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STUDIES IN THE INDOLE SERIES—IV[1]
THE SYNTHESIS OF THE VOBASINE SKELETON[2]

T. SHIOIRI and S. YAMADA

Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Tokyo, Japan

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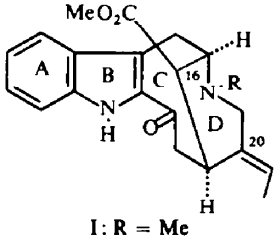
Abstract—The first synthesis of 1-methyl-16-demethoxycarbonyl-20-desethylidenevobasine (IV) having the carbon skeleton of the 2-acylindole alkaloids as represented by vobasine (I) has been carried out.

Dimethyl esters (VIIIa and VIIIb), obtained from N-benzyltryptophan methyl ester (VIIa) and its 1-methyl derivative (VIIb) respectively, underwent Dieckmann cyclization to give the methyl β-ketoesters (IXa and IXb). Alcoholysis of IXa and IXb followed by alkylation furnished the dibenzyl esters (XVIa and XVIb), which were reduced and decarboxylated to the carboxylic acids (XVIIa and XVIIb). The Huang-Minlon reduction of XVIIa and XVIIb was followed by cyclization with polyphosphoric acid to the tetracyclic ketolactams XXa and XXb, which were reduced with LAH, and oxidized with chromic acid to the ketones XXIIa and XXIIb. Compound XXIIa and XXIIb resisted the catalytic debenzylation and only XXIIb yielded a small amount of the carbinolamine (XXVIb).

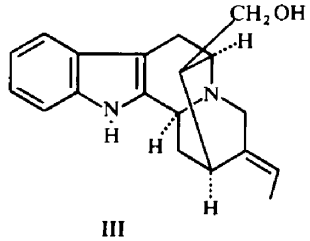
Thus XIXb-1 was debenzylated with sodium in liquid ammonia, and the product (XXIIIb) was successively treated with polyphosphoric acid, LAH and chromic acid to give XXVIb. Finally methylation of XXVIb afforded the desired vobasine derivative (IV).

RECENTLY a large number of 2-acylindole alkaloids have been isolated from a variety of apocynaceous plants and their structures elucidated.[3]

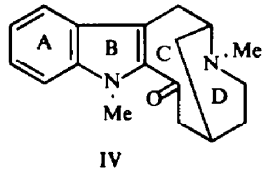
Vobasine (I), a principal member of this class of alkaloids, was the first to be structurally investigated. The correct gross structure was established in 1961,[4] and an X-ray crystallographic study confirmed this structure.[5] Its absolute configuration



I: R = Me
II: R = H



III



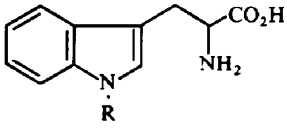
IV

was also determined[6] by transformation of perivine (II), i.e. des-N_b-methylvobasine, to normacusine-B(III),[7] but to date no synthetic efforts toward vobasine-type alkaloids have been recorded. We now describe the synthesis of 1-methyl-16-

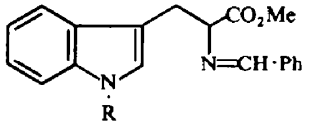
demethoxycarbonyl-20-desethylidenevobasine (IV), a totally synthetic compound containing the full carbon skeleton of vobasine and its congeners.

As an indole was an obvious choice as starting material for the synthesis of the vobasine skeleton, rac-tryptophan (Va) and its 1-methyl derivative[8] (Vb) were chosen. The synthetic experiments involved indole-N unsubstituted compounds (suffix "a") and indole-N methyl derivatives (suffix "b").

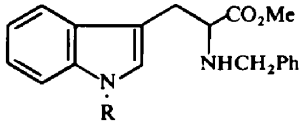
Tryptophan (Va) and 1-methyltryptophan (Vb) were converted to N-benzylidene-tryptophan methyl ester[9] (VIa) and its 1-methyl derivative[10] (VIb) respectively.



Va: R = H
Vb: R = Me



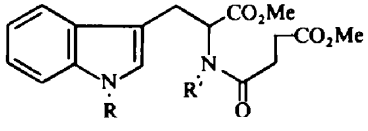
VIa: R = H
VIb: R = Me



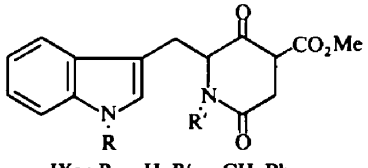
VIIa: R = H
VIIb: R = Me

Catalytic hydrogenation of the Schiff bases (VIa and VIb) over PtO_2 in MeOH afforded the corresponding N-benzyl derivatives (VIIa and VIIb) which were characterized in the form of their crystalline hydrochlorides. VIIa and VIIb were transformed to their dimethyl esters (VIIIa and VIIIb) by reaction with methyl 3-chloroformylpropionate under Schotten–Baumann conditions, whereas 1-methyltryptophan methyl ester furnished a secondary amide (VIIIc) by a similar reaction.

The Dieckmann condensation of the dimethyl esters (VIIIa, VIIIb and VIIIc) completed the carbon skeleton of ring D. The reaction conditions for the Dieckmann condensation have been varied according to substrates, i.e. a combination of sodium hydride-tetrahydrofuran,[11] sodium hydride-DMSO,[12] or sodium hydride-toluene-



VIIIa: R = H, R′ = CH_2Ph
VIIIb: R = Me, R′ = CH_2Ph
VIIIc: R = Me, R′ = H



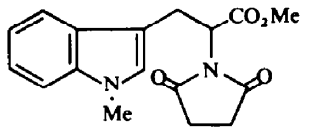
IXa: R = H, R′ = CH_2Ph
IXb: R = Me, R′ = CH_2Ph
IXc: R = Me, R′ = H

MeOH[10] may be used. In the condensation of the secondary amide (VIIIc), the action of sodium hydride in dioxan proved to be the most effective as shown in Table 1, but as the β-ketoester (IXc) and the imide (Xc) are both formed in this case,[13] the best yield of the former was 34·4%. The imide (Xc) was not isolated but its hydrolysis product (XIc) was obtained and gave VIIIc with diazomethane. Dioxan is a suitable solvent for VIIIb, and one molar equivalent of sodium hydride was sufficient to cause cyclization. The condensation of VIIIa was consistent with these results, and as imide formation is not possible with the tertiary amides (VIIIa and VIIIb), the β-ketoesters (IXa and IXb) were obtained in good yields.

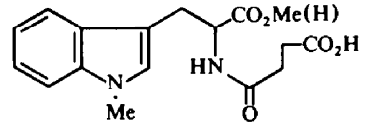
Conversion of the methyl β-ketoesters (IXa, IXb and IXc) to their benzyl derivatives (XIIa, XIIb and XIIc) was smoothly accomplished by treatment with hot benzyl alcohol in accord with the previous work.[11] Catalytic hydrogenation of the benzyl β-ketoesters (XIIb and XIIc) over Pd–C in ethanol was accompanied by spontaneous

TABLE 1. DIECKMANN CYCLIZATION OF DIMETHYL ESTERS (VIII)

s.m.	Base	Base mole	Solvent	Bath Temp	Time	Yield of IX
	NaH	2	Dioxan	105°	4 hr	34·4%
	NaH	1	Dioxan	45° 85°	1 hr 10 min	6·0
	t-BuOK	2	Dioxan	Reflux	6 hr	27·6
VIIIc	t-BuOK	3	Dioxan–Toluene	Reflux	12	12·7
	t-BuOK	2	THF	Reflux	13	6·1
	t-BuOK	2	t-BuOH	Reflux	2	8·0
	t-BuOK	2	DMSO	85°	1	trace
	NaH	2	Dioxan	105°	5 hr	68·8%
VIIIb	NaH	1	Dioxan	105°	5·5	79·3
	NaH	1·5	Toluene	Reflux	6·5	8·6
	NaH	2	Dioxan	105°	3·5 hr	83·9%
VIIIa	NaH	2	DMSO	Room temp	6	39
	LiH	2	Dioxan	105°	5	trace

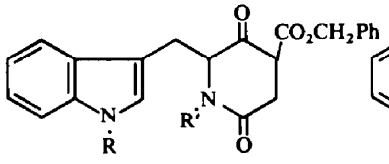


Xc

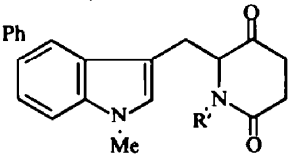


XIc

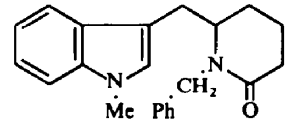
decarboxylation to give the ketones (XIIIb and XIIIc), the former of which on Huang–Minlon reduction gave the lactam (XIVb).



XIIa: R = H, R' = CH_2Ph
XIIb: R = Me, R' = CH_2Ph
XIIc: R = Me, R' = H



XIIIb: R' = CH_2Ph
XIIIc: R' = H



XIVb

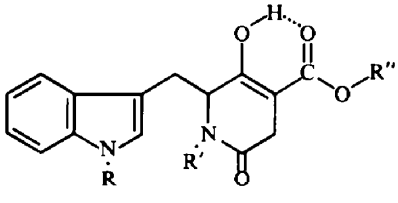
Structures of β-ketoesters. The β-ketoesters (IX and XII) appear to be mainly enolic, since they give an instantaneous and intense coloration (reddish-purple) with ferric chloride,[14] and show the CO stretching vibrations of the chelated enolic tautomers at 1670–1690 cm^{-1} in their IR spectra. The UV spectra show maxima at about 258 mμ (ε 9000) in addition to the usual indolic absorptions at about 220 mμ (ε 40,000) and 280–285 mμ (ε 6000). These characteristic spectral features[14] are shown in Table 2 in comparison with those of the reference compounds (XIIIb, XIIIc and XIVb). It is, therefore, concluded that the β-ketoesters possess the enol

TABLE 2. IR AND UV SPECTRA OF β-KETOESTERS (IX AND XII)

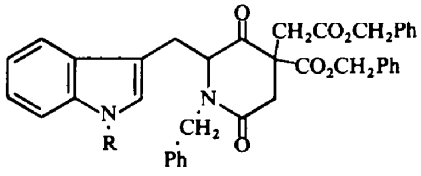
Compd	IR cm^{-1} in KBr	IR cm^{-1} in $CHCl_3$	UV mμ (ε × 10^{-3}) in 90% aqueous EtOH			
IXa	1690, 1640	1682, 1636	218 (42·0)	258 (8·93)	278 (7·21)*	289 (5·42)
IXb	1683, 1642	1681, 1636	222·5 (39·9)	258 (7·81)	286 (6·17)*	301 (3·72)*
IXc	1673, 1636	1666, 1637	222·5 (42·8)	260 (9·58)	287 (7·09)*	299 (5·05)*
XIIa	1679, 1643	1679, 1633	217 (41·8)	258 (10·0)	278 (7·31)*	289 (5·34)
XIIb	1684, 1632	1680, 1635	222 (39·7)	257 (8·83)	287 (6·14)*	302 (3·65)*
XIIc	1673, 1639	1662, 1631	223 (38·4)	258 (9·92)	287 (6·66)*	301 (3·96)*
XIIIb	1729, 1633	1734, 1646	221·5 (39·9)		287·5 (6·06)	
XIIIc	1736, 1676	1735, 1676	222·5 (38·8)		287·5 (6·25)	
XIVb	1632	1622	224 (32·6)		290 (5·16)	

* shoulder.

structures (XV) rather than the tautomeric ketoester structures (IX and XII) both in the solid state and in solution.



XV



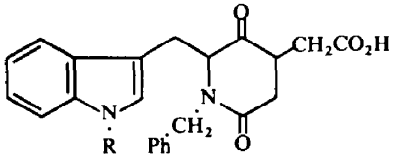
XVIa: R = H
XVIb: R = Me

Construction of the vobasine skeleton. Treatment of XIIa and XIIb with benzyl bromoacetate in acetone in the presence of potassium carbonate furnished the oily dibenzyl esters (XVIa and XVIb), which show a negative ferric chloride test and were found to be diastereoisomeric mixtures of possible C-alkylated products by TLC, spectral data, and reaction sequences. Alkylation in dioxan in the presence of sodium hydride or in xylene in the presence of potassium carbonate was not as effective as a combination of acetone and potassium carbonate as observed in the alkylation of 3,3′-bioxindoles.[15] Further work is required to explain this interesting observation.*

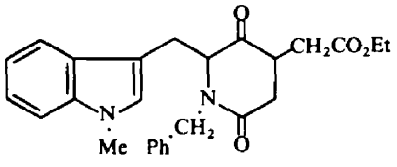
The oily dibenzyl esters (XVIa and XVIb) were subjected to catalytic debenzylation and subsequent decarboxylation over Pd–C in EtOH or tetrahydrofuran to give the required keto-carboxylic acids (XVIIa and XVIIb). It was not clear whether these compounds were diastereoisomeric mixtures although they were homogeneous in an extensive TLC investigation. When a mixture of EtOH and ethyl acetate was used as a solvent in the reduction of XVIb, the ethyl ester (XVIIIb) was obtained in addition to the desired XVIIb. The ester (XVIIIb) was easily hydrolysed with aqueous potassium hydroxide to give XVIIb. XVIIb was also obtained by the hydrolysis of

* The effects of solvent, halide, base and temperature on the alkylation of the ambident anion derived from ethyl acetoacetate have been investigated.[16]

XVIb with one molar equivalent of base, followed by hydrogenolysis and decarboxylation, but this route resulted in a lower yield than the direct catalytic debenzylation and decarboxylation of XVIb.

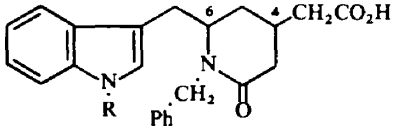


XVIIa: R = H
XVIIb: R = Me



XVIIIb

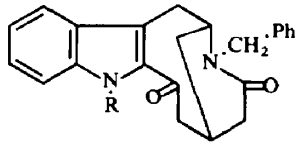
The Huang–Minlon reduction of the keto-carboxylic acid (XVIIa) furnished the carboxylic acid (XIXa) or a mixture of diastereoisomers. A similar reduction of XVIIb gave a mixture of XIXb-1 and XIXb-2 separable by fractional crystallization (Experimental). A diastereoisomeric relation of the products (XIXb-1 and XIXb-2) was evident by comparison of their similar but not identical IR and NMR spectra measured in DMSO solution. The NMR spectra of both compounds reveal the



XIXa: R = H
XIXb-1: R = Me (4,6-*cis*)
XIXb-2: R = Me (4,6-*trans*)

methylene protons of the N-benzyl group as an AB system with chemical shifts 4·71 and 5·53 τ (XIXb-1, J = 14 c/s) and 4·79 and 5·73 τ (XIXb-2, J = 15 c/s). This marked magnetic nonequivalence of benzylic protons suggests the restricted rotation around the methylene C—N bond of the N-benzyl group. A similar phenomenon has been observed in a number of N-benzyl lactams.[17]

As polyphosphoric acid (PPA) is an effective cyclizing agent in the synthesis of cycloalkan[b]indolones from 3-indolealkanoic acids,[18] treatment of the carboxylic acids (XIXa and XIXb-1) with PPA yielded the tetracyclic keto-lactams (XXa and XXb). XXa on methylation[19] afforded XXb. The first evidence of the desired tetracyclic compounds (XXa and XXb) was provided by the UV spectra which show maxima at about 236 and 316 mμ (ε ≥ 10,000) in agreement with those of 2-acylindoles.[1,3,18] The IR spectra exhibit broad peaks at 1620–1630 cm^{-1} attributable to the additive lactam carbonyl and the 2-acylindole moiety, the latter being considered a vinylogous amide.[1] The NMR spectra show that both compounds lack a



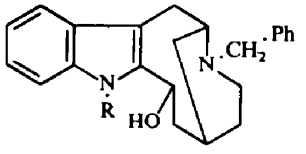
XXa: R = H
XXb: R = Me

peak ascribable to an indolic α-proton,[18] and the lowfield shift of the N–Me group of XXb (5·87 τ) is due to the CO group at the indolic α-position.[1] The methylene protons of the N-benzyl group of XXa and XXb are similar to the AB system of the

carboxylic acids (XIXb-1 and XIXb-2). Finally the mass spectra confirm these conclusions.*

Treatment of the carboxylic acid (XIXb-2) with PPA yielded a compound, m.p. >290°, together with recovered starting material. Although the structure of the product has not been elucidated and it may be impossible to decide the configuration of XIXb-1 and XIXb-2, the reaction with PPA suggests that XIXb-1 is the 4,6-cis isomer which could be cyclized to the 8-membered ring compound.

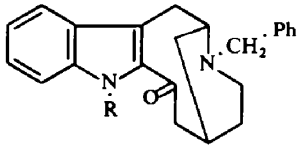
The action of LAH in refluxing tetrahydrofuran proved efficient in the simultaneous reduction of both the lactam and ketone functions in XXa and XXb. The reduction products, which were probably mixtures of stereoisomers, were the expected amino-alcohols (XXIa and XXIb) as shown by strong new peaks at about 1070 cm^{-1} (ν_{C-O}) and the almost complete disappearance of the CO absorptions in the IR. The OH absorptions were not clearly assignable. The UV spectra show the presence of a typical, non conjugated 2,3-dialkyl substituted indole chromophore.



XXIa: R = H
XXIb: R = Me

Borohydride reduction of vobasine (I) and perivine (II), both of which have a methoxycarbonyl group at C-16, was reported[4,6] to give 3β-hydroxy compounds because of the attack of borohydride ion from the sterically less crowded side of each molecule. Both XXa and XXb lack a substituent at the position corresponding to above C-16, and although it was not clear which hydroxy compound was predominantly produced by LAH reduction, the asymmetry introduced at this point was eliminated during the next stage.

Mild oxidation of the amino-alcohols (XXIa and XXIb) with chromium trioxide in pyridine[20] furnished the corresponding ketones (XXIIa and XXIIb) whose IR



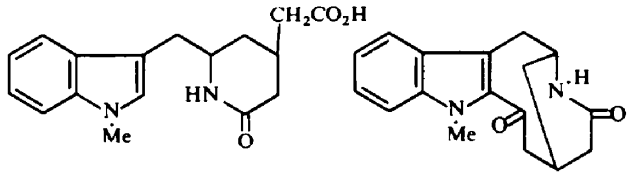
XXIIa: R = H
XXIIb: R = Me

and UV spectra are typical of 2-acylindoles.[1,3,18] The attempted catalytic debenzylation of XXIIa was unsuccessful, but XXIIb afforded a debenzylated product in low yield. Its structure will be discussed later.

Finally, debenzylation of XIXb-1 with sodium in liquid ammonia yielded the debenzylated carboxylic acid (XXIIIb) according to the procedure described by Sugasawa and Fujii[21] for N-benzyl lactams. Cyclization of XXIIIb to the tetracyclic keto-lactam (XXIVb) was effected with PPA. Reduction with LAH afforded the amino-alcohol (XXVb) which was subsequently oxidized with chromic acid to furnish the same compound as that obtained by debenzylation of XXIIb.

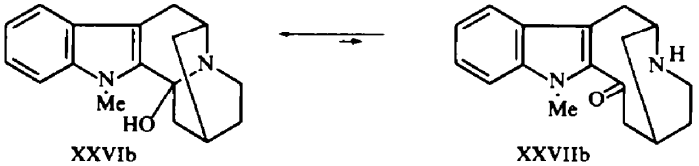
* The mass spectra of vobasine type compounds in this report will be discussed in the subsequent publication in this series. T. Shioiri, T. Nakashima, and S. Yamada, *Tetrahedron*, in press.

A portion of the work was presented before the 2nd *Symposium on the Mass Spectrometry of Organic Compounds* Abstracts p. 20. Tokyo, 24–25 November (1966).



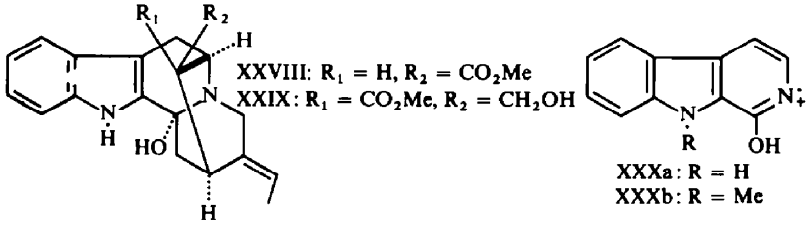
XXIIIb XXIVb XXVb

The IR spectrum (KBr) of this product shows no CO absorption and a weak OH band at 3555 cm^{-1}. In chloroform solution it has a weak CO absorption at 1643 cm^{-1}. The UV spectrum (90% EtOH aq) exhibits maxima at 227·5 (ε 31,800) and 285 mμ (ε 6770) with shoulders at 292 (ε 6450) and 316 mμ (ε 2490). This clearly displays an equilibrium between carbinolamine (XXVIb) and 2-acylindole (XXVIIb). On the assumption that the UV spectrum of the former corresponds to that of the



XXVIb XXVIIb

amino-alcohol (XXVb) and the spectrum of the latter to that of IV obtained below, it could be calculated that the compound consisted of 87% of the carbinolamine (XXVIb) and 13% of the 2-acylindole (XXVIIb) forms. This equilibrium was virtually unchanged in acid and several other solutions. Gorman *et al.*[6a] reported that perivine exists primarily in the 2-acylindole form (II) but epiperivine obtained by base treatment of perivine was the carbinolamine (XXVIII). Voacarpine, a minor alkaloid of *Voacanga chalotiana* Pierre ex Stapf, was also shown by Martin *et al.*[22] to have mainly the carbinolamine structure (XXIX). The above spectral data indicate that



XXVIII: R_1 = H, R_2 = CO_2Me
XXIX: R_1 = CO_2Me, R_2 = CH_2OH

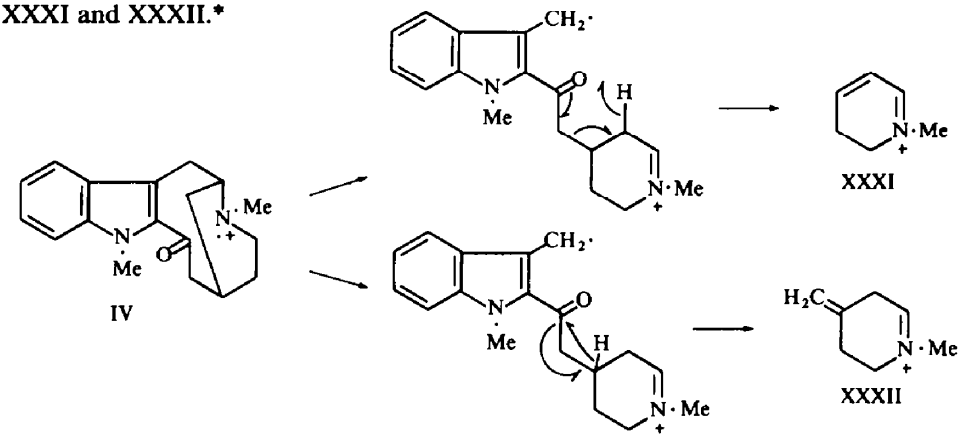
XXXa: R = H
XXXb: R = Me

our product is almost entirely in the carbinolamine form (XXVIb) in the solid state but in solution 2-acylindole (XXVIIb) exists in equilibrium with carbinolamine (XXVIb). This was verified by the similarity of the mass spectral fragmentation patterns between our product and voacarpine (XXIX), both showing strong M-17 (OH) peaks and the β-carbolinium ions (XXXa from XXIX and XXXb from XXVIb).*

Now only one carbon atom at N_b was required to complete the synthesis of the vobasine skeleton. Treatment of carbinolamine (XXVIb) with a mixture of formic acid and formalin yielded the desired compound (IV). Its IR spectrum, which exhibits a single CO at 1642 cm^{-1} in chloroform, as well as the UV spectrum in 90% EtOH aq

* See footnote * on page 4162.

(239, 316 mμ; ε 16,100, 18,700) confirm the structure, 1-methyl-16-demethoxycarbonyl-20-desethylidenevobasine (IV). No transannular interaction between N_b and the CO group[23] analogously to vobasine[4] (I) has been observed even in acidic solution. The mass spectrum of IV provides further support for the proposed structure and its fragmentation pattern bears significant similarities to that of vobasine[4,24] as shown below. Two peaks at *m/e* 96 (base peak) and 110 are attributed to the ions XXXI and XXXII.*



The completion of this synthetic sequence will provide a method for the total synthesis of vobasine (I) and related 2-acylindole alkaloids.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were measured on a JASCO-DS-301 or -402G spectrophotometer in KBr discs unless otherwise stated; UV spectra on a Cary Model 11 spectrophotometer in 90% EtOH aq unless otherwise stated, and NMR spectra on a Varian HR-100 instrument at 100 Mc and given in the τ scale with reference to TMS as the internal standard. Solvents used for extraction were dried over anhyd. Na_2SO_4 after extraction, and removed under reduced pressure. Specimens for analysis were dried over P_2O_5 at 5 mm Hg. Experiments about compounds of indole-N methyl series are described as typical examples.

N-Benzylidene-1-methyltryptophan methyl ester (VIb)

Benzaldehyde (146 g, 1·4 mole) was added to 1-methyltryptophan methyl ester[8] (295 g, 1·3 mole) in abs benzene (500 ml). The reaction mixture became hot and turbid. After removal of the separated water the solvent was evaporated. Addition of benzene (3 × 300 ml) followed by vacuum evaporation quantitatively afforded the Schiff base VIb as a yellow viscous oil;[10] ν_{max}^{cap} cm^{-1} 1740 (CO_2Me), 1640 (C=N), 738, 692 (benzene).

N-Benzylidenetryptophan methyl ester (VIa)

The condensation of tryptophan methyl ester[25] (33 g, 0·15 mole) with benzaldehyde (18 g, 0·17 mole) was carried out as above in benzene to give a colorless solid (43·7 g, 95·2%). Recrystallization from MeOH afforded colorless small needles, m.p. 128–129° (lit. 129°,[9a] 132–133°[9b]). ν_{max}^{Nujol} cm^{-1} 1740 (CO_2Me), 1635 (C=N), 746, 690 (benzene).

N-Benzyl-1-methyltryptophan methyl ester (VIIb)

The base VIb (50·9 g) in MeOH (150 ml) was hydrogenated over PtO_2 (0·24 g) at room temp and atm press; the reaction ceased after 6 hr (H_2 uptake a slight excess of one molar equiv). Filtration and evaporation of the filtrate gave a slightly yellow viscous oil[10] (51·6 g, quantitative); ν_{max}^{cap} cm^{-1} 1740 (CO_2Me), 738, 698 (benzene).

* See footnote on page 4162

The hydrochloride, obtained by treatment of the base with 10 w/v % MeOH–HCl, was recrystallized from MeOH; colorless small needles, m.p. 232–233° (dec) (lit. 232° (dec)[10]). (Found: C, 66·96; H, 6·35; N, 7·78. Calc. for $C_{20}H_{22}O_2N_2 \cdot HCl$: C, 66·93; H, 6·46; N, 7·81%); ν_{max} cm^{-1} 2800–2300 (NH_2^+), 1743 (CO_2Me), 742, 735, 694 (benzene).

N-*Benzyltryptophan methyl ester* (VIIa)

The ester VIIa was obtained quantitatively from VIa as above in the form of a slightly yellow viscous oil.[9b]

The hydrochloride was recrystallized from benzene–MeOH (10:1) to colorless small pillars, m.p. 188° (dec). (Found: C, 65·89; H, 6·22; N, 8·30. $C_{19}H_{20}O_2N_2 \cdot HCl$ requires: C, 66·18; H, 6·14; N, 8·12%); ν_{max} cm^{-1} 3400 (ind. NH), 1749 (CO_2Me), 752, 740, 694 (benzene).

N-*Benzyl*-N-(3-*methoxycarbonylpropionyl*)-1-*methyltryptophan methyl ester* (VIIIb)

A soln of methyl 3-chloroformylpropionate[26] (241 g, 1·6 mole) in abs benzene (0·5 l.) was added dropwise to a stirred mixture of VIIb (409·4 g, 1·27 mole), benzene (2 l.), and 15 w/v %. K_2CO_3 aq (1·5 l., 1·63 mole) at 6–10° (internal temp) during 0·5 hr. The reaction mixture was allowed to warm to room temp and after the addition of 30 w/v % K_2CO_3 aq (100 ml, 0·22 mole), the mixture was stirred at room temp for 3·5 hr. Further addition of 30 w/v % K_2CO_3 aq (146 ml, 0·32 mole) was followed by the addition of methyl 3-chloroformylpropionate[26] (45 g, 0·3 mole) and the mixture was stirred at room temp for 1 hr. The benzene layer was washed successively with 10% HCl aq, water and sat NaCl aq. Drying and evaporation of the solvent gave a yellowish brown oil.[10] (539 g, 97·3%); ν_{max}^{cap} cm^{-1} 1740 (CO_2Me), 1655 (CON$\langle$), 745, 700 (benzene).

N-*Benzyl*-N-(3-*methoxycarbonylpropionyl*)*tryptophan methyl ester* (VIIIa)

This was produced in a yield of 94·8%. For analysis a sample was recrystallized 3 times from benzene–n-hexane (1:1) to give colorless crystals, m.p. 135–135·5°. (Found: C, 68·48; H, 6·11; N, 6·77. $C_{24}H_{26}O_5N_2$ requires: C, 68·23; H, 6·20; N, 6·63%); ν_{max} cm^{-1} 3380 (ind. NH), 1741 (CO_2Me), 1635 (CON$\langle$), 740, 690 (benzene); λ_{max} mμ (ε) 220·5 (37,300), 283·5 (5750), 291·5 (5070).

N-(3-*Methoxycarbonylpropionyl*)-1-*methyltryptophan methyl ester* (VIIIc)

1-Methyltryptophan methyl ester (160·5g, 0·69 mole) was allowed to react with methyl 3-chloroformylpropionate[26] (114 g, 0·76 mole) as above. In this case 7 w/v % K_2CO_3 aq (2050 ml, 1·04 mole) and Et_2O (3000 ml) were used. The product VIIIc crystallized out during the reaction and was filtered off, washed with MeOH–Et_2O, and dried giving 191 g of colorless crystals, m.p. 100–103°. The Et_2O layer was washed with 10% HCl aq and water, and combined with the above washings. Drying and evaporation gave 16·5 g of colorless crystals, m.p. 96–99°, total yield 209·5 g (87·7%). Two recrystallizations from benzene gave colorless needles, m.p. 103·5–104·5°. (Found: C, 62·79; H, 6·67; N, 8·15. $C_{18}H_{22}O_5N_2$ requires: C, 62·41; H, 6·40; N, 8·09%); ν_{max} cm^{-1} 3358 (NH), 1737 (CO_2Me), 1638 (Amide I), 1535 (Amide II), 730 (benzene).

1-Methyltryptophan methyl ester was recovered from 10% HCl aq layer as its hydrochloride (6·9 g).

N-(3-*Carboxypropionyl*)-1-*methyltryptophan*. The ester VIIIc (1·04 g, 3 mmole) was dissolved in a mixture of 20 w/v % EtOH–KOH (0·39 g, 6 mmole) and water (0·39 ml) with slight warming. The reaction mixture was allowed to stand at room temp for 24 hr. After evaporation of EtOH, the mixture was acidified with conc HCl aq and extracted with AcOEt. The AcOEt layer was washed with water and sat NaCl aq, dried and evaporated to give slightly yellowish white solid (0·87 g, 90·5%), m.p. 163–166°. Recrystallization from Me_2CO afforded colorless needles, m.p. 165–166°. (Found: C, 60·20; H, 5·78; N, 8·92. $C_{16}H_{18}O_5N_2$ requires: C, 60·37; H, 5·70; N, 8·80%); ν_{max} cm^{-1} 3340 (NH), 1734, 1725 (CO_2H), 1631 (Amide I), 1545 (Amide II), 739 (benzene).

The dicarboxylic acid was easily reconverted to VIIIc with excess diazomethane in MeOH–Et_2O.

Dieckmann cyclization of dimethyl esters (VIII)

See Table 1 for the various conditions employed. Typical condensations are described below.

Methyl 1-*benzyl*-6-[(1-*methyl*-3-*indolyl*)*methyl*]*piperidine*-2,5-*dione*-4-*carboxylate* (IXb). A suspension of NaH (obtained from 6·2 g (0·13 mole) of a 50% oil dispersion by washing with abs benzene and dioxan) in abs dioxan (50 ml) was added to a soln of VIIIb (48·3 g, 0·11 mole) in abs dioxan (100 ml) stirred under N_2. The mixture was heated at 100–110° (bath temp) for 5·5 hr. (Since the condensation was started vigor-

ously at about 50° in the case of use of large quantities of starting material, the reaction was carried out without external heating, and at 100–110° after the initial reaction subsided.) After removal of the solvent the residue was treated with water (70 ml), AcOEt (30 ml) and benzene (10 ml). The cold aqueous layer was adjusted to pH 8·5 by the addition of conc HCl aq to give the slightly yellow ppts (26·5 g), m.p. 152–154°. The filtrate was extracted with AcOEt. The AcOEt layer was combined with above AcOEt–benzene layer, dried and evaporated to give an oil (8·8 g) which was solidified by the tritulation with Me_2CO, total yield 35·3 g (79·3%). Two recrystallizations from benzene–n-hexane (1:1) gave colorless prisms, m.p. 153–154·5°. (Found: C, 71·26; H, 5·83; N, 7·02. $C_{24}H_{24}O_4N_2$ requires: C, 71·27; H, 5·98; N, 6·93%).

Methyl 1-Benzyl-6-(3-indolylmethyl)piperidine-2,5-dione-4-carboxylate (IXa). The condensation was carried out as above using a mixture of VIIIa (93 g, 0·22 mole), a 50% NaH oil dispersion (24 g, 0·50 mole) and abs dioxan (800 ml). After evaporation of the dioxan the residue was dissolved in water (300 ml), and the aqueous layer was acidified with conc HCl aq (90 ml) under ice-cooling, and extracted with AcOEt (200 ml, 3 × 100 ml). The AcOEt layer was washed successively with water, sat $NaHCO_3$ aq, water, and sat NaCl aq. Drying and evaporation gave the solid residue which was washed with Et_2O (200 ml) to afford white crystals (72 g, 83·9%), m.p. 141–143°. Three recrystallizations from benzene–n-hexane (1:1) gave colorless prisms, m.p. 144–145°. (Found: C, 70·59; H, 5·57; N, 7·19. $C_{23}H_{22}O_4N_2$ requires: C, 70·75; H, 5·68; N, 7·18%).

Methyl 6-[(1-methyl-3-indolyl)methyl]piperidine-2,5-dione-4-carboxylate (IXc). The ester VIIIc (52 g, 0·15 mole) was allowed to react with a 50% NaH oil dispersion (16 g, 0·33 mole) in abs dioxan (400 ml), and the reaction mixture was treated as above. From the AcOEt layer, the product IXc (16·25 g, 34·4%) was obtained, m.p. 140–141°. An analytical sample recrystallized from benzene and benzene–n-hexane in the form of colorless prisms had m.p. 148–150°. (Found: C, 65·16; H, 5·90; N, 9·08. $C_{17}H_{18}O_4N_2$ requires: C, 64·95; H, 5·77; N, 8·90%).

When the above analytical sample was kept in a KOH–$CaCl_2$ desiccator at room temp for a month, it showed slight changes in the IR spectrum in nujol (for example, ν_{max} in the CO region, 1673 and 1636 cm^{-1} → 1680, 1655 and 1640 cm^{-1}). However, its m.p. and IR spectrum in $CHCl_3$ remained unchanged. A sample recrystallized again from benzene had the same m.p. and IR spectrum in the solid state. This fact revealed their dimorphic relation.

On the other hand, the $NaHCO_3$ aq layer was acidified with conc HCl aq and extracted with AcOEt. Washing the extract with water, drying, followed by evaporation afforded a reddish brown amorphous substance XIc (35 g), whose IR spectrum resembled that of the dicarboxylic acid obtained from VIIIc. Esterification of the amorphous substance with diazomethane furnished VIIIc.

Benzyl esterification of methyl β-ketoesters (IX)

Benzyl 1-benzyl-6-[(1-methyl-3-indolyl)methyl]piperidine-2,5-dione-4-carboxylate (XIIb). The ester IXb (4·04 g, 0·01 mole) in benzyl alcohol (5·4 ml, 0·05 mole) was heated in an oil bath at about 170° for 6 hr, while MeOH produced was subjected to distillation in a stream of N_2. Evaporation of benzyl alcohol furnished a reddish brown viscous oil, which was dissolved in Me_2CO while hot, followed by the addition of Et_2O to yield colorless crystals. Filtration and washing with Et_2O gave 4·45 g (92·7%) of XIIb, m.p. 109–114°. Two recrystallizations from benzene–n-hexane (2:3) afforded colorless needles, m.p. 119–120°. (Found: C, 75·05; H, 5·84; N, 6·01. $C_{30}H_{28}O_4N_2$ requires: C, 74·98; H, 5·87; N, 5·83%).

Benzyl 1-benzyl-6-(3-indolylmethyl)piperidine-2,5-dione-4-carboxylate (XIIa). The ester IXa was treated as above, yield 93%. For analysis the crude product was recrystallized from benzene–n-hexane (1:1): colorless needles, m.p. 160–162°. (Found: C, 74·62; H, 5·56; N, 6·14. $C_{29}H_{26}O_4N_2$ requires: C, 74·66; H, 5·62; N, 6·01%).

Benzyl 6-[(1-methyl-3-indolyl)methyl]piperidine-2,5-dione-4-carboxylate (XIIc). The ester XIIc was obtained from IXc in nearly quantitative yield, and crystallized twice from Me_2CO to yield colorless needles, m.p. 136–137·5°. (Found: C, 70·96; H, 5·80; N, 7·41. $C_{23}H_{22}O_4N_2$ requires: C, 70·75; H, 5·68; N, 7·18%).

Catalytic debenzylation and decarboxylation of benzyl β-ketoesters (XII)

1-Benzyl-6-[(1-methyl-3-indolyl)methyl]piperidine-2,5-dione (XIIIb). The ester XIIb (4·8 g) in AcOEt soln (50 ml) was hydrogenated over 10% Pd–C[27] (1·6 g) at room temp and atm press for 2 hr. A slurry of 30% Pd–C[27] (0·5 g) in AcOEt (20 ml) was added to the reaction mixture, which was hydrogenated for 1·5 hr to absorb 80% of the calculated amount of H_2. The catalyst was filtered and washed with benzene. The combined filtrates were evaporated to give a slightly yellow foam (2·9 g, 83·8%) which crystallized by the addition of Me_2CO, m.p. 101–103°. After 3 recrystallizations from benzene–n-hexane (1:5) the colorless

small needles had m.p. 115–116°. (Found: C, 76·45; H, 6·63; N, 7·86. $C_{22}H_{22}O_2N_2$ requires: C, 76·27; H, 6·40; N, 8·09%).

6-[(1-*Methyl*-3-*indolyl*)*methyl*]*piperidine*-2,5-*dione* (XIIIc). The ester XIIc in EtOH was hydrogenated as above to give XIIIc in 94% yield. Recrystallization from benzene–n-hexane afforded colorless small needles, m.p. 118·5–119·5°. (Found: C, 70·25; H, 6·15; N, 11·05. $C_{15}H_{16}O_2N_2$ requires: C, 70·29; H, 6·29; N, 10·93%).

1-*Benzyl*-6-[(1-*methyl*-3-*indolyl*)*methyl*]*piperid*-2-*one* (XIVb). A mixture of XIIIb (1·04 g), triethylene glycol (68 ml), hydrazine dihydrochloride (2·52 g) and 80% aqueous hydrazine hydrate (12·4 g) was stirred at 130° (internal temp) for 2·5 hr. After the addition of KOH (4·36 g), the internal temp was raised to 210° during 1 hr while removing low boiling materials, and kept there for 2·5 hr.[28] After dilution with water (68 ml) the reaction mixture was extracted with Et_2O (250 ml), and the extract was washed successively with water, 2% HCl aq, water and sat NaCl aq. Drying and evaporation gave a slightly yellow oil (0·54 g, 54%) which crystallized with Me_2CO. Two recrystallizations from benzene–n-hexane (1:5) yielded colorless small needles, m.p. 117–118°. (Found: C, 79·39; H, 7·16; N, 8·44. $C_{22}H_{24}ON_2$ requires: C, 79·48; H, 7·28; N, 8·43%).

Alkylation of benzyl β-ketoesters (XII)

Benzyl bromoacetate. A mixture of bromoacetic acid (50 g, 0·36 mole) and benzyl alcohol (43 ml, 0·40 mole) in benzene (50 ml) containing *p*-TsOH (0·4 g) was refluxed for 8 hr while removing water separated with a Cope's apparatus. The mixture was washed with sat $NaHCO_3$ aq and sat NaCl aq, and dried. Evaporation of the benzene gave an oily residue which was distilled at 136–137°/11 mm Hg (lit.[29] b.p.[10] 143°) to afford colorless benzyl bromoacetate (70·2 g, 85·2%), n_D^{24} 1·541.

Benzyl 1-*benzyl*-4-*benzyloxycarbonyl*-6-[(1-*methyl*-3-*indolyl*)*methyl*]*piperidine*-2,5-*dione*-4-*acetate* (XVIb). A stirred mixture of XIIb (33 g, 0·069 mole), benzyl bromoacetate (19 g, 0·083 mole) and powdered dry K_2CO_3 (20 g, 0·14 mole) in Me_2CO (150 ml) was refluxed for 7 hr. The inorganic materials were filtered and washed with hot Me_2CO and benzene. Evaporation of the combined filtrates gave an oily residue which was dissolved in benzene, and washed with water and sat NaCl aq. Drying and evaporation left a yellow viscous oil (43 g, quantitative), showing a negative $FeCl_3$ test; ν_{max}^{cap} cm^{-1} 1740 (CO), 1675 (CON$\langle$), 745, 700 (benzene). λ_{max} 285 mμ, λ_{min} 246 mμ. Two spots (R_f 0·55, 0·43) were detected on a TLC plate (Merck silica gel GF_{254}, benzene–EtOH (20:1)).* The mixture was used directly for the next step.

Benzyl 1-*benzyl*-4-*benzyloxycarbonyl*-6-(3-*indolylmethyl*)-*piperidine*-2,5-*dione*-4-*acetate* (XVIa). The ester XIIa was converted quantitatively to XVIa as above in the form of a yellow viscous oil, showing a negative $FeCl_3$ test; ν_{max}^{cap} cm^{-1} 3430, 3320 (ind. NH), 1740 (CO), 1665 (CON$\langle$), 750, 700 (benzene); λ_{max} 280, 289 mμ, λ_{min} 241 mμ.

Catalytic debenzylation and decarboxylation of dibenzyl esters (XVI)

1-*Benzyl*-6-[(1-*methyl*-3-*indolyl*)*methyl*]*piperidine*-2,5-*dione*-4-*acetic acid* (XVIIb). (i) *in THF*. The ester XVIb (96 g) in THF (700 ml) was hydrogenated over 5% Pd–C† (14·7 g) at room temp and atm press for 7 hr. A slight excess of the calculated amount (two mole equivs) of H_2 was absorbed. The catalyst was filtered and washed with THF. The combined filtrates were evaporated to the residue, which was tritulated with Me_2CO–Et_2O (1:2, 50 ml). The crystals (51 g, 82·5%) was filtered off, washed with a small amount of Me_2CO–Et_2O (1:2), and recrystallized twice from MeOH to afford colorless prisms, m.p. 186–188°. (Found: C, 71·37; H, 6·16; N, 7·05. $C_{24}H_{24}O_4N_2$ requires: C, 71·27; H, 5·98; N, 6·93%); ν_{max} cm^{-1} 1724 (CO), 1617 (CON$\langle$), 745, 711 (benzene). λ_{max} mμ (ε) 222 (37,100), 287 (6850).

(ii) *in* EtOH–AcOEt. A suspension of XVIb (37 g) and 30% Pd–C[30] (7 g) in EtOH (280 ml) and AcOEt (20 ml) was hydrogenated at 40° and atm press for 5 hr. To the reaction mixture was added a slurry of

* M. Yui in our laboratory separated one epimer (R_f 0·55) as crystals by allowing the oily mixture to stand and treating with EtOH and AcOEt. Recrystallizations from toluene–n-hexane (3:2) gave colorless pillars, m.p. 118–119°. (Found: C, 74·56; H, 5·81; N, 4·43. $C_{39}H_{36}O_6N_2$ requires: C, 74·50; H, 5·77; N, 4·46%). ν_{max} cm^{-1} 1746, 1733 (CO), 1663 (CON$\langle$), 738, 696 (benzene). ν_{max}^{Chlf} cm^{-1} 1740 (CO), 1657 (CON$\langle$); λ_{max} 286 mμ (ε 6190), λ_{min} 248 mμ (ε 3470). Catalytic debenzylation and decarboxylation of this isomer afforded the same acid XVIIb as that obtained from the oily diastereoisomeric mixture.

† Purchased from Japan–Engelhard Co. Ltd.

10% Pd–C[27] (1·9 g) in AcOEt (15 ml), and the catalytic hydrogenation was carried out at 40° for 6 hr to absorb 90% of the calculated amount of H_2. Filtration, washing the catalyst, and evaporation of the filtrates afforded a mixture of oil and foam which crystallized by the addition of Me_2CO and was washed with Me_2CO (5 ml)–EtOH (15 ml)–Et_2O (180 ml) to give colorless crystals (4·85 g). After evaporation of the mother liquor the residue was dissolved in benzene–AcOEt and extracted with sat $NaHCO_3$ aq. The $NaHCO_3$ layer was acidified and extracted with benzene–AcOEt. Drying and evaporation of the extract gave a foam which on trituration with Me_2CO yielded colorless crystals (2·98 g), total yield of XVIIb was 7·83 g, 33%.

On the other hand, after extraction with $NaHCO_3$ aq the benzene–AcOEt layer was washed with water, dried and evaporated to give colorless crystals (3·08 g), m.p. 136–140°. Two recrystallizations from benzene–n-hexane (2:3) afforded colorless small pillars, m.p. 141–142°. Its structure was determined as the corresponding ethyl ester XVIIIb from analytical and spectral data. (Found: C, 72·42; H, 6·60; N, 6·48. $C_{26}H_{28}O_4N_2$ requires: C, 72·20; H, 6·53; N, 6·48%); ν_{max} cm^{-1} 1737 (CO_2Et), 1725 (C=O), 1665 (CON<), 750, 699 (benzene). λ_{max} mμ (ε) 221 (37,300), 287·5 (5750).

When the catalytic reduction was carried out with 5% Pd–C* in the same solvent system, H_2 uptake (two mole equiv) was observed at room temp and atm press. However, a small amount of XVIIIb was produced and the yield of XVIIb was low.

(iii) *Hydrolysis of ethyl ester* (XVIIIb). The ester XVIIIb (2·65 g, 6·13 mmole) in dioxan (10 ml) was allowed to react with a soln of 85% KOH (0·44 g, 6·74 mmole) in water (3 ml) at room temp for 24 hr. Most of the solvent was removed, the remaining foam was dissolved with water, and the soln was washed with a mixture of benzene and AcOEt. The acidified aqueous layer was extracted with benzene–AcOEt. The organic layer was washed with water, dried and evaporated to give XVIIb (2·1 g, 85%), m.p. 175–177°.

(iv) *Hydrolysis and catalytic debenzylation.* The ester XVIb (3·5 g, 5·6 mmole) was heated under gentle reflux for 4·5 hr with a soln of 85% KOH (0·39 g, 5·9 mmole) in water (2 ml). After 24 hr standing work-up as above (iii) gave a foam (2·1 g), which was hydrogenated in EtOH (30 ml) at 50° and atm press in the presence of 30% Pd–C[30] (0·5 g). During 3 hr a slight excess of one mole equiv of H_2 was absorbed. The catalyst was removed and washed with EtOH, the filtrate was distilled off, and the residue (1·7 g) was crystallized from Me_2CO–Et_2O to give XVIIb (0·5 g, 21% from XVIb), m.p. 176–182°.

1-*Benzyl*-6-(3-*indolylmethyl*)*piperidine*-2,5-*dione*-4-*acetic acid* (XVIIa). The ester XVIa (90 g, 0·146 mole) in EtOH (500 ml) was hydrogenated over 30% Pd–C[27] (15 g) at room temp and atm press for 2·5 hr and then at 40° for 4·5 hr. After addition of 30% Pd–C[27] (4 g) in EtOH (50 ml), the reduction was carried out at room temp for 3 hr and again at 40° for 2·5 hr. H_2 uptake was slightly less than that of the calculated amount. Conventional work-up afforded colorless crystals (52 g, 91%), which was washed with EtOH–Et_2O and Et_2O, and recrystallized twice from Me_2CO to give colorless prisms, m.p. 212–213° (dec). (Found: C, 70·61; H, 5·61; N, 7·30. $C_{23}H_{22}O_4N_2$ requires: C, 70·75; H, 5·68; N, 7·18%); ν_{max} cm^{-1} 3340 (ind. NH), 1731 (C=O), 1714 (CO_2H), 1605 (CON<), 733, 699 (benzene). λ_{max} mμ (ε) 217·5 (41,300), 281 (6200), 290 (5120).

Huang–Minlon reduction of keto-carboxylic acids (XVII)

1-*Benzyl*-6-[(1-*methyl*-3-*indolyl*)*methyl*]-2-*piperidone*-4-*acetic acids* (XIXb-1 and XIXb-2). A soln of XVIIb (101 g), 80% aqueous hydrazine hydrate (500 ml), and 85% KOH (70 g) in triethylene glycol (2500 ml) was stirred at 130° (internal temp) for 1 hr. The internal temp was raised to 190° during 1 hr while water and excess hydrazine were removed. Heating was continued at 190–200° for 1 hr. The cooled reaction mixture was made up to 10 l. by dilution with water and acidification with conc HCl aq (350 ml). After chilling in a refrigerator overnight, the ppts were collected, washed with water (5 l.) and dried. The half-dried product (315 g) was washed with Me_2CO (300 ml)–Et_2O (200 ml) and Me_2CO (50 ml)–Et_2O (50 ml) to give 51 g of solid, which was extracted with hot MeOH (300 and 200 ml) to leave 26 g of solid (A), m.p. 224–229°. The MeOH extracts on standing gave 0·7 g of crystals (B), m.p. 228–229°. The identity of A and B (XIXb-2) was confirmed by their IR comparison. Total yield of XIXb-2 was 26·7 g (27·4%). For analysis a sample was recrystallized 3 times from MeOH: colorless small needles, m.p. 233–234°. (Found: C, 73·73; H, 6·67; N, 7·48. $C_{24}H_{26}O_3N_3$ requires: C, 73·82; H, 6·71; N, 7·18%); ν_{max} cm^{-1} 1719 (CO_2H), 1594,

* See footnote on page 4162

1584 (CON<), 733, 717, 693 (benzene); ν_{max}^{DMSO} cm^{-1} 1715 (CO_2H), 1631 (CON<), 785, 758 (benzene); λ_{max} mμ (ε) 224 (37,500), 289 (5990); NMR (DMSO) 6·28 (3H s, N·Me), 5·73, 4·78 (2H doublet-d, AB type J = 15 c/s, N·CH_2·Ph), 2·89 (1H, ind. α-H).

The MeOH extracts after collecting B was evaporated and the residue crystallized from Me_2CO to give 6 g of colorless crystals (C), m.p. 182–187°. On the other hand the first washings (Me_2CO–Et_2O soln) were evaporated to the residue which was washed with Me_2CO (3 × 50 ml) to yield 13·1 g of colorless solid (D), m.p. 182–188°. The IR spectra of C and D (XIXb-1) were indistinguishable. The total yield of XIXb-1 was 19·1 g (19·6%). For analysis a sample was recrystallized 3 times from MeOH: colorless prisms, m.p. 191–193°. (Found: C, 73·56; H, 6·85; N, 7·12. $C_{24}H_{26}O_3N_2$ requires: C, 73·82; H, 6·71; N, 7·18%); ν_{max} cm^{-1} 1720 (CO_2H), 1594 (CON<), 735, 705 (benzene); ν_{max}^{DMSO} cm^{-1} 1715 (CO_2H), 1632 (CON<), 782, 757 (benzene). λ_{max} mμ (ε) 223 (37,600), 288 (5740). NMR (DMSO) 6·28 (3H s, N·Me), 5·53, 4·71 (2H doublet–d, AB type J = 14 c/s, N·CH_2·Ph), 2·98 (1H s, ind. α-H).

1-*Benzyl*-6-(3-*indolylmethyl*)-2-*piperidone*-4-*acetic acid* (XIXa). The Huang–Minlon reduction of XVIIa gave XIXa in 49·1% yield. Successive recrystallizations from Me_2CO, EtOH and MeCN afforded colorless prisms, m.p. 225–227°. (Found: C, 73·16; H, 6·41; N, 7·85. $C_{23}H_{24}O_3N_2$ requires: C, 73·38; H, 6·43; N, 7·44%); ν_{max} cm^{-1} 3340 (ind. NH), 1695 (CO_2H), 1591, 1580 (CON<), 745, 721, 699 (benzene). λ_{max} mμ (ε) 220 (35,200), 282·5 (5260), 291 (4920).

6-[(1-*Methyl*-3-*indolyl*)*methyl*]-2-*piperidone*-4-*acetic acid* (XXIIIb).

(i) *Debenzylation of* XIXb-1. Metallic Na (2·5 g, 0·11 atom) was added with stirring in small pieces to XIXb-1 (15·6 g, 0·04 mole) in liquid NH_3 (4 l.) during 2 hr. After evaporation of NH_3, the white residue was dissolved in water (150 ml). The aqueous layer was washed with Et_2O and acidified with conc HCl aq (20 ml) to afford a gum which was solidified by the addition of AcOEt (50 ml). The pale brown solid was collected and washed with Me_2CO–Et_2O: yield 7·1 g, m.p. 161–163°. The washings were combined with the AcOEt soln and washed with water and sat NaCl aq. Evaporation of the dried soln yielded a foam, which was crystallized by the addition of Me_2CO and was washed with Me_2CO–Et_2O to give 2·95 g of pale brown solid, m.p. 159–161°, total yield of XXIIIb was 10·05 g.

(ii) *Hydrolysis of methyl ester of* XXIIIb. To the ester of XXIIIb (0·13 g, 0·41 mmole) obtained below in MeOH (3 ml) 85% KOH (0·05 g, 0·82 mmole) and water (1 ml) was added. The mixture was heated to obtain a soln and left at room temp for 3 hr. The residue on evaporation was dissolved in water (4 ml), acidified with 10% HCl aq (1 ml) and the white ppts were extracted with $CHCl_3$ containing a small amount of MeOH. The extract was washed with water, dried and evaporated to give a slightly yellow oil. Crystallization from a large amount of Me_2CO afforded colorless small prisms, which were dried over P_2O_5 at 90°/5 mm Hg for 3 days, m.p. 170–171°. (Found: C, 65·88; H, 6·70; N, 9·10. $C_{17}H_{20}O_3N_2 \cdot \frac{1}{2}H_2O$ requires: C, 66·00; H, 6·84; N, 9·06%); ν_{max} cm^{-1} 3265, 3180 (NH), 1731 (CO_2H), 1637 (CONH), 737 (benzene); λ_{max} mμ (ε) 224 (32,400), 288 (5080),

Methyl 6-[(1-*methyl*-3-*indolyl*)*methyl*]-2-*piperidone*-4-*acetate*

The acid XXIIIb (0·5 g) was dissolved in THF (10 ml) and MeOH (4 ml). A cold Et_2O soln (18 ml) of fresh diazomethane prepared from N-nitrosomethylurea (1·8 g)[31] was added at 5° during 10 min. After addition of Et_2O (12 ml), the reaction mixture was stirred at room temp. The crystals separated after 45 min. MeOH (3 ml) was added to dissolve the crystals, and stirring was continued at room temp for 3 hr. Excess diazomethane was destroyed with a few drops of AcOH, and the solvents were distilled off. The residual crystals were washed with Et_2O: 0·50 g (96%) of colorless crystals, m.p. 154–158°. Three recrystallizations from MeOH gave colorless fluffy needles, m.p. 165–166°. (Found: C, 68·68; H, 7·03; N, 8·96. $C_{18}H_{22}O_3N_2$ requires: C, 68·77; H, 7·05; N, 8·91%); ν_{max} cm^{-1} 3280, 3190 (NH), 1735 (CO_2Me), 1666 (NHCO), 741 (benzene); λ_{max} mμ (ε) 224 (38,200), 288 (6030).

PPA cyclization of lactam-carboxylic acids (XIX and XXIIIb)

3-*Benzyl*-9-*methyl*-1,2,3,4,5,6,7,8-*octahydro*-9H-2,6-*methanoazecino*[5,4-b]*indole*-4,8-*dione* (XXb). (i) *PPA cyclization of* XIXb-1. The acid XIXb-1 (2·0 g) was added to hot PPA (102 g), and the mixture was stirred vigorously at 100–110° (internal temp) for 30 min. Addition of the mixture to ice–water (500 ml) was followed by extraction with AcOEt (500 ml). The AcOEt extract was washed successively with 10%

K_2CO_3 aq (100 ml), sat $NaHCO_3$ aq (100 ml), water (50 ml) and sat NaCl aq (50 ml), dried and evaporated to leave a mixture of oil and foam, which was solidified by the addition of Me_2CO. Washing with Me_2CO–Et_2O afforded pale yellow crystals (0·94 g), m.p. 189–193·5°. From the washing another crop (0·14 g, m.p. 188–193°) was obtained, total yield: 1·08 g (56·8%). Recrystallizations from Me_2CO gave colorless prisms, m.p. 194–195°. (Found: C, 77·63; H, 6·71; N, 7·46. $C_{24}H_{24}O_2N_2$ requires: C, 77·39; H, 6·50; N, 7·52%); ν_{max} cm^{-1} 1623 (broad, C=O, CON<), 737, 700 (benzene); $\nu_{max}^{CHCl_3}$ cm^{-1} 1630 (broad, C=O, CON<). λ_{max} mμ (ε) 238 (16,100), 316 (19,600). NMR ($CDCl_3$) 5·87 (3H s, N·CH_3), 5·68, 4·44 (2H doublet–d, AB type J = 14·0 c/s, N·CH_2·Ph). Mass *m/e* 372 (M^+), 187, 186 (base peak), 91.

(ii) *Methylation of* XXa. To a stirred soln of XXa (9·4 mg) in Me_2CO (1 ml) was added 66 w/v % KOH aq (1·2 ml), followed by the dropwise addition of Me_2SO_4 (1·5 ml) during 10 min. After stirring at room temp for 20 min, the reaction mixture was diluted with water (20 ml) and extracted with AcOEt (50 ml). The AcOEt extract was washed successively with sat $NaHCO_3$ aq, water and sat NaCl aq, dried and evaporated leaving an oil which crystallized with Me_2CO to give 3·05 mg (32%) of colorless crystals, m.p. 180–185°. The product was indistinguishable with XXb obtained in (i) on TLC and IR spectra.

PPA cyclization of XIXb-2. The condensation of XIXb-2 (2·9 g) in PPA (150 g) was carried out as above to yield pale yellow crystals (0·40 g), m.p. >290°. Two recrystallizations from $CHCl_3$ afforded colorless crystals, m.p. >290°. (Found: C, 67·42; H, 5·64; N, 6·94%). ν_{max} cm^{-1} 1627 (broad), 751, 713 (benzene); λ_{max} mμ 256, 303, 347, unchanged in acid. From the alkaline layer 1·10 g of the starting material (XIXb-2) was recovered.

3-*Benzyl*-1,2,3,4,5,6,7,8-*octahydro*-9H-2,6-*methanoazecino*[5,4-b]*indole*-4,8-*dione* (XXa). PPA cyclization of XIXa afforded XXa in 11·4% yield. Recrystallizations from Me_2CO gave slightly yellow crystals, m.p. 240–242°. (Found: C, 76·76; H, 6·23; N, 7·61. $C_{23}H_{22}O_2N_2$ requires: C, 77·07; H, 6·19; N, 7·82%); ν_{max} cm^{-1} 3300 (ind. NH), 1621 (broad, C=O, CON<), 754, 702 (benzene); $\nu_{max}^{CHCl_3}$ cm^{-1} 3440 (ind. NH), 1633 (broad, C=O, CON<); λ_{max} mμ (ε) 235 (9800), 317 (14,900). NMR ($CDCl_3$) 5·66, 4·36 (2H doublet–d, AB type J = 14·6 c/s, N·CH_2·Ph). Mass *m/e* 358 (M^+), 172 (base peak), 91.

9-*Methyl*-1,2,3,4,5,6,7,8-*octahydro*-9H-2,6-*methanoazecino*[5,4-b]*indole*-4,8-*dione* (XXIVb). The acid XXIIIb (9·2 g) in PPA (500 g) was allowed to react as above. The reaction mixture was poured into ice–water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed successively with 10 w/v % K_2CO_3 aq, water and sat NaCl aq. Drying and evaporation yielded a mixture (5·4 g) of a foam and crystals, which was chromatographed on silicagel (180 g) (Kanto Kagaku Co. Ltd., 100–200 mesh). Elution with $CHCl_3$–Me_2CO (1:1) yielded a white solid (1·30 g, 15·4%), m.p. 269–271°. One recrystallization from Me_2CO gave colorless prisms, m.p. 269–270°. (Found: C, 72·20; H, 6·49; N, 10·22. $C_{17}H_{18}O_2N_2$ requires: C, 72·32; H, 6·43; N, 9·92%); ν_{max} cm^{-1} 3200 (NH), 1648 (NHCO), 1640 (C=O), 733 (benzene); λ_{max} mμ (ε) 238 (15,200), 314·5 (20,200).

LAH reduction of keto-lactams (XX and XXIVb)

3-*Benzyl*-9-*methyl*-1,2,3,4,5,6,7,8-*octahydro*-9H-2,6-*methanoazecino*[5.4-b]*indol*-8-*ol* (XXIb). To a soln of XXb (2·06 g) in abs THF (100 ml) was added LAH (1·0 g). The reaction mixture was stirred at reflux for 4 hr and cooled, the excess hydride was decomposed with THF (30 ml)–water (3 ml), and water (3 ml). The Al salts were filtered and washed with THF (70 ml), and the combined filtrates were dried and concentrated. The residue was washed with benzene–Et_2O and Et_2O to yield a colorless solid (1·19 g, 60·1%), m.p. 200–210°. Two recrystallizations from Me_2CO afforded colorless plates, m.p. 210–212° (dec). (Found: C, 79·95; H, 7·69; N, 7·74. $C_{24}H_{28}ON_2$ requires: C, 79·96; H, 7·83; N, 7·77%); ν_{max} cm^{-1} 1077 (C—O), 737, 701 (benzene). λ_{max} mμ (ε) 229 (34,850), 291 (7530); Mass *m/e* 360 (M^+), 342 (M^+—H_2O), 186 (base peak), 91).

3-*Benzyl*-1,2,3,4,5,6,7,8-*octahydro*-9H-2,6-*methanoazecino*[5,4-b]*indol*-8-*ol* (XXIa). The LAH reduction of XXa was carried out as above. The crude product (yield 96%) was solidified with Et_2O, m.p. 127–138°. Although repeated recrystallizations from Me_2CO gave colorless small needles, the m.p. did not become sharp and constant. So the crude product was used without purification for the next step; ν_{max} cm^{-1} ca. 3400 (broad, ind. NH, OH), 1071 (C—O), 735, 696 (benzene); λ_{max} mμ 222, 284, 292. Mass *m/e* 346 (M^+), 328 (M^+—H_2O), 172, 91 (base peak).

9-*Methyl*-1,2,3,4,5,6,7,8-*octahydro*-9H-2,6-*methanoazecino*[5,4-b]*indol*-8-*ol* (XXVb). The lactam XXIVb was reduced with LAH for 11 hr. The crude product (yield 64·5%) was crystallized from Me_2CO. Two more recrystallizations from Me_2CO afforded colorless prisms, m.p. 218–221°. (Found: C, 75·51; H, 8·08;

N, 10·39. $C_{17}H_{22}ON_2$ requires: C, 75·52; H, 8·20; N, 10·36%); ν_{max} cm^{-1} 3270 (NH, OH), 1071 (C—O), 740 (benzene); λ_{max} mμ (ε) 226·5 (34,700), 288 (7830). Mass *m/e* 270 (M^+), 252 ($M^+ - H_2O$), 175 (base peak), 82.

Chromic acid oxidation of amino-alcohols (XXI and XXVb)

3-*Benzyl*-9-*methyl*-1,2,3,4,5,6,7,8-*octahydro*-9H-2,6-*methanoazecino*[5,4-b]*indol*-8-*one* (XXIIb). To alcohol XXIb (0·72 g) in abs pyridine (20 ml) was added a slurry of CrO_3 (0·72 g) in abs pyridine (20 ml). The dark-colored reaction mixture was kept at room temp for 5 min with occasional shaking, poured into water (250 ml), and extracted with AcOEt (400 ml). The AcOEt layer was washed with water, sat NaCl aq, dried and evaporated. The solid brown residue (0·7 g, 97%) was washed with Me_2CO–Et_2O (1:1) and Me_2CO, and recrystallized twice from EtOH to give colorless needles, m.p. 166–168°. (Found: C, 80·07; H, 7·34; N, 7·67. $C_{24}H_{26}ON_2$ requires: C, 80·41; H, 7·31; N, 7·82%); ν_{max} cm^{-1} 1635 (C=O), 741, 734, 697 (benzene); λ_{max} mμ (ε) 241 (14,700), 317 (15,200). Mass *m/e* 358 (M^+), 172 (base peak), 91.

3-*Benzyl*-1,2,3,4,5,6,7,8-*octahydro*-9H-2,6-*methanoazecino*-[5,4-b]*indol*-8-*one* (XXIIa). The alcohol XXIa was oxidized with CrO_3 in pyridine to give XXIIa in 86·7% yield. For analysis a sample was recrystallized twice from EtOH to yield colorless small needles, m.p. 211–212°. (Found: C, 80·17; H, 7·11; N, 8·32. $C_{23}H_{24}ON_2$ requires: C, 80·20; H, 7·02; N, 8·13%); ν_{max} cm^{-1} 3300 (ind. NH), 1632 (C=O), 748, 731, 694 (benzene). λ_{max} mμ (ε) 237 (12,500), 318 (16,000); Mass *m/e* 344 (M^+), 172 (base peak), 91.

12-*Methyl*-1,2,3,4,6,7,12,12b-*octahydro*-2,6-*methanoindolo*[2,3-a]*quinolizin*-12b-*ol* (XXVIb)

(i) CrO_3 *Oxidation of* XXVb. The amine XXVIb was obtained from XXVb by CrO_3 oxidation in 75·8% yield. Two recrystallizations from THF afforded colorless small prisms, m.p. 257–258°. (Found: C, 76·08; H, 7·12; N, 10·37. $C_{17}H_{20}ON_2$ requires: C, 76·08; H, 7·51; N, 10·44%); ν_{max} cm^{-1} 3555 (OH), 1124 (C—O), 744 (benzene); ν_{max}^{Chlf} cm^{-1} 1643 (C=O), 1125 (C—O); λ_{max} mμ (ε) 227·5 (31,800), 285 (6770); λ_{sh} mμ (ε) 292 (6450), 316 (2490); $\lambda_{max}^{EtOH-HCl}$ mμ (ε) 223·5 (33,150), 276 (6265), 285 (6440), 317 (4100); $\lambda_{sh}^{EtOH-HCl}$ 295 (ε 5940); λ_{max}^{Chlf} 297 mμ (ε 6170); λ_{sh}^{Chlf} 315 mμ (ε 5040); λ_{max}^{THF} 295 mμ (ε 6900); λ_{sh}^{THF} 314·5 mμ (ε 5090); λ_{max}^{MeCN} mμ (ε) 229 (32,000), 286·5 (6180), 293 (6190); Mass *m/e* 268 (M^+, base peak), 251 (M^+—OH), 212, 198 (XXXb).

(ii) *Catalytic debenzylation of* XXIIb. The ketone XXIIb (0·52 g) in THF (20 ml) was hydrogenated over 5% Pd-C* (0·60 g) at 40° and atm press for 3 hr. Addition of the catalyst* (0·1 g) was followed by reduction at the same temp for 6 hr. After further addition of 30% Pd–C[30] (0·1 g) in THF (3 ml), the hydrogenation was carried out at room temp for 1·5 hr and at 40° for 2 hr. Removal of the catalysts, washing with THF, Me_2CO and benzene, and evaporation of the combined filtrates afforded a solid which was washed with Me_2CO–Et_2O to give 0·1 g of a brown white solid. It was washed with hot Me_2CO (100 ml) to leave 0·01 g of an undissolved white solid, m.p. 249–253°. Concentration of the Me_2CO soln to 50 ml gave 0·02 g of a white solid. A third crop (0·03 g) of crystals was obtained from the mother liquor by allowing it to stand at room temp. Total yield of XXVIb was 0·05 g (13%). Recrystallization from Me_2CO afforded colorless small prisms, m.p. 256–258°.

The identity of the products obtained in (i) and (ii) was confirmed by mixed melting point test and IR comparison.

3,9-*Dimethyl*-1,2,3,4,5,6,7,8-*octahydro*-9H-2,6-*methanoazecino*[5,4-b]*indol*-8-*one*≡1-*Methyl*-16-*demethoxycarbonyl*-20-*desethylidenevobasine* (IV)

To the amine XXVIb (0·13 g) was added 98% HCO_2H aq (1·5 ml) and 37% HCHO aq (1·5 ml). The mixture was heated on a water bath for 2 hr, and poured into a mixture of water (50 ml) and 10% HCl aq (5 ml). After washing with Et_2O (30 ml), the aqueous layer was made alkaline with NaOH pellet, and extracted with AcOEt. The AcOEt extract was washed with water and sat NaCl aq, dried and evaporated to leave a mixture (0·12 g) of oil and solid, which was chromatographed on silicagel (6 g) (Kanto Kagaku Co. Ltd., 100–200 mesh). Fractions of 3 ml were collected. Elution with $CHCl_3$–MeOH (10:1) yielded 72 mg (53%) of the desired IV in the fractions 3–5. Two recrystallizations from Me_2CO afforded colorless prisms, m.p. 163·5–164°. (Found: C, 76·12; H, 7·38; N, 9·52. $C_{18}H_{22}ON_2$ requires: C, 76·56; H, 7·85; N, 9·92%; ν_{max} cm^{-1} 1631 (C=O), 740 (benzene); ν_{max}^{Chlf} cm^{-1} 1642 (C=O). λ_{max} mμ (ε) 239 (16,100), 316 (18,700); $\lambda_{max}^{EtOH-HCl}$ mμ (ε) 239·5 (15,350), 316 (20,100); Mass *m/e* 282 (M^+), 110 (XXXII), 96 (XXXI, base peak).

* See footnote * on page 4162

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