Novel Reactions of Indolenines †

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3,3-Disubstituted indolenines readily undergo addition by Grignard reagents to afford 2,3,3-trisubstituted indolines; the reaction is stereospecific if one of the 3-substituents is considerably larger than the other. The diastereoisomeric indolines may be obtained by hydrogenation of the appropriate 2,3,3-trisubstituted indolenines. 2,3,3-Trialkylindolenines are alkylated by Grignard reagents at the α-methylene group of the 2-alkyl substituent. Such indolenines easily autoxidise, *e.g.*, 2-ethyl-3,3-dimethylindolenine affords 2-acetyl-3,3-dimethylindolenine. Mass and n.m.r. spectra of most of the indolenines and indolines are recorded.

DURING the course of our studies [1,2] of electrophilic substitution in indoles, a number of 3,3-dialkylindolenines (I) were prepared in order to study their rearrangement to 2,3-disubstituted indoles. On one occasion, when preparing 3,3-dimethylindolenine (I; R = Me) by methylation of the Grignard derivative of skatole (following Hoshino's procedure [3]), we obtained an oily basic product instead of the expected crystalline material. The spectral characteristics (Table 2) of the anomalous product clearly showed that it was 2,3,3-trimethylindoline (II; $R^1 = R^2 = Me$), and this was confirmed

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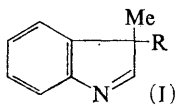
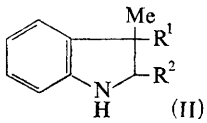
[1] A. H. Jackson and A. E. Smith, *Tetrahedron*, 1965, **21**, 989.
[2] A. H. Jackson and P. Smith, *Tetrahedron*, 1968, **24**, 2227.
[3] T. Hoshino, *Annalen*, 1935, **500**, 35.

by elemental analysis of the hydrochloride. This result was attributed to the addition of an excess of methylmagnesium iodide * to the indolenine 1,2-double bond, because (i) the use of only one equivalent of methylmagnesium iodide in the methylation of skatole gave the expected 3,3-dimethylindolenine (I; R = Me), and (ii) treatment of 3,3-dimethylindolenine (prepared either by monomethylation of skatole or by Fischer indole synthesis [4]) with methylmagnesium iodide gave 2,3,3-trimethylindoline (II; $R^1 = R^2 = Me$).


(I)


(II)

* In all the alkylations of indole derivatives described in Hoshino's paper,[3] 2 equivalents of Grignard reagent and 2 equivalents of alkyl halide are used to each equivalent of indole, but he does not report the isolation of any indolines, only indoles or indolenines.

Several other indolines were also prepared by Grignard addition to 3,3-dialkylindolenines (see Experimental section), and details of their spectra are in Tables 1 and 2. The magnesium derivative of malonic ester can also be added to the 1,2-double bond of indolenines (see Experimental section), and these reactions are clearly of potential use in indole alkaloid synthesis. This type of Grignard addition reaction to alkyl indolenines has not hitherto been observed, but it is not very surprising, since there are many examples of nucleophilic addition to the 1,2-double bond, *e.g.*, the cyclisation of aminoethyl and hydroxyethyl side-chains in the synthesis (and biosynthesis) of the tricyclic ring systems present in physostigma and related alkaloids [5] [*i.e.* (III) ⟶ (IV)], and the metal hydride reductions of indolenines to indolines.[6] Grignard addition to reactive double bonds

[4] K. Brunner, *Monatsh.*, 1895, **16**, 849.
[5] B. Robinson, *Chem. and Ind.*, 1963, 218 and refs. therein.
[6] B. Witkop and J. B. Patrick, *J. Amer. Chem. Soc.*, 1953, **75**, 4474.

TABLE 1

Nuclear magnetic resonance spectra of indolenines in deuteriochloroform and trifluoroacetic acid (τ-values)

Indolenine (substituents)	2-Substituent			3-Substituents			Aromatic-*H* *
		$CDCl_3$	TFA		$CDCl_3$	TFA	TFA
2,3,3-Me_3	$-CH_3$	7·72	7·21				
2,3-Me_2, 3-Et	$-CH_3$	7·80	7·37	$-CH_3$	8·72	8·39	2·45
				$-CH_3$	8·77	8·55	2·41
				$-CH_2CH_3$	8·20q, 9·63t	8·92q, 9·55t	
3,3-Me_2, 2-Et	$-CH_2CH_3$	7·39q, 8·60t	6·92q, 8·42t	$-CH_3$	8·69	8·43	2·45
2,3-Me_2, 3-CH_2Ph	$-CH_3$	7·76	7·20	$-CH_3$	8·72	8·33	~2·5
				$-CH_2C_6H_5$	7·07q, 3·0m (J_{AB} 13·5)	6·70q, 2·75—3·35m (J_{AB} 14)	
3,3-Me_2, 2-Ac	$-COCH_3$	7·31	7·05	$-CH_3$	8·50	8·13	~2·4
3,3-Me_2, 2-C(OH)Me_2	$-C(OH)(CH_3)_2$	6·7b, 8·36	8·09	$-CH_3$	8·47	8·17	~2·5
2,3-$(CH_2)_4$, 3-CH_3	$-CH_2(CH_2)_3$	7·2m, 7·6—8·5m	6·7m, 7·0—8·6m	$-CH_3$	8·72	8·44	2·49
2,3-$(CH_2)_4$, 3-CH_2Ph	$-CH_2(CH_2)_3$	7·15m, 7·5—8·3m	6·8m, 7·0—8·6m	$-CH_2C_6H_5$	6·92q, 2·9m (J_{AB} 14·5)	6·45q, 2·7—3·4m (J_{AB} 14)	2·48
2,3-$CH(CH_2)_3$, 3-CH_3	$-CH(CH_2)_3$	6·4m, 7·5—8·5m	6·4m, 6·8—8·4m	$-CH_3$	8·70	8·36	2·40
CH_2Ph	$-CH_2C_6H_5$	7·1, 2·73	6·6m, 2·5—2·9m				

* In $CDCl_3$, *ca.* 2·4—3·0m.

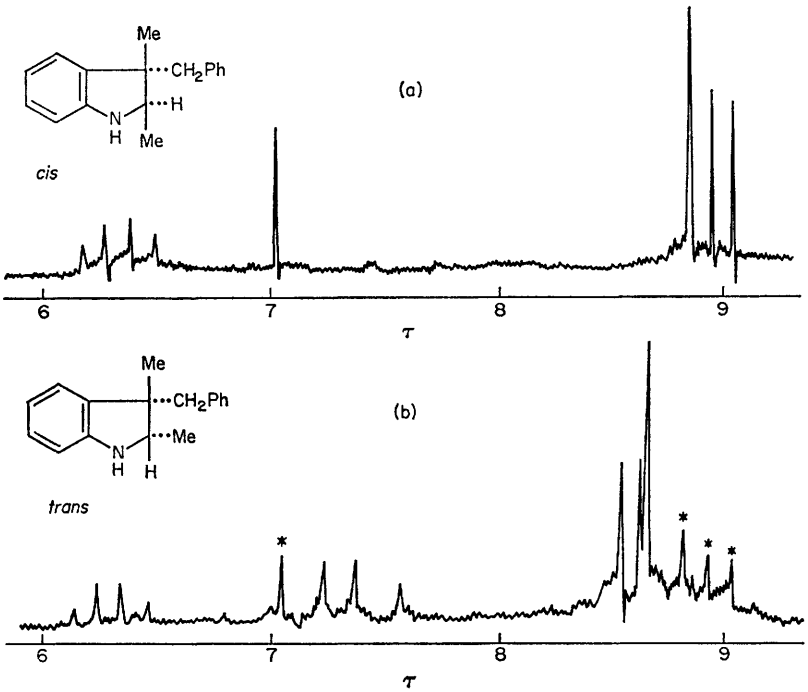
TABLE 2

Nuclear magnetic resonance spectra of indolines in deuteriochloroform and trifluoroacetic acid (τ-values)

Indoline (substituents)	2-*H*		2-Substituent			3-Substituents			N-*H*
	$CDCl_3$	TFA		$CDCl_3$	TFA		$CDCl_3$	TFA	$CDCl_3$
2,3,3-Me_3	6·50q	6·12q	$-CH_3$	8·84d	8·50d	$-CH_3$	8·96	8·80	6·40
							8·73	8·60	
3,3-Me_2, 2-Et	6·77q	6·25t	$-CH_2CH_3$	8·4—9·2m	7·8—9·0m	$-CH_3$	8·97	8·82	6·15
							8·71	8·56	
2,3-Me_2, 3-Et	6·35q	5·8b	$-CH_3$	8·88d	8·48d	$-CH_3$	8·92	8·75	6·48
						$-CH_2CH_3$	8·2—9·4m	8·0—8·6m, 9·14t	
2,3-Et_2, 3-Me	6·58q	6·04t	$-CH_2CH_3$	8·0—9·5m	7·7—9·3m	$-CH_3$	8·92	8·76	6·20
						$-CH_2CH_3$	8·0—9·5m	7·7—9·3m	
2,3-Me_2, 3-Pr^i	6·18q	5·57q	$-CH_3$	8·87d	8·45d	$-CH_3$	8·85	8·68	6·48
						$-CH(CH_3)_2$	7·7—8·4m	{9·08d, 9·13d} 8·0m, 9·05d	
2,3-Me_2, 3-CH_2Ph	6·32q	5·76q	$-CH_3$	9·06d	8·60d	$-CH_3$	8·85	8·64	6·54
						$-CH_2C_6H_5$	7·09, 2·75	6·95, 2·7	
3,3-Me_2, 2-$CH(CO_2Et)_2$	5·91d	5·62d	$-CH$	6·30d	5·85d	$-CH_3$	8·82	8·71	
			$(CO_2CH_2CH_3)_2$	5·75q, 8·70t	5·59q, 8·71t		8·69	8·51	
				5·80q, 8·76t	5·82q, 8·73t				
3,3-Me_2[1]	6·75	—		—	—	$-CH_3$	8·75	—	6·52
3-Me, 3-Pr^{n}[1]	6·73q	—		—	—	$-CH_2CH_2CH_3$	8·5—8·8m, 9·12t		

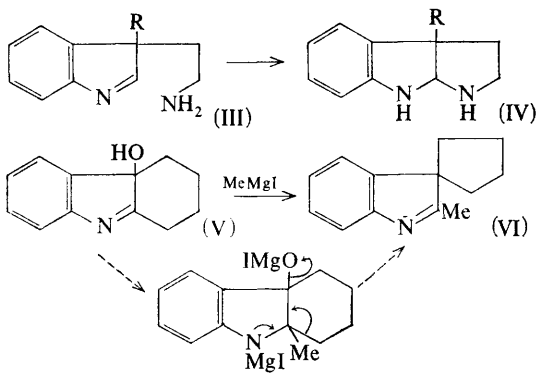
Ar-*H*: in $CDCl_3$ 2·6—3·6m; in TFA 2·4—2·7m.

in other nitrogen heterocycles, *e.g.*, quinolines,[7] isoquinolines,[8] and pyrromethanes,[9] is also well known. Witkop and Patrick[10] reported that treatment of 11-hydroxytetrahydrocarbazolenine (V) with methylmagnesium iodide affords the spirocyclic indolenine (VI); presumably initial addition occurs at the 10-position followed by elimination of the hydroxy-group and rearrangement as indicated (possibly during the acid work-up).



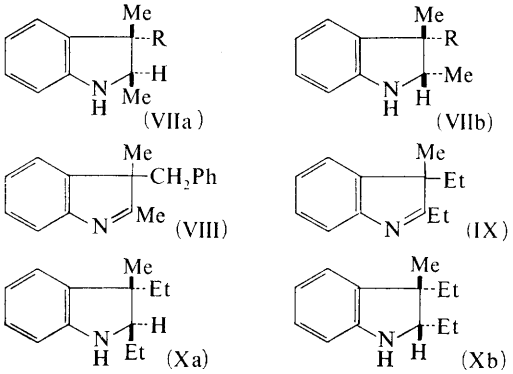
Nuclear magnetic resonance spectra of the diastereoisomeric 3-benzyl-2,3-dimethylindolines in deuteriochloroform prepared (a) by addition of methylmagnesium iodide to 3-benzyl-3-methylindolenine, and (b) by catalytic hydrogenation of 3-benzyl-2,3-dimethylindolenine. The aliphatic regions only are shown and the NH resonances have been eliminated by shaking the solutions with deuterium oxide

The aliphatic regions of the n.m.r. spectra of the indolines (II; $R^1 = R^2 = Et$) and (II; $R^1 = Et$, $R^2 = Me$) were somewhat complex, and insufficiently well resolved to analyse satisfactorily, whereas the spectra of indolines (II; $R^1 = R^2 = Me$) and (II; $R^1 = Me$, $R^2 = Et$) were readily interpreted. The complexity of the former spectra could be explained on the assumption that the two products obtained were diastereoisomeric mixtures (the latter two compounds are of course only simple racemates). To confirm this supposition, and to discover whether a bulky 3-substituent would induce stereospecific addition of the Grignard reagent, 3-benzyl- and 3-isopropyl-3-methylindolenines (I; $R = CH_2Ph$ and $R = Pr^i$) were treated with methylmagnesium iodide. The n.m.r. spectra [Table 1 and the Figure (a)] of the resulting indolines clearly showed that only one compound was formed in each reaction, *i.e.*, that the reactions had been entirely stereospecific. The products were assigned structures (VIIa; $R = CH_2Ph$ and $R = Pr^i$) on the assumption that methyl addition had taken place *trans* to the bulky group and *cis* to the 3-methyl group. Confirmation of this assignment was provided by catalytic hydrogenation of the indolenine (VIII) which had been prepared by benzylation of the Grignard derivative of 2,3-dimethylindole. The major product obtained was the expected diastereoisomeric indoline (VIIb; $R = CH_2Ph$) corresponding to addition of hydrogen to the opposite face of the molecule to the bulky benzyl group. However, the n.m.r. spectrum showed that about 10% of the same isomer (VIIa; $R = CH_2Ph$) as obtained by Grignard addition was also formed [cf. low-intensity resonances



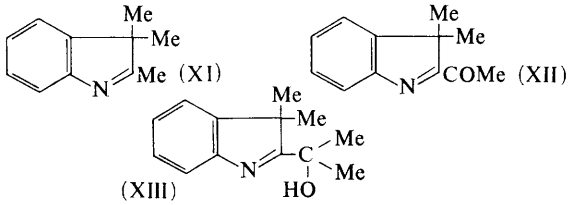
[7] D. Craig, *J. Amer. Chem. Soc.*, 1938, **60**, 1458.
[8] C. Djerassi, F. C. Markley, and R. Ehrlich, *J. Org. Chem.*, 1956, **21**, 975.
[9] H. Booth, A. W. Johnson, F. Johnson, and R. A. Langdale-Smith, *J. Chem. Soc.*, 1963, 650.
[10] B. Witkop and J. B. Patrick, *J. Amer. Chem. Soc.*, 1951, **73**, 1558.

asterisked in the Figure (b)]. The n.m.r. spectra (Figure) also confirmed the stereochemical assignments of the two diastereoisomers, since in the major hydrogenation product (VIIb; R = CH_2Ph) the methylene protons of the benzyl group are in a more crowded environment and give rise to an AB quartet, whereas in

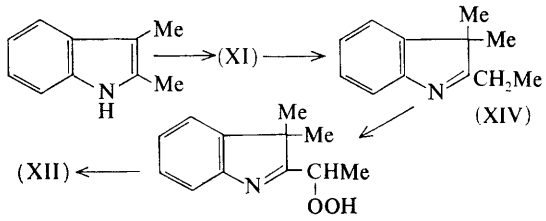


the diastereoisomer (VIIa; R = CH_2Ph) a singlet is observed; the 2-methyl protons in the isomer (VIIb; R = CH_2Ph) resonate at lower field than those in the isomer (VIIa; R = CH_2Ph) as they are closer to the plane of the ring current of the benzyl group and would thus experience a deshielding effect. Catalytic reduction of 3-ethyl-2,3-dimethylindolenine (IX) was also investigated. The resulting mixture of indolines gave a fairly complex n.m.r. spectrum but the major product (80%) appeared to be the indoline (Xb). Comparison of this spectrum with that of the corresponding Grignard addition product to 3-ethyl-3-methylindolenine (I; R = Et) indicated that the latter was also a mixture of diastereoisomers but with the other isomer (Xa) predominating.

Grignard addition to 2,3,3-trisubstituted indolenines was next investigated, and 2,3-dimethylindole was treated directly with 2 mol. of methylmagnesium iodide and 2 mol. of methyl iodide by analogy with the first reaction described above (*i.e.*, following Hoshino's experimental direction [4]). The product was not, however, either 2,3,3-trimethylindolenine (XI) (which could be obtained by monomethylation or by Fischer indole synthesis [11]) or 2,2,3,3-tetramethylindoline, as might perhaps have been expected. Instead, a crystalline material, m.p. 130°, $C_{11}H_{13}NO$ (elemental analysis and mass spectrum) was obtained, corresponding not only to addition of two carbon atoms but also to introduction of oxygen. The u.v. spectrum ($\lambda_{max.}$ 229, 234, and 305 mμ) was rather similar to that of an indolenine salt (232, 236, and 280 mμ) (cf. refs. 1 and 2), and the i.r. spectrum showed an intense band at 1600 $cm.^{-1}$. The n.m.r. spectrum (Table 2) clearly showed resonances corresponding to four aromatic protons and three methyl groups, and on the basis of these results the anomalous product was assigned structure (XII). The presence of an acetyl group was confirmed by a positive iodoform test, by formation of a dinitrophenylhydrazone, and by the mass spectrum (see Experimental section). Treatment with methylmagnesium iodide gave the hydroxypropylindolenine (XIII) (fully characterised by analytical and spectroscopic methods). Final confirmation was provided by comparison of the acetyl derivative and its oxime with the products obtained by oximination of 2-ethyl-3,3-dimethylindolenine (XIV) and described by Plancher.[12]



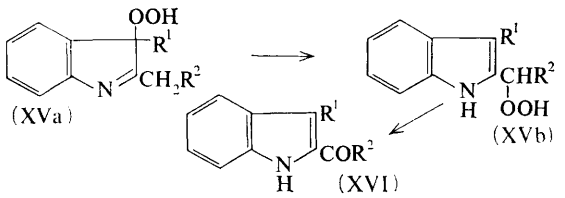
The probable course of this remarkable reaction of 2,3-dimethylindole is indicated schematically. The last stage involves autoxidation by atmospheric oxygen, and



even if air was vigorously excluded during the Grignard reaction the major product was nevertheless the 2-acetylindolenine (XII) (owing to autoxidation during work-up). Indeed, 2-ethyl-3,3-dimethylindolenine (XIV) (prepared by methylation of 2-ethyl-3-methylindole) readily peroxidised in air, either in solution or in the solid state. Peroxidation of indoles, especially 2,3-substituted indoles, is a well known process,[13-15] and although the initial product is usually the 3-hydroperoxide [*e.g.* (XVa)], the latter can be readily converted into the corresponding 2-acyl-3-alkylindole (XVI) [probably through the rearrangement product (XVb) as suggested by Leete [14]]. Modifications of this scheme have been discussed by Wasserman and Floyd,[15] and also by Taylor.[16] Our results to some extent support Leete's scheme, although no rearrangement is involved, and the peroxidation must involve direct electrophilic attack on the β-carbon of a potential enamine system. A somewhat analogous peroxidation reaction has recently been reported [17] in the isoquinoline series, involving the

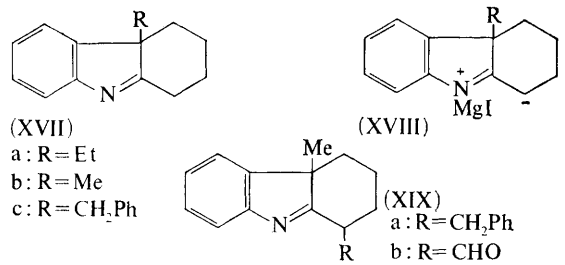
[11] G. Plancher, *Ber.*, 1898, 31, 1496; *Gazzetta*, 1898, **28** (II), 426.
[12] G. Plancher, *Atti. R. Acad. Lincei*, 1900, [5], 9 I, 118; 1909, [5], **18**, II, 395.
[13] R. J. S. Beer, L. McGrath, and A. Robertson, *J. Chem. Soc.*, 1950, 2118, 3283; B. Witkop and J. B. Patrick, *J. Amer. Chem. Soc.*, 1951, **73**, 2188, 2196.
[14] E. Leete, *J. Amer. Chem. Soc.*, 1961, **83**, 3645; E. Leete and Y.-H. Chen, *Tetrahedron Letters*, 1963, 2013.
[15] H. H. Wasserman and M. B. Floyd, *Tetrahedron Letters*, 1963, 2009.
[16] W. I. Taylor, *Proc. Chem. Soc.*, 1962, 247.
[17] S. Kubota, T. Masui, E. Fujita, and S. M. Kupchan, *J. Org. Chem.*, 1966, **31**, 516

oxidation of a 1-benzyl-3,4-dihydroisoquinoline to the corresponding 1-benzoyl derivative. It may well be that an excess of Grignard reagent facilitates the oxidation by proton abstraction from the methylene group at the 2-position in (XIV). Indeed, the methylation of



the potential enamine system in the trimethylindolenine (XI) to give the 2-ethyl-3,3-dimethylindolenine (XIV) is presumably also assisted in this way by the Grignard reagent.[18] The presence of both of these indolenines in the basic mother-liquors from the crystallisation of the 2-acetylindolenine (XII) was shown by both t.l.c. and i.r. comparisons, and the 2-ethylindolenine (XIV) could be isolated in moderate yield when the initial reaction was carried out under nitrogen, and work-up was carried out as quickly as possible with minimum exposure to air. Treatment of 2,3,3-trimethylindolenine (XI) with methylmagnesium iodide and methyl iodide also gave mixtures of the ethyl- and acetyl-indolenines (XIV) and (XII).

These results contrast with those [10] obtained by treatment of 11-hydroxycarbazolenine (V) with methylmagnesium iodide, and discussed above, but it may well be that reaction of the Grignard reagent with the hydroxy-group, and formation of an essentially anionic species, inhibits the abstraction of a proton from the 1-position whilst allowing Grignard addition to the 9,10-double bond. However, Witkop and Patrick also reported [10] that treatment of 11-ethyltetrahydrocarbazolenine (XVIIa) with ethylmagnesium bromide yields 1 mol. of ethane, and starting material was recovered on decomposition of the complex. They suggested that reaction occurred at the 1-position, and we have now confirmed this by alkylation of the Grignard reaction



product [which we formulate as (XVIII)] with benzyl bromide to give 1-benzyl-11-methylcarbazolenine (XIX; R = CH_2Ph). Further evidence for the reactivity of the 1-position in carbazolenines of this type is provided by their ready formylation [19] under Vilsmeier conditions to give the 1-formyl derivatives (XIX; R = CHO).

Mass Spectra of Indolenine and Indolines (Tables 3 and 4).—The mass spectra of the simple trialkylindolenines show fairly similar characteristics to those of the dialkyl analogues recorded previously,[2] except that rearrangement to indoles cannot occur. Loss of one of the 3-substituents is usually a major process, although the 2-acetyl- and 2-(2-hydroxypropyl)-3,3-dimethylindolenines undergo primary fission of the 2-substituent (presumably because of the stability of the ejected neutral fragment). The marked loss of acetyl (accompanied by the appropriate metastable ion) which also occurs in the latter case must involve a complex rearrangement.

The spectra of the two tetrahydrocarbazolenines (XVIIc) and (XIXa) also exhibit ions corresponding to loss of the 3-substituent, and the latter also exhibits, as expected, a moderately intense ion due to fragmentation of the 1-benzyl group. However, the major cleavage of this compound to give an ion *m/e* 145 must involve loss of the 1-benzyl group and the 1-, 2-, and 3-carbons, the

TABLE 3

Mass spectra of indolenines

2,3,3-*Trimethylindolenine*. 159 (66) M^+, 158 (34), 144 (100), 131 (21), 130 (13), 118 (20), 117 (50), 115 (25), 103 (35), 91 (21), 78 (21), 77 (38). *m**: 157 (159 → 158)

3-*Ethyl*-2,3-*dimethylindolenine*. 173 (68) M^+, 172 (18), 159 (15), 158 (100), 146 (13), 145 (50), 144 (10), 131 (8), 130 (7), 129 (5), 128 (7), 117 (25), 116 (8), 115 (20), 103 (12), 91 (16), 77 (21). *m**: 171 (173 → 172), 144·3 (173 → 158), 129·5 (158 → 143)

3-*Benzyl*-2,3-*dimethylindolenine*. 235 (70) M^+, 234 (3), 220 (2), 178 (4), 158 (3), 145 (5), 144 (20), 143 (7), 130 (3), 128 (3), 115 (5), 103 (4), 102 (4), 91 (100), 77 (11). *m**: 233 (235 → 234), 206 (235 → 220)

2-*Ethyl*-3,3-*dimethylindolenine*. 173 (40) M^+, 172 (30), 158 (47), 145 (80), 144 (100), 143 (23), 130 (50), 129 (7), 128 (10), 117 (23), 116 (12), 115 (27), 104 (20), 103 (23), 102 (15), 91 (22), 78 (20), 77 (28). *m**: 171 (173 → 172), 145 (173 → 158), 143 (145 → 144), 129·5 (158 → 143), 116·5 (145 → 130). The spectrum also showed a substantial ion at *m/e* 187 due to the autoxidation product 2-acetyl-3,3-dimethylindolenine

2-*Acetyl*-3,3-*dimethylindolenine*. 187 (6) M^+, 186 (2), 172 (2), 145 (11), 144 (14), 143 (2), 130 (6), 118 (9), 117 (100), 116 (10), 115 (1), 90 (40), 89 (35). *m**: 185 (187 → 186), 158 (187 → 172), 143 (145 → 144), 116·5 (145 → 130), 88 (90 → 89), 69·5 (117 → 90)

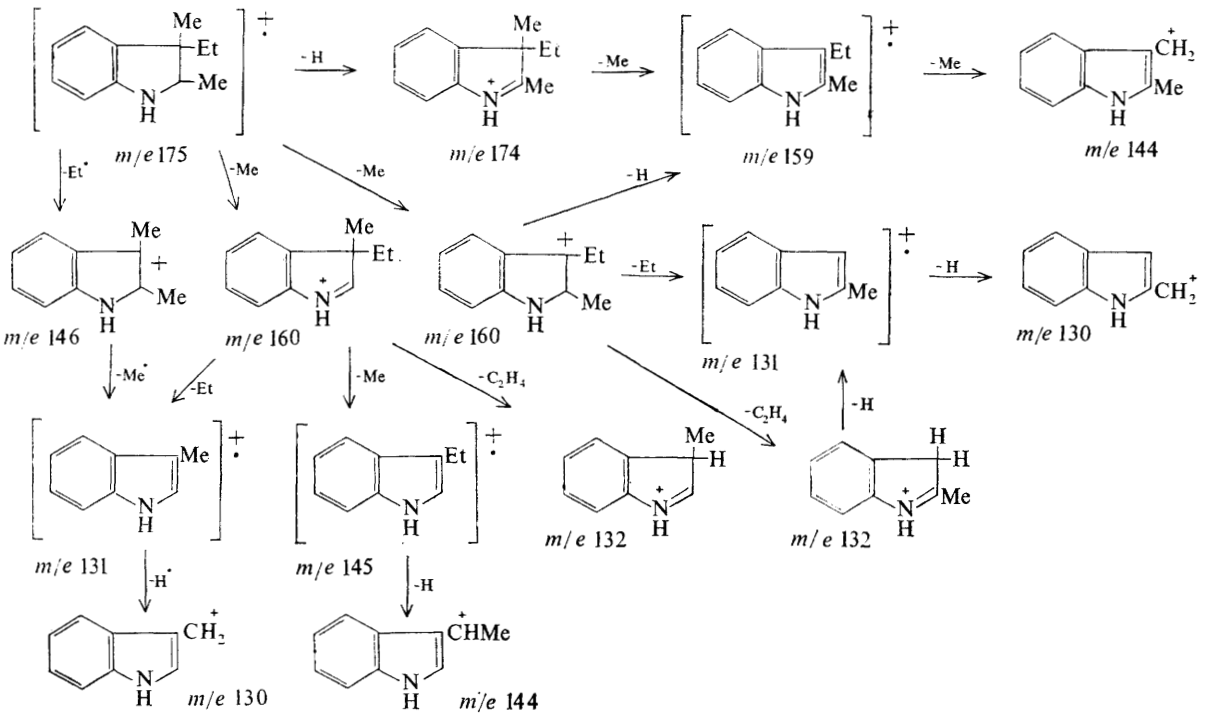
2-(2-*Hydroxyisopropyl*)-3,3-*dimethylindolenine*. 203 (17) M^+, 160 (100), 146 (39), 145 (50), 144 (94), 131 (11), 130 (50), 129 (16), 117 (8), 115 (10), 104 (28), 103 (14), 102 (6), 101 (29), 91 (9), 78 (9), 77 (16). *m**: 143 (145 → 144), 131·5 (160 → 145), 126 (203 → 160), 117·5 (146 → 131)

11-*Benzyl*-1,2,3,4-*tetrahydrocarbazolenine*. 261 (100) M^+, 259 (18), 233 (44), 232 (30), 218 (6), 184 (4), 170 (35), 169 (7), 168 (26), 167 (11), 154 (7), 143 (19), 142 (15), 128 (9), 116 (8), 115 (22), 102 (6), 91 (100), 77 (12). *m**: 259 (261 → 260), 231 (233 → 232), 208·5 (261 → 233), 204 (233 → 208)

1-*Benzyl*-11-*methyl*-1,2,3,4-*tetrahydrocarbazolenine*. 275 (63) M^+, 274 (10), 272 (6), 260 (22), 246 (8), 233 (5), 232 (12), 230 (6), 218 (5), 217 (5), 185 (14), 184 (33), 182 (7), 170 (17), 169 (7), 168 (14), 167 (10), 157 (9), 156 (7), 154 (11), 145 (100), 144 (69), 143 (9), 131 (5), 130 (24), 129 (7), 128 (9), 117 (5), 116 (5), 115 (21), 91 (31), 77 (18). *m**: 143 (145 → 144), 76·5 (275 → 145)

11-*Methyl*-1,2,3,4-*tetrahydrocarbazolenine*. 185 (100) M^+, 184 (40), 175 (53), 168 (9), 157 (29), 156 (22), 144 (15), 143 (17), 130 (12), 129 (17), 128 (14), 116 (10), 115 (24), 102 (7), 101 (10), 91 (11), 89 (10), 77 (19). *m**: 183 (185 → 184), 156 (185 → 170)

[18] Cf. G. Stork and S. R. Dowd, *J. Amer. Chem. Soc.*, 1963, **85**, 2178.
[19] H. Fritz, *Chem. Ber.*, 1959, **92**, 1809.



product being 3,3-dimethylindolenine, or 2,3-dimethylindole, or perhaps more likely, the isomeric quinoline (by ring expansion; see refs. 2 and 20). In the other carbazolenine (XVIIc) an important fragmentation process (*m/e* 261 ⟶ 233, attested by a metastable peak) is loss of ethylene, presumably the 2- and 3-methylene groups of the saturated ring, and several alternative structures may be written for the ion *m/e* 233, all involving rearrangements.

In the fragmentation of indolines, either a 2- or a 3-substituent may be cleaved in the primary process, and the base peak in most of the spectra corresponds to loss of the most stable neutral fragment, *e.g.*, loss of ethyl from both 2-ethyl-3,3-dimethylindoline and 3-ethyl-2,3-dimethylindolenine. Subsequent fragmentations are unexceptional and follow similar lines to those of related indoles and indolenines.[2,20] The accompanying Scheme illustrates some of the pathways involved in fragmentation of 3-ethyl-2,3-dimethylindoline.

There was no apparent difference (either in fragmentation pattern or peak intensity) between the spectra of the diastereoisomeric indolines synthesised by Grignard addition to, and by hydrogenation of, indolenines. This is not unexpected insofar as the most bulky group is the one ejected in the major fragmentation step, and this also gives the most stable neutral fragment.

TABLE 4
Mass spectra of indolines

2,3,3-*Trimethylindoline*. 161 (18) M^+, 160 (12), 147 (14), 146 (100), 145 (7), 144 (10), 132 (9), 131 (53), 130 (40), 91 (40), 77 (19). *m**: 132·5 (161 ⟶ 146), 117·5 (146 ⟶ 131)

2-*Ethyl*-3,3-*dimethylindoline*. 175 (29) M^+, 174 (7), 160 (33), 159 (6), 158 (12), 147 (15), 146 (100), 145 (9), 144 (23), 143 (13), 141 (9), 138 (8), 133 (6), 132 (16), 131 (34), 130 (37), 129 (6), 128 (6), 118 (6), 117 (10), 116 (5), 115 (10), 111 (7), 103 (10), 101 (17), 97 (8), 91 (18), 86 (39), 83 (8), 81 (9), 77 (18). *m**: 121·5 (175 ⟶ 146)

3-*Ethyl*-2,3-*dimethylindoline*. 175 (18) M^+, 174 (6), 160 (19), 159 (8), 158 (7), 147 (11), 146 (100), 145 (11), 144 (30), 143 (5), 132 (15), 131 (30), 130 (26), 117 (9), 115 (8), 103 (6), 91 (9), 86 (8), 77 (13). *m**: 129 (131 ⟶ 130), 121·5 (175 ⟶ 146), 117·5 (146 ⟶ 131)

2,3-*Diethyl*-3-*methylindoline*. 189 (17) M^+, 174 (4), 161 (12), 160 (100), 145 (6), 144 (14), 132 (26), 131 (27), 130 (31), 117 (6), 115 (6), 103 (5), 91 (6), 77 (8). *m**: 160 (189 ⟶ 174), 135·5 (189 ⟶ 160), 109 (160 ⟶ 132), 107 (160 ⟶ 131)

3-*Isopropyl*-2,3-*dimethylindoline*. 189 (12) M^+, 147 (12), 146 (100), 144 (5), 143 (8), 132 (10), 131 (35), 130 (37), 103 (5), 91 (5), 77 (9). *m**: 129 (131 ⟶ 130), 117·5 (146 ⟶ 131), 113 (189 ⟶ 146)

3-*Benzyl*-2,3-*dimethylindoline*. 237 (7) M^+, 146 (100), 145 (6), 144 (40), 131 (40), 130 (39), 91 (44). *m**: 129 (131 ⟶ 130), 117·5 (146 ⟶ 130)

2-(2-*Hydroxyisopropyl*)-3,3-*dimethylindoline*. 191 (10) M^+, 158 (5), 152 (30), 147 (12), 146 (100), 145 (6), 144 (10), 132 (8), 131 (32), 130 (16), 117 (6), 115 (4), 103 (4), 91 (5), 81 (7), 77 (8). *m**: 129 (131 ⟶ 130), 117·5 (146 ⟶ 130), 111·5 (191 ⟶ 146)

2-(1,1-*Diethoxycarbonylmethyl*)-3,3-*dimethylindoline*. 305 (2) M^+, 160 (5), 147 (29), 146 (83), 145 (100), 144 (6), 133 (35), 130 (60), 117 (6), 115 (90), 104 (25), 103 (27), 102 (9), 91 (8), 89 (6), 87 (24), 86 (10), 78 (23), 77 (25), 76 (8), 75 (6). *m**: 115·5 (144 ⟶ 129)

EXPERIMENTAL

Ultraviolet spectra were determined with a Unican SP 800 spectrophotometer, n.m.r. spectra with a Varian A-60 instrument, and mass spectra with an A.E.I. MS9 spectrometer operating at 50 μA and 70 ev. T.l.c. was carried out on silica gel (for indoles) or alumina (for indolenines and indolines) in benzene–light petroleum mixtures. The pre-

[20] J. H. Beynon and A. E. Williams, *Appl. Spectroscopy*, 1959, **13**, 101; C. Djerassi, H. Budzikiewicz, and D. H. Williams, 'Interpretation of Mass Spectra of Organic Compounds,' vol. 1, Holden-Day, San Francisco, 1964, pp. 251—253.

paration of some of the indoles and indolenines required in this work has been described previously.[2]

Indolenines

3-*Ethyl*-2,3-*dimethylindolenine*.—To magnesium turnings (1·2 g.) in dry ether (30 ml.), an excess of ethyl bromide (7·0 g.) was added slowly. When all the magnesium had reacted, dry benzene (30 ml.) was added and the ether and excess of ethyl bromide were distilled out. 2,3-Dimethylindole (7·2 g.) in benzene (20 ml.) was then added slowly, and the resulting dark fluorescent solution boiled under reflux for 15 min. Ethyl bromide (5·6 g.) was added and the mixture boiled under reflux for 2 hr. The golden brown solution was then poured into 2N-hydrochloric acid (50 ml.) to decompose the complex. The acidic layer was separated, traces of neutral products were extracted from the acidic layer with ether (30 ml.), and after basification with 2N-sodium hydroxide, the organic material was isolated by ether extraction (3 × 40 ml.). The combined ether extracts were washed with water (2 × 30 ml.), dried ($MgSO_4$) and evaporated to leave a red mobile liquid which after distillation at 56°/0·25 mm. gave 3-ethyl-2,3-dimethylindolenine (2·8 g., 32%) as a pale green oil. The picrate formed yellow needles (from alcohol), m.p. 152—154° (lit.,[12] 152—153°) (Found: C, 53·7; H, 4·7; N, 13·8. Calc. for $C_{18}H_{18}N_4O_7$: C, 53·7; H, 4·5; N, 13·9%).

2-*Ethyl*-3,3-*dimethylindolenine*.—This was prepared in a similar manner from 2-ethyl-3-methylindole in 55% yield. It formed needles, m.p. 52° (lit.,[12] 52—53°) [from light petroleum (b.p. 60—80°)]. The picrate formed yellow needles (from alcohol), m.p. 138—139° (lit.,[12] 137—138°). The free base readily became partly autoxidised in the solid state to the 2-acetyl analogue.

3-*Benzyl*-2,3-*dimethylindolenine*.—This was prepared in a similar manner to the foregoing compound except that benzyl bromide was added to a cooled solution of 2,3-dimethylindolylmagnesium bromide. Distillation of the crude product at 135°/0·8 mm. gave 3-*benzyl*-2,3-*dimethylindolenine* (7·0 g., 60%) as a fluorescent green oil. The picrate formed yellow needles (from alcohol), m.p. 142—144° (Found: C, 59·3; H, 4·3; N, 11·8. $C_{23}H_{20}N_4O_7$ requires C, 59·5; H, 4·3; N, 12·1%).

The following 1,2,3,4-tetrahydrocarbazolenines were prepared in a similar manner to the above indolenines but using 1,2,3,4-tetrahydrocarbazole instead of skatole, and the appropriate halide. 11-Methyl-1,2,3,4-tetrahydrocarbazolenine (methyl iodide) (20%), m.p. 65° (lit.,[21] 65°); picrate, m.p. 169° (lit.,[21] 169°). 11-*Benzyl*-1,2,3,4-*tetrahydrocarbazolenine* (benzyl bromide) (35%), m.p. 83—84°; picrate, m.p. 175—177° (Found: C, 61·3; H, 4·4; N, 11·5. $C_{25}H_{22}N_4O_7$ requires C, 61·2; H, 4·5; N, 11·4%).

1-*Benzyl*-11-*methyl*-1,2,3,4-*tetrahydrocarbazolenine*.— To magnesium turnings (1·2 g.) in ether (30 ml.), an excess of ethyl bromide (7·0 g.) was added slowly. When all the magnesium had reacted, dry benzene (30 ml.) was added and the ether and excess of ethyl bromide were distilled out. 11-Methyl-1,2,3,4-tetrahydrocarbazolenine[21] (4·7 g.) in ether (20 ml.) was added slowly. After boiling under reflux for 15 min. the mixture was cooled in ice and benzyl bromide (8·5 g.) added. The mixture was then removed from the ice-bath and the temperature rose to 30° and the solution darkened considerably. When the temperature started to fall, the solution was boiled under reflux for 10 min., cooled, and poured into 2N-hydrochloric acid (50 ml.) to decompose the complex. The acidic layer was separated, traces of neutral products were extracted with ether (30 ml.), and after basification with 2N-sodium hydroxide, the organic material was isolated by ether extraction (3 × 40 ml.). The combined extracts were washed with water (2 × 30 ml.), dried ($MgSO_4$), and evaporated to leave a pale red oil (4·0 g.) which slowly crystallised from petroleum (b.p. 60—80°) to give 1-*benzyl*-11-*methyl*-1,2,3,4-*tetrahydrocarbazolenine*, needles, m.p. 123—125° (Found: C, 87·1; H, 7·5; N, 5·1. $C_{20}H_{21}N$ requires C, 87·2; H, 7·7; N, 5·1%).

Indolines

(A) *By Grignard Addition to Indolenines.*

2,3,3-*Trimethylindoline*.—To magnesium turnings (2·4 g.) in dry ether (30 ml.), methyl iodide (14·2 g.) was added slowly. When the exothermic reaction had subsided, skatole (6·0 g.) in benzene (50 ml.) was added slowly and the resulting greenish solution boiled under reflux for 15 min. After cooling, methyl iodide (7·2 g.) was added, and the solution heated under reflux for 2 hours. The fluorescent purple solution was then poured into 2N-hydrochloric acid (50 ml.) to decompose the complex. The acidic layer was separated, traces of neutral products were extracted with ether (30 ml.), and after basification with 2N-sodium hydroxide, the basic organic material was isolated by ether extraction (3 × 40 ml.). The combined ether extracts were washed with water (2 × 30 ml.), dried ($MgSO_4$), and evaporated, to leave 2,3,3-trimethylindoline as an oil (2·4 g., 36%), b.p. 60°/0·4 mm., $\lambda_{max.}$ (log ε) (95% EtOH) 243 (3·86) and 291 (3·39), $\nu_{max.}$ (film) 3450 and 1620 cm.$^{-1}$. The hydrochloride formed as an amorphous solid (from ether–alcohol), m.p. 197—199° (lit.,[22] 198—199°) (Found: C, 67·2; H, 7·7; N, 7·1. Calc. for $C_{11}H_{16}ClN$: C, 67·2; H, 7·9; N, 7·0%).

3-*Ethyl*-2,3-*dimethylindoline*.—To magnesium turnings (0·05 mole) in dry ether (30 ml.), an excess of ethyl bromide (0·075 mole) was added slowly. When all the magnesium had reacted, dry benzene (30 ml.) was added and the ether and excess of ethyl bromide were distilled out. Skatole (0·05 mole) in benzene (20 ml.) was then added slowly, and the resulting yellow solution boiled under reflux for 15 min. After cooling, ethyl bromide (0·05 mole) was added and the mixture boiled under reflux for 2 hr. A solution of methylmagnesium iodide in benzene, prepared from magnesium turnings (0·05 mole) and an excess of methyl iodide (0·075 mole) (the excess of methyl iodide being removed by distillation), was then added slowly and the mixture boiled under reflux for a further 2 hr. The deep orange fluorescent solution was then cooled and poured into 2N-hydrochloric acid (50 ml.) to decompose the complex. The acidic layer was then separated, traces of neutral products were extracted from the acidic layer with ether (30 ml.), and after basification with 2N-sodium hydroxide, the organic material was isolated by ether extraction (3 × 40 ml.). The combined extracts were washed with water (2 × 30 ml.), dried ($MgSO_4$), and evaporated to leave a dark green oil (4·0 g.). This oil was separated into three fractions by chromatography on silica using redistilled petroleum as solvent. The second fraction, after distillation at 50°/0·07 mm., yielded 3-*ethyl*-2,3-*dimethylindoline* (2·5 g., 29%) as a pale green oil (Found: C, 82·0; H, 9·5; N, 8·3. $C_{12}H_{17}N$ requires C, 82·2; H, 9·8; N, 8·0%).

[21] G. Plancher, B. Cecchetti, and E. Ghigi, *Gazzetta*, 1929, **59**, 334.

[22] E. Ferratini, *Gazzetta*, 1893, **23** II, 115.

The following indolines were also prepared in the same manner. 2,3-*Diethyl*-3-*methylindoline*, b.p. 70°/0·06 mm. (1·0 g., 10%) (Found: C, 82·3; H, 10·1; N, 7·4. $C_{13}H_{19}N$ requires C, 82·5; H, 9·9; N, 7·7%). 2-*Ethyl*-2,3-*dimethylindoline*, b.p. 60°/0·2 mm. (2·4 g., 27%) (Found: C, 82·3; H, 9·6; N, 8·2. $C_{12}H_{17}N$ requires C, 82·2; H, 9·8; N, 8·0%). The foregoing indolines could also be prepared by isolation of the intermediate indolenine and treatment of the latter with Grignard reagent in a separate step.

3-*Isopropyl*-2,3-*dimethylindoline*.—To magnesium turnings (0·05 mole) in dry ether (30 ml.), an excess of ethyl bromide (0·075 mole) was added. When all the magnesium had reacted, dry benzene (30 ml.) was added and the ether and excess of ethyl bromide were distilled out. Skatole (0·05 mole) in benzene (30 ml.) was then added slowly, and the resulting yellow solution boiled under reflux for 15 min. After cooling, isopropyl bromide (0·05 mole) was added and the mixture boiled under reflux for 2 hr. A solution of methylmagnesium iodide in benzene prepared from magnesium turnings (0·05 mole) and an excess of methyl iodide (0·075 mole) (the excess of methyl iodide being removed by distillation) was then added slowly and the mixture boiled under reflux for 2 hr. The solution was then cooled and poured into 2N-hydrochloric acid (50 ml.) to decompose the complex. The acidic layer was separated, traces of neutral products were extracted from the acidic layer with ether (30 ml.), and after basification with 2N-sodium hydroxide, the organic material was isolated by ether extraction (3 × 40 ml.). The combined extracts were washed with water (2 × 30 ml.), dried ($MgSO_4$), and evaporated to leave a dark oil (2·9 g.) which was shown by t.l.c. to contain a small amount of indoline but to be mainly 3-isopropyl-3-methylindolenine.

To an ethereal solution of methylmagnesium iodide prepared from magnesium turnings (0·50 mole) and methyl iodide (0·05 mole), the above crude indolenine (2·6 g.) in ether (15 ml.) was added, and the mixture refluxed for 1·5 hr. The red-brown solution was then cooled and poured into 2N-sodium hydroxide (50 ml.) to decompose the complex. The organic material was isolated by ether extraction (3 × 40 ml.). The combined extracts were washed with water (2 × 40 ml.), dried ($MgSO_4$), and evaporated to leave a yellow oil (2·8 g.). This oil was separated into three components by chromatography on grade 1 alumina using redistilled petroleum (b.p. 60—80°) and benzene as solvents. The second fraction, after distillation at 65°/0·1 mm., yielded 3-*isopropyl*-2,3-*dimethylindoline* as a pale green oil (1·0 g., 11%) (Found: C, 82·8; H, 9·9; N, 7·3. $C_{13}H_{19}N$ requires C, 82·5; H, 10·1; N, 7·4%).

3-*Benzyl*-2,3-*dimethylindoline*.—This was prepared in a similar manner, as an oil after distillation at 110°/1·0 mm. (1·0 g., 9%) (Found: C, 85·9; H, 8·1; N, 6·0. $C_{17}H_{19}N$ requires C, 86·0; H, 8·1; N, 5·9%).

These experiments were repeated several times but it was found that *in situ* addition of methylmagnesium iodide to the crude reaction product never gave more than traces of indoline (in contrast to the other preparations described above), and it was always necessary to isolate the intermediate indolenine and treat it with more Grignard reagent.

2-*Di*(*ethoxycarbonyl*)*methyl*-3,3-*dimethylindoline*.—Magnesium turnings (1·2 g.) in ethanol (15 ml.) were mixed with dry tetrahydrofuran (30 ml.) and heated to boiling. Diethyl malonate (8 ml.) and ethanol (10 ml.) were then added and the mixture boiled under reflux until all the magnesium had dissolved. The solvents were removed under a vacuum, and benzene (25 ml.) was added and evaporated to dryness. The residual pale green viscous oil was then taken up in a little benzene and added to 3,3-dimethylindolenine in benzene (100 ml.) which had previously been prepared from skatole (6·5 g.) by methylation of its Grignard derivative. The mixture was heated under reflux for 2 hr., cooled, and poured into 2N-hydrochloric acid (50 ml.). The aqueous layer was separated, basified with dilute sodium hydroxide, and extracted with ether (3 × 50 ml.). The dried ($MgSO_4$) ether extracts were evaporated to dryness, and the residual brown oil (1·5 g.) was distilled at 90—95°/0·2 mm., to give the *indoline* (Found: C, 67·2; H, 7·5; N, 4·8. $C_{17}H_{23}NO_4$ requires C, 66·9; H, 7·6; N, 4·6%), $\lambda_{max.}$ (log ε) (95% EtOH) 241 (4·02) and 290 (3·53) mμ, $\nu_{max.}$ 3470 (NH), 1765, and 1740 (C=O) cm.$^{-1}$.

(B) *By Hydrogenation of Indolenines*

3-*Ethyl*-2,3-*dimethylindoline*.—Platinum oxide (0·0003 mole) was added to a solution of 3-ethyl-2,3-dimethylindolenine (0·003 mole) in methanol (20 ml.) and concentrated hydrochloric acid (1·0 ml.), and the solution hydrogenated until hydrogen (95 ml.) had been taken up (theoretical uptake, 80 ml.). The catalyst was filtered off, the filtrate basified with 2N-sodium hydroxide (10 ml.), and the organic material isolated by ether extraction (3 × 40 ml.). The combined extracts were washed with water (2 × 30 ml.), dried ($MgSO_4$), and evaporated, to leave 3-*ethyl*-2,3-*dimethylindoline* (0·5 g.) as a pale green oil.

The hydrochloride formed an amorphous solid, m.p. 180° (with subl.) (from ether–alcohol) (Found: C, 68·2; H, 8·6; N, 6·4. $C_{12}H_{18}ClN$ requires C, 68·1; H, 8·6; N, 6·6%).

3-*Benzyl*-2,3-*dimethylindoline*.—This was prepared in a similar manner by hydrogenation of the corresponding indolenine. The green, highly fluorescent oil obtained slowly solidified but could not be recrystallised owing to its high solubility in all organic solvents. The *hydrochloride* formed an amorphous solid, m.p. 248—249° (from alcohol–ether) (Found: C, 74·3; H, 7·4; N, 5·1. $C_{17}H_{20}ClN$ requires C, 74·6; H, 7·4; N, 5·1%).

Action of Methyl Iodide (2 *mol.*) *and Methylmagnesium Iodide* (2 *mol.*) *on* 2,3-*Dimethylindole*.—To magnesium turnings (0·05 mole) in dry ether (30 ml.), an excess of methyl iodide (0·075 mole) was added. When all the magnesium had reacted, dry benzene (30 ml.) was added and the ether and excess of methyl iodide were distilled out. 2,3-Dimethylindole (0·05 mole) in benzene (30 ml.) was then added slowly, and the resulting reddish solution boiled under reflux for 15 min. After cooling, methyl iodide (0·05 mole) was added, and the mixture boiled under reflux for 2 hr. A solution of methylmagnesium iodide in benzene, prepared from magnesium turnings (0·05 mole) and an excess of methyl iodide (0·075 mole) (the excess of methyl iodide being removed by distillation), was then added, and the mixture boiled under reflux for 2 hr. The dark red solution was then cooled and poured into 2N-hydrochloric acid (50 ml.) to decompose the complex.

The basic material was extracted into the acidic layer which was then separated. Traces of neutral products were extracted from the acidic layer with ether (30 ml.), and after basification with 2N-sodium hydroxide the organic material isolated by ether extraction (3 × 40 ml.). The combined ether extracts were washed with water (2 × 30 ml.), dried ($MgSO_4$), and evaporated, to leave a fluorescent orange oil (6·8 g.) which slowly crystallised from alcohol to

give 2-acetyl-3,3-dimethylindolenine (2 g., 22%) as pale yellow crystals, m.p. 129—130° (lit.,[12] 130°) (Found: C, 76·9; H, 7·0; N, 7·6. Calc. for $C_{12}H_{13}NO$: C, 77·0; H, 7·0; N, 7·5%), $\lambda_{max.}$ (log ε) (95% EtOH) 229 (3·88), 234 (3·88), and 305 (4·02) mμ unchanged on addition of a few drops dil. HCl.; mol. wt., 185 (mass spectrum). Oxime, m.p. 175° (lit.,[12] 175—176°); 2,4-dinitrophenylhydrazone, m.p. 298—300°.

The residual oil (4·1 g.) was shown to contain 2,3,3-trimethylindolenine by comparison with an authentic sample (i.r. and t.l.c.). A trace of 2-ethyl-3,3-dimethylindolenine was also detected by t.l.c.

2-(2-*Hydroxyisopropyl*)-3,3,-*dimethylindolenine*.— To magnesium turnings (1·2 g.) in dry ether (30 ml.), an excess of methyl iodide (10·7 g.) was added. When all the magnesium had reacted, dry benzene (30 ml.) was added, and the ether and excess of methyl iodide were distilled out. 2-Acetyl-3,3-dimethylindolenine (2·00 g.) was then added in benzene, and the red mixture boiled under reflux for 2 hr. The brown solution was then cooled, poured into 2N-sodium hydroxide (50 ml.) to decompose the complex, and the organic material isolated by ether extraction (3 × 40 ml.). The combined extracts were washed with water (2 × 30 ml.), dried ($MgSO_4$), and evaporated to leave a red oil (2·0 g.) which crystallised from light petroleum (b.p. 40—60°) to give 2-(2-*hydroxyisopropyl*)-3,3-*dimethylindolenine* (1·3 g., 60%) as pinkish needles, m.p. 85°, very sensitive to aerial oxidation (Found: C, 65·2; H, 7·6; N, 5·9. $C_{13}H_{17}NO$ requires C, 65·1; H, 7·6; N, 5·8%), $\lambda_{max.}$ (log ε) (95% EtOH) 224 (4·06) and 257 (3·81), (95% EtOH + HCl gas) 233 (3·80), 239 (3·76) and 285 (3·78) mμ. The hydrochloride had m.p. 165—166° (from ethanol–ether).

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