AZASTEROIDAL HORMONE ANALOGUES RELATED TO DOISYNOLIC ACID[1]

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ABSTRACT

Condensation of β-*m*-methoxyphenethylamine with methyl coumalate followed by saponification of the ester gave N-(*m*-methoxyphenethyl)-5-carboxy-2-pyridone (I). Cyclization of the pyridone using phosphorus oxychloride gave 3-carboxy-6,7-dihydro-9-methoxybenzo[*a*]-quinolizinium chloride (II*e*), which, on catalytic reduction, afforded the two possible racemic 3-carboxy-1,3,4,6,7,11*b*-hexahydro-9-methoxy-2H-benzo[*a*]quinolizines (III*b* and IV*b*). The corresponding ethyl esters were prepared in an analogous manner and their stereochemistry was assigned on the basis of equilibration experiments. Mercuric acetate oxidation of the racemic esters gave 3-carbethoxy-1,2,3,4,6,7-hexahydro-9-methoxybenzo[*a*]quinolizinium perchlorate (V).

In continuing our work on the preparation of amino acid analogues of artificial estrogens (1), we became interested in incorporating a nitrogen atom into the skeleton of compounds related to doisynolic acid. Several isomers of the latter compound are known to be potent estrogens (2). This paper describes the preparation of some polyhydrobenzo[*a*]quinolizines (III–V) which represent 8-aza analogues of doisynolic acid.

By the method of Wiley, Smith, and Knabeschuh (3), treatment of methyl coumalate (4) with an excess of *m*-methoxyphenethylamine and saponification of the crude product gave N-(*m*-methoxyphenethyl)-5-carboxy-2-pyridone (I) in 82% yield. Cyclization of this pyridone using phosphorus oxychloride in xylene (3) followed by treatment of the intermediate acid chloride with absolute ethanol gave 3-carbethoxy-6,7-dihydro-9-methoxybenzo[*a*]quinolizinium chloride (II*a*) in 72% yield. Treatment of the crude reaction mixture with potassium iodide gave the corresponding iodide (II*b*). Hydrolysis of the intermediate acid chloride gave the quinolizinium acid salts II*d* and II*e*.

A number of attempted cyclizations of pyridones to produce substituted quinolizinium compounds have yielded simply the corresponding pyridinium salts (ref. 5 and references therein). That N-(*m*-methoxyphenethyl)-5-carboxy-2-pyridone did undergo cyclization to the quinolizinium ring system is evidenced by the fact that the products II*a*–II*e* have ultraviolet absorption spectra characteristic of this ring system (3), but different from what would be expected from a composite of the isolated *m*-methoxyphenyl and carboxychloropyridinium chromophores had cyclization not occurred. It is generally found that Bischler-Napieralski reactions of N-*m*-methoxyphenethylamides and lactams occur preferentially with cyclization para to the methoxyl group (6–8). That a para ring closure occurred in the present work is indicated by spectral means, and will be discussed later under the preparation of III*a*.

Catalytic hydrogenation of the quinolizinium ester salts II*a*–II*c* using Adams catalyst resulted in the isolation of the two possible racemic forms of the free amino ester. The best results were obtained when the chloride salt II*a* was used because of its greater

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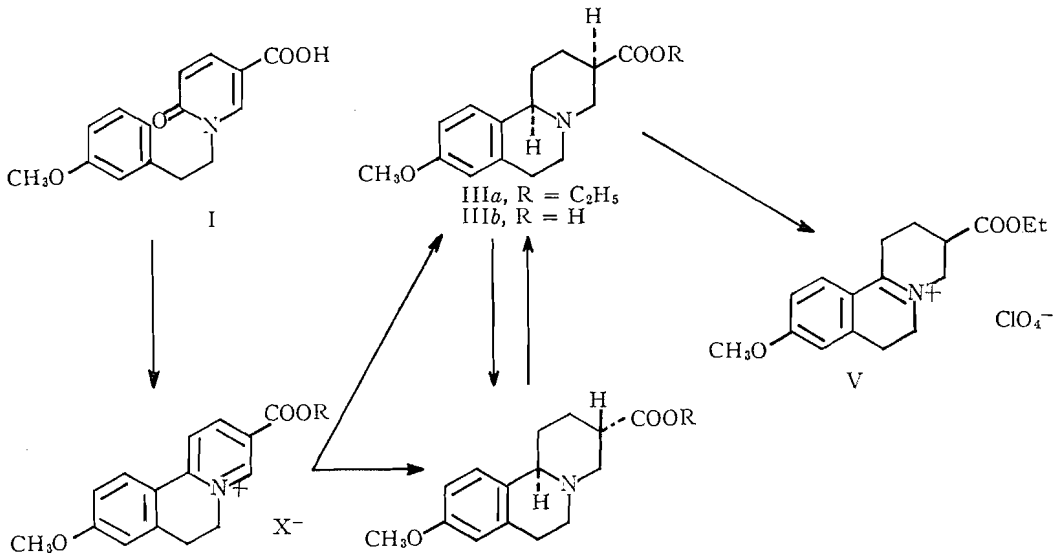
solubility as compared with the iodide and perchlorate salts II*b* and II*c*. Thus, when 3-carbethoxy-6,7-dihydro-9-methoxybenzo[*a*]quinolizinium chloride (II*a*) was reduced catalytically using Adams catalyst and a solvent mixture composed of 2 parts ethanol, 2 parts water, and 1 part acetic acid, 3 molecular equivalents of hydrogen were absorbed, and the product obtained in 76% yield was the hydrochloride of 3-carbethoxy-1,3,4,6,7,11*b*-hexahydro-9-methoxy-2H-benzo[*a*]quinolizine IV*a* in which the relationship of the hydrogen atoms attached to C-3 and C-11*b* is *trans*. The basis for this assignment will be given below. Also isolated from this reduction was 16% of a lower-melting hydrochloride salt which was a mixture of the two racemic forms. That the reduction took place in the pyridinium ring rather than the benzene ring is shown by the ultraviolet absorption spectrum. The hydrochloride of compound IV*a* has maxima at 277 (ϵ 1 750) and 284 mμ (ϵ 1 720) while 6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride has maxima at 278 (ϵ 1 960) and 285 mμ (ϵ 1 840).

Treatment of the hydrochloride of IV*a* with dilute sodium hydroxide liberated *trans*-3-carbethoxy-1,3,4,6,7,11*b*-hexahydro-9-methoxy-2H-benzo[*a*]quinolizine IV*a* in 95% yield.



II*a*, R = C_2H_5, X = Cl
II*b*, R = C_2H_5, X = I
II*c*, R = C_2H_5, X = ClO_4
II*d*, R = H, X = ClO_4
II*e*, R = H, X = Cl

IV*a*, R = C_2H_5
IV*b*, R = H

On the other hand, catalytic reduction of II*a* using Adams catalyst in glacial acetic acid again resulted in an uptake of 3 molecular equivalents of hydrogen. After evaporation of the reduction mixture, treatment of the crude oil with dilute ammonium hydroxide resulted in the isolation of 86% of the isomeric *cis* ester III*a*. The ultraviolet spectra of compounds III*a* and IV*a* are consistent with the presence of a 6-methoxy-1,2,3,4-tetrahydroisoquinoline chromophore and are inconsistent with an 8-methoxy-1,2,3,4-tetrahydroisoquinoline chromophore (7). This rules out the possibility that cyclization of I occurred at the less favorable position ortho to the methoxy group. Further conformation for the para ring closure of I can be found in the n.m.r. spectrum of III*a*. The aromatic region of the curve is typical of a 1,2,4-trisubstituted benzene of the estrone type (cf. ref. 8).

Equilibration studies on the isomeric esters III*a* and IV*a* indicated that III*a* is the less stable isomer and that the equilibrium position lies approximately 80% on the side of IV*a*. The isomer IV*a* was therefore assigned the thermodynamically more stable configuration in which the carbethoxy group is equatorial. Treatment of both esters with mercuric acetate in aqueous acetic acid followed by the addition of perchloric acid (6) resulted in the formation of the same dehydro product, 3-carbethoxy-1,2,3,4,6,7-hexahydro-9-methoxybenzo[*a*]quinolizinium perchlorate (V), in about 90% yield. Catalytic hydrogenation of V using Adams catalyst in glacial acetic acid gave a mixture of the two esters III*a* and IV*a* with the more stable isomer IV*a* predominating in about the same ratio as found in the equilibration of the amino ester.

The ease with which the mercuric acetate oxidation proceeds under the mild conditions used for both esters is indicative of a *trans* quinolizine system having an axial hydrogen at the bridgehead (9). Further evidence for the *trans* ring juncture is given by the fact that infrared spectra of both esters show four characteristic peaks in the carbon–hydrogen stretching region when a calcium fluoride prism is used: the major band at 2 940 cm^{-1} and three peaks of medium intensity at 2 850, 2 815, and 2 780 cm^{-1}. Such bands appear to be associated with tertiary amines which have two or more adjacent hydrogens *trans* diaxial to the electron pair of the nitrogen (refs. 10, 11; see, however, ref. 12 for possible exceptions).

On the basis of the above evidence for *trans*-fused rings, and the results of the equilibration studies, the more stable low-melting material is assigned structure IV*a* with the carbethoxy group equatorial. The isomeric ester is assigned the configuration with an axial carbethoxy and is represented by III*a*. After this work had been completed, Ohki and Noike (13) published independently the structural assignment of the isomeric 3-carbethoxyquinolizidines, in which essentially the same methods of elucidation were employed.

Once the configuration of the amino esters had been determined, the preparation of the corresponding amino acids was investigated. Hydrogenation of 3-carboxy-6,7-dihydro-9-methoxybenzo[*a*]quinolizinium chloride (II*a*), using Adams catalyst in glacial acetic acid and in aqueous acetic acid solution, resulted in the formation of mixtures of amino acids as their hydrochlorides. Separation of the isomeric compounds by fractional crystallization from absolute ethanol gave 46% of the less soluble higher-melting isomer later shown to be the hydrochloride of IV*b*. The filtrate gave the lower-melting hydrochloride of III*b* in 50% yield. The homogeneity of the different isomers was shown by paper chromatography.

Treatment of the hydrochloride of IV*b* with exactly 1 equivalent of sodium hydroxide afforded the amino acid IV*b* in 94% yield. The relationship of this amino acid and therefore of its antecedent hydrochloride to the amino esters was determined by treating an ethanolic solution of the free amino acid with ethereal diazoethane. The amino acid IV*b* was converted to the amino ester IV*a* (equatorial carbethoxy) in a 93% yield.

In the same manner as above, the hydrochloride of III*b* was converted to the free amino acid III*b* in 89% yield and this in turn was transformed into the amino ester III*a* (axial carbethoxy) in 72% yield by treatment with ethereal diazoethane.

The infrared spectra of these isomeric acids are of interest, in that III*b* with its axial carboxyl group can form an intramolecular hydrogen bond while the isomeric amino acid IV*b* cannot form such a bond unless the nitrogen atom undergoes inversion to give the less favorable cisoid ring juncture with the electron pair on nitrogen oriented equatorially and the N-alkyl group oriented axially. Spectra of the amino acids in potassium

bromide pellets show that III*b* (axial carboxyl) has absorption peaks at 2 860 cm^{-1} (m, C—H stretching), 2 740–2 580 cm^{-1} (w, broad, characteristic of amine salts), and two peaks associated with carboxyl absorption: 1 675 cm^{-1} (s, broad, hydrogen-bonded associated carboxyl) and 1 590 cm^{-1} (m, ionized carboxyl).

The isomeric amino acid IV*b* shows essentially the same peaks but there are significant differences in intensity and exact location. The 2 860 cm^{-1} peak is almost nonexistent and the absorption at 2 720–2 580 cm^{-1} is more intense than in III*b*. The carboxyl absorption, however, shows the greatest change. The free-carboxyl absorption has shifted to 1 650 cm^{-1} and is present only as a shoulder. The ionized carboxyl at 1 590 cm^{-1} has increased greatly in intensity and is the most intense band in the spectrum.

Paper chromatography of the two amino acid preparations indicated that the preparations were homogeneous. The more soluble *cis* material III*b* moved faster under the conditions employed and a mixture of the two isomers was separated without difficulty.

EXPERIMENTAL

Infrared spectra were determined with a Perkin–Elmer (model 21) spectrophotometer fitted with a sodium chloride prism unless otherwise specified. Ultraviolet spectra were determined in 95% ethanol with a Cary recording spectrophotometer (model 11 MS). The microanalyses were performed by Dr. S. M. Nagy and his associates. Melting points are uncorrected.

N-(m-Methoxyphenethyl)-5-carboxy-2-pyridone (I)

A mixture of 2.0 g of methyl coumalate (4) and 5 ml of *m*-methoxyphenethylamine was converted to 3.0 g (82%) of crude product, m.p. 179–181°, by the method of Wiley *et al.* (3). Recrystallization of the material twice from 95% ethanol gave white crystals of I, m.p. 180.5–181°. The ultraviolet spectrum showed peaks at 261 mμ (ϵ 16 100) and 303 mμ (ϵ 5 310). The infrared spectrum (KBr pellet) showed carbonyl peaks at 1 700 and 1 640 cm^{-1}.

Anal. Calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.55; N, 5.13. Found: C, 65.62; H, 5.54; N, 5.08.

3-Carbethoxy-6,7-dihydro-9-methoxybenzo[a]quinolizinium Iodide (IIb)

Following a known method (3), we converted 1.4 g of N-(*m*-methoxyphenethyl)-5-carboxy-2-pyridone to 1.8 g of II*b*, m.p. 215–219° (decomp.) (recrystallized from ethanol–ether). The ultraviolet spectrum showed maxima at 220 (ϵ 23 800), 291 (ϵ 6 620), and 364 mμ (ϵ 27 320) and a shoulder at 258 mμ (ϵ 5 090). The infrared spectrum showed a carbonyl peak at 1 725 cm^{-1}.

Anal. Calcd. for $C_{17}H_{18}INO_3$: C, 49.65; H, 4.41; N, 3.41. Found: C, 49.72; H, 4.37; N, 3.51.

3-Carbethoxy-6,7-dihydro-9-methoxybenzo[a]quinolizinium Chloride (IIa) and Perchlorate (IIc)

Cyclization of 5.0 g of I using phosphorus oxychloride (3) gave a product which was recrystallized from 25 ml of water to give 4.2 g (72%) of II*a*, m.p. 200–201°, raised to 208–209° after recrystallization from ethanol–ether. The ultraviolet and infrared spectra showed essentially the same characteristics as described above for the corresponding iodide salt (II*b*).

The filtrates from the above crystallizations were combined and treated with 2 ml of 72% perchloric acid to give 1.9 g (27%) of the perchlorate salt II*c*, m.p. 210–212°. An analytical sample recrystallized from aqueous methanol had m.p. 209–210° and suitable infrared and ultraviolet spectra.

Anal. Calcd. for $C_{17}H_{18}ClNO_7$: C, 53.20; H, 4.74; N, 3.65. Found: C, 53.32; H, 4.64; N, 3.50.

3-Carboxy-6,7-dihydro-9-methoxybenzo[a]quinolizinium Perchlorate (IIa)

N-(*m*-Methoxyphenethyl)-5-carboxy-2-pyridone (1.9 g) was cyclized as described above in the preparation of II*b*; however, water (20 ml) rather than ethanol was used in the reaction with the intermediate acid chloride. The aqueous mixture was allowed to stand at room temperature for 10 min, then 70 ml of water was added to dissolve the precipitate. To the solution was added 2.0 g of sodium perchlorate, a precipitate forming immediately. The suspension was cooled at 5° overnight and then filtered. Recrystallization of the precipitate from ethanol–water gave 2.0 g (81%) of product, m.p. 270° (decomp.). The ultraviolet spectrum has maxima at 220 (ϵ 23 800), 284 (ϵ 6 650), and 355 mμ (ϵ 23 400) and a shoulder at 254 mμ (ϵ 4 900).

Anal. Calcd. for $C_{15}H_{14}ClNO_7$: C, 50.80; H, 3.97; N, 3.95. Found: C, 50.78; H, 4.01; N, 3.88.

3-Carboxy-6,7-dihydro-9-methoxybenzo[a]quinolizinium Chloride (IIe)

To 5.0 g of N-(*m*-methoxyphenethyl)-5-carboxy-2-pyridone was added 25 ml of phosphorus oxychloride and 25 ml of xylene. After the mixture was heated gently under reflux for 2 h, the volatile material was removed under reduced pressure. The residue was dissolved in 125 ml of water and allowed to cool slowly.

Filtration gave 5.3 g (98%) of product, m.p. 265–266°. Maxima in the ultraviolet spectrum occur at 220 (ε 9 600), 283 (ε 7 460), and 355 mμ (ε 24 200) and a shoulder at 254 mμ (ε 5 520).

Anal. Calcd. for $C_{15}H_{14}ClNO_3$: C, 61.75; H, 4.84; N, 4.81. Found: C, 61.71; H, 4.96; N, 4.58.

trans-3-Carbethoxy-1,3,4,6,7,11b-hexahydro-9-methoxy-2H-benzo[a]quinolizine (IVa) Hydrochloride

To a solution of 3.0 g of II*a* dissolved in a mixture of 24 ml of acetic acid, 50 ml of ethanol, and 50 ml of water was added 500 mg of Adams catalyst. Hydrogen was introduced at atmospheric pressure and the suspension was stirred vigorously. After the hydrogen uptake ceased (8 h), the suspension was filtered and the filtrate was evaporated to dryness. The oil was dissolved in 15 ml of absolute ethanol, treated with Norit, and filtered. The product was crystallized from absolute ethanol–ether giving 2.3 g (76%) of IV*a* hydrochloride, m.p. 194–197°, raised to 201–202.5° after recrystallization. The ultraviolet spectrum shows maxima at 227 (ε 8 630), 277 (ε 1 755), and 284 mμ (ε 1 720).

Anal. Calcd. for $C_{17}H_{24}ClNO_3$: C, 62.66; H, 7.42; N, 4.30. Found: C, 62.55; H, 7.40; N, 4.10.

The filtrate yielded an additional 500 mg of material, m.p. 115–170°, which appeared to be a mixture of the two isomeric hydrochlorides.

trans-3-Carbethoxy-1,3,4,6,7,11b-hexahydro-9-methoxy-2H-benzo[a]quinolizine (IVa)

Treatment of a solution of 5.3 g of IV*a* hydrochloride in 25 ml of water with a slight excess of dilute sodium hydroxide solution and recrystallization of the crude product from ethanol–water gave 4.5 g (96%) of IV*a*, m.p. 47–50°, raised to 51–52.5° after one recrystallization. The ultraviolet spectrum of IV*a* has maxima at 220 (ε 9 275), 278 (ε 1 890), and 286 mμ (ε 1 840). The infrared spectrum (in CCl_4, calcium fluoride prism) shows maxima at 2 850, 2 815, 2 780, and 2 760 cm^{-1} (C—H stretching of transoid-ring system) and (with sodium chloride prism) 1 730 cm^{-1} (ester C=O) and two peaks at 1 110 and 990 cm^{-1} (characteristic of this *trans* isomer).

Anal. Calcd. for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.54; H, 7.96; N, 4.75.

cis-3-Carbethoxy-1,3,4,6,7,11b-hexahydro-9-methoxy-2H-benzo[a]quinolizine (IIIa)

A mixture of 2.5 g of II*a*, 100 ml of glacial acetic acid, and 200 mg of Adams catalyst was shaken in the presence of hydrogen at atmospheric pressure until the theoretical amount of hydrogen was absorbed (7 h). The suspension was filtered and evaporated to dryness. The residue was dissolved in 50 ml of water to which dilute ammonium hydroxide was added until the mixture was alkaline. The aqueous suspension was extracted with ether and the ether extract was washed with water until neutral. The solvent was removed under reduced pressure and the oil was crystallized from aqueous methanol yielding 1.85 g (86%) of product III*a*, m.p. 83–86°, raised to 85–86° on recrystallization from aqueous ethanol. The ultraviolet spectrum of III*a* has maxima at 220 (ε 9 720), 278 (ε 1 925), and 286 mμ (ε 1 850). The infrared spectrum (in CCl_4, calcium fluoride prism) shows maxima at 2 850, 2 815, and 2 780 cm^{-1} (C—H stretching of transoid-ring system) and (with sodium chloride prism) 1 735 cm^{-1} (ester C=O) and two peaks at 1 100 and 1 076 cm^{-1} (characteristic of this *cis* isomer). The n.m.r. spectrum of III*a* in $CDCl_3$ shows signals centered at about 6.64, 6.74, and 7.12 p.p.m. (tetramethylsilane = 0) for the 8-, 10-, and 11-hydrogens, respectively.

Anal. Calcd. for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.67; H, 7.93; N, 4.80.

The hydrochloride salt of III*a* was prepared by passing hydrogen chloride into an ethereal solution of pure III*a*. The product was recrystallized from ethanol–ether, m.p. 210–211°, and gave normal ultraviolet and infrared spectra.

Equilibration Studies of the cis and trans Isomers of 3-Carbethoxy-1,3,4,6,7,11b-hexahydro-9-methoxy-2H-benzo[a]quinolizine

Standard curves of optical density vs. concentration were prepared from infrared data of synthetic mixtures (10% solutions in CCl_4) of III*a* and IV*a* using the 987 cm^{-1} peak and 1 076 cm^{-1} peak of the *trans* and *cis* isomers respectively.

(A) To 500 mg of IV*a* (m.p. 50.5–51.5°) was added 10 ml of sodium ethoxide solution prepared from 500 mg of sodium in 50 ml of absolute ethanol. The solution was kept under a nitrogen atmosphere at room temperature for 48 h. The solution was poured into 100 ml of ice water which was then extracted with ether. The ether extract was washed until neutral and evaporated to give 450 mg of mixed amino esters. The oil was dried for 24 h at 50° *in vacuo*. An infrared spectrum of the mixture and utilization of the standard curves indicated the presence of 86% of IV*a* and 17% of III*a*. Normalization gives the equilibrium position as 83.5% IV*a* and 16.5% III*a*.

(B) To 250 mg of III*a* (m.p. 85–85.4°) was added 5.0 ml of sodium ethoxide prepared from 500 mg of sodium and 50 ml of absolute ethanol. The solution was kept under a nitrogen atmosphere at room temperature for 48 h. The solution was worked up in the same manner as above to give 240 mg of mixed amino esters. The oil was dried for 24 h at 50° *in vacuo*. From the infrared spectrum of the mixture and utilization of the standard curves the mixture appeared to consist of 86% of IV*a* and 28% III*a*. Normalization gives the equilibrium position as 75.5% IV*a* and 24.5% III*a*.

3-Carbethoxy-1,2,3,4,6,7-hexahydro-9-methoxybenzo[a]quinolizinium Perchlorate (V)

Both III*a* and IV*a* gave the same quinolizinium perchlorate after mercuric acetate oxidation. The procedure used for each isomer was exactly the same and it is described below for the equatorial isomer IV*a*.

To a solution of 4.5 g of mercuric acetate in 25 ml of 5% acetic acid was added 1.0 g of *trans* ester IV*a*. Mercurous acetate began precipitating within 3 min as the temperature of the mixture was raised to 60° and kept there for 2 h. Filtration gave 1.7 g (95%) of mercurous acetate. The filtrate was saturated with hydrogen sulfide and the suspension filtered through Celite. The solution was concentrated under reduced pressure to 10 ml, at which point it was diluted to 50 ml with absolute ethanol. The solution was again concentrated to a volume of 10 ml under reduced pressure and 15 ml of absolute ethanol containing 0.5 ml of 70% perchloric acid was added. The solution was diluted with ether giving 1.1 g of V, m.p. 131.5–132.5°, and 90 mg, m.p. 129–131°. The sample melting at 131.5–132.5° was analytically pure. The ultraviolet spectrum of V has maxima at 230 (ϵ 5 890), 237 (ϵ 7 400), and 323 mμ (ϵ 18 900) and a shoulder at 244 mμ (ϵ 5 680).

Anal. Calcd. for $C_{17}H_{22}ClNO_7$: C, 52.65; H, 5.72; N, 3.62. Found: C, 52.52; H, 5.76; N, 3.64.

The *cis* amino ester gave 90% yield of V, m.p. 131.0–132.0°. The infrared spectra of the products obtained from the isomeric esters are superimposable and mixed melting point determination showed no depression.

Reduction of 3-Carbethoxy-1,2,3,4,6,7-hexahydro-9-methoxybenzo[a]quinolizinium Perchlorate (V)

To a suspension of 1.1 g of V in 50 ml of glacial acetic acid was added 100 mg of Adams catalyst. Hydrogen was introduced at atmospheric pressure and the uptake was completed in 6 h. The suspension was filtered and the filtrate evaporated to dryness. The oil was dissolved in 50 ml of water and dilute ammonium hydroxide was added until the mixture was basic. The suspension was extracted with ether. The ether extract was washed with water to neutrality. The ether was evaporated to give an oil which was a mixture of the amino esters III*a* and IV*a*. The oil was dissolved in a methanol–water solution and 110 mg of III*a*, m.p. 80.5–83°, precipitated. Addition of water to the filtrate followed by slow cooling precipitated 300 mg of IV*a*, m.p. 46–48°.

Hydrochlorides of cis- and trans-3-Carboxy-1,3,4,6,7,11b-hexahydro-9-methoxy-2H-benzo[a]quinolizines (IIIb and IVb)

A mixture of 4.5 g of 3-carboxy-6,7-dihydro-9-methoxybenzo[*a*]quinolizinium chloride (II*e*), 400 ml of acetic acid, and 400 mg of Adams catalyst was shaken in a hydrogen atmosphere at atmospheric pressure until the theoretical uptake of hydrogen had occurred (12 h). The catalyst was removed and the filtrate evaporated to dryness. The residue was leached with 30 ml of boiling absolute ethanol. The insoluble material amounted to 2.1 g (46%) of the *trans* isomer IV*b*, m.p. 274–280°, raised to 287–288° after two recrystallizations from 95% ethanol.

Anal. Calcd. for $C_{15}H_{20}ClNO_3$: C, 60.50; H, 6.77; N, 4.70. Found: C, 60.34; H, 6.79; N, 4.71.

The ethanol leach solution above was diluted to a volume of 100 ml with ether giving 1.75 g (38%) of the *cis* isomer III*b*, m.p. 231–235°, raised to 235–239° on recrystallization from aqueous ethanol–ether.

Anal. Calcd. for $C_{15}H_{20}ClNO_3$: C, 60.50; H, 6.77; N, 4.70. Found: C, 60.58; H, 6.88; N, 4.75.

Paper chromatography of the isomeric amino acid hydrochlorides indicated that the above materials were homogeneous as far as was indicated by the development techniques used. From a spot of 100 γ of each material was obtained a single spot. A mixture of 50 γ of each was separated into two spots. The mobile phase for these experiments was methyl ethyl ketone to which 1% methanol was added. Whatman No. 1 paper was used and the spots were developed by passing the dried paper strip through a solution of iodine in carbon tetrachloride. The compounds showed up as yellow spots.

cis-3-Carboxy-1,3,4,6,7,11b-hexahydro-9-methoxy-2H-benzo[a]quinolizine (IIIb)

A solution of 1.1 g of the hydrochloride of III*b* in 10 ml of water was neutralized to pH 7 with dilute sodium hydroxide. The solution was evaporated to dryness under reduced pressure and the residue was triturated with 50 ml of absolute ethanol. The suspension was diluted to a volume of 100 ml with ether and then filtered, giving 859 mg (89%) of III*b*, m.p. 219–224°, raised to 224–225° (with sintering at 218°). The ultraviolet spectrum of III*b* has maxima at 227 (ϵ 9 110), 277 (ϵ 1 720), and 285 mμ (ϵ 1 680). The infrared spectrum (KBr pellet) exhibits a strong band at 1 675 cm^{-1} (hydrogen-bonded carboxyl) and a medium band at 1 590 cm^{-1} (ionized carboxyl).

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.95; H, 7.32; N, 5.36. Found: C, 68.98; H, 7.37; N, 5.41.

Paper chromatography of the material melting at 224–225° with the same system used for the hydrochloride indicated that the material was homogeneous. The *cis* isomer moves more rapidly than the *trans* isomer (described below) and a mixture of the two isomers is separated.

trans-3-Carboxy-1,3,4,6,7,11b-hexahydro-9-methoxy-2H-benzo[a]quinolizine (IVb)

Conversion of 500 mg of the hydrochloride of IV*b* by essentially the same process as described above for the preparation of III*b* gave 410 mg (93%) of IV*b*, m.p. 231–240°, raised to 240–242° on recrystallization from aqueous ethanol. The ultraviolet spectrum of IV*b* has maxima at 227 (ϵ 9 200), 277 (ϵ 1 790), and 285 mμ (ϵ 1 730). The infrared spectrum (KBr pellet) exhibits a shoulder at 1 650 cm^{-1} (hydrogen-bonded carboxyl) and a strong band at 1 590 cm^{-1} (ionized carboxyl).

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.95; H, 7.32; N, 5.36. Found: C, 69.10; H, 7.39; N, 5.42.

Paper chromatography of a sample of IV*b* melting at 240–242° indicated that it was homogeneous.

Mixtures of the isomeric amino acids III*b* and IV*b* could be separated effectively by leaching them with

anhydrous benzene. The axial isomer III*b* is much more soluble in benzene and it was removed completely from the mixture. Concentration of the benzene followed by slow cooling gave III*b* in well-defined crystals.

Correlation of the Amino Acids IIIb and IVb with the Corresponding Axial and Equatorial Esters. Treatment with Diazoethane

(A) To a solution of 150 mg of IV*b* in 15 ml of 95% ethanol was added an excess of ethereal diazoethane solution (14). The solution was stirred at room temperature for 2 h and then evaporated to dryness. The residue was dissolved in 50 ml of anhydrous ether, filtered, and evaporated to dryness to give 160 mg (97.5%) of crude product. An infrared spectrum indicated that the material was the equatorial ester. Recrystallization of the oil from ethanol–water gave 145 mg (88%) of the equatorial amino ester IV*a*, m.p. 49–50°. The amino acid IV*b* and the corresponding hydrochloride therefore have equatorial carboxyl groups.

(B) To a solution of 150 mg of III*b* (softening 210°, m.p. 219–222°) in 15 ml of an ethanol–water mixture was added an excess of ethereal diazoethane. The solution was stirred for 2 h and then evaporated to dryness. The residue was dissolved in 50 ml of anhydrous ether, filtered, and evaporated to dryness to give 155 mg (93.5%) of crude product. Comparison of the infrared spectrum to that of the pure axial ester indicated that there was a small amount of the low-melting equatorial isomer present. The oil was crystallized from an ethanol–water mixture to give 119 mg (72%) of the axial ester III*a*, m.p. 83–84°. The amino acid III*b* and its corresponding hydrochloride therefore have axial carboxyl groups.

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