

SYNTHESIS AND STRUCTURE ASSIGNMENTS OF DIETHYL CIS- AND
TRANS-5-ETHYL-2-OXO-4-PIPERIDINEMALONATE

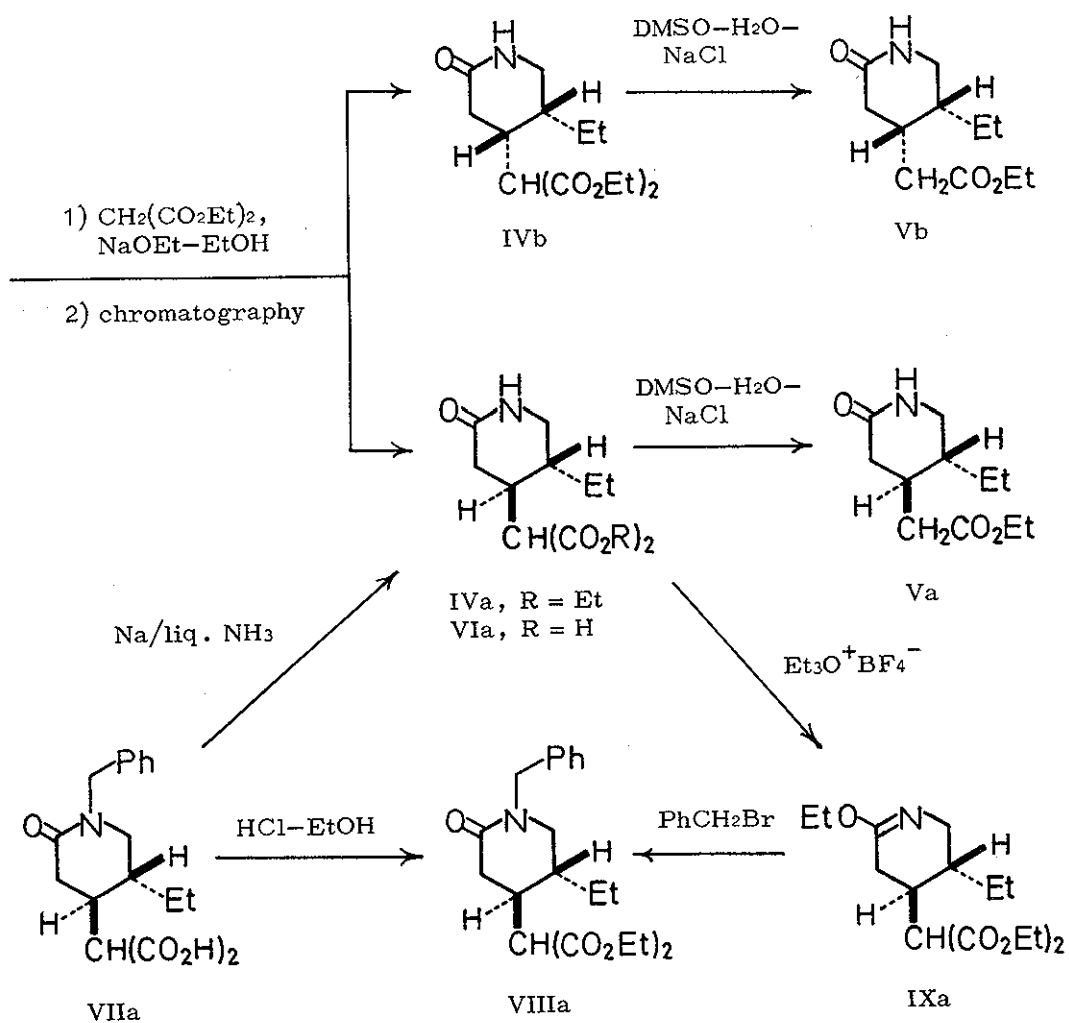
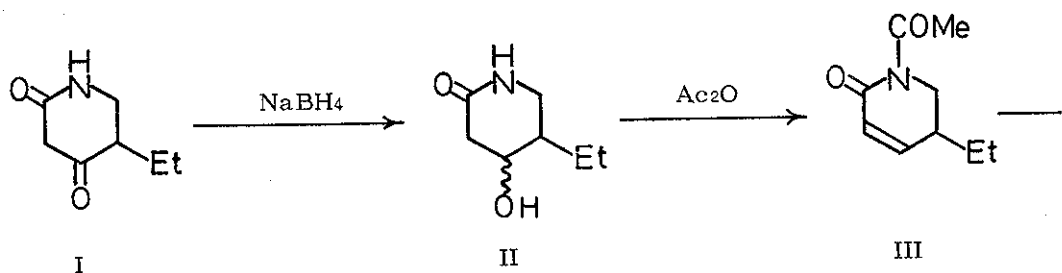
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The Michael addition of diethyl malonate to 1-acetyl-5-ethyl-5,6-dihydro-2(1H)-pyridone (III) produced an 85 : 15 mixture of the trans- (IVa) and the cis-isomer (IVb) of the title lactam diester. The configuration of both isomers has been established by chemical interrelation of them with substances of known stereochemistry.

Our recent syntheses of (\pm)-emetine,^{1,2} (\pm)-ankorine,² and (\pm)-alanguanine³ from ethyl (\pm)-trans-5-ethyl-2-oxo-4-piperidineacetate (Va)^{4,5} by employing the "lactim ether method"⁶ have emphasized the assumed importance of the lactam ester Va as a common starting material for the syntheses of structurally related alkaloids which yet remain to be synthesized. In his earlier study on the synthesis of Va, one (T. F.) of the present authors prepared a crystalline isomer (IVa) of the title compound by the addition of diethyl malonate to the Michael acceptor III, but refrained from assignment of stereochemistry to that isomer for the reasons described previously.⁴ This communication describes the results of our further chemical studies, which have established the stereochemistry of



IVa as well as that of a newly isolated crystalline isomer (IVb).

The Michael acceptor III used in the present study was prepared through the lactam ketone I as reported before,⁴ but the reduction of I to the lactam alcohol II was effected with NaBH₄ (EtOH, 0–20°, 4 hr). The subsequent dehydration of II with Ac₂O (reflux, 4.5 hr) gave III in 82% overall yield (from I). Condensation of III with diethyl malonate (NaOEt, EtOH, 55°, 1 hr) and column chromatographic purification of the resulting Michael products (alumina, benzene–EtOH; silica gel, AcOEt) furnished IVa (36% yield; mp 82–83°), identical with a sample previously characterized,⁴ together with IVb (4% yield; mp 72.5–74°).⁷

Since analytical and spectral data of both lactam diesters (IVa,b) suggested that they are probably isomers due to the difference in stereochemical relationship between the two side chains, we tried to interrelate them with materials of known stereochemistry. Krapcho *et al.*^{8,9} have recently reported that geminal diesters undergo decarbalkoxylation when heated with NaCl in wet dimethyl sulfoxide (DMSO) at 140–183°. Under similar reaction conditions (DMSO–H₂O–NaCl, 160°, 3 hr),⁹ IVa produced the lactam monoester Va (92% yield; mp 93–94°), identical with authentic ethyl trans-5-ethyl-2-oxo-4-piperidineacetate.^{4,5} Likewise, IVb afforded Vb (88% yield) as an oil, which was identical (by means of ir spectroscopy and thin-layer chromatography) with an authentic sample of the cis-ester (Vb) prepared in 97% yield from cis-5-ethyl-2-oxo-4-piperidineacetic acid^{4,5} by esterification [10% (w/w) HCl–EtOH, 15°, 16 hr].^{10,11} The trans structure of IVa was further supported by the conversion of IVa into the lactim ether IXa (100% yield),^{2,12} which was then benzylated⁶ (PhCH₂Br, HCO–NMe₂, 60°, 15 hr) to give VIIIa (54% yield) as an oil, identical with a sample obtained quantitatively from trans-1-benzyl-5-ethyl-2-oxo-4-piperidinemalonic acid [VIIIa, mp 152–153° (dec.)]¹ by esterification [10% (w/w) HCl–EtOH, 15°,

24 hr].

On the other hand, debenzoylation of VIIa (Na, liq. NH₃, -33°)¹³ gave VIa [25% yield; mp 140-142° (dec.)],¹⁴ which was identified with a sample prepared previously⁴ by alkaline hydrolysis of IVa. This interrelation of IVa with VIIa through VIa has not only multiplied the evidence in support of the assignments of trans configuration to IVa and of cis configuration to IVb, but also made it possible to establish the stereochemistry of VIa which remained unsettled.

In the Michael reaction of III described above a preciser ratio of both isomers (IVa : IVb = 85 : 15) was measured C-13 nmr spectroscopically in a manner similar to that reported before.⁵ Although it is not certain whether both isomers had been equilibrated¹⁵ under the reaction conditions adopted, the observed stereoselectivity is roughly compared with the semi-quantitative results reported for similar Michael reactions of analogous derivatives^{4,16-18} and may reflect a preference for the formation of the trans-isomer (IVa) over that of the cis-isomer (IVb) in both the kinetically controlled and the thermodynamically controlled process.¹⁵

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isomerization of the cis-lactam acid⁵ did not occur at all during the esterifica-
tion at 15°, but the same esterification at 32° (16 hr) or at reflux (2.5 hr) gave
a 97 : 3 or an 80 : 20 mixture of the cis- (Vb) and the trans-ester (Va) in 92% or
93% yield.
- 11 It has already been shown⁵ in this laboratory that heating cis- or trans-
5-ethyl-2-oxo-4-piperidineacetic acid at 180–210° for 8 min gave an equilibrat-
ed 33 : 67 mixture of the cis and the trans acid, whereas the corresponding
methyl or ethyl esters (Va, b) failed completely in undergoing such cis-trans
isomerization at 180° over a period of at least 1 or 5 hr. We have also confirm-
ed that neither the cis nor the trans isomer of the lactam monoester (V) under-
went the isomerization under these particular decarboxylation conditions.
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14 About 50% of the starting material (VIIa) was recovered from the reaction mixture. The low yield of VIa and the recovery of a large portion of VIIa were probably due to the poor solubility of the disodium salt of VIIa, which had initially formed, in liquid ammonia.

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