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

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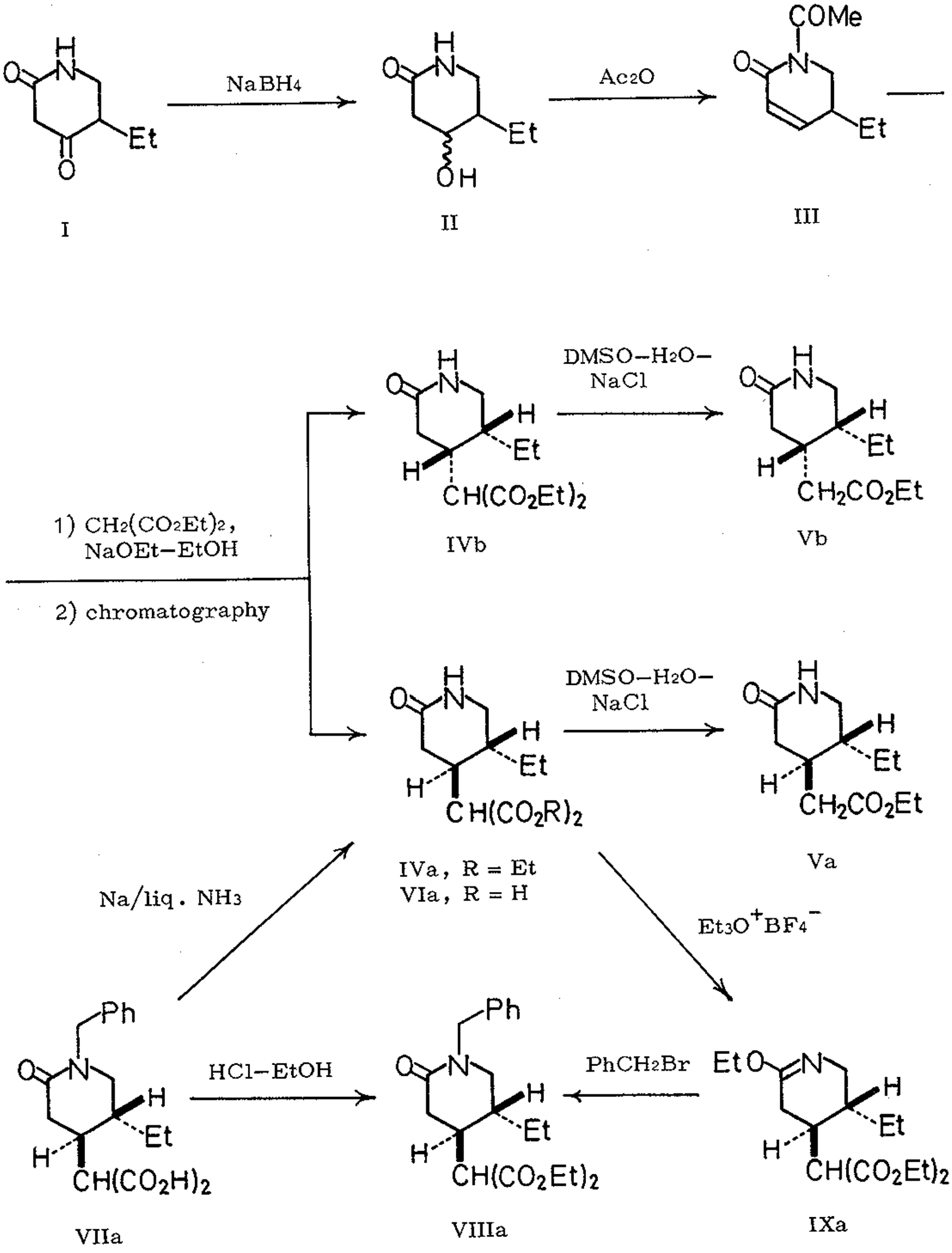
The Michael addition of diethyl malonate to 1-acetyl-5-ethyl-5,6-dihydro-2(1H)-pyridone (III) produced an 85 : 15 mixture of the trans- (IVa) and the cis-isomer (IVb) of the title lactam diester. The configuration of both isomers has been established by chemical interrelation of them with substances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

Our recent syntheses of (±)-emetine,[1,2] (±)-ankorine,[2] and (±)-alangicine[3] from ethyl (±)-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


NaBH4
Ac2O
COMe
I
II
III
1) CH2(CO2Et)2, NaOEt–EtOH
2) chromatography
DMSO–H2O–NaCl
IVb
Vb
IVa, R = Et
VIa, R = H
Va
Na/liq. NH3
Et3O+BF4−
HCl–EtOH
PhCH2Br
VIIa
VIIIa
IXa

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 $NaBH_4$ (EtOH, 0–20°, 4 hr). The subsequent dehydration of II with Ac_2O (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 ($DMSO–H_2O–NaCl$, 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 benzylated[6] ($PhCH_2Br$, $HCONMe_2$, 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 [VIIa, mp 152–153° (dec.)][1] by esterification [10% (w/w) HCl–EtOH, 15°, 24 hr].

On the other hand, debenzylation of VIIa (Na, liq. NH_3, −33°)[13] gave VIa [25% yield; mp 140–142° (dec.)],[14] which was identified with a sample prepared previously[4] 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 equilibrated[15] 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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10 We have confirmed by means of C-13 nmr spectroscopy[5] that *cis* → *trans* isomerization of the *cis*-lactam acid[5] did not occur at all during the esterification 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 shown[5] in this laboratory that heating *cis*- or *trans*-5-ethyl-2-oxo-4-piperidineacetic acid at 180–210° for 8 min gave an equilibrated 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 confirmed that neither the *cis* nor the *trans* isomer of the lactam monoester (V) underwent the isomerization under these particular decarbethoxylation 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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