Tetrahedron Vol 32, pp 1019 to 1023. Pergamon Press 1976 Printed in Great Britain

SYNTHESIS OF CORYNANTHEIDINE ALKALOIDS—II[1]

AN UNUSUAL EPIMERIZATION OF INDOLO[2,3-a]- AND BENZO[a]QUINOLIZIDINE DERIVATIVES

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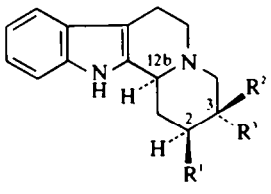
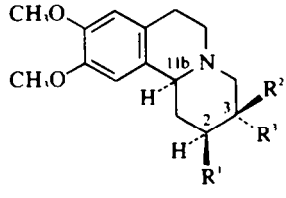
(*Received in UK 24 September 1975; Accepted for publication 24 November 1975*)

Abstract—2,3-*cis*-Substituted quinolizidine-enamines can be epimerized to the corresponding *trans* compounds, if suitable substituents are attached to the CH group linked to C atom No. 2. This observation allows the transformation of indolo[2,3-a]- and benzo[a]quinolizidines of *allo* configuration into their *normal* stereoisomers. Starting from optically active compounds, it has been established on the basis of their CD curves that the epimerization proceeds at C(2).

For the synthesis of (−)-corynantheidine (**1a**‡)[1] and dimethoxy-despyrrolo-corynantheidine (**2a**)[2] the *allo* nitrileester racemates (**1b** and **2b**), readily obtained in a stereoselective sequence, were used as starting materials. These compounds can be oxidized [e.g. with $Pb(OAc)_4$ or



1a–c

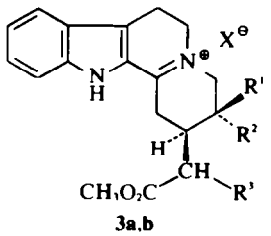


2a–g

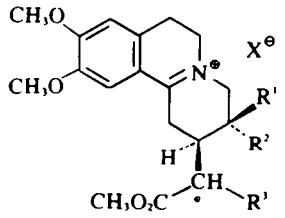
	R¹	R²	R³
a	$CH_3O_2C-C(R^1)=CH-OCH_3$	$-C_2H_5$	H
b	$CH_3O_2C-CH(R^1)-CN$	$-C_2H_5$	H
c	$CH_3O_2C-CH(R^1)-CN$	H	$-C_2H_5$
d	$CH_3O_2C-CH(R^1)-CO_2CH_3$	$-C_2H_5$	H
e	$CH_3O_2C-CH(R^1)-CO_2CH_3$	H	$-C_2H_5$
f	$-CH_2CO_2CH_3$	$-C_2H_5$	H
g	$-CH_2-CO_2CH_3$	H	$-C_2H_5$

Thus, e.g. during 6–7 hr the benzo[a]quinolizidine derivative (**6a**) is mostly transformed into a new compound, which has been isolated in the form of its perchlorate salt (**4b**). The reduction of **4b** with $NaBH_4$ gave another cyanoacetate (**2c**), epimeric with the starting

$Na_2Cr_2O_7$ in acetic acid medium] to the immonium salts **3a** and **4a**. These, as well as the enamines (**5a** and **6a**) obtained from them with ammonium hydroxide, can be reduced with sodium borohydride back to the starting *allo* nitrile-esters **1b** and **2b**. However, if the solutions of the enamines (**5a** and **6a**) are left to stand at room temperature in an inert gas atmosphere, a slow transformation can be observed by TLC.



3a,b



4a–c

3,4	R¹	R²	R³
a	Et	H	CN
b	H	Et	CN
c	Et	H	CO_2CH_3
d	H	Et	CO_2CH_3

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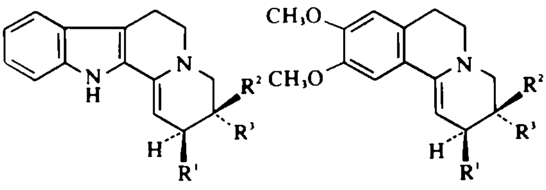
‡In the paper, the structural formula is given only for one of the enantiomers of racemic compounds. The optically active compounds are indicated by marking the relevant arabic number with an asterisk *.



5a,b **6a,-d**

5,6	R^1	R^2	R^3
a	$CH_3O_2C—CH—CN$	C_2H_5	H
b	$CH_3O_2C—CH—CN$	H	C_2H_5
c	$CH_3O_2C—CH—CO_2CH_3$	C_2H_5	H
d	$LCH_3O_2C—CH—CO_2CH_3$	H	C_2H_5

2b. The identification of the stereostructure of the product was facilitated by the fact that all the possible stereoisomers of **2b** were synthesized and investigated earlier.[2] On the basis of physical-chemical data (UV, IR, ^{1}H-NMR, MS, TLC), the new compound (**2c**) proved to be of *normal* steric structure. In an analogous way, the normal cyano-acetate was obtained from the *allo* indolo[2,3-a]quinolizidine derivative (**1b**) via the reaction sequence **1b** → **3a** → **5a** → **5b** → **3b** → **1c**, the steric structure of which was supported (in addition to the experiences with the benzoquinolizidine series) by its mass spectroscopic[4] and TLC[3] behaviour. The evaluation of the comparative investigation[3,4] was facilitated by the fact that in the course of the synthesis of (−)-corynantheidine,[1] the *pseudo* epimer of **1b** and **1c** have also been prepared.

To sum up it can be stated that when the racemates **5a** and **6a** are left standing in solution, the hydrogens (or substituents) originally in the 2,3-*cis* position are transformed by the inversion of *one* of the chirality centres of the enamines into the *trans* position.

To decide whether the epimerization takes place at position C(2) or at C(3) the reaction sequence described above was carried out with optically active *allo* nitrile-esters. CD investigation of the product then allows comparison of the absolute configurations of the starting *allo* nitrile-ester and the saturated *normal* compound resulting from the reaction series.

The optical activity of indolo[2,3-a]- and benzo[a]quinolizidines, as well as that of 1-substituted-tetrahydroisoquinolines, is affected by the aromatic chromophore.[5] The sign of the Cotton-effect depends primarily on the chirality of the immediate environment of the achiral aromatic chromophore, i.e. on the chirality of the tetrahydropyridine ring, forming the chiral second sphere. On the other hand, the position of the equilibrium between the two possible conformation of this ring is determined by the C(1) configuration of the tetrahydroisoquinoline compound (by the annelation carbon configuration of quinolizidines). It is to be expected, therefore, that the CD spectra of different compounds will offer unambiguous information on the configuration at C(11b) relative to each other.

On the other hand, experience shows that in the course of the catalytic or $NaBH_4$ reduction of 2,3-disubstituted immonium- and enamine compounds, the hydrogen generally enters the molecule in such a way that the new C–H bond will occupy a 1,3-*cis*-diaxial position with respect to the hydrogen at C(2), resulting in the formation of the thermodynamically more stable stereoisomer.[6]

It follows from the above that if the epimerization of the enamines occurs at C(3) [e.g. **6a*** 2(S), 3(S) → **6b*** 2(S), 3(R)], in the *normal* compound obtained after the reduction the absolute configuration of the annelation C atom will remain identical with that of the starting *allo* compound, and accordingly, it is to be expected that the CD curves of the epimeric nitrile-esters [e.g. **2b*** → **2c***] will be of similar character. However, if the epimerization proceeds at C(2) [e.g. **6a*** 2(S), 3(S) → **6b*** 2(R), 3(S)], the absolute configuration of the annelation C atom in the hydrogenation product will be the opposite of that of the starting compound, and this necessarily means that the CD curves of the *allo* and *normal* nitrile-esters will show Cotton effects of opposite sign.

The benzo[a]quinolizidine-cyano-acetate derivative (**2b**) was therefore resolved with dibenzoyl-D-tartaric acid, and the reaction series was carried out separately with both enantiomers. The course of the CD curves of the *normal* compounds obtained from both *allo* enantiomers had a mirror image character with respect to the CD curves of the starting compounds (Fig. 1). Thus, the (−)-**2b*** 11b(S), 2(S), 3(S) *allo* nitrile-ester led to the (+)-**2c*** 11b(R), 2(R), 3(S) *normal* stereoisomer. Similarly, the allo compound "11b(R)" gave the normal cyano-ester "11b(S)". The absolute configurations of the dextrorotatory and levo-rotatory enantiomers of **2b** and **2c** were assigned only on the basis of the similarity of their CD curves with the CD curve of the *normal* acetic acid ester (−)-**2g*** 11b(S), 2(S), 3(R), which leads to (−)-emetine of known absolute configuration (Fig. 1).

Our findings concerning the absolute configuration are supported by the fact that the CD spectra of the compound (−)-**2g***, and of the compounds (−)-**2b*** and (−)-**2c*** are analogous with respect to the positions as well as the signs of the Cotton-effects with the CD spectra of the unsubstituted 12b(S)-indolo[2,3-a]quinolizidine and of 1(S)-1-methyl-1,2,3,4-tetrahydro-β-carboline.[7] Experi-

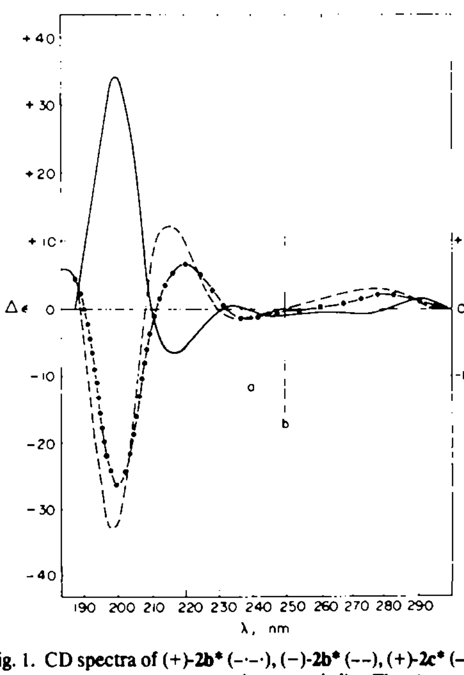


Fig. 1. CD spectra of (+)-**2b*** (–·–·), (−)-**2b*** (– –), (+)-**2c*** (———); (−)-**2c*** (–··–··) and **2g*** (—) in acetonitrile. The Δε values of (+)-**2c*** and (−)-**2c*** from line *a*, those of (+)-**2b***, (−)-**2b*** and **2g*** from line *b* are drawn on a tenfold larger scale.

ments with optically active compounds unequivocally prove that the epimerization of enamines of type **5** and **6** proceeds at the *C atom at position* 2. Presumably, the epimerization proceeds by an ionic mechanism, which is supported, in addition to the base-catalysability of the process, by the fact that in the case of the diester **2d**[2] containing less electron-attracting groups in the side-chain, the **6c** → **6d** epimerization proceeded considerably slower (as a result of the reaction, the **2e** *normal* diester[8] can also be prepared); further, the **2f** → **2g** *allo* → *normal* transformation could not be realised with the acetic acid ester derivative containing only one electron-attracting group. Moreover, further investigations *proved* that the transformation of enamines proceeds through reversible steps; starting from whatever stereoisomer the same position of equilibrium (**5a** ⇌ **5b**, **6a** ⇌ **6b** ~ 1:10; TLC evaluation) could be achieved.

To gain further insight into the mechanism of the epimerisation, the behavior of the deuterated compound 2S-**6a** generated from 2D-**2b** was investigated (Experimental).

Further investigations concerning the mechanism of the interesting observation are in progress.

The *allo* → *normal* stereochemical transformation, observed for the first time for indolo[2,3-a]- and benzo[a]quinolizidines, furnishes in addition to its theoretical interest a means of extending the synthesis of (−)-corynantheidine (**1a***)[1] and dimethoxy-despyrrolo-corynantheidine (**2a**)[2] developed by us to the preparation of alkaloids with the *normal* quinolizidine skeleton.[8]

EXPERIMENTAL

UV spectra were measured on a Spectromom Model 201 spectrophotometer. IR spectra were recorded in KBr with a Spectromom 2000 spectrophotometer. The ^{1}H-NMR spectra were obtained using a Perkin-Elmer R12 (60Mc) instrument; chemical shifts are reported as ppm (δ) downfield from TMS. Mass spectra (MS) were recorded with an AEI MS 902 instrument (70 eV, ion source temp. 150°, direct insertion).

Optical rotations were measured with an automatic polarimeter Model Polamat A. CD curves were recorded with a Roussel-Jouan Model III dichrograph, in acetonitrile soln ($c = 10^{-4}$ to 10^{-3} M), in 1–5 mm cells at room temp.

The course of the reaction was checked by qualitative TLC, for which Silicagel GF_{254} (Merck) inactive adsorbent was used. The developing systems used in the experiments are:

System A: spotting with AcOH, drying, 5′ NH_3 saturation, benzene-MeOH 12:1

System B: ether

System C: spotting with AcOH, drying, 10′ NH_3 saturation, ether

System D: 5′ NH_3 saturation, benzene–MeOH 8:1.

The evaporation of solutions is carried out *in vacuo* under argon. M.ps are uncorrected.

Transformation of indolo[2,3-a]*quinolizidine-cyanoacetic acid ester* (**1b**) *of* allo *structure to the corresponding normal product* (**1c**)

Oxidation of cyano-acetic-acid-ester **1b** *to immonium salt* (**3a**), *i.e. to enamine* (**5a**). The hydrochloride of the **1b** *allo* nitrile-ester[1] (1·22 g; 3 mmole) was dissolved under magnetic stirring and heating to 80° in glacial AcOH (80 ml). After quick cooling to 17°, $Pb(OAc)_4$ (1·40 g; 3·15 mmole) was added in 10 min. The suspension, containing precipitated $PbCl_2$, was agitated at 17° for 3 hr. The oxidation could be followed by TLC. (In System A R_f **1b**: 0·7; R_f **3a** and **5a**: 0·6). If necessary, further $Pb(OAc)_4$ was added to the mixture. The mixture was kept overnight in a refrigerator, saturated with H_2S, and the PbS formed was filtered off. The soln was evaporated to dryness, the residue dissolved in a mixture of water (25 ml) and AcOH (3 ml), and unreacted **1b** extracted with ether from the weakly acidic soln. Then on cooling with ice the aqueous soln was made alkaline with 25% NH_4OHaq (pH 10), and the base ppt extracted with ether (3 × 40 ml). Enamine **5a** obtained in this way was epimerized without isolation. This **5a** could be reduced with $NaBH_4$ to the starting cyano acetate **1b**.

Epimerization of the 2,3-cis *enamine* **5a** *to* 2,3-trans *enamine* **5b**. *Preparation of the immonium salt* **3b**. The ether soln of enamine **5a**, was diluted with CH_2Cl_2 (100 ml), and allowed to stand in argon atmosphere for 24–48 hr. The epimerization was followed by TLC (in System "B" R_f **5a**: 0·2; R_f **5b**: 0·3). When equilibrium was achieved (**5a**: **5b** = ~1:10), MeOH (60 ml) was added to the soln, which is then acidified with 1N perchloric acid in MeOH to pH 2, so that **5a** was converted to **3b**. On evaporation of the solvent crystals begin to separate from the soln. This process was promoted by the addition of ether. The yellow crystals of **3b** (0·75 g; 56% referred to the starting **1b**) decomposed at 205–206°. (Found: C, 55·90; H, 5·13. Calc. for $C_{21}H_{24}N_3O_8Cl$; (449·88) C, 56·06; H, 5·38%). IR (KBr): 1745 (C=O ester); 1640, 1580 (C=$\dot{N}$<); 2270 (CN); 3300 cm^{-1} (NH). ^{1}H-NMR (DMSO-d_6): 1·04 (3H, m, $C\underline{H}_3$–CH_2); 3·90 (3H, s, CH_3O_2C–); 3·30 (2H, t, Ph–CH_2–); 4·13 (2H, t, –CH_2–$\dot{N}$=); 4·87 (1H, m, C(1)-$\underline{H}$ equat.); 7·00–7·83 (4H, m, aromatic); 12·32 (1H, s, >NH). UV (EtOH): λ_{max} (log ϵ) 226 (4·36); 310 (4·28); 320 (4·22); 367 (broad, 3·46); 522 nm (2·88).

Preparation of the normal indolo[2,3-a]*quinolizidine-cyano-acetate derivative* (**1c**) *by the reduction of enamine* **5b** *or of immonium perchlorate* **3b**, *respectively*. Compound **3b** perchlorate (1·35 g, 3 mmol) was dissolved in a mixture of CH_2Cl_2 (100 ml), MeOH (25 ml) and AcOH (13 ml), and at 0–5° under magnetic stirring, $NaBH_4$ (110 mg; ~2·5 mmol) was poured during ~30 min. The reduction was checked by TLC (in System "C" R_f **3b**: 0·25; R_f **1**: 0·5). If necessary, further reducing agent was added. When the main part of the solvent had distilled off, ice water (~20 g) was added to the residue, which was then made weakly alkaline (pH 8–9) with 25% NH_4OHaq, and the base separated was extracted with an ether-MeOH (9:1) mixture (3 × 40 ml). The organic phase was washed with sat. NaClaq dried ($MgSO_4$), and evaporated to dryness. The residue was dissolved in ether–MeOH (1:1) mixture, and slightly acidified with HCl in MeOH. The colourless crystals of the **1c**-hydrochloride (1·1 g, 91%) decomposed at 220°. IR (KBr): 1740 (C=O); 2500, 3140 (>$\dot{N}$H); 3400 cm^{-1} (indole NH). If after evaporation the base extracted with ether–MeOH mixture was treated with a mixture of ether–hexane, the *normal* nitrile-ester base **1c** was obtained (0·83 g; 79%), m.p. 165–166°. (Found: C, 71·57; H, 7·15; N, 12·08. Calc. for $C_{21}H_{25}N_3O_2$: (351·43) C, 71·77; H, 7·17; N, 11·96%). IR (KBr): 1750 (C=O); 2350 (CN); 3470 cm^{-1} (NH). UV (EtOH): λ_{max} (log ϵ) 274 (sh); 282 (3·88); 290 nm (3·80). ^{1}H-NMR ($CDCl_3$): 1·03 (3H, m, $C\underline{H}_3$–CH_2); 3·76 and 3·90 (3H, $C\underline{H}_3O$); 7·06–7·60 (4H, m, aromatic CH); 8·00 and 8·21 ppm (indole NH). MS (*m/e*; %) 351 (M^+; 100); 350 (91); 336 (1); 322 (3); 320 (2); 292 (3); 253 (79); 251 (10); 225 (16); 224 (6); 223 (6); 221 (4); 184 (9); 170 (15); 169 (13); 156 (11).

Transformation of the **2b** *benzo*[a]*quinolizidine-cyano-acetate into the corresponding stereoisomer of normal configuration* (**2c**)

Oxidation of benzo[a]*quinolizidine cyano-acetate* (**2b**) *to the corresponding immonium salt* (**4a**) *and to the enamine* (**6a**), *respectively*. Compound **2b**[2] (11·16 g; 30 mmol) was oxidized with $Pb(OAc)_4$, as described. The oxidation was checked by TLC (in System "A" R_f **2b**: 0·7; R_f **6a**: 0·58). From the **4a** salt present in the AcOH soln, **6a** was liberated with NH_4OHaq, and epimerization was carried out without isolation.

The base **2b** (0·372 g; 1 mmol) was dissolved in AcOH (6 ml), and, under magnetic stirring, a lukewarm (~40°) soln of $Na_2Cr_2O_7 \cdot 2H_2O$ (0·36 g; 1·2 mmol) in AcOH (9 ml) was added drop by drop. Oxidation was carried out as described: it proceeded at room temp. in ~72 hr. Next, the soln was poured on

ice (~100 g), and made alkaline with 25% NH_4OH (pH 9–10). The base was extracted with ether. The **6a** obtained was identical with the enamine obtained according to 2.1.a; the $NaBH_4$ reduction of the oxidation product prepared via both routes gave the initial cyano acetate **2b**.

Epimerization of the 2,3-cis *enamine* **6a** *to* 2,3-trans *enamine* **6b**. *Preparation of the immonium salt* **4b**. The ether soln of **6b**, was diluted with an equiv volume of CH_2Cl_2, and allowed to stand in a place protected from light. According to TLC tests (System "D" R_f **6a**: 0·63; R_f **6b**: 0·70), epimerization equilibrium was achieved in about 5–6 hr. **6b** enamine was obtained as its perchlorate salt **4b** (8·15–9·7 g; 54–64%). The yellow crystals decomposed at 142–145°. (Found: C, 52·27; H, 5·63; N, 5·75. Calc. for $C_{21}H_{27}N_2O_8Cl{\cdot}CH_3OH$ (502·94): C, 52·53; H, 6·21; N, 5·57%). IR (KBr): 1750 (C=O ester); 2280 (CN); 2000 ($ClO_4^{\ominus}$); 1610 (arom.); 1645, 1575 cm^{-1} ($\rangle C{=}\overset{\oplus}{N}\langle$). ^{1}H-NMR (DMSO-$d_6$): 0·90 (3H, m, CH_3CH_2); 3·28 (3H, s, CH_3OH); 3·89 (3H, s, CO_2CH_3); 3·93 (3H, s, C(9)–OCH_3); 3·99 (3H, s, C(10)–OCH_3); 4·65 (1H, 2xs; J_1 = 3cps, J_2 = 12cps; C(1)–H equat.); 7·10 (1H, s, C(8)–H); 7·41 ppm (1H, s, C(11)–H). UV (EtOH): λ_{max} (log ϵ) 247 (4·32); 266 (sh.); 305 (4·12); 356 (4·11); 420 nm (sh.).

Preparation of **2c** *by the reduction of enamine* **6b** *or immonium perchlorate* **3b**, *respectively*. Compound **4b** perchlorate (20·12 g; 40 mmol) was suspended under magnetic stirring in a mixture of CH_2Cl_2 (250 ml), MeOH (50 ml) and AcOH (80 ml), and then reduced with $NaBH_4$ (1·9 g; ~40 mmol). (TLC checking in System "D" R_f **4b**: 0·1; R_f **2c**: 0·25). To the soln obtained after reduction, ice (~20 g) was added, and the soln was made slightly alkaline with NH_4OH. The CH_2Cl_2 phase was separated, and the aqueous phase washed with CH_2Cl_2 (100 ml). Hereinafter, **2c** was obtained as a colourless crystalline hydrochloride according to the procedure described (15·7–16·8 g; 93–99%), m.p. 170–175°. The base obtained from the hydrochloride of **2c** proved to be identical in every respect (IR, ^{1}H-NMR, m.p., m. m.p., MS, TLC) with the *normal* nitrile-ester obtained via another method.[2] UV (EtOH): λ_{max} (log ϵ) 282 (3·53), 286 nm (sh).

Transformation of benzo[a]*quinolizidine diester* (**2d**) *of allo configuration*[2] *to the corresponding normal diester* **2e**

Oxidation of the **2d** *allo diester to immonium salt* **4c** *and enamine* **6c**, *respectively*. The soln of **2d** (1·62 g; 4 mmol) in AcOH (20 ml) was oxidized with $Pb(OAc)_4$ (2·1 g; 4·8 mmol). Extraction was carried out with CH_2Cl_2 (4 × 25 ml), and the soln of **6c** used directly for the epimerization. (After extraction, the $NaBH_4$ reduction of a small sample of the soln gave the initial **2d**.)

Epimerization of the 2,3-cis *enamine* **6c** *to* 2,3-trans *enamine* **6d**. The CH_2Cl_2 soln of **6c**, was filtered through a Whatmann phase-separating paper, and refluxed in argon atmosphere for 100 hr. The epimerization was followed by TLC of small samples reduced with $NaBH_4$ (in system "D" R_f **2d**: 0·75; R_f **2e**: 0·4). After refluxing 100 hr the **6c**/**6d** ratio was ~1:2 according to TLC.

Reduction with $NaBH_4$ *of the* **6c**/**6d** *epimer mixture enamines*. To the cooled CH_2Cl_2 soln, MeOH (20 ml) was added, and henceforward under argon $NaBH_4$ (40 mg, ~1 mmol) at 0–5° under magnetic stirring. Reduction was checked by TLC (in system "D" R_f **6c**: 0–0·09; R_f **6d**: 0·09–0·11; R_f **2d**: 0·75; R_f **2c**: 0·4). The mixture was evaporated, the residue dissolved in 1N HCl (40 ml), and, on ice cooling, cautiously neutralized with 2N NH_4OH to pH 6. Next, the liberation of the base was continued with small portions of 0·2N NH_4OH, and after each portion the ppt was extracted with ether. The first few extracts contained mainly **2d**, the next extracts the allo-normal mixture, while the last ones contained the normal **2e**. The latter was dried, evaporated, and the residue converted to the HCl salt with HCl in MeOH. The crystals of the **2e** normal diester HCl salt obtained by crystallization from MeOH-ether and the base obtained from it, were identical in every respect (IR, ^{1}H-NMR, m.p. TLC) with the product prepared in another way.[4]

Resolution of allo *benzo*[a]*quinolizidine-cyano-acetate* **2b**

The **2b** base[2] (3·72 g; 10 mmol) was admixed with an equiv quantity of (−)-dibenzoyl-D-tartaric acid hydrate (3·76 g; 10 mmol), and dissolved under heating in MeOH (60 ml). The soln was allowed to stand overnight, and the crystals filtered off with suction. This crystalline substance (2·25 g; 31%), as well as the crystalmass (1·24 g; 17%), separating from the aceton soln (50 ml) of the evaporation residue of the mother-liquor, decomposed at 153–155°C; $[\alpha]_D$-102° (*c* = 2, MeOH). These data do not change after recrystallisation (MeOH). Evaporation of the acetone mother liquor to dryness gave a pulverizing pale yellow foam (3·3 g; 45·5%), m.p. 129–130° (deco), $[\alpha]_D$-10° (*c* = 2, MeOH). From the dibenzoyl tartarate of $[\alpha]_D$-102°, a nitrile-ester *base* [(−)-**2b***] melting at 117–119° (ether-hexane) was obtained; $[\alpha]_D$-100° (*c* = 2·5, MeOH), the absolute configuration of which was: 11b(S), 2(S), 3(S). From the acidic dibenzoyl tartarate of $[\alpha]_D$-10° a nitrile-ester base [(+)-**2b*** 11b(R), 2(R), 3(R)] was obtained. Its m.p. as well as the degree of rotation was identical with, the direction of the latter was of opposite to that of (−)-**2b***. Spectroscopical data of the optically active bases agreed with those of the corresponding spectra of the racemic compound.[2] The CD curves of the dextro-rotating and levo-rotating nitrile-esters of allo stereostructure are shown in Fig. 1.

The comparison of these curves with the CD curve of (−)-**2b*** made the determination of their absolute configuration (see above) possible.

Preparation of the optically active normal benzo[a]*quinolizidine-cyano-acetate* (+)-**2c*** *and* (−)-**2c***

Transformation of (−)-**2b*** *to* (+)-**2c***. The acidic dibenzoyl tartarate of (−)-**2b*** (7·30 g; 10 mmol) was suspended in CH_2Cl_2 (150 ml), and shaken with a mixture of ice water (50 ml) and 25% NH_4OH (4 ml). The aqueous phase was extracted with ether (2 × 200 ml). The combined organic phase was washed with water, dried ($MgSO_4$) and evaporated. The residual colourless oil [(−)-**2b***; 11b(S), 2(S), 3(S)] (3·8 g; 100%) was oxidized and subsequently epimerized. The mixture obtained after epimerization was slightly acidified with AcOH (2 ml), and reduced with $NaBH_4$ (~0·8 g). The CH_2Cl_2 soln was concentrated to ~50 ml and shaken with 10% HClaq (5 × 50 ml). Under external and internal cooling with ice, the aqueous phase was made alkaline with 25% NH_4OH, and the liberated base extracted with ether (3 × 100 ml). After drying ($MgSO_4$), the ether phase was evaporated to dryness, the residue dissolved in MeOH (~10 ml), and made slightly acid with HCl in MeOH. Thus, normal (+)-**2c*** hydrochloride containing about 10% of the starting material, was obtained. This was purified by fractional crystallization from MeOH-ether; the colourless crystals of the normal (+)-**2c***, obtained from the hydrochloride salt (1·3 g; 32%), melted at 137–138° (ether-hexane); $[\alpha]_D$ + 62·5° (*c* = 0·7; MeOH). The UV, IR, ^{1}H-NMR and TLC data are the same as the corresponding data of the racemic **2c**. On the basis of its CD curve the absolute configuration of the product was 11b(R), 2(R), 3(S) (Fig. 1).

Transformation of the allo *nitrile-ester* (+)-**2b*** *into the normal nitrile-ester* (−)-**2c***. Repeating the last experiment with the acidic dibenzoyl-D-tartarate of (+)-**2b***, the base (−)-**2c*** was obtained, the spectroscopical and TLC behaviour of which is identical with that of the racemate or (+)-**2c***, m.p. 137–138°; $[\alpha]_D$ − 64° (*c* = 0·7; MeOH). Its absolute configuration [11b(S), 2(S), 3(R)] is unambiguously proved by the CD curve (Fig. 1).

Investigation with 2-*deuterated compounds*

Preparation of 2-*deuterated* allo *nitrile-ester* (2-D-**2b**). The $\Delta^{2,3}$-unsaturated nitrile-ester[2] (3·70 g; 10 mmol) was reduced with sodium tetradeutero-borate (0·143 g; 3·5 mmol). The pale yellow crystals of 2-D-**2b** (3·05 g; 82%) melted at 137–138°. ^{1}H-NMR ($CDCl_3$): 3·52 and 3·55 $\left(1H,\ 2xs,\ -CH\begin{matrix}CN\\ CO_2CH_3\end{matrix}\right)$. (In the ^{1}H-NMR spectrum of **2b** the corresponding signals are splitted by the C(2)-H). MS *m/e* (rel. intensity): 373 (M^+; 18); 372 (20); 358(3); 275(100); 246(7); 205(11); 191(18); 190(8); 176(5).

Oxidation and subsequent epimerization of 2-D-**2b**. The oxidation and epimerization processes of 2-D-**2b** (2·60 g; 7 mmol) were accomplished, but the latter was performed in a mixture of CH_2Cl_2 and MeOH (~1·1). The yellow crystals of 2-D-**4b** perchlorate (1·80 g; 52%) melted at 141–145°. IR and UV data were identical with those of **4b**.

Preparation of 2-D-**2c** *by the reduction of* 2-D-**4b**. After

reduction of 2-D-**4b** (1·51 g; 3 mmol), the spectroscopical investigations of the 2-D-**2c** base (0·88 g; 79%) unambiguously proved the deuterium to remain in the position 2: ^{1}H-NMR ($CDCl_3$): 4·01 $\left(1H, s, -CH\begin{smallmatrix}CN\\CO_2CH_3\end{smallmatrix}\right)$. (In the ^{1}H-NMR spectrum of **2c** the corresponding signal at 4·02 is splitted because of the C(2)-H.) MS *m/e* (rel. intensity): 373 (M$^+$; 25); 372(30); 358(4); 275(100); 246(20); 205(10); 191(20); 190(10); 176(5).

Acknowledgements—The authors wish to thank the Hungarian Academy of Sciences for financial support; Dr. J. Tamás for the high-resolution mass spectra and their interpretation, Dr. P. Kolonits and his co-workers for IR and ^{1}H-NMR spectra. Thanks are expressed to Mrs. S. Krakoviczer for technical assistance.

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