Pyrazine Chemistry. Part 11.[1] Chemical Studies on Cyclic Tautomers of *cyclo*-L-Propyl-L-tryptophyl and its Derivatives

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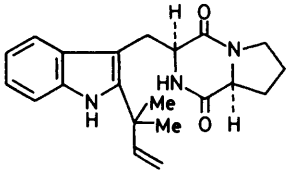
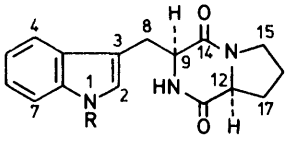
Simple derivatives of tryptophan, including *cyclo*-L-propyl-L-tryptophyl, can form cyclic tautomers involving formation of the hexahydropyrrolo[2,3-*b*]indole system (6) by treatment with strong protic or Lewis acids. The cyclic tautomers are useful in synthetic transformations since selective acylation or alkylation of the indolic nitrogen atoms is possible. In this manner a 3,3-dimethylallyl substituent can be introduced into the indolic nitrogen of the title compound to produce (1). The *N*-substituted derivatives readily open up, under acid catalysis, to regenerate the *N*-substituted indole system (3).

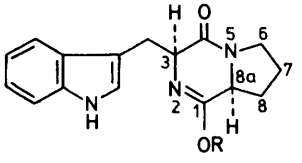
DIMETHYLALLYL derivatives of several naturally occurring dioxopiperazines have been isolated and these include the brevianamides [2] and austamides.[3a] A likely precursor to this family of compounds is the simple derivative (1) named desoxybrevianamide E.[3a] The



(1)



(2) ; R = H
(3) ; R = $CH_2CH{=}CMe_2$
(14) ; R = COMe

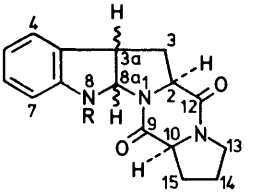


(4) ; R = Me
(5) ; R = Et

presence, at position 2 of the indole residue in such structures, of the 1,1-dimethylallyl residue, linked through the more hindered centre, has led to much biosynthetic speculation.[4-7] The simplest hypothesis involves direct insertion of the dimethylallyl residue by an enzyme-mediated S_N2' process which controls these sites of allylation.[8] Chemical methods for introducing the 2-substituent are known.[9]

RESULTS AND DISCUSSION

An alternative biosynthetic process involves migration of a 3,3-dimethylallyl residue from the indolic nitrogen atom to position 2. Casnati *et al.* have demonstrated the possibility of such migrations, using model systems, although yields are generally poor.[10] As part of a general study of the chemistry of dioxopiperazines we have prepared the *N*-(3,3-dimethylallyl) derivative (3) from the unsubstituted dioxopiperazine (2). Since competing alkylation of the secondary amide group would interfere with base-catalysed alkylation of the indolic nitrogen atom, we sought to protect this function by preparing the *O*-methyl derivative (4) which can be formed by reaction of such amides with the Meerwein salt, trimethyloxonium fluoroborate. Thus reaction of *cyclo*-L-prolyl-L-tryptophyl (2) with an excess of the salt was attempted several times but always, after work-up, only a small amount of the desired imino-ether (4) had formed, isolated together with recovered starting material (2). In each case an excess of the trimethyloxonium fluoroborate was present, suggesting that the starting material was mainly being removed from the reaction mixture before alkylation could occur. In turn, this suggested salt formation by the small quantity of free fluoroboric acid always present in fresh preparations of the oxonium salt. T.l.c. examination of the reaction mixture, after quenching aliquots with sodium hydrogencarbonate solution, indicated the presence of starting material and two new products, the imino-ether (4) and a less polar material. The same less polar compound also formed when triethyloxonium salt was used on the dioxopiperazine (2), along with the homologous imino-ether (5). The new product was isomeric with the starting dioxopiperazine but it had a completely different u.v. spectrum, indicating loss of the indole chromophore. Addition of base caused a rapid change in the u.v. spectrum, changing it to that of the starting dioxopiperazine (2) within 20 min. A similar, but slower, change was effected by dilute protic acids. On the basis of these results and its ^1H n.m.r. pattern, the isomeric



(6) ; R = H
(13) ; R = COMe
(17) ; R = $CH_2CH{=}CMe_2$

compound was assigned as the hexahydropyrrolo[2,3-*b*]-indole (6). That the formation of the indoline (6) was caused by free acid liberated during the attempted alkylation with Meerwein salts was readily shown by

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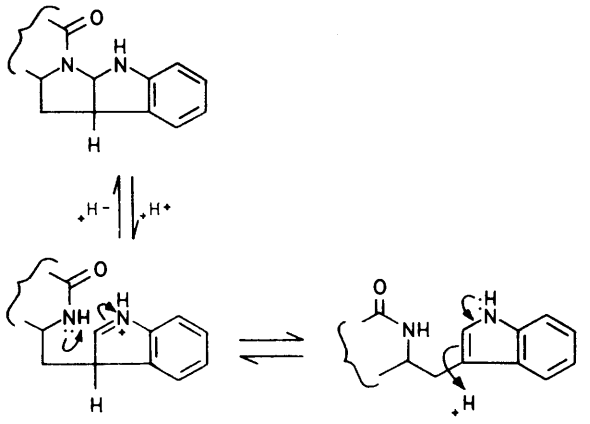
treating the starting dioxopiperazine (2) with strong acid. For example, in trifluoroacetic acid, the dioxopiperazine (2) immediately formed the indoline (6), and a quantitative yield of this could be isolated by rapid quenching



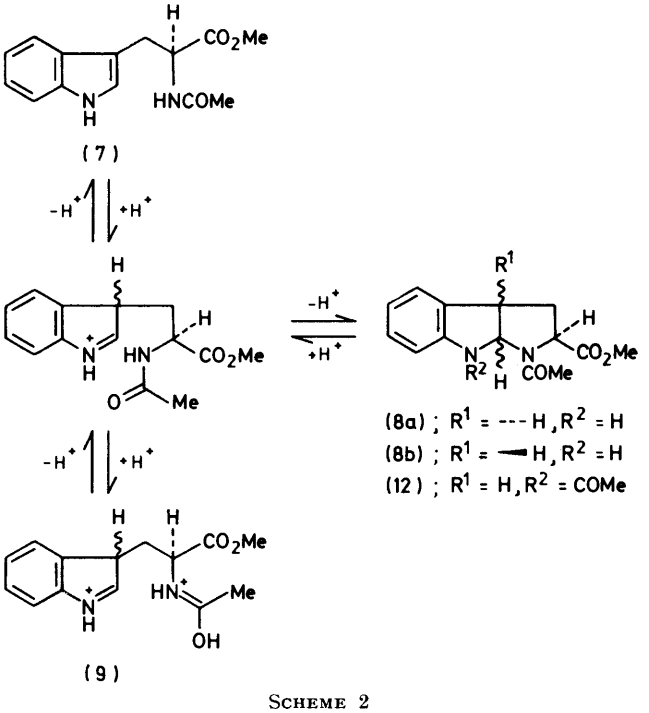
SCHEME 1

with sodium hydrogencarbonate solution and extraction into dichloromethane. Similarly, efficient alkylation of the dioxopiperazine (2) with triethyloxonium fluoroborate was achieved by conducting it in the presence of a well-stirred suspension of calcium carbonate, which removes any acid formed during the reaction. Under these conditions no indoline (6) could be detected amongst the reaction products, and a good yield of the imino-ether (5) formed.

Formation of the indoline (6) must be initiated by protonation of the indole nucleus at position 3, followed by intramolecular trapping of the indolenium species so formed (Scheme 1). Although examples of such processes are know,[11] the only example involving tryptophan utilises an electrophile other than a proton.[12] One reaction, which might involve an indoline intermediate, is recorded in the literature [13] and, subsequent to our work, a short report, revealing similar, independent studies, was published by Hino and Taniguchi.[14]

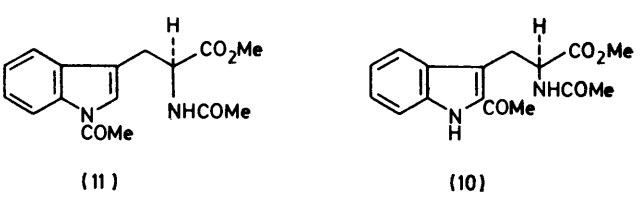
The isolation of the indoline (6) in such high yield was thought to have important implications in peptide chemistry involving tryptophan. In order to test the generality of Scheme 1, *N*-acetyl-L-tryptophan methyl ester (7) was subjected to treatment with trifluoroacetic acid. In this case, however, very little of the desired tautomer (8) could be detected after work-up, despite the fact that examination of the ^1H n.m.r. spectrum in trifluoroacetic acid indicated formation of two new, isomeric protonated species, assigned as the indolines (8a) and (8b). A peak at δ 6.0 occurred as a doublet (J 6 Hz) assigned as the methine proton at position 8a, coupled with the *cis*-proton at position 3a. The u.v. spectrum of the indoline ester (7) in trifluoroacetic acid was also similar to that obtained for the protonated indoline (6), both showing a weak maximum at 280 nm, consistent with that expected for a protonated aniline.[15] Different n.m.r. results were obtained in concentrated sulphuric acid. In this solvent the ester (7) appeared to be perfectly stable over long periods, but the spectrum indicated the formation of two new compounds which were different from those found in trifluoroacetic acid. Work-up gave back unchanged starting material. It is assumed that, with the much stronger sulphuric acid full protonation of the amide function also occurs, so that cyclisation of the intermediate indolenium species does not occur. Since protonation, at position 3 of the indole species can occur from either side, two isomeric salts (9) are observed.

Because the indolines (8a) and (8b) could not be readily isolated, attempts were made to trap them by acetylation. Addition of acetic anhydride to the solution in trifluoroacetic acid produced two new products, identified by their spectroscopic properties as the 2,N^b-diacetyl-L-tryptophan methyl ester (10) and the N^aN^b-diacetyl-L-tryptophan methyl ester (11); the latter had a u.v. spectrum virtually identical to that of *N*-acetylskatole.[15] Addition of propylamine to the u.v. solution of (11) rapidly regenerated the spectrum of the parent tryptophan (7). Whereas formation of the 2,N^b-



SCHEME 2

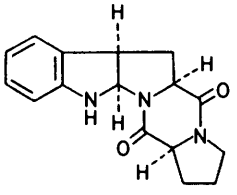
diacetyl derivative probably occurs by the direct acetylation of the indole species, acetylation of the indolic nitrogen under these conditions probably occurs *via* intermediacy of the indoline (8), followed by rapid equilibration of this acetylated species (12) with the open



form (11) (Scheme 2). It should be noted that direct acetylation of indolic nitrogen does not occur under acidic conditions.[16] The relative instability of the acetylated indolines (12) was repeated in the *cyclo*-L-prolyl-L-tryptophan series. Thus when the indoline (6) was treated either with acetic anhydride in trifluoroacetic acid for short periods (10 min) or with acetic anhydride alone, the acetyl derivative (13) could be isolated in good yield. When the 1-acetylindoline (13) was treated with acid in ethanol a conversion into the N^a-acetylindole tautomer (14) occurred.

The more favoured formation of the indoline species from the dioxopiperazine (2), compared to the acetyl derivative (7) must be as a consequence of the more conformationally fixed structure of the rigid dioxopiperazine unit and of the presence of the *cis*-amide function of the former compound compared to the *trans*-amide bond of the latter.

The stereochemistry of the indoline (6) bears comment. Although two isomers would be expected from cyclisation of the precursor (2), by protonation on either face of the indole nucleus, only one product could be detected. The selectivity can be explained either by selective protonation on one face of the indole to form only one indolenium salt followed by cyclisation to the indoline, or by protonation from both sides of the ring but preferential cyclisation of only one of the two indolenine salts. ^{1}H N.m.r. studies did not allow a categoric assignment of stereochemistry to the isolated indoline (6). Extensive studies on the conformations of 2,5-dioxopiperazines bearing an aromatic side-chain have demonstrated that, for 3,6-*cis*-substituted dioxopiperazines containing proline the fully folded conformation commonly encountered is *not* preferred, owing to both steric hindrance between the proline ring and the aromatic (indole) residue, and to strain introduced by the proline ring.[3,8] The ^{1}H n.m.r. spectrum of compound (2) reflects this change by the size of the coupling constants, between the methine proton (9-H) and the adjacent methylene protons (8-H_2), of 4 and 10 Hz; in



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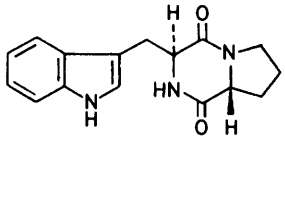

(15)

the fully folded conformation these would be of the order of 4 and 6 Hz, as is observed, for example, in *trans*-substituted systems, such as the isomer (15). The coupling constants of 4 and 10 Hz in (2) reflect a partially folded conformation (the ' extended ' conformation [3b]) in which only one of the amide bonds of the dioxopiperazine ring overlaps with the aromatic ring. If these steric effects persist in the intermediate indolenium species, cyclisation to give the all-*cis*-indoline (*syn*) isomer (16) would be expected to occur.

One further example was chosen to study the generality of the tautomerism, *cyclo*-D-prolyl-L-tryptophyl (15). Treatment of this with trifluoroacetic acid, however, did not cause cyclisation to the indoline, protonation only proceeding to the indolenium state. Since, in *trans*-substituted cases the folded conformation can be adopted (coupling constants 9-H–8-H_2 of 4 and 6 Hz) [3,8] this cannot be essential for tautomerism to occur. Presumably the lack of cyclisation in this case is because of ring strain. The proline ring imparts to the dioxopiperazine ring a conformation in which the 3,5-*trans*-oriented substituents try to adopt pseudo-equatorial positions. Fusion of a further pyrrolidine ring onto the system imparts strain into both of the attached five-membered rings. A similar situation exists in the *cyclo*-pro-pro series, in which the *trans*-substituted system is less stable than the 3,5-*cis*-oriented isomer.[17]

The indoline (6) provides a useful alternative to the imino-ethers, wherein the secondary amide function of the starting dioxopiperazine is protected, allowing either selective substitution on the indolic nitrogen or the introduction of groups into positions 5 and 7 of the benzene nucleus. Alkylation of the indolic nitrogen was achieved using 3,3-dimethylallyl bromide and sodium hydride in dimethylformamide. The product was generally a mixture of the alkylated indoline (17) and the uncyclised tautomer (3), formed by the exposure of the indoline to acid during the work-up procedure. The indoline (17) could be converted into the tryptophan derivative (3) by treatment with dilute aqueous acid, but was stable to base. Likewise, treatment of the tryptophan derivative (3) with trifluoroacetic acid catalysed its quantitative conversion to the indoline (17); again only one isomeric indoline could be detected during this process.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. ^{1}H N.m.r. spectra were recorded on either Varian T-60 or JEOL MH-100 instruments for solutions in deuteriochloroform, unless otherwise stated, with tetramethylsilane as internal (or for trifluoroacetic acid solutions, external) reference. U.v. spectra were recorded for solutions in ethanol on a Pye-Unicam SP 800 instrument and i.r. spectra were recorded for Nujol mulls, unless otherwise stated, using a Pye-Unicam SP 1000 spectrophotometer. Mass spectra were recorded either on an AEI MS 9 instrument at Imperial College, London, or by the Physical and Chemical Measurements Unit, Harwell.

T.l.c. was carried out on silica gel GF_{254} (1-mm layer for preparative work). Solvents were generally distilled before use and light petroleum refers to the fraction of boiling range 40—60 °C. Solutions were dried over anhydrous sodium sulphate.

Tautomeric equilibria were studied either by examination of solutions in the u.v. spectrometer, operating in the continuous scanning mode, or by studying solutions in the MH-100 n.m.r. spectrometer, again by continuous scanning of the resonance spectrum.

The numbering system used for ^{1}H n.m.r. spectral assignments is shown in the relevant formulae in the text and is non-systematic.

cyclo-L-*Prolyl*-L-*tryptophyl* (2).—L-Proline methyl ester hydrochloride (24 g) in dichloromethane (200 ml) was treated with a stream of ammonia gas, with cooling in an ice-bath, and the liberated ammonium chloride removed by filtration. The filtrate was evaporated to small volume, to remove ammonia, and fresh dichloromethane (300 ml) added. *N*-Benzyloxycarbonyl-L-tryptophan (46 g) and dicyclohexylcarbodi-imide (28 g) were added and the solution stirred for 23 h. The mixture was filtered, and the filtrate washed with 2N HCl, saturated aqueous sodium hydrogencarbonate, and water (200 ml portions). Drying and evaporation afforded *N*-Benzyloxycarbonyl-L-tryptophyl-L-proline methyl ester as a foam (49.3 g, 80%). A portion (17 g) was dissolved in methanol (100 ml) and reduced under hydrogen at atmospheric pressure in the presence of palladium–charcoal (1 g, 5% Pd) and acetic acid (10 drops). Work-up gave, after removal of solvent and trituration with ether, the *dioxopiperazine* (2) (8.3 g, 77%), m.p. (acetone) 173—174 °C (lit.,[3] 174 °C); $[\alpha]_D^{24}$ −99° (*c* 1.2, AcOH).

cyclo-D-*Prolyl*-L-*tryptophyl* (15).—*cyclo*-L-Prolyl-L-tryptophyl (842 mg) was heated in refluxing methanol (15 ml) containing potassium t-butoxide (1 mg) for 3 h. The solution was cooled, diluted with dichloromethane (25 ml), and washed with 2N HCl, saturated aqueous sodium hydrogencarbonate, and water (25 ml portions), and dried. Evaporation gave an amorphous foam (586 mg) which was separated by preparative t.l.c. to give back the starting material (83 mg, 10%) and the *epimer* (15) (250 mg, 30%), m.p. (acetone–light petroleum) 191—193 °C; $[\alpha]_D^{20}$ +120° (*c* 1.3, AcOH); $\lambda_{max.}$ (log ε), 220 (4.37), 273 (3.66), 279 (3.66), 279 (3.69), and 289 (3.63) nm; δ 8.50 (1 H, br s, exchangeable, N*H*), 7.60—6.90 (5 H, m, 1 H exch, amide N*H*, aromatic-*H*), 6.80 (1 H, s, 2-*H*), 4.16 (1 H, br s, collapsing to br t after D_2O exchange, *J* 4 Hz, 9-*H*), 3.60—2.78 (4 H, m, 12-*H*, 8-*H*, 15-H_2), 2.60 (1 H, m, 8-*H*), and 2.10—1.10 (4 H, m, 16-H_2, 17-H_2) (Found: C, 67.8; H, 6.1; N, 14.7. $C_{16}H_{17}N_3O_2$ requires C, 67.8; H, 6.05; N, 14.8%).

Preparation of Imino-ethers.—(a) *Methyl ether*. *cyclo*-L-Prolyl-L-tryptophyl (2.83 g) was stirred with trimethyloxonium tetrafluoroborate (4 g) in refluxing dichloromethane (50 ml) under dry N_2 for 8 h. After cooling, the mixture was poured into saturated aqueous sodium hydrogencarbonate solution (50 ml), and the organic phase was separated, washed with water (25 ml), dried, and evaporated to give a brown, oily mixture. Purification of a sample of this mixture by column chromatography (SiO_2) followed by preparative t.l.c. afforded (3S,8aS)-3-[(1H-*indol*-3-*yl*)-*methyl*]-1-*methoxy*-3,6,7,8-*tetrahydropyrrolo*[1,2-a]*pyrazin*-4-*one* (4) (*ca.* 10% yield), m.p. 98—100 °C; $\nu_{max.}$ 3 260, 1 710, 1 690, and 1 620 cm^{-1}; $\lambda_{max.}$ (log ε) 290 (3.70), 282 (3.77), 274 (3.73), and 222 (4.56) nm; δ 8.30 (1 H, s, exchangeable, N*H*), 7.90—7.00 (5 H, m, aromatic), 4.30 (1 H, nm 3-*H*), 5.75 (3 H, s, MeO), 5.70—5.10 (3 H, m, 8a-*H*, NCH_2), and 2.20—1.0 (6 H, m, pyrrolo-protons) (Found: C, 68.6; H, 6.4; N, 14.2. $C_{17}H_{19}N_3O_2$ requires C, 68.7; H, 6.4; N, 14.1%).

(b) *Ethyl ether*. A similar procedure to that employed for the methyl ether gave only *ca.* 10% yield. Addition of calcium carbonate to the reaction mixture, and then stirring at room temperature for 7 h improved the yield to 63%. The *ethyl imino-ether* (5) had m.p. (acetone–light petroleum) 128—130 °C; $\nu_{max.}$ 3 260, 1 710, 1 690, and 1 620 cm^{-1}; $\lambda_{max.}$ (log ε) 290 (3.62), 282 (3.69), 275 (3.65), and 221 (4.87) nm; δ 8.20 (1 H, s, exchangeable, N*H*), 7.70—7.00 (5 H, m, aromatic), 4.40—3.90 (3 H, q superimposed on m, *J* 7 Hz, OCH_2CH_3 + 3-*H*), 3.90—2.95 (3 H, m, N-CH_2 + 8a-*H*), and 2.25—1.00 (9 H, m, CH_3CH_2O, CH_2–CH_2 and 8a-H-CH_2); *m/e* 311 (24%, M^+), 182 (98), 153 (10), 130 (100), 103 (5), 77 (5), and 70 (7) (Found: C, 69.5; H, 6.8; N, 13.4. $C_{18}H_{21}N_3O_2$ requires C, 69.4; H, 6.8; N, 13.5%).

Indoline (6).—The dioxopiperazine (2) (17 g) was dissolved in trifluoroacetic acid (50 ml) and after a few minutes the solution was added slowly to a well-stirred suspension of sodium hydrogencarbonate (60 g) in water (100 ml) at room temperature. After addition, the mixture was extracted with dichloromethane (2 × 150 ml) and the combined organic extracts washed with water (100 ml), dried, and evaporated to give the *indoline* as a foam; trituration with ether gave a crystalline solid (16 g, 94%), m.p. (acetone–light petroleum) 187—188 °C, $[\alpha]_D^{21}$ −44° (*c* 0.97, EtOH); $\nu_{max.}$ 3 405, 3 320, and 1 660 cm^{-1}; $\lambda_{max.}$ (log ε) 297 (3.31), 242 (3.78), 207 (415) nm; δ 7.20—6.50 (4 H, m, aromatic), 5.50 (1 H, d, *J* 7 Hz, C^{8a}-*H*), 5.10 (1 H, br s, exchangeable, N*H*), 4.15—3.83 (3 H, m, C^2H, $C^{10}H$, $C^{3a}H$), 3.60—3.35 (2 H, m, $C^{13}H_2$), and 2.75—1.75 (6 H, m, C^3H_2, $C^{14}H_2$, $C^{15}H_2$); *m/e* 283 (84%, M^+), 153 (67), 130 (100), 117 (71), and 7 (51) (Found: M^+, 283.131 8; C, 68.1; H, 6.1; N, 14.9%. $C_{16}H_{17}N_3O_2$ requires *M*, 283.132 1; C, 67.8; H, 6.05; N, 14.8%).

1-*Acetylindoline* (13).—The indoline (6) (100 mg) was stirred in acetic anhydride (10 ml) for 40 min at room temperature before removing the solvent *in vacuo* to give, in quantitative yield, the *acetylindoline*, m.p. (acetone–light petroleum) 253—257 °C; $\nu_{max.}$ 1 670 and 1 660 cm^{-1}; $\lambda_{max.}$ (log ε) 283 (3.33), 276 (3.36), and 244 (3.3) nm; δ 8.10 (1 H, d, *J* 8 Hz, C^7H), 7.4—7.04 (3 H, m, aromatic), 6.25 (1 H, d, *J* 6 Hz, $C^{8a}H$), 4.28—3.85 (3 H, m, C^2H, $C^{10}H$, $C^{3a}H$), 3.56 (2 H, m, $C^{13}H_2$), 2.65 (3 H, s, MeCO), and 2.60—1.80 (6 H, m, $C^{14}H_2$, $C^{15}H_2$, C^3H_2) (Found: C, 66.3; H, 5.9; N, 13.0. $C_{18}H_{17}N_3O_3$ requires C, 66.4; H, 5.9; N, 12.9%).

N^aN^b-*Diacetyl*-L-*tryptophan Methyl Ester* (11) *and* N^b,2-*Diacetyl*-L-*tryptophan Methyl Ester* (10).—N^b-Acetyl-L-tryptophan methyl ester (7) (m.p. 147—150 °C; lit.,[18] 152.5 °C) (110 mg) was stirred in redistilled acetic anhydride (5 ml) at room temperature and trifluoroacetic acid (4 ml) was quickly added. All solids dissolved to form a yellow solution within 10 min. The solution was poured slowly into a solution of sodium hydrogencarbonate (20 g) in water. The mixture was extracted with dichloromethane and the separated organic layer washed with water (2 × 20 ml) and dried. Evaporation afforded a solid which was separated by preparative t.l.c. to give, as the less polar product, the *acetate* (11) (36 mg, 31%), m.p. (ethyl acetate–light petroleum) 156—158 °C; $\nu_{max.}$ 3 290, 3 110, 1 740, 1 705, and 1 650 cm^{-1}; $\lambda_{max.}$ (log ε) 299 (3.86), 291 (3.83), 270 (sh) (3.90), 262 (3.90), and 239 (4.26) nm; δ 8.6—8.4 (1 *H*, m, C^7H), 7.8—7.25 (4 H, m, aromatic), 6.45 (1 H, br d, *J* *ca.* 8 Hz, exchangeable, N*H*), 5.25—4.8 [1 H, dt, *J* 8.6 Hz, collapse to t (*J* 6 Hz) with D_2O, C^9H], 3.75 (3 H, s, OMe), 3.30 (2 H, d, *J* 6 Hz, C^8H_2), 2.60 (3 H, s, $MeCON^a$), and 2.0 (3 H, s, $MeCON^b$); *m/e* 302 (6%, M^+), 243 (17), 201 (19), 172 (11), 130 (100), and 43 (27) (Found: C, 63.3; H, 6.0; N, 9.4. $C_{16}H_{18}N_2O_4$ requires C, 63.6; H, 6.0; N, 9.3%).

The more polar product was the acetate (10) (64 mg, 58%), m.p. (acetone–light petroleum) 202—204 °C; $\nu_{max.}$ 3 230, 3 080, 1 745, 1 658, and 1 650 cm^{-1}; $\lambda_{max.}$ (log ε) 312 (4.27) and 236 (4.20) nm; δ 9.40 (1 H, br s, exchange-

able, indole-N*H*), 7.9—7.0 (5 H, m, 1 H exchangeable, aromatic + amide N*H*), 5.2—4.8 (1 H, dt, collapses to t with D_2O, C^9*H*), 4.2—3.35 (5 H, s, superimposed upon d, 1 C^8*H*$_2$ and OMe), 2.65 (3 H, s, C^2-COMe), and 2.05 (3 H, s, MeCON[b]); *m/e* 302 (5%, M^+), 243 (5), 184 (31), 172 (100), 130 (16), and 43 (34) (Found: C, 63.3; H, 6.0; N, 9.1. $C_{16}H_{18}N_2O_4$ requires C, 63.6; H, 6.0; N, 9.3%).

cyclo-L-*Prolyl*-L-[N^a-(3,3-*dimethylallyltryptophyl* (3).—3,3-Dimethylallyl bromide was prepared from 2-methylbut-3-en-2-ol by the method of Crombie *et al.*[19] and stored over 4A molecular sieves. To sodium hydride (3.5 mmol, as a 65% emulsion in mineral oil) in dimethylformamide (5 ml) under nitrogen was added a solution of the indoline (6) (1 g) and dimethylallyl bromide (6.4 g; 10 equiv.) in dimethylformamide (30 ml). The mixture was stirred for 1 h and then poured into water (50 ml) containing sodium hydrogencarbonate (1.5 g). The solution was extracted with dichloromethane (50 ml) and the organic phase washed with more water, the aqueous washings being back-extracted with more dichloromethane (25 ml). The combined organic extracts were dried and evaporated to small volume. Column chromatography on silica (50 g) afforded, with dichloromethane–methanol (97 : 3) as eluant, the *title compound* (1.05 g, 85%), m.p. (acetone–light petroleum) 147—150 °C; $[\alpha]_D^{21}$ −99° (*c* 1.06, EtOH); $\nu_{max.}$ 3 220, 1 685, and 1 640 cm^{-1}; $\lambda_{max.}$ (log ε) 278 (sh) (3.60), 288 (3.63), and 292 sh (3.56) nm; δ 7.45—6.95 (4 H, m, aromatic), 6.90 (1 H, s, C^2*H*), 5.90 (1 H, s, exchangeable, N*H*), 5.28 (1 H, t, *J* 7 Hz, vinyl-*H*), 4.55 (2 H, d, *J* 7 Hz, NC*H*$_2$), 4.25 (1 H, X part of AMX system), 3.94 (1 H, br t, *J* 6 Hz, C^{12}*H*), 3.77—3.58 (3 H, m, C^8*H*, C^{15}*H*$_2$), 3.03—2.76 (1 H, A part of AMX system, C^8*H*), and 2.4—1.6 [10 H, Me_2C, C^{16}H$_2$, C^{17}*H*$_2$]; *m/e* 351 (5%, M^+), 198 (61), 130 (100), 73 (20), 69 (35), and 41 (34) (Found: M^+, 351.194 0; C, 72.1; H, 7.0; N, 12.2%. $C_{21}H_{25}N_3O_2$ requires *M*, 351.794 7; C, 71.8; H, 7.2; N, 12.0%).

8-(3,3-*Dimethylallyl*)*indoline* (17).—The dioxopiperazine (3) (200 mg) was dissolved in trifluoroacetic acid (5 ml) and then immediately added, dropwise with vigorous stirring, to saturated aqueous sodium hydrogencarbonate solution (150 ml). Work-up in the usual manner afforded, in quantitative yield, the *indoline* (17), m.p. (acetone–light petroleum) 128—133 °C; $[\alpha]_D^{19.5}$ −348° (*c* 0.93, EtOH); $\nu_{max.}$ 1 665 and 1 605 cm^{-1}; $\lambda_{max.}$ (log ε) 209 (4.37), 256 (3.91), and 306 (3.28) nm; δ 7.05—6.20 (4 H, m, aromatic), 5.80 (1 H, d, *J* 7 Hz, C^2*H*), 5.10 (1 H, t, *J* 7 Hz, vinyl-*H*), 4.24—3.75 (5 H, m, indole-N*H*, C^9*H*, C^{12}*H*, C^3*H*), 3.66—3.42 (2 H, m, C^{15}*H*$_2$), and 2.60—1.55 (12 H, remaining protons); *m/e* 351 (13%, M^+), 198 (79), and 130 (100) (Found: C, 71.8; H, 7.1; N, 11.7. $C_{21}H_{25}N_3O_2$ requires C, 71.8; H, 7.2; N, 12.0%).

Treatment of the indoline with dilute ethanolic hydrochloric acid reconverted it into the open dioxopiperazine (3).

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