ORMOSIA ALKALOIDS

IV. STEREOCHEMISTRY OF ORMOJANINE; STRUCTURE AND STEREOCHEMISTRY OF PIPTANTHINE, DASYCARPINE, AND ORMOSININE[1]

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ABSTRACT

By using the known structure and stereochemistry of the alkaloid ormosanine, $C_{20}H_{35}N_3$ (I), as reference, the structure and stereochemistry of the isomeric compounds piptanthine (II), tetrahydro-ormojanine (XIV), isotetrahydro-ormojanine (XIII), and dasycarpine (XX) have been elucidated by isomerization and reduction experiments. Three additional $C_{20}H_{35}N_3$ bases possessing the ormosanine skeleton have been prepared by the reduction of pyridine VII. Thus, of the 15 possible stereoisomers of ormosanine, 7 are now known.

The study leads to the stereo-formula XIX for the alkaloid ormojanine, $C_{20}H_{31}N_3$. The alkaloid ormosinine has been found to be a dimer of panamine.

Stereochemical aspects of the catalytic and chemical reductions of the double bonds and pyridine rings contained in the described compounds are discussed. A possible biogenetic intermediate is proposed which explains the presence of both antipodal series of *Ormosia* alkaloids in nature.

The isolation of a number of alkaloids with the empirical formula $C_{20}H_{35}N_3$ has been reported; these are ormosanine from *Ormosia jamaicensis* (1), piptanthine from *Piptanthus nanus* (2), and dasycarpine from *Ormosia dasycarpa* (3). Recently, the structure and stereochemistry of ormosanine were found by X-ray crystallography to be as represented in I (4).[2] It appeared to be an interesting challenge to use the known structure and configuration of ormosanine as a point of departure and to establish the structure and stereochemistry of all the isomeric bases by correlative experiments and configurational arguments. Our interest in this problem was enhanced by the fact that we obtained two additional $C_{20}H_{35}N_3$ bases, tetrahydro-ormojanine and isotetrahydro-ormojanine, in reduction experiments on ormojanine, $C_{20}H_{31}N_3$, another constituent of *O. jamaicensis*.

Disregarding absolute configuration[2] and taking account of the fact that the two asymmetric centers C_7 and C_9 are configurationally interdependent, one arrives at 16 possible compounds containing the ormosanine skeleton. It now remains to establish whether tetrahydro-ormojanine, isotetrahydro-ormojanine, piptanthine, and dasycarpine all possess the same skeleton as ormosanine and, if so, to select for each of these compounds the correct configuration out of the 15 remaining stereochemical possibilities.

Piptanthine

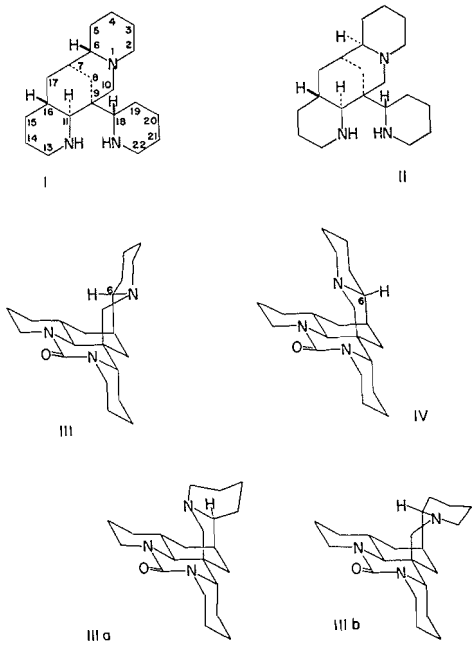
The solution in the case of the alkaloid piptanthine proved to be remarkably easy. We have been able to show (5) that a prolonged treatment of ormosanine with platinum in acetic acid in a hydrogen atmosphere at room temperature converted it into piptanthine.[3] On the basis of this isomerization, the structure and stereochemistry of piptanthine must be II for the following reasons.

Homoxy-ormosanine (III), the urea derivative of ormosanine (8), was found to undergo the same catalytic isomerization to homoxypiptanthine (IV). Consequently, C_6 must be

[1]*For part III in this series, see ref. 8.*

[2]*The absolute configuration of ormosanine and related compounds is unknown, and none is implied in any of the formulae in this communication.*

[3]*Since natural ormosanine is racemic (6), the catalytically produced piptanthine is also racemic. Piptanthine from P. nanus is levorotatory ($[\alpha]_D$ −24.3°) (7).*



considered the most likely reaction center, since this process, which probably proceeds via dehydrogenation–hydrogenation, can be expected to be sufficiently rapid only in the vicinity of the basic nitrogen atom. The configurational assignments at C_6 are confirmed by infrared spectroscopy. A potassium bromide pellet spectrum of homoxy-ormosanine shows bands in the 2 800 cm^{-1} region characteristic of the *trans*-diaxial arrangement of the tertiary nitrogen electron pair and at least two α-hydrogen atoms (9), in agreement with conformation III (4). A spectrum of homoxy-ormosanine in chloroform, on the other hand, shows no bands in this region and indicates that the compound assumes conformation III*a* or III*b* in solution. In contrast, the infrared spectrum of homoxypiptanthine shows the diagnostic bands both in solid state and in solution, in agreement with the stable all-chair all-*trans* conformation IV (5).

This difference in spectroscopic behavior and the selectivity and efficiency of this essentially irreversible isomerization process can only be explained by the configuration II for piptanthine. It should be added parenthetically that a direct proof for the platinum-catalyzed exchange of hydrogen atoms situated alpha to the tertiary nitrogen atom in *Ormosia* alkaloids is also available. During our investigation of the alkaloid ormojanine, dihydro-ormojanine (VI) was reduced with deuterium gas and platinum in CH_3COOD and the product was dehydrogenated with palladium on charcoal to the pyridine VII (8). A nuclear magnetic resonance study of the resulting pyridine showed a complete absence of deuterium in the aromatic rings and at C_{17}, whereas analysis indicated the presence of 2.3 deuterium atoms in the molecule (8). Since the deuteration was done under very mild conditions (normal pressure and room temperature), it appears reasonable to assume that the incorporated deuterium atoms must be situated alpha to the tertiary nitrogen atom (C_2, C_6, and (or) C_{10}).

It is also interesting to note that the deep-seated rearrangement taking place during the catalytic dehydrogenation of ormosanine and tetrahydro-ormojanine to 3-pentyl-6,8-dipropylquinoline requires the removal of the C_6-hydrogen atom as one of the initial steps (8).

Tetrahydro-ormojanine and Isotetrahydro-ormojanine

As reported in the accompanying communication (8), the gross structure of the alkaloid ormojanine, $C_{20}H_{31}N_3$, a constituent of *O. jamaicensis*, can be represented by formula V.[4] The following three compounds were obtained by the reduction of ormojanine. A short catalytic reduction yielded dihydro-ormojanine (VI), whereas a longer hydrogenation saturated the double bond and gave pure tetrahydro-ormojanine (8, 10). A reduction of dihydro-ormojanine (VI) with lithium in boiling ethylene diamine (17) also saturated the double bond and gave an isomeric $C_{20}H_{35}N_3$ compound, isotetrahydro-ormojanine, in a good yield. The two isomeric reduction products were found to be distinctly different from ormosanine (I) and piptanthine (II) in their physical and chemical properties.

Dehydrogenation experiments showed clearly that ormosanine and ormojanine possess the same skeleton (8). Dehydrogenation of ormosanine and of tetrahydro-ormojanine at 280° with palladium on charcoal yielded 3-*n*-pentyl-6,8-dipropylquinoline (8, 10), whereas both ormosanine and dihydro-ormojanine gave the pyridine VII on dehydrogenation with the same catalyst at a lower temperature (8, 11). It should be noted that the hydrogen atom at C_6 in pyridine VII is assigned a configuration *cis* to the C_7—C_9 bridge, requiring an isomerization at C_6 during the dehydrogenation of ormosanine (5). This configuration follows from the presence of strong bands in the 2 800 cm^{-1} region of the infrared spectrum of pyridine VII both in solid state and in solution, in complete analogy to the spectral properties of piptanthine (see above), and is proved by the reduction study described below.

The question now arises whether ormojanine and its reduction products have the ormosanine or the piptanthine configuration at C_6. Several lines of evidence clearly show that the C_6-hydrogen atom is *cis* to the C_7—C_9 bridge (analogous to II and VII) in ormojanine and all its derivatives.

(*a*) Ormojanine and all its reduction products show infrared bands in the 2 800 cm^{-1} region analogous to those of piptanthine (II) and pyridine VII.

(*b*) Neither tetrahydro-ormojanine nor isotetrahydro-ormojanine change under conditions used for the ormosanine–piptanthine isomerization.

(*c*) Isomerization of dasycarpine to isotetrahydro-ormojanine (see below) proves that the C_6-hydrogen atom in the latter is *cis* to the C_7—C_9 bridge.

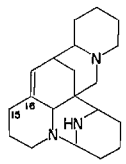
(*d*) Catalytic reduction of dihydro-ormojanine gives only one compound, tetrahydro-ormojanine.

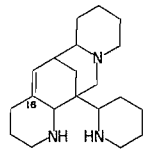
(*e*) The absence of an isomerization at C_6 during the catalytic reduction of ormojanine to dihydro-ormojanine is proved by the following evidence. *N*,*N*-Dimethyldihydro-ormojanine has been prepared from dihydro-ormojanine in three steps (8, 10). The identical dimethyl compound has also been prepared from ormojanine itself in a sequence in which no catalytic reduction was involved (8, 10).

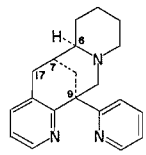
If tetrahydro-ormojanine, isotetrahydro-ormojanine, and piptanthine (II) have the same relative configuration at C_6, C_7, and C_9, they must obviously differ at some or all of the asymmetric centers C_{11}, C_{16}, and C_{18}. In other words, with the structure of piptanthine determined as II, tetrahydro-ormojanine and isotetrahydro-ormojanine must be two of the seven remaining possible compounds represented by formula VIII. Since the pyridine VII possesses the same configuration at C_6, C_7, and C_9 as the three compounds in question, it is clear that a detailed study of its reduction could provide a complete solution to the problem.

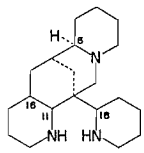
This opportunity was exploited in the following way. Pyridine VII was first reduced under mild catalytic conditions, which saturated only the monosubstituted pyridine ring.

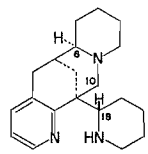
[4] *An alternative position of the double bond at* C_{15}—C_{16} *in ormojanine is not rigorously excluded by our evidence.*

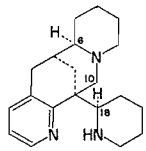

V


VI


VII


VIII


IX


X

Clearly, this reduction could be expected to give two compounds, IX and X, differing only in the configuration at C_{18}. In fact, the reduction product gave only one spot in thin-layer chromatography and was also reported (11) to appear homogeneous in vapor-phase chromatography. We have found, however, that acetylation of the reduction product gave two acetyl derivatives which could be separated chromatographically. To facilitate a reconversion into the secondary amines, the procedure was repeated with the corresponding carbobenzyloxy derivatives, which were separated by column chromatography and individually hydrogenolyzed to pure IX and pure X. The two secondary amines have the same R_f value in thin-layer chromatography, but show distinct differences in their infrared and nuclear magnetic resonance spectra. Most significantly, the two hydrogen atoms at C_{10} appear as a singlet (A_2) at 8.2 τ in the spectrum of one of the isomers and as a quadruplet (AB) centered at 8.11 τ (δ_{AB} = 19 c.p.s., J_{AB} = 10 c.p.s.) in the spectrum of the other isomer.

It must now be established which of these isomers is IX and which is X. To simplify the discussion, the results of the subsequent reduction experiments are anticipated; these demonstrate unambiguously that the isomer showing a singlet corresponding to the C_{10}-methylene group is X, and that the other isomer (quadruplet corresponding to C_{10}-methylene) is IX.

Pyridine IX was reduced catalytically with platinum in acetic acid at high pressure. Since the resulting mixture of completely saturated bases did not appear to be sufficiently stable for an extended experimentation, it was immediately treated with phosgene and thus converted into the corresponding cyclic urea derivatives. Purification by chromatography yielded two crystalline ureas, A_1 and A_2. Reduction of pyridine IX with sodium and isoamyl alcohol, followed by a treatment with phosgene and chromatography, also yielded A_1 and A_2.

Similarly, a high-pressure hydrogenation of pyridine X, followed by a treatment with

phosgene and chromatography, yielded two crystalline ureas, B_1 and B_2, whereas the chemical reduction of X with sodium and isoamyl alcohol resulted, after treatment with phosgene, in two ureas, B_1 and B_3.

These transformations can be summarized by the following scheme.

$$A_1, A_2 \xleftarrow[2.\ COCl_2]{1.\ H_2/Pt} IX \xrightarrow[2.\ COCl_2]{1.\ Na/alcohol} A_1, A_2$$

$$B_1, B_2 \xleftarrow[2.\ COCl_2]{1.\ H_2/Pt} X \xrightarrow[2.\ COCl_2]{1.\ Na/alcohol} B_1, B_3$$

The five homoxy derivatives (ureas) obtained in this way are all pure, stable compounds with the expected molecular ion in their mass spectra (*m/e* 343) and showing distinct differences in thin-layer chromatography and infrared and nuclear magnetic resonance spectroscopy. Furthermore, their spectra show the complete absence of olefinic or aromatic hydrogen atoms. They must therefore be the homoxy derivatives of five of the eight possible $C_{20}H_{35}N_3$ isomers depicted by the general formula VIII.

Comparison with known compounds has shown that A_1 is identical with homoxypiptanthine (IV) and that B_3 is identical with homoxytetrahydro-ormojanine. Since the complete stereochemistry of piptanthine is known, it is clear that these findings rigorously differentiate between the two monopyridines IX and X. Furthermore, ormojanine and its reduction products must clearly have a configuration at C_{18} opposite to that of piptanthine.

Just as significantly, however, the homoxy derivatives of ormosanine, dasycarpine, and isotetrahydro-ormojanine were found not to be identical with any one of the remaining reduction products, A_2, B_1, and B_2. The absence of homoxy-ormosanine (III) was to be expected and confirms our assignment of a configuration at C_6 in pyridine VII opposite to that of ormosanine (I) (5). Homoxy-dasycarpine cannot be expected to be present among the hydrogenation products on the basis of experiments described below.

The absence of the urea of isotetrahydro-ormojanine among the reduction products of X was, however, unexpected. It must be remembered that isotetrahydro-ormojanine is produced by the chemical reduction of dihydro-ormojanine (VI), whereas tetrahydro-ormojanine results from a catalytic reduction of VI. Since we now know that ormojanine possesses the more stable configuration at C_6 and since, furthermore, there is no evidence in our work of any isomerizations under the conditions of a chemical reduction, it must be assumed that the two tetrahydro isomers differ only in the configuration at the reduced center C_{16}.[5] It follows, therefore, that isotetrahydro-ormojanine must correspond to the missing fourth possible reduction product of X (B_4).

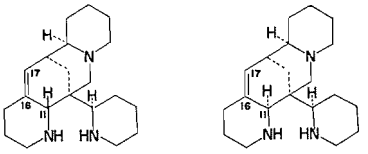
This postulate gives rise to a paradoxical situation. Since isotetrahydro-ormojanine is formed in a high yield in the chemical reduction of VI, it should be more stable than tetrahydro-ormojanine. How is it possible, then, that the less-stable compound, tetrahydro-ormojanine, is formed in the chemical reduction of pyridine X and that the more stable compound, isotetrahydro-ormojanine, is not obtained from X at all?

Actually, there is one, and only one, satisfactory solution to this dilemma. First of all, as stated above, the results of the hydrogenation of pyridines IX and X clearly show that the ormojanine series has a configuration at C_{18} opposite to that of ormosanine (I) and piptanthine (II). Dihydro-ormojanine (VI) can therefore definitely be represented by one of two complete stereo-formulae, XI and XII, differing in the configuration at C_{11}.

[5]*That isotetrahydro-ormojanine has a configuration at* C_6 *identical with that of X also follows clearly from our work on dasycarpine (see below).*

Scheme 1 now shows the tetrahydro compounds to be expected from the two possibilities. Clearly, XI would, on reduction, give rise to XIII and XIV, whereas XII would be reduced to XV and XVI.

Should XI be the correct representation of dihydro-ormojanine, then XIII must be the formula for isotetrahydro-ormojanine and XIV for tetrahydro-ormojanine for the following reasons. Clearly, a catalytic reduction of the C_{16}—C_{17} double bond in XI should proceed from the less-hindered side. In this case, the two rings containing the tertiary nitrogen

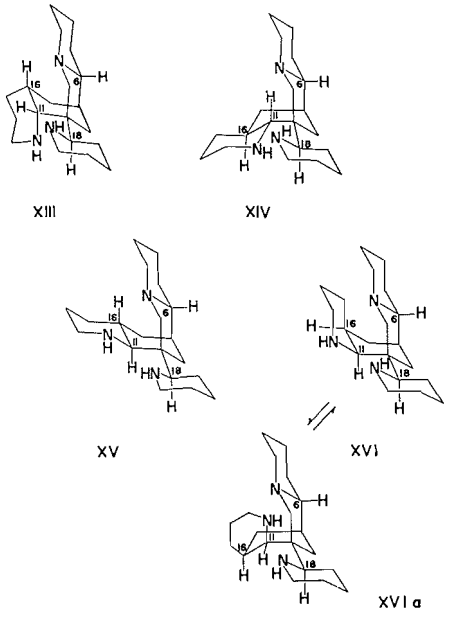


XI XII

atom completely screen the upper side of the molecule, and the catalytic addition of hydrogen, which is found to be completely stereospecific, must therefore take place from the bottom. Thus, tetrahydro-ormojanine would be XIV. On the other hand, the chemical reduction of the C_{16}—C_{17} double bond in XI would be expected to give the more stable compound, and an inspection of models shows that XIII could well be more stable than XIV. This leads to formula XIII for isotetrahydro-ormojanine.

Similar considerations apply if XII were the structure of dihydro-ormojanine. Again, the catalytic reduction would be expected to proceed from the side opposite to the two rings containing the tertiary nitrogen; tetrahydro-ormojanine would therefore be XVI. Furthermore, XV is clearly more stable than XVI; isotetrahydro-ormojanine would thus have structure XV.

The decision between these two possibilities is now quite simple. It can be seen that the



XIII XIV XV XVI XVI a

SCHEME 1.

configuration at the important centers C_6, C_{11}, and C_{16} in formula XV is identical with that of piptanthine (II).[6] Since piptanthine is produced both by a catalytic and a chemical reduction of pyridine IX (see above), it can be expected that compound XV would be formed by both reductions, or at the very least one of the reductions, of pyridine X. Since B_3 is identical with homoxytetrahydro-ormojanine, structure XV must therefore definitely correspond to one of the two remaining reduction products of pyridine X, B_1 or B_2. However, neither B_1 nor B_2 are identical with homoxyisotetrahydro-ormojanine (see above); *isotetrahydro-ormojanine must therefore have structure XIII, tetrahydro-ormojanine structure XIV, and dihydro-ormojanine structure XI.*[7] Mechanistic considerations (see below), furthermore, clearly indicate that formula XV must correspond to reduction product B_1 and formula XVI to reduction product B_2.

It still remains to be explained, however, why the chemical reduction of pyridine X gives no isotetrahydro-ormojanine (XIII). It can be seen immediately that this and all other reported facts find a ready explanation when the reasonable assumption is made that the reduction of the pyridine ring with sodium and alcohol is a multistage process in which the tetrahydro-pyridines XVII and XVIII (or the corresponding dihydro-pyridines with an additional double bond at C_{13}—C_{14}) are intermediates.[8] The reduction of XVII can give XIII and XV, but if XV is the more stable compound of the two, only XV and no isotetrahydro-ormojanine (XIII) will be produced. Similarly, the reduction of XVIII can give XIV and XVI; only tetrahydro-ormojanine (XIV) will be produced if it is more stable than compound XVI.

The apparent paradox is thus seen to arise because, in the chemical reduction of dihydro-ormojanine, the stability of isotetrahydro-ormojanine is compared with that of tetrahydro-ormojanine, whereas in the chemical reduction of pyridine X, it is compared with that of isomer XV. In the first case, isotetrahydro-ormojanine is the more stable compound; in the second case, it is the less-stable one.

The above analysis thus explains all the known experimental facts satisfactorily and provides a unique solution of the stereochemistry of the ormojanine reduction products. *Based on the previously deduced gross structure V, ormojanine itself can then be represented by the complete formula XIX.* The opposite configuration at C_{22} in this structure is sterically impossible.

It is interesting to note that, on the basis of the hydrogenation study described above, the synthesis of pyridine VII will represent the total synthesis of one natural product, piptanthine, and four alkaloid reduction products, including tetrahydro-ormojanine. Stereochemically, the synthesis thus simplifies to the preparation of two possible diastereoisomers (VII and its epimer at C_6), which are furthermore connected by the described isomerization at C_6.

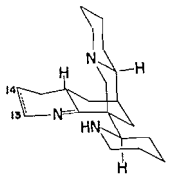
Dasycarpine

After the stereochemical relationships in the ormojanine series had been clarified, the structure and stereochemistry of dasycarpine, $C_{20}H_{35}N_3$, an alkaloid of *Ormosia dasycarpa* (3), were solved in the following simple way. A sample of dasycarpine was subjected to a

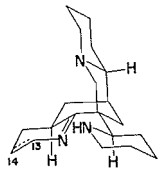
[6]*The two compounds only differ in their configuration at* C_{18}, *and this difference would not be expected to affect significantly the following arguments.*

[7]*Another argument, independent of the piptanthine series, leads to the same conclusion. The assignment of formula XV to isotetrahydro-ormojanine and of XVI to tetrahydro-ormojanine cannot be correct, since it requires that compound XVI not be formed in the catalytic reduction of pyridine X, although an addition of two* α*-hydrogen atoms during this hydrogenation would be expected to be particularly favorable.*

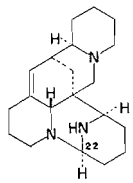
[8]*It is known that the reduction of pyridines with sodium and alcohol proceeds via 1,4-dihydropyridines (12), and it can be expected that an enamine–imine isomerization will precede further reduction.*



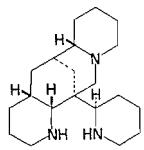
XVII



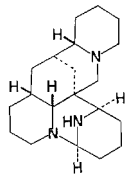
XVIII



XIX



XX



XXI

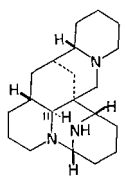
prolonged treatment with platinum in acetic acid in a hydrogen atmosphere at room temperature under conditions identical with those necessary for the ormosanine–piptanthine isomerization. The resulting product was found to be isotetrahydro-ormojanine. *Dasycarpine is therefore epimeric with isotetrahydro-ormojanine at* C_6 *and can be represented by the stereo-formula XX.*

An oily alkaloid isolated from *O. jamaicensis* has been found to give dasycarpine in a mild hydrogenation. This compound is probably identical with ormosajine, $C_{20}H_{33}N_3$, which has been isolated and hydrogenated to dasycarpine by Hassall and Wilson (13, 14). Since the presence of an N—C—N linkage in this alkaloid is indicated by spectroscopy, it can be assigned the structure and stereochemistry XXI.

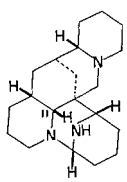
Panamine and Ormosinine

These two alkaloids of *Ormosia panamensis* have been studied under the assumption that they both have the composition $C_{20}H_{33}N_3$ (6, 15).

On the basis of the fact that panamine is converted into ormosanine by a reduction with sodium borohydride (6), and to ormosanine (6) and piptanthine (5) by catalytic hydrogenation, structure XXII was proposed for panamine (15). A recent X-ray analysis (16) confirmed the correctness of this proposal. Thus, panamine is a simple oxidative derivative of ormosanine.



XXII



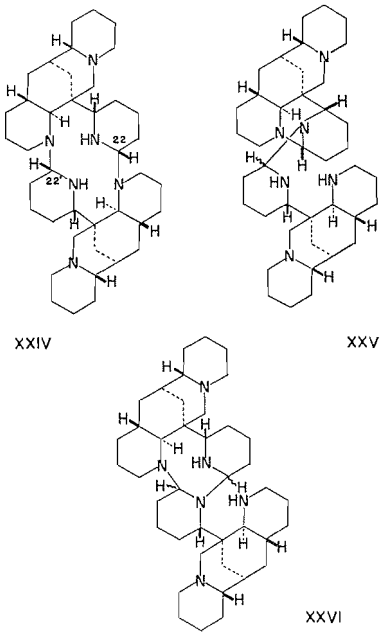
XXIII

It was furthermore proposed that the alkaloid ormosinine can be represented by formula XXIII (15). The conversion of ormosinine into some derivatives of panamine (6), which requires an epimerization at C_{11} on the basis of this structural assignment, was explained by rather involved isomerization mechanisms (15).

Our own interest in ormosinine was based on the following considerations. Should XXIII be the correct representation of this alkaloid, then one of its hydrogenation products would clearly be a C_{18}-epimer of dasycarpine and should, after isomerization at C_6, fit into our pyridine reduction series A. We have, however, found that vigorous hydrogenation of ormosinine produces, in addition to ormosanine and piptanthine, two reduction products, neither of which gives A_2 on conversion into the corresponding urea derivatives.

All published data and the above hydrogenation can readily be explained by the fact that *ormosinine is not an isomer but a dimer of panamine.* This follows from the following new findings. (*a*) Sublimation of ormosinine in a high vacuum gave pure panamine. (*b*) A molecular weight determination with a Mechrolab osmometer gave a value of 640 for ormosinine.

The identity of the mass spectra of panamine and ormosinine (6) and the conversion of ormosinine into panamine derivatives (6) can thus be explained in a very simple way.



SCHEME 2.

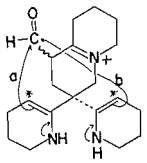
The only remaining question is the exact nature of the dimer. There are several ways in which two molecules of panamine (in the open imine form) can dimerize, and the available evidence does not lead to a unique solution. The structural possibilities are given in Scheme 2.[9] On the basis of steric considerations and a study of urea formation (see Experimental), we consider formula XXIV as the most probable structure of ormosinine.

Biogenesis

One of the unusual aspects of *Ormosia* alkaloid stereochemistry is the fact that the natural alkaloid ormosanine is racemic (6). Furthermore, our work has shown (5) that piptanthine from *Piptanthus nanus* and panamine from *Ormosia panamensis* belong to antipodal series.[10]

[9] *Additional structures with an opposite configuration at* C_{22} *and (or)* $C_{22'}$ *in XXIV are also sterically possible.*

[10] *Piptanthine form P. nanus is levorotatory (7), whereas piptanthine formed by the reduction and isomerization of panamine is dextrorotatory (5, 6).*



XXVII

It is interesting to note that the existence of both antipodal series in this class of alkaloids can be explained in a particularly simple manner by the postulate of a biogenetic intermediate of the type XXVII, formed by the condensation of four lysine units (10, 15). The enol of aldehyde XXVII has a plane of symmetry, and the two corresponding enantiomeric aldehydes can condense with the appropriate C*-atom (arrows *a* or *b* in formula XXVII) to give the two antipodal pentacyclic derivatives.

EXPERIMENTAL

Nuclear magnetic resonance spectra were recorded in $CDCl_3$ on a Varian HR-60 spectrometer, and chemical shifts are reported in parts per million relative to an internal tetramethylsilane reference. Infrared spectra were obtained with Perkin–Elmer model 21 and 137B Infracord instruments, and ultraviolet spectra were recorded on a Beckman DK-2 instrument and mass spectra on a Hitachi Perkin–Elmer RMU-6D instrument. All melting points are uncorrected.

Isomerization of Ormosanine

Ormosanine (35 mg) was stirred in a hydrogen atmosphere in acetic acid (10 ml) in the presence of platinum oxide (100 mg) at room temperature and normal pressure for 1 day. The catalyst was removed by filtration and the solution evaporated. Distribution between ether and 1 *N* hydrochloric acid, followed by basification of the aqueous layer with ammonia and its extraction with ether gave 29 mg of a basic material. To convert it into the corresponding urea, the residue was dissolved in dry benzene, one drop of triethylamine was added, and phosgene gas was bubbled through the solution for 1 min. The solution was then extracted with 1 *N* hydrochloric acid, and the aqueous layer was basified with ammonia and extracted with ether. The resulting mixture of two homoxy-derivatives (thin-layer chromatography (t.l.c.)) was purified by preparative t.l.c., using alumina and ether–benzene (1:4).

The faster moving fraction (11 mg) crystallized from petroleum ether and was found to be identical with homoxypiptanthine (IV) (2)[11] in t.l.c. and infrared and nuclear magnetic resonance spectra.

The slower moving fraction (8 mg) was homoxy-ormosanine (III) (8) on the basis of melting point, t.l.c., and infrared spectrum.

The same catalytic isomerization was performed, starting with homoxy-ormosanine (52 mg). Preparative t.l.c. again gave pure homoxypiptanthine (7 mg) and homoxy-ormosanine (27 mg).

Chemical Reduction of Dihydro-ormojanine

Dihydro-ormojanine (200 mg) (8) and ethylene diamine (40 ml) were heated to 90 °C in a purified nitrogen atmosphere in a dried apparatus protected with a mercury seal. Lithium wire (2.5 g) was then added in small portions to the stirred solution over a period of 45 min, the temperature being maintained at 90–100° (17). The mixture was then refluxed for 1 h and allowed to stand at room temperature for 15 h. After a careful addition of water under ice cooling, the mixture was acidified with concentrated hydrochloric acid and extracted with ether. The aqueous layer was basified with sodium hydroxide and extracted with ether to give 110 mg of a basic material. Crystallization from acetone gave pure isotetrahydro-ormojanine, m.p. 135–136°. The mass spectrum shows the expected molecular ion peak at *m/e* 317. Infrared maximum (CCl_4) at 3 300 cm^{-1} (NH, sharp).

Treatment of isotetrahydro-ormojanine with phosgene in the usual manner gave the homoxy derivative, showing a molecular ion peak at *m/e* 343 in its mass spectrum and an amide maximum at 1 610 cm^{-1} in its infrared spectrum ($CHCl_3$).

Isotetrahydro-ormojanine was found to be distinctly different from tetrahydro-ormojanine (8), ormosanine (1), and piptanthine (2) in melting point and infrared and nuclear magnetic resonance spectra.

Catalytic Reduction of Pyridine VII

Pyridine VII (1.08 g), prepared by the dehydrogenation of dihydro-ormojanine (8), was hydrogenated in the presence of platinum oxide (100 g) in acetic acid (70 ml) for 20 h at room temperature and normal pressure. The solution was filtered and evaporated, and the residue was distributed between aqueous ammonia and ether. The dried ether extract (1.10 g) showed only one spot in t.l.c. Maxima in the nuclear magnetic

[11] *We thank the Czech workers for a sample of piptanthine from P. nanus.*

resonance spectrum (CCl_4) at 1.83 (1 H, multiplet) and 2.80–3.40 τ (2 H's, multiplet) together with the ultraviolet spectrum (inflection 263, λ_{max} 268 (ϵ 3 400), inflection 275 mμ) clearly show that only one (α,β-substituted) pyridine ring is present in the product. Purification and characterization of this product as a mixture of pyridines IX and X is described below.

N-Acetyl Derivatives of Pyridines IX and X

The above mixture (68 mg) was acetylated with acetic anhydride (5 ml) in pyridine (5 ml) for 15 h at room temperature. The usual work-up gave 65 mg of a basic material which showed two spots in t.l.c. on alumina with benzene–ether (1:1) as eluent. Preparative t.l.c. gave one compound (R_f 0.6) as an oil (26 mg).

Anal. Calcd. for $C_{22}H_{31}N_3O$: C, 74.74; H, 8.88; O, 4.53; N, 11.88. Found: C, 74.12; H, 8.73; O, 4.42; N, 10.89.

Nuclear magnetic resonance maxima at 1.73 (1 H, multiplet), 2.70–3.20 (2 H's, multiplet), and 7.80 τ (*N*-acetyl, singlet).

The second acetyl derivative (R_f 0.4) weighed 31 mg and, after crystallization from ether, melted at 195–197°.

Anal. Found: C, 74.26; H, 8.60; O, 4.39; N, 10.99.

Nuclear magnetic resonance maxima at 1.70 (1 H, multiplet), 2.70–3.20 (2 H's, multiplet), and 7.65 and 7.70 τ (*N*-acetyl, two singlets).

N-Carbobenzyloxy Derivatives of Pyridines IX and X

The above mixture of pyridines IX and X (1.10 g) was dissolved in methylene chloride (175 ml), and the solution was mixed with water (50 ml) and magnesium oxide (280 mg). Benzyl chloroformate (3.6 g) in methylene chloride (75 ml) was added to the stirred mixture over a period of 90 min at ice-bath temperature. The stirring was continued for an additional hour, the mixture was acidified with dilute hydrochloric acid, and the organic layer was extracted exhaustively with 2 *N* hydrochloric acid. The combined aqueous layers were basified with ammonia and extracted with ether to give 1.54 g of a basic material. Thin-layer chromatography on alumina with ether indicated two compounds different from the starting material.

These were separated by column chromatography on neutral alumina (Woelm, activity 2, 80 g), taking 100 ml fractions and analyzing them by t.l.c. Elution with benzene – petroleum ether (1:2 (2.5 l) and 1:1 (500 ml)) gave pure *N*-carbobenzyloxy IX (630 mg), elution with benzene – petroleum ether (3:1, 800 ml) gave a mixture of the two isomers (120 mg), and elution with ether (500 ml) gave pure *N*-carbobenzyloxy X (790 mg). The two compounds, which could not be induced to crystallize, were found to be homogeneous by t.l.c. and showed the expected ultraviolet (λ_{max} 268 mμ), infrared (maxima at 1 680 and 1 580 cm^{-1}), and nuclear magnetic resonance spectra (a multiplet at 1.7 τ for 1 H, a multiplet at 2.8–3.3 τ for 7 H's, and a broad singlet at 5.0 τ for the benzylic CH_2).

Pyridines IX and X

N-Carbobenzyloxy IX (200 mg) was hydrogenolyzed in acetic acid (95%, 10 ml) with palladium on charcoal (10%, 40 mg) in a hydrogen atmosphere for 12 h. The usual work-up gave 140 mg of pure oily pyridine IX, homogeneous in t.l.c. Infrared maxima (CCl_4) at 3 300 (NH) and 1 560 cm^{-1} (broad); nuclear magnetic resonance maxima (CCl_4) at 1.81 (1 H, multiplet), 2.8–3.3 (2 H's, multiplet), and 8.11 τ (C_{10}-methylene, quadruplet).

N-Carbobenzyloxy X (156 mg) was hydrogenolyzed in the same manner to give 108 mg of pure oily pyridine X. Infrared maxima (CCl_4) at 3 300 (NH) and 1 560 cm^{-1} (broad); nuclear magnetic resonance maxima at 1.83 (1 H, multiplet), 2.8–3.3 (2 H's, multiplet), and 8.20 τ (C_{10}-methylene, singlet).

The pyridines IX and X show identical R_f values in all t.l.c. systems tried; their separation was therefore found to be possible only through the above derivatives.

Catalytic Reduction of IX

Pyridine IX (75 mg) was hydrogenated in acetic acid (10 ml) with platinum oxide (110 mg) at 100° and 2 200 p.s.i. for 12 h. The usual work-up gave 58 mg of a basic material. Since a preliminary study indicated that the product slowly decomposed on chromatography, it was immediately treated with phosgene and triethylamine in benzene (see above). The product (50 mg) was shown to be a mixture of two homoxy derivatives by t.l.c.

Separation was achieved by preparative t.l.c., using alumina and benzene–ether (1:1). The faster moving fraction was further purified by a second preparative t.l.c. under the same conditions, and the resulting crystalline product, A_1 (12 mg), m.p. 153–155°, was found to be identical in infrared spectrum and t.l.c. with homoxypiptanthine (2).

The second compound, A_2 (8 mg), crystallized from petroleum ether and melted at 164–165°. Its mass spectrum (molecular ion peak at *m/e* 343) confirms its composition. Its infrared spectrum contains the urea maximum at 1 620 cm^{-1} ($CHCl_3$); the fingerprint region, furthermore, shows that A_2 is not identical with the homoxy derivative of any of the known $C_{20}H_{35}N_3$ *Ormosia* isomers.

Chemical Reduction of IX

To a solution of pyridine IX (200 mg) in boiling isoamyl alcohol (30 ml) was added sodium (2.0 g) in small pieces during 90 min. The cooled solution was extracted with 1 *N* hydrochloric acid, and the aqueous

layer was washed with ether, basified, and extracted with ether. The residue was treated with phosgene in the usual way to give 156 mg of two homoxy derivatives (t.l.c.).

The faster moving fraction was obtained in a pure state (39 mg) by column chromatography with benzene on neutral alumina (Woelm, grade 2, 7.5 g) and identified as homoxypiptanthine, A_1.

The second compound could not be obtained in a pure state by column chromatography. The preparative t.l.c. method gave the pure product (10 mg), identical in all respects with A_2 (see above).

Catalytic Reduction of X

Pyridine X (76 mg) was hydrogenated in acetic acid (10 ml) with platinum oxide (20 mg) at 115° and 2 500 p.s.i. for 3 days. The usual work-up gave 40 mg of a basic material, which was immediately treated with phosgene as above. The product (40 mg), containing two compounds (t.l.c.), was subjected to preparative t.l.c. on alumina, with benzene–ether (1:1) as eluent.

The faster moving fraction, B_2 (15 mg), crystallized from petroleum ether and melted at 224–225°. Its mass spectrum shows the expected molecular ion peak at m/e 343; the infrared spectrum ($CHCl_3$) shows the urea peak at 1 610 cm^{-1}.

The second fraction, B_1 (11 mg), crystallized from petroleum ether and melted at 158–159°. Its mass spectrum shows the expected molecular ion peak at m/e 343, and its infrared spectrum ($CHCl_3$) contains the urea peak at 1 610 cm^{-1}.

The physical properties of B_1 and B_2 (melting point and infrared, nuclear magnetic resonance, and mass spectra) clearly show the non-identity of these compounds with the homoxy derivatives of ormosanine, piptanthine, tetrahydro-ormojanine, and isotetrahydro-ormojanine.

Chemical Reduction of X

Sodium (1.2 g) was added in small pieces during 90 min to a boiling solution of pyridine X (108 mg) in isoamyl alcohol (15 ml). The usual work-up (see above) gave 100 mg of a basic material, which was subjected to an additional reduction with sodium (1.2 g) in isoamyl alcohol (15 ml). The resulting basic material (70 mg) was subjected to preparative t.l.c. on silica, using 4% dimethylamine in petroleum ether as eluent.

The faster moving fraction (10 mg) was treated with phosgene as described above, and the resulting homoxy derivative was purified by preparative t.l.c. on alumina with benzene–ether (1:1). The pure product (7 mg) melted at 158–159° and was found to be identical with B_1, produced by the catalytic reduction of pyridine X.

The second fraction (7 mg) was also treated with phosgene and the product purified by preparative t.l.c. on alumina with benzene–ether (1:1). The resulting pure compound (4 mg) crystallized from petroleum ether and melted at 203–205°. This compound, B_3, was found to be identical in all respects (melting point, t.l.c., and infrared and mass spectra) with homoxytetrahydro-ormojanine (8).

Isomerization of Dasycarpine

(*a*) Dasycarpine (34 mg) (3)[12] was stirred in a hydrogen atmosphere in acetic acid (10 ml) in the presence of platinum oxide (100 mg) at room temperature and normal pressure for 3 weeks. The usual work-up gave 34 mg of a basic material, which was treated with phosgene as described above. Thin-layer chromatographic analysis of the product on alumina with ether – petroleum ether (1:1) as eluent showed the presence of two compounds with R_f values of 0.4 and 0.5, respectively.

Preparative t.l.c. on alumina with ether – petroleum ether (7:3) as eluent achieved a complete separation. The faster moving compound was found to be identical in all respects with homoxyisotetrahydro-ormojanine (see above). The slower moving compound was homoxydasycarpine (3). The two compounds were isolated in approximately equal quantities.

Although homoxyisotetrahydro-ormojanine shows a strong band at 2 750 cm^{-1} in the infrared spectrum ($CHCl_3$), this band is completely absent from the spectrum of homoxydasycarpine. This is analogous to the piptanthine–ormosanine pair.

(*b*) Mother liquors from the crystallization of ormosanine and ormojanine from *O. jamaicensis* (8) were subjected to a nine-funnel countercurrent distribution, using ether and McIlvaine's buffer (pH 7.3), with the buffer as a moving phase. Fraction 7 (1.95 g from 13.5 g of the original mixture) contained a foam which was homogeneous in t.l.c. and showed an R_f value of 0.4 on alumina with 4% methanol in benzene. Sublimation in a high vacuum gave a colorless oil; nuclear magnetic resonance maximum at 6.50 τ (1 H, broad singlet). This compound is probably identical with the alkaloid ormosajine (13, 14).

The oily sublimed alkaloid (215 mg) was hydrogenated for 16 h in 2% aqueous hydrochloric acid (40 ml) in the presence of platinum oxide (400 mg) at room temperature and normal pressure. The usual work-up gave 200 mg of a basic material which, on the basis of t.l.c. analysis (3% diethylamine in petroleum ether on silica), consisted of approximately equal amounts of two products with R_f values of 0.4 and 0.3, respectively.

Preparative t.l.c. with the above system achieved a complete separation. The component, R_f 0.3, was found to be identical with dasycarpine (3), and the second component, R_f 0.4, was isotetrahydro-ormojanine.

[12]*We thank Drs. Clarke and Grundon for this sample.*

Ormosinine

The alkaloids ormosinine, m.p. 219–220°, and panamine were isolated from *O. panamensis* by the procedure reported by Lloyd and Horning (18). Ormosinine shows a strong sharp NH maximum at 3 300 cm^{-1} in the infrared spectrum (CCl_4) and a broad singlet at 6.56 τ characteristic of the N—CH—N grouping in the nuclear magnetic resonance spectrum.

A molecular weight determination with Mechrolab osmometer model 301 in carbon tetrachloride (four independent measurements) gave a value of 640 ∓ 30 for ormosinine.

Sublimation of ormosinine at 250° and 0.4 mm gave a quantitative yield of panamine (sublimate), identified by infrared and nuclear magnetic resonance spectra.

Thin-layer chromatographic analysis of crystalline ormosinine on silica with 7% diethylamine in petroleum ether (double elution) revealed the presence of two components, R_f 0.5 and 0.45, respectively. It is not yet certain whether crystalline ormosinine consists of two different dimers or whether a partial conversion takes place during chromatography.

Vigorous hydrogenation of ormosinine in acetic acid with platinum oxide at 40° and 1 850 p.s.i. for 20 h gave, in addition to starting material, four reduction products. After the conversion of the mixture into the corresponding homoxy derivatives, homoxy-ormosanine and homoxypiptanthine were isolated from the mixture by column chromatography on alumina. The two remaining compounds were separated by preparative t.l.c. on alumina, with ether as eluent. One of them crystallized from petroleum ether and melted at 245°, and the second one remained oily. Both compounds are almost certainly dimeric, since their mass spectra show fragments with *m/e* above 400.

Homoxy-ormosinine

Ormosinine (130 mg) was treated in the usual way with phosgene in dry benzene (15 ml) and triethylamine (0.5 ml). The usual extraction gave a quantitative yield of a basic material. The infrared spectrum of the product in chloroform showed a carbonyl absorption at 1 720 and a double maximum at 1 630 cm^{-1}. Although it has so far not been possible to achieve a separation, it appears possible that the maxima at 1 630 cm^{-1} indicate the presence of ureas formed after a partial opening of the dimer, and the maximum at 1 720 cm^{-1} corresponds to the homoxy derivative of XXIV, in which the geometry of the relevant orbitals would not allow the usual amide resonance.

Hydrogenation of Panamine

Panamine (18) (1.4 g) was hydrogenated in 4% hydrochloric acid (50 ml) in the presence of platinum oxide (550 mg) at room temperature and normal pressure for 16 h. The resulting basic material, obtained in a quantitative yield, was converted into the homoxy derivative on treatment with phosgene and triethylamine in benzene (see above). Separation of a portion of this product by t.l.c. on alumina with ether – petroleum ether (1:1) gave pure homoxy-ormosanine and pure homoxypiptanthine.

The original hydrogenation mixture could, without conversion into ureas, be separated by preparative t.l.c. on silica with 5% diethylamine in petroleum ether. The two components were identified as ormosanine and piptanthine.

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