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# MODELS FOR ULEINE-ALKALOID BIOGENESIS

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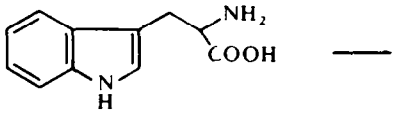
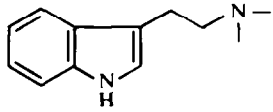
**Abstract**—Possible mechanisms by which the $C_2$-unit of the tryptamine bridge of condylocarpine-type alkaloids can be lost to give the uleine skeleton are considered. A terminally-oxidized $\beta$-$C_2$ substituent on an $\alpha$-methyleneindoline system could not be cleaved, but a $\beta$-$C_1$ acid unit fragmented readily.

MOST complex indole alkaloids contain a tryptamine moiety (**2**) which is derived biogenetically from tryptophan (**1**).[1] There are a number of indole alkaloids, however, whose $\beta$-ethylamine side chain of the tryptamine unit is partially or totally absent.

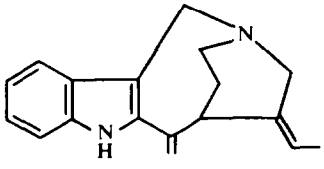


**1**

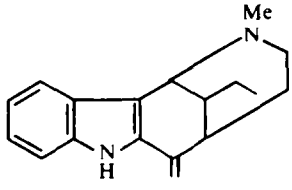


**2**

Apparicine (**3**), for example, lacks one of the carbons of the $C_2$-bridge; uleine (**4**) and ellipticine (**5**) lack both carbons of the bridge. In still another variation, there are alkaloids which retain the $C_2$-bridge, but have it detached from the $\beta$-N such as in *Cinchona* species (**6**).



**3**



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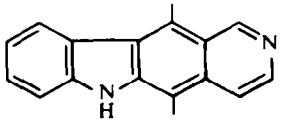

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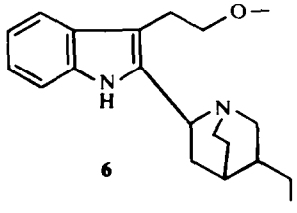
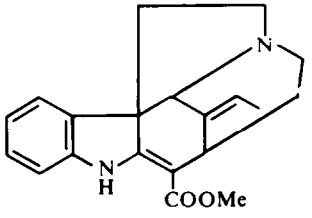


**6**

While tryptophan serves as a precrusor of the tryptamine unit in apparicine[2] and the *Cinchona* types,[1] it was not incorporated into uleine.[2] This suggests, but does not prove since negative results of this type must be interpreted with a good deal of caution, that a precursor other than tryptophan is involved in the construction of the uleine indolic moiety.[3]

When the biogenetic origin of the uleine alkaloids is being considered, the similarities in structure between these alkaloids and those of the condylocarpine (7) group cannot go unnoticed. Except for the tryptamine bridge, their skeletal structures are the same. Moreover, both types co-occur in certain plant species (*Aspidosperma tomentosum* Mart.[4]). A chemically feasible pathway for loss of the β-$C_2$-unit would interrelate, in a biogenetically consistent fashion, these two groups of alkaloids.

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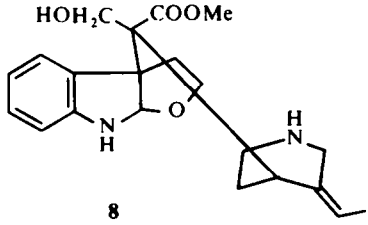


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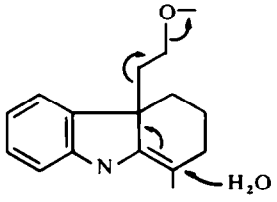
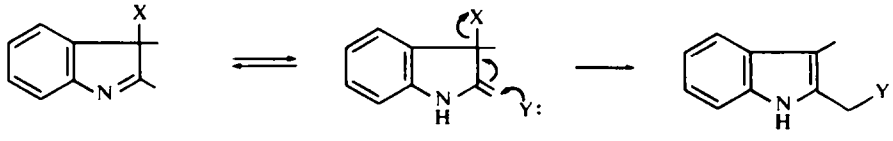
In 1965 Joule and co-workers,[5] noting the co-occurrence of uleine alkaloids with aspidodasycarpine (8), an alkaloid with the tryptamine bridge oxidatively detached from $N_b$, postulated a mechanism for the expulsion of the β-$CH_2$-unit from an α-methylene-indoline to give the indolic system:




This type of fragmentation, as noted by the authors, is an ethylogue of a well-known reaction of indole systems first generalized by Taylor:[6]

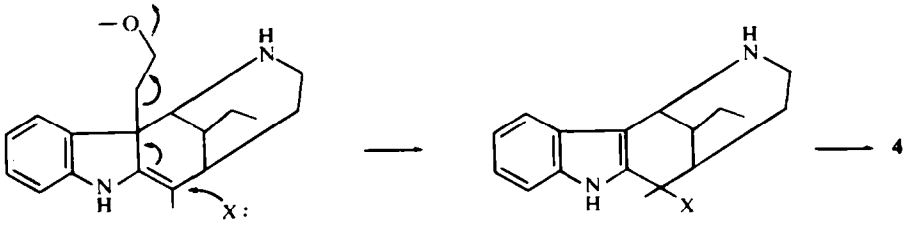



X = Cl, Br, $Pb(OAc)_3$, OOH, OH
Y = $H_2O$, OAc, $NR_3$, CN, OMe

Other workers[7,8] have since utilized this reaction. Buchi and Manning[7] used it in their preparation of 18-cyanoibogaine (9).


9

If a condylocarpine-like structure undergoes oxidative cleavage of the β-C—$N_b$ bond an intermediate such as **10** would result. A nucleophilic attack such as that suggested by Joule would lead to **11**, which, after loss of HX and methylation, would give uleine. The two major difficulties with this type of transformation are the poor




**10** **11**

leaving group and nucleophilic attack at a somewhat hindered position (although the latter has precedent in the formation of **9** above). Nevertheless, these adverse factors do not rule out the possibility that this type of fragmentation can occur. We were interested in determining the feasibility of such a reaction with the side chain in a higher oxidation state, presumably providing a better leaving group.

TABLE 1

| Compound | Nucleophile | Solvent | $C_2$-Side Chain Cleavage | Products |
|---|---|---|---|---|
| **15** | $OMe^-$ | MeOH | none | **13** + tar |
| **15** | $OAc^-$ | MeOH | none | **13** + tar |
| **15** | $CN^-$ | MeOH | none | **24** |
| **15** | $CN^-$ | MeCN | none | starting material |
| **19** | $CN^-$ | MeOH | none | **25** |
| **21** | $OMe^-$ | MeOH | none | none identified |
| **21** | $CN^-$ | MeOH | none | none identified |
| **21** | $CN^-$ | MeCN | none | starting material |
| **23** | $CN^-$ | MeOH | none | **26** |

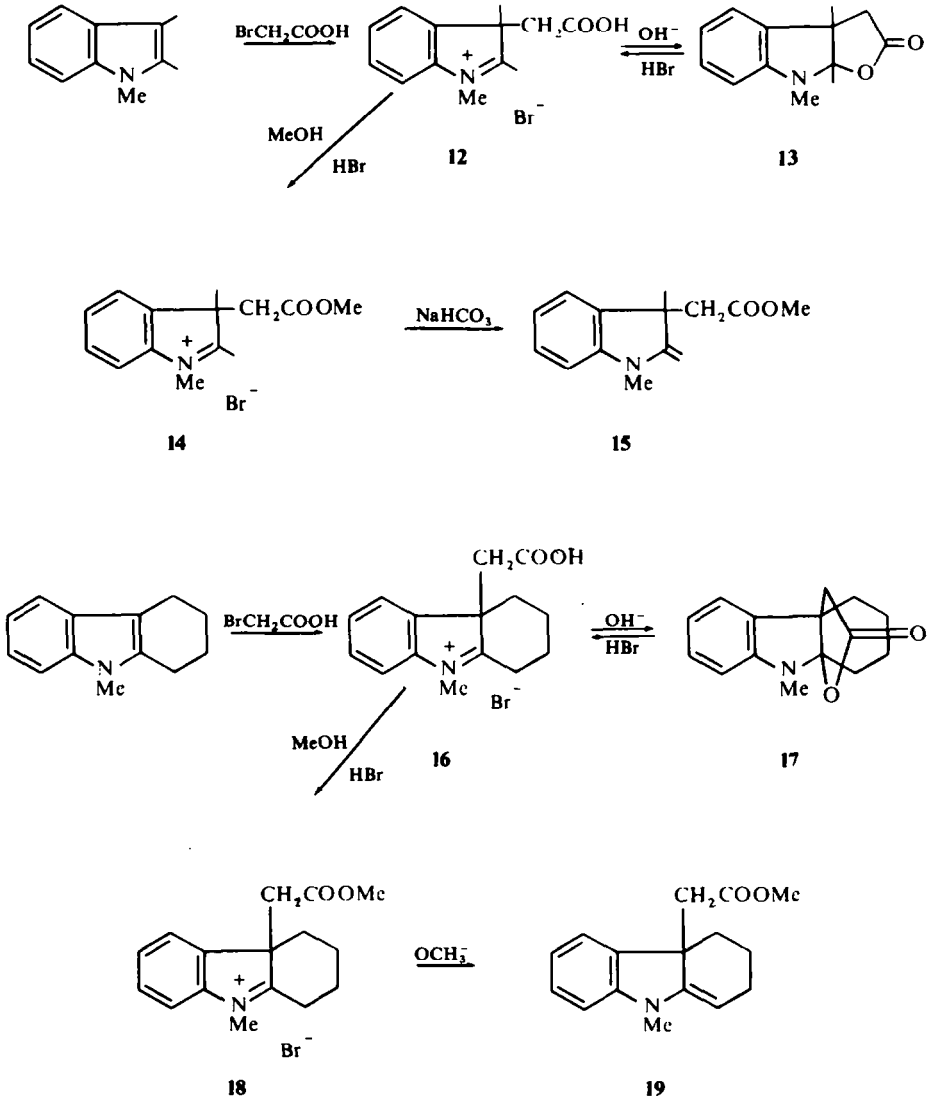
The compounds studied were **15**, **19**, **21** and **22**. Their syntheses are outlined in Schemes I–III. Attempts to prepare the tetrahydrocarbzole analog of **22** gave instead lactol **23** (Scheme III).

Compounds **15**, **19**, **21** and **22** were extremely unstable to air and decomposed to a red gum in its presence. The α-methylene-indoline chromophore is characteristically

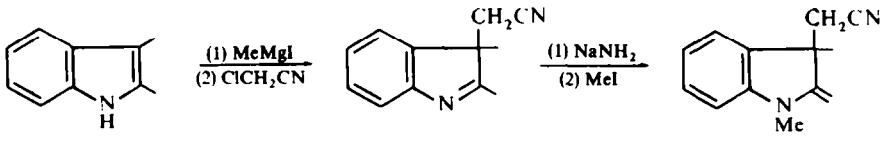
very sensitive to oxidation.[9] All compounds containing such a group were stored as salts and generated just prior to use by passage through an anion exchange column.

The results of the reaction of **15**, **19**, **21** and **22** with nucleophiles are summarized in Table 1. In no case was any $C_2$-side chain cleavage observed. Compounds **24** and **25** arise from HCN addition across the double bond, and **26** can be rationalized as

SCHEME I

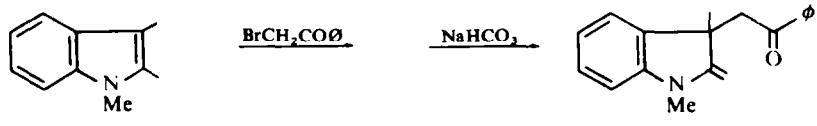


SCHEME II

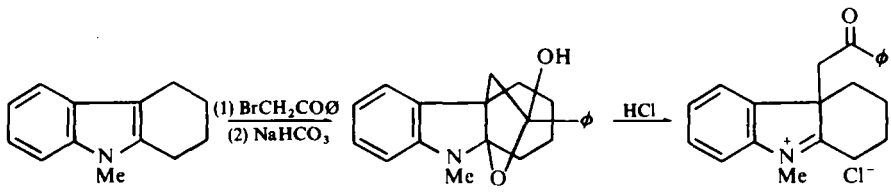



20 21

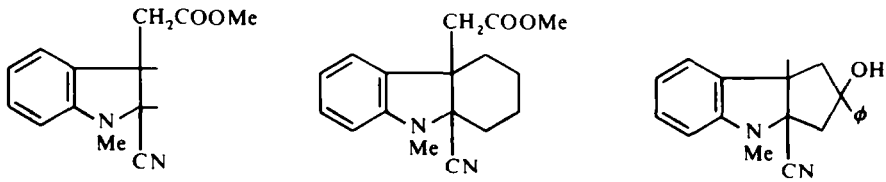
SCHEME III




22

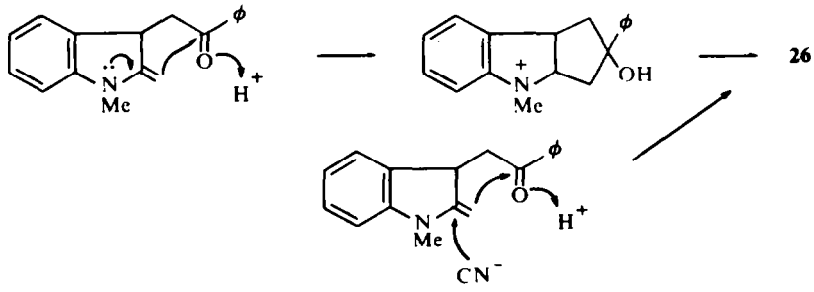



23 23a

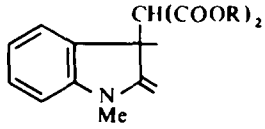



24 25 26

attack of the double bond on the carbonyl followed by addition of cyanide or as a concerted attack as illustrated below:



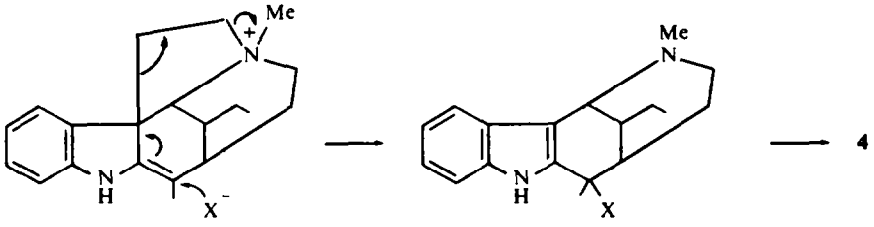

Since the acetate, acetonitrile and acetophenone groupings could not be displaced from the β-position of the α-methylene-indoline system, attention was turned to the preparation of a malonyl derivative (**27**) which would provide a more reasonable




27

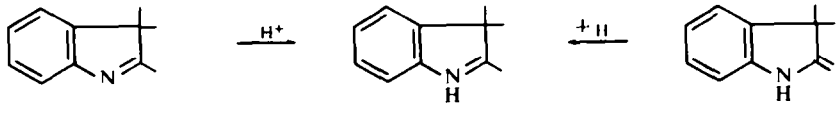
leaving group.[10] Numerous attempts to synthesize such a compound met with no success, however. Acylation of **13**, **15**, **17** and **19** with a variety of acylating agents and catalysts gave none of the desired products. Direct introduction of the malonyl group by condensation of 1,2,3-trialkyl-substituted indoles with halomalonates was also unsuccessful.

Our failure to induce cleavage of the oxidized β-$C_2$-side chain by nucleophilic displacement casts doubt on this mechanism as a route for elimination of the β-alkyl group. However, Joule's original suggestion of fragmentation of the side chain in a lower oxidation state (as in **10**) is still feasible as this possibility has not been tested. The Joule mechanism becomes even more attractive if one allows a quaternized nitrogen to serve as the leaving group:



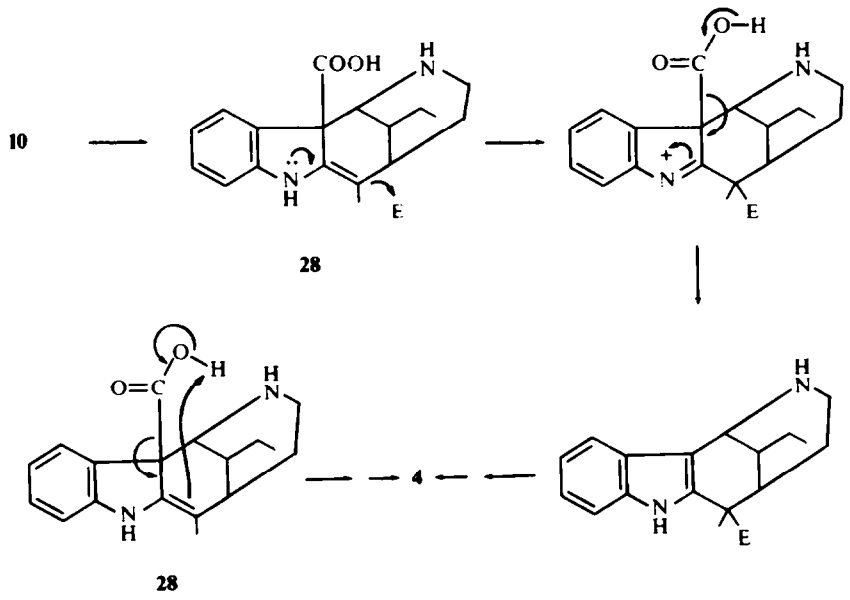

It will be of interest to determine if a fragmentation of this type can be effected in these systems.

While we were working with the oxidized β-$C_2$ model compounds, our attention was drawn to another process which could result in elimination of the β-side chain, *e.g.*, a step-wise degradation of the chain to a one carbon acid fragment followed by decarboxylation either intramolecularly or with external electrophilic attack (Scheme IV). Acids such as **28** might be expected to decarboxylate readily. Since such systems have not been reported in the literature, we prepared several model compounds to determine if the β-$C_1$ acid group would be lost readily. Indolenine compounds were used since they give the same indolenium salts as α-methyleneindolines when treated with acids:



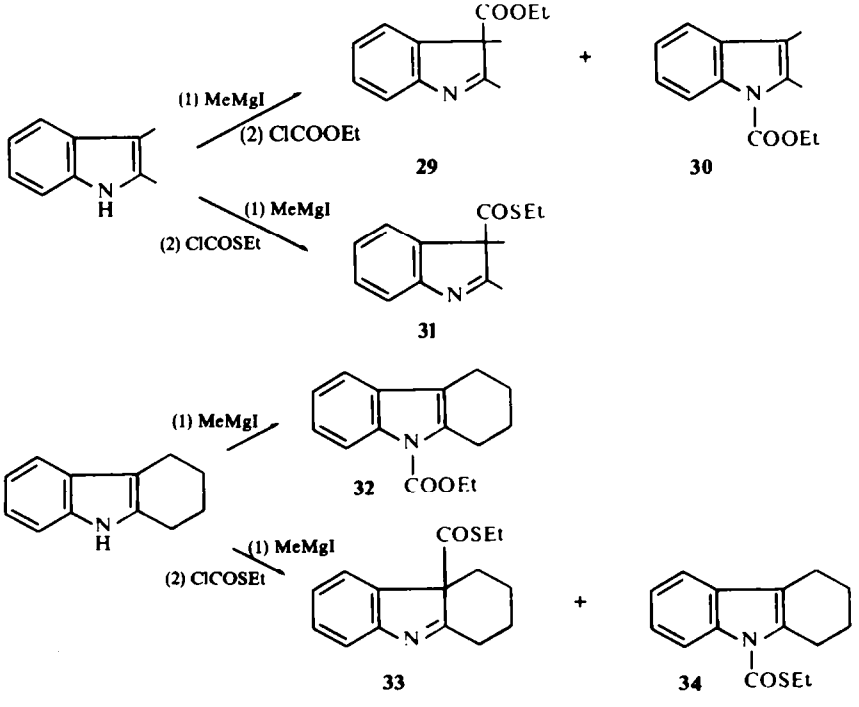

Attempts at preparing 3-indolenine carboxylic acids by condensation of the 3-indolenine Grignard reagent with carbon dioxide resulted only in recovered indole. The ethyl ester (**29**) and ethyl thioesters (**31** and **33**) could be made in this fashion, however (Scheme V). Mixtures of N-substituted and C-substituted products were generally observed, but with 1,2,3,4-tetrahydrocarbazole and ethyl chloroformate

SCHEME IV

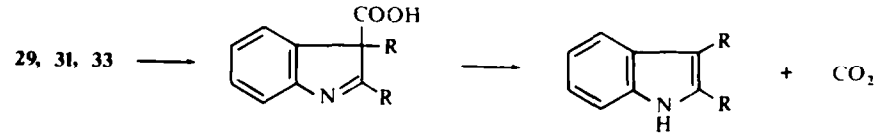



only **32** was isolated; with 2,3-dimethylindole and ethyl chlorothioformate, only **31** was obtained in amounts large for characterization.

SCHEME V



Compounds **29**, **31** and **33** reacted with acid under hydrolytic conditions with loss of carbon dioxide to give the corresponding indoles. Thus, **29** and **31** gave 2,3-dimethylindole and **33** gave 1,2,3,4-tetrahydrocarbazole when treated with aqueous hydrochloric acid. Quantitative decarboxylation of **29** was also achieved in a medium of aqueous base. Although they could not be isolated, the free acids (or acid salts) (**35**) are undoubtedly intermediates in these reactions. (IR evidence for their intermediacy is given in the Experimental).




35

This facile cleavage of a β-$C_1$ acid fragment from an α-methylene-indoline system provides an attractive pathway by which the tryptamine $C_2$-bridge may be lost in alkaloids of the condylocarpine type. It necessitates oxidative cleavage at the C—$N_b$ bond followed by oxidative degradation to a $C_1$ acid unit. This is not an unreasonable process.[11] However, other equally attractive mechanisms for the elimination of the β-alkyl group have yet to be tested.

## EXPERIMENTAL

M. and B. ps are uncorrected. IR spectra were determined using Perkin–Elmer Model 137 and 337 spectrophotometers. UV spectra were determined on a Perkin–Elmer Model 202 spectrophotometer. NMR spectra were obtained on a Jeolco Model C-60H or a Varian HA-60 spectrometer with TMS as an internal standard. Elemental analyses were performed by M–H–W Laboratories, Garden City, Michigan and Galbraith Laboratories, Inc., Knoxville, Tennessee.

1·2,3-*Trimethylindole*. A 3-neck flask was fitted with an overhead stirrer, gas inlet tube, dry-ice condenser and NaOH drying tube. The flask was cooled in a dry-ice acetone bath, and liquid ammonia was distilled into the flask until a volume of 150 ml was reached. With vigorous stirring, about 0·1 g ferric nitrate (nonahydrate) was added, and then, in small portions, 1·5 g Na. After dissolution was complete, a soln of 8·4 g (0·058 mol) 2,3-dimethylindole was added slowly. Ten min after complete addition, a soln of 10 g MeI in 10 ml anhyd ether was added dropwise. Stirring was continued for 15 min, and the ammonia was allowed to evaporate overnight. Water was cautiously added followed by 100 ml ether. The ether layer was dried ($MgSO_4$) and the ether removed *in vacuo*. The residue was distilled to give 7·6 g (83%) colorless liquid, b.p. 102–105°/0·6 mm (lit.[12] b.p. 89°/0·75 mm); picrate, m.p. 151° (lit.[13] m.p. 148–149°).

*Methyl* 1,2,3-*trimethylindolenium*-3-*acetate bromide* (**14**). To 12·5 g (0·99 mol) molten bromoacetic acid was added 4·77 g (0·03 mol) 1,2,3-trimethylindole, and the mixture was heated in a $N_2$ atmosphere for 2 hr at a bath temp of 140°. The mixture was cooled, and the ppt was washed successively with ether and $CH_2Cl_2$ to give 7·39 g (83%) of acid salt **12**. Crystallization from acetonitrile gave pure white crystals, m.p. 245–245·5° (dec); UV (MeOH) 245 (indoline), 230 and 237 (indolenium), and a broad band centered at 282 mμ (indoline and indolenium). In 95% EtOH soln, the spectrum was typical for the indoline structure only: $\lambda_{max}$ 243 and 292 mμ. The indoline bands are arising from solvent addition to the double bond[14,15] or lactone formation. IR (nujol) 5·80 (C=O), 6·16 μ (C=$N^+$).

This same indolenium bromide was obtained from lactone **13** when it was treated with gaseous HBr.

The ester **14** was obtained in 91% yield by refluxing **12** for 3 days in MeOH saturated with HBr. Recrystallization from acetonitrile gave white needles, m.p. 189–189·5° (dec); IR (nujol) 5·80 (C=O), 6·13 μ (C=$N^+$); UV (EtOH) 227, 234, 278 mμ; NMR ($CDCl_3$) δ 1·80 (s, 3H, β-$CH_3$), 3·23 (s, 3H, α-$CH_3$), 3·48 (s, 3H, $COOCH_3$), 3·68 (AB quartet, 2H, $J$ = 17 Hz, β-$CH_2$), 4·35 (s, 3H, $N^+CH_3$), 7·7 (m, 4H, ArH). (Found: C, 54·10; H, 5·88; N, 4·46. Calc. for $C_{14}H_{18}NO_2Br$: C, 53·84; H, 5·88; N, 4·49%).

Attempts to prepare this ester by direct condensation of 1,2,3-trimethylindole with methyl bromoacetate gave poor yields of lactone **13**.

*Methyl 1,3-dimethyl-2-methyleneindoline-3-acetate* (**15**). Indolenium salt **14** was basified with 10% $NaHCO_3$aq which was then extracted with ether. The ether extract gave a crude pink oil, which, upon washing with hexane, gave a near quantitative yield of **15** as a viscous yellow oil, unstable to air and light. UV (MeOH) 279, 315 (sh) mμ; IR (neat) 5·75 (C=O), 6·06 μ (C=C); NMR ($CDCl_3$) δ 1·35 (s, 3H, β-$CH_3$), 2·60 (s, 2H, $CH_2COOR$), 2·90 (s, 3H, $NCH_3$), 3·35 (s, 3H, $COOCH_3$), 3·80 (s, 2H, C=$CH_2$),* 6·25–7·15 (m, 4H, ArH). The picrate melted at 128·8–129°. (Found: C, 52·14; H, 4·48; N, 12·12 (picrate). Calc. for $C_{20}H_{20}N_4O_9$: C, 52·17; H, 4·35; N, 12·42%).

*1,2,3-Trimethyl-2-hydroxyindoline-3-acetic acid γ-lactone* (**13**). To 1·30 g (0·01 mol) β-methyl levulinic acid[16] was added 1·22 g (0·01 mol) N-methylphenylhydrazine. The resulting hydrazone was subjected to vacuum distillation to remove the water and then treated with 20 ml boiling 10% $HSO_4$. The mixture was neutralized with dil $NH_4OH$ and then extracted with ether. The ether extract was stored at 0° until white crystals formed. Recrystallization from $CH_2Cl_2$–light petroleum gave 0·57 g (30% of lactone **13**, m.p. 128–129°; UV (EtOH) 244, 295 mμ; IR (nujol) 5·66 μ (C=O); NMR ($CDCl_3$) δ 1·30 (s, 3H, β-$CH_3$), 1·65 (s, 3H, α-$CH_3$), 2·85 (AB quartet, 2H, $J$ = 17 Hz, β-$CH_2$; in DMSO-$d_6$ this quartet is better resolved), 2·90 (s, 3H, $NCH_3$), 6·40–7·30 (m, 4H, ArH). (Found: C, 72·16; H, 6·98; N, 6·27. Calc. for $C_{13}H_{15}NO_2$: C, 71·88; H, 6·91; N, 6·45%).

This lactone was readily formed when **12** was basified.

*9-Methyl-1,2,3,4-tetrahydrocarbazole.* This compound was obtained in 90% yield following the procedure used for 1,2,3-trimethylindole. Recrystallization of the crude product gave colorless clusters, m.p. 49° (lit.[9] m.p. 46–47°).

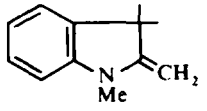
*Methyl 9-methyl-2,3,4,4a-tetrahydrocarbazolenium-4a-acetate bromide* (**18**). To 1·12 g (0·008 mol) molten bromoacetic acid was added 0·55 g (0·003 mol) 9-methyl-1,2,3,4-tetrahydrocarbazole, and the mixture was heated under $N_2$ for 1 hr at a bath temp of 140°. The ppt was washed successively with ether and $CH_2Cl_2$ to give 0·78 g (80%) of **16**. Recrystallization from acetonitrile gave pure white crystals, m.p. 249–251° (dec); UV (MeOH) 231, 237, 245, 284 mμ; UV (95% ethanol) 241 and 292 mμ; IR (nujol) 5·85 (C=O), 6·13 μ (C=$N^+$). (Found: C, 55·51; H, 5·56; N, 4·53. Calc. for $C_{15}H_{18}O_2NBr$: C, 55·56; H, 5·56; N, 4·32%).

The corresponding ester **18** was obtained in 97% yield by heating the acid salt for 2 days in refluxing MeOH saturated with dry HBr. Recrystallization from acetonitrile gave white crystals, m.p. 87° (dec); UV (EtOH) 229, 236, 278 mμ; IR (nujol) 5·81 (C=O), 6·15 μ (C=$N^+$); NMR ($D_2O$) δ 1·3–2·1 (m, 6H, $CH_2CH_2CH_2$; the α-$CH_2$ exchanges under these conditions), 3·5 (s, 3H, $COOCH_3$), 3·7 (AB quartet, 2H, $J$ = 17 Hz, $CH_2COOR$), 4·2 (s, 3H, $N^+CH_3$), 7·7–8·0 (m, 4H, ArH).

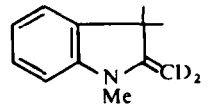
*Methyl 9-methyl-2,3,4,4a-tetrahydrocarbazole-4a-acetate* (**19**). A soln of 0·52 g of **18** in dry MeOH was loaded onto a column of Rexyn 201 (methoxide form), and 150 ml of anhyd MeOH was eluted and collected in 3 portions. The first portion contained **19** while the third portion contained **17**. Evaporation of the MeOH from the first fraction gave crude **19** as a yellow oil, UV (MeOH) 280, 315 (sh) mμ; IR (neat) 5·75 (C=O), 5·94 μ (C=C).[9] This material was not obtained pure without traces of oxidation and/or polymeric products.

*9-Methyl-9a-hydroxy-1,2,3,4,4a,9a-hexahydrocarbazole-4a-acetic acid γ-lactone* (**17**). Ethyl 2-ketocyclohexylacetate was prepared from cyclohexanone, piperidine and ethyl bromoacetate by the Stork[17] method. The corresponding acid was obtained in quantitative yield by hydrolysis of the ester with concentrated HCl. The acid displayed m.p. 73° (lit.[18] m.p. 73°); 2,4-DNP, m.p. 190° (lit.[18] m.p. 193–194°).

* The anomalously high chemical shift value for the vinyl protons is surprising. The assignment was confirmed, however, by comparison with the chemical shift of the vinyl protons of 1,3,3-trimethyl-α-methyleneindoline (**i**), which also appear as a singlet at 3·80 δ. The deuterated compound (**ii**) lacks this signal.




i




ii

To 4·71 g of the acid was added 3·6 g N-methylphenylhydrazine. The water was evaporated from the resulting solution *in vacuo*, and the residue was treated with 20 ml boiling 10% $H_2SO_4$. The mixture was extracted with water, and the water layer was neutralized with dil $NH_4OH$. The ether extracts of this aqueous soln gave 1·63 g (22%) of **17**, m.p. 134·5–135°. Silica gel chromatography followed by sublimation at reduced pressure gave an analytical sample, m.p. 139–140°; UV (EtOH) 242, 285 mμ; IR (nujol) 5·67 μ (C=O); NMR ($CDCl_3$) δ 1·17–1·67 (m, 8H, $CH_2CH_2CH_2CH_2$), 2·60 (m, 2H, $CH_2CO$; in DMSO-$d_6$ this signal is an AB quartet, $J$ = 17 Hz), 2·92 (s, 3H, $NCH_3$), 6·50–7·33 (m, 4H, ArH). (Found: C, 74·20; H, 7·04; N, 5·83. Calc. for $C_{15}H_{17}NO_2$: C, 74·05; H, 7·04; N, 5·76%).

This same lactone was obtained by basifying the carbazolenium salt **16**.

2,3-*Dimethylindolenine*-3-*acetonitrile* (**20**). To an ethereal soln of 2,3-dimethylindole magnesium iodide (prepared from 1·34 g Mg, 3·6 ml MeI, and 7·25 g, 2,3-dimethylindole)[19] at 0° was added 5·0 g (25% excess) of freshly distilled chloroacetonitrile in ether. The soln was stirred at room temp for 20 min and then refluxed for 30 min. The Grignard complex was decomposed with ice-water and neutralized with AcOH. The mixture was extracted thoroughly with ether, which was then washed with $NaHCO_3$ aq followed by water. The ether layer was then extracted with 2N HCl. After basifying the acid extract with NaOH, it was re-extracted with ether. The ether layer was washed with water, dried ($MgSO_4$) and the ether removed to give 3·73 g (41%) of **20** as a viscous yellow oil. Upon washing the oil with a small amount of ether, a yellow solid was obtained. Recrystallization from hexane gave 2·1 g (23%) light yellow crystals, m.p. 77·5–78·5° (lit.[20,21] m.p. 75–76°, 81–83°). The picrate melted at 176·5–177° (lit.[20,21] m.p. 175–178°, 177–178°). Compound **20** displayed UV (EtOH) 257 mμ; IR (neat) 4·43 (C≡N), 6·30 μ (C=N).

1,3-*Dimethyl*-2-*methyleneindoline*-3-*acetonitrile* (**21**). This compound was obtained by methylation of **20** with a 10% excess Na and MeI in liquid ammonia according to the procedure used for the preparation of 9-methyl-1,2,3,4-tetrahydrocarbazole. Purification by column chromatography on silica gel gave a colorless liquid, UV (MeOH) 278, 315 (sh) mμ; IR (neat) 4·47 (C≡N), 6·05 μ (C=C); NMR ($CDCl_3$) δ 1·5 (s, 3H, β-$CH_3$), 2·5 (s, 2H, $CH_2CN$), 3·0 (s, 3H, $NCH_3$), 4·0 (s, 2H, C=$CH_2$),* 6·5–7·3 (m, 4H, ArH).

The hydrochloride salt crystallized from acetonitrile as white crystals, m.p. 168° (dec). (Found: C, 66·43; H, 6·30. (hydrochloride) Calc. for $C_{13}H_{15}N_2Cl$: C, 66·52; H, 6·40%).

This same indoline was obtained in very poor yield by alkylation of 1,2,3-trimethylindole with chloroacetonitrile in a sealed tube at 130° for 4 hr.

2-(1,3-*Dimethyl*-2-*methyleneindoline*-3-*yl*)-*acetophenone* (**22**). A soln of 5·92 g of 1,2,3-trimethylindole and 19·62 g (2 eq) α-bromoacetophenone in 40 ml benzene and 29 ml water was refluxed for 10 days. The water layer was separated each day, and to the benzene layer was added 20 ml fresh water and refluxing was then resumed. The combined water layers were neutralized with 10% $NaHCO_3$ aq. The ether extract of this aqueous soln gave **22** as a pale yellow oil, UV (MeOH) 250, 280 mμ; IR (neat) 5·91 (C=O), 6·07 μ (C=C); NMR ($CDCl_3$) δ 1·50 (s, 3H, β-$CH_3$), 2·93 (s, 2H, $CH_2CO\emptyset$), 3·03 (s, 3H, $NCH_3$), 3·40 (s, 2H, C=$CH_2$),* 6·9–7·5 (m, 9H, ArH).

The hydrochloride salt (acetonitrile–ether) melted at 177–179° (dec); UV (MeOH) 251, 290 (sh) mμ; IR (nujol) 5·95 (C=O), 6·16 μ (C=$N^+$).

(Found: C, 72·42; H, 6·21. (hydrochloride) Calc. for $C_{19}H_{20}NOCl$: C, 72·66; H, 6·44%).

2-(9-*Methyl*-9a-*hydroxy*-1,2,3,4,4a,9a-*hexahydrocarbazole*-4a-*yl*)-*acetophenone* γ-*lactol* (**23**). A soln of 0·37 g (0·002 mol) 9-methyl-1,2,3,4-tetrahhdrocarbazole and 1·07 g (0·0054 mol) α-bromoacetophenone in 6 ml EtOH and 3·6 ml water was heated at 85° for 12 hr. The mixture was treated with water and ether. The water layer was separated and basified with $Na_2CO_3$ aq. The ether extract of this water layer gave white crystals which were recrystallized from chloroform–hexane to give 0·15 g (23%) of **23**, m.p. 102° (dec); UV (EtOH) 249, 297 mμ; IR (nujol) 2·94 μ (OH); NMR ($CDCl_3$) σ 1·2–2·4 (m, 8H, $CH_2CH_2CH_2CH_2$), 2·7 (AX quartet, 2H, $J$ = 8 Hz, $CH_2C\emptyset OH$), 2·9 (s, 3H, $NCH_3$) 6·3–7·8 (m, 9H, ArH). (Found: C, 78·44; H, 7·21; N, 4·29. Calc. for $C_{21}H_{23}NO_2$: C, 78·50; H, 7·17; N, 4·37%).

The lactol gave hygroscopic white crystals when treated with HCl gas, UV (MeOH) 248, 297 mμ; IR (nujol) 5·96 (C=O), 6·12 μ (C=$N^+$). The structure assigned to this compound is that of the open chain system **23a**.

*Reaction of α-methyleneindolines with nucleophiles—General procedure.* The α-methyleneindolines were generated from their hydrochloride or hydrobromide salts by passage through a basic ion exchange resin which had been dried in a vacuum desiccator for 3 days to constant weight. The specified ionic form of the resin was obtained by washing with the appropriate ionic soln. The solns of the α-methyleneindolines from the column were generally used directly without isolation of the air-sensitive compounds.

The mixtures were worked-up as follows: the mixture was cooled and the solvent removed *in vacuo*. The

residue was extracted with an organic solvent then dried over $MgSO_4$. The solvent was then removed *in vacuo*.

1. *Reaction of* **15** *with various nucleophiles*

(a) *With sodium methoxide in methanol.* A soln of 0·50 g (0·0016 mol) of **14** in dry MeOH was loaded onto a column of Dowex 2-X4 (methoxide form), and 300 ml dry MeOH was eluted. The first 100 ml eluent was refluxed under $N_2$ for 3 days with a MeOH soln containing 0·0067 mol NaOMe. A hexane extract of the mixture gave lactone **13** as the major product together with a small amount of red, tar-like material, containing no indole chromophore by UV.

(b) *With sodium acetate in methanol.* A soln of 0·5 g of **14** in dry MeOH was loaded onto a column of Dowex 2-X4 (methoxide form), and 300 ml of dry MeOH was eluted. The first 100 ml eluent was refluxed with 0·40 g anhyd NaOAc under a $N_2$ atmosphere for 3 days. Ether extraction gave lactone **13** as a minor product together with non-indolic (UV) red tar as the major product.

(c) *With potassium cyanide in methanol.* A soln of 0·31 g of **14** in dry MeOH was loaded onto a column of Rexyn 201 (methoxide form), and 300 ml of dry MeOH was eluted. The first 100 ml eluent was refluxed with 0·33 g KCN for 3 days under a $N_2$ atmosphere. Ether extraction gave a white crystalline compound. Recrystallization from hexane afforded an analytical sample of **24**, m.p. 103–104°; UV (EtOH) 250, 293 mμ; IR (nujol) 4·50 (C≡N), 5·77 μ (C=O); NMR ($CDCl_3$) δ 1·55 (s, 3H, β-$CH_3$), 1·70 (s, 3H, α-$CH_3$), 2·45 (AB quartet, 2H, $J$ = 15 Hz, $CH_2COOR$), 2·75 (s, 3H, $NCH_3$), 3·50 (s, 3H, $COOCH_3$), 6·37–7·20 (m, 4H, ArH). (Found: C, 69·65; H, 7·08; N, 10·62. Calc. for $C_{15}H_{18}N_2O_2$: C, 69·77; H, 6·98; N, 10·85%).

(d) *With potassium cyanide in acetonitrile.* A soln of 1 g of **14** in dry MeOH was loaded onto a column of Rexyn 201 (methoxide form), and 200 ml of acetonitrile was eluted. The first 150 ml eluent was refluxed with 0·08 g KCN in acetonitrile under $N_2$ for 3 days. $CH_2Cl_2$ extraction gave only recovered starting material.

2. *Reaction of* **19** *with potassium cyanide in methanol*

A soln of 0·49 g of **18** in dry MeOH was loaded onto a column containing 20 g of Rexyn 201 (methoxide form), and 300 ml of dry MeOH was eluted. The first 150 ml eluent was refluxed with KCN in dry MeOH under $N_2$ for 3 days. The ether extract gave **25** after several recrystallizations from hexane (white needles), m.p. 58·5°; UV (EtOH) 251, 296 mμ; IR (neat 4·5 (very weak, C≡N), 5·74 μ (C=O); NMR ($CDCl_3$) δ 1·10–2·20 (m, 8H, $CH_2CH_2CH_2CH_2$), 2·75 (s, 3H, $NCH_3$), 2·85 (AB quartet, 2H, $J$ = 15 Hz, $CH_2COOR$), 3·70 (s, 3H, $COOCH_3$) 6·35–7·24 (m, 4H, ArH). (Found: C, 72·02; H, 6·99. Calc. for $C_{17}H_{20}N_2O_2$: C, 71·83; H, 7·04%).

3. *Reaction of* **21** *with various nucleophiles*

(a) *With sodium methoxide in methanol.* A soln of 0·32 g of **21** in 20 ml dry MeOH was refluxed with NaOMe (0·44 g) under $N_2$ for 2 days. Ether extracts gave mixtures of unidentified non-indolic (UV) products.

(b) *With potassium cyanide in methanol.* A soln of 0·63 g of **21** in 40 ml dry MeOH was refluxed with KCN (0·65 g, 3 eq) under $N_2$ for 2 days. Ether extracts gave mixtures of unidentified, non-indolic (UV) products.

(c) *With potassium cyanide in acetonitrile.* A soln of 0·63 g of **21** in acetonitrile was refluxed with 0·33 g KCN under $N_2$ for 2 days. Only starting material was recovered.

4. *Reaction of* **23** *with potassium cyanide in methanol*

A soln of 0·63 g hydrochloride salt of **23** in water was neutralized with 10% $Na_2CO_3$ aq and extracted with ether. The ether extract was dried and the ether removed *in vacuo*. The residue was refluxed with MeOH containing 0·20 g KCN under $N_2$ for 3 days. Ether extraction gave a semisolid. Crystallization from hexane gave **26**, m.p. 147°; UV (MeOH) 253, 302 mμ; UV (MeOH, $H^+$) 260, 268 (sh) mμ;[22] IR (nujol) 2·85 (OH), 4·46 μ (C≡N); NMR ($CDCl_3$) δ 1·8 (s, 3H, β-$CH_3$), 2·0 (s, 1H, OH), 2·4–2·8 (m, 4H, α- and β-$CH_2$), 2·9 (s, 3H, $NCH_3$), 6·3–7·5 (m, 9H, ArH). (Found: C, 79·09; H, 6·46. Calc. for $C_{20}H_{20}N_2O$: C, 78·95; H, 6·58%).

*Ethyl 2,3-dimethylindolenine-3-carboxylate* (**29**). To an ethereal solution of 2,3-dimethylindole magnesium iodide (prepared from 0·025 mol of 2,3-dimethylindole, 0·025 mol Mg and 0·025 mol MeI) at 7–8° was added 2 ml (0·025 mol) of freshly distilled ethyl chloroformate in anhyd ether. After the mixture was stirred at 8–10° for 90 min, crushed ice was added, and then it was neutralized with AcOH. The combined ether

extracts of the aqueous mixture were dried and concentrated under reduced pressure. The residue was distilled at 120–145°/2–4 mm. The yellowish distillate was dissolved in ether and chromatographed on silica gel. Elution of the column with hexane–ether (5:1) gave 1·4 g (26%) of **30**. UV (EtOH) 229, 265, 282, 295 mμ;[23] IR (neat) 5·77 μ (C=O); NMR ($CD_3COCD_3$) δ 1·2 (t, 3H, $J$ = 7 Hz, $CH_2C\underline{H}_3$), 2·0 (s, 3H, β-$CH_3$), 2·2 (s, 3H, α-$CH_3$), 4·2 (quartet, 2H, $J$ = 7 Hz, $C\underline{H}_2CH_3$), 7·1 (m, 3H, 4,5,6-ArH), 8·0 (m, 1H, 7-ArH). The picrate melted at 89–90° (lit.[9] m.p. 90–90·5°).

The 1:1 hexane–ether eluent gave 1·52 g (28%) of indolenine **29**, b.p. 95–106°/1·4 mm; UV (EtOH) 260 mμ; IR (neat) 5·75 (C=O), 6·30 μ (C=N);[9] NMR ($CD_3COCD_3$) δ 1·1 (t, 3H, $J$ = 7·0 Hz, $CH_2C\underline{H}_3$), 1·6 (s, 3H, β-$CH_3$), 2·4 (s, 3H, α-$CH_3$),[14] 4·1 (quartet, further split, 2H, $J$ = 7·0 and 2·0 Hz, $C\underline{H}_2CH_3$), 7·4 (m, 4H, ArH). The picrate melted at 143°. (Found: C, 50·88; H, 4·03; N, 12·35. (picrate) Calc. for $C_{19}H_{18}N_4O_9$: C, 51·15; H, 4·04; N, 12·56%).

*Ethyl 2,3-dimethylindolenine-3-thiocarboxylate* (**31**). To an ethereal soln of 2,3-dimethylindole magnesium iodide (prepared from 0·025 mol of 2,3-dimethylindole, 0·025 mol Mg, and 0·025 mol MeI) at 8–9° was added with stirring 3·02 g (0·025 mol) ethyl chlorothioformate in dry ether. After 95 min between 7–13°, crushed ice was added, the mixture was neutralized with AcOH and then extracted with ether. The combined ether extracts were concentrated under reduced pressure, and the residue was distilled at 143–152°/3–5 mm. The yellow distillate (1 ml) was dissolved in ether and chromatographed on silica gel. Elution of the column with light petroleum ether (1:1) gave **31** as a yellow solid, m.p. 44–45°; UV (EtOH) 230, 272 (sh) mμ; IR (neat) 5·98 (C=O), 6·34 μ (C=N); NMR ($CDCl_3$) δ 1·1 (t, 3H, $J$ = 7 Hz, $CH_2C\underline{H}_3$), 1·6 (s, 3H, β-$CH_3$), 2·3 (s, 3H, α-$CH_3$), 2·7 (quartet, 2H, $J$ = 7 Hz, $C\underline{H}_2CH_3$), 7·2–7·7 (m, 4H, ArH).

*Ethyl 1,2,3,4-tetrahydrocarbazole-9-carboxylate* (**32**) To an ethereal soln of 1,2,3,4-tetrahydrocarbazole magnesium iodide[19] (0·02 mol) at 9° was added 0·02 mol freshly distilled ethyl chloroformate in anhyd ether with stirring. After 45 min between 8–10°, crushed ice was added, and then the mixture was neutralized with AcOH and extracted with ether. The combined ether extracts were concentrated *in vacuo*, and the residue afforded, after several recrystallizations from hexane, indole ester **32**, m.p. 62·5–63·5° (lit.[24] m.p. 65°); IR (nujol) 5·75 μ (C=O); UV (EtOH) 229, 265, 283, 295 mμ;[23] NMR ($CDCl_3$) δ 1·4 (t, 3H, $J$ = 7 Hz, $CH_2C\underline{H}_3$), 1·8 (m, 4H, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 2·6 (distorted t, 2H, β-$CH_2$), 2·9 (distorted t, 2H, α-$CH_2$), 4·4 (quartet, 2H, $J$ = 7 Hz, $C\underline{H}_2CH_3$), 7·2 (m, 3H, 5,6,7-ArH), 8·0 (m, 1H, 8-ArH).

*Ethyl 2,3,4,4a-tetrahydrocarbazolenine-4a-thiocarboxylate* (**33**). To an ethereal soln of 1,2,3,4-tetrahydrocarbazole magnesium iodide (prepared from 0·025 mol of 1,2,3,4-tetrahydrocarbazole, 0·025 mol Mg and 0·025 mol MeI) at 8–10° was added with stirring 3·02 g (0·025 mol) of ethyl chlorothioformate in dry ether. After 100 min at 10°, crushed ice was added, the reaction mixture was neutralized with AcOH and then extracted with ether. The combined ether extracts were concentrated under reduced pressure and adsorbed onto a silica gel column. The hexane–ether (4:1) eluent gave **34** as the major product, a yellow oil. UV (EtOH) 220, 233, 252, 268 (sh), 295, 303 mμ; IR (neat) 5·98 (C=O), 13·35 (*o*-disubstitution pattern). The $CH_2CH_2$–EtOAc eluent gave carbazolenine **33** as a yellow oil (minor product). UV (EtOH) 230 mμ; IR (neat) 5·98 (C=O), 6·33 μ (C=N). (Found: C, 69·36; H, 6·66. Calc. for $C_{15}H_{17}NOS$: C, 69·50; H, 6·53%).

*Decarboxylation reactions of* **29**

(a) *In acid.* A soln of 0·40 g of **29** in 20 ml 1N HCl was refluxed for 1 hr. The mixture was cooled and extracted with ether. The ether layer was dried and the ether removed *in vacuo*. Crystallization of the residue from hexane gave 0·30 g (92%) 2,3-dimethylindole.

The same results were obtained with 6N and 0·1N HCl, but with 0·01N HCl only starting ester (**29**) was recovered.

(b) *In base.* A soln of 0·085 g of **29** in alcohol containing 0·044 g KOH was kept at room temp for 20 hr. A quantitative yield of 2,3-dimethylindole was obtained.

*Decarboxylation reactions of* **31**

A soln of 0·41 g of **31** in acetone–water with 1·15 g lead acetate was kept 19 hr at room temp. An IR spectrum of an ether extract was almost identical to that of starting indolenine ester. After one day at reflux, the IR spectrum of an ether extract showed carbonyl absorption at 5·85 μ (COOH) while the thioester absorption at 5·98 μ was markedly diminished in intensity. Strong C=N absorption at 6·33 μ remained as well as the typical indolenine absorptions in the finger print region. After 4 days at reflux, the IR spectrum of an ether extract showed only very weak thioester, imine, and indolenine absorptions, and it was essentially the spectrum of 2,3-dimethylindole.

*Decarboxylation reactions of* **33**

A soln of **33** in 12 ml 1N HCl was refluxed for 1 day. The mixture was extracted with ether to give, after recrystallization (hexane), 1,2,3,4-tetrahydrocarbazole.

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