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CYCLIC TAUTOMERS OF TRYPTOPHANS AND TRYPTAMINES—4[1]

SYNTHESIS OF CYCLIC TAUTOMERS OF TRYPTOPHANS AND TRYPTAMINES[2]

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Abstract—N_b-Methoxycarbonyltryptophan methyl ester (DL- and L-**13**) was cyclized to the corresponding *trans* cyclic tautomer (**14**) in excellent yield in various acids such as 85% phosphoric acid or trifluoroacetic acid. The *cis* cyclic tautomer (**15**) was formed as the less stable and kinetically controlled product and converted to the more stable *trans* isomer (**14**) under the reaction condition. The *trans* isomer (**14**) was reverted to **13** on treatment with 10% sulfuric acid in methanol. Other tryptophan and tryptamine derivatives (**6** and **19a**) also cyclized to the corresponding cyclic tautomers in similar acidic media.

There are three possible tautomers, the indole (**1**), the indolenine (**2**), and the cyclic (**3**) tautomers, in tryptophans and tryptamines, though the indole tautomer is strongly favoured in neutral solvents and no detectable amount of the indolenine and the cyclic tautomer was observed in their NMR spectra.[3] To our knowledge only one report on the synthesis of tautomeric pyrroloindoles of type **3** has appeared in the literature, although 3a-substituted pyrrolo[2,3-b]indole derivatives such as as physostigmine,[4] sporidesmins,[5] chimonanthine,[6] folicanthine,[6] 3a-hydroxypyrroloindoles,[7] and 3a-alkylpyrroloindoles[8] are well known. N_a,N_b-dimethylpyrrolo[2,3-b]indole (**4**), a cyclic tautomer, was proposed as a tentative structure of folicanthine,[9] and an attempt to synthesize **4** was reported to be unsuccessful.[10] The cyclic tautomer of tryptophan (**5**) was recently postulated as a hypothetical intermediate of the enzymic prenylation of tryptophan at the 4-position.[11] The first and only example of the cyclic tautomer was reported by Witkop *et al.*[12] who prepared its N_b-acetyl derivatives (**8a, b**) by the catalytic hydrogenation of the pyrroloindole derivative (**7**) obtained by the halogenation of the tryptophan derivative (**6**).

The cyclic tautomer lost the enamine reactivity of the indole ring at 3-position and the reactivity at the 2-position, and its benzene ring should gain an aniline reactivety. Therefore, the cyclic tautomer (**3**) would be an attractive intermediate to prepare tryptophan derivatives substituted at the benzene ring, because the electrophilic substitution of the indolic form (**1**) of 3-substituted indoles usually occurs at the 2-position and the regioselective substitution at the benzene ring is not feasible.[13] Furthermore, there are many natural indole derivatives which are derived from tryptophan and carry substituents at the benzene ring, and the cyclic tautomer (**3**) may play an important role in these biosynthesis as shown by Baldwin in the prenylation of tryptophan.[11]

We report here a facile synthesis of the cyclic tautomer of tryptophans and tryptamines. The tryptamine derivatives (**1**) are known to give the pyrroloindole derivative (**10**) via **9** on alkylation,[8] halogenation,[12,14] dye-sensitized oxygenation,[7] and peracid oxidation.[15] On the other hand, N-alkyltryptamine and tryptamine itself in a strong acid do not cyclize to **10** (E=H) and stay at the diprotonated form such as **11**[16] or dimerize to **12**.[17] However, we may obtain the cyclic tautomer (**10**, E=H) when we choose a proper acid and a proper protective group for the N_b-nitrogen such as that the indole ring is protonated and N_b-nitrogen retains enough nucleophilicity to attack at the 2-position of the protonated form (**9**) in the media.

When N_b-methoxycarbonyl-DL-tryptophan methyl ester (DL-**13**) was dissolved in 85% phosphoric acid at ambient temperature for 3 hr and the mixture was poured into an excess of 10% sodium carbonate, the pyrroloindole (DL-**14**), m.p. 104.5–106.5°, was obtained as stable crystals in 85% yield. The similar cyclization proceeded to give DL-**14** in various acidic conditions such as 85–70% sulfuric acid, 85–50% sulfuric acid in methanol, and trifluoroacetic acid (Table 1). However, the cyclic tautomer was not formed in acetic acid, formic acid and conc sulfuric acid. Tryptophan derivative **13** does not dissolve in more dilute phosphoric acid and sulfuric acid, and the indole ring was not sufficiently protonated in formic acid or less acidic media. On the other hand, **13**, is protonated both at the 3-position and the N_b-nitrogen in conc sulfuric acid.

Acetylation of DL-**14** with acetic anhydride-pyridine gave a N_a-acetyl derivative (DL-16), m.p. 162–163.5°. In 85% phosphoric acid DL-**13** dissolved slowly and DL-**14** was isolated as a sole product. On the other hand when DL-**13** was dissolved in 70% sulfuric acid in methanol at room temperature and quenched after 15 min, the NMR spectrum of the mixture showed the presence of the other isomer (DL-**15**) besides DL-**14**. Direct isolation of DL-**15** failed due to its facile reversion to DL-**13** during isolation. However, the acetylation of the mixture of DL-**14** and **15** made it possible to isolate DL-**16** and DL-**17**, m.p. 177–178.5° in 51% and 30% yields respectively. The reaction of DL-**13** in trifluoroacetic acid at 16° for 60 min followed by acetylation gave DL-**16** and **17** in 56% and 13% yields. When DL-**13** was treated with trifluoroacetic acid in different conditions, the ratio of DL-**16** and **17** (DL-**16**/DL-**17**) was changed as follows: 0.05 (15°, 2–3 min), 0.91 (15°, 30 min), 4.3 (16°, 60 min), and 0.1 (−18 to −10°, 30 min). Furthermore, the NMR spectrum of the mixture obtained by the reaction of DL-**13** in trifluoroacetic acid followed by neutralization indicated that DL-**15** was the major isomer at 17° for 2–3 min or at −15 to −10° for 30 min, while DL-**14** became the major

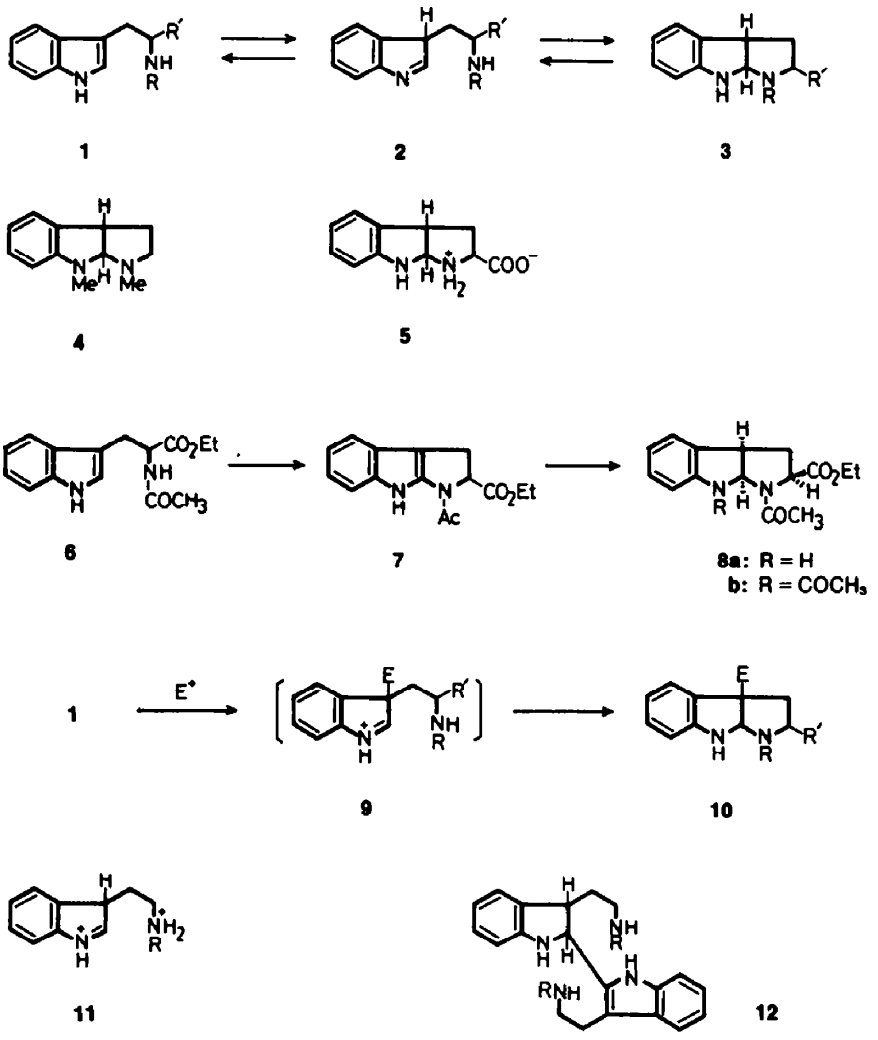

Chart 1.

Table 1. Formation of the cyclic tautomer (DL-14) in various acid media

Acid	Reaction time	DL-14 yield %	DL-13 recovered %
85% H_3PO_4	3 hr	85	8
70% H_3PO_4	3 days	0	95
CF_3COOH	2 hr	75	5
conc. H_2SO_4	4 hr	0	97
85% H_2SO_4	30 min	67	20
70% H_2SO_4	2 hr	57	9
50% H_2SO_4	3 days	0	64
85% H_2SO_4-MeOH	1.5 hr	60	16
70% H_2SO_4-MeOH	2 hr	62	23
50% H_2SO_4-MeOH	4 hr	38	52
30% H_2SO_4-MeOH	10 hr	0	96

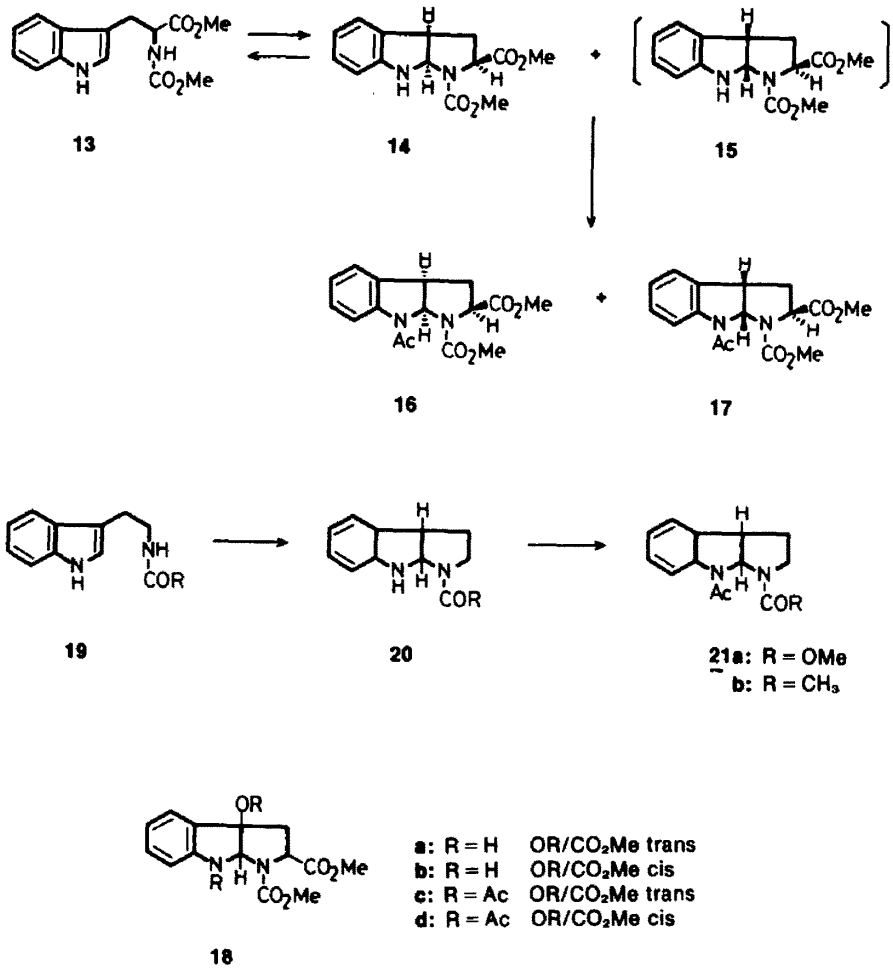

Chart 2.

isomer at 50° for 2–3 min. These results showed that the DL-**14** was the thermodynamically stable isomer and DL-**15** was the less stable one and the kinetically controlled product.

The cyclic tautomer (DL-**14**) is stable as crystals at room temperature, but reverted to **13** by dissolving in acetic acid or by addition of a small amount of hydrochloric acid in its methanolic solution at room temperature. The N_a-acetyl derivative (DL-**16**), however, is stable in acetic acid, but reverted to **13** on treatment with 10% sulfuric acid in methanol at room temperature and converted to N_a-acetyl-**13** on treatment with 10% sulfuric acid in acetic acid. On the other hand, the other isomer (DL-**17**) was transformed to Na-acetyl-**13** rapidly and then slowly changed to **13** on treatment with 10% sulfuric acid in methanol at room temperature.

The structures of these cyclic tautomers were confirmed by their spectral data (Table 2). The UV and NMR spectra of **14**, **16**, and **17** are similar to those of 3a-hydroxy derivatives (**18**). Two singlets for N–CO_2Me and two doublets for 8a–H in the NMR spectrum of **14** in deuterochloroform are probably due to the presence of the rotamers by the hindered rotation between C–N bond in the N_b-carbamate group.[7c] This was verified by the NMR in deuteropyridine; Two singlets at 3.55 and 3.63 ppm for N–CO_2Me and two doublets at 5.63 and 5.73 ppm for 8a–H observed at room temperature changed to a singlet at 3.55 ppm and a doublet at 5.62 ppm at 80° respectively.

The stereochemistry of **14**, **16** and **17** was assigned by comparison of NMR spectra of **16** and **17** with those of 3a-hydroxy derivatives (**18c** and **18d**) whose stereochemistry was established previously.[7d] The Me signal in the ester group was observed in a higher field (3.10 ppm) in **18c** where the ester group was shielded by the benzene ring, while it was observed at a normal position (3.64 ppm) in **18d**. Therefore DL-**16** and DL-**14** having a higher field Me signal are *trans* relationship between 2–CO_2Me and 3a–H with *cis* ring fusion between two 5-membered rings, while DL-**17** is *cis* relationship between 2–CO_2Me and 3a–H.

When N_b-methoxycarbonyl-L-tryptophan methyl ester (L-**13**) prepared from L-tryptophan was dissolved in 85% phosphoric acid, the optical active cyclic tautomer (L-**14**), m.p. 85–86°, was obtained in 85% yield. The corresponding acetylated isomers, L-**16** and L-**17** were obtained in 80% and 6% yields respectively by direct acetylation of the reaction mixture. The both L-**16** and L-**17** were reverted to L-**13** in 10% sulfuric acid in methanol, demonstrating that the racemization did not take place practically during cyclization and acetylation. The CD spectra of L-**16** and L-**17** (Fig. 1) showed similar but opposite sign, supporting epimeric configuration at the ring junctions in the both isomers. The optical active L-**16** could be con-

Table 2. Spectral data of cyclic tautomers

	DL-14	DL-16	DL-17
UV λ_{max}nm(ε) in MeOH	243(7100), 299(2400)	246(12000), 277(1750) 284.5(1550)	244(12500), 275.5(1900), 283(1700)
Mass m/e(rel. intens.)	276(M^+,64), 217(37), 185(28), 130(100)	318(M^+, 21), 276(100), 217(43), 185(15), 130(83)	318(M^+, 20), 276(77) 217(47), 185(28), 130(100)
Nmr δ in $CDCl_3$ 3-CH_2	2.4-2.8(m)	2.3-2.9(m)	2.1-2.8(m)
CO_2Me	3.14(s), 3.16(s)	3.11(s)	3.63(s), 3.72(s)
N-CO_2Me	3.66(s), 3.79(s)	3.73(s)	
3a-H	3.9(m)	4.05(t,J=6 Hz)	4.0(m)
2-H	4.8(m), 5.12(m)	4.59(dd,J=8 and 2 Hz)	
NH	4.4-4.7(br.)	-	-
N-Ac	-	2.59(s)	2.52(s)
8a-H	5.49(d, J=6 Hz), 5.53(d, J=6 Hz)	6.22(d,J=8 Hz)	6.13(d,J=6 Hz)
arom H	6.5-7.1(m)	6.9-7.4(m)	7.0-7.4(m)
7-H	-	7.92(d,J=8 Hz)	7.93(d,J=8 Hz)

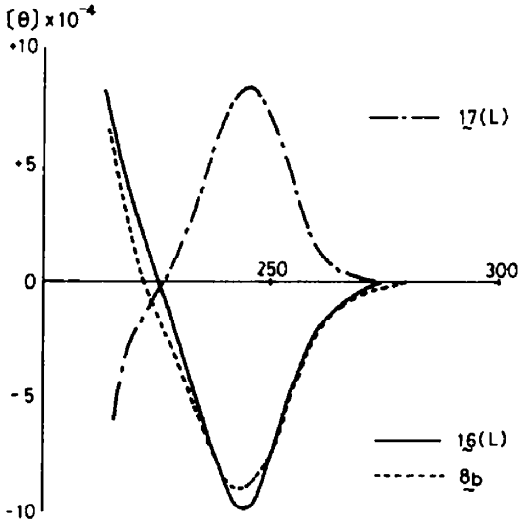

Fig. 1. CD spectra of L-16, 17 and 8b.

verted directly to L-tryptophan with partial racemization on heating in 2N-NaOH.

In order to examine the scope and limitation of these cyclization in acid media we carried out the reactions of other tryptophan derivatives in acids. N_b-Acetyl-L-tryptophan ethyl ester (L-6) in 85% phosphoric acid cyclized similarly to the corresponding cyclic tautomer (L-8a) but in lower yield (29%) which was identical with a sample prepared by Witkop's method, providing further support for the structure of the cyclic tautomer. In contrast to the L-13, when L-6 was treated in 85% phosphoric acid, the competitive acid-catalyzed dimerization occured besides the cyclization, probably due to the less nucleophilic character of the N_b-acetyl group compared to that of the N_b-methoxycarbonyl group. The stereochemistry of L-8a was assigned as the *trans* regard to the ester group and 3a-hydrogen by comparison fo the CD spectrum of L-8a and L-8b with those of L-14, 16 and 17.

N_b-Methoxycarbonyltryptamine (19a) in 85% phosphoric acid was also shown to cyclize to the cyclic tautomer (20a) which was detected by the NMR spectrum and tlc of the mixture, but 20a was not stable and failed to purify. However, acetylation of 20a gave 21a as stable crystals in 71% yield. Prolonged treatment of 19a with the acid decreased the yield of 21a and dimeric products were formed. On the other hand, N_b-acetyltryptamine (19b) in 85% phosphoric acid does not form the cyclic tautomer. The NMR spectrum of 19a in trifluoroacetic acid showed that nearly complete conversion of 19a to the corresponding cyclic tautomer (20a) after dissolution and a small amount of dimers was formed after 24 hr, while the NMR spectrum of 19b immediately taken after dissolving in trifluoroacetic acid showed the predominant formation of dimeric products along with a small amount of the cyclic tautomer (20b). This demonstrates again the methoxycarbonyl group was a better protecting group for the N_b-nitrogen for the cyclization reaction in an acid media. N_b-Benzyloxycarbonyltryptamine and N_b-methoxycarbonyl-DL-tryptophan (free carboxylic acid) were also found to cyclize to the corresponding cyclic tautomer in trifluoroacetic acid by their NMR spectra. However, tryptamine and tryptophan themselves do not form the corresponding cyclic tautomer in trifluoroacetic acid or 85% phosphoric acid, due to the protonation of N_b-nitrogen instead of the indole ring.

The mechanism of the formation of these cyclic tautomers in acid media may be rationalized by Chart 3.

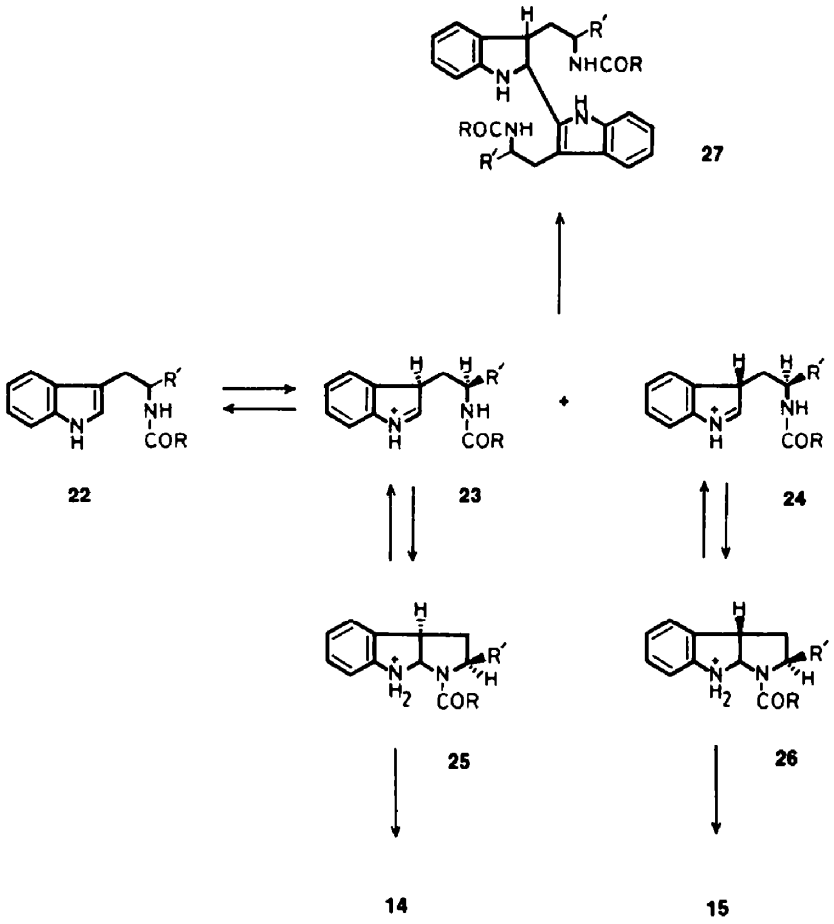

Chart 3.

Reversible protonation at the 3-position of the indole (**22**) occurs both from top and below of the indole ring to form **23** and **24**, but the cyclization of **24** to form *cis* isomer (**26**) occurs more rapidly than the other. The *cis* isomer (**26**), kinetically controlled product, gradually transformed to the thermodynamically stable *trans* isomer (**25**) through the equilibrium (**26**⇄**24**⇄**22**⇄**23**⇄**25**) on prolonged reaction time or at higher temperature. The presence of the equilibrium has been shown by the NMR spectrum of DL-**14** in deuterophosphoric acid at ambient temperature which indicated rapid deuteration at both 3a- and 8a-hydrogens, accompanying slow partial deuteration of the aromatic hydrogens.[16] The protonation at the 8-position in **25** and **26** was proved by the benzenoid UV absorption of DL-**14** in 85% phosphoric acid. The acid-catalyzed dimerization of **23** and **24** to **27** may compete with the cyclization in an acid media. As the tryptophan derivatives may dimerize to **27** less readily than the tryptamine derivatives due to the presence of the carboxyl group which may hinder the attack of another molecule of **22** to **23** or **24**, the cyclic tautomers of tryptophans were formed more smoothly than those of tryptamines, providing acyl group is the same. And more nucleophilic N_b-methoxycarbonyl derivatives prefer the cyclization over the dimerization, while less nucleophilic N_b-acetyl derivatives prefer the dimerization.

The cyclic tautomers of various N_b-acyltryptophans and tryptamines[19] thus prepared by simply dissolving these compounds in an acid may serve as promising intermediates to tryptophans and tryptamines carrying substituents at the benzene ring.[1,20] Researches along this line are now under investigation.

EXPERIMENTAL

All m.ps were determined with a Yamato MP-1 or Yanagimoto micro m.p. apparatus (hot stage), and are not corrected. The UV spectra are recorded on a Hitachi 323 spectrophotometer, and the IR spectra are run on a Hitachi 215 and 295 spectrophotometer. The NMR spectra were measured with a JEOL MH-100 spectrometer with TMS as an internal standard. The mass spectra were obtained by a Hitachi RMU-6E spectrometer.

1,2,3,3a,8,8a - Hexahydro - 1,2 - dimethoxycarbonylpyrrolo[2, 3 - b]indole (**14**)

(i) *Formation of* DL-**14** *in phosphoric acid.* DL-**13** (1.38 g, 5 mmol) was dissolved in 85% H_3PO_4 (15 ml) at room temp. The soln was stirred for 3 hr and then poured into 10% Na_2CO_3 (500 ml) with ice cooling. The mixture was extracted with CH_2Cl_2. The organic layer was washed with sat NaClaq, dried over Na_2SO_4, and evaporated. The residual colorless oil was crystallized from benzene-hexane to give colorless prisms (DL-**14**, 1.045 g), m.p. 104–107° (hot stage). Preparative tlc (silica gel, benzene–acetone (5:1)) of the mother liquor gave further **14** (129 mg, total 1.174 g, 85%) and recovered **13** (109 mg, 8%). Recrystallization of DL-**14** from acetone gave colorless prisms, m.p. 104.5–106.5°. IR(KBr) cm^{-1}: 3380(NH), 1763(CO_2Me), 1718(NCO_2Me). NMR δ in CF_3COOH: 2.6–3.3(m, 3–CH_2), 3.50(s, CO_2Me), 3.69, 4.02(s, N–CO_2Me), 4.56(m, 3a–H), 4.93(m, 2–H), 6.45(d, J = 7 Hz, 8a–H), 7.0–8.0(m, arom. H). UV(in 85% H_3PO_4)

$\lambda_{max}(\epsilon)$: 255.5(320), 261(420), 267.5(420). Other spectral data are shown in Table 2. (Found: C, 60.90; H, 5.84; N, 10.19. $C_{14}H_{16}O_4N_2$ requires: C, 60.86; H, 5.84; N, 10.14%). The other isomer (DL-15) was detected on a tlc, but it reverted to 13 on the preparative tlc.

(ii) *Formation of* DL-14 *in various acids.* DL-13 (55 mg, 0.2 mmol) was dissolved in various acids (1 ml) with stirring at room temp. The mixture was poured into 10% Na_2CO_3 (20 ml) after an appropriate time, and extracted with CH_2Cl_2. The organic layers were washed with sat NaClaq, dried, and evaporated to give a residue which was separated by preparative tlc. The results are summarized in Table 1.

(iii) *Detection of the formation of* DL-14 *and* 15. A soln of DL-13 (55 mg), in 70% (w/w) H_2SO_4 in MeOH (1 ml) was stirred for 15 min and the mixture was worked up as above. The NMR spectrum of the crude mixture in $CDCl_3$ showed additional signals probably due to the unstable isomer (DL-15) besides those for 14 at 2.4(m, 3-CH_2), 4.26(q, J = 6 Hz, 2-H), 5.70(d, J = 6 Hz, 8a-H) ppm. The ratio of 14 and 15 was assumed to be roughly 1:1 by comparison of intensities of 8a-H signals. The additional signals disappeared after standing at 25° for 1 hr and new signals corresponding to 13 were observed besides those of 14. DL-13 was dissolved in CF_3COOH in various conditions and work-up as above. The NMR spectra of these crude mixture showed the ratio of 14 and 15 (15/14) as follows: 8(17°, 2–3 min), 0.8(50°, 2–3 min), 9(−15 to −10°, 30 min) and 2.5(16°, 30 min).

(iv) *Formation of* L-14. A soln of L-13 (276 mg, 1 mmol) in 85% H_3PO_4 (3 ml) was stirred for 3 hr at room temp. The soln was poured into 10% Na_2CO_3 (90 ml) with cooling and extracted with benzene. The benzene layer was washed with H_2O, dried, and evaporated to leave an oil which was crystallized from benzene–i-Pr_2O to give L-14 (188 mg). Separation of the mother liquor by preparative tlc (silica gel, benzene–acetone (10:1)) gave further L-14 (48 mg, total 236 mg, 85%) and recovered L-13 (21 mg). Recrystallizations of L-14 from benzene-i-Pr_2O gave colorless needles, m.p. 85–86°; $[\alpha]_D^{24} = +224°$ ($c = 0.2$, MeOH) (Found: C, 60.74; H, 5.79; N, 10.07. $C_{14}H_{16}O_4N_2$ requires: C, 60.86; H, 5.84; N, 10.14%). IR(KBr) cm^{-1}: 3380, 1762, 1710. The UV and NMR spectra were identical with those of DL-14.

8 - *Acetyl* - 1,2 - *dimethoxycarbonyl* - 1,2,3,3*a*,8,8*a* - *hexahydropyrrolo*[2, 3 - *b*]*indole* (16 *and* 17).

(i) DL-16 *and* 17. A soln of DL-13 (553 mg, 2 mmol) in 85% H_3PO_4 (5 ml) was stirred for 1.5 hr at room temp and worked up as above. The crude mixture was dissolved in pyridine (10 ml) and Ac_2O (3 ml) was added to the soln. The mixture was stirred at room temp overnight, and evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with 5% HCl, sat $NaHCO_3$ and then H_2O. The organic layer was dried and evaporated to leave a residue which was crystallized from acetone–hexane to give DL-16 (493 mg). Separation of the mother liquor by preparative tlc (silica gel, AcOEt–hexane (1:2)) gave further DL-16 (27 mg, total 520 mg, 82%), DL-17 (37 mg, 6%) and recovered DL-13 (28 mg, 5%). Further recrystallizations of DL-16 from acetone–hexane gave colorless crystals, m.p. 162–163.5°. Recrystallizations of DL-17 from acetone gave colorless crystals, m.p. 177–178.5°. DL-16 (Found: C, 60.51; H, 5.65; N, 8.77. $C_{16}H_{18}O_5N_2$ requires: C, 60.37; H, 5.70; N, 8.80%). IR(KBr) cm^{-1}: 1740, 1712, 1669, 1607.

DL-17 (Found: C, 60.17; H, 5.71; N, 8.78. $C_{16}H_{18}O_5N_2$ requires: C, 60.37; H, 5.70; N, 8.80%). IR(KBr) cm^{-1}: 1766, 1759, 1728, 1690, 1679.

(ii) *Cyclization followed by acetylation*; *various conditions.* A soln of DL-13 (553 mg, 2 mmol) in 70% H_2SO_4 in MeOH (5 ml) was stirred for 15 min at room temp. The similar work-up as above gave a mixture of DL-16 and 17 which were separated by a silica gel column. Elution with AcOEt–hexane (1:1) gave DL-13 (67 mg, 12%). Elution with AcOEt–hexane (1:1 − 2:1) gave DL-17 (193 mg, 30%) and DL-16 (327 mg, 51%). DL-13 was dissolved in CF_3COOH in various conditions and workup as above. The ratio of DL-16 and 17 (16/17) was as follows: 0.05(15°, 2–3 min), 0.91(15°, 30 min), 4.3(16°, 60 min), and 0.1(−18 to −10°, 30 min).

(iii) L-16 *and* 17. A soln of L-13 (1.0 g, 3.6 mmol) in 85% H_3PO_4 (10 ml) was stirred for 3.5 hr at room temp. The work-up as above (i) gave L-16 (918 mg, 80%), L-17 (70 mg, 6%), and L-13 (22 mg, 2%). L-16, m.p.150–151.5° (from acetone–i-Pr_2O), $[\alpha]_D^{24} = +74°$ ($c = 0.2$, MeOH) (Found: C, 60.21; H, 5.62; N, 8.84%). $C_{16}H_{18}O_5N_2$ requires: C, 60.37; H, 5.70; N, 8.80%). IR(KBr) cm^{-1}: 1760, 1730, 1671. L-17, m.p. 185–186.5° (from acetone-i-Pr_2O), $[\alpha]_D^{31} = -165°$ ($c = 0.2$, MeOH) (Found: C, 60.53; H, 5.69; N, 8.79.) CD spectra: L-16, $[\theta]_{244} = -97{,}800$; L-17, $[\theta]_{244} = +83{,}600$. The UV and NMR spectra were identical with those of DL-16 and 17.

Ring-opening of 14 *to* 13

A soln of DL-14 (55 mg, 0.2 mmol) in AcOH (1 ml) was stirred at room temp for 40 min. The tlc of the soln revealed complete reversion to 13. The soln was evaporated *in vacuo* and the residue was crystallized from benzene–hexane to give DL-13 (51 mg, m.p. 112–114°, which was identical with an authentic sample (m.m.p., IR). Addition of a drop of 10% HCl to a soln of DL-14 in MeOH resulted in complete conversion to DL-13 within several min (followed by UV spectrum).

Ring-opening of 16 *and* 17 *to* 13

(i) DL-16 *and* 17. A soln of DL-16 (64 mg, 0.2 mmol) in 10% (w/w) H_2SO_4–MeOH (2 ml) was stirred for 2 hr at room temp. The mixture was poured into sat $NaHCO_3$aq (10 ml), and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried, and evaporated to leave a residue (55 mg) which showed a single spot for 13 in its tlc. The residue was crystallized from acetone–hexane to give DL-13 (44 mg), m.p. 112–114°, which was identical with a standard sample (m.m.p., IR). DL-17 in 10% H_2SO_4 in MeOH at room temp transformed to Na-acetyl-13 within a few hr and slowly changed to 13 (tlc).

(ii) L-16 *and* 17. A soln of L-16 (500 mg, 1.57 mmol) in 10% H_2SO_4–MeOH (20 ml) was stirred for 3.5 hr at room temp. The soln was treated as above (i) to give a crude L-13 (427 mg) which showed almost single spot on its tlc. The residue after filtration through a short silica gel column was submitted to take the optical rotation, $[\alpha]_D^{23} = -1.3°$ ($c = 3.85$, MeOH), which was nearly identical with that of L-13 ($[\alpha]_D^{23} = -1.2$ ($c = 3.90$, MeOH). The crude 13 was recrystallized from acetone–iPr_2O to give L-13, m.p. 101–102.5°, which was identical with an authentic sample (m.m.p., IR).

A soln of L-17 (30 mg) in 10% H_2SO_4–MeOH (1 ml) was stirred for 96 hr at room temp. The same work up gave a crude L-13 (24 mg) which was purified by preparative tlc. Its ORD and CD spectra were nearly identical with those of L-13.

Ring-opening of DL-16 *to* N_a - *acetyl* - N_b - *methoxycarbonyl* - DL - *tryptophan methyl ester*

A soln of DL-16 (500 mg, 1.57 mmol) in 10% H_2SO_4–AcOH (10 ml) was stirred for 6 hr at room temp. The soln was poured into H_2O (100 ml), and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried and evaporated to leave a white solid which was crystallized from acetone–i-Pr_2O to give N_a-acetyl-13 (380 mg) as colorless prisms, m.p. 125–130°. Separation of the mother liquor by preparative tlc (silica gel, AcOEt–hexane (2:1)) gave further N_a-acetyl-13 (66 mg, total, 446 mg, 89%) and DL-16 (15 mg, 3%). Recrystallization of acetyl-13 from acetone–hexane gave colorless prisms, m.p. 125–130°. IR(KBr) cm^{-1}: 3350, 1748, 1707. UV (in EtOH) λ_{max}nm(ϵ); 239(18,700), 260.5(8400), 269°(7500), 291(6500), 299.5(6900). Mass *m/e*(rel. intens.): 318(M^+, 8), 172(17), 130(100). NMR (in $CDCl_3$) δ: 2.56(3H, s, Ac) 3.21(2H, d, J = 6 Hz, β-CH_2), 3.66, 3.68(6H, CO_2Me, NCO_2Me), 4.72(1H, m, α-CH), 5.40(1H, br. d, J = 7 Hz, NH), 7.1–7.7(3H, m, arom H), 8.38(1H, m, 7-H)(Found: C, 60.37; H, 5.69; N, 8.84. $C_{16}H_{18}O_5N_2$ requires; C, 60.37; H, 5.70; N, 8.80%).

1-*Acetyl* - 2 - *ethoxycarbonyl* - 1,2,3,3*a*,8,8*a* - *hexahydropyrrolo*[2, 3 - *b*]*indole* (8a)

A soln of L-6 (1.371 g, 5 mmol) in 85% H_3PO_4 (50 ml) was stirred for 3 hr in an ice bath. The soln was poured into 10% Na_2CO_3 with cooling, and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried and evaporated to leave an oil

(1.36 g) which was chromatographed over silica gel (70 g). Elution with CH_2Cl_2–acetone (50:1) gave L-**8a** (393 mg, 29%), a mixture of L-**8a** and L-**6** (170 mg), and recovered L-**6** (531 mg). Further elution with the same solvent gave dimeric products (118 mg, 9%) which were not purified further, but the mass spectrum showed a peak at *m/e* 584 corresponding to the dimer. Separation of the mixture by preparative tlc gave further L-**6** (53 mg, total 584 mg, 43%). Recrystallization of L-**8a** from acetone gave colorless prisms, m.p. 121–123° (reported m.p. 104–105°[12]), $[\alpha]_D^{17} = +287$ ($c = 0.2$, EtOH, reported value +242°[12]). IR(KBr) cm^{-1}: 3285, 1760, 1644, 1630, 1609. UV (in EtOH) λ_{max} nm(ϵ); 243.5(7450), 300.5(2400). Mass *m/e*(rel intens); 274(M^+, 74), 174(76), 159(92), 132(56), 130(100). NMR (in $CDCl_3$) δ: 0.94(3H, t, J = 7 Hz, CH_2CH_3), 1.98, 2.24(3H, two s, Ac), 2.4–2.9(2H, m 3-CH_2), 3.3–4.0(3H, m, CH_2CH_3, 3a–H), 4.4(1H, dd, J = 8 and 2 Hz, 2–CH), 5.18(1H, br, NH) 5.62(1H, d, J = 6 Hz, 8a–H), 6.4–7.2(4H, m, arom H)(Found : C, 65.79; H, 6.60; N, 10.31. $C_{15}H_{18}N_2O_3$ requires: C, 65.67; H, 6.61; N, 10.21%). The sample was identical with a sample prepared by Witkop's procedure[12] (m.m.p., NMR).

1,8 - *Diacetyl* - 2 - *ethoxycarbonyl* - 1,2,3,3*a*,8,8*a* - *hexahydropyrrolo*[2, 3 - *b*]*indole* (**8b**)

A soln of L-**6** (1.371 g, 5 mmol) in 85% H_3PO_4 (50 ml) was stirred for 2.5 hr in an ice bath. The same work-up as above gave a residue (1.34 g) which was dissolved in pyridine (15 ml) and Ac_2O(5 ml). The mixture was stirred for 2 hr at room temp, and evaporated *in vacuo* to leave a residue. The residue was dissolved in CH_2Cl_2, and the organic layer was washed with 2% HCl, H_2O, and dried. The solvent was removed to give white solid (1.67 g) which was crystallized from acetone to give L-**8b** (428 mg), m.p. 204–206° (reported m.p. 204–206°[12]). The mother liquor was chromatographed over silica gel (50 g). Elution with AcOEt–benzene (1:1) gave L-**6** (620 mg, 45%). Elution with AcOEt-benzene (2:1–3:1) gave further L-**8b** (98 mg, total 526 mg, 33%). Further elution with the same solvent and AcOEt gave monoacetylated dimeric products (183 mg).

8b: IR(KBr) cm^{-1}: 1732, 1668. UV (in EtOH) λ_{max}nm(ϵ); 246(11,500), 277.5(1850), 284.5(1700). Mass *m/e*(rel intens); 316(M^+, 27), 274(97), 174(100), 159(58), 132(30), 130(56). NMR (in $CDCl_3$) δ: 0.95(3H, t, J = 6 Hz, CH_2CH_3), 1.8–3.0(8H, m, N_a–Ac, N_b–Ac, 3-CH_2), 3.3–3.9(2H, m, CH_2CH_3), 4.04(1H, t, J = 6 Hz, 3a–H), 4.42, 4.84(1H, br, 2–CH), 6.31, 6.64(1H, br, 8a–H), 6.8–7.4(3H, m, arom H), 7.92(1H, d, J = 7 Hz, 7–H)(Found: C, 64.41; H, 6.57; N, 8.82. $C_{17}H_{20}N_2O_4$ requires: C, 64.54; H, 6.37; N, 8.86%).

1,2,3,3*a*,8,8*a* - *Hexahydro* - 8 - *acetyl* - 1 - *methoxycarbonylpyrrolo*[2, 3 - *b*]*indole* (**21a**) *from* **19a**

A soln of **19a** (437 mg, 2 mmol) in 85% H_3PO_4 (10 ml) was stirred at room temp for 30 min. The mixture was poured into 10% Na_2CO_3 (200 ml) and extracted with benzene. The organic layer was washed with H_2O, dried and evaporated to give a residue which was dissolved in pyridine (10 ml) and Ac_2O(1 ml) and stirred overnight at room temp. A residue obtained on evaporation of the solvent was chromatographed over silica gel column to afford **21a** (371 mg, 71%. Recrystallizations from acetone–hexane gave **21a**, m.p. 126.5–128°. Monoacetylated dimers (9 mg, 2%, 3 spots, *m/e* 478(M^+)) were also isolated.

21a: IR(KBr) cm^{-1}: 1717, 1665, 1603. UV (in EtOH) λ_{max}nm(ϵ); 245(12,400), 276(2180), 283(1920). Mass *m/e*(rel. intens): 260(M^+, 30), 218(98), 143(20), 131(44), 130(100). NMR (in $CDCl_3$) δ: 2.0–2.4(2H, m, 3-CH_2), 2.53(3H, s, Ac), 2.90(1H, m, 2-CH_2), 3.72(3H, s, OMe), 3.8(1H, m, 2-CH_2), 4.07(1H, m, 3a–H), 6.21(1H, d, J = 6 Hz, 8a–H), 7.0–7.4(3H, m, arom H), 8.04(1H, d, J = 8 Hz, 7–H)(Found: C, 64.70; H, 6.19; N, 10.81. $C_{14}H_{16}N_2O_3$ requires: C, 64.60; H, 6.20; N, 10.76%).

The reaction of **19a** in 85% H_3PO_4 for 2 hr and 24 hr gave **21a** in 36% and 28% yield respectively, and monoacetylated dimers were obtained in 37% and 26% yield respectively. The similar reaction in CF_3COOH for 10 min gave **21a** in 69% yield, monoacetylated dimers (3%) and **19a** (16%).

Isolation of **20a**

A soln of **19a** (44 mg, 0.2 mmol) in 85% H_3PO_4 (1 ml) was stirred for 45 min at room temp. The mixture was poured into 10% Na_2CO_3 (20 ml) and extracted with benzene. The organic layer was dried and evaporated to leave a residue which was separated by preparative tlc (alumina, CH_2Cl_2) to give **20a** (14 mg). Further purification was not carried out owing to instability. **20a**: UV (in EtOH) λ_{max}nm: 243, 295. NMR (in pyridine-d_5) δ: 2.04(2H, m, 3-CH_2), 3.1(1H, m, 2-CH_A), 3.61, 3.70(3H, two s, OMe), 3.4–4.0(2H, m, 2-CH_B, 3a–H), 5.64(1H, t, 8a–H), 6.6–7.3(m, arom, H).

N_b-Acetyltryptamine (**19b**) *in* 85% H_3PO_4

A soln of **19b** (101 mg, 0.5 mmol) in 85% H_3PO_4 (3 ml) was stirred for 2.5 hr at room temp. The mixture was poured into 10% Na_2CO_3 (50 ml) and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried and evaporated to give a residue which was separated by preparative tlc (silica gel, CH_2Cl_2–acetone (5:1)). A dimeric product (68 mg, 68%) was obtained as major product besides a trace amount of the cyclic tautomer (**20b**) and recovered **19b** (5 mg, 5%). A dimer, caramel. UV (in EtOH) λ_{max}nm; 226.5, 286, 293.5. NMR (in $CDCl_3$) δ: 1.73 s, Ac), 1.82 (s, Ac), 4.72 (1H, d, J = 8 Hz, 2–CH(indoline)), 9.00(1H, s, indolic NH).

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REFERENCES

[1]Part 3. T. Hino, M. Taniguchi and M. Nakagawa, *Heterocycles* **15**, 187 (1981).

[2]A part of this work has been published as a communication: T. Hino and M. Taniguchi, *J. Am. Chem. Soc.* **100**, 5564 (1978).

[3]L. A. Cohen, J. W. Daly, H. Kny and B. Witkop, *Ibid.* **82**, 2186 (1960).

[4]E. Coxworth, *The Alkaloids* (Edited by R. H. F. Manske) Vol. VIII, p. 27 (1965); B. Robinson, *Ibid*, Vol. X, p. 383 (1968); Vol. XII, p. 213 (1971).

[5]P. G. Sammes, *Fortschritte Chem. Org. Naturstoffe* **32**, 51 (1974).

[6]R. H. F. Manske, *The Alkaloids*, Vol. VIII, p. 581 (1965); B. Robinson, *Chem. Ind* 218 (1963).

[7a]M. Nakagawa, T. Kaneko and H. Yamaguchi, *J. Chem. Soc.* Chem. Commun. 1972, 603; *Tetrahedron* **30**, 2591 (1974); [b]M. Nakagawa, T. Kaneko, K. Yoshikawa and T. Hino, *J. Am. Chem. Soc.* **96**, 624 (1974); M. Nakagawa, K. Yoshikawa and T. Hino, *Ibid.* **97**, 6496 (1975); [c]M. Nakagawa, H. Okajima and T. Hino, *Ibid.* **98**, 635 (1976); **99**, 4424 (1977); [d]M. Nakagawa, H. Watanabe, S. Kodato, H. Okajima, T. Hino, J. L. Flippen and B. Witkop, *Proc. Natl. Acad. Sci. USA* **74**, 4730 (1977); [e]M. Nakagawa, S. Kato, S. Kataoka and T. Hino, *J. Am. Chem. Soc.* **101**, 3136 (1979).

[8]A. Fontana and C. Toniolo, *Fortschritte, Chem. Org. Naturstoffe*, **33**, 309 (1976).

[9]H. F. Hodson and G. F. Smith, *Chem. Ind.* 740 (1956).

[10]S. Sugasawa and M. Murayama, *Chem. Pharm. Bull.* **6**, 194 (1958).

[11]J. E. Baldwin and N. R. Tzodikow, *J. Org. Chem.* **42**, 1878 (1977).

[12]M. Ohno, T. F. Spande and B. Witkop, *J. Am. Chem. Soc.* **92**, 343 (1970).

[13]R. J. Sundberg, *The Chemistry of Indoles*. Academic Press (1970); W. A. Remers, *Indoles* (Edited by W. J. Houlihan) Part I, p. 1. Wiley Interscience (1972).

[14]T. Hino, H. Miura, T. Nakamura, R. Murata and M. Nakagawa, *Heterocycles* **3**, 805 (1975); T. Hino, H. Miura, R. Murata and M. Nakagawa, *Chem. Pharm. Bull.* **26**, 3695 (1978).

[15]W. E. Savige, *Aust. J. Chem.* **28**, 2275 (1975).

[16]A. H. Jackson and A. E. Smith, *J. Chem. Soc.* 5510 (1964). cf.

M. J. Kamlet and J. C. Dacons, *J. Org. Chem.* **26**, 220 (1961); R. L. Hinman and J. Lang, *J. Am. Chem. Soc.* **86**, 3796 (1964); R. L. Hinman and E. B. Whipple, *Ibid.* **84**, 2534 (1962).

[17]Y. Omori, Y. Matsuda, S. Aimoto, Y. Shimonishi and M. Yamamoto, *Chem. Lett.* 805 (1976).

[18]For the deuteration of the aromatic hydrogens in the indole ring, see: S. Kang, T. Witherup and S. Gross, *J. Org. Chem.* **42**, 3769 (1977).

[19]Recently similar cyclic tautomers were reported. P. G. Sammes and A. C. Weedon, *J. Chem. Soc.* Perkin I, 3048 (1979).

[20]T. Hino, M. Taniguchi, A. Gonsho and M. Nakagawa, *Heterocycles* **12**, 1027 (1979).