Pyrazine Chemistry. Part 12.[1] Acid-catalysed Rearrangements of *cyclo*-L-Prolyl-L-[N^a-(3,3-dimethylallyl)]tryptophyl

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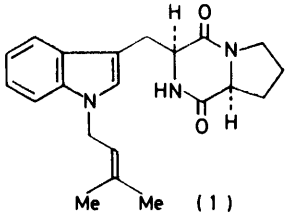
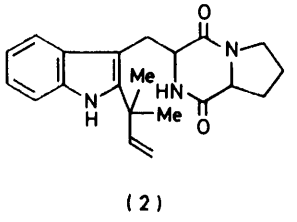
Rearrangements of the title compound under the influence of trifluoroacetic and Lewis acids have been studied. Under no circumstances was deoxybrevianamide E formation observed. Amongst the rearrangement products isolated were two resulting from intramolecular Friedel–Crafts alkylations and two resulting from cleavage of the nitrogen–allyl bond. The chemical relationships between the rearrangement products has been explored. Lead tetra-acetate oxidation of the Friedel–Crafts product (6) introduced an acetate function at position 3 of the indole nucleus and acid catalysed a novel rearrangement of this, to the indolic nitrogen substituent, to give the epimeric aminol acetates (19) and hence the aminols (20); the latter were remarkably resistant to ring-opening under a variety of conditions.

In the preceding paper of this series [1] a simple route to *cyclo*-L-prolyl-L-[N^a-(3,3-dimethylallyl)]tryptophyl (1) was described. This compound has been suggested as a possible precursor to deoxybrevanamide E (2) and,



(1)



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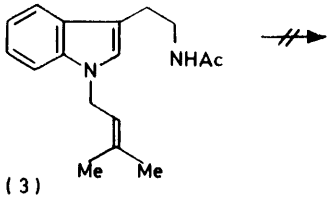

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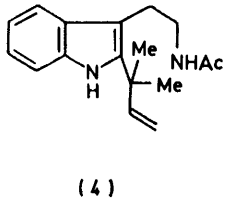
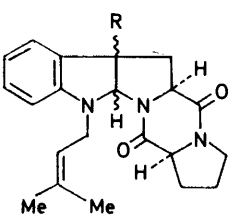


(4)

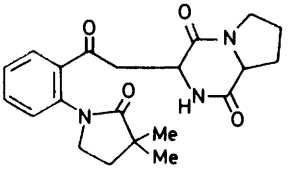
thereafter, to a range of naturally occurring dioxopiperazines,[2] including the austamides,[3] brevianamides,[4] and fumitremorgens.[5] Considerable work has been reported on the acid-catalysed rearrangements of a variety of *N*-allylindole derivatives,[6] culminating in a study of the rearrangements of N^a-(3,3-dimethylallyl)-N^b-acetyltryptamine (3).[7] The latter study showed that migrations of the allyl residue onto the carbon nucleus of the indole moiety occurred but that, in this case, none of the rearranged isomer (4) was observed. It was of interest, therefore, to study the behaviour of compound (1) under different acidic conditions.

RESULTS AND DISCUSSION

Treatment of the dioxopiperazine (1) with boron trifluoride–ether in either dichloromethane or carbon tetrachloride at room temperature slowly produced two new products, neither of which corresponded to the indoline, (5). The more polar product was identified as the pyrroloindole derivative (6), and the less polar product as the isomer (7). Both analysed as isomers of the starting material, showed the characteristic indole chromophore in their u.v. spectra, and replacement of the vinylic dimethyl group with an aliphatic *gem*-dimethyl signal, suggesting, in both instances, the occurrence of an intramolecular Friedel–Crafts alkylation of the aromatic residue. The more polar product (6) gave a negative Urk test,[8] indicating a substituent at position 2 of the indole nucleus, which was confirmed by the absence of a 2-H resonance in the ^{1}H n.m.r. spectrum. The isomer (7) did possess this proton, and did give a positive Urk test. Further structural evidence was obtained by cleavage of the indole nucleus. Both ozonolysis and singlet-oxygen oxidation [9] selectively oxidised the 2,3-double bond to give, from the pyrroloindole (6) the pyrrolidone (8) and, from the less polar compound (7), the *N*-formyl derivative (9).



(5); R = H
(10); R = BBr_2



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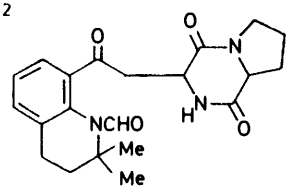

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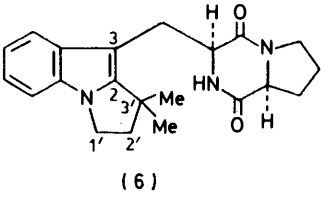
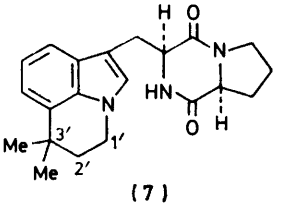


(6)

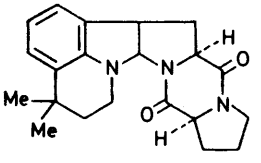


(7)

Neither of the compounds (6) or (7) appeared to tautomerise to the corresponding indolines when treated with trifluoroacetic acid.[1] Variations in the reaction conditions using boron trifluoride–ether did not lead to products containing the vinylic signals associated with

the presence of dimethylallyl residues. At temperatures up to 100 °C the major products were still compounds (6) and (7), although the ratio of these changed slightly, the proportion of pyrroloindole (6) increasing. Above 100 °C a variety of minor products began to form, accompanied by charring of the materials. When small quantities of water were added to the reaction mixtures the proportion of pyrroloindole (6) was further increased and yields of up to 50% of this isomer could be formed.

Since boron trifluoride–ether had failed to give any of desired product (2), other Lewis acids were employed. With boron tribromide, a much stronger Lewis acid than boron trifluoride–ether,[10] a single major product was formed along with numerous, more polar by-products. The major product was the pyridinoindole (7); no trace of the pyrroloindole (6) was detected. This rather unexpected result is rationalised by assuming that boron tribromide is sufficiently strong to complex to position 3 of the indole nucleus, as well as the allylic double bond. Cyclisation to position 7 of the indole nucleus can then proceed in the indoline form (10), position 2 being blocked. The product indoline (11) is unstable, since cyclisation of

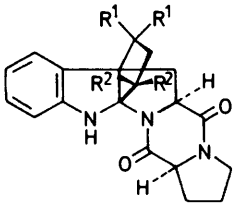


(11)

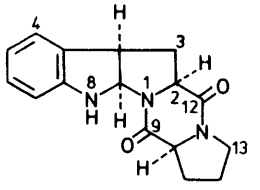
(7) to (11) does not occur in trifluoroacetic acid and on work-up yields the open product (7). A similar result was observed with the indoline (5) and boron tribromide whereas, with boron trifluoride–ether, the indoline again produced both compounds (6) and (7).

Stannic chloride was also used as a catalyst to rearrange the dioxopiperazine (1). In this case an insoluble complex precipitated out from the dichloromethane solution. Work-up of the complex after a few minutes of reaction re-formed the starting material but, after longer periods, three products formed. The major products were again the cyclised materials (6) and (7) but these were accompanied by a much less polar material. This non-polar compound had spectral properties indicating an indoline structure, but did not contain any vinylic protons indicative of an allyl group. Furthermore, the characteristic resonance at positions 3a and 8a of the indoline system was absent, suggesting substitution at these positions, and an NH resonance was observed indicating liberation of the indolic nitrogen. The assignment of the indoline structure was confirmed by the ^{13}C n.m.r. spectrum.*

Whilst the u.v. spectrum of the product was similar to that of the indoline (5), it did not alter to the open, indole form by treatment with dilute acid, in agreement with the presence of two substituents at position 3. Two gross structures are possible for this product, the bridged species (12) or (13). N.m.r. evidence did not help to distinguish between these structures, except that the positions of the *gem*-dimethyl signals (δ 1.15 and 0.70)



(12) ; R^1 = H ; R^2 = Me
(13) ; R^1 = Me , R^2 = H



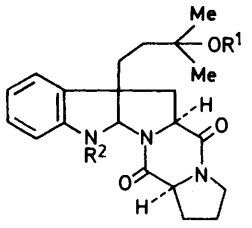
(14)

were very similar to those of the derivative (6) (see below), in which models indicate that the methyl groups are spatially oriented in a very similar environment and occur at δ 1.56 and 0.97. Further evidence that the structure is (12) was obtained by attempted acetylation; unlike the *N*-unsubstituted indoline (14), acetylation did not occur, indicating a large degree of steric hindrance about the N–H bond; acetylation would be expected for systems of the type (13) but not for (12). As with other instances of indoline formation,[1] two stereoisomers would be expected but again only one product of this gross type could be detected. By analogy with the tentative assignment made for the other indolines,[1] *cf.* (14), compound (12) is tentatively assigned the *syn*-orientation. Formation of the compound (12) does indicate that allyl migrations are possible in this series. Treatment of either of the Friedel–Crafts products (6) or (7) with stannic chloride did not produce further quantities of (12), and essentially starting material was recovered in both instances.

The rearrangement of the dioxopiperazine (1) in trifluoroacetic acid was also investigated. Although brief treatment produced quantitative yields of the indoline (5), prolonged exposure produced, mainly, the pyrroloindole (6) and three other minor products of similar polarity, none of which possessed vinylic protons and so were not investigated further. One less polar product was also formed, the u.v. spectrum of which indicated an indoline structure. In this compound the proton at position 8a was present, as a singlet at δ 5.25, suggesting a new substituent at position 3a. The nitrogen at position 8 possessed a hydrogen substituent, indicating migration of the dimethylallyl group to position 3a. Incorporation of a trifluoroacetate group into the dimethylallyl group was suggested by the i.r. spectrum ($\nu_{max.}$ 1 780 cm^{-1}) and the shift of the methyl signals as a singlet at δ 1.48. Hydrolysis of the trifluoroacetate group gave a tertiary alcohol. On the basis of this evidence the product was assigned structure (15), and the alcohol structure (16). As anticipated, the indoline (15) was readily acetylated by acetic anhydride to produce the amide (17). Prolonged treatment of the cyclic products (6) and (17) with trifluoroacetic acid did

* The n.m.r. data are deposited as Supplementary Publication No. SUP 22614 (11 pp.). For details see Notice to Authors No. 7, *J.C.S. Perkin I*, 1978, Index issue.

not give the ester (15), suggesting that this is produced by a non-concerted rearrangement pathway, probably involving ion pairs which then collapse by attack at position 3 of the indole ring, followed by quenching of the

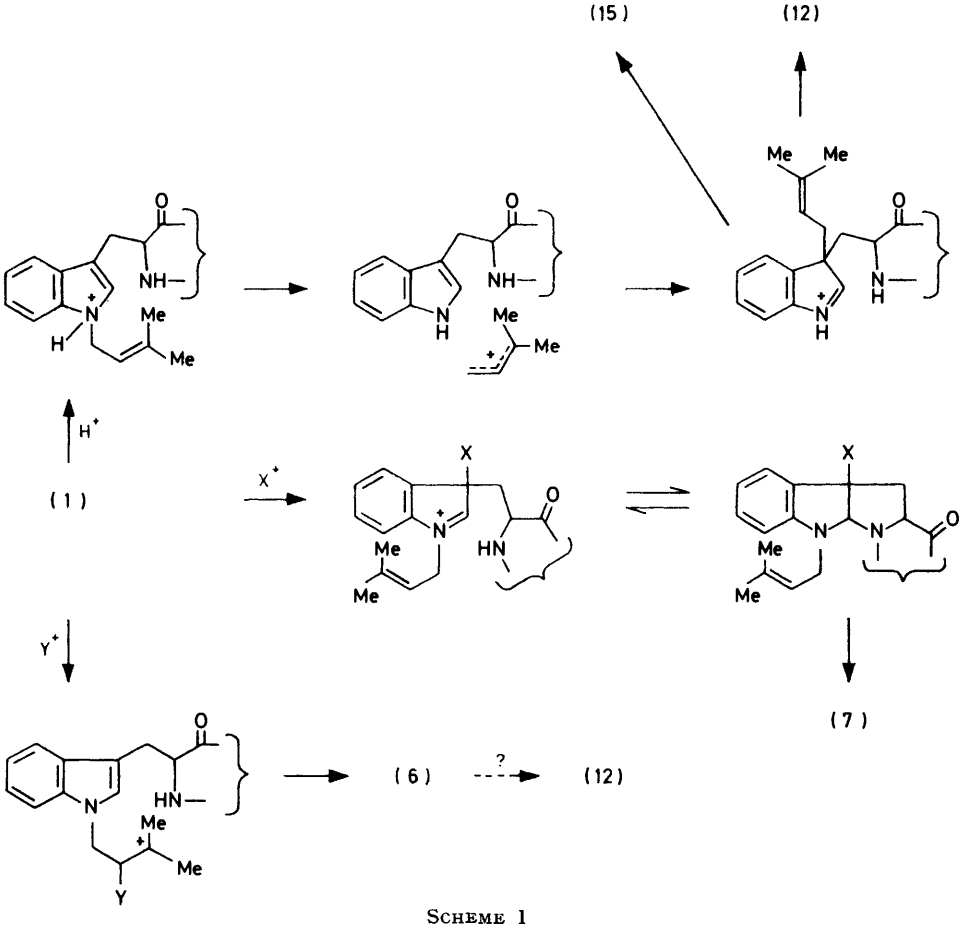


(15) ; $R^1 = CF_3CO$, $R^2 = H$
(16) ; $R^1 = R^2 = H$
(17) ; $R^1 = CF_3CO$, $R^2 = Ac$

indolenium species by attack of the dioxopiperazine ring. Again only one stereoisomer could be isolated. The rationale forwarded to explain the observed results is presented in Scheme 1.

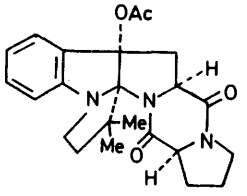
Because of the failure of the above acid-catalysed processes to produce desoxybrevianamide E (2), an attempt was made to convert the major product, the pyrroloindole (6), into it by further chemical processes. In principle this conversion requires opening of the tetrahydropyrrole ring by an elimination of the indolic substituent. It was initially felt that electrophilic attack on the indole ring at position 3, creating an indolenium species, would enhance the electrofugacity of the leaving group, provided indoline formation, *via* participation of the dioxopiperazine, did not interfere. In the event, the latter process did occur. Thus oxidation of (6) with lead tetra-acetate in acetic acid gave two major products. The least polar of these was identified as the acetate (18), existing as a single isomer. The fact that only one isomer is formed in this case is of mechanistic interest and suggests that electrophilic attack is the selective step. (In indoline formation by protonation it could also be argued that protonation is an equilibrium process, occurring from either face of the indoline, with the cyclisation process selectively occurring to only one of the indolenium species.) This result supports the contention that the *cyclo*-L-prolyl-L-tryptophyl system occurs in a partially folded conformation and that electrophilic attack occurs preferentially to the least hindered side of the indole ring, leading to the *syn*-configuration, previously assigned on a tentative basis, for the compounds (5), (12), (15), and (18).

The more polar product from the lead tetra-acetate oxidation was identified, on spectroscopic evidence, as a mixture of two diastereoisomers. Analytical t.l.c. only effected a partial separation and preparative t.l.c.

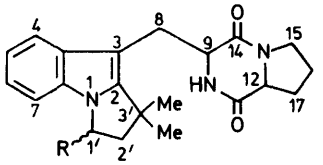


SCHEME 1

separation was not possible. These isomers were assigned the structure (19); partially purified material rapidly re-equilibrated to the mixture.



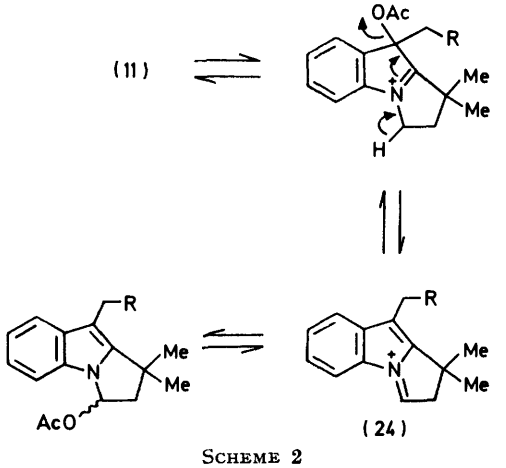
(18)



(19); R = OCOMe
(20); R = OH
(25); R = NHNHSO$_2$C$_6$H$_4$Me-p
(27); R = S[CH$_2$]$_3$SH

The relative proportions of the oxidation products (18) and (19) varied from reaction to reaction until it was realised that the isomeric acetates (19) were formed from (18) by treatment with acetic acid, the initial oxidation product being the expected acetate (18). Treatment of the acetates (19) did not form any of the indoline (18). A scheme for their conversion is presented (Scheme 2).

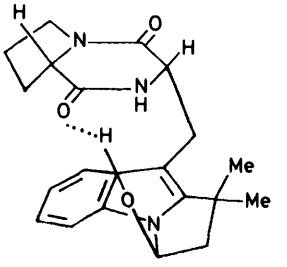
It was considered that the acetates (19) could be used to synthetic advantage, since their corresponding alcohols, the aminols (20), were expected to equilibrate with the open, aldehydo-amine form (21). Hydrolysis to a mixture of the alcohols (20) was effected efficiently under acidic conditions; crystallisation of the mixture afforded only one of the diastereoisomeric alcohols. This alcohol exhibited a typical indole chromophore in its u.v. spectrum. The coupling constants observed between the protons at positions 8 and 9 (<3 and 9 Hz), is indicative of a preference for the partially unfolded (extended) conformation for the system. The occurrence of an intramolecular hydrogen bond to the amide bond was observed by comparing the frequency of amide bond stretch in the acetate(s) (19) and the isolated alcohol (1 690, 1 685 and 1 670, 1 685 cm^{-1}, respectively). These results suggest the conformation illustrated by (22). No observation for any aldehyde tautomer was present in these spectroscopic studies; a similar situation is observed for the alkaloid eburnamine.[11]



(24)

SCHEME 2

Since sodium borohydride reduction in methanol of eburnamine produced the ring-opened alcohol, the reaction was applied to the aminol (20). No reduction occurred and, instead, epimerisation about position 12 gave the two new aminols (23); control experiments showed that, under these reaction conditions, no epimerisation occurred at position 9. Sodium in liquid ammonia did not rapidly epimerise the dioxopiperazine unit and reduction occurred, but only to give back the



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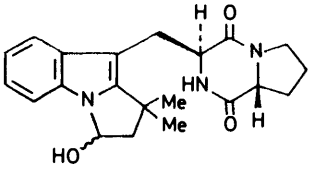

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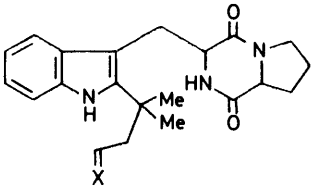
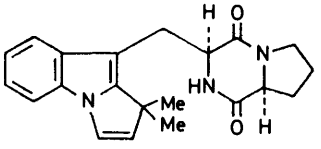


(21) X = O
(28) X = S(CH$_2$)$_3$S

pyrroloindole (6). Attempts were then made to utilise the transiently formed iminium intermediate (24), formed from the alcohol (20) under acidic conditions. A Bamford–Stevens reaction was attempted, *via* the hydrazine (25). After preparation, this showed it had



(26)

the cyclic structure, rather than the open, hydrazone form, and that it existed as a mixture of epimers. Heating either isomer at 160 °C *in vacuo* gave complete and clean decomposition, again to give the pyrroloindole (6). Related reductive reactions of tosylhydrazines are known.[13] The action of base on the tosylhydrazine (25) gave complex mixtures, the major component always being the reduction product (6). Treatment of the acetates (19), alcohols (20), or the hydrazines (25) with trifluoroacetic acid all produced the enamine (26), presumably by initial formation of the iminium species (24).

One further attempt at opening the aminol ring was made using the concept of intramolecular competition. Thus, reaction of the aminol with propane-1,3-dithiol was

made. The intermediate monosulphide (27) was expected to equilibrate with the dithioacetal (28) and instances related to this are recorded in the literature.[14] However, none of the dithioacetal (28) was detected, only the monothioacetal (27) being formed. Ethane-1,2-dithiol gave analogous products. At this point further attempts to utilise the alcohols (20) as a route to desoxybrevianamide E were abandoned.

The resistance of the animol structure to equilibrate with the amino-aldehyde tautomer must reflect the very close encumbrance of the latter groups if the opening can occur. The methyl groups at position 3′ probably help to lock the conformation of the pyrrolo-residue such that the methylene substituent at position 3 of the indole nucleus is held between the two methyl groups. The energy required to rotate tertiary alkyl groups in such a disposition is not known, although in analogous *o*-disubstituted benzene systems it is known to be high.[15] Thus, even if the aldehydo-amine tautomer could exist, strong entropy effects would be present to make it recyclise. To date no natural products have been isolated containing the part structures with the modified isoprenyl substituents represented in compounds (6), (7), (19), and (26), although several compounds, including the tremorgans, bear N^a-(3,3-dimethylallyl) substituents.[5]

EXPERIMENTAL

General experimental procedures were as described in the preceding paper.[1]

Lewis-acid-catalysed Rearrangements of the Dioxopiperazine (1).—(a) *Boron trifluoride–ether*. The complex (100 ml, freshly distilled) and water (1 ml) were added to the dioxopiperazine (6.33 g) in carbon tetrachloride (100 ml) and the mixture heated to reflux for 1 h. The solution was cooled, poured into aqueous sodium hydrogencarbonate solution, then extracted with dichloromethane (300 ml), and washed with more sodium hydrogencarbonate solution and water. The dried organic extract was evaporated to give a foam. Column chromatography (SiO_2), using dichloromethane–methanol (98 : 2) as eluant, gave cyclo-L-*prolyl*-L-(3′,3′-*dimethyl*-1′,2′,3′H-*pyrrolo*[1,2-a]*tryptophyl*) (6) (5.37 g; 86%), contaminated with a little of the isomer (7). Crystallisation (acetone–light petroleum) gave the pyrroloindole, m.p. 145—147 °C; $[\alpha]_D^{22}$ −85° (*c* 1.06, EtOH); $\nu_{max.}$ 3 200, 1 675, and 1 655 cm^{-1}; $\lambda_{max.}$ (log ε) 227 (4.47), 278 (sh) (3.76), 284 (3.70), and 292 (3.65) nm; δ 7.82—6.99 (4 H, m, aromatic), 5.75 (1 H, br s, exchangeable, N*H*), 4.42 (1 H, dd, X part of AMX system, J_{XM} 3, J_{XA} 10 Hz, C^9*H*), 4.12 (1 H, br t, *J* 7 Hz, C^{12}*H*), 3.83—3.46 (3 H, m, C^8*H*, C$^{15}H_2$), 3.20—2.80 (3 H, dd superimposed upon t; X part of AMX system, J_{AX} 10, J_{MX} 15 Hz, C^3*H*; *J* 8 Hz, C$^{5'}H_2$), 2.63—2.25 (3 H, t superimposed upon m; *J* 8 Hz, C$^{4'}H_2$, C-*H*), and 2.25—1.52 (9 H, 2 × Me, C*H*, C$^{17}H_2$); *m/e* 351 (5%, M^+), 198 (100), 143 (9), 41 (11), and 56 (14) (Found: C, 71.7; H 7.3; N, 11.85. $C_{21}H_{25}N_3O_2$ requires C, 71.8; H, 7.2; N, 12.0%).

(b) *Boron tribromide*. The dioxopiperazine (0.51 g) was stirred in dichloromethane (50 ml) containing boron tribromide (5.5 ml) for 50 h at ambient temperature. The solution was then poured into water (50 ml) and neutralised with sodium hydrogencarbonate. The mixture was extracted with dichloromethane (50 ml), washed with water (50 ml), dried, and evaporated to give an amorphous solid (0.47 g), which was purified by preparative t.l.c. to give cyclo-L-*prolyl*-L-1,7-(3,3-*dimethylpropano*)*tryptophyl* (7) (123 mg, 24%) as an amorphous powder, melting range 70—85 °C; $[\alpha]_D^{27}$ −161° (*c* 1.1, EtOH); $\nu_{max.}$ (CCl_4) 3 490, 3 240, and 1 680 cm^{-1}; $\lambda_{max.}$ (log ε) 223 (4.34), 248 (sh) (3.53), 290 (3.64), and 300 (3.62) nm; δ 7.44—6.92 (3 H, m, aromatic), 6.99 (1 H, s, C^2*H*), 5.98 (1 H, br s, exchangeable, N*H*), 4.38 (1 H, br dd, *J* 4 and 10 Hz, C^9*H*), 4.20—3.44 (6 H, m, C^{12}*H*, NCH_2, C^8*H*, C$^{15}H_2$), 2.98 (1 H, dd, *J* 10 and 14 Hz, C^8*H*), 2.42—1.55 (6 H, m, C$^{16}H_2$, C$^{17}H_2$, NCH_2CH_2), 1.35 (6 H, s, 2 × Me); *m/e* 351 (29%, M^+), 198 (100); 143 (18), 109 (22), 70 (21), 70 (21), 56 (64), and 41 (24) (Found: M^+, 351.194 7. $C_{21}H_{25}N_3O_2$ requires *M*, 351.194 7).

(c) *Boron trifluoride on the* N-*allylindoline* (5). The *N*-allylindoline (5) (72 mg) was stirred in freshly distilled boron trifluoride–ether (10 ml) for 24 h and poured into saturated aqueous sodium hydrogencarbonate (100 ml). More sodium hydrogencarbonate was added until evolution of carbon dioxide ceased, and the mixture extracted with dichloromethane (50 ml). The organic extract was washed with aqueous sodium hydrogencarbonate solution (100 ml), water (100 ml), and dried. Evaporation and purification by preparative t.l.c. gave the pyrroloindole (6) (12 mg, 17%), the pyridinoindole (7) (16 mg, 22%), and the *N*-allylindole (1) (9 mg, 13%).

(d) *Stannic chloride*. The allylindole (1) (0.53 g) in dichloromethane (35 ml) was added to stannic chloride (2 ml) and the suspension stirred for 22 h at room temperature. The mixture was slowly poured into saturated aqueous sodium hydrogencarbonate solution (100 ml), containing an excess of the base, and stirred until gas evolution ceased and the white precipitate had dissipated (*ca.* 1 h). The mixture was filtered from insoluble tin oxides and the organic phase separated, backwashing the aqueous layer with more solvent. The combined organic extracts were washed with water (50 ml), dried, and evaporated to afford a foam (0.49 g). Separation of this by preparative t.l.c. afforded the *indoline* (12) (0.10 g, 21%) and a mixture of the pyrroloindole (6) and pyridinoindole (7) (0.27 g); further separation of the latter compounds gave (6) (0.12 g; 25%) and (7) (0.06 g; 12%). The indoline (12) was obtained as a colourless powder by trituration with light petroleum; $[\alpha]_D^{23}$ −303° (*c* 1.04, EtOH); $\nu_{max.}$ (CCl_4) 3 430 and 1 675 cm^{-1}; $\lambda_{max.}$ (log ε) 229 (3.91), 244 (3.80), and 296 (3.42) nm; δ 7.2—6.45 (4 H, aromatic), 5.50 (1 H, br s, exchangeable, N*H*), 4.03 (2 H, br t, *J* 8 Hz, C^9*H*, C^{12}*H*), 3.70—3.37 (2 H, m, C$^{15}H_2$), 2.25—2.30 (10 H), 1.15 (3 H, s, Me), and 0.70 (3 H, s, Me); *m/e* 351 (100%, M^+), 198 (63), 185 (49), 170 (46), 143 (38), 70 (37), 56 (50), and 41 (30) (Found: M^+, 351.194 0. $C_{21}H_{25}N_3O_2$ requires *M*, 351.194 7).

Oxidation of the Pyrroloindole (6).—A procedure based on the method of Meyer *et al.* was used. An ozone–oxygen mixture (*ca.* 5% v/v ozone) was bubbled into dichloromethane at −78 °C and the solution estimated iodimetrically. To the solution of ozone (0.14 mmol) was added the pyrroloindole (40 mg, 0.11 mmol) in dichloromethane at −78 °C. The blue colour discharged immediately, and the solution was warmed to room temperature and the solution was warmed to room temperature and the solution evaporated to dryness. The residue was dissolved in ethyl acetate, shaken under hydrogen in the presence of palladium (14 mg) (as 10% Pd–C) for 45 min and filtered. Preparative

t.l.c. of the product afforded, as a colourless powder, the pyrrolidone (8) (11 mg). A similar product was isolated by oxidation of the pyrroloindole (6) (44 mg) in methanol (75 ml) containing Methylene Blue (0.5 mg) with a stream of oxygen, whilst irradiating the flask with a 500-W tungsten lamp for 15 h and keeping the temperature below 25 °C. Preparative t.l.c. gave the pyrrolidone (8) (33 mg); $[\alpha]_D^{20}$ −56° (c 1.07, EtOH); $\nu_{max.}$ (CCl_4) 3 280, 1 705, and 1 680 cm^{-1}; $\lambda_{max.}$ (log ε) 281 (3.0), 225 (4.11), and 211 (4.13) nm; δ 7.80—7.17 (4 H, m, aromatic), 7.20—6.40 (1 H, br s, exchangeable, N*H*), 5.65 (1 H, br d, *J ca.* 8 Hz, $ArCOCH_2$-C*H*), 4.20 (1 H, m, NHCOC*H*), 4.0—3.0 (4 H, m, $ArCOCH_2$, NCH_2), 2.75—1.80 (8 H, m), 1.54 (3 H, s, Me), and 1.40 (3 H, s, Me); *m/e* 383 (32%, M^+), 366 (9), 351 (8), 217 (35), 16 (46), 189 (51), 174 (100), 70 (86), and 41 (4); *m** 350 (383→366).

When the pyridinoindole (7) (20 mg) was ozonised, under the conditions reported above, the crude product showed an n.m.r. resonance at δ 9.1, indicating the presence of a formyl proton; the product (9) was not formally characterised.

Action of Trifluoroacetic Acid on the Dioxopiperazine (1).—The dioxopiperazine (238 mg) was stirred in trifluoroacetic acid (10 ml) at room temperature with nitrogen for 17 h. The solution was then dropped slowly into an excess of sodium hydrogencarbonate in water (25 ml) with vigorous stirring. After cessation of gas evolution, dichloromethane (25 ml) was added and the organic extract washed with water, backwashing all aqueous washings with more dichloromethane (10 ml). The combined organic extracts were dried, evaporated to dryness, and the residue subjected to preparative t.l.c. to afford the pyrroloindole (6) (34 mg, 14%), the trifluoroacetoxyindoline (15) (51 mg, 21%), and a further fraction comprised of a mixture of compounds (82 mg, 34%). The trifluoroacetoxyindoline was unstable to storage and the freshly isolated material had $[\alpha]_D^{24}$ −275° (*c* 0.8, EtOH); $\nu_{max.}$ (CCl_4) 400, 1 780, and 1 665 cm^{-1}; $\lambda_{max.}$ (log ε) 295 (3.29), and 241 (3.70) nm; δ 7.20—6.40 (4 H, m, aromatic), 5.25 (1 H, s, C^2H), 5.20 (1 H, br s, exchangeable, N*H*), 4.04 (2 H, br t, C^9H, $C^{12}H$), 3.65—3.40 (2 H, m, $C^{15}H_2$), 2.80—1.60 (10 H, m), and 1.48 (6 H, s, Me_2C); *m/e* 351 (67%), 282 (35), 198 (20), 185 (15), 143 (35), 130 (67), 99 (47), 93 (44), 69 (50), 56 (100), and 45 (73).

Hydrolysis of the ester function was achieved by treating the ester (150 mg) with sodium hydrogencarbonate (0.6 g) in 1 : 1 aqueous tetrahydrofuran (10 ml) at room temperature for 2 d. On work-up the alcohol (16) was obtained (66 mg, 55%) as an amorphous solid; $\nu_{max.}$ ($CHCl_3$) 3 600, 3 410, and 1 665 cm^{-1}; δ 7.16—6.50 (4 H, m, aromatic), 5.27 (1 H, s, C^2H), 4.04 (2 H, br t, $C^{12}H$, C^9H), 3.70—3.35 (3 H, $C^{15}H_2$, O*H*), 2.68 (1 H, dd, *J* 7 and 13 Hz, C^8H) 2.42—1.30 (9 H, m), and 1.15 (6 H, s, Me_2C); *m/e* 369 (3%, M^+), and thereafter as for the ester.

Acetylation of the indoline (15) with acetic anhydride afforded one major product, which showed no evidence for an NH bond in its i.r. or ^1H n.m.r. spectra, and which also showed a new $\nu_{max.}$ at 1 670 cm^{-1} (amide CO) as expected for the *N*-acetylated derivative (17); this was not further characterised.

Lead Tetra-acetate Oxidation of the Pyrroloindole (6).—The indole (67 mg) and lead tetra-acetate (100 mg) were stirred together in glacial acetic acid (10 ml) for 13 h. The solvent was evaporated and the residual gum extracted between dichloromethane (15 ml) and water (25 ml), backwashing with more water and dichloromethane. The organic extract was washed with saturated sodium hydrogencarbonate solution (10 ml) and water (2 × 20 ml), dried, evaporated, and separated by preparative t.l.c. The less polar material was the acetoxyindoline (18) (13.7 mg, 18%); crystallised from acetone–light petroleum this had m.p. 222—225 °C; $\nu_{max.}$ (CCl_4) 1 755, 1 690, and 1 235 cm^{-1}; $\lambda_{max.}$ (log ε) 256 (3.88) and 299 (3.25) nm; δ 7.69—6.77 (4 H, m, aromatic), 3.98 (2 H, m, C^9H,$C^{12}H$), 3.73 (2 H, br t, $C^{15}H_2$), 3.50 (2 H, br t, indoline NCH_2), 3.24—1.76 (8 H, m), 1.94 (3 H, s, MeCO), 1.56 (3 H, s, Me), and 0.97 (3 H, s, Me); *m/e* 409 (60%, M^+), 394 (36), 334 (31), 243 (28), 201 (52), 198 (100), and 182 (59) (Found: M^+, 409.199 4; C, 67.5; H, 6.55; N, 10.4%. $C_{23}H_{27}N_3O_4$ requires M^+, 409.200 1; C, 67.5; H, 6.65; N, 10.4%).

The more polar material was a mixture of the epimers, cyclo-L-*prolyl*-L-{3′,3′-*dimethyl*-1′-(R,S)-*acetoxy*-1′,2′,3′H-*pyrrolo*[1,2-a])*tryptophyl*} (19) (38 mg, 49%), obtained as an amorphous powder; $\nu_{max.}$ (CCl_4) 3 360, 1 750, 1 680, and 1 230 cm^{-1}; $\lambda_{max.}$ (log ε) 226 (4.60), 280 (sh) (3.83), 286 (3.86), and 294 (sh) (3.80) nm; δ 7.70—6.95 (4 H, m, aromatic), 6.20 (1 H, m, C^2H), 5.35 (1 H, br s, exchangeable, N*H*), 4.30 (1 H, br d, C^9H), 3.97 (1 H, m, $C^{12}H$), 3.80—3.30 (3 H, m, C^8H, $C^{15}H_2$), 3.10—2.70 (1 H, m, C^8H), 2.70—2.40 (1 H, m, $C^{3'}H$), 2.40—1.60 (5 H, m, $C^{16}H_2$, $C^{17}H_2$, $C^{3'}H$), 2.09 and 2.22 (3 H, s, MeCO), and 1.70—1.60 (6 H, Me_2C); *m/e* 409 (4%, M^+), 349 (9), 256 (100), and 196 (86).

Equilibration of the Acetates (18) *and* (19).—The ester (18) (6.7 mg) in acetic acid (2 ml) was left at room temperature for 8 d. Evaporation afforded a mixture of the two isomers, (18) and (19), in the ratio 2 : 1, respectively. Similar treatment of (19) afforded none of the isomer (18).

Hydrolysis of the Acetate (19).—The ester (140 mg) was stirred for 16 h in acetonitrile (15 ml) and water (6 ml) containing trifluoroacetic acid (0.3 ml). The mixture was evaporated to small bulk, poured into an excess of aqueous sodium hydrogencarbonate solution and extracted with dichloromethane. Work-up in the normal manner afforded a mixture of the alcohols (20) (110 mg, 88%). Crystallisation, from acetone–light petroleum selectively gave crystals of one of the isomers, m.p. 165—167 °C; $\nu_{max.}$ ($CHCl_3$) 3 300 and 1 675 cm^{-1}; $\nu_{max.}$ (Nujol) 3 310, 3 220, 1 690, and 1 670 cm^{-1}; $\lambda_{max.}$ (log ε) 280 (sh) (3.86), 286 (3.89), and 293 (sh) (3.85) nm; δ 8.33 (1 H, br s, exchangeable, N*H*), 7.70—7.00 (4 H, m, aromatic), 5.68 (1 H, br s, exchangeable, O*H*), 5.38 (1 H, m, $C^{2'}H$), 4.16 (1 H, m, C^9H), 3.90 (1 H, m, $C^{12}H$), 3.84—3.35 (3 H, m, C^8H, $C^{15}H_2$), 2.97 (1 H, dd, *J* 9 and 14 Hz, C^8H), 2.72 (1 H, dd, *J* 14 and 6 Hz, $C^{3'}H$), 2.40 (1 H, dd, *J* 14 and 4 Hz, $C^{3'}H$), and 2.35—1.55 (10 H, m); *m/e* 367 (7%, M^+), 349 (11), 214 (100), 196 (84), and 158 (19) (Found: M^+, 367.187 3; C, 68.6; H, 6.8; N, 11.4%. $C_{21}H_{25}N_3O_3$ requires M^+, 367.189 5; C, 68.6; H, 6.9; N, 11.4%).

Reactions of the Alcohols (20).—(a) *Epimerisation.* The alcohols (160 mg) were treated with sodium borohydride (100 mg) in propan-2-ol (10 ml) in the dark at room temperature for 60 h. [More sodium borohydride (100 mg) was added after the first 40 h.] The solution was evaporated to small bulk and extracted with dichloromethane and washed with brine to afford, after work-up, a mixture of two compounds, more polar than the starting epimers, which were separated by preparative t.l.c. The more polar epimer (23a) (65 mg, 41%) crystallised from acetone–light petroleum, m.p. 240—243 °C; $[\alpha]_D^{20}$ +9° (*c* 1.17, EtOH); $\nu_{max.}$ (CCl_4) 3 430, 3 270, 1 675, and 1 650 cm^{-1};

$\lambda_{max.}$ (log ε) 226 (4.51), 279 (3.73), 285 (3.78), and 291 (3.73) nm; δ 7.80—6.95 (5 H, m, 1 exchangeable H, N*H* and aromatic), 5.40 (1 H, m, C^{21}*H*), 4.57 (1 H, br s, exchangeable, O*H*), 4.30 (1 H, m, C^{9}*H*), 3.75—3.10 (4 H, m), 3.10—2.10 (3 H, m), and 2.10—1.50 (10 H, m); *m/e* 367 (9%, M^+), 349 (3), 214 (100), 196 (18), 158 (13), and 130 (5).

The less polar product (23b) (21 mg, 13%) had m.p. (acetone–light petroleum) 135—137 °C; $[\alpha]_D^{23}$ +5° (*c* 1.03, EtOH); $\nu_{max.}$ 3 390, 3 260, and 1 670 cm^{-1}; $\lambda_{max.}$ (log ε) 226 (4.50), 280 (3.74), 296 (3.79), and 293 (3.75) nm; δ 7.75—6.95 (4 H, m, aromatic), 6.90 (1 H, br d, exchangeable, N*H*), 5.35 (1 H, m, C$^{2'}$*H*), 4.35 (2 H, m, OH, C^{9}*H*), 3.82—3.15 (4 H, m, C^{8}*H*, C^{12}*H*, C$^{15}H_2$), 3.15—2.25 (3 H, m, C^{8}*H*, C$^{3'}H_2$), and 2.25—1.15 (10 H, m); *m/e* 367 (11%, M^+), 349 (2), 214 (100), 196 (8), 158 (14), and 130 (6).

(b) *Reduction.* The alcohol (17 mg) was dissolved in liquid ammonia (5 ml) at its boiling point and sodium (4 mg) added in portions. The blue colour due to the excess of metal persisted at the end of 10 min when acetone (1 ml) and ammonium sulphate (200 mg) were added. The solvent was removed, the residue worked-up by dichloromethane extraction, and the products separated by preparative t.l.c. Some starting material (9 mg, 55%) was removed, together with the pyrroloindole (6) (2.0 mg, 12%), m.p. and mixed m.p. 140—145 °C.

(c) *Attempted Bamford–Stevens reaction.* To the alcohol (425 mg), tosylhydrazine (1.2 g), and dichloromethane (7 ml), was added trifluoroacetic acid (0.3 ml) and the mixture was cooled to 5 °C in ice–water. After 1 h the mixture was poured into 2N hydrochloric acid (50 ml) and extracted with dichloromethane (30 ml). Work-up gave a mixture of the epimeric hydrazides (25) (583 mg). These were separated by preparative t.l.c. to give the more polar isomer as an amorphous solid (65 mg, 12%); $[\alpha]_D^{23}$ −130° (*c* 1.2, EtOH); $\nu_{max.}$ ($CHCl_3$) 3 360, 3 250, 1 665, 1 160, and 908 cm^{-1}; $\lambda_{max.}$ (log ε) 229 (4.50), 278 (3.68), 2.86 (3.73), and 293 (3.69) nm; δ 8.00—7.00 (10 H, aromatic and 2 exchangeable H), 6.88 (1 H, br s, exchangeable, N*H*), 4.90—4.25 (2 H, m, C^{21}*H*, C^{9}*H*), 4.25—3.80 (1 H, m, C^{12}*H*), 3.80—3.10 (3 H, m, C$^{15}H_2$, C^{8}*H*), 2.80—2.10 (6 H, m), and 2.10—1.30 (10 H, m); *m/e* 535 (1%, M^+), 351 (14), 198 (100), 155 (14), and 91 (50).

The less polar isomer (103 mg, 19%) had $[\alpha]_D^{20}$ −78° (*c* 0.96, EtOH); $\nu_{max.}$ ($CHCl_3$) 3 360, 3 250, 1 665, 1 160, and 908 cm^{-1}; $\lambda_{max.}$ (log ε) 229 (4.50), 278 (3.68), 286 (3.73), and 293 (3.69) nm; δ 8.00—7.00 (10 H, aromatic and 2 exchangeable H), 6.49 (1 H, br s, exchangeable, N*H*), 4.68—4.20 (2 H, m, C^{21}*H*, C^{9}*H*), 4.20—3.80 (1 H, m, C^{12}*H*), 3.80—3.05 (3 H, m, C$^{15}H_2$, C^{8}*H*), 3.0—2.40 (3 H, m, C^{8}H, C$^{3'}H_2$), 2.38 (3 H, s, Me), and 2.35—1.30 (10 H, m); *m/e* 535 (<1%, M^+), 351 (14), 198 (100), 155 (14), and 91 (50).

Heating a sample of either of the hydrazide isomers (25) *in vacuo* at 160 °C for 5 min. caused complete and clean decomposition to a less polar material identified, by comparison with authentic material, as the pyrroloindole (6).

(d) *Dehydration.* A solution of the alcohols (134 mg), in benzene (20 ml) containing a crystal of toluene-*p*-sulphonic acid monohydrate was heated to reflux in a Soxhlet assembly, containing molecular sieve in the upper chamber, for 5 h. Work-up afforded, by preparative t.l.c., the enamine (26) (122 mg, 97%) as an amorphous solid; $[\alpha]_D^{20}$ −30° (*c* 0.84, EtOH); $\nu_{max.}$ (CCl_4) 3 390 and 1 680 cm^{-1}; $\lambda_{max.}$ (log ε) 220 (4.25), 232 (sh) (4.16), 245 (sh) (3.90), 313 (3.86), 325 (sh) (3.74), and 341 (3.34) nm; δ 7.63—7.00 (4 H, m, aromatic), 6.60 (2 H, vinylic-*H*), 5.73 (1 H, br s, exchangeable N*H*), 4.35 (1 H, dd, *J* 4 and 10 Hz, C^{9}*H*), 4.03 (1 H, br t, C^{12}*H*), 3.90—3.48 (3 H, m, C^{8}*H*, C$^{15}H_2$), 3.00 (1 H, m, C^{8}*H*), 2.40—1.70 (4 H, m, C$^{16}H_2$, C$^{17}H_2$), 1.64 (3 H, s, Me), and 1.57 (3 H, s, Me); *m/e* 349 (7%, M^+) and 196 (100) (Found: M^+, 349.179 3. $C_{21}H_{23}N_3O_2$ requires *M*, 349.179 0).

(e) *Attempted dithioacetal formation.* The alcohol (112 mg) was stirred in dichloromethane (10 ml) containing propane-1,3-dithiol (341 mg) and trifluoroacetic acid (267 mg) for 90 min, and then the solution was poured into an excess of aqueous sodium hydrogencarbonate solution. Work-up and preparative t.l.c. gave two major products. The more polar isomer of (27) (32 mg, 23%) showed δ 7.60—7.00 (4 H, m, aromatic), 5.80 (1 H, exchangeable, NH), 4.65—4.35 (2 H, m, C^{9}H, C$^{2'}$*H*), 4.20—3.95 (1 H, m, C^{12}*H*), 3.90—3.44 (3 H, m, C^{8}*H*, C$^{15}H_2$), 3.35—3.04 (1 H, dd, *J* 11 and 14 Hz, C^{8}*H*), 3.03—2.45 (6 H, m, C$^{3'}H_2$, 2 × SCH_2), and 2.20—1.50 (13 H, m, 1 exchangeable H). The ^{1}H n.m.r. spectrum of the less polar isomer (18 mg, 13%) had a very similar pattern except that the amide proton appeared at δ 6.45. For a mixture of the two isomers; *m/e* 457 (5%, M^+), 349 (21), 304 (13), and 196 (100) (Found: M^+, 457.186 9. $C_{24}H_{31}N_3O_2S_2$ requires *M*, 457.185 7).

The reaction was repeated using ethane-1,2-dithiol. In this case the *more polar isomer* (9%) had $\nu_{max.}$ ($CHCl_3$) 3 360, 2 460, and 1 670 cm^{-1}; δ 7.60—7.00 (4 H, m, aromatic), 6.44 (1 H, br s, exchangeable, NH), 4.65—4.35 (2 H, m), 4.10—3.90 (1 H, m), 3.90—3.35 (3 H, m), 3.14 (1 H, dd, *J* 9 and 12 Hz, C^{8}*H*), 3.03—2.77 (5 H, m, SCH_2-CH_2S, C$^{3'}$*H*), 2.77—2.48 (1 H, dd, *J* 4 and 13 Hz, C^{31}*H*), and 2.32—1.50 (11 H, m); *m/e* 443 (1%, M^+), 349 (5), 290 (5), 196 (100), and 94 (21) (Found: M^+, 443.170 4. $C_{23}H_{29}N_3O_2S_2$ requires *M*, 443.170 2). The less polar isomer (31 mg, 18%) had $\nu_{max.}$ ($CHCl_3$) 3 360, 2 450, and 1 670 cm^{-1}; δ 7.60—7.00 (4 H, m, aromatic), 5.79 (1 H, br s, exchangeable, NH), 6.46—4.40 (2 H, m, C^{21}*H*, C^{9}*H*), 4.15—3.90 (1 H, m, C^{12}*H*), 3.80—3.40 (3 H, m, C$^{15}H_2$, C^{8}*H*), 3.34—3.08 (1 H, dd, *J* 14 and 10 Hz), 3.00—2.68 (5 H, m, C^{31}*H*, SCH_2CH_2S), 2.68—2.45 (1 H, dd, *J* 4 and 12 Hz, C^{31}*H*), and 2.45—1.50 (C11H, m); *m/e* 443 (2%, M^+), 349 (5), 290 (17), 288 (15), 230 (25), 196 (100), and 94 (7) (Found: M^+, 443.171 4. $C_{23}H_{29}N_3O_2S_2$ requires *M*, 443.170 2).

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