Tetrahedron. Vol. 26, pp. 1961 to 1965. Pergamon Press 1970. Printed in Great Britain

A SHORT SYNTHESIS OF SEVERAL GAMBIR ALKALOIDS

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(*Received in the USA* 24 *November* 1969; *Received in the UK for publication* 22 *December* 1969)

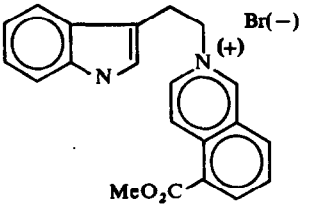
Abstract—A high-yield, one-step synthesis of *dl*-dihydrogambirtannine (II) is described in which a novel tetrahydro-β-carboline synthesis by reductive cyclization plays a key role. Ourouparine (III) has been oxidized with peroxide in dioxane solution to form oxogambirtannine (IV). Some improvements on the synthesis of 5-carbomethoxyisoquinoline are presented.

EVAPORATION of the aqueous extracts of the leaves and stems of *Rubiacea Uncaria gambier*, Roxb. (*Ourouparia gambir*, Baillon) provides a complex substance used commercially in the tanning of leather. Small quantities of fluorescent indole alkaloids have been separated from the extracts of which dihydrogambirtannine[1] (II), ourouparine[2] (III), and oxogambirtannine[1, 2] (IV) are pertinent to this synthetic study.

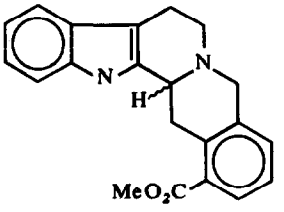
Since Potts and Robinson[3] reported that 2-[2-(3-indolyl]-isoquinolinium chloride could be converted to a tetrahydro-β-carboline derivative *via* a LAH reduction, there has been considerable activity[4] surrounding the attractive prospect of reducing an indolylethylpyridinium salt to a dihydropyridine which, in turn, could be ring closed to the tetrahydro-β-carboline. Clearly, a suitable procedure would give an unencumbered synthetic access to alkaloids having a variation of the hexahydroindolo [2.3-*a*]quinolizine structure (e.g. of the yohimbine or corynantheine types). This intriguing reaction, if it were to become incorporated into organic synthesis as a general method, would require that (a) the reducing agent be sufficiently mild, not only to avoid undesired reductions of functionalities elsewhere in the molecule, but also to ensure that the reduction would stop at the dihydropyridine stage, (b) that side reactions be effectively suppressed to render the procedure synthetically useful in terms of yield and ease of product isolation, (c) and that, in the case of an unsymmetrically substituted pyridinium compound (i.e. derived from a 3-substituted pyridine or from an isoquinoline), the correct orientation of the substituent with respect to the indole nucleus would prevail. The last mentioned, as the early experiments and mechanistic interpretation given by Potts and Robinson would suggest, proved not to be a difficulty, but the remaining two conditions have been met with varying degrees of success.

Thus, using THF as solvent for the LAH reduction of 2-[2-(3-indolyl)-2-oxoethyl]-pyridinium salts,[4c] good yields of the ring-closed product were generally realized. Unfortunately, the vigor of the reducing agent limits the utility of the reaction. Sodium borohydride, heretofore, has been useless to provide an intermediate for ring closure[4a, b, d, f]; further reduction to the tetrahydropyridine was ostensibly unavoidable. Moreover, the deactivated metal hydride, $LiAlH(OtBu)_3$, gave complex products in low yield[4d] and therefore is essentially a reagent with little to recommend itself.

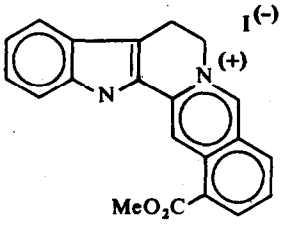
The hope at the outset of this work that the reduction capability of sodium borohydride, when appropriately modified, might yet satisfy all the conditions outlined above was amply rewarded. The multiple-phase reduction of 2-[2-(3-indolyl)ethyl]-5-carbomethoxyisoquinolinium bromide (I) slurried in a methanol-water-ether system containing a high concentration of the cyanide nucleophile gives an intermediate which when heated with mineral acid evolves hydrogen cyanide with the subsequent formation of *dl*-dihydrogambirtannine (II) hydrochloride in an overall yield of 83%. These events are not inconsistent with the earlier borohydride reductions of pyridinium salts in the presence of cyanide reported by Fry.[5]



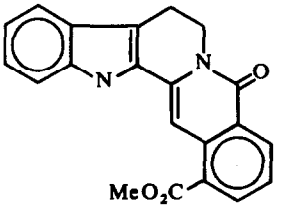
I



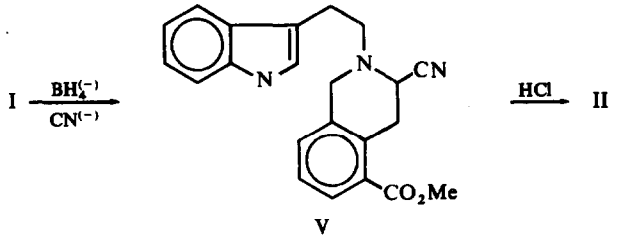
II



III



IV



V

By analogy[5] a possible course of the reaction can be envisaged. Acceptance of a hydride ion at the 1-position of the isoquinolinium nucleus generates an enamine (alternatively, through equilibration or double bond migration, an azomethine) which can be trapped by cyanide ion to give an intermediate that can be formulated as V. However, the intermediate was obtained as a gum and no attempt was made to characterize it beyond the observation of a nitrile band (ν_{max} 2211 cm^{-1}) in the IR. Contact of V with the reducing medium is minimized by providing the reaction mixture with a layer of ether into which lipophilic products can enter as they are formed. Heating the reduction product (V) briefly with dilute acid regenerates the dihydropyridine which may then cyclize, presumably under acid catalysis, to a tetrahydro-β-

carboline.* Only one product was isolated from the reaction and no apparent reduction of the carbomethoxy group occurred. The *dl*-dihydrogambirtannine synthesized with this economic, one-step method was identical in melting point, IR, UV and MS with II prepared by catalytic reduction of gambirtannine.[1]

This synthesis of II represents an improvement on the more lengthy procedure previously described[6] which necessitated a doubly substituted isoquinoline (dimethyl isoquinoline-4,5-dicarboxylate) in the condensation with tryptophyl bromide. The borohydride-cyanide procedure obviates the need for a prosthetic 4-carboalkoxy group to arrest the reduction of the isoquinolinium salt.

It is relevant at this point to discuss the synthesis of 5-carbomethoxyisoquinoline which when condensed with tryptophyl bromide affords the salt I. With several practical modifications, the scheme of Jeiteles[7] was followed to substitute a nitrile function at the 5-position of isoquinoline. Accordingly, an aqueous solution of the sulfonation product of isoquinoline sulfate was fractionally crystallized to give colorless needles of what subsequently proved to be isoquinoline-5-sulfonic acid in a good state of purity.† The critical point in the synthesis is the fusion of the sulfonic acid with inorganic cyanide. Earlier workers[7] were only able to realize a 15–20% yield for this conversion, but by the simple expediency of increasing the porosity of the pyrolysis mixture with ordinary sea sand, a dramatic increase in yield was achieved. The product, which was free of the 8-isomer, had a m.p. identical to that recorded in the literature[10] for 5-cyanoisoquinoline prepared by an alternate synthesis. Acid hydrolysis and esterification completed the preparation.

Using Elderfield's[11] general method for aromatizing the D-ring of hexahydroindole[2,3-*a*]quinolizines, Merlini and Nasini[12] were able to make ourouparine iodide (III) from (-)dihydrogambirtannine. Because of the instability of *dl*-dihydrogambirtannine, similar to other compounds of this class,[13] it was a considerable advantage to find that the stable hydrochloride of the racemic base also dehydrogenated quantitatively under Elderfield's conditions to give III.

Thus, with useful quantities of alkaloid III on hand, acquired by two efficient reactions starting from I, the final objective in the synthesis of the Gambir alkaloids was undertaken, namely, the oxidation of III to give oxogambirtannine (IV).

It was observed that dilute solutions of III in dioxane rapidly develop a blue fluorescence (under UV light), which is characteristic[1, 12] of oxogambirtannine. Indeed, the formation of IV could be readily followed by TLC. Because other common laboratory solvents did not cause this behavior, or with a much lesser facility, peroxides present in the dioxane were suspected as being the oxidizing agents for the reaction. As anticipated, moderate quantities of hydrogen peroxide added to mixtures of III and dioxane effectively accelerated the formation of the pyridone IV and rendered the reaction practical. The oxogambirtannine (IV) obtained in this way was identical in melting point, UV, IR and MS to the plant alkaloid[1] and to the synthetic alkaloid[12] made by an unrelated route.

* Further studies of this useful, potentially general reaction are in progress and will be reported at a later date.

† Some of the 8-isomer was also to be expected[8] although the sulfonation was run at moderate temperatures[9] to minimize its formation.

EXPERIMENTAL

IR spectra were recorded with a Perkin–Elmer Model 421 spectrophotometer. The Beckman grating spectrophotometer Model DB-G was used to determine UV spectra. Mass spectra were measured at 80 eV using an Hitachi–Perkin–Elmer RMU-6 double focusing spectrometer. M.ps were taken with a Kofler block and are uncorrected. Where necessary, Na_2SO_4 was used to dry organic sols.

Isoquinoline-5-sulfonic acid. To 35 g of isoquinoline sulfate was added 60 g of 65% oleum while cooling the reaction flask in an ice bath. After standing at room temp for 16 hr an additional 20 g fuming acid was added to the viscous reaction soln and heated on a steam bath for 1 hr. When cool, the syrup was poured over 170 g ice chips. The following day 14·1 g of large needles were removed by filtration and rapidly washed with acetone. Storing the mother liquor at −25° caused an additional 11·0 g to crystallize bringing the total yield to 61%.

5-Cyanoisoquinoline. A one-necked flask, which had been charged with an intimate mixture of 4·0 g (19·6 mmole) isoquinoline-5-sulfonic acid, 8·0 g KCN, and 40 g coarse sea sand, was fitted with an elbow adapter and inclined to near horizontal to facilitate short-path distillation of the reaction product. The apparatus was evacuated to 15 mm with a water pump while the reaction mixture was heated uniformly on all sides with a Bunsen flame, until no more product distilled over (ca. 20 min). When cool, the product, which had condensed as a hard wax in the elbow adapter, was collected. The yield from two such runs totaled 3·94 g (65%). Recrystallization from benzene-cyclohexane (charcoal) gave 3·30 g needles, m.p. 137–140° (subl), which was of sufficient purity for the next synthetic step. Sublimation raised the m.p. to 140–141° (subl). The literature[10] m.p. for 5-cyanoisoquinoline is 139°.

5-Carboxyisoquinoline. A soln of 3·15 g 5-cyanoisoquinoline in 25 ml 48% HBr was refluxed for 5 hr. Crystals of the amino acid hydrobromide crystallized quantitatively from soln on cooling.

An aqueous soln of the salt on neutralization with ammonia water precipitated the free amino acid in good yield. The crude 5-carboxyisoquinoline [m.p. 275° (subl); lit.,[10] m.p. 280–282°] was of sufficient purity to carry through to the esterification procedure.

5-Carbomethoxyisoquinoline. The procedure of Tyson[10] was followed without changes to convert 5-carboxyisoquinoline to its methyl ester in excellent yield, m.p. 64–66° (hexane); lit.,[10] m.p. 66°; ν_{max} 1722 (aryl ester), 1141 (Me ester) cm^{-1}.

2-[2-(3-Indolyl)ethyl]-5-carbomethoxyisoquinolinium bromide (I). Condensation of tryptophyl bromide[14] and 5-carbomethoxyisoquinoline according to the instructions[4b] readily gave the quaternary bromide as compact orange crystals, m.p. 243–245° after recrystallization from MeOH (lit.,[4b] m.p. 248°).

dl-Dihydrogambirtannine (II). A soln of 800 mg NaCN and 65 mg $NaBH_4$ in a mixture of 1·0 ml water and 2·0 ml MeOH was layered with 10 ml ether. While stirring vigorously with a magnetic stirrer, 800 mg of I was added in one portion. The stirring was continued until all the orange salt had been consumed (ca. 5 min), then the mixture was diluted with ether and water and separated. The dried ether soln was stripped under vacuum, the residue taken up in fresh ether (flocculent material separates) and combined with 10 ml 3N HCl. After the ether had been boiled off on a steam cone, the heating was continued for 10 min with periodic swirling. When cool a few milliliters of acetone were added and the product (597 mg, 83%) was collected by filtration. The crude *dl*-dihydrogambirtannine hydrochloride was recrystallized from a large volume of MeOH which provided 545 mg (76%) of platelets, m.p. 241–243 (dec). One further recrystallization raised the m.p. to 244–245° (dec) [lit.,[6] m.p. 248–250° (dec)].

The free base (II) was obtained from 150 mg of the hydrochloride by neutralizing a MeOH soln with 10% K_2CO_3 aq. Concentration of the MeOH soln under vacuum, partitioning between water and CH_2Cl_2, and recrystallization from methylene chloride-cyclohexane gave 127 mg near-white needles (II). The alkaloid so prepared exhibited a double m.p.: 155–160° then 174–178°;[15] IR ($CHCl_3$): 3450 (indolic NH), 2840, 2790, 2742 (Bohlmann bands), 1715 (aryl ester), 1143 (Me ester) cm^{-1}. The UV and mass spectra were identical to those previously recorded.[1] A freshly chromatographed (neutral Woelm alumina, activity II) sample of the base gave a single m.p. at 175–176° (lit., m.p. 175°[1] and 176–178°[6]).

Ourouparine iodide (III) *from* dl-*dihydrogambirtannine hydrochloride.* The dehydrogenation procedure developed by Elderfield[11] was adopted with slight modifications. Thus, a warm soln of 100 mg (0·027 mmole) of the hydrochloride in 10 ml 0·1 M ethanolic AcOK was added to a warm soln of 500 mg I_2 crystals and 1·0 g AcOK in 20 ml EtOH. The soln was heated on the steam cone until crystals began to separate (5 min) from soln. Filtration of the chilled soln provided 127 mg orange needles after thoroughly washing with EtOH. Recrystallization from MeOH gave 98 mg (80%) of the quaternary iodide in two crops. The product did not have a clear m.p. but rather decomposed at temps greater than ca. 300°[12]. (Found: C, 55·45; H, 3·80; I, 27·59. $C_{21}H_{16}N_2O_2I$ requires: C, 55·39; H, 3·54; I, 27·87%); IR (KBr): 1721

(aryl ester), 1639, 1602, 1311, 1263 and 1154 cm^{-1}. The UV spectrum was consistent with literature[2, 12] descriptions.

The picrate of III was formed from a MeOH soln of III containing sodium picrate. The picrate (orange needles) melted with decomposition when placed on a block preheated to 295° (lit.,[2] m.p. 267°).

Oxogambirtannine (IV). A slurry of III (40 mg) in 10 ml dioxane containing 0·2 ml 30% H_2O_2 was stirred at room temp for 16 hr. An additional 0·1 ml peroxide was added, and the reaction mixture was stirred and heated intermittently on the steam cone until a complete soln was obtained. The solvent was removed under vacuum, the residue taken up in CH_2Cl_2, washed with water, dried and evaporated. The resulting oil was dissolved in 20 ml benzene and applied to a 1 × 11 cm column of Woelm, neutral, activity III alumina. Elution with benzene and benzene-EtOAc (10:1) moved a yellow band down the column which when retrieved from the eluate gave 20 mg (66%) of an oil that crystallized on addition of a drop MeOH. The TLC plate (silica G; φH-EtOAc, 7:1) showed only one spot (blue fluorescence under UV). Recrystallization from MeOH gave 15 mg solvated (strong *m/e* 32) yellow needles, m.p. 201–205° (crystal change at ca. 165°). Recrystallization from CH_2Cl_2-cyclohexane produced yellow, fluorescent (UV) microcrystals, m.p. 208–209° (lit.,[1] m.p. 205°); IR ($CHCl_3$): 3462, 2998, 2953, 2850, 1708, 1645, 1608 and 1129 cm^{-1}. The UV and mass spectra were identical to those reported.[1]

Useful amounts of IV could not be obtained by repeating the above reaction procedure *without* the addition of H_2O_2.

Acknowledgements—The author would like to express his gratitude to Dr. E. M. Fry of this laboratory for his valuable advice and to whom all credit is due for the borohydride procedure adapted to the synthesis described herein. For their assistance and cooperation in this work the author is obliged to Dr. W. C. Alford (elemental analysis), Mr. W. R. Landis (mass spectrometry) and Mrs. E. G. Peake (infrared).

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