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# THE STRUCTURES OF AMURINE AND NUDAURINE

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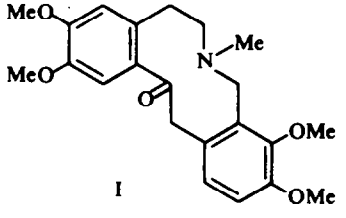
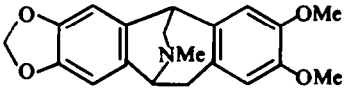
**Abstract**—The structures of the related alkaloids amurine (IV) and nudaurine (V) are elucidated mainly from spectroscopic studies. Supporting evidence for these structures is provided by the Hofmann degradation of amurine to 2-hydroxy-3-methoxyphenanthrene and by the rearrangement of amurine, under acidic conditions, to the phenanthrene XIV (R = H). Similarly, nudaurine with acid is shown to afford the phenanthrene XVIII (R = H). The biogentic origin of IV and V is discussed.

THE species *Papaver amurense* Hart (syn. *P. nudicaule* L. var *amurense*) has been reported to contain five alkaloids.[1] The structures of muramine (I),[2] amurensine (II)[3] amuronine (IIIa)[4] and amuroline (IIIb)[4] have been discussed previously. The structure determination of the remaining alkaloid amurine (IV) and the related base nudaurine (V), which occurs together with IV in P. *nudicaule* var *aurantiacum*[1b] forms the subject of this paper.[5]




I

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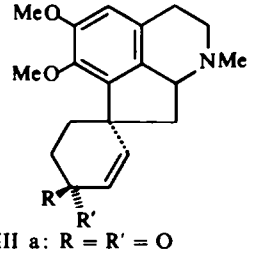
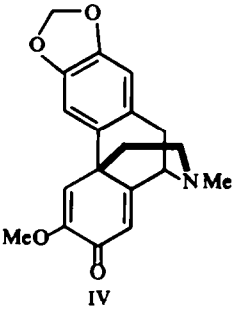
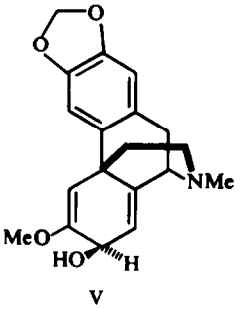



III a: R = R' = O
b: R = H R' = OH




IV

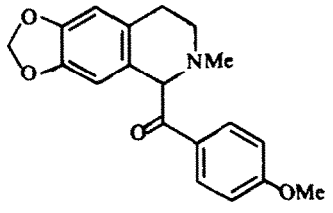



V

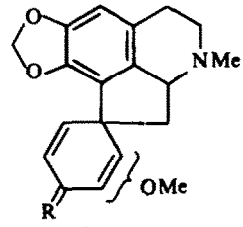
*NMR spectral investigations of nudaurine and amurine*

Earlier investigations of amurine had established the molecular formula as $C_{19}H_{19}O_4N$. The oxygen functions were accounted for in a conjugated CO, an O-Me, and methylenedioxy groups. An N-Me group also was present. The tentative suggestion[6] that amurine was represented as structure VI was subsequently refuted

by the synthesis of VI and its demonstrated non-identity with the alkaloid.[7] Further studies by Šantavý and *et al.*[8] showed that the IR spectrum of amurine was consistent with the presence of a cross-conjugated dienone, and on the basis of a comparison of the UV spectra and half-wave reduction potentials of this alkaloid with similar data from several cross-conjugated dienones, including the 4,4-spirocyclohexadienone alkaloids mecambrine[9] and pronuciferine,[10] the partial structure VIIa was assigned. In view of the previously demonstrated relationship between amurine and nudaurine, the latter was represented by structure VIIb.




VI




VII a: R = O
b: R = H, OH

Our investigations on the structures of amurine and nudaurine were pursued when it was found that the NMR spectrum of nudaurine (Fig. 1) was inconsistent with the structure assigned by Šantavý *et al.*

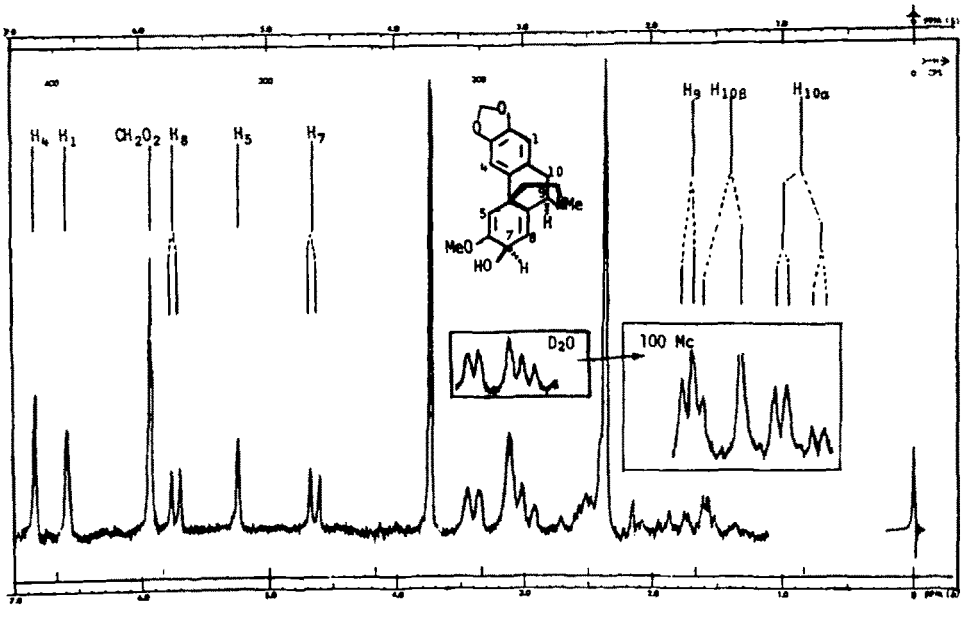



FIG. 1. NMR Spectrum of nudaurine (V).

The presence of two aromatic hydrogens is clearly indicated from the occurrence of singlet resonances at 6·82 $\delta$ and 6·58 $\delta$ and serves to eliminate structure VIIb from further consideration. The chemical shifts are typical for aryl hydrogens located next to oxygen functions[11] and in conjunction with the presence of a 2-proton singlet at

5·92 $\delta$ attributable to a methylenedioxy group attached to an aromatic ring, nudaurine could be assigned the partial structural unit VIII.

In addition the spectrum contains olefinic hydrogen resonances as a doublet at 5·76 $\delta$ ($J$ = 4·0 Hz), and a singlet at 5·28 $\delta$. The olefinic hydrogen giving rise to the former signal is coupled to a proton whose signal appears as a doublet at 4·76 $\delta$ ($J$ = 4·0 Hz). An assignment of these signals to a dienol system as shown in partial structure IX could be made after inspection of the NMR spectrum (Fig. 2) of the related

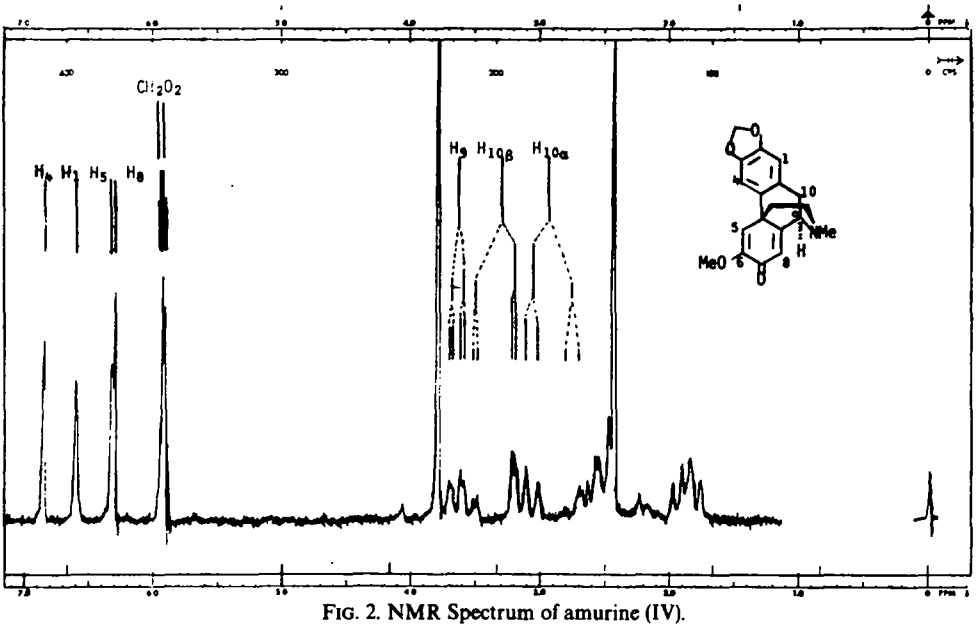
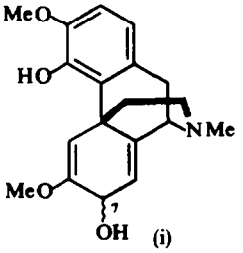


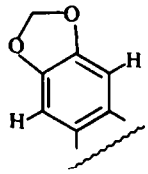

FIG. 2. NMR Spectrum of amurine (IV).

alkaloid amurine and the knowledge that amurine contained a cross-conjugated dienone chromophore.† The low field position of the MeO resonance in the spectra of nudaurine and amurine indicated that this group was attached to an unsaturated C atom. Its placement at C6 rather than the alternate C5 or C8-positions was guided initially by biogenetic arguments and was subsequently substantiated by chemical studies. The presence of an N-Me group is confirmed by the occurrence of a 3-proton singlet at 2·35 $\delta$, and a signal from a OH proton was located at 3·14 $\delta$ by its diminution on exchange with $D_2O$. A 3-proton multiplet at 2·60–3·45 $\delta$ becomes clearly recognizable as an ABX system in the 100 MHz spectrum (see inset in Fig. 1), which on

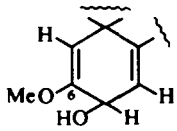



(i)

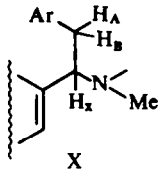
† Ample support for these assignments has recently become available since our original structural proposal[5] from the NMR data published for the salutaridinols(i)(epimeric at the C7-position).[12]



VIII



IX

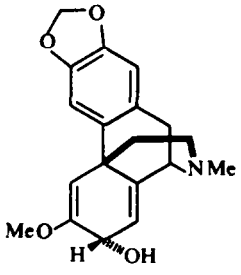


X

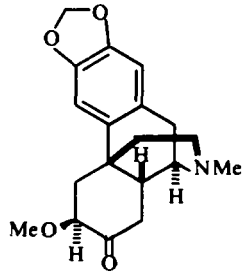
first order analysis† gives the values $J_{AB} = -18$ Hz, $J_{AX} < 1{\cdot}0$ Hz, $J_{BX} = 6{\cdot}0$ Hz. The large coupling between the AB protons is characteristic of geminal coupling augmented by the presence of an adjacent $\pi$-system.[13] This fact, in conjunction with the chemical shift values, leads to their assignment as non-equivalent protons of a benzylic methylene group. The location of the X-proton signal at 3·39 $\delta$ suggests it is attached to a carbon bearing a nitrogen substituent, and in fact the chemical shift agrees well with the values reported for the C9-hydrogen signal of alkaloids in the morphine series containing $\Delta^8$-unsaturation.[14] From this it may be inferred that the ABX system is contained in the structural unit X. The remaining four hydrogens are responsible for the two complex multiplets centered at 2·50 $\delta$ and 1·70 $\delta$, which is consistent with the signals expected from the four methylene hydrogens in an ethanamine moiety. Combination of the latter with the partial structural units VIII–X leads to the most reasonable representations of nudaurine as structure V (no stereochemical implications).

In view of the previously demonstrated oxidation of nudaurine to amurine, the latter may be formulated as indicated in structure IV. Further evidence on the simple relationship between these alkaloids is obtained from the results of the borohydride reduction of amurine, which affords nudaurine as the main product accompanied by the epimeric alcohol XI.‡

The NMR spectrum of amurine is in complete accord with the proposed structure. Aromatic hydrogen resonances are located at 6·93 and 6·77 $\delta$ as singlets. Since the latter signal is somewhat shorter and broader it is ascribed to the C1-hydrogen resonance on the basis of its expected weak coupling with the benzylic hydrogens.[15] Strongly deshielded olefinic signals occur at 6·40 and 6·35 $\delta$ as evidenced by the absence of these peaks in the NMR spectrum of tetrahydroamurine (XII).



XI



XII

† Since the analysis is first order, the values reported for $J_{AX}$ and $J_{BX}$ are only apparent coupling constants. However, this makes no difference to the subsequent structural assignments deduced therefrom.

‡ Alcohol XI is extremely unstable in air and its identity rests upon its oxidation to amurine with manganese dioxide in chloroform.

A 12-line ABX pattern occurs between 3·60–2·72 $\delta$ and its assignment to the signals from the hydrogens at the C9- and C10-positions follows from the same arguments presented for the similar pattern found in the spectrum of nudaurine. Differentiation of the C10α- and the C10β-hydrogen signals was possible from consideration of the magnitude of their apparent coupling against the C9-hydrogen. The observed values are in reasonably good agreement with the calculated values[16] derived from the appropriate dihedral angles measured from a Drieding model of amurine and nudaurine (Table 1).

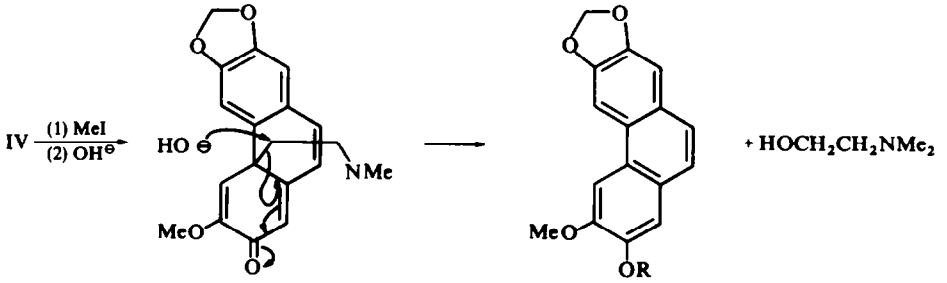
TABLE 1

| | Dihedral angle | Calc $J$ (Hz) | Observed splitting (Hz) | |
|---|---|---|---|---|
| | | | IV | V |
| $H_9$–$H_{10\beta}$ | 90° | 0 | 2·0 | <0·5 |
| $H_9$–$H_{10\alpha}$ | 30° | 7·3 | 6·0 | 6·0 |

*Hofmann degradation and acid catalysed rearrangement products*

Supporting chemical evidence for the structures of amurine and nudaurine was forthcoming from a study of the products obtained from the acid catalyzed rearrangement of these alkaloids and more directly from the Hofmann degradation of amurine.

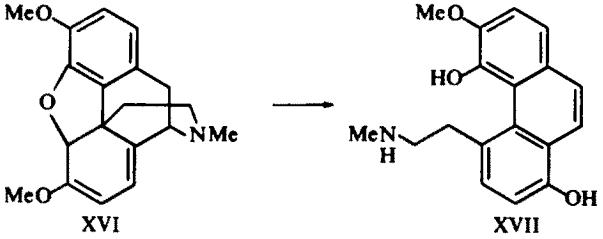
The latter reaction afforded a basic fraction characterized as β-dimethylaminoethanol (XIII) and a crystalline phenolic compound XIV (R = H), m.p. 216–217°. The structure of XIV (R = H) was inferred from its methylation with dimethyl sulfate and base to 2,3-dimethoxy-6,7-methylenedioxyphenanthrene (XIV, R = Me). Formation of the phenol XIV (R = H) is readily explicable on the grounds that the primary Hofmann product XV would be expected to have a strong driving force to aromatise by nucleophilic attack of hydroxide in effecting the displacement of the ethanamine moiety as illustrated below.

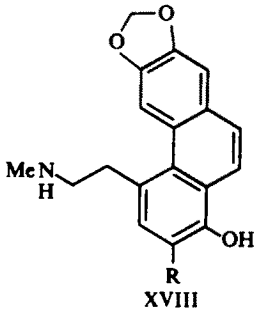



XV XIV XIII

The reaction of either amurine or nudaurine on exposure to acid took an intriguing but parallel course. Brief heating of amurine with dilute acid gave an air sensitive product, $C_{18}H_{17}NO_4$, isolated as its hydrochloride. The compound was optically inactive and showed both OH and NH absorption in its IR spectrum. A series of intense bands between 264 mμ and 450 mμ in the UV spectrum suggested the presence of extended conjugation, as in a polycyclic aromatic hydrocarbon.

Further structural investigation of this compound was continued with the more stable product obtained after acetylation. Strong bands at 1765 $cm^{-1}$ and 1635 $cm^{-1}$ in the IR spectrum of the acetylation product were indicative of the presence of a phenolic acetate and an N-acetate groups. Its formulation as an O,O,N-triacetate was indicated from both elemental analysis, $C_{24}H_{23}NO_7$, and the NMR spectrum which contained signals ascribable to Me resonances from an N-acetyl, two phenolic acetates, and the expected N-Me function. The foregoing spectral data indicate that acid treatment of amurine generates a secondary amine accompanied by aromatization of rings B and C. This change which obviously involves cleavage of a C—N bond, is reminiscent of the acid-catalysed rearrangement of thebaine (XVI) to thebenine (XVII). Accordingly, the structure of the rearrangement product could be tentatively represented as XVIII (R = OH). The suggested mechanism of the rearrangement is shown in Chart 1 and is analogous to that proposed for the thebaine–thebenine change by Stork.[17]




The tentative proposal for the structure of the rearrangement product is substantiated by the conversion of its O,O,N-triacetyl derivative to the salt XIX (R = OMe, $A^- = \frac{1}{2}\ SO_4^{--}$) by dimethyl sulfate in refluxing base and the subsequent degradation of this salt as follows. Hofmann degradation of the methohydroxide XIX (R = OMe, $A^-$ = OH) gave the vinylphenanthrene XX (R = OMe), which shows a characteristic ABX pattern for the vinyl hydrogens in the NMR spectrum. Location of the oxygen substituents in this compound followed from its oxidation to 1,2-dimethoxy-6,7-methylenedioxyphenanthrene-4-carboxylic acid (XXI, R = OMe) and the subsequent decarboxylation of the acid to the known 1,2-dimethoxy-6,7-methylenedioxyphenanthrene (XXII, R = OMe). With the knowledge of the position of the oxygen functions in XXI, the vinyl function in this compound could be placed at the C4-position on the basis of the NMR spectrum which contains aromatic hydrogen signals as three 1-proton singlets at 8·26 $\delta$ (H(5)), 7·22 $\delta$ (H(3)),

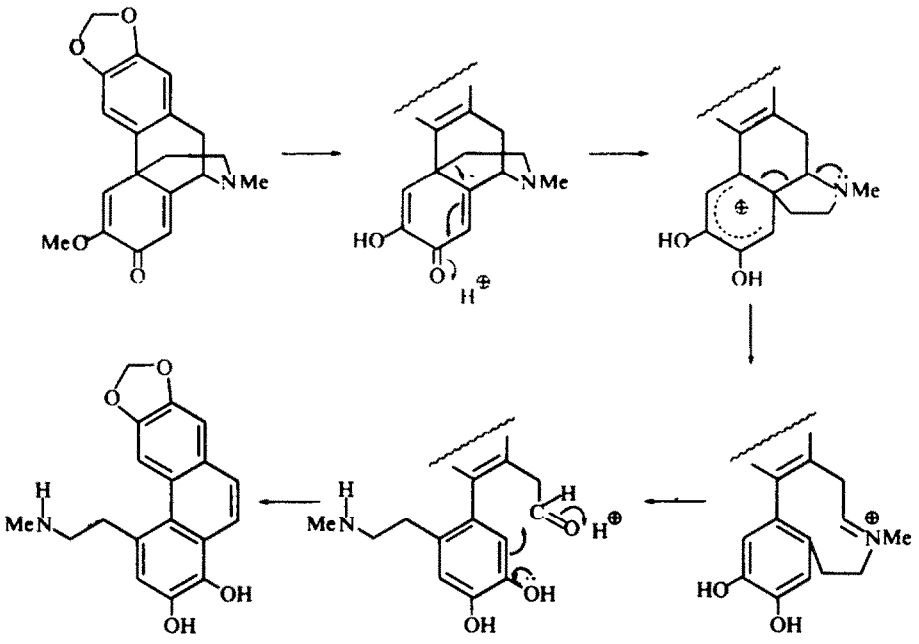


CHART 1 Suggested course for the acid catalysed rearrangement of amurine.

7·16 $\delta$ (fine splitting) (H(1)), and an AB quartet at 7·95 ($\delta_A$) and 7·55 ($\delta_B$) ascribed to the C9- and C10-protons. The reactions described are summarized in Chart 2.

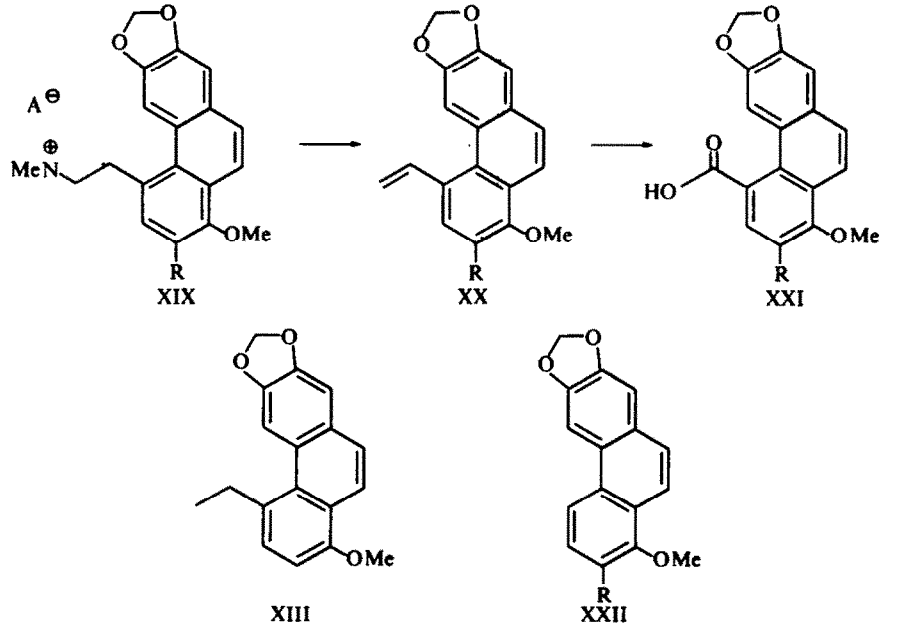


CHART 2. Chemical transformations of the acid catalysed rearrangement products derived from nudaurine and amurine.

With the course of the rearrangement of amurine known and the structure of the product established it was a simple matter to assign structure XVIII (R = H) to the product obtained from the acid catalysed rearrangement of nudaurine. Confirmation of this structure was forthcoming from the results of the degradation of its O,N-diacetate by the sequence XIX (R = H) → XX (R = H) → XXI (R = H) → 1-methoxy-6,7-methylenedioxyphenanthrene (XXII, R = H), which paralleled the series of reactions carried out to establish the structure of the product derived from amurine. In addition the vinyl compound XX (R = H) could be hydrogenated to the ethyl-phenanthrene XXIII. (Chart 2).

The NMR spectra of the acetylation products of XVIII (R = H) and XVIII (R = OH) showed certain interesting and unusual features in that several protons showed two peaks instead of a single resonance line expected for these signals. In the spectrum (Fig. 3a) of the O,O,N-triacetate of XVIII (R = OH) recorded at 38° (the normal probe temperature of the Varian A-60 used in this work), the three protons of the N-Me group are distributed between two signals occurring at 2·88 $\delta$ and 2·79 $\delta$ with an intensity ratio of approximately 1:3. The N-acetyl methyl group (1·95 $\delta$ and 1·83 $\delta$), methylenedioxy group (6·0 $\delta$ and 5·96 $\delta$), the C6- and C4-hydrogens (7·18 and 7·23 $\delta$; 7·90 and 8·42 $\delta$) similarly each showed two bands in which the ratio of intensities in each pair was also approximately 1:3. A similar multiplicity of the corresponding signals was observed in the NMR spectrum of the O,N-diacetate of XVIII (R = H) when recorded at 38°.

The spectral characteristics of each of these compounds are consistent with the occurrence of two slowly interconverting forms which are attributed to the presence of the conformers arising from restricted rotation about the amide C—N bond. The observation of this phenomena by NMR spectroscopy is well documented[21] and in accord with this explanation the spectrum of the O,N,N-triacetate showed a marked temperature dependence. Complete coalescence of the two peaks in the N-acetyl methyl, N-methyl, methylenedioxy C4- and C6-hydrogen signals in the spectrum was not observed until a temperature of 120° was attained (Fig. 3b). This suggests that there is a considerable energy barrier to rotation around the amide bond in this compound.

Assignments of the aromatic hydrogen signals were made on the basis of previous studies in the phenanthrene series[19] and by the $\Delta\nu$ values observed in the spectrum of the two conformers at 38°. Consideration of the $\Delta\nu$ values was helpful in distinguishing the C1-hydrogen signal ($\Delta\nu$ = 0) from that of the C6-hydrogen ($\Delta\nu$ = 4·5 Hz). The C4-hydrogen signals in the spectrum of the two conformers, which are unequivocally assigned from their chemical shifts, show the large $\Delta\nu$ value of 31·0 Hz. This suggests that the amide group in one, and maybe both, of the conformers involving rotation around the carbonyl–nitrogen bond is in closer proximity to the C4-hydrogen than the C6-hydrogen. However, the situation may be complicated by the 1,2-disubstituted ethane group possessing a different rotamer population around the C—C bond for each amide conformer.

*Hydrogenation products and absolute configuration of amurine*

Catalytic hydrogenation of amurine, as might be expected, gives rise to a variety of products. Depending on the conditions, a tetrahydroamurine (XII) or hexahydro-amurine (XXIV), m.p. 136–137°, can be obtained as the major product. Hydrogenation

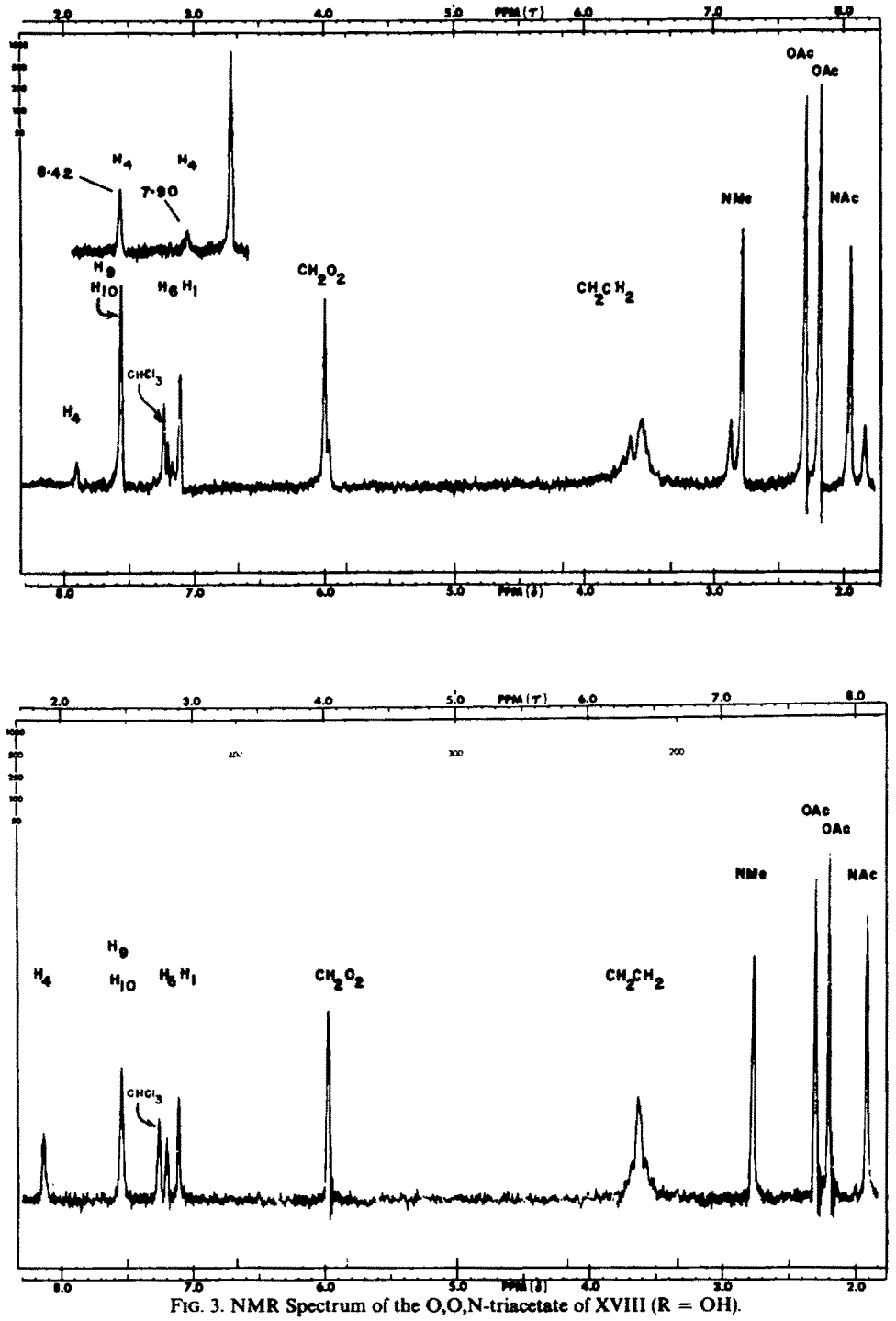
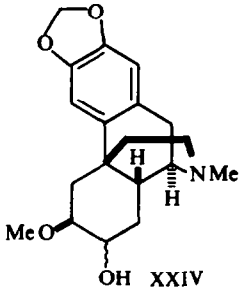


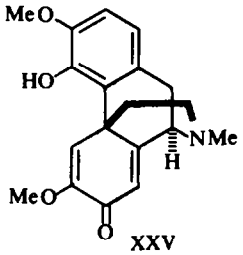

FIG. 3. NMR Spectrum of the O,O,N-triacetate of XVIII (R = OH).
(a) Probe temperature 38°;
(b) Probe temperature 120°.

over a Pd–$BaSO_4$ catalyst afforded XII as the major product in 65% yield, together with 13% of the hexahydroamurine (XXIV), and two uncharacterized minor products. Catalytic reduction over Adams catalyst gave the hexahydro compound XXIV in 40% yield as the only product isolated.

Tetrahydroamurine, which is amorphous, shows a strong CO absorption at 1725 $cm^{-1}$ typical of a cyclohexanone. Its gross structural assignment as represented by XII is fully supported by its NMR spectrum which in addition to having the expected signals (Experimental) shows the absence of olefinic hydrogen resonances. Reduction of amurine to tetrahydroamurine creates two new centers of asymmetry at the C5 and C14-positions. The configuration at C5 could be readily ascertained from the NMR spectrum of tetrahydroamurine in which the C5-hydrogen signal appears at 3·75 $\delta$ as a 4-line X part of an ABX system. Full analysis of this system was not possible since the signals of the C4-methylene hydrogens, which comprise the AB part, were obscured by other signals. However, the axial nature of the C5-hydrogen could be assigned with confidence since the value of $J_{AX} + J_{BX}$ obtained from the X-pattern was 18·5 Hz. With this value the minimum coupling for either $J_{AX}$ or $J_{BX}$ is at least 9·2 Hz which, when considering the ring involved is a chair-form cyclohexanone, is only consistent with coupling between *trans* diaxial hydrogens.




XXIV




XXV

In order to deduce the relative stereochemistry at the C14-position it was first necessary to elucidate the absolute configuration of amurine.

Fortunately the closely related compound salutaridine (XXV)† and its enantiomer, sinoacutine[20] have recently had their absolute configurations established[12, 20b] and we were able to use a comparison of the molecular rotations of these alkaloids with that of amurine in deducing that amurine is related to the same stereochemical series as salutaridine.‡ The absolute configuration of nudaurine, aside from the relative stereochemistry of the C7-OH,§ follows from its interelationship with amurine.

The ORD spectrum of tetrahydroamurine shows a negative Cotton effect at 317 mμ associated with the n → π* transition of the carbonyl chromophore. With a knowledge of the absolute configuration of amurine application of the octant rule[23] permitted the assignment of a β-configuration to the C14-hydrogen as in structure

† See footnote † on page

‡ Professor Snatzke was subsequently able to corroborate this assignment by a study of the circular dichroism spectra of amurine and sinoacutine.[21]

§ The relative and absolute stereochemistry of nudaurine and epinudaurine as shown in formulas V and XI, respectively is based upon independent evidence.[22]

XII. The octant projection and predicted signs for the cotton effects of XII and the C14-epimer XXVI are shown in Chart 3.

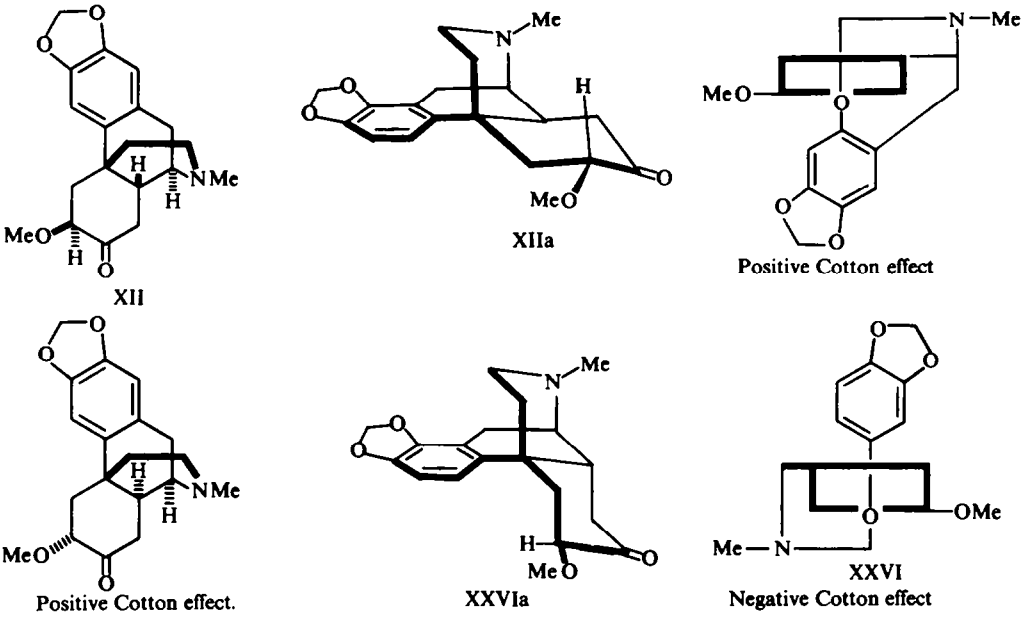



CHART 3. Conformational representation of the tetrahydroamurines XII and XXVI and their octant projections.

The conformational limitation placed upon ring C in tetrahydroamurine (see XIIa) implies that the C5-equatorial MeO is necessarily β-oriented.

Independent support for the 14β-hydrogen configuration was obtained from the mass spectrum of XII which shows an ion at *m/e* 59 of high relative abundance, $\%\Sigma_{40} = 5{\cdot}3$, to which the structure XXVII is assigned. Mandelbaum and Ginsberg[24] in a study of the mass spectra of various morphine derivatives which are epimeric at at C14 found that only those possessing a *cis*-fused B:C ring gave rise to a high intensity peak at *m/e* 59. The genesis of ion XXVII is shown in Chart 4 and involves the necessary proximity of the C14-hydrogen to the C15-carbon, a condition which is met only by compounds possessing the *cis*-fused B:C ring. It should be mentioned

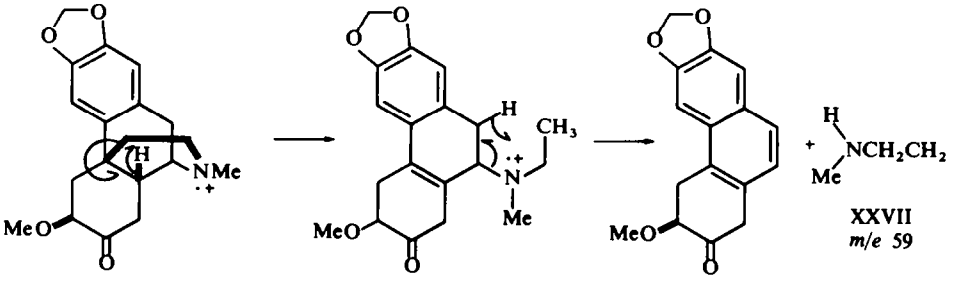



CHART 4. Origin of the fragment ion, *m/e* 59 in the mass spectrum of tetrahydroamurine.

that since tetrahydroamurine was isolated by chromatography over alumina it is conceivable that the stereochemistry at C5 as defined in XII is a consequence of an equilibration to the more stable form on the column, and therefore it may not represent the original stereochemistry of the hydrogenation product.

The structure and stereochemistry of hexahydroamurine, with the exception of

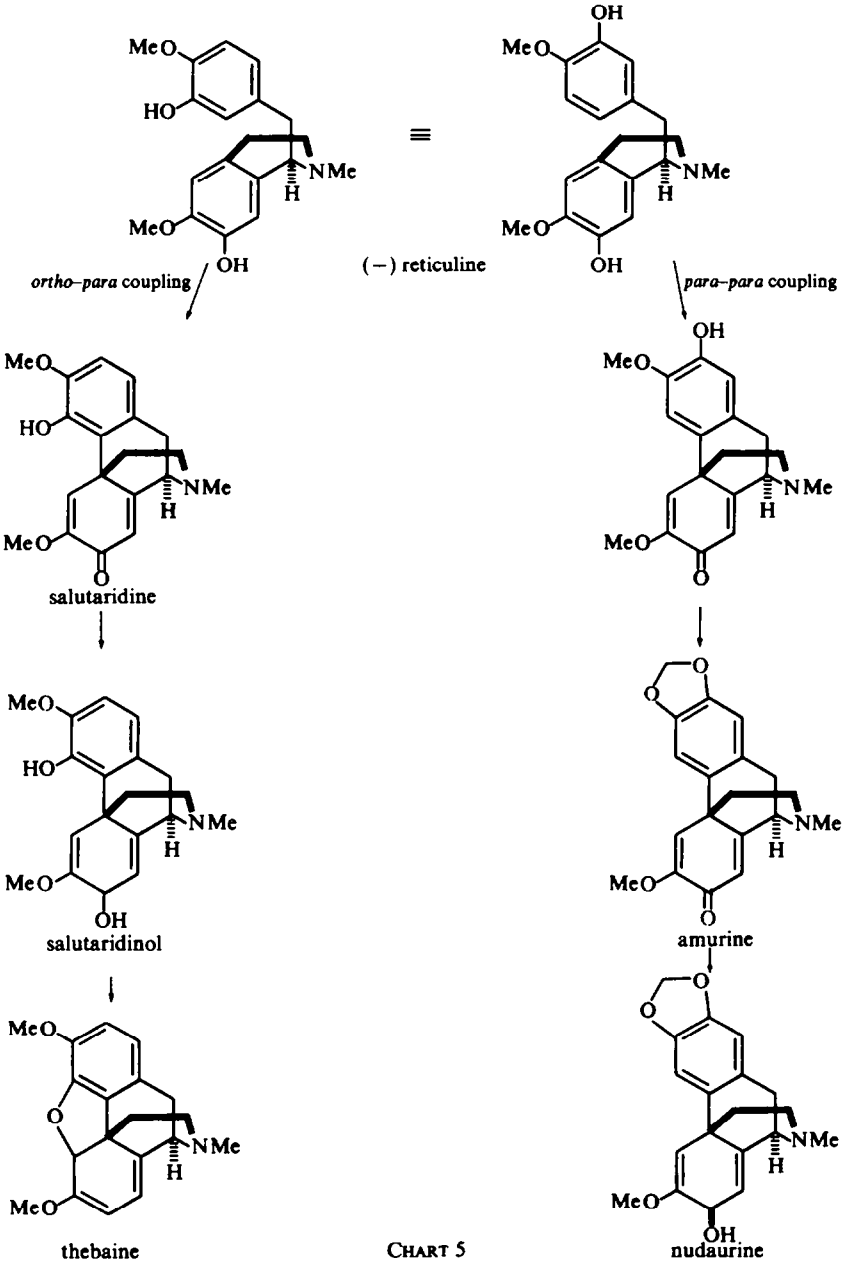



CHART 5

Proposed biosynthetical scheme for amurine and nudaurine from (−)-reticuline.

the hydroxyl group, is defined as shown in structure XXIV* by virtue of its oxidation to tetrahydroamurine (XII) with Jones[25] reagent.

*Biosynthesis*

Extensive tracer studies have established the importance of reticuline in the biosynthesis of the morphine alkaloids† as well as many other classes of benzylisoquinoline alkaloids.[26]

The utilization of this ubiquitous precursor in the biosynthesis of morphine involves its conversion to salutaridine by an *ortho–para oxidative coupling* process. Salutaridine is then subsequently reduced to the corresponding alcohol, salutaridinol, which undergoes an allylic elimination to afford the morphine alkaloid thebaine. (Chart 5).

The structural similarity of amurine and nudaurine with salutaridine and salutaridinol suggests a close biogenetic relationship between these substances. In the light of current theories it may be postulated that the biosynthesis of amurine involves para–para oxidative coupling of (−)-reticuline followed by subsequent cyclization of the resulting *o*-methoxyphenol.[27] Biological reduction of amurine may then proceed to give nudaurine. Thus it would appear that amurine and nudaurine are the first examples of alkaloids which result from an obvious *para–para* oxidative coupling of reticuline.‡

## EXPERIMENTAL

NMR spectra were recorded at 60 MHz on a Varian A-60 spectrometer in $CDCl_3$ soln with TMS as an internal standard. Mass spectra were obtained on a Perkin–Elmer Hitachi RMU6 mass spectrometer operating at 70 eV.

*Oxidation of nudaurine* (V) *to amurine* (IV). To a soln of 50 mg of nudaurine in 10 ml dry $CHCl_3$, 300 mg active $MnO_2$ was added and the suspension stirred at room temp. Samples were removed at 10 min intervals and checked by TLC. After 20 min the presence of nudaurine was no longer detectable; the stirring was continued for a further 40 min. The residue, obtained after filtration and evaporation of the filtrate, crystallized from acetone to give 45 mg amurine, m.p. 212–213°, $[\alpha]_D^{24}$ +9·6° (*c* 0·8, in $CHCl_3$) identical in every respect to an authentic sample (mixed m.p. and IR).

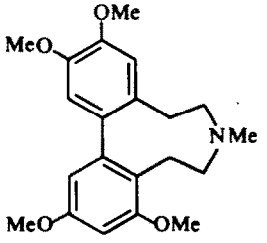
*Reduction of amurine* (IV) *to nudaurine* (V) *and epinudaurine* (XI)

(a) $NaBH_4$ (100 mg) was added slowly to a stirred soln of amurine (100 mg) in MeOH (10 ml) and the mixture heated under reflux for 1 hr. The MeOH was removed and the residue dissolved in dil AcOH;

* From this single experiment it is not possible to state with confidence that epimerization of the C(5)-methoxyl does not occur under the acidic conditions of the oxidation.

† See footnote † on page

‡ It is possible that the biosynthesis of protostephanine (ii) may involve an intermediate formed by *para–para* coupling of a reticuline type precursor.[28]




(ii)

‡ Since the completion of this manuscript a second morphandienone alkaloid, flavinine, which may be formed by *para-para* oxidative coupling, has been described.[29]

basification with ammonia followed by extraction with $CHCl_3$ afforded an amorphous material from the

TABLE 2

| Fraction No. (25 ml) | Solvent | Eluted material | TLC‡ |
|---|---|---|---|
| 1–19 | B-BE 23:2 | | |
| 20–23 | BE 23:2 | 5 mg gum | 0·32 |
| 24–25 | BE 22:3 | 3 mg amurine | 0·50 |
| 26 | BE 21:4 | 2 mg amurine-nudaurine | 0·28 |
| 27–33 | BE 21:4–18·7 | 30 mg nudaurine | 0·28 |
| 34–35 | BE 15:10 | | |
| 36–41 | BE 10:15-E | 22 mg epinudaurine | 0·26 |
| 42–45 | E-EM 20:5 | 23 mg dark brown gum | 0·00–0·26 |

‡ B (benzene), E (EtOAc), M (MeOH).

‡ Silica gel G; solvent benzene–EtOAc–MeOH 1:1:1.

*Nudaurine*, m.p. 200–201°, $[\alpha]_D^{19}$ −48° (*c* 0·42, in $CHCl_3$), isolated from the chromatographic separation gave no depression of m.p. on admixture with the natural alkaloid; the IR spectra of the two samples also were identical.

*Epinudaurine*, $[\alpha]_D^{19}$ −23° (*c* 1·06, in $CHCl_3$) could not be crystallized and samples of this compound rapidly oxidized on standing. Treatment of a soln of epinudaurine with $MnO_2$, in the manner described above for the oxidation of nudaurine, gave amurine.

(b) To amurine (80 mg), in 10 ml dry THF, a soln of LAH (ca. 200 mg) in THF (20 ml) was added and the mixture allowed to stand at room temp for 17 hr. The excess reagent was decomposed with EtOAc and water, and the precipitated hydroxides filtered off. The ppt was washed with MeOH, the washings combined and evaporated to dryness to give a gum. Chromatography of this gum as described in (a) gave amurine (2 mg), nudaurine (28 mg), and epinudaurine (11 mg).

*Amurine methiodide.* MeI (4 ml) was added to a soln of 200 mg amurine in 3 ml MeOH and the mixture allowed to stand under a $N_2$ for 4 hr. Removal of the solvent left a solid (288 mg) which was crystallized twice from MeOH to afford the pure *methiodide* as colorless prisms, m.p. 202–206° (dec) $[\alpha]_D^{22}$ +13° (*c* 1·075, in water). (Found: C, 50·94; H, 4·91; N, 2·90. $C_{20}H_{22}NO_4I$ requires: C, 51·40, H, 4·75; N, 3·00%). The methiodide turned yellow on exposure to air and light.

*Hofmann degradation of amurine.* A soln of 115 mg amurine methiodide in 2 ml water was added to 2 ml 20% NaOHaq and the mixture heated for 1 hr at 120–140° in a stream of $N_2$. The exiting $N_2$ gas was passed through a trap containing 1N HCl. Extraction of the alkaline soln with ether afforded the basic fraction as an intractable brown gum (ca. 5 mg). Acidification of the basic soln and ether extraction gave crude phenolic material which was chromatographed in benzene over 3 g neutral alumina. Concentration of the benzene eluates and crystallization of the residue from benzene afforded 39 mg *2-hydroxy-3-methoxy-6,7-methylenedioxyphenanthrene* as colorless glistening plates, m.p. 216–217° (changed to prisms at ca. 170°); $\nu_{max}^{CHCl_3}$ 3550 $cm^{-1}$ (phenolic OH). (Found: C, 71·70; H, 5·60. $C_{16}H_{12}O_4$ requires: C, 71·63; H, 4·51%).

Concentration of the 1N HCl from the trap and addition of chloroauric acid to the concentrate gave a chloroaurate, m.p. 202–205° (in vac; dec)[30] identified as β-dimethylaminoethanol chloroaurate.

*2,3-Dimethoxy-6,7-methylenedioxyphenanthrene* (XIV, R = Me). 2-Hydroxy-3-methoxy-6,7-methylenedioxyphenanthrene (20 mg) was treated in the usual manner with base and $Me_2SO_4$. The product was extracted with benzene and chromatographed on neutral alumina (0·5 g). Removal of the solvent from the first 10 ml eluate and crystallization of the residue from MeOH gave 14 mg of *2,3-dimethoxy-6,7-methylenedioxyphenanthrene* as pale yellow prisms, m.p. 193–195° (Reported[31] 192°): $\nu_{max}^{CHCl_3}$, no absorption in the OH stretching region; $\lambda_{max}^{CH_3OH}$ 245 mμ (log ε 4·59) 252 (4·86), 287 (4·40), 300 (4·25), 323 (3·35), 338 (3·33) and 352 (2·87). The picrate crystallized as red-brown needles, m.p. 181–185° (vac) (Reported[31] m.p. 182–183°).

*Acid catalyzed rearrangement of amurine.* Amurine (100 mg) in 2 ml of 3N HCl was covered with a $N_2$ atm and heated for 3 hr at 100° on a water bath. The soln slowly changed to a dark brown and a yellow crystalline ppt formed. Filtration of the soln afforded 103 mg (92% theoretical) of the hydrochloride which

was washed successively with water and EtOH–ether and then dried at 100° for 6 hr *in vacuo* to give XVIII (R = OH) as the pure *hydrochloride*, m.p. 238–240° (vac; dec), $[\alpha]_D$ = 0° (*c* 2·0, pyridine): $\nu_{max}^{Nujol}$, 3390, 3295 and 3140 $cm^{-1}$ (OH and NH absorptions); $\lambda_{max}^{H_2O}$, 264 mμ (log ε, 4·75), 305 (3·94), 3·52 (3·71), 368 (3·74) and 450 (3·05). (Found: C, 59·48; H, 5·40; N, 3·83; OMe, 0·00. $C_{18}H_{17}NO_4 \cdot HCl \cdot H_2O$ requires: C, 59·10; H, 5·51; N, 3·83%).

The free base was oxidized rapidly in air to an olive-green product.

O,O,N-*Triacetyl derivative of* XVIII (R = OH). A soln of the hydrochloride of XVIII (R = H) in 6 ml pyridine and 3 ml $Ac_2O$ was allowed to stand 40 hr at room temp. The solvent was removed *in vacuo* and the residue taken up in 5 ml $CHCl_3$. After washing the $CHCl_3$ soln successively with 2 ml 1N $H_2SO_4$, 2 ml 5% NaOH aq and water, the soln was dried and the solvent removed to leave 110 mg crystalline product, m.p. 165–170°. Recrystallization from benzene-pet ether afforded the pure O,O,N-*triacetate* (XVIII, R = Ac) as colorless prisms, m.p. 172–173°: $\nu_{max}^{KBr}$, 1765 and 1200 $cm^{-1}$ (phenolic acetate), 1635 $cm^{-1}$ (amide); $\lambda_{max}^{MeOH}$ 262 mμ (log ε 4·94), 279 (4·52), 342 (3·56) and 359 (3·61). (Found: C, 65·84; H, 5·13; N, 2·79; Acetyl 30·3. $C_{24}H_{23}NO_7$ requires: C, 65·89; H, 5·30; N, 3·20; 3 Acetyl, 29·52%).

1,2-*Dimethoxy*-4 *vinyl*-6,7-*methylenedioxyphenanthrene* (XX, R = OMe). A suspension of 188 mg of the hydrochloride of XVIII (R = H) in water was covered with a $N_2$ atm and 0·3 ml 30% NaOH aq added. The resulting greenish-brown soln was stirred and 0·3 ml $Me_2SO_4$ was added slowly over 30 min. The addition of 0·3 ml $Me_2SO_4$ and 0·3 ml 30% NaOH aq was repeated twice. The excess $Me_2SO_4$ was hydrolysed by a brief warming of the pale yellow acid soln. The soln on cooling deposited 240 mg colorless crystals, which after crystallization from MeOH gave the methosulfate of 1,2-dimethoxy-4(β-N,N-dimethylaminoethyl)-6,7-methylenedioxyphenanthrene, m.p. 224–230° (234–238° vac). (Found: C, 57·90; H, 6·00; N, 2·60; O, 26·40; S, 7·20. $C_{23}H_{29}NO_8S$ requires: C, 57·60; H, 6·10; N, 2·92; O, 26·69; S, 6·69%). A suspension of the methosulfate (240 mg) in 5 ml of 20% NaOH aq was heated for 4 hr at 80–100° in a stream of $N_2$ and the exiting gases passed through a trap containing 1N HCl. As the reaction proceeded the methosulfate dissolved and a ppt of the vinyl compound formed. Filtration of this ppt gave 14·6 mg (95%) of yellow-green solid which on recrystallization afforded pure 1,2-*dimethoxy*-4-*vinyl*-6,7-*methylenedioxyphenanthrene* as colorless needles, m.p. 133–135°: NMR,† 3-proton singlets 3·94 δ, 3·98 δ (aromatic MeO's), 8-line AB part of ABX system, 534, 535, 544, 546, 559, 560, 575, 577 Hz, 4-line X part at 630, 638, 645, 656 Hz (vinyl hydrogens), 1-proton singlets at 7·15 δ, 7·23 δ and 8·26 δ (aromatic hydrogens at C1, C6 and C4) and 1-proton doublets at 7·55 δ, 7·95 δ (*J* = 9·0 Hz) (C9 and C10-hydrogens). (Found: C, 74·60; 5·10; O, 20·90; OMe, 20·60. $C_{19}H_{16}O_4$ requires: C, 74·01; H, 5·23; O, 20·76; 2 OMe, 20·13%). Concentration of the HCl soln from the trap gave a hygroscopic solid. Addition of gold chloride soln to a concentrated soln of the solid in 1N HCl gave a yellow ppt which on crystallization from EtOH afforded trimethylaminechloroaurate, m.p. 226–230 (vac). The sample showed no depression of m.p. on admixture with authentic trimethylaminechloroaurate and the IR spectrum was identical with the spectrum of trimethylaminechloroaurate.

1,2-*Dimethoxy*-6,7-*methylenedioxyphenanthrene*-4-*carboxylic acid* (XXII, R = OMe). To an ice cold soln of XX (R = OMe) a soln of 180 mg of $KMnO_4$ in 10 ml acetone was added dropwise with stirring during 1 hr. The reaction was then allowed to come to room temp and the $MnO_2$ which had precipitated was filtered off and washed first with acetone followed by several washings with 30 ml portions boiling water. The original filtrate and the acetone washings were combined and the solvent removed to leave a residue. This residue was extracted several times with ether and the remaining insoluble residue was combined with the aqueous washings which were concentrated to ca. 2 ml. Acidification of the concentrated soln with HCl precipitated the crude acid as brown flakes. Recovery of the acid fraction was completed by extraction of the ppt with ether. The crude material thus obtained (65 mg) was crystallized from MeOH to give the pure *acid* XXII (R = OMe), m.p. 203–206°: $\nu_{max}^{KBr}$, 3430, 1740 (sh), 1725 and 1675 $cm^{-1}$. (Found: C, 65·80; H, 4·4. $C_{18}H_{14}O_6$ requires: C, 66·25; H, 4·32%). Evaporation of the ethereal soln left 38 mg which on crystallization gave an additional 11 mg of XXII (R = OMe) and 17 mg of a solid, m.p. 173–174° (MeOH) which from its IR spectrum, $\nu_{max}^{KBr}$ 1670 $cm^{-1}$ and mass spectrum $M^+$ 310, is presumably 1,2-*dimethoxy*-6,7-*methylenedioxyphenanthrene*-4-*aldehyde* ($C_{18}H_{14}O_5$, MW 310·3).

1,2-*Dimethoxy*-6,7-*methylenedioxyphenanthrene* (XXII, R = OMe). The acid XXII (R = OMe) was placed in a sublimation apparatus containing a cold finger and heated at 180°/$10^{-2}$ mm. Chromatography of the sublimate in benzene soln over 0·5 g neutral alumina (activity 1) gave a solid in the first eluate which

† Recorded on a Varian HA-100 spectrometer by Mrs. M. G. Miller of North Carolina State University, Raleigh, through the courtesy of Professor C. A. Moreland.

crystallized from MeOH to give 1,2-*dimethoxy*-6,7-*methylenedioxyphenanthrene* as colorless needles, m.p. 178–179° (Reported[31] m.p. 175–176·5°): $\lambda_{max}^{MeOH}$, 259 mμ (log ε, 4·80), 285 (4·26), 331 (3·51), 345 (3·53), 361 (3·53), 380 (2·35) and 402 (2·74). Addition of picric acid to the mother liquors from the crystallization afforded the *picrate* of XXII (R = OMe) as red needles, m.p. 163–165° (Reported[31] m.p. 165°).

*Acid catalysed rearrangement of nudaurine*

(a) *Hydrochloride.* A soln containing 100 mg nudaurine in 2 ml 1N HCl was heated on a water bath for 10 min and the crystalline ppt which formed was collected. Crystallization of the ppt (91 mg) from water gave the *hydrochloride* of 1-*hydroxy*-4-(β-N-*methylaminoethyl*)6,7-*methylenedioxyphenanthrene* (XVIII, R = H), m.p. 255–260° (vac, dec): $\lambda_{max}^{H_2O}$, 262 mμ (log ε, 4·84), 304 (3·96), 315 (3·95), 347 (3·69), and 363 (3·77). (Found: C, 63·80; H, 5·55; N, 4·24. $C_{18}H_{17}NO_3 \cdot HCl \cdot \frac{1}{2} H_2O$ requires: C, 63·44; H, 5·62; N, 4·11%).

(b) *Free base.* A soln of the hydrochloride (100 mg) in 4 ml water was taken to pH 8–9 with ammonia and the ppt which formed filtered, washed with water, and then dissolved in MeOH (2·0 ml). Concentration of the methanolic soln to 10 ml afforded XVIII (R = H) as the free base (45 mg), prisms, m.p. 219–220° (dec): $\nu_{max}^{Nujol}$, 3295 $cm^{-1}$ and 2550 $cm^{-1}$ (N—H); $\lambda_{max}^{MeOH}$, 256 mμ (log ε, 4·78), 305 (3·94) 317 (3·95), 332 (3·62), 348 (3·71) and 346 (3·80). The base is insoluble in $CHCl_3$, acetone and MeOH, fairly soluble in DMF and is somewhat sensitive to air oxidation in soln. (Found: C, 72·94; H, 5·78; N, 4·92; OMe, 0·00. $C_{18}H_{17}NO_3$ requires: C, 73·20; H, 5·80; N, 4·74%).

(c) O,N-*Diacetate.* The hydrochloride of XVIII (R = H) was suspended in 3 ml pyridine containing 1·5 ml $Ac_2O$ and the mixture was left to stand at room temp for 24 hr. Evaporation of the solvent left a residual gum which was taken up in $CHCl_3$ and the soln was washed successively with 6% NaOH aq and water. Removal of the $CHCl_3$ left a colorless gum which crystallized from acetone–ether to afford the O,N-*diacetate*, prisms, m.p. 160–162°: $\nu_{max}^{KBr}$, 1765 and 1205 $cm^{-1}$ (phenolic acetate), 1640 $cm^{-1}$ (acetamide); $\lambda_{max}^{MeOH}$, 261 mμ (log ε, 4·82), 279 (4·37), 301 (3·94), 312 (inf.) (3·88), 343 ( 3·42) and 359 (3·47). (Found: C, 69·41; H, 5·73; N, 3·77, Ac, 21·4. $C_{22}H_{21}NO_5$ requires: C, 69·64; H, 5·58; N, 3·69; 2 Ac, 22·69%).

1-*Methoxy*-4-*vinyl*-6,7-*methylenedioxyphenanthrene* (XX, R = H).

(a) *Methosulfate.* A stream of $N_2$ was passed through a suspension of 240 mg of the hydrochloride of XVIII (R = H) in 1 ml water, and 2 ml 1N NaOH and 0·2 ml $Me_2SO_4$ was added over 15 min. The addition of above amounts of NaOH and $Me_2SO_4$ was repeated twice. The resulting red-brown acid soln was warmed briefly on a water bath and then concentrated *in vacuo*. On cooling the concentrated soln deposited pale yellow prisms (267 mg), m.p. 214–235°. Recrystallization from water gave the pure *methosulfate*, m.p. 235–237°. (Found: C, 59·15; H, 5·95; N, 3·15. $C_{22}H_{27}NO_7S$ requires: C, 58·78; H, 6·06; N, 3·12%).

(b) *Hofmann degradation.* The methosulfate (130 mg) in 4 ml 10% NaOH aq was heated at 90–110° in a stream of $N_2$ and the exit gas was passed through a trap containing 1N HCl. After 5 hr the ppt (39 mg) which had formed was filtered and the filtrate was heated for an additional 6 hr. The total yield of crude product obtained was 68 mg which on crystallization from MeOH afforded XX (R = H), pale yellow needles, m.p. 125–126°. (Found: C, 77·94; H, 5·45. $C_{18}H_{14}O_3$ requires: C, 77·68, H, 5·07%). Concentration of the HCl from the trap gave $Et_3N$ which was characterized as its chloroaurate as described previously.

1-*Methoxy*-6,7-*methylenedioxyphenanthrene* (XXIII, R = H). To an ice cold soln of 45 mg of XX (R = H) in 2 ml acetone the calculated amount of $KMnO_4$ (86 mg) in 4 ml acetone was added with stirring. After 3 hr the $MnO_2$ was filtered off and washed first with acetone and then with water. The aqueous washings were acidified and the yellow ppt which formed was extracted into ether. Removal of the ether left a brown residue (15 mg), m.p. 160–165°, which is insoluble in water but soluble in $NaHCO_3$ aq. The crude acid was heated in a sublimator at 140–160°/5 × $10^{-3}$ mm for 2 hr. The sublimed material was dissolved in benzene and passed through a small column of alumina. Removal of the solvent from the benzene eluates and crystallization of the resulting residue from MeOH gave 4 mg of XXIII (R = H), pale yellow prisms, m.p. 147–149°: $\lambda_{max}^{MeOH}$, 257 mμ (log ε, 4·67), 275 (4·19), 297 (3·91), 309 (3·97), 324 (3·63), 339 (3·82) and 355 (3·88), identical with an authentic sample of 1-methoxy-6,7-methylenedioxyphenanthrene,[32] m.p. 150° by IR spectral comparison and mixture, m.p. 147–149°. The neutral fraction (10 mg) obtained from the acetone washings was chromatographed on 0·5 g of alumina (neutral, activity 1) and eluted with benzene. The first eluates contained 2 mg of XX (R = H) followed by 5 mg of a compound crystallizing in brown needles, m.p. 230–231°: $\nu_{max}^{KBr}$, 2740 and 1662 $cm^{-1}$ (1-methoxy-6,7-methyldioxyphenanthrene-4-aldehyde).

*Hydrogenation of* XX (R = H). A soln of 25 mg of XX (R = H) in 5 ml MeOH was added to 50 mg of prereduced $PdO_2$–$BaSO_4$ catalyst suspended in 10 ml of MeOH and the mixture shaken in a $H_2$ atm

at 20° for 75 min. After this time 2·6 ml $H_2$ had been absorbed (calc for 1 mole, 2·2 ml). The catalyst was removed by filtration through kieselguhr and the hydrogenation product recovered from the filtrate and crystallized from MeOH to afford 15 mg of *1-methoxy-4-ethyl-6,7-methylenedioxyphenanthrene* (XXI), pale brown prisms, m.p. 92–94°. (Found: C, 77·15; H, 5·80. $C_{18}H_{16}O_3$ requires: C, 77·12; H, 5·75%).

*Hydrogenation of amurine.* To a suspension of 500 mg of prereduced $PdO_2$–$BaSO_4$ sulfate catalyst was added amurine (190 mg) in 5 ml MeOH and the mixture shaken in a $H_2$ atm at 20°. The uptake of $H_2$ was very rapid and after 10 min 29 ml had been adsorbed (calc. 2 mole, 28 ml). The crude product (190 mg), isolated in the usual way, showed at least 5 different spots on TLC. It was dissolved in benzene and chromatographed over 25 g of alumina; eluates were collected in 100 ml fractions. Elution with benzene–EtOAc (95:5) in fractions 8–9 gave 14 mg of colorless gum which could not be crystallized, $[\alpha]_D^{20}$ +14° (*c*, 0·7 in $CHCl_3$): $\nu_{max}^{KBr}$, 1725 $cm^{-1}$ (cyclohexanone). The compound, which is probably a stereoisomer of XII, showed a single spot on TLC at $R_f$ = 0·48 in benzene–EtOAc–MeOH 1:1:1 on silica gel G, but was not further characterized. Fractions 11–14 containing benzene–EtOAc (95:5–90:10) afforded 56 mg *tetrahydroamurine* (XII), colorless gum, $[\alpha]_D^{20}$ −111° (*c* = 1·97, in $CHCl_3$): ORD,† (*c* 0·018, in dioxan at 25°), $[\Phi]_{430}$ +1060°; $[\Phi]_{317}$ −2418°, $[\Phi]_{310}$ −1920°; $[\Phi]$ −1991°; $[\Phi]_{278}$ +3830°; $\nu_{max}^{KBr}$, 1725 $cm^{-1}$ (cyclohexanone); NMR, 3-proton singlets, 2·40 $\delta$ (N-Me) and 3·43 $\delta$ (C6-MeO), 2-proton singlet, 5·94 $\delta$ (methylenedioxy), 4-line X part of ABX system, 215·5, 220, 227·5 and 233 Hz (C6-hydrogen), 1-proton singlets 6·65 $\delta$ C4-hydrogen) and 6·92 $\delta$ (C1-hydrogen); mass spectrum *m/e* 329 ($M^+$) (64%), 314 (13%), 211 (14%), 185 (18%), 149 (13%), 141 (10%), 128 (11%), 115 (15%), 85 (66%), 84 (40%), 83 (100%), 59 (96%). The substance showed a single spot on TLC at $R_f$ = 0·23 in benzene–EtOAc–MeOH 1:1:1 on silica gel G. (Found: C, 69·26; H, 7·00; N, 4·30. $C_{19}H_{23}NO_4$ requires: C, 69·28; H, 7·04; N, 6·25%). Tetrahydroamurine formed a yellow picrate, m.p. 140–145° which turned red after a short time.

Fractions 23–33 containing benzene–EtOAc (75:25–50:50) afforded a red colored product. Crystallization of the material from ether gave *hexahydroamurine* (XXIV) as colorless prisms, m.p. 136–137°, $[\alpha]_D^{21}$ −56° (*c* 0·25, in $CHCl_3$): $\nu_{max}^{KBr}$, 3370 $cm^{-1}$, no CO absorption. (Found: C, 68·80; H, 7·66, N, 4·34; M.W. 331 (mass spec.) $C_{19}H_{25}NO_4$ requires: C, 68·86; H, 7·60; N, 4·23%; N.W. 331·4). Compound XXIV shows a single spot on TLC at $R_f$ 0·06 under the same conditions referred to above for tetrahydromurine.

Continued elution with benzene–EtOAc (40:60–20:80) gave from fractions 26–40 a crystalline product (11 mg), which on recrystallization from ether afforded 6 mg of pale yellow prisms, m.p. 110–117°: $\nu_{max}^{KBr}$, 3430 $cm^{-1}$ no CO absorption. This compound which is presumably a stereoisomer of XXIV was not further characterized.

*Oxidation of hexahydroamurine.* A soln of 15 mg hexahydroamurine in 3 ml $CHCl_3$ was stirred for 3 hr at room temp in the presence of 150 mg active $MnO_2$. After filtering the soln, the filtrate was concentrated *in vacuo* and the residue which was obtained was treated with a soln of picric acid in acetone to give a yellow ppt of tetrahydroamurine picrate which was identical in all respects with a sample obtained directly from tetrahydroamurine.

† Recorded on a Cary 60 spectropolarimeter by kind permission of Professor C. Tanford, Department of Biochemistry, Duke University.

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