Tetrahedron. Vol 32, pp. 1153 to 1159 Pergamon Press 1976. Printed in Great Britain

SYNTHESIS OF CORYNANTHEIDINE ALKALOIDS—III[1]

THE STEREOSELECTIVE TOTAL SYNTHESIS OF (±)-DIHYDROCORYNANTHEINE

M. BÁRCZAI-BEKE, G. DORNYEI, G. TÓTH†, J. TAMÁS‡ and CS. SZÁNTAY*
Department of Organic Chemistry, Technical University Budapest, Hungary

(*Received UK* 20 *September* 1975; *Received UK for publication* 25 *November* 1975)

Abstract—Starting from the *normal* cyano-acetate derivative **3b**, obtained from the *allo* stereoisomer **3a** via an unusual epimerization,[1] the stereoselective totalsynthesis of (±)-dihydrocorynantheine (**1a**) was accomplished.

The normal structure of (+)-dihydrocorynantheine (**1a**), isolated[2] from the bark of *Corynanthe yohimbe* and *Pseudocinchona africana* A. Chev., has been established[3] by the help of chemical and physical means and substantiated by synthesis. In the course of all known syntheses of corynantheidine-type alkaloids the characteristic β-methoxy-acrylate group was developed from the corresponding ester derivatives **3c** and **3d** in a two-step sequence. First the hydrogen in the α-position to the ester-carbonyl function was substituted by a formyl group with methyl formate in the presence of strong base (generally triphenylsodium). This step was followed by methylation of the desmethylcorynantheidine-epimers (**3h, 3i**).

In connection with the syntheses of (−)-corynantheidine (**1b***)[5] and dimethoxy-despyrrolo-corynantheidine (**2b**)[6]—both having the *allo* structure—we reported a new process yielding the desired α-formyl-esters **3h** and **4h**, which exist partly in the β-hydroxy-acrylate tautomeric form. The corresponding dimethyl-malonates **3e** and **4e** were reduced partially to the malon-aldehyde-esters (**3h, 4h**) with LAH in dry ether at −70°. The malonate derivatives **3e** and **4e** used for the reduction were obtained from the *allo* nitrile-esters **3a** and **4a**.

A very good opportunity was offered to extend the above synthetic method,[5,6] when we succeeded in producing via 2,3-*cis*⇌*trans* epimerization[1] the *normal* nitrile-esters (**3b, 4b**) suitable for the syntheses of the (±)-dihydrocorynantheine (**1a**) and dimethoxy - despyr-rolo - dihydrocorynantheine (**2a**).

It may be mentioned that the reaction sequences[5,6] resulting in the *allo* nitrile-esters **3a** and **4a** have been improved; while maintaining a high-degree of stereoselectivity the yield has been significantly increased, as follows. The benzo [a]-[7] and indolo[2·3-a]quinolizidine-ketones[8] were transformed into the unsaturated dinitriles **5** and **6**[9] in almost quantitative yield. During the condensation epimerization occurs at C(3), as in the case of the analogous reaction with cyano-acetic-esters. Furthermore on reduction with $NaBH_4$ **5** and **6** furnish the saturated dinitriles of *allo* structure (**3g, 4g**). In accordance with previous experience[10] the latter could be transformed into the stable nitrile-iminoether bases **3j** and **4j**. Investigations concerning the imine-enamine tautomeric equilibrium were also extended. IR and ^{1}H NMR technique revealed that the position of the equilibrium is almost independent of the dielectric constant of the medium.§ If, however, there is a possibility to form intermolecular H-bonds with the solvent molecules the enamine form is preferred as a function of increasing solvent-basicity.

In the presence of aqueous acid the nitrile-imino-ethers (**3j, 4j**) furnish the *allo* nitrile-esters **3a** and **4a** in excellent yield.

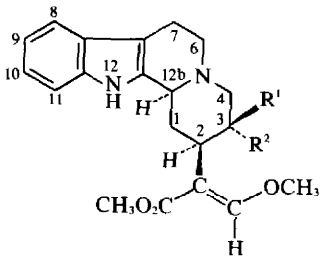
The *normal* nitrile-esters **3b** and **4b** obtained from the *allo* stereoisomers via 2,3-*cis*⇌*trans* epimerization[1] could be easily transformed into the corresponding *normal* diesters **3f** and **4f** with MeOH/HCl. The LAH reduction of the latter compounds gives the α-formyl-ester derivatives **3i** and **4i**, which can exist also in the tautomeric (*Z*)- and (*E*)-enol forms. The position of equilibrium depends on the solvent applied (Experimental). It is worth mentioning that also the otherwise rarely observed *trans*-enol forms **3i″** and **4i″** could be shown by the aid of ^{1}H-NMR spectroscopy, moreover these are the very forms dominating in DMSO solutions. The desmethyl-dihydrocorynantheine (**3i**) and the corresponding benzo[a]quinolizidine-derivative (**4i**) obtained were submitted to methylation under the condition of methyl-acetal formation with MeOH/HCl.[4b] Using excess methanol the target molecule (**1a**) is contaminated by **3k** dimethyl-acetal. In methylene-chloride, however, with 1·1 equivalent of methanol no by-product could be detected.

In contrast to the almost quantitative methylating process[5,6] of the desmethyl-corynantheidine (**3h**), on treatment with dimethyl-sulphate in heterogeneous phase, the sodium salt derived from the enol-forms of **3i** and **4i** could only be transformed into the target molecules in poor yield. Even if an equivalent amount of methylating agent is used the (±)-dihydrocorynantheine (**1a**) and the benzo[a]quinolizidine analogue **2a** are contaminated by the corresponding quaternary quinolizidine compounds. The ^{1}H NMR spectra of these by-products show $\overset{+}{\underset{}{\text{N}}}\text{–CH}_3$ signals. In their MS spectra the fragmentation patterns correspond to those of the target molecules, but

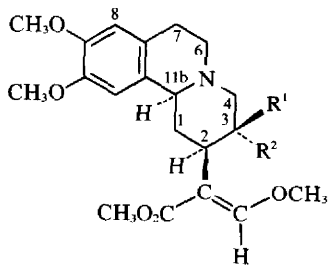
†Institute of Organic Chemistry, Faculty of Pharmaceutical Sciences, Semmelweis Medical University, Budapest, Hungary.

‡Central Research Institute for Chemistry, Hungarian Academy of Sciences, Budapest, Hungary.

§The measurements were performed only in aprotic solvents to avoid the fast proton-exchange, which would have prevented us from assigning the N–H protons.

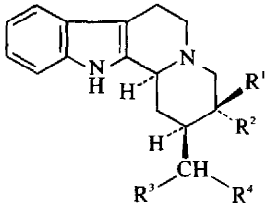


1a,b

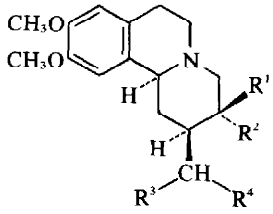


2a,b

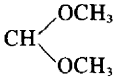
1,2	R^1	R^2
a	H	C_2H_5
b	C_2H_5	H

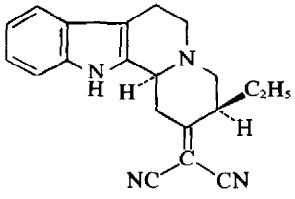


3a–k

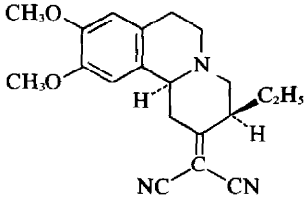


4a–j

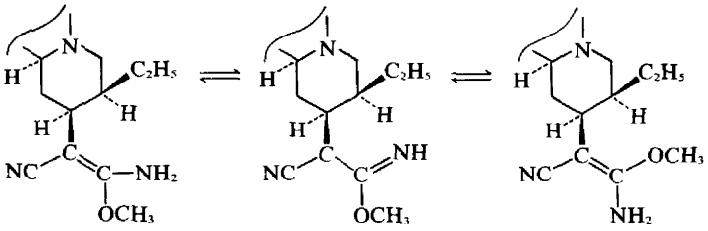
3,4	R^1	R^2	R^3	R^4
a	C_2H_5	H	CN	CO_2CH_3
b	H	C_2H_5	CN	CO_2CH_3
c	C_2H_5	H	H	CO_2CH_3
d	H	C_2H_5	H	CO_2CH_3
e	C_2H_5	H	CO_2CH_3	CO_2CH_3
f	H	CO_2CH_3		CO_2CH_3
g	C_2H_5	H	CN	CN
h	C_2H_5	H	CHO	CO_2CH_3
i	H	C_2H_5	CHO	CO_2CH_3
j	C_2H_5	H	CN	
k	H	C_2H_5	CO_2CH_3	



5



6

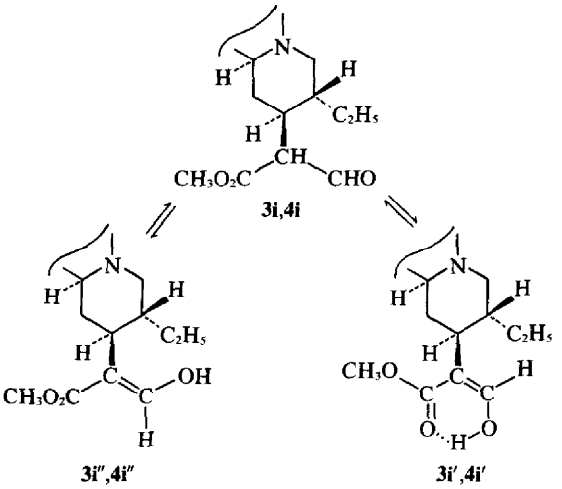


(Z)-enamine **3j,4j** imine (E)-enamine

additional peaks at *m/e* 382 [M (**1a**) + 14] and 403 [M (**2a**) + 14] as well as at 50 and 52 (MeCl) are observable.

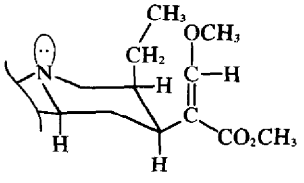
This different behaviour of the *allo* and *normal* sodium-enolates **3h**-Na and **3i**-Na towards dimethylsulphate may be interpreted by the conformational analysis of Trager *et al.*[11] In the most stable conformer of the *allo* compound (**A**) the ethyl-group exists in the axial position, and hinders the attack on the quinolizidine-nitrogen owing to 1,3-diaxial interaction. The lack of this steric factor in the most stable conformer of the *normal* compound (**N**) increases significantly the likelihood of nitrogen quaternerization.

1a and **2a** obtained during the reaction sequence could be easily purified from the by-products. On the basis of its ^{1}H NMR spectrum, identical with that of natural (+)-dihydro-corynantheine, the β-methoxy-acrylate group of the synthetic product possesses *E* geometry. The correspondence of the racemic synthetic product with the natural alkaloid was also proven by their TLC, IR in CCl_4 and MS data.

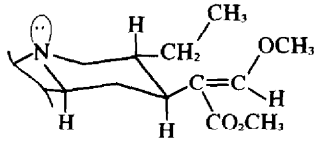


3i,4i

3i″,4i″ **3i′,4i′**



A



N

3β - Ethyl - 1,3,4,7,12,12bα - hexahydro - 2H,6H - indolo[2,3-a]quinolizin - 2 - ylidenemalononitrile (**5**)

To a stirred soln of malononitrile (10 g; 152 mmol) in CH_2Cl_2 (25 ml) 3β - ethyl - 1,3,4,7,12,12bα - hexahydro - 2H,6H - indolo[2,3-a]quinolizin - 2 - on (6·7 g; 25 mmol), NH_4OAc (0·1 g) and MeOH (15 ml) were added under argon. The mixture was refluxed for 3 min, and the homogenious soln obtained left to stand at room temp. for 48 hr. Gradually yellow crystals separated. Then the CH_2Cl_2 was distilled off *in vacuo* and the crystalline mass filtered off, and washed with MeOH and diethyl ether. The yellow crystals of **5** base (7·84 g; 99%) melted at 206–207°. (Found: C, 75·60; H, 6·34; N, 17·86. Calc. for $C_{20}H_{20}N_4$ (316·39): C, 75·92; H, 6·37; N, 17·71%). IR (KBr): 1600 (C=C and arom.); 2235 (conj. C ≡ N); 3300 cm^{-1} (NH). ^{1}H NMR (DMSO-d_6): 0·98 (3H, as, t, $-CH_2-CH_3$); 6·95–7·40 (4H, m, arom.); 11·15 (1H, s, NH).

3β - Ethyl - 9,10 - dimethoxy - 1,3,4,6,7,11bα - hexahydro - 2H - benzo[a]quinolizin - 2 - ylidenemalononitrile (**6**)

A mixture of malononitrile (6·6 g; 100 mmol), 3α - ethyl - 9,10 - dimethoxy - 1,3,4,6,7,11bα - hexahydro - 2H - benzo[a]quinolizin - 2 - on (14·47 g; 50 mmol), MeOH (20 ml) and NH_4OAc (0·1 g) was homogenized with stirring at 50°. The soln was left for 24 hr at room temp. and 2 hr in a cooler under argon atmosphere. The yellow crystals of **6** (16·25 g; 96·5%) obtained after filtration melted at 160–161° (lit.[9] m.p. 159–160°). IR data corresponded with those reported.[9] (Found: C, 71·16; H, 7·02; N, 12·65. Calc. for $C_{20}H_{23}N_3O_2$ (337·40): C, 71·19; H, 6·87; N, 12·45%). ^{1}H NMR ($CDCl_3$): 0·98 (3H, as.t, $-CH_2-CH_3$); 3·88 (6H, s, $-OCH_3$); 6·64 and 6·68 (2H, C8- and C11-H).

3β - Ethyl - 1,3,4,7,12,12bα - hexahydro - 2H,6H - indolo[2,3-a]quinolizin - 2β - ylmalononitrile **3g**)

To a stirred suspension of **5** unsaturated dinitrile (0·95 g; 3 mmol) in MeOH (10 ml), CH_2Cl_2 (16 ml) and AcOH (0·1 ml) $NaBH_4$ (300 mg) was added little by little at 5°, until the reduction of the double bond was complete. The reaction could be controlled by TLC (system "C" R_f **5**: 0·80; R_f **3g**: 0·45). The soln can be directly used for the preparation of **3j** and subsequently the **3a** *allo* nitrile-ester. To isolate the **3g** *allo* dinitrile the soln was evaporated and the residue dissolved in CH_2Cl_2, washed with water, the pH value of which was carefully adjusted to 8 with NH_4OH. Having been dried the organic phase was rendered slightly acidic (pH 3) with 1 N HCl in MeOH. MeOH was added to the soln, from which the CH_2Cl_2 was distilled off. To the remaining MeOH suspension ether was added, and the colourless crystals of **3g**-HCl (0·93 g; 87%) obtained after filtration melted at 243° (dec.).

To recover the base the suspension of its HCl salt (0·355 g; 1 mmol) in CH_2Cl_2 (50 ml) was treated with water containing 1·1 equiv of NH_3. After shaking the organic layer was dried ($MgSO_4$) and evaporated. The residue crystallized from ether/hexane (0·26 g; 82%), m.p. 162–163°. (Found: C, 75·00; H, 7·05; N, 17·46. Calc. for $C_{20}H_{22}N_4$ (318·41); C, 75·44; H, 6·97; N, 17·60%). IR (KBr): 1610 (arom); 2250 (C≡N); 2750, 2795 cm^{-1} (Bohlmann bands). ^{1}H NMR (DMSO-d_6): 0·94 (3H, as.t, $-CH_2-CH_3$); 4·94 [1H, d, J = 9·5 cps; $-CH(CN)_2$]; 6·80–7·05 and 7·20–7·35 (2–2H, m, arom.); 10·64 (1H, s, indol NH). MS *m/e* (rel. intensity): 318(70; M$^+$); 317(60); 253(100); 237(2); 225(5); 224(8); 184(9); 170(13); 169(13); 156(11); 144(7); 143(10).

EXPERIMENTAL

IR spectra were recorded in KBr and in soln with Perkin Elmer 221 and Perkin Elmer 457 spectrophotometers. The ^{1}H NMR spectra were obtained using Perkin Elmer R12 (60 Mc) and JEOL PS 100 instruments; 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 temperature 150°, direct insertion).

The course of reactions 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" CH_2Cl_2–MeOH, 15:1
"B" benzene–MeOH, 8:1
"C" $CHCl_3$–MeOH, 50:1
"D" CH_2Cl_2–MeOH, 25:1.

The evaporation of solns was carried out *in vacuo* under argon, m.ps are uncorrected.

3β - Ethyl - 9,10 - dimethoxy - 1,3,4,6,7,11bα - hexahydro - 2H - benzo[a]*quinolizin - 2β - ylmalononitrile* (**4g**)

The reduction of **6** unsaturated dinitrile (6·75 g; 20 mmol) as well as the isolation of the **4g** *allo* dinitrile was carried out by the method applied to the corresponding indoloquinolizine derivative (Exp. 3.). TLC: system "B" R_f **6**: 0·70; R_f **4g**: 0·64. The soln obtained after the dosage of $NaBH_4$ can be directly used for the preparation of **4j** and subsequents **4a** *allo* nitrile-ester. The colourless crystals of **4g**-HCl (6·01 g; 80%) melted at 231–232° (dec., MeOH–ether). (Found: C, 64·02; H, 6·78; N, 11·39; Cl, 9·71. Calc. for $C_{20}H_{26}N_3O_2Cl$ (375·89): C, 63·90; H, 6·97; N, 11·18; Cl, 9·43%). IR (KBr): 1605 (arom.); 2250 (C≡N); 2460 cm^{-1} (broad; $\overset{\oplus}{\text{N}}$–H).

To recover the **4g** base the soln of its HCl salt (6·01 g; 16 mmol) in CH_2Cl_2 (100 ml) was shaken for some min with water containing an equiv amount of NH_3. The organic phase was dried, evaporated and the residue crystallized from ether/hexane (4·79 g; 71%), m.p. 153–154°. (Found: C, 70·48; H, 7·61; N, 12·65. Calc. for $C_{20}H_{25}N_3O_2$ (339·42): C, 70·77; H, 7·42; N, 12·38%). IR (KBr): 1605 (arom.); 2250 (C≡N); 2750, 2780 and 2800 cm^{-1} (Bohlmann bands). ^{1}H NMR ($CDCl_3$): 1·02 (3H, as.t, $-CH_2-CH_3$); 3·72 [1H, d, J = 10 cps; $-CH(CN)_2$]; 3·93 (6H, s, OCH_3); 6.54 (1H, s, C8-H); 6·59 (1H, s, C11-H).

Methyl cyano - 3β - ethyl - 1,3,4,7,12,12bα - hexahydro - 2H,6H - indolo[2,3-a]*quinolizin - 2β - ylacetimidate* (**3j**)

The **5** unsaturated dinitrile (0·95 g, 3 mmol) was reduced in CH_2Cl_2 (16 ml) and MeOH (10 ml) with $NaBH_4$ (75 mg). Without isolation of the **3g** *allo* dinitrile, MeOH (10 ml) and 1N NaOMe/MeOH (0·5 ml) were added to the mixture, which was then refluxed until TLC investigation showed the complete disappearence of **3g** (*ca* 80 min; R_f **3g**: 0·45 R_f **3j**: 0·15 in developing system "C"). The soln obtained can be directly used for producing **3a** nitrile-ester.

To isolate the **3j** imino-ether the solvent was evaporated, the residue dissolved in CH_2Cl_2 (30 ml), washed with water, dried ($MgSO_4$) and evaporated. The **3j** base crystallized from MeOH–ether (0·59 g; 56%), m.p. 205–206°. (Found: C, 72·16; H, 7·14; N, 15·65. Calc. for $C_{21}H_{26}N_4O$ (350·44): C, 71·96; H, 7·48; N, 15·99%). IR (KBr): 1655 (C=N); 2245 (C≡N); 2750, 2790 (Bohlmann-bands); 3200 and 3290 cm^{-1} (NH and NH_2). IR ($CHCl_3$) 1655, 1650 (shoulder) (C=N imine); 2245 (C≡N imine) 2185 w (C≡N enamine); 2750, 2800 and 2825 (Bohlmann-bands); 3295, 3325 and 3465 (NH and NH_2). ^{1}H NMR: see Table 1. MS *m/e* (rel. intensity): 350 (M^+; 30); 335(65); 318(21); 319(19); 253(100); 252(30); 251(65); 225(15); 224(15); 223(23); 221(22); 210(5), 184(15); 169(25); 168(25); 156(17).

Methyl cyano - 3β - ethyl - 1,3,4,6,7,11bα - hexahydro - 2H - benzo[a]*quinolizin - 2β - ylacetimidate* (**4j**)

The soln obtained after the reduction of **6** unsaturated dinitrile (20 mmol) was treated with 1N NaOMe/MeOH (5 ml) and MeOH (100 ml). The mixture was then refluxed until TLC investigation showed the total disappearance of **4g** (*ca.* 1 hr; R_f **4g**: 0·64; R_f **4j**: 0·46 in system "B"). This mixture can be used for preparing **4a** *allo* nitrile-ester without isolating the **4j** acetimidate.

To obtain the **4j**, the soln was evaporated to dryness; the residue was dissolved in CH_2Cl_2 (150 ml), washed with water, dried and evaporated. The residue was recrystallized from MeOH/ether. The colourless crystals of **4j** (4·60; 62%) melted at 144–145°. (Found: C, 68·20; H, 8·14. Calc. for $C_{21}H_{29}N_3O_3$ (371·46): C, 67·90; H, 7·87%). IR (KBr): 1610 (arom.); 1660 (C=N); 2250 (C≡N); 2740, 2790 (Bohlmann-bands); 3280 cm^{-1} ($\diagdown$NH). ^{1}H NMR ($CDCl_3$): 0·97 (3H, as.t, CH_2-CH_3); 3·40 (1H, 2xd, J = 6·0 c/s, NC–$\underset{|}{C}$H–); 3·82–3·86 (9H, OCH_3); 6·50 and 6·60 (2H, two singlets, arom. H); 7·48 (1H, broad; =NH). IR and ^{1}H NMR data for the imine ⇌enamine equilibrium (for ^{1}H NMR deuterated solvent were used): see Table 2. MS *m/e* (rel. intensity): 371 (M^+; 3); 370(2); 357(9); 356(35); 275(19); 274(100); 272(16); 246(5); 244(5); 205(11); 192(12); 191(15).

Table 1. ^{1}H NMR of **3j**

Solvent	CH_3-CH_2	OCH_3	indol NH	enamine =C–NH_2 / OCH_3	%	imine NH	%	Aromatic protons
DMFA	0·91 as.t (3)	3·74–3·86 (3)	10·72 s 10·83 s 10·98 s(1)	6·42 s 6·64 s	39	8·83 broad	61	6·93–7·50 m (4)
DMSO	0·93 as.t (3)	3·74–3·80 3 s(3)	10·66–10·83 3 s(1)	6·53 s 6·42 s	63	8·78 s	37	6·90–7·42 m (4)

Table 2. IR and ^{1}H NMR data of **4j**

Solvent	IR: imine C≡N	IR: imine C=N	IR: enamine conj. C≡N	^{1}H NMR: imine =NH[b]	%	^{1}H NMR: enamine $-NH_2$	%
C_2Cl_4	2245 m	1660	—	7·66 s 7·44 s	>95	—	—
C_6H_6	2245 m	1655	—	7·56 s	~93	—	—
$CHCl_3$	2245 m	1658	2185 vw	7·50 s 7·30 s	~90	—	—
$C_6H_5NO_2$	2245 m	—[a]	2185 w	8·13 s 7·95 s	>95	—	—
CH_3NO_2	2245 m	—[a]	2185 w	7·90 s 7·55 s	~90	—	—
CH_3CN	—[a]	1662	—[a]	7·92 s 7·70 s	~90	—	—
DMFA	2245 w	—[a]	2185 m	8·90 broad	63	6·36 s 6·60 s 39: 61[c]	37
DMSO	2245 vw	—[a]	2170 m	8·70 s 8·30 s	34	6·34 s 6·47 s 37: 63[c]	64

[a] the corresponding bounds could not be evaluated because of absorption of the solvent.
[b] splitting is because of the chirality of meso-C atom.
[c] the two singulett and the proportion represent the E and Z geometry of the C=C.

Methyl cyano - 3β - ethyl - 1,3,4,7,12,12bα - hexahydro - 2H,6H - indolo[2,3-a]quinolizin - 2β - ylacetate (**3a**)

To the cooled soln, obtained in Exp. 5, after being refluxed with NaOMe, water (5 ml) and HCl/MeOH was added until the pH remained slightly acidic. After removal of the CH_2Cl_2 colourless crystals separated from the aqueousmethanolic mixture. The **3a**-HCl–H_2O (1·06; 87%) as well as the **3a** base recovered from the salt were identical (m.p., TLC, IR, ^{1}H NMR) with the **3a** *allo* nitrile-ester previously reported.[5] MS *m/e* (rel. intensity): 351 (M^+; 97); 350(90); 336(2); 322(2); 320(1); 292(4); 253(100); 251(12); 225(11); 224(10); 223(8); 184(14); 170(13); 169(12); 156(11).

Methyl cyano - 3β - ethyl - 9,10 - dimethoxy - 1,3,4,6,7,11bα - hexahydro - 2H - benzo[a]quinolizin - 2β - ylacetate (**4a**)

To the cooled soln, obtained in Exp. 6. after being refluxed with NaOMe, water (10 ml) and HCl/MeOH were added until the pH remained slightly acidic. The **4j** acetimidate was converted completely into **4a** *allo* nitrile-ester over a period of about 10 min. (TLC R_f **4j**: 0·46; R_f **4a**: 0·61 in system "B"). Then the mixture was concentrated to a small volume, diluted with ice-water and neutralized with 2N NH_4OH while cooling. The base was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and evaporated. The methanolic soln of the residue was acidified with HCl in MeOH (pH 3) and treated with ether. The colourless crystals of **4a**-HCl salt (6·87 g; 84% counted upon **6**), as well as the base recovered from it were identical (m.p., TLC, IR, ^{1}H NMR, MS) with the *allo* nitrile-ester prepared earlier.[6]

Dimethyl 3α - ethyl - 1,3,4,7,12,12bα - hexahydro - 2H,6H - indolo[2,3-a]quinolizin - 2β - ylmalonate (**3f**)

The hydrochloride salt of **3b** *normal* nitrile-ester[1] (1·94 g; 5 mmol) was suspended in dry MeOH (50 ml) which was saturated with anhyd HCl at −10°. The soln was left at room temp. for 48 hr and afterwards refluxed for 4 hr. Most of the solvent was then removed, and the colourless crystals of **3f**-HCl salt separated were filtered off (1·79 g; 85%), m.p.: 245° (dec). R_f **3b**: 0·40; R_f **3f**: 0·31 in system "D".

To recover the corresponding base the cooled CH_2Cl_2 suspension of the **3f**-HCl (4·20 g; 10 mmol) was treated with an equiv amount of 2N NaOMe in MeOH. The mixture was washed with ice-water, dried ($MgSO_4$) and evaporated. The foam resulted in an almost quantitative yield and satisfactory purity for use in the LAH reduction. An analytical sample was prepared by recrystallization from chloroform-hexane containing a little EtOH. The colourless crystals of **3f** (1·83–2·00 g; 85–93%) melted at 136–139°. (Found: C, 66·94; H, 7·72; N, 6·58. Calc. for $C_{22}H_{28}N_2O_4$. C_2H_5OH (430·53): C, 66·95; H, 7·96; N, 6·51%). IR (KBr): 1720, 1745 (C=O); 2730, 2740 (Bohlmann-bands); 3160 cm^{-1} (NH). ^{1}H NMR ($CDCl_3$): 0·97 (3H, as.t, $-CH_2-C\underline{H}_3$); 1·25 (3H, t, $C\underline{H}_3-CH_2-O-$); 2·35 (1H, s, $C_2H_5-O\underline{H}$); 3·75 and 3·85 (3–3H, 2s, OCH_3); 3·74 (2H, q, $-OC\underline{H}_2CH_3$); 6·95–7·25 (3H, m, arom.); 7·35 (1H, m, arom.); 8·27 (1H, s, >NH). MS *m/e* (rel. intensity): 384 (M^+; 100); 383(83); 369(5); 355(4); 353(5); 325(6); 321(3); 253(48); 251(20); 225(20); 184(7); 170(16).

Dimethyl 3α - ethyl - 9,10 - dimethoxy - 1,3,4,6,7,11bα - hexahydro - 2H - benzo[a]quinolizin - 2β - ylmalonate (**4f**)

The hydrochloride of the *normal* nitrile-ester **4b**[1] (4·44 g; 10 mmol) was suspended in dry MeOH (100 ml), and saturated at −10° with dry HCl. Next, it was allowed to stand for 2 days at room temp. and then boiled for 4 hr. After cooling, it was evaporated, the residue dissolved in ice-water (50 ml), and neutralized with 2N NH_4OH. The ppt was extracted with ether (2 × 25 ml), the combined ether phase dried ($MgSO_4$) and evaporated. The oily residue was dissolved in MeOH (2–3 ml) and slightly acidified with HCl in MeOH (pH 2). Ether was added to the warm soln until it became turbid. After standing, colourless crystals of **4f**-HCl (3·80 g; 86%) separated, which decomposed at 200–205°. IR (KBr): 1740 and 1720 (C=O); 2500, 3350 cm^{-1} (⊕N–H).

The base was liberated from the hydrochloride, and the product recrystallized from ether-hexane, to yield colourless **4f** diester, m.p. 76–78°. (Found: C, 64·96; H, 7·62; N, 3·45. Calc. $C_{22}H_{31}NO_6$ (405·48): C, 65·16; H, 7·71; N, 3·46%). IR (KBr): 1745 (C=O); 2730, 2790 cm^{-1} (Bohlmann-bands). ^{1}H NMR ($CDCl_3$): 3·73 and 3·81 (3–3H, 2s, $-CO_2CH_3$); 3·88 (6H, s, OCH_3); 6·66 (1H, s, C8-H); 6·77 (1H, s, C11-H). MS *m/e* (rel. intensity): 405 (M^+; 70); 404(80); 390(41); 375(14); 349(61); 347(8); 274(100); 246(55); 205(30); 191(40); 176(9).

(±)-Desmethyl-dihydrocorynantheine (**3i** and **3i′**, **3i″**, resp.)

The soln of the crude foamy **3f** *normal* diester (1·92 g; 5 mmol) in freshly dehydrated ether (100–120 ml) was poured into a desiccated flask under argon. The soln was cooled to −70° and LAH in ether (0·5 mmol/ml; 8·75 ml = 4·375 mmol = 3·5 equiv) was added over a period of 1 hr. After stirring for 2 hr the excess reagent as well as the complex were destroyed by dropwise addition of sat. Na_2SO_4 (15–20) ml) while maintaining the temp. at −70°. The mixture was kept cool overnight. The ether phase was decanted and the slurry extracted with ether (2 × 40 ml) thereafter with CH_2Cl_2 (10 × 30 ml), until the extract did not give a positive Fe(III) chloride test. The extraction should be carried out cautiously to avoid the formation of an emulsion. The combined ether phase contained starting material (**3f**) and **3i** target molecule (TLC R_f **3f**: 0·41; R_f **3i**: 0·37 in system "B"). The **3i** α-formyl-ester derivative can be extracted from the ether soln with 2N NaOH, and the unreacted **3f** can be recovered (0·66 g; 34·5%). The 2N NaOH phase was neutralized and extracted with CH_2Cl_2. All the CH_2Cl_2 extracts containing **3i** α-formyl-ester were combined, washed with sat NaCl, dried and evaporated. The oily residue (0·66–0·75 g; 56–64% estimated on the unrecovered **3f**) can be recrystallized from EtOAc; its m.p. however, was not constant, presumably because of the varying proportion of the tautomer forms **3i**, **3i′** and **3i″**. The **3i**-HCl salt melted at 233–234° (lit.[4c] m.p. 236·2–238°). The (±)-**3i** obtained was identical (TLC, MS, IR, ^{1}H NMR) with an authentic sample[12] prepared from natural (+)-dihydrocorynantheine. (Found: C, 71·47; H, 7·63; N, 7·78. Calc. for $C_{21}H_{26}N_2O_3$ (354·43): C, 71·16; H, 7·40; N, 7·90%). IR (KBr): aldehyde form 1730 (C=O ester) 1695 (shoulder C=O aldehyde) *cis* enol form 1680 (C=O conj. ester) 1640 (C=C); 2740 and 2800 cm^{-1} (Bohlmann-bands). IR ($CHCl_3$): 1670 (C=O of **3i′**

Table 3. ^{1}H NMR of **3i**

				aldehyde form		*cis*-enol form			*trans* form enol		
Solvent	CH_3CH_2	OCH_3	NH	–CHO	%	=CH	OH	%	=CH	–OH	%
$CDCl_3$	0·90 as.t.	3·65–3·86 4 or 5 s (3)	7·95 s	9·60 s 9·70 s	10	unvaluable	12·50 s	65	7·70 s	8·21 s	~25
$(CD_3)_2CO$	0·92 as.t.	3·65 s 3·86 s (3)	9·77 s (1)	—	—	unvaluable			7·87 s	4·40 broad	65
DMSO-d_6	0·90 as.t.	3·64 s	10·37 s	—	—	—	—	—	7·69 s	7·30 s	>90

and C=C of **3i''**); 1620 (C=C of **3i'**); 1725 (week, C=O of **3i''**); 2750 and 2800 (Bohlmann-bands); 3480 cm^{-1} MS *m/e* (rel. intensity): 354·1940 (M^+ 45, $C_{21}H_{26}N_2O_3$); 353(35); 339(12); 326(9); 325(12); 322(20); 321(16); 311(12); 253(24); 251(13); 225(19); 197(5); 184(22); 171(80); 170(78); 169(79); 156(100); 143(20); 129(15); 128(26); 115(14). ^1H NMR: see Table 3.

The Na *salt of* **3i'** *or* **3i''**. To the stirred suspension of **3i** in ether/CH_2Cl_2 1:1 equiv amount of 1N NaOMe in MeOH was added. The soln obtained was then evaporated, the residue treated with ether/hexane. The tan crystals of the enol-Na were filtered off and dried over P_2O_5. IR (KBr): 1650 (C=O conj., chel; C=C); 2730 and 2795 (Bohlmann-bands); 3390 cm^{-1} (broad, >NH).

Methyl formyl - 3α - ethyl - 9,10 - dimethoxy - 1,3,4,6,7,11bα - hexahydro - 2H - benzo[a]*quinolizin - 2β - ylacetate* (**4i**) *and the tautomeric* (Z)- *and* (E) - *methyl β - hydroxy - acrylate derivatives* (**4i'** and **4i''**)

The reduction of **4f** diester (3·24 g; 8 mmol) to **4i** α-formyl-ester was accomplished by the method described from **3i** with prolonged reaction time (6 hr). In the course of processing the unreacted **4f** was recovered (0·70 g; 22%). The tan crystals of **4i** (exactly of the tautomer mixture of **4i**, **4i'** and **4i''**) (1·47 g; 62% estimated on the unrecovered **4f**) obtained by digestion of the oily residue with ether/hexane melted at 112–113°. R_f **4f**: 0·40; R_f **4i**: 0·29 in system "B". (Found: C, 66·82; H, 8·03; N, 3·70. Calc. for $C_{21}H_{29}NO_5$ (375·45): C, 67·18; H, 7·79; N, 3·73%). IR (KBr): 1720 (C=O ester) 1700 (shoulder, C=O aldehyde); 1680 (C=O conj. chel. ester); 1640 (C=C); 1605 (arom.) 2740 cm^{-1} (Bohlmann-bands). IR ($CHCl_3$): 1730 (weak C=O ester); 1670 (strong C=O conj. chel. ester); 1620 (C=C and arom.); 2760 and 2810 cm^{-1} (Bohlmann-bands). IR (DMSO-d_6): 1705 (strong; C=O conj. ester of **4i''**); 1670 cm^{-1} (medium; C=O conj. chel. ester of **4i'**) MS *m/e* (rel. intensity): 375·2048 (M^+; 45, $C_{21}H_{29}NO_5$); 374(36); 360(40); 347(11); 346(12); 343(16); 342(36); 316(6); 274(70); 272(29); 246(61); 244(12); 205(100); 192(52); 191(78); 190(50); 176(20). ^1H NMR: see Table 4.

The Na *salt of* **4i'** *or* **4i**. To the solution of **4i** (0·375 g; 1 mmol) in MeOH (1 ml) equiv. amount of 1N NaOMe in MeOH and ether were added till the lukewarm soln became turbid. The colourless crystals which separated after 12 hr were filtered off (0·32 g; 80%), m.p.: 165–166°. IR (KBr): 1700–1620 cm^{-1} (broad, conj. chel. ester). ^1H NMR ($CDCl_3 + CD_3OD$): 0·92 (3H, as.t. CH_3CH_2–); 3·59 (3H, s, CO_2CH_3); 3·80 and 3·82 (3–3H, s, OCH_3): 6·58 (1H, s, C8-H); 6·72 (1H, s, C11-H); 8·75 (1H, s, =CH).

(±)-*Dihydrocorynantheine* (**1a**)

Methylation process under the condition of acetalformation: Methylation with equivalent amount of methanol in CH_2Cl_2. The suspension of **3i** (35 mg; 0·1 mmol) in CH_2Cl_2 (4·5 ml) was saturated with dry HCl at 0°. Then 1% MeOH in CH_2Cl_2 0·11 mmol) was added to the soln which was left to stand for 6 days in a cooler. The reaction could be controlled by TLC (R_f **3i**: 0·44; R_f **1a**: 0·49 in system "A"). The mixture was evaporated, the residue taken up in ether, extracted with 2N NaOH (3 × 1 ml), washed with sat NaCl aq and dried ($MgSO_4$). After evaporating the ether phase, **1a** was obtained as an oily residue (25 mg; 68%). From the 2N NaOH soln, **3i** (4·8 mg; 13·7%) could be recovered via neutralization, extraction with ether and subsequent evaporation. The yield of **1a** estimated on the unrecovered starting material was 78%. The spectroscopical (IR in CCl_4, MS[13]) and TLC behaviour of the synthetic product corresponded to that of the natural (+)-dihydrocorynantheine. IR (CCl_4): 1640 (C=C); 1710 (C=O); 2740, 2800 and 2840 (Bohlmann-bands); 3480 cm^{-1} (indol NH). MS: M (measured) = 368·2097; $C_{22}H_{28}N_2O_3$; M (Calc.): 368·2100

Methylation with excess amount of methanol: The preparation of desmethyl-dihydrocorynantheine-dimethylacetal (**3k**). The soln of **3i** (35 mg; 0·1 mmol) in MeOH (4 ml) was saturated with dry HCl at −5°, and left to stand in a cooler. The reaction was checked by TLC. After 3 days the starting material disappeared; beside the desired **1a**, however, a spot of **3k** dimethylacetal appeared, (R_f **3i**: 0·44, R_f **1a**: 0·49, R_f **3k**: 0·56 in system "A"). The two compounds could be separated by preparative TLC (20 × 20 × 0·5 mm sheet of silica gel PF_{254} in system "A"). The **1a** (12 mg; 33%) obtained was identical with the synthetic product described, its spectroscopical data corresponded to those of the natural product.

The yield of **3k** dimethylacetal is 16 mg; (40%). IR (CCl_4): 1740 (C=O); 1620 (arom.); 2740, 2800 and 2820 cm^{-1} (Bohlmann-bands). MS *m/e* (rel. intensity): 400·2359 (M^+; 99, $C_{23}H_{32}N_2O_4$); 390(95); 385(40); 369(20); 253 [M–CH(CH(OCH$_3$)$_2$)(CO$_2$CH$_3$); 70]; 251(100); 225(30); 184(20); 170(30); 169(40); 156(25).

Methylation with dimethylsulphate. To the stirred suspension of desmethylcorynantheine-sodium (**3i**-Na) (37 mg; 0·1 mmol) in dry benzene (5 ml), 1N dimethylsulphate in benzene (0·1 ml) was added. After a 3–4 hr reaction period at room temp. the mixture was left in a cooler overnight, then diluted with ether (10 ml) extracted with 2N NaOH (3 × 2 ml) to remove the unreacted **3i**. The organic phase was washed with sat NaCl aq, dried ($MgSO_4$) and evaporated (9·7 mg; 24%). The spectroscopical (IR, MS) and TLC behaviour of the oily residue (**1a**) corresponded to that of the synthetic racemate described and that the natural (+)-dihydrocorynantheine.

Methyl (E) - *methoxymethylene - 3α - ethyl - 9,10 - dimethoxy - 1,3,4,6,7,11bα - hexahydro - 2H - benzo*[a]*quinolizin - 2β - ylacetate* (*dimethoxy - despyrrolo - dihydrocorynantheine*) (**2a**)

Methylation under the condition of acetal formation (HCl/MeOH). An abs. MeOH (10 ml) soln of **4i** (376 mg; 1 mmol) was saturated with dry HCl at −10°, and left to stand at room temp. for 48 hr. It was then concentrated to ~1 ml, diluted with ice-water (30 ml) and made alkaline with 2N NaOH (pH 10). The **2a** was extracted from the alkaline mixture with ether (3 × 20 ml). The combined organic phase was washed with sat NaCl aq until it became neutral, then dried and evaporated. The residue was taken up in MeOH (3 ml), and acidified slightly (pH 3) with HCl in MeOH. The **2a** HCl (215 mg; 50%) obtained by crystallization from MeOH/ether (1:3) melted at 155–158°. IR (KBr): 1690 (C=O conj.); 1640 (C=C); 1610 (arom.); 2400 and 3400 cm^{-1} (broad >N–H). MS *m/e* (rel. intensity): 389·2205 [M^+ (basis), 30, $C_{22}H_{31}NO_5$]; 388(28); 375(20); 374(76); 360(5); 358(7); 342(2·5); 332(8); 260(11); 246(32); 205(100); 191(35).

From the aqueous solution of the hydrochloride salt the base

Table 4. ^1H NMR of **4i**

Solvent	CH_3CH_3–	OCH_3 CO_2CH_3	C8-H	C11-H	=CH–OH Z	=CH–OH E	=CH–OH Z	=CH–OH E	CHO	aldehyde:Z:E
$CDCl_3$	0·93 as.t. (3)	3·85 s (3) 3·91 s (6)	6·52 s (1)	6·58 s (1)	7·05 s	7·60 s	11·45 s	—	9·63 s 9·73 s	10:80:10
DMSO-d_6	0·90 as.t. (3)	3·66 (3) 3·75 s (6)	6·64 s (1)	6·68 s (1)	7·29 s	7·72 s	—	—	—	0:10:90

can be prepared by treating with NH_4OH and by subsequent ether extraction. The tan foam (90%) obtained after evaporation had a fragmentation pattern identical with that of the HCl salt. IR (KBr): 1695 (C=O conj.); 1630 (C=C); 1605 (sh. arom.); 2740 and 2780 cm^{-1} (Bohlmann-bands). ^1H NMR ($CDCl_3$): 0·93 (3H, as.t. CH_3CH_2–); 3·75 (3H, s, =CH–OCH_3); 3·81 (3H, s, CO_2CH_3); 3·86 (6H, s, OCH_3); 6·62 (1H, s, C8-H); 6·72 (1H, s, C11-H); 7·42 (1H, s, =CH–).

Methylation with dimethylsulphate. To the stirred suspension of **4i**-Na (200 mg; 0·5 mmol) in benzene (10 ml) and hexane (20 ml) 0·1 N dimethylsulphate in benzene (5 ml) was added at 50° over a period of about 15 min. After stirring for 1 hr the unreacted **4i** was removed from the mixture by extraction with 2N NaOH. The organic phase was dried ($MgSO_4$) and evaporated. The preparation of **2a**-HCl (83 mg; 39%) from the residue was accomplished as described. From the basic-aqueous extracts 80 mg of **4i** could be recovered; the yield of **2a**-HCl estimated on the unrecovered **4i** was 65%. The **2a**-HCl as well as the base obtained proved to be identical in every respect with the compound prepared previously.

Acknowledgements—The authors wish to thank the Hungarian Academy of Sciences for financial support, Prof. R. Goutarel, Gif-sur-Yvette, France, for providing sample of natural (+)-dihydrocorynantheine; Mrs. I. Balogh-Batta and her co-workers for the microanalyses; Dr. P. Kolonits and his co-workers for IR and NMR spectra. Thanks are expressed to Mrs S. Krakoviczer for technical assistance.

REFERENCES

[1]Part II: M. Bárczai-Beke, G. Dörnyei, M. Kajtár and Cs. Szántay, Tetrahedron.

[2a]P. Karrer and H. Salomon, *Helv. Chim. Acta* **9**, 1059 (1926); [b]Raymond-Hamet, *C. R. Acad Sci. Paris* **197**, 860 (1933); [c]M. Janot and R. Goutarel, *Ibid.* **206**, 1183 (1938); [d]A. Blumenthal, C. H. Eugster and P. Karrer, *Helv. Chim. Acta* **37**, 787 (1954).

[3a]J. E. Saxton, *The Indole Alkaloids in The Alkaloids* (Edited by R. H. F. Manske), Vol. VII. p. 37. Academic Press New York (1960); [b]R. H. F. Manske, *Alkaloids of Pseudocinchona and Yohimbe in The Alkaloids* (Edited by R. H. F. Manske), Vol. VIII. p. 639. Academic Press, New York (1965); [c]H. J. Monteiro, *Yohimbe and Related Alkaloids in The Alkaloids* (Edited by R. H. F. Manske), Vol. XI. p. 145. Academic Press, New York (1968).

[4a]E. E. van Tamelen and J. B. Hester, *J. Am. Chem. Soc.* **81**, 3805 (1959); [b]J. A. Weisbach, J. L. Kirkpatrick, K. R. Williams, E. L. Anderson, N. C. Yim and B. Douglas, *Tetrahedron Letters* 3457 (1965); [c]E. E. van Tamelen and J. B. Hester, *J. Am. Chem. Soc.* **91**, 7342 (1969); [d]E. E. van Tamelen and I. G. Wright, *Tetrahedron Letters* 295 (1964); [e]R. L. Autrey and P. W. Scullard, *J. Am. Chem. Soc.* **90**, 4917 (1968).

[5]Cs. Szántay and M. Bárczai-Beke, *Tetrahedron Letters* 1405 (1968); *Chem. Ber.* **102**, 3963 (1969).

[6]M. Bárczai-Beke, G. Dörnyei, J. Tamás und Cs. Szántay, *Chem. Ber.* **105**, 3244 (1972).

[7]D. Beke and Cs. Szántay, *Ibid.* **95**, 2132 (1962).

[8]Cs. Szántay and L. Töke, *Tetrahedron Letters* 251 (1963).

[9]A. Brossi, M. Baumann, L. H. Chopard-dit-Jean, J. Würsch, F. Schnider and O. Schnider, *Helv. Chim. Acta* **42**, 772 (1959).

[10]L. Töke, G. Blaskó, L. Szabó and Cs. Szántay, *Tetrahedron Letters* 2459 (1972); L. Töke, G. Blaskó, L. Szabó, G. Tóth and Cs. Szántay, *Acta Chim. Acad, Sci. Hung.* **81**, 97 (1974).

[11]W. F. Trager, C. M. Lee and A. H. Beckett, *Tetrahedron* **23**, 365, 375 (1967).

[12]J. P. Kutney and R. T. Brown, *Ibid.* **22**, 321 (1966).

[13]A. H. Beckett, D. Dwuma-Badu and R. E. Haddock, *Ibid.* **25**, 5961 (1969).