-green precipitate was purified on silica gel with adsorption from benzene–petroleum ether (b.p. 80–100°) (1:1) and elution with benzene to yield, after recrystallization from benzene–petroleum ether (b.p. 100–120°), 5,6-diacetoxy-7-iodo-2-methylindole (1.5 g.), m.p. 164–165°, identical with the acetylation product of 5,6-dihydroxy-7-iodo-2-methylindole.

Anal. Calcd. for $C_{13}H_{12}INO_4$: C, 41.84; H, 3.24; N, 3.75; I, 34.07; *o*-acetyl, 23.07. Found: C, 41.67; H, 3.17; N, 3.73; I, 34.01; *o*-acetyl, 23.42.

5,6-Diacetoxy-2-methylindole (XXI, R = CH_3).—Deiodination of 5,6-diacetoxy-7-iodo-2-methylindole (1.5 g.) was carried out as described above in the deiodination of XVII (R = CH_3) with zinc (10 g.) and acetic acid (20 ml.). The dried (Na_2SO_4) ether extracts were evaporated *in vacuo*. The crude product was purified by repeated recrystallization from benzene–petroleum ether (b.p. 100–120°) to yield 5,6-diacetoxy-2-methylindole as a colorless crystalline solid (0.46 g.), m.p. 133–136°. After further purification on silica gel with adsorption from, and elution with, benzene–petroleum ether (b.p. 60–80°) (1:1) colorless crystals, m.p. 140–141.5°, were obtained which did not depress the melting point of 5,6-diacetoxy-2-methylindole (XIII) prepared by acetylation of 5,6-dihydroxy-2-methylindole.[24]

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67; *o*-acetyl, 34.80. Found: C, 63.44; H, 5.36; N, 5.72; *o*-acetyl, 35.35.

II. Unambiguous Synthesis of 5,6-Dimethoxy-7-iodoindoles. 3,4-Dimethoxy-5-iodo-β-nitrostyrene (V).—A solution of 3,4-dimethoxy-5-iodo-α-nitromethylbenzyl alcohol (0.2 g.)[19] in acetic anhydride (1 ml.) containing fused sodium acetate (0.8 g.) was refluxed for 10 minutes and poured into water. The crude product, after recrystallization from ethanol, afforded yellow needles of 3,4-dimethoxy-5-iodo-β-nitrostyrene (0.18 g.), m.p. 127°, undepressed on admixture with an authentic sample.[26]

3,4-Dimethoxy-5-iodo-β-methyl-β-nitrostyrene (VII).—A solution of 5-iodoveratraldehyde (5.0 g.) and nitroethane (12 ml.) in acetic acid (18 ml.) containing ammonium acetate (1.0 g.) was refluxed for 3 hours. The oily product which separated after the reaction mixture had been poured into water was extracted with benzene. The benzene extract was stirred with saturated aqueous sodium bisulfite for 10 minutes and then separated and dried (Na_2SO_4). After evaporation, recrystallization from aqueous ethanol gave yellow needles of 3,4-dimethoxy-5-iodo-β-methyl-β-nitrostyrene (3.8 g.), m.p. 70°.

Compound VII (0.14 g.) was also synthesized from 3,4-dimethoxy-5-iodo-α-(1-nitroethyl)-benzyl alcohol,[19] (0.2 g.) in analogy to the preparation of V.

Anal. Calcd. for $C_{11}H_{12}INO_4$: C, 37.84; H, 3.47; N, 4.02; I, 36.35. Found: C, 37.96; H, 3.42; N, 4.12; I, 37.74.

3,4-Dimethoxy-5-iodo-β,6-dinitrostyrene (VIII). (A) By Nitration of VII.—A solution of 3,4-dimethoxy-5-iodo-β-nitrostyrene (4.0 g.) in acetic anhydride (80 ml.) was added dropwise to a stirred volume (150 ml.) of nitric acid (*d.* 1.4) at −5°. The reaction mixture was cautiously heated to 40° and then poured into a large excess of an ice–water mixture. The yellow precipitate was purified by recrystallization first from ethanol and then from benzene–petroleum ether (b.p. 60–80°). Yellow needles of 3,4-dimethoxy-5-iodo-β,6-dinitrostyrene (2.8 g.), m.p. 158–160°, were obtained.

(B) By Dehydration of the Parent Nitro Alcohol.—A solution of 3,4-dimethoxy-5-iodo-6-nitro-α-nitromethylbenzyl alcohol[19] (1.5 g.) in acetic anhydride (6 ml.) containing anhydrous sodium acetate (1.5 g.) was refluxed for 10 minutes. The yellow solid, which was obtained on pouring the reaction mixture into water, was recrystallized from ethanol to yield yellow needles of 3,4-dimethoxy-5-iodo-β,6-dinitrostyrene (1.2 g.), m.p. 158–160°, identical with the product as prepared by method A.

(C) By Condensation of VI with Nitromethane.—A solution of 6-nitro-5-iodoveratraldehyde (VI)[19] (0.2 g.), nitromethane (0.5 ml.) and ammonium acetate (0.05 g.) in acetic acid (1.5 ml.) was refluxed for 3 hours. On pouring the reaction mixture into water a yellow solid was obtained which, on recrystallization from aqueous ethanol, afforded yellow needles of 3,4-dimethoxy-5-iodo-β,6-dinitrostyrene (0.1 g.) identical in all respects with the material prepared by methods A and B.

Anal. Calcd. for $C_{10}H_9IN_2O_6$: C, 31.60; H, 2.87; N, 7.37; I, 33.39. Found: C, 31.75; H, 2.65; N, 7.34; I, 33.55.

3,4-Dimethoxy-5-iodo-β-methyl-β,6-dinitrostyrene (IX) was prepared by methods analogous to those described above for the preparation of the lower homolog VIII. By the nitration method A 2.65 g. of 3,4-dimethoxy-5-iodo-β-methyl-β-nitrostyrene (VII) gave 2.5 g. of the dinitrostyrene IX, m.p. 110–111°. By the dehydration method B 0.21 g. of the dinitrostyrene IX was obtained from 0.25 g. of the corresponding nitro-alcohol. By the condensation method C 0.08 g. of the dinitrostyrene IX was obtained from 6-nitro-5-iodoveratraldehyde (0.2 g.), nitroethane (0.7 ml.) and ammonium acetate (0.1 g.) in acetic acid (1.5 ml.).

Anal. Calcd. for $C_{11}H_{11}IN_2O_6$: C, 33.52; H, 2.82; N, 7.11; I, 32.20. Found: C, 33.78; H, 2.86; N, 7.11; I, 32.33.

5-Iodo-6-nitroveratraldehyde (VI). (A) By Oxidation of the Dinitrostyrene V.—A saturated solution of potassium permanganate in acetone, purified by distillation from potassium permanganate, was added dropwise with shaking to a solution of 3,4-dimethoxy-5-iodo-β,6-dinitrostyrene (V) (0.10 g.) in acetone (30 ml.) until a permanent pink color persisted. The reaction mixture was filtered and the residue, after evaporation of the acetone, was recrystallized from 90% ethanol. 5-Iodo-6-nitroveratraldehyde (0.07 g.) was obtained in the form of pale yellow needles, m.p. 153°, undepressed on admixture with a sample of this compound prepared by nitration of 5-iodoveratraldehyde.[19]

(B) 3,4-Dimethoxy-5-iodo-β-methyl-β,6-dinitrostyrene (VII) (0.1 g.) was oxidized with potassium permanganate in acetone in a similar manner to give 0.03 g. of 5-iodo-6-nitroveratraldehyde, m.p. 153°.

5,6-Dimethoxy-7-iodoindole (X). (A) *Via* **Dinitrostyrene VIII.**—A solution of 3,4-dimethoxy-5-iodo-β,6-dinitrostyrene (VIII) (1.0 g.) in a mixture of ethyl acetate (300 ml.), ethanol (26 ml.) and acetic acid (3 ml.) containing 0.5 g. of 10% palladium-on-charcoal catalyst was shaken in a hydrogen atmosphere at 55 p.s.i. at 45–50° for 5 hours. The reaction mixture was filtered, neutralized with solid sodium bicarbonate, washed with water, dried (Na_2SO_4), and concentrated *in vacuo* under nitrogen. The crude product was purified first on silica gel with adsorption from 1:1 and elution with 95:5 benzene–petroleum ether (b.p. 80–100°) and then by recrystallization from benzene–petroleum ether (b.p. 60–80°). 5,6-Dimethoxy-7-iodoindole (0.182 g.) was obtained in colorless prisms, m.p. 130–131°.

Anal. Calcd. for $C_{10}H_{10}INO_2$: C, 39.61; H, 3.32; N, 4.62; I, 41.87. Found: C, 39.82; H, 3.48; N, 4.77; I, 41.83.

Further elution of the above column with benzene–ethyl acetate (95:5) gave, after recrystallization of the product from light petroleum, colorless prisms of 5,6-dimethoxyindole (VI) (0.085 g.), m.p. 154°, undepressed on admixture with an authentic specimen.[27]

(B) *Via* **Iodonoradrenochrome.**—A solution of diazomethane in ether (1.5 ml.; containing 15.3 mg. of diazomethane) was added to a solution in ether (10 ml.) of 5,6-dihydroxy-7-iodoindole, prepared by the reduction of 7-iodonoradrenochrome (0.05 g.).[11] The reaction mixture was allowed to stand under nitrogen at room temperature for 10 minutes. The ether was removed *in vacuo* (under nitrogen) and the methylation procedure was repeated five times. The methylation product was purified on alumina-G, with absorption from benzene–petroleum ether (b.p. 80–100°) (4:1) and elution with benzene–petroleum ether (b.p. 80–100°) (9:1), giving elongated prisms of 5,6-dimethoxy-7-iodoindole, m.p. 127–128°, undepressed on admixture with a sample prepared by method A. A small quantity of unreacted 5,6-dihydroxy-7-iodoindole could be obtained by further elution of the column with ethyl acetate.

5,6-Dimethoxyindole (XI).—A solution of 7-iodo-5,6-dimethoxyindole (30 mg.) in ethyl acetate (10 ml.), ethyl alcohol (2 ml.) containing concentrated ammonia solution (1 drop) and a

(26) X. A. Dominguez, G. L. Diez and F. V. Gonzalez, *Ciencia* (Mexico), **15**, 208 (1955).

(27) C. F. Huebner, H. A. Troxell and D. C. Schroeder, *J. Am. Chem. Soc.*, **75**, 5887 (1953).

10% palladium-on-charcoal catalyst (20 mg.) was shaken in the presence of hydrogen at room temperature and under atmospheric pressure for 3 hours. The reaction mixture, after filtration, was concentrated to dryness *in vacuo* and the crude deiodination product was purified on silica gel with adsorption from benzene and elution with ethyl acetate–benzene (5:95), and then by recrystallization from benzene–petroleum ether (b.p. 80–100°) giving colorless prisms of 5,6-dimethoxyindole, m.p. 154°, undepressed on admixture with an authentic specimen.[27]

5,6-Dimethoxy-7-iodo-2-methylindole (XII). (A) Reductive Cyclization with Palladium.—A solution of 3,4-dimethoxy-5-iodo-β-methyl-β,6-dinitrostyrene (1.0 g.) in a mixture of ethyl acetate (300 ml.), ethanol (26 ml.) and acetic acid (3 ml.), containing 0.5 g. of 10% palladium-on-charcoal catalyst was shaken in a hydrogen atmosphere at 55 p.s.i. at 40° for 3 hours. The product was isolated and purified by the procedure described above for the preparation of 5,6-dimethoxy-7-iodoindole (XXXII). 7-Iodo-5,6-dimethoxy-2-methylindole (0.08 g.), m.p. 130–131°, was obtained as colorless needles or prisms from benzene–petroleum ether (b.p. 80–100°).

Anal. Calcd. for $C_{11}H_{12}INO_2$: C, 41.66; H, 3.82; N, 4.42; I, 40.02. Found: C, 41.77; H, 3.76; N, 4.57; I, 40.12.

4-Iodo-5,6-dimethoxy-2-methylindole.—Further elution of the silica gel column with ethyl acetate–benzene (5:95) yielded after recrystallization from benzene–petroleum ether (b.p. 80–100°) a colorless crystalline solid (XIII), 0.12 g., m.p. 127°, which depressed the m.p. of 7-iodo-5,6-dimethoxy-2-methylindole and gave a different infrared spectrum. The compound was isomeric with 7-iodo-5,6-dimethoxy-2-methylindole and it has been formulated as the 4-iodo isomer on the basis of n.m.r. data (see above).

Anal. Calcd. for $C_{11}H_{12}INO_2$: C, 41.66; H, 3.82; N, 4.42; I, 40.02. Found: C, 41.35; H, 3.94; N, 4.44; I, 39.94.

(B) Reductive Cyclization with Iron Powder.—A solution of 3,4-dimethoxy-5-iodo-β-methyl-β,6-dinitrostyrene (0.05 g.) in a 1:1 ethanol–acetic acid mixture (10 ml.) to which iron powder (0.1 g.) had been added over a period of 15 minutes was refluxed with vigorous stirring. The reaction mixture was filtered from the residual iron, neutralized with solid sodium bicarbonate and was then extracted with ether. The crude product obtained on concentration of the dried (Na_2SO_4) ether extract was purified on silica gel with adsorption from, and elution with, benzene–petroleum ether (b.p. 80–100°) (95:5) followed by recrystallization from benzene–petroleum ether (b.p. 80–100°) to yield crystals of 5,6-dimethoxy-7-iodo-2-methylindole (0.019 g.), m.p. 125–127°, identical in all respects with the material obtained by method A.

(C) By O-Methylation of the Parent Dihydroxyindole.—A solution of sodium methoxide in methanol (2.27 ml.) prepared by dissolving 0.5 g. of sodium in 50 ml. of methanol was added to a solution of 5,6-dihydroxy-7-iodo-2-methylindole (0.1 g.) in methanol under nitrogen. The methanol was removed *in vacuo* under nitrogen. The solid residue was treated with an excess of dimethyl sulfate in dry benzene and the reaction mixture was then refluxed in a nitrogen atmosphere overnight. The product was filtered, and the filtrate stirred vigorously with 2 *N* sodium hydroxide solution to decompose the excess dimethyl sulfate. The benzene layer was separated, washed with alkali, water, and dried (Na_2SO_4). Purification over silica gel and recrystallization from light petroleum (b.p. 80–100°) afforded 7-iodo-5,6-dimethoxy-2-methylindole, m.p. 130°, undepressed on admixture with a sample prepared by method A.

5,6-Dimethoxy-2-methylindole (XIV). (A) By Deiodination of XII with Palladium.—A solution of 5,6-dimethoxy-7-iodo-2-methylindole (XII) (0.25 mg.) in ethyl acetate (25 ml.), ethanol (2.5 ml.) containing concentrated ammonia solution (1 drop) and a 10% palladium-on-charcoal catalyst (15 mg.) was shaken in the presence of hydrogen at room temperature and atmospheric pressure for 3 hours. After filtration, the reaction mixture was concentrated to dryness *in vacuo*. The crude product was purified on silica gel with adsorption from benzene and elution with ethyl acetate–benzene (5:95) and then by recrystallization from benzene–petroleum ether (b.p. 80–100°) to yield 5,6-dimethoxy-2-methylindole (7 mg., 47%), m.p. 90°, undepressed on admixture with an authentic specimen.[24]

(B) By Deiodination of the Isomeric Iodoindole XIII.—The isomeric 5,6-dimethoxy-4-iodo-2-methylindole (XIII) was found to be inert to the above conditions of catalytic hydrogenation. A solution of XIII (30 mg.) in acetic acid to which zinc powder had been added was refluxed for 10 minutes. The solution, after cooling, was treated with excess 40% sodium hydroxide solution and was then extracted with ether. Purification on silica gel, followed by recrystallization from benzene–petroleum ether (b.p. 80–100°), gave 5,6-dimethoxy-2-methylindole (7 mg., 39%), m.p. 90°, undepressed on admixture with an authentic specimen.[24] A small quantity (3 mg.) of a pale yellow crystalline by-product, m.p. 218–220° (probably dimeric), which did not react positively with Ehrlich reagent, was also obtained.

III. Compounds Derived from the Oxidation of Noradrenaline and Adrenaline. 7-Iodonoradrenochrome (XVI, R = H) was prepared as described by Heacock and Scott[21] as deep violet needles, decomposition point 122–127°, yield 35%.

Anal. Calcd. for $C_8H_5INO_3$: C, 33.01; H, 2.08; N, 4.81; I, 43.61. Found: C, 33.19; H, 1.94; N, 4.96; I, 43.70.

7-Iodo-3,5,6-triacetoxyindole (XVII, R = H).[21]—A solution of 7-iodonoradrenochrome (1.9 g.) in acetic anhydride (25 ml.) and dry pyridine (25 ml.) was allowed to stand at room temperature overnight and was then added dropwise, with stirring, to an ice–water mixture (500 ml.). The resulting aqueous suspension was extracted with ether (5 × 150 ml.), and the combined ether extracts were washed with 5% aqueous sodium bicarbonate solution (3 × 50 ml.) and water (100 ml.). After drying (Na_2SO_4), the ether extract was concentrated *in vacuo*, below 30°. The crude product was purified on silica gel with absorption from benzene–petroleum ether (1:1) and elution with ethyl acetate–benzene (5:95), followed by recrystallization from benzene–petroleum ether (b.p. 80–100°), giving 7-iodo-3,5,6-triacetoxyindole in pale yellow plates, m.p. 207–208°. (The literature reports[22] m.p. 208–209° for this compound which was, however, assigned an incorrect structure.)

Anal. Calcd. for $C_{14}H_{12}INO_6$: C, 40.30; H, 2.89; N, 3.36; I, 30.43. Found: C, 40.32; H, 2.92; N, 3.14; I, 30.53.

3,5,6-Triacetoxyindole (XIX, R = H).[21]—Deiodination of the parent XVII (R = H) was carried out in the usual manner starting with 0.8 g. of 7-iodo-3,5,6-triacetoxyindole (XVII, R = H), 6 g. of zinc and 12 ml. of acetic acid. Dry benzene (20 ml.) was added to the residue from the ether extract and the crude product, dissolved in benzene, was purified on silica gel by elution with ethyl acetate–benzene (5:95). Pure 3,5,6-triacetoxyindole (0.8 g.) was obtained in colorless needles, m.p. 123–124°, after recrystallization from benzene–petroleum ether (b.p. 80–100°). (The literature reports[22] m.p. 125–127° for the same compound but incorrectly assigned structure.)

Anal. Calcd. for $C_{14}H_{13}NO_6$: C, 57.73; H, 4.50; N, 4.82. Found: C, 57.79; H, 4.53; N, 4.81.

5,6-Dihydroxyindole (XXIII, R = H).—Deiodination of 0.8 g. of 5,6-dihydroxy-7-iodoindole[11] was carried out as described using zinc (5.3 g.) and 10% aqueous acetic acid (11 ml.). Dry benzene (200 ml.) was added to the dried (Na_2SO_4) ether extract and the ether was removed *in vacuo* under nitrogen, below 30°. The crude product in benzene was purified on silica gel using benzene as eluent. It was then recrystallized from benzene–petroleum ether (b.p. 80–100°) to yield 5,6-dihydroxyindole in colorless needles (0.3 g.), m.p. 138–139°, undepressed on admixture with an authentic sample.[23]

3,5,6-Triacetoxy-7-bromo-N-methylindole.—7-Bromoadrenochrome[4] (0.4 g.) was dissolved in a 1:1 mixture of acetic anhydride and dry pyridine (20 ml.) and the solution allowed to stand at room temperature for 48 hours. The acetylation mixture was poured into an ice–water mixture and the colorless precipitate so obtained was purified by repeated recrystallization from petroleum ether (b.p. 100–120°), giving colorless needles of 3,5,6-triacetoxy-7-bromo-N-methylindole, m.p. 137.5–138.5°.

Anal. Calcd. for $C_{15}H_{14}BrNO_6$: C, 46.89; H, 3.67; N, 3.65. Found: C, 47.23; H, 3.94; N, 3.52.

7-Iodoadrenochrome Methyl Ether Semicarbazone.—A mixture of 7-iodoadrenochrome methyl ether (1.4 g.),[10] semicarbazide hydrochloride (1.25 g.) and sodium acetate (anhydrous, 1.25 g.) was suspended in water, and the resulting suspension stirred at room temperature for 1 hour. The orange-red product was collected and washed with a small volume of cold water. The dried crude product (1.5 g.) was extracted with chloroform. Concentration of the chloroform extracts afforded 7-iodoadrenochrome methyl ether semicarbazone (XLVIII) (0.5 g.) as bright cherry-red prisms after recrystallization from chloroform–petroleum ether (b.p. 60–80°).

Anal. Calcd. for $C_{11}H_{12}IN_4O_3$: C, 35.12; H, 3.48; N, 14.90; I, 33.75. Found: C, 35.24; H, 3.57; N, 14.69; I, 33.88.