532. *The Chemistry of Extractives from Hardwoods. Part XXXII.* Adifoline, an Alkaloid from* Adina cordifolia.

By A. D. Cross, F. E. King, and T. J. King.

A new alkaloid, adifoline, $C_{22}H_{20}N_2O_8$, has been isolated from the heartwood of *Adina cordifolia*. Benzoic acid, umbelliferone, and β-sitosterol are other minor constituents. Adifoline, which contains two acidic groups, belongs to the β-carboline series and is ultimately degraded to apoadifoline, $C_8H_8N_2$, an isomer of apoharmine. Syntheses of certain indoles and oxindoles incidental to the structural problem are described.

The S.E. Asian tree *Adina cordifolia* Hook (family Rubiaceae) possesses a hard, yellow, heartwood known as keli-kadem (Bengal), haldu (N. India), or kwow (Burma and Siam). In 1938 Lal and Dutt [1] described the isolation of a yellow constituent "adinin" and attributed to it the formula $C_{16}H_{14}O_7$. The more detailed examination described here confirms the occurrence of a compound agreeing in physical properties with "adinin" which, however, is shown to be an alkaloid, $C_{22}H_{20}N_2O_8$, of the β-carboline series. In view of possible confusion with the purine adenine we have re-named the compound *adifoline*. One other *Adina* species, *A. rubrostipulata* K. Schum., has previously been examined and contains mitraphylline.[2]

An oily, light-petroleum extract of the ground heartwood, when separated into acid and neutral portions, afforded benzoic acid and β-sitosterol. Ether-extraction of the residual wood then yielded umbelliferone. Adifoline was thereafter obtained from the remaining wood by extraction with boiling acetone; the yield varied (0—0·27% of the wood); it formed bright yellow crystals, slightly soluble in, *e.g.*, ethanol, to give intensely coloured solutions with a brilliant green fluorescence.

Adifoline, $C_{22}H_{20}N_2O_8$ (but normally obtained as a trihydrate), dissolves in aqueous ammonia and sodium hydrogen carbonate, indicating presence of at least one carboxyl group, and titration gave an equivalent weight of 284. Heating it with aqueous alkali liberated acetic acid, corresponding to one acetyl group. One further oxygen atom was identified as methoxyl (Zeisel), and one *C*-methyl group in addition to that present as acetyl was detected by the Kuhn–Roth method. The presence of two acidic groups was established by the formation of a (gummy) dimethyl derivative with diazomethane or methyl sulphate and potassium carbonate. Both adifoline and the dimethyl derivative are weakly basic and dissolve sparingly in mineral acid, but none of the salts, not even derivatives of organic compounds, *e.g.*, picric acid, methyl iodide, was obtained crystalline.

Adifoline was unchanged by hydrogenation over Adams catalyst in a variety of solvents. The low solubility hampered reduction by lithium aluminium hydride, and other methods using hydrochloric acid with tin, zinc, or magnesium were also unsuccessful.

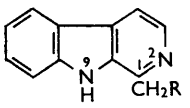
Some indications of the structure were obtained when a close resemblance was observed between the ultraviolet absorption of adifoline and that of 1-ethyl-β-carboline [3] (I; R = Me) and of yobyrine [4] (I; R = *o*-tolyl). Moreover, acidification produced absorption shifts to maxima typical of the β-carbolinium cation chromophore, as exemplified by alstonine or serpentine salts (II).[5] In each case, however, although all absorption intensity values remain strictly comparable, there is a bathochromic shift of the longest-wavelength maximum of adifoline relative to that of the reference compounds (see Table).

In the infrared spectrum of adifoline (in Nujol) measured by Dr. Meakins (Oxford),

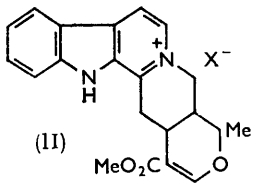
* Part XXXI, *J.*, 1961, 702.

[1] Lal and Dutt, *J. Indian Chem. Soc.*, 1938, **12**, 257.
[2] Michiels, *J. Pharm. Belg.*, 1935, **17**, 1049.
[3] Leonard and Elderfield, *J. Org. Chem.*, 1942, **7**, 556.
[4] Pruckner and Witkop, *Annalen*, 1943, **554**, 127.
[5] Schlittler and Schwarz, *Helv. Chim. Acta*, 1950, **33**, 1463.

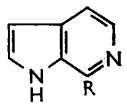
bands of medium intensity are discernible at 3510, 3330, and 3075 cm.$^{-1}$, which together with general broad absorption over the range 3570—2530 cm.$^{-1}$, suggest the presence of one or more carboxylic acid groups, while not excluding OH and NH groups.* Complex absorption occurs in the 1710—1550 cm.$^{-1}$ region with bands at 1709s, 1706s, 1689m, 1678m, 1664m, 1658m, 1638s, 1607s, and 1577 cm.$^{-1}$. Other strong bands appear at 1220



(I)



(II)



(III)

and 1124 cm.$^{-1}$, and weak or medium absorption at 1515, 1312, 1250, 1241, 1193, 1081, 1024, 812, 790, 769, and 719 cm.$^{-1}$. Complete interpretation of this multiplicity of bands is as yet impossible although the absence of absorption above 1710 cm.$^{-1}$ excludes γ-lactone, unconjugated δ-lactone or aldehyde, phenolic ester, and unconjugated ester groups from the molecular structure.

Ultraviolet spectra of adifoline and its degradation products, and of reference compounds, in ethanol unless otherwise stated.

Substance	$\lambda_{max.}$ (log ε)				Ref.
Adifoline in EtOH	235(4·59),	285(4·38),	365(3·67)		
in 0·01N-HCl–EtOH	248(4·47),	299(4·44),	418(3·79)		
in 0·01N-NaOH–EtOH	244(4·65),	269(4·56),	390(3·72)		
1-Ethyl-β-carboline (I; R = Me)	235(4·51),	286(4·20),	351(3·73)		3
Serpentine nitrate (II; X = NO_3)	252(4·5),	305(4·35),	378(3·6)		5
Apoadifoline	219(4·47),	261(3·62),	294(3·73)		
Apoharmine (III; R = Me)	220(4·49),	263(3·68),	292(3·78)		*a*
1,7-Diazaindene	—	—	288(3·92)		*b*
2-Methyl-1,4-diazaindene	—	—	297(4·0)		*b*
2-Methyl-1,5-diazaindene	—	267(3·51)	—		*b*
peri-Fused pentacyclic product (VIII) from selenium reaction	232(4·13),	266(3·89), 373(4·50),	354(4·14) 392(4·59)		
Perylene	252(4·64),	386(4·09),	407(4·43),	434(4·53)	
β-Carboline S_1 from selenium dehydrogn.	231	289	331		
Phenolic β-carboline S_2 from selenium dehydrogn.	231	297	339		
Norharman	232	285	340		4
Harmol	242	300	337		*c*
Tetrahydrocarbazole	229	282	—		*d*
Tetrahydro-6-methoxycarbazole	226	289	—		*c*
Yobyrine	237	290	237, 338, 348		4, *e*
11-Hydroxy-yobyrine	244	302	336		*f*

Refs.: *a*, Schwartz and Schlittler, *Helv. Chim. Acta*, 1951, **34**, 629. *b*, G. A. Swann, personal communication. *c*, Schlittler, Burckhardt, and Gellért, *Helv. Chim. Acta*, 1953, **36**, 1337. *d*, Beer, McGrath, and Robertson, *J.*, 1950, 2118. *e*, Schwartz, *Experientia*, 1950, **6**, 330. *f*, Dorfman, Furlemeier, Huebner, Lucas, MacPhillamy, Müller, Schlittler, and St. André, *Helv. Chim. Acta*, 1954, **37**, 59.

The absence of spectroscopic evidence for a normal *O*-acetyl group and the known instability of *N*-acetylcarbazoles and related carbolines require that the molecule of acetic acid formed on alkaline hydrolysis arises from some secondary decomposition.

Oxidation confirmed the presence of the β-carboline system disclosed by ultraviolet spectroscopy. Treatment of adifoline with alkaline permanganate yielded no identifiable products, but use of hot concentrated nitric acid led to an amorphous, weak, tetracarboxylic acid with the ferrous reaction of a pyridine-α-carboxylic acid.[6] Analysis of

* For tabulated infrared absorption frequencies and correlations with structural units, see A. D. Cross, "An Introduction to Practical Infra-red Spectroscopy," Butterworths, London, 1960.

[6] Ley, Schwartz, and Münnich, *Ber.*, 1924, **57**, 349.

the methyl ester gave the formula $C_{16}H_{16}N_2O_8$ which contains four methoxyl (Zeisel) and one *C*-methyl group (Kuhn–Roth). Since the methoxyl content of the acid is nil, the derivative is a tetramethyl ester. It is insoluble in alkali and possesses one active hydrogen (Zerewitinoff), which is therefore present as NH. Hydrolysis with 2% aqueous sodium hydroxide regenerated the tetracarboxylic acid, but saponification with 10% alkali was accompanied by decarboxylation and resulted in a hydrated tricarboxylic acid which was readily converted into a trimethyl ester. Thermal decarboxylation of the tetracarboxylic acid gave the anhydrous tricarboxylic acid, estimations of the evolved carbon dioxide and water being consistent with $C_{12}H_8N_2O_8,2H_2O$ as the formula of the amorphous tetracarboxylic acid. The triacid was also obtained directly from adifoline by oxidation with concentrated nitric acid at 140° under pressure.

Distillation with zinc dust or freshly precipitated copper powder effected total decarboxylation of the tetracarboxylic acid, and nitrogen analysis of the resulting viscous, alkali-insoluble product, apoadifoline, was in good agreement with the expected molecular formula $C_8H_8N_2$. The ultraviolet absorption of apoadifoline very closely resembles that of apoharmine [7] (III; R = Me) (see Table) but differs noticeably from those of 1,4-, 1,5-, and 1,7-diazaindene which possess only one maximum above 250 mμ. Apoharmine and apoadifoline also exhibit similar colour changes in Dische's carbazole test.[8] The analytical and spectroscopic evidence therefore reveals 1,6-diazaindene $C_7H_6N_2$ (III; R = H) as the parent nucleus of apoadifoline and its derivatives, strong hydrogen-bonding between the NH and adjacent methoxycarbonyl groups accounting for the absence of a characteristic N–H stretching absorption band in the infrared spectrum of the tetramethyl ester.

In addition to alternatives represented by the expression (IV), structures of type (V) require consideration also for the tetracarboxylic acid since the side-chain $CH_2{\cdot}CO_2H$ would lead ultimately through decarboxylation to the generation of acetic acid in the Kuhn–Roth oxidation.

Through the co-operation of Dr. L. M. Jackman (Imperial College, London) a nuclear magnetic resonance spectroscopic study has been made of the tetramethyl ester.* A peak at 2·70 requires the presence of an aromatic hydrogen atom and thus excludes structures of type (IV) in which all available sites are substituted since the NH group is not substituted (see above). Moreover, the value 2·70 corresponds closely to that for the hydrogen at a pyridine β-position [10] (3·015) diminished by 0·2—0·3 p.p.m. owing to an α-methoxycarbonyl group.[11] α-Pyridine-hydrogen causes absorption at 1·50.[10]

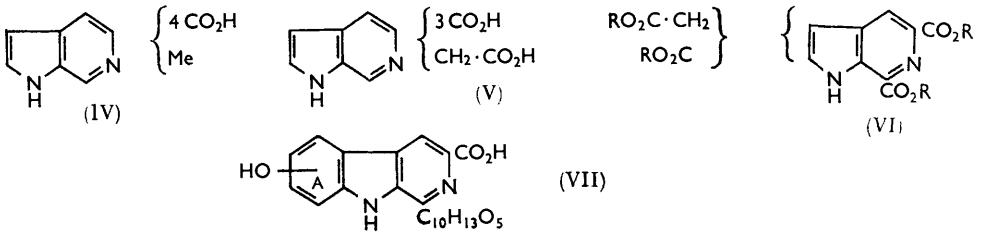
Four peaks appear in the region normally occupied by aromatic methyl ester protons, *e.g.*, 6·10 for ester-hydrogen in methyl benzoate.[12] Three of these (at 5·96, 6·03, and 6·07) are approximately equal in area, but the fourth, at 5·93, is more than half as large again. This extra absorption is attributable to the allylic methylene of $CH_2{\cdot}CO_2Me$. Shoolery's rules [13] predict that this methylene group should absorb very approximately at 6·3, but an appreciable lowering can be expected from a *cis*-α-methoxycarbonyl group [14] (compare, for example, *cis*-dimethyl β-methylglutaconate: allylic methylene absorption at 0·5 p.p.m. lower than that of the *trans*-dimethyl ester [15]). Of the various alternatives based on (IV) and (V), therefore, two isomers of structure (V) alone agree with the nuclear magnetic resonance observations. The preferred structures based on (V) appear to find

* These spectra were obtained with a solution in deuterochloroform and a Varian Associates V-4311 spectrometer with 56·4 Mc./sec. oscillator. Absorption bands are quoted as τ values.[9]

[7] Schwarz and Schlittler, *Helv. Chim. Acta*, 1951, **34**, 629; Perkin and Robinson, *J.*, 1919, **115**, 933.
[8] Dische, *Biochem. Z.*, 1927, **189**, 77.
[9] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon, London, 1959, p. 47.
[10] Ref. 9, p. 64.
[11] Ref. 9, p. 123.
[12] Ref. 9, p. 55.
[13] Ref. 9, p. 59.
[14] Ref. 9, p. 121.
[15] Jackman and Wiley, *Proc. Chem. Soc.*, 1958, 196.

confirmation in the infrared absorption of the tetramethyl ester in chloroform, since of the four ester carbonyl bands (at 1713, 1718, 1722, and 1738 cm.$^{-1}$) that occurring at the significantly highest frequency may be regarded as indicating the non-conjugated carbonyl group.

Since the carboxymethylene group clearly results from the destruction of an aromatic ring, there remain only two possible structures for apoadifolinetetracarboxylic acid, namely,



those represented by formula (VI; R = H). A tentative partial structure (VII) may therefore be derived for the parent alkaloid. The expression (VII) is in agreement with conclusions based on biogenetic considerations which presume the synthesis of the carboline alkaloids from tryptophan or a related precursor. The 5-carboxyl group in (VI; R = H) corresponds to that of the tryptophan precursor, while the 7-carboxyl group is derived from the substituent—$C_{10}H_{13}O_5$ in the case of adifoline—common to all known β-carboline alkaloids. Moreover, formation of adifoline from tryptophan would leave $C_{(6)}$ of the carboline nucleus unsubstituted, in agreement with the nuclear magnetic resonance measurements on tetramethyl apodifolinetetracarboxylate.

The destruction of ring A by oxidation appears to require the presence therein of oxygenated substituents, and chemical evidence on this point was sought from selenium treatment of adifoline. This gave two oily products (S1 and S2), with the characteristic spectra of β-carbolines (see Table). S1 was non-phenolic, but product S2, though insoluble in aqueous sodium hydrogen carbonate, dissolved in sodium hydroxide solution and with ferric chloride developed a bright yellow colour. Further, the longer-wavelength ultraviolet absorption maximum of compound S2 exhibited a bathochromic shift compared with that for S1 of *ca.* 10 mμ, which is comparable with the differences observed (see Table) in the ultraviolet spectra of norharman and harmol, tetrahydrocarbazole, tetrahydro-6-methoxycarbazole, yobyrine, and 11-hydroxy-yobyrine. Compounds S1 and S2 appear to contain respectively a β-carboline and a hydroxy-β-carboline chromophore.

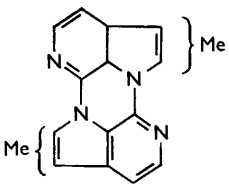
In contradiction to this chemical evidence, however, the ultraviolet absorption of adifoline suggests that the alkaloid A-ring is devoid of phenolic (or phenol ether) substituents, and this anomaly has yet to be resolved. High-pressure hydrogenation in butanol with Raney nickel at 200°, conditions likely to result in *N*-alkylation, afforded a product shown by ultraviolet examination of distillation and chromatographic fractions to be a mixture of indoles and indolenines. However, each fraction was insoluble in alkali, including one fraction $C_{15}H_{21}NO$ which was methoxyl-free and had the spectrum of a typical αβ-disubstituted indole [231 (log ε 4·03), 289 mμ (log ε 3·62)].

Alkali-fusion has not yielded any recognisable product except the acetic acid obtained by milder saponification. Evidence from ultraviolet absorption data suggests that adifoline resembles the simple carbolines, *e.g.*, harmine and norharmine, in its absorption maxima and in the characteristic band shifts in acid media. The N(*b*) atom thus appears to be tertiary and part of an aromatic system and in this respect adifoline is exceptional among the more complex carboline alkaloids. Yet it is noteworthy that other evidence from light absorption, particularly in the infrared region, is compatible with the presence of a conjugated vinyl ether fragment $MeO_2C{-}C{=}C{-}O{-}$ found in several indole

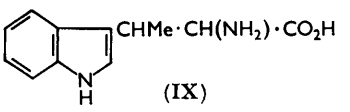
alkaloids [16] that contain a fourth ring fused to ring C *via* the nitrogen atom. Before the partial structure (VII) can be extended, further experimental work is required. This unfortunately has been precluded by difficulties in finding wood samples containing significant amounts of the alkaloid.

When apoadifolinetetracarboxylic acid was heated with selenium a small quantity of a product was isolated having an ultraviolet absorption of general resemblance to that of perylene (see Table). This result may be interpreted as the "*peri*"-fusion of two 1,6-diazaindene residues at the 1- and 7-positions to yield the hitherto unknown heterocycle, 5,5*b*,10,10*b*-tetrazadicyclopent[*de*,*kl*]anthracene,* carrying two methyl substituents (VIII), and it affords further support for the conclusion that the 7-position of apoadifoline cannot bear a *C*-methyl substituent.

Indole and Oxindole Syntheses.—Before nuclear magnetic resonance spectrometry had eliminated a methoxy-α-methyltryptophan structure, *e.g.*, (IX), as a possible adifoline precursor three synthetic routes to this amino-acid were explored. In the first, *N*-chloroacetyl-*p*-anisidine [17] (X) was converted into 5-hydroxyoxindole (XI; R = R′ = H) by a modification of the Stollé method,[18] and 5-methoxyoxindole (XI; R = Me, R′ = H) (35%) accompanied by 5-methoxy-1,3,3-trimethyloxindole (XII; R = Me) obtained from



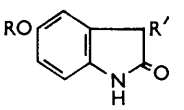
(VIII)



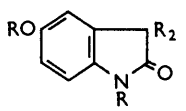
(IX)

p-MeO·C$_6$H$_4$·NH·CO·CH$_2$Cl

(X)



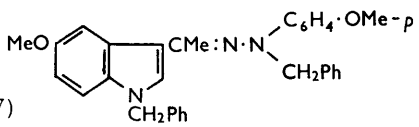
(XI)



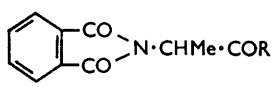
(XII)

p-MeO·C$_6$H$_4$·NR·CH$_2$Ph

(XIII)



(XIV)



(XV)

it with dimethyl sulphate. Others [19] obtained unsatisfactory yields of 5-hydroxyoxindole with the standard Stollé procedure.[20] The properties of 5-methoxyoxindole agree with those of the product previously prepared by cyclisation of 2-amino-5-methoxyphenylacetic acid; [21] Robertson and his co-workers [19] have already shown that the compound prepared by Giovannini and Portmann [22] using vigorous conditions in the Stollé synthesis is in fact 5-hydroxyoxindole, as suggested earlier by Julian *et al.*[23]

Acetylation of 5-methoxyoxindole with sodium ethoxide and ethyl acetate [24] gave 3-acetyl-5-methoxyoxindole (XI; R = Me, R′ = Ac) but the acetyl group was removed during attempted preparation of the ethylene ketal required for conversion into the corresponding indole. With cold acetic anhydride–pyridine 5-hydroxyoxindole was converted

* Ring Index nomenclature, suggested by the Editor.

[16] Janot and Goutarel, *Bull. Soc. chim. France*, 1951, 588; Bader, *Helv. Chim. Acta*, 1953, **36**, 215.
[17] Hill and Kelsey, *J. Amer. Chem. Soc.*, 1922, **44**, 2357.
[18] Abramovitch and Hey, *J.*, 1954, 1697.
[19] Beer, Davenport, and Robertson, *J.*, 1953, 1262; Kellie, O'Sullivan, and Sadler, *J.*, 1956, 3809.
[20] Stollé, *Ber.*, 1914, **47**, 2120.
[21] Koelsch, *J. Amer. Chem. Soc.*, 1944, **66**, 2019.
[22] Giovannini and Portmann, *Helv. Chim. Acta*, 1948, **31**, 1381.
[23] Julian, Meyer, and Printy, in Elderfield's "Heterocyclic Compounds," Wiley, New York, 1952, Vol. III, p. 145.
[24] Horner, *Annalen*, 1941, **548**, 117.

into 5-acetoxy-1,3,3-triacetyloxindole (XII; R = Ac). The preparation and light absorption of some 3-acyl-5-methoxyindoles have been reported recently.[25]

A novel approach to 3-acetyl-5-methoxyindole was investigated in which an *N*-benzyl substituent was incorporated to exclude pyrazole formation during a Fischer indole reaction of the appropriate hydrazone (XIII; R = N:CH·CH_2·COMe). *N*-Benzyl-*p*-anisidine was prepared from *N*-benzylidene-*p*-anisidine by three reduction methods (see Experimental section). Low hydrogenation temperatures were necessary since those recommended for hydrogenation of azomethines [26] caused debenzylation. The amine (XIII; R = H) was converted into *N*-benzyl-*N*-nitroso-*p*-anisidine (XIII; R = NO), and the nitrosamine reduced with lithium aluminium hydride [27] to *N*-benzyl-*N*-*p*-methoxyphenylhydrazine (XIII; R = NH_2), which was characterised as its hydrochloride and benzylidene and *p*-nitrobenzylidene derivatives. Other reduction procedures gave low yields, or cleaved the N–N bond, forming the amine (XIII; R = H). The weakness of the N–N bond was illustrated in the reaction of the hydrazine (XIII; R = NH_2) with the sodio-derivative of acetylacetaldehyde [28] in cold aqueous acetic acid, in which Fischer indole cyclisation rapidly occurred. Formation of 3-acetyl-1-benzyl-5-methoxyindole as its *N'*-benzyl-*N'*-*p*-methoxyphenylhydrazone (XIV) under these extremely mild reaction conditions is unusual. Other products isolated from the reaction mixture were *N*-benzyl-*p*-anisidine (XIII; R = H) and benzaldehyde *N'*-benzyl-*N'*-*p*-methoxyphenylhydrazone (XIII; R = N:CHPh); these two products apparently come from a disproportionation of either the hydrazine (XIII; R = NH_2) or the initial hydrazone (XIII; R = ·N:CH·CH_2·COMe) to give *N*-benzyl-*p*-anisidine and *N*-benzylidene-*p*-anisidine, cleavage of the latter yielding *p*-anisidine (not isolated) and benzaldehyde as the source of (XIII; R = ·N:CHPh). This synthetic route was therefore abandoned.

α-Phthalimidopropionic acid (XV; R = OH), prepared from phthalic anhydride and DL-alanine, was converted by thionyl chloride quantitatively into α-phthalimidopropionyl chloride [29] (XV = Cl). This acid chloride and indolylmagnesium bromide produced 3-α-phthalimidopropionylindole (XV; R = 3-indolyl) in only 3% yield, insufficient to merit further investigation of this route to the desired tryptophan.

Syntheses have since been announced of α-methyltryptophan, involving a Mannich reaction of indole with an appropriate ketimine,[30] and of α-methyltryptamine.[31]

Experimental

Except where otherwise stated, ultraviolet absorption spectra were measured for ethanol solutions with a Unicam S.P. 500 spectrophotometer, and analytical samples of solids were dried at 120° in a vacuum for 3 hr. Rotations are for chloroform solutions. Light petroleum refers to the fraction of b. p. 60—80°. Figures for light absorption are $\lambda_{max.}$ in mμ followed by log ε in parentheses.

Extraction of Adina cordifolia *Heartwood.*—Continuous extraction of the coarsely powdered heartwood (12 kg.) with boiling light petroleum for 24 hr. afforded a yellow-brown syrup (11 g., 0·09%). Benzoic acid was obtained from an ether solution of the syrup by extraction with sodium hydrogen carbonate. The recrystallised acid (1·68 g.), its anilide, and its *p*-bromophenacyl ester had m. p.s in accord with those of authentic preparations and gave no depression on admixture therewith.

After extraction with aqueous 2N-alkali and with 2N-acid the dried ether solution was evaporated to yield a neutral oil from which, by chromatography on alumina, " β "-sitosterol was separated as plates (from methanol), m. p. 136—137°, $[\alpha]_D$ −34° (*c* 0·47). In the

[25] Ballantine, Barrett, Beer, Boggiano, Eardley, Jennings, and Robertson, *J.*, 1957, 2227.
[26] Magee and Henze, *J. Amer. Chem. Soc.*, 1940, **62**, 910.
[27] Schueler and Hanna, *J. Amer. Chem. Soc.*, 1952, **74**, 3693.
[28] Johnson, Woroch, and Mathews, *J. Amer. Chem. Soc.*, 1947, **66**, 566.
[29] Gabriel, *Ber.*, 1905, **38**, 630.
[30] Snyder and Matteson, *J. Amer. Chem. Soc.*, 1957, **79**, 2217.
[31] Abramovitch and Muchowski, *Canad. J. Res.*, 1960, **38**, 554.

Liebermann–Burchard test this sterol underwent the colour changes, red → purple → blue → green. The derived acetate [32] had m. p. 127·5—128·5° [Found: C, 81·3; H, 11·4%; *M* (Rast), 455. Calc. for $C_{31}H_{52}O_2$: C, 81·6; H, 11·4%; *M*, 456·5], and the benzoate [32] had m. p. 144—145° (Found: C, 83·1; H, 10·2. Calc. for $C_{36}H_{54}O_2$: C, 83·3; H, 10·5%).

The wood was next extracted with boiling ether for 24 hr. A gum containing crystals was obtained. Crystallisation from hot water (charcoal) afforded prisms of umbelliferone (7-hydroxycoumarin), m. p. 227—228° (0·03% of the wood) [Found: C, 66·5; H, 4·1%; *M* (Rast), 168. Calc. for $C_9H_6O_3$: C, 66·7; H, 3·7%; *M*, 162]. The coumarin gave an acetate, m. p. 140°, and a methyl ether (treatment with diazomethane), m. p. 116° (Found: C, 67·9; H, 4·9; OMe, 16·7. Calc for $C_{10}H_8O_3$: C, 68·2; H, 4·6; 1OMe, 17·6%), and with aqueous bromine a tribromo-derivative, pale yellow rods (from ethanol), m. p. 197—198° (Found: C, 26·9; H, 1·0; Br, 59·5. Calc. for $C_9H_3Br_3O_3$: C, 27·1; H, 0·8; Br, 60·1%). These physical constants are in close agreement with those recorded [33] for umbelliferone and its derivatives.

Finally, the ground wood was extracted with boiling acetone during 24 hr., and the extract treated in one of two ways. Either it was evaporated, and the residual gum (90—120 g. per 3 kg. of wood) leached with warm water (2 l.) and dissolved in glacial acetic acid (30 c.c.), whereupon crude yellow solid (0—5·1 g.) separated slowly from the syrupy solution ; or the extracts were concentrated to 300—400 c.c. and set aside; after 2—3 days crude alkaloid separated, and further quantities of alkaloid were collected at intervals until no further separation occurred on further concentration. In later extractions, ground heartwood was extracted directly with hot acetone, the light petroleum and ether extractions being omitted, and the yellow principle was obtained from the concentrated extracts as outlined above.

Adifoline.—Crude alkaloid from the modified extraction procedure was extracted successively in a Soxhlet apparatus with benzene (3 days) and ether (3 days). Recrystallisation of the residue several times from ethanol or acetic acid afforded pure *adifoline* as small bright yellow needles or prisms, respectively, which did not melt but darkened slowly above 183° and blackened rapidly at 195—196° with shrinking (Found: C, 53·6; H, 5·6; N, 5·7; OMe, 6·3; Ac, 8·3; *C*-Me, 4·9%; equiv., 284. $C_{22}H_{20}N_2O_8,3H_2O$ requires C, 53·4; H, 5·3; N, 5·7; 1OMe, 6·3; 1Ac, 8·7; 2*C*-Me, 6·1%; equiv., 247). The water of crystallisation was removed at 150° *in vacuo* (Found: C, 60·1; H, 5·1; N, 6·6; OMe, 6·25. $C_{22}H_{20}N_2O_8$ requires C, 60·0; H, 4·8; N, 6·4; OMe, 7·0%). Both sets of analyses agree less well for a formula $C_{22}H_{22}O_8N_2$ for adifoline. Accurate determination of the equivalent weight by titration was hindered by the intense yellow colour of solutions of the alkaloid, which masked the end-point (phenolphthalein).

Neither a picrate nor a methiodide of adifoline could be prepared, nor could crystalline salts be obtained with oxalic, perchloric, sulphuric, nitric, hydrochloric, or hydriodic acid, or with brucine, strychnine, cinchonine, piperidine, triethylamine, or morpholine. Adifoline gave no carbonyl derivatives; negative reactions with ferric chloride, in tests for methylenedioxy, and in the Ehrlich test for indoles were obtained.

Methylation of Adifoline.—(a) *With diazomethane.* An ice-cold solution of adifoline (0·5 g.) in butan-1-ol (175 c.c.) was treated repeatedly with an excess of ethereal diazomethane. After removal of the ether, the alcoholic solution was boiled (charcoal) and evaporated. The residual gum gave a yellow solution in ethanol with an intense green fluorescence. A solution of the product in benzene (100 c.c.) was washed with aqueous 2N-alkali and with water, dried, and concentrated to 40 c.c. before being placed on a column of alumina (20 g.). Elution with benzene–ether (2 : 1) afforded *adifoline dimethyl ester* as a clear, yellow, alkali-insoluble glass (0·31 g., 65%) (Found, for a specimen purified by further chromatography: OMe, 17·9. $C_{24}H_{24}N_2O_8$ requires 3OMe, 19·9%), $\lambda_{max.}$ 240 (4·48), 282 (4·48), 352 mμ (3·69). The ester had the same solubilities in dilute or concentrated mineral acid as had adifoline itself.

(b) *With dimethyl sulphate.* Adifoline was methylated in boiling acetone solution with dimethyl sulphate–potassium carbonate, and the viscous oily product thus obtained chromatographed as described above. Adifoline dimethyl ester, after rechromatography, was gained as a clear yellow glass (Found: OMe, 18·5%).

Oxidation of Adifoline.—A solution of adifoline (1·17 g.) in nitric acid (75 c.c.; *d* 1·4) was heated on the steam-bath for 20 hr. and then evaporated under reduced pressure. More nitric

[32] King and Jurd, *J.*, 1953, 1192.
[33] Markley, Nelson, and Sherman, *J. Biol. Chem.*, 1937, **118**, 433.

acid (75 c.c.; *d* 1·4) was added and the procedure repeated. Water (50 c.c.) was then added to the residues and the mixture boiled for 0·5 hr. before it was again evaporated to dryness under reduced pressure. A solution of the pale yellow residue (0·53 g.) in boiling water was filtered and allowed to cool; over a period of several days, three or four crops of nearly colourless, amorphous apoadifolinetetracarboxylic acid (0·468 g.) were collected (Found: OMe, absent). The acid, which effervesced at 223—225° without melting, dissolved readily in dilute aqueous sodium hydrogen carbonate and sparingly in dilute mineral acid, but was practically insoluble in the usual organic solvents. It gave a negative test with ferric chloride, but an aqueous solution with ferrous sulphate produced a red-brown colour.[6]

Methylation of the Tetracarboxylic Acid.—(*a*) Diazomethane and the tetracarboxylic acid in methanolic suspension gave *tetramethyl apoadifolinetetracarboxylate* as needles (from ethanol), m. p. 210—211° [Found: C, 52·9; H, 4·1; N, 7·6; OMe, 34·1; *C*-Me, 3·7; active H, 0·28%; *M* (Rast), 368. $C_{16}H_{16}N_2O_8$ requires C, 52·8; H, 4·4; N, 7·7; 4OMe, 34·1; 1*C*-Me, 4·1; 1H, 0·28%; *M*, 364]. Ethanolic solutions of the ester fluoresced strongly blue. Light absorption was at 240 (4·69) and 296 mμ (3·97). The infrared spectrum showed no band between 3200 and 3570 cm.$^{-1}$.

(*b*) Dimethyl sulphate (4 c.c.), potassium carbonate (10 g.), and the tetracarboxylic acid (1 g.) were heated together in boiling acetone (150 c.c.) for 24 hr. More dimethyl sulphate (4 c.c.) was added and boiling continued a further day. The tetramethyl ester (686 mg.) was isolated from the filtered mixture by concentration and crystallisation.

Apoadifolinetricarboxylic Acid.—(*a*) The tetracarboxylic acid (250 mg.) and nitric acid (25 c.c.; *d* 1·4) were heated together at 140° in a sealed Carius tube for 20 hr. Crystals separated from the cooled solution. These were collected and the filtrate evaporated to give a residue which recrystallised from water. Further recrystallisations of the solids afforded *apoadifolinetricarboxylic acid* as a monohydrate, pale yellow prisms (64 mg.), m. p. 308—310° (Found: C, 46·6; H, 3·8; N, 10·3. $C_{11}H_8N_2O_6,H_2O$ requires C, 46·8; H, 3·6; N, 9·9%). The anhydrous *acid* was obtained as an amorphous powder, decomp. >300°, when the monohydrate was dried to constant weight at 160° (Found: C, 49·6; H, 3·2; loss in wt., 7·2. $C_{11}H_8N_2O_6$ requires C, 50·0; H, 3·05; loss in wt., 6·4%).

(*b*) Adifoline (1 g.) was heated with nitric acid (30 c.c.; *d* 1·4) in a sealed Carius tube at 140° for 24 hr. and apoadifolinetricarboxylic acid (134 mg.) isolated as described above.

Thermal Decarboxylation of Apoadifolinetetracarboxylic Acid.—Apoadifolinetetracarboxylic acid (300 mg.) was heated at 225° (oil-bath) in a slow stream of carbon dioxide-free, oxygen-free, dry nitrogen, and the effluent nitrogen bubbled through standard barium hydroxide solution. The oil-bath temperature was maintained at 225° until effervescence had diminished and then increased to 250° for 5 min. Carbon dioxide evolved was estimated by titration of the excess of baryta against standard hydrochloric acid (phenolphthalein). The amorphous residue (218 mg.) gave no colour with ferrous sulphate and, on crystallisation from water, afforded pale-yellow prisms, m. p. 312—314° undepressed on admixture with the hydrated tricarboxylic acid [Found: CO_2 evolved, 49·2 mg.; water of crystallisation lost (by difference), 32·8 mg. Calc. for $C_{12}H_8N_2O_8,2H_2O$: loss of $1CO_2$, 43 mg.; loss of $2H_2O$, 31·4 mg.].

Esterification of the Tricarboxylic Acid.—Ethereal diazomethane converted the tricarboxylic acid into the *trimethyl ester*, needles (from methanol), m. p. 196—197° (Found: OMe, 30·5. $C_{14}H_{14}N_2O_6$ requires 3OMe, 30·0%).

Saponification of the Tetramethyl Ester.—(a) *With* 10% *alkali.* The tetramethyl ester (0·40 g.) and 10% aqueous sodium hydroxide (10 c.c.) were heated together on the steam-bath for 2 hr. After filtration, the yellow solution was made just acid to litmus, methanol was added to the hot solution to incipient precipitation, and the solution allowed to cool. Crystallisation of the precipitated solid from aqueous methanol yielded apoadifolinetricarboxylic acid as its monohydrate, prisms (0·28 g.), m. p. 318—320° (Found: C, 47·1; H, 3·9; N, 9·9; *C*-Me, 5·55%; equiv., 87·3. Calc. for $C_{11}H_8N_2O_6,H_2O$: *C*-Me, 5·3%; equiv., 94).

(b) *With* 2% *alkali.* 2% Aqueous potassium hydroxide (25 c.c.) and the tetramethyl ester (190 mg.) were heated together at 100° for 0·5 hr. and an amorphous carboxylic acid (154 mg.) was isolated from the solution by neutralisation, evaporation, and leaching out of inorganic material from the residue with cold water. The acid was identified as apoadifolinetetracarboxylic acid by converting it into the tetramethyl ester, m. p. and mixed m. p. 209—210°.

Neither the tetramethyl ester nor the tricarboxylic acid gave condensation products with benzaldehyde or *p*-nitrobenzaldehyde when piperidine was used as a catalyst.

Apoadifoline.—An intimate mixture of clean, dry, activated zinc dust (6 g.) and finely powdered apoadifolinetetracarboxylic acid (200 mg.) was placed in the bulb of a microdistillation tube and covered with a layer of the pure zinc dust. Distillation was effected at atmospheric pressure, with gradual heating to 270° (0·5 hr.). Freshly precipitated copper powder replaced zinc dust in a similar experiment. In both cases, a small quantity of *apoadifoline* distilled over as a nearly colourless, viscous oil, b. p. 222° (bath)/755 mm. on redistillation (Found: N, 21·5. $C_8H_8N_2$ requires N, 21·2%), $\lambda_{max.}$ 219 (4·47), 261 (3·62), 294 mμ (3·73).

Addition of a trace of formaldehyde to a solution of apoadifoline in concentrated sulphuric acid (Dische's carbazole test) gave a yellow-brown colour accompanied by a green fluorescence. When diluted, the solution became colourless and fluoresced pale violet. Apoharmine shows the same colour changes.[34]

Action of Selenium on the Tetracarboxylic Acid.—Apoadifolinetetracarboxylic acid (0·70 g.) and selenium powder (2 g.) were kept at 280—290° for 20 hr. and then extracted with ether (Soxhlet) overnight. Evaporation of the filtered extracts afforded an oil (44 mg.), which was dissolved in benzene for chromatography on alumina (3 g.). Evaporation of the benzene eluate left a small quantity of pale yellow prisms, m. p. 203—205° after two recrystallisations from benzene. The prisms, believed to be a dimethyl 5,5*b*,10,10*b*-tetra-azadicyclopent[*de*,*kl*]-anthracene (VIII), showed light absorption at 232 (4·13), 266 (3·89), 354 (4·13), 372 (4·50), 392 mμ (4·59) (log ε values for $C_{16}H_{12}N_4$).

Selenium Dehydrogenation of Adifoline.—Adifoline (2 g.) and selenium (2 g.) were heated gradually to 250° and after 0·25 hr. thereat were heated at 300—310° for 0·75 hr. The cooled tube and its contents were crushed, mixed with sand, and extracted (Soxhlet) successively with benzene, ether, and methanol, each extraction being for 24 hr. Evaporation of the benzene extracts afforded a neutral yellow oil (16 mg.), purified by elution with benzene from an alumina column, but showing a negative reaction in the Ehrlich test for indoles. Negligible material resulted from ether-extraction. A yellow-brown gum (123 mg.) was obtained by evaporation of the methanol extracts. After passage through alumina this gum (75 mg.) was fractionally distilled under reduced pressure. The lower-boiling fraction constituted a viscous, colourless oil (10 mg.), b. p. 182—184° (bath)/0·01 mm., insoluble in alkali but dissolving in dilute mineral acids. An ethanolic solution showed no change in light absorption pattern on addition of alkali, and no colour developed on addition of ferric chloride. The higher-boiling fraction was a clear, yellow gum (25 mg.), b. p. 225—235° (bath)/0·03 mm., which was readily soluble in dilute aqueous sodium hydroxide but insoluble in carbonate or sodium hydrogen carbonate solution. Ethanolic solutions, light yellow in colour with intense green-blue fluorescence, became deep yellow on addition of ferric chloride. Insufficient was available for further investigations (Found: OMe, absent). Neither fraction crystallised. Light absorption data are given in the Discussion section.

Hydrogenation of Adifoline.—Anhydrous adifoline (1·2 g.) in dry butan-1-ol (240 c.c.) was hydrogenated at 200°/200 atm. over Raney nickel (*ca.* 1 g.) during 10 hr. Evaporation of the filtered solution yielded oils (1·05 g.) which were promptly chromatographed on alumina (30 g.). Acetone removed a yellow oil (*A*, 536 mg.), acetone–ethanol (1 : 1) eluted a yellow-brown oil (B, 384 mg.), and ethanol eluted a brown gum (C, 97 mg.). No single substance could be isolated from the second (B; $\lambda_{max.}$ 213, 245, 251, 285) or third (C) components from the column.

The yellow oil (A) was separated by vacuum-distillation into a mobile, yellow oil, b. p. 105—110° (bath)/0·01 mm. [Found: OMe, absent; *M* (Rast), 190], and a viscous, yellow oil, b. p. 143—148° (bath)/0·01 mm. [Found, for a sample purified by further distillation: C, 77·8; H, 9·4; N, 6·0%, OMe, absent; *M* (Rast), 211. $C_{15}H_{21}NO$ requires C, 77·9; H, 9·1; N, 6·1%; *M*, 231]. Formulation of the lower-boiling oil as a 2,3-disubstituted *N*-butylindoline was compatible with the ultraviolet spectrum ($\lambda_{max.}$ 208, 253, 280). The higher-boiling fraction had a typical αβ-disubstituted indole spectrum (see Discussion section).

None of the hydrogenation products dissolved in alkali, and none gave a positive reaction with ferric chloride.

Similar results were obtained when the hydrogenation was performed on a solution in dioxan with the expected exception that no *N*-alkylated products appeared.

Action of Alkali on Adifoline.—Adifoline (430 mg.) was boiled in aqueous 2N-sodium

[34] Lawson, Perkin, and Robinson, *J.*, 1924, **125**, 646.

hydroxide (25 c.c.) for 1 hr. The mixture was acidified, and distilled, water being added at the same rate as distillate was collected. The organic acid in the distillate (500 c.c.) was neutralised by titration against 0·02N-sodium hydroxide, and the sodium salt (50 mg.), which remained on evaporation, was boiled with ethanolic *p*-bromophenacyl bromide (15 mg. in 2 c.c.). A crystalline ester was collected which, after recrystallisation from ethanol, had m. p. 85°, alone or on admixture with *p*-bromophenacyl acetate. The acid reaction solution, after removal of the acetic acid in the aqueous distillate, was neutralised. Orange-brown solids which were precipitated were filtered off and extracted with a large volume of ethanol (charcoal). Evaporation of the extracts afforded a solid, purified by reprecipitation from aqueous ethanol to give a yellow amorphous solid which darkened at 258—261° (Found, for a specimen dried at 150°: OMe, absent; equiv., 242).

Some Unsuccessful Experiments.—No crystalline product was obtained when adifoline was treated at 100° with acetic anhydride and pyridine, sulphuric acid, perchloric acid, or acetic acid–sodium acetate.

No hydrogenation products of adifoline proved isolable when Adams platinum catalyst was used in ethanol or acetic acid at room or elevated temperatures. Chemical methods attempted included zinc, magnesium, and tin with acid; sodium and liquid ammonia; and lithium aluminium hydride in tetrahydrofuran (Soxhlet extractor technique). Adifoline dimethyl ester was unchanged after 24 hr. with the last reagent in ether.

5-Hydroxyoxindole.—*N*-Chloroacetyl-*p*-anisidine (25·0 g.) was added to a vigorously stirred melt of aluminium chloride (100 g.) and sodium chloride (20 g.) at 140°. Rapid heating to 235—240° caused brisk evolution of hydrogen chloride, but this slackened after 3—5 min. Care was taken to prevent a temperature rise to above 245° since this caused decomposition of the oxindole. The hot melt was poured on to a marble slab, allowed to cool, pulverised, and decomposed by addition to crushed ice containing a little dilute hydrochloric acid. A yellow solid was collected, washed with small quantities of water and a minimum of cold ethanol, and recrystallised from ethyl acetate (charcoal) as nearly colourless prisms of 5-hydroxyoxindole (8·44 g., 45%), m. p. 270° (decomp.) on rapid heating. The compound decomposed without melting at 252—254° when heated slowly (Found: C, 64·4; H, 4·5; N, 9·1. Calc. for $C_8H_7NO_2$: C, 64·4; H, 4·7; N, 9·4%).

Methylation of 5-Hydroxyoxindole.—5-Hydroxyoxindole (5·1 g.), when boiled with dimethyl sulphate (4·3 g.) and potassium carbonate (12 g.) in acetone during 24 hr., gave, on filtration and evaporation, an oil which crystallised from benzene (charcoal) as pale pink rods of 5-methoxyoxindole (1·93 g., 35%), m. p. 149—151° (Found: C, 66·2; H, 5·3. Calc. for $C_9H_9NO_2$: C, 66·3; H, 5·2%). Koelsch [21] recorded m. p. 152—154°.

When an excess (1·1—1·3 mol.) of dimethyl sulphate had been employed in the same procedure the oily product was fractionally distilled. The second fraction, b. p. 178—198° (bath)/0·8 mm., when triturated with ethanol, afforded *5-methoxy-1,3,3-trimethyloxindole* (1·85 g.), yellow plates (from benzene–light petroleum), m. p. 191—193° (Found: N, 7·2; OMe, 15·4. $C_{12}H_{15}NO_2$ requires N, 6·8; 1OMe, 15·1%). The oil remaining in the mother-liquors and the first fraction, b. p. 149—177° (bath)/0·08 mm., crystallised from benzene to give 5-methoxyoxindole (1·28 g.).

3-Acetyl-5-methoxyoxindole.—Ethyl acetate (0·43 g.) and 5-methoxyoxindole (0·40 g.) were added to sodium (0·06 g.) in dry ethanol (1·5 c.c.) and heated at 100° until a thick paste developed (12—15 min.). The mixture was broken up immediately with crushed ice (20 g.) containing 2N-hydrochloric acid (5 c.c.), and the precipitate collected and washed with a little water. The *3-acetyl-5-methoxyoxindole* (0·23 g.) thus obtained crystallised from aqueous ethanol as pale yellow needles, which gave a purple colour with ferric chloride and had m. p. 181° (Found: C, 64·1; H, 5·6; N, 7·3. $C_{11}H_{11}NO_3$ requires C, 64·4; H, 5·4; N, 6·8%). The *2,4-dinitrophenylhydrazone* separated from benzene–acetone as orange prisms, m. p. 256—257° (decomp.) (Found: C, 53·4; H, 3·8. $C_{17}H_{15}N_5O_6$ requires C, 53·0; H, 3·9%).

5-Methoxyoxindole was isolated from attempted ethylene ketal formation of 3-acetyl-5-methoxyoxindole. The latter (0·74 g.) was treated with boiling benzene (50 c.c.), ethylene glycol (3 c.c.), and toluene-*p*-sulphonic acid (0·15 g.) for 5 hr., and the cooled mixture treated with saturated sodium hydrogen carbonate solution. 5-Methoxyoxindole (0·42 g.) was obtained from the benzene layer.

Acylation of 5-Hydroxyoxindole.—Acetylation of 5-hydroxyoxindole with acetic anhydride–pyridine at room temperature gave *5-acetoxy-1,3,3-triacetyloxindole*, crystallising from benzene

in needles, m. p. 204—205° (Found: C, 60·9; H, 4·9; N, 4·57; Ac, 57·2. $C_{16}H_{15}NO_6$ requires C, 60·6; H, 4·7; N, 4·4; 4Ac, 54·3%). This compound was alkali-insoluble and gave no colour with ferric chloride.

N-*Benzyl*-p-*anisidine*.—(*a*) A hot, stirred, ethanolic solution of *N*-benzylidene-*p*-anisidine was treated portionwise with sodium and, after one hour's boiling, ethanol was removed and water added. The yellow oil obtained by extraction with ether had b. p. 160—164°/0·6 mm. and crystallised from light petroleum as plates of *N*-benzyl-*p*-anisidine, m. p. 52° (yield 88%).

(*b*) *N*-Benzylidene-*p*-anisidine was reduced in ethereal solution with lithium aluminium hydride, and the mixture worked up in the normal manner. *N*-Benzyl-*p*-anisidine was isolated by extraction with ether and crystallised from ethanol as plates, m. p. 51—52° (86% yield).

(*c*) *N*-Benzylidene-*p*-anisidine in ethanol was shaken at 20° for 0·5 hr. with Raney nickel catalyst and hydrogen at 100 atm. *N*-Benzyl-*p*-anisidine was obtained in 93% yield. Similar experiments conducted at 60° (0·5 hr.) and 75° (0·5 hr.) afforded 37 and 0% respectively of the secondary amine. Distillation of the latter reaction solution gave a quantitative yield of *p*-anisidine, needles (from light petroleum), m. p. and mixed m. p. 56°. Ammonia gas was also formed (strong odour).

N-*Benzyl*-N-*nitroso*-p-*anisidine*.—A stirred ethanolic solution of *N*-benzyl-*p*-anisidine and sulphuric acid at 0° was treated portionwise with sodium nitrite (1 equiv.) and diluted with water. N-*Benzyl*-N-*nitroso*-p-*anisidine* was collected. This nitrosamine, needles from ethanol (charcoal), had m. p. 78° (90% yield) and gave a positive Liebermann reaction (Found: C, 69·1; H, 5·8; N, 11·3. $C_{14}H_{14}N_2O_2$ requires C, 69·4; H, 5·8; N, 11·6%).

N-*Benzyl*-N-p-*methoxyphenylhydrazine*.—(*a*) The above nitrosamine was added in ether to a boiling stirred suspension of lithium aluminium hydride in the same solvent. After being boiled for 2 hr. the mixture was worked up in the usual way, saturated sodium potassium tartrate solution being used to dissolve the inorganic precipitate. *N*-Benzyl-*N*-*p*-methoxyphenylhydrazine was obtained as a pale yellow oil (93% yield), b. p. 155—156°/0·2 mm., which decomposed slowly in air. The *hydrazine hydrochloride* separated from ethyl acetate–ethanol as needles, m. p. 146—147° (Found: C, 63·8; H, 6·5; N, 10·4; Cl, 13·4. $C_{14}H_{16}N_2O$,HCl requires C, 63·5; H, 6·8; N, 10·6; Cl, 13·4%). The *benzaldehyde hydrazone* was obtained as pale yellow needles, m. p. 119°, from an ethanolic solution of the hydrazine hydrochloride and benzaldehyde (Found: C, 79·9; H, 6·2; N, 8·8. $C_{21}H_{20}N_2O$ requires C, 79·7; H, 6·4; N, 8·9%). Similarly prepared, the p-*nitrobenzaldehyde hydrazone* crystallised from aqueous ethanol as orange needles, m. p. 134—136° (Found: C, 69·8; H, 5·0; N, 11·5. $C_{21}H_{19}N_3O_3$ requires C, 69·8; H, 5·3; N, 11·6%).

(*b*) Reduction of the nitrosamine with sodium in boiling ethanol for 0·5 hr., evaporation and extraction with ether, gave an oil which crystallised from ethanol as plates (91% yield), m. p. 51—52° alone or mixed with *N*-benzyl-*p*-anisidine. When the mother-liquors were warmed with benzaldehyde and 2N-sulphuric acid, and cooled, the above benzaldehyde hydrazone, m. p. 118°, was obtained in a quantity equivalent to 7% of hydrazine formation.

(*c*) Attempted reduction of the nitrosamine with zinc and acetic acid, with hydrogen sulphide, or catalytically failed. The starting materal was recovered or *N*-benzyl-*p*-anisidine and ammonia were formed.

Reaction of Acetylacetaldehyde with N-*Benzyl*-N-p-*methoxyphenylhydrazine*.—The sodium derivative of acetylacetaldehyde [29] (9·47 g., 0·085 mole) in ice-water (20 c.c.) was added dropwise to a cooled, stirred solution of the hydrazine (20·0 g., 0·086 mole) in acetic acid (11·0 g., 0·18 mole). The mixture was then stirred a further hour, warmed on the water-bath for 0·5 hr., diluted with water (80 c.c.), neutralised with sodium hydrogen carbonate, and extracted with ethyl acetate. Yellow needles (3·58 g.) separated from the extracts and evaporation to 50 c.c. gave a further small quantity of the same product. Recrystallisation from ethyl acetate afforded 3-*acetyl*-1-*benzyl*-5-*methoxyindole* N-*benzyl*-N-p-*methoxyphenylhydrazone* (3·61 g., 17%), m. p. 200° (Found: C, 78·3; H, 6·1; N, 8·7; OMe, 12·7. $C_{32}H_{31}N_3O_2$ requires C, 78·5; H, 6·4; N, 8·6; 2OMe, 12·7%).

Distillation of the ethyl acetate mother-liquors afforded a fraction, b. p. 138—170° (bath)/0·08 mm., which on trituration with ethanol gave *N*-benzyl-*p*-anisidine (7·47 g., 40%) as plates, m. p. and mixed m. p. 50—51° after further recrystallisation from light petroleum; the second fraction, b. p. 205—235° (bath)/0·08 mm., crystallised from methanol as needles (4·51 g., 31%) of benzaldehyde *N*-benzyl-*N*-*p*-methoxyphenylhydrazone, m. p. and mixed m. p. 119°.

In a similar experiment with the hydrazine, acetic acid, and sodioacetylacetaldehyde in a 2 : 3 : 1 molecular ratio the yields of the indole hydrazone, the benzaldehyde hydrazone, and *N*-benzyl-*p*-anisidine, were 11, 28, and 49% respectively. In other experiments the indole hydrazone was isolated without the reaction temperature's rising above 0°.

α-Phthalimidopropionyl Chloride.—Equimolecular proportions of phthalic anhydride and DL-alanine were heated together at 150° until no more steam was evolved. Crystallisation of the residue from hot water gave needles, m. p. 163—164° (lit.,[30] m. p. 160—162°), of α-phthalimidopropionic acid. The latter was treated with an excess of thionyl chloride and, after being boiled under reflux during 1 hr., the solution was distilled. α-Phthalimidopropionyl chloride was collected; it had b. p. 110—113°/0·04 mm., m. p. 72—73° (lit.,[30] m. p. 73°).

Reaction of Indolylmagnesium Bromide with α-Phthalimidopropionyl Chloride.—A solution of α-phthalimidopropionyl chloride (21·83 g., 1·06 mol.) in dry ether (50 c.c.) was added dropwise to a stirred, ice-cold ethereal suspension of indolylmagnesium bromide (18·8 g., 1 mol., in 30 c.c.) at <5°. After addition of the acid chloride stirring was continued for 5 hr. and the mixture kept for 2 days at 0°. After decomposition of the red reaction complex by ice-water, and acidification, ethyl acetate extracts of the aqueous layer were combined with the ethereal layer and this solution was washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated. The resultant red oil was fractionally distilled to give indole, m. p. 50—51° (5·0 g., 50% recovery), and a higher-boiling orange oil, b. p. 250—305° (bath)/0·03 mm., which crystallised from acetone–light petroleum as colourless needles of *3-α-phthalimidopropionylindole*, m. p. 207° (0·80 g., 3% yield) (Found: C, 71·2; H, 4·3; N, 8·7. $C_{19}H_{14}N_2O_3$ requires C, 71·4; H, 4·4; N, 8·8%). The 2,4-dinitrophenylhydrazone was formed with difficulty and crystallised from benzene as orange prisms, m. p. 219—220°.

Acidification of the bicarbonate washings precipitated α-phthalimidopropionic acid, m. p. 162—163° (7·95 g., 40%).

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