STEREOSELECTIVE SYNTHESIS OF A DIBENZO[*a*,*g*]QUINOLIZINE ANALOG OF 18-HYDROXYEPIALLOYOHIMBANE

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Received April 7, 1965

ABSTRACT

Starting from *cis*-Δ^4-cyclohexenedicarboxylic acid anhydride, a stereoselective synthesis of *cis*-Δ^4-tetrahydrohomophthalic acid (IX) is described (Chart 1). The synthesis involves selective reduction to Δ^4-tetrahydrophthalide (III) and reaction of the latter with cyanide to give mainly the *cis*-nitrile acid V in good yield. Alkaline hydrolysis leads to the *cis*-homodiacid IX which was characterized as its corresponding anhydride. The nitrile acid intermediate could be transformed to stereoisomeric decahydroisoquinolines (VIII). Bromolactonization of the *cis*-diacid IX afforded the bromo-γ-lactone XIII (R = Br; Chart 2) which underwent hydrogenolysis to the already described γ-lactone homoacid intermediate XV in good yield. Transformation of the latter to the dihydroisoquinoline XVIII was uneventful. Reduction with sodium borohydride gave XIX which on heating gave the two isomeric lactams XX and XXII. The former was identical to a lactam already obtained by a different route (ref. 1). The latter was reduced to the tetracyclic base XXIII which is believed to exist in conformation XXIV*c*. The corresponding trimethoxybenzoic acid ester was prepared and tested for reserpine-like activity. It was found to be inactive. The significance of this result is briefly discussed.

In an accompanying paper (1), a rationale was presented which led to the suggestion that dibenzo[*a*,*g*]quinolizine analogs of certain indole alkaloids may be of physiological interest. In particular, attention was centered on the 18-hydroxyepialloyohimbane analog XXIII (Chart 2), a substance which is related both to the physiologically long-acting molecule of reserpine and the short-acting drug Tetrabenazine (2). If, as suggested by Quinn *et al.* (3), the same receptors are involved in the binding of the two drugs, it may be expected that the analog XXIII should produce protracted effects when interacting at the same level. Our initial attempts to obtain XXIII led instead to a stereospecific synthesis of the "allo"-epimer XXI which, however, is related to the physiologically ineffective 3-isoreserpine. It is the purpose of this communication to describe an alternative approach to the desired epimer XXIII (epiallo configuration). The new approach is based on the use of *cis*-Δ^4-tetrahydrohomophthalic acid (IX) as a key intermediate. The technical procedures provide for large scale preparations and are free of the hazards associated with the handling of large quantities of diazo compounds as was the case in our first approach (1). The ready availability of the *cis*-diacid intermediate IX suggests a number of applications in the field of the synthesis of indole alkaloids.

The preparation of intermediate IX was accomplished as shown in Chart 1. Its use in the synthesis of XXIII is described in Chart 2. A key finding is that 4-cyclohexene-*cis*-1,2-dicarboxylic anhydride (I) can be readily converted in 60–70% yields to Δ^4-*cis*-tetrahydrophthalide (III) by reduction with sodium borohydride in dry dimethyl formamide (DMF). The aldehydo-acid salt II is an obvious candidate as an unisolatable intermediate in this reaction. The phthalide III was characterized by its elemental composition, its equivalent molecular weight and its infrared spectrum. The same structure III was assigned by others (4) to a solid m.p. 100° (hydrazide m.p. 170°) obtained by a different and somewhat ambiguous route. Our preparation is liquid and no well defined crystalline hydrazide could be obtained. The discrepancy may be attributable to *cis–trans* isomerism. That our liquid phthalide III has the *cis* configuration was shown by its stability to potassium *t*-butoxide in *t*-butanol (5).

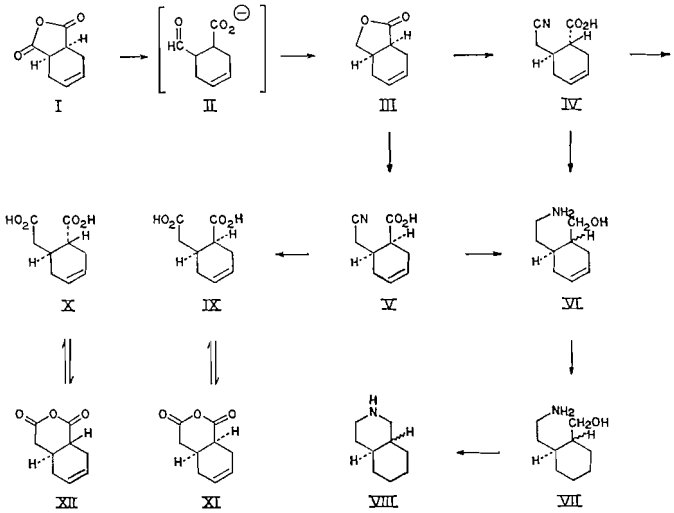


CHART 1.

On the basis of the known reactivity of γ-lactones in nucleophilic carbon–oxygen fission reactions (6), the phthalide III was reacted with cyanide ion using a variety of experimental conditions with a view to obtaining the nitrile-acid V. In the absence of a solvent, only tarry material was produced. In dimethylsulfoxide (DMSO) as the solvent the reaction proceeded smoothly and in good yield but extensive epimerization to the *trans*-nitrile acid IV occurred. Separation of the isomeric nitrile acids IV and V was not feasible on a preparative scale, but the corresponding diacids IX and X resulting from alkaline hydrolysis could be readily separated. In this way it could be established that the *trans*-nitrile acid IV accounted for 40–50% of the mixture when DMSO was used as the solvent. Reduction of the crystalline mixture of isomeric nitrile acids with lithium aluminium hydride gave VI which was converted to VII by catalytic hydrogenation and then to decahydroisoquinoline VIII after treatment with thionyl chloride followed by basification. The melting point behavior of the picrate and hydrochloride salts of VIII was consistent with that expected for a mixture of *cis* and *trans* isomers. Paper chromatography confirmed the presence of the isomeric bases thus pointing to the correctness of the assigned structures for the nitrile acids IV and V. It was eventually found that the proportion of *trans*-nitrile acid IV could be reduced to about 20% of the total yield of nitrile acid product by reacting the lactone III with sodium cyanide in DMF as the solvent. The mixture thus obtained (*cis*:*trans* ratio of 80:20) was hydrolyzed with boiling dilute sodium hydroxide to give a mixture of *cis*- and *trans*-Δ^4-tetrahydrohomophthalic acids (IX and X). The *cis* isomer IX crystallized in pure form from water in 60% yield. From the mother liquors, a mixture of *cis* and *trans* isomers was obtained. Recently, an alternative synthesis of the *cis*- and *trans*-homodiacids IX and X based on the Arndt–Eistert homologation reaction was described (7). The reported melting points for the isomers (7, 8) are in satisfactory agreement with our observations. It was essential at this point to establish the correctness of our configurational assignment to the *cis*-homodiacid IX. The melting points could hardly be relied upon to distinguish between the two isomers because, as was also noted by others (7), they are nearly identical. Recourse was made therefore to the corresponding anhydrides. Using a variety of conditions, Brutcher and Rosenfeld (7) were able to obtain only the *trans*-anhydride XII

either from the *cis*-diacid IX or the *trans* isomer X. However, under appropriate conditions, we have been successful in preparing in nearly quantitative yield the *cis*-anhydride XI, m.p. 67–68°. The two isomeric anhydrides exhibit a difference of 100° in their m.p. and have different infrared spectra. Hydrolysis with water regenerated the pure diacid precursor. A mixture of the two anhydrides can be readily separated by crystallization. It is obvious that the conditions applied by Brutcher and Rosenfeld (7) are too vigorous for the *cis*-anhydride to retain its configurational integrity. We found it expedient to isolate and purify the *cis*-diacid IX as its *cis*-anhydride prior to use in subsequent steps. Large scale preparations of this useful intermediate IX have been successfully carried out.

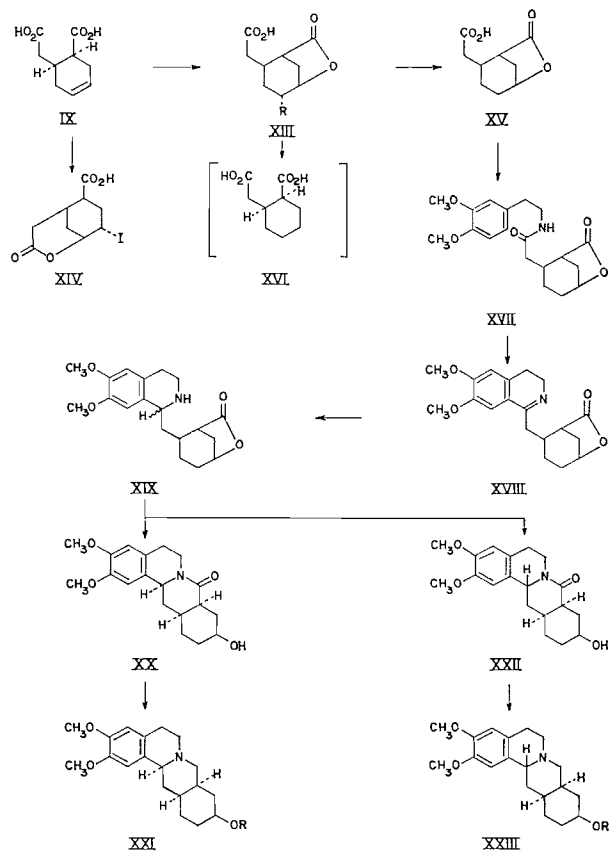
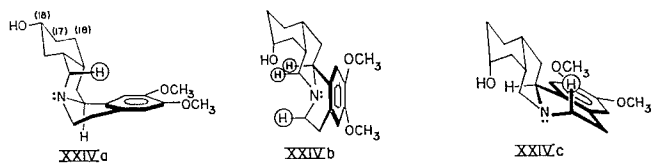


CHART 2.

The synthesis of XXIII from IX is summarized in Chart 2. As a means of introduction of the *cis*-hydroxyl function on ring D of XXIII, we initially submitted the *cis*-homodiacid IX to the Bougault iodolactonization reaction (9). Two likely reaction paths are available, one leading to the desired γ-lactone XIII, the other to the isomeric δ-lactone XIV. In practice, the γ-lactone XIII (R = I) was the major product of the reaction but was uniformly contaminated by small quantities of an isomeric lactone showing strong absorption at 1 720 cm^{-1} in the infrared. Although we have not established the structure of this minor product we suspect that it corresponds to the expected iodo-δ-lactone XIV. The iodo-γ-lactone XIII (R = I) had poor crystallization properties and was somewhat unstable. These difficulties were obviated when it was found that bromolactonization of

IX gave a well crystallized, stable bromo-γ-lactone XIII (R = Br) free of contaminating isomers. If any bromo-δ-lactone isomer was formed, its presence was not detectable by infrared. Hydrogenolysis of the carbon–bromine bond of XIII (R = Br) proceeded best using Raney nickel as the catalyst and afforded the already known lactone homoacid XV (1). A small amount of a by-product lacking the γ-lactone bond but absorbing strongly at 1 700 cm^{-1} was detected. It seems likely on the basis of previous experience (1) that this compound corresponds to *cis*-hexahydrohomophthalic acid (XVI) although no effort was made to characterize it further. The proportion of this contaminant in the hydrogenolysis mixture was found to be a function of the reaction time. Hydrogen uptake was initially very rapid and, if the reaction was stopped as soon as stoichiometry was attained, the amount of by-product (XVI?) was negligible thus suggesting that the homoacid lactone XV can suffer further attack by hydrogen albeit at a slow rate (see preceding paper (1)).

The homoacid lactone XV was next converted in high yield to the previously described (1) oily amide XVII by the mixed anhydride technique. The latter amide was ring closed the the dihydroisoquinoline lactone XVIII (1) which was purified as the crystalline hydrochloride. At this stage, our previous experience (1) suggested that reduction of the double bond of XVIII ought to be accomplished before the formation of ring C to provide for the formation of the two possible isomers at the position 1 of the tetrahydroisoquinoline ring. No stereoselectivity in the reduction of XVIII is to be expected and in agreement with theory, sodium borohydride reduction of XVIII afforded a mixture of epimers (XIX) which was used as such in the next step. Heating in boiling DMF caused smooth cyclization of XIX to two isomeric lactams which could be readily separated by crystallization. From benzene, a lactam m.p. 213–216° (XX) separated whereas a lactam m.p. 161–163° (XXII) was obtained from ethyl acetate. A rapid and quantitiative method of separation of these two isomers consists in digesting the mixture with tetrahydrofuran in which the high-melting isomer is insoluble in contrast to the low-melting one. The lactam m.p. 213–216° proved identical in every respect with the lactam previously obtained by another route (1) and consequently has the configuration XX. Moreover, lithium aluminium hydride reduction of this lactam gave the expected crystalline base (XXI, R = H) already described by Belleau and Dvornik (1). Similar treatment of the low-melting isomer XXII afforded the corresponding tetracyclic base XXIII (R = H) in high yield. In agreement with the configurational assignment, this latter base did not give rise to Bohlmann bands (10) in the infrared (in contrast to its isomer XXI (1)), an observation which might be taken to indicate that the dimethoxyphenyl substituent assumes the axial orientation with respect to ring C (as shown in XXIV*a*). However,



XXIV*a* XXIV*b* XXIV*c*

this is unlikely in view of the fact that the *A* value for a phenyl ring is from 3 to 6 times greater than that of a hydroxyl function (11). Of the alternative conformations XXIV*b* and XXIV*c* only the latter satisfies the criterion of thermodynamic stability (*A* values) and that of the infrared absorption characteristics (absence of Bohlmann bands). Conformation XXIV*b* places more than two axial hydrogens (circled atoms) *trans* to the α-electrons on the nitrogen. It follows that XXIII would not exist in a reserpine-like

conformation because of the absence of the 17 and 16 substituents which in reserpine stabilize conformation XXIV*a*. The possibility must be recognized that ring D of XXIV*c* may exist in a twisted boat conformation which would serve to relieve the 1,3-interactions introduced by the axial hydroxyl. The base XXIII was converted in moderate yield to the corresponding 3,4,5-trimethoxybenzoic acid ester for pharmacological evaluation.

Pharmacological results.—In a variety of standard tests Dr. M. Pindell, Bristol Laboratories, Syracuse, found that the analog XXIII (R = trimethoxybenzoyl) is devoid of reserpine-like activity. It could be argued that the absence in XXIII of the 16 and 17 substituents of reserpine may be responsible for the observed lack of activity either because these substituents participate in the binding of reserpine onto its physiological receptors or because they impose the proper conformation (equivalent to XXIV*a*) to the molecule. However, after our work was completed, we have learned from Dr. G. Muller (Roussel-Uclaf, Romainville, France) that the analog of XXIII in which both the 16 and 17 substituents of reserpine are present (synthesized by the Woodward method for reserpine (12) is also inactive. We are led to the conclusion that the indole ring of reserpine is critical for activity. These observations cast some doubt on the proposed identity of the receptors for Tetrabenazine and reserpine (3).

EXPERIMENTAL

Melting points and boiling points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer Infracord instrument; chloroform solutions were used unless otherwise noted. Microanalyses were by Midwest Microlab, Indianapolis, and by Daessle Organic Microanalyses, Montreal. The sentence "worked up in the usual manner" signifies that the reaction mixture was extracted with ether or chloroform, and that the extract was washed successively with water and dilute base (or dilute acid when appropriate), dried over sodium sulfate, and evaporated to dryness *in vacuo*.

cis-6-Hydroxymethyl-3-cyclohexene-1-carboxylic Acid γ-Lactone (III)

A solution of 152 g of *cis*-Δ^4-tetrahydrophthalic acid anhydride (I) in 475 ml of dry DMF was added dropwise over a period of 1 h to a stirred, ice-cold solution of 30 g sodium borohydride in 475 ml of dry DMF. The temperature of the reaction was kept below 20°. The solvent was removed under reduced pressure and the residue was carefully treated with 2.1 l of 2 *N* aqueous sulfuric acid. After standing for 16 h the turbid solution was extracted with chloroform and the extract was processed in the usual manner. The residue was distilled *in vacuo* to give 71 to 83 g (52–60% yield) of colorless liquid, b.p. 128–130° at 2.8 mm, n^{22} 1.499. Yields as high as 73% were obtained when the starting anhydride I was purified before use. Solvents other than DMF such as diglyme gave inferior yields.

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.30; Sap. Equiv. 138. Found: C, 68.91; H, 7.27; Sap. Equiv. 140. Infrared: λ_{max} 1 770 cm^{-1}.

Attempts to prepare a crystalline hydrazide were unsuccessful (see ref. 4).

cis- and trans-Δ^4-Tetrahydrohomophthalonitrile (V and IV)

(A) DMF as Solvent

To a boiling suspension of 9.0 g sodium cyanide in 1.3 l of DMF was added in portions a solution of 25 g of the preceding tetrahydrophthalide III in 200 ml of DMF. The mixture was heated under reflux for 18 h, cooled, and filtered, and the filtrate was then evaporated under reduced pressure. The residue was dissolved in water, acidified to pH 3 with dilute sulfuric acid, and thoroughly extracted with chloroform. The extract was washed several times with aqueous sodium bicarbonate, and the combined washings were acidified and cooled in ice whereupon crystals separated. They were collected, the filtrate was extracted with chloroform, and the extract was worked up in the usual manner to give a crystalline mass. The combined solids were recrystallized from water to give 18.7 g (56% yield) of a mixture of *cis*- and *trans*-nitrile acid IV and V, m.p. 72–76°.

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 64.90; H, 6.90; N, 8.55. λ_{max} (Nujol mull): 2 240, 1 700 cm^{-1}.

(B) DMSO as Solvent

Using one fifth as much of this solvent as of DMF, the same reaction as described in (A) above was carried out. It was found that in DMSO the optimum reaction time (which minimizes epimerization to IV) is 4 h. The mixture was worked up as described above to give the nitrile acid mixture in 60–65% yield. However, the proportion of *trans* isomer IV in this mixture was increased by a factor of 2–3.

cis- and trans-Decahydroisoquinoline (VIII) from the cis- and trans-Nitrile Acids IV and V

The sequence of reactions followed conventional lines. Thus, the nitrile acid (IV + V) was reduced in hot tetrahydrofuran (THF) with excess lithium aluminium hydride for 6 h. The mixture was decomposed with water and aqueous sodium hydroxide, and the liberated amino alcohol VI was isolated in crude form in the usual manner. It was purified by a short path distillation (bath temp. 100° under reduced pressure (1.2 mm) to give a colorless oil which was catalytically hydrogenated over Adams' catalyst in ethanol under a pressure of 40 p.s.i. of hydrogen. The reduced base VII was isolated in the usual manner (no olifinic absorption in the infrared, converted to the oily hydrochloride, and treated in dry chloroform with a 10% excess of pure thionyl chloride. After boiling the mixture for 1 h, the solvent was evaporated and the residue was treated at 100° with an excess of 10% aqueous sodium hydroxide. The mixture was cooled and worked up in the usual manner to give a liquid which was purified by distillation to give a colorless liquid, b.p. 80° (bath temp.) at 0.2 mm. It was converted to a crystalline picrate and crystalline hydrochloride which had respective m.p. 151–160° and 165–188° after several recrystallizations from ethanol (reported (13) for the *cis* isomer, 150° and 175–178°). The liquid base gave rise to two distinct spots on paper chromatograms (pyridine–methanol–water).

Anal. Calcd. for the picrate $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47. Found: C, 49.22; H, 5.53.

cis-Δ^4-Tetrahydrohomophthalic Acid (IX)

A solution of 33 g of the preceding mixture of nitrile acids IV and V in 600 ml of 1 *N* aqueous sodium hydroxide was heated under reflux until ammonia was no longer evolved (about 66 h). The solution was cooled in ice and acidified to pH 3 whereupon the *cis*-homodiacid IX separated as a white crystalline mass. It was collected, washed, and recrystallized from water to give 22 g (60% yield) of the pure *cis* isomer, m.p. 162–164° (reported (7): 155–157°). Extraction of the combined mother liquors with chloroform yielded 5.3 g of a mixture of *cis* and *trans* isomers (IX and X), m.p. 130–140° (reported for a 50:50 mixture, 130–144° (7). Separation of the *trans* isomer could be more readily accomplished by conversion to the anhydride.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.83; H, 6.57. λ_{max} (Nujol): 2 600, 1 700 cm^{-1}.

cis-Δ^4-Tetrahydrohomophthalic Anhydride (XI)

A solution of 400 mg of the preceding *cis*-homodiacid IX in 4 ml of benzene containing 1 ml of acetic anhydride was heated under reflux for 2 h and the solution was taken to dryness *in vacuo*. The residue crystallized from ether–hexane to give 320 mg of crystals, m.p. 67–68° unchanged after recrystallization.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.07; H, 6.15. λ_{max}: 1 795, 1 750, 1 022, 960 cm^{-1}.

Hydrolysis with cold water regenerated the *cis*-homodiacid precursor, m.p. and mixed m.p. 162–164°.

trans-Δ^4-Tetrahydrohomophthalic Anhydride (XII) from a Mixture of cis- and trans-Diacids

When the above mixture of *cis*- and *trans*-homodiacids IX and X (m.p. 130–140°) was treated as described in the preceding experiment, there was obtained a solid which when recrystallized from benzene gave in 50% yield the *trans*-anhydride XII, m.p. 166– 8° (reported (7, 8): 166– 7° and 167– 8°). λ_{max}: 1 798, 1 750, 1 070, 980 cm^{-1}. Hydrolysis of the pure anhydride XII with cold water gave *trans*-Δ^4-tetrahydrohomophthalic acid (X) m.p. 154–155° (reported (7): 154–156°). Mixed m.p. with the *cis* isomer IX, 130–140° (reported (7): 130–144°).

5-Iodo-cis-4-hydroxy-2-carboxy-cyclohexaneacetic Acid γ-Lactone (XIII, R = I)

The *cis*-homodiacid IX was submitted to the conditions of iodolactonization exactly as described for Δ^4-cyclohexene-*cis*-dicarboxylic acid in an accompanying paper (1). After the acidification step, however, the iodolactone did not separate spontaneously. It was extracted with ether and the extract was processed in the usual manner to give a solid which was recrystallized from ethanol–water. Repeated recrystallizations gave crystals of m.p. 133–135° (40% yield.

Anal. Calcd. for $C_9H_{11}IO_4$: C, 34.83; H, 3.54. Found: C, 35.11; H, 3.38. λ_{max}: 1 780, 1 705 cm^{-1}.

On standing, the mother liquors deposited some solid which after repeated recrystallizations from methanol had m.p. 185–188°. This material was tentatively assigned structure XIV on the basis of its infrared spectrum; λ_{max} (Nujol): 1 720, 1 695 cm^{-1}.

Anal. Calcd. for $C_9H_{11}IO_4$: C, 34.83; H, 3.54. Found: C, 34.70; H, 3.44.

5-Bromo-cis-4-hydroxy-2-carboxy-cyclohexaneacetic Acid γ-Lactone (XIII, R = Br)

A solution of 22 g of the *cis*-homodiacid IX in 300 ml of 0.8 *N* aqueous sodium hydroxide was prepared. To this was added a solution of 20.2 g of sodium hydrogen carbonate in 150 ml of water followed by the dropwise addition of 13.2 ml of bromine. Stirring was maintained during the addition and for 1 h at room temperature. Some solid sodium thiosulfate was added to remove some light-yellow color and the solution was acidified to Congo red. After chilling for 2 h, a crystalline mass was collected and recrystallized from methanol–water to give 20.2 g (64% yield) of colorless crystals, m.p. 127–129°, unchanged by further recrystallizations.

Anal. Calcd. $C_9H_{11}BrO_4$: C, 41.08; H, 4.21; Br, 30.37. Found: C, 41.48; H, 4.16; Br, 29.51. λ_{max}: 1 770, 1 700 cm^{-1}.

cis-4-Hydroxy-2-carboxy-cyclohexaneacetic Acid γ-Lactone (XV)

A solution of 13.15 g of the preceding bromolactone acid XIII (R = Br) in 150 ml of ethanol containing 3.65 g of pure diethylamine and 2 teaspoonfuls of freshly prepared Raney nickel was shaken in a hydrogen atmosphere under an initial pressure of 80 p.s.i. After a pressure drop of 4.5 p.s.i. the mixture was worked up in the usual manner and the residue was taken up in hot benzene. The diethylamine hydrobromide was filtered off and the filtrate was concentrated and set aside in the cold whereupon 7.5 g (80% yield) of crude lactone homoacid XV, m.p. 95–102°, was obtained. Recrystallization from benzene raised the m.p. to 111–116° (crystal change at 100–110°). Repeated recrystallizations did not alter the m.p. The crude material proved satisfactory for use in the next step. (Reported m.p. (1): 119–120°, 111–116°). This material proved identical as ascertained by mixed m.p. determination and infrared spectroscopy with a sample prepared by another route (1).

From the mother liquors a small amount of chloroform-insoluble material lacking the lactone band at 1 760 cm^{-1} but absorbing strongly at 1 700 cm^{-1} was obtained. It did not decolorize bromine in chloroform and behaved as an acid. It is tentatively assigned the structure XVI. No attempt was made to further characterize this minor component.

Lactone Homoamide XVII by the Mixed Anhydride Technique

A solution of 4.8 g of the preceding lactone homoacid XV in 150 ml of benzene containing 2.6 g triethylamine was cooled in ice and treated dropwise with 2.8 g of freshly distilled ethyl chloroformate. The insoluble salt was filtered; to the ice-cold filtrate 4.7 g of homoveratrylamine was added. After standing for 1 h, the solution was evaporated to dryness to give a viscous yellow oil which proved identical in the infrared with a sample prepared by another method (1). The yield was quantitative.

Cyclization to XVIII

This reaction has been described in an accompanying paper (1). The hydrochloride salt was obtained in crystalline form. It gave yellow crystals from toluene–chloroform, m.p. 175–176°.

Anal. Calcd. for $C_{19}H_{24}ClNO_4$: C, 62.37; H, 6.61; N, 3.83. Found: C, 61.86; H, 6.71; N, 3.69.

Reduction to the Tetrahydroisoquinoline Lactone XIX and Ring Closure to XX and XXII

To a solution of 5.5 g of the preceding hydrochloride salt of XVIII in 66% aqueous ethanol was added in portions 0.75 g of sodium borohydride. After 30 min at room temperature the reaction was complete as ascertained by the disappearance in the ultraviolet of the long-wavelength chromophore at 310 mμ. The solution was concentrated *in vacuo*, and was then saturated with carbon dioxide and thoroughly extracted with chloroform. The extract yielded 3.5 g (70% yield) of a solid absorbing strongly in the infrared at 1 760 cm^{-1} (γ-lactone band). This mixture of epimers (XIX) was used as such in the next step.

The solid thus obtained was heated under reflux in 100 ml of dry DMF for 3 h under an oxygen-free atmosphere of nitrogen. The solvent was removed *in vacuo* and the residue was taken up in benzene whereupon crystals m.p. 191–196° separated. Recrystallization from benzene–methanol raised the mp. to 213–216° (yield: 1.0 g). This lactam XX proved identical in every respect with the lactam previously obtained by Belleau and Dvornik (1).

From the benzene mother liquors there was obtained a crude crop of the isomer XXII which after recrystallization from ethyl acetate had m.p. 161–163°, unchanged after further recrystallizations (yield: 1.10 g).

Anal. Calcd. for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.25; H, 7.92; N, 4.25. λ_{max}: 3 400, 1 600 cm^{-1}.

The crude mixture of isomeric lactams XX and XXII could be readily separated by taking advantage of the insolubility in THF of the former isomer.

Reduction of XXII to the Tetracyclic Base XXIII (Epiallo Configuration)

A solution of 900 mg of the lactam XXII in 50 ml of dry THF was added dropwise to a stirred and cooled suspension of 1 g lithium aluminium hydride in 50 ml of dry ether. The mixture was heated under reflux for 20 h and carefully decomposed with 1.1 ml of water followed by the addition of 0.9 ml of 20% aqueous sodium hydroxide and 4.0 ml of water. The solids were filtered, the filtrate was evaporated and the residue was taken up in dilute sulfuric acid. The solution was washed with ether and then made strongly alkaline whereupon a solid separated. It was collected and recrystallized from acetone; m.p. 197–199°, unchanged after additional recrystallizations (yield: 450 mg).

Anal. Calcd. for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.97; H, 9.00; N, 4.44. λ_{max}: 3 600, 3 400 cm^{-1}.

In a similar way, the lactam XX gave the isomeric base XXI which proved identical in every respect with a sample prepared as described in an accompanying paper (1).

The *3,4,5-trimethoxybenzoic acid ester* of the epiallo base XXIII was prepared according to the method of Lucas *et al.* (14). After several recrystallizations from methanol it had m.p. 164–165°.

Anal. Calcd. for $C_{29}H_{37}NO_7$: C, 68.08; H, 7.29; N, 2.74. Found: C, 67.76; H, 7.24; N, 2.95. λ_{max}: 1 700, 1 580 cm^{-1}.

ACKNOWLEDGMENTS

The financial support of this work by Bristol Laboratories, Syracuse, was highly appreciated.

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