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THE ALKALOIDS OF *ABUTA IMENE* AND *ABUTA RUFESCENS*

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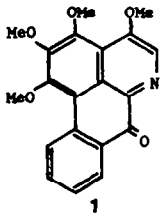
Abstract—The alkaloid fraction of either *Abuta imene* or *Abuta rufescens* was found to contain the oxoaporphines imenine, homomoschatoline, and imerubrine, as well as the azafluoranthenes imeluteine, rufescine and norrufescine. Structures are proposed for the new alkaloids imerubrine and norrufescine, and a synthesis of homomoschatoline is described.

Many alkaloids have been isolated from the family Menispermaceae.[1] The genus *Abuta*, which occurs mainly in the lowlands of Central and South America,[2-4] has been described as "the most rapidly growing genus in the American Menispermaceae",[3] but has not been previously examined chemically. As part of a broader phytochemical study of this genus, we now report an investigation of the alkaloids of *Abuta imene* and *Abuta rufescens*. These two species, which are large woody climbing vines (bush ropes), have been stated to be used as curare ingredients by the Juris of the Rio Japuras basin of the state of Amazonas, Brazil.[5]

The two species contained the same six alkaloids. The structures and synthesis of the first three of these have been discussed by us elsewhere, and details will not be repeated here. The alkaloids in question are imenine (**1**), the first 4-oxygenated oxoaporphine,[6,7] and imeluteine (**2**) and rufescine (**3**), the first azafluoranthene alkaloids.[8]



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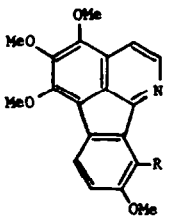


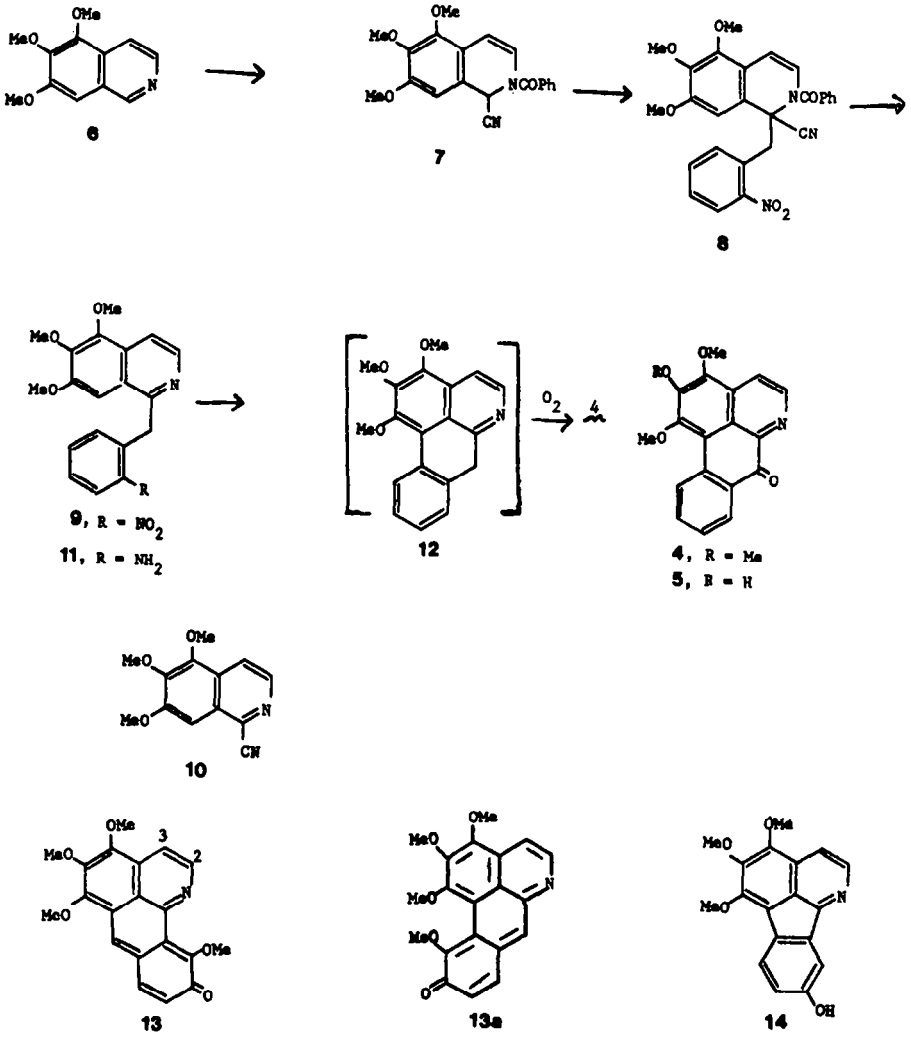
2 R = OMe
3 R = H

The fourth alkaloid proved to be identical with the 0-methyl derivative (**4**) of the phenolic oxoaporphine, moschatoline (**5**).[9,10,*] Recently, compound **4** has been found in both *Guatteria subsessilis*[11] and *Triclisia gillettii*,[12] and has been named homomoschatoline.[11] We have carried out a simple synthesis of **4** which is patterned upon our synthesis of imenine (**1**).[7] Thus, conversion of 5,6,7-trimethoxyisoquinoline (**6**) to the Reissert compound **7**,[13] followed by alkylation of **7** with *o*-nitrobenzyl chloride and direct basic hydrolysis of intermediate **8**, gave the desired nitroisoquinoline **9** as well as some 1-cyano-5,6,7-trimethoxy-isoquinoline (**10**). Catalytic reduction of **9** to the amine **11**, followed by diazotization and Pschorr cyclization, afforded homomoschatoline (**4**) in 27% overall yield from **9**. As in the imenine synthesis,[7] the intermediary ring-B aromatic aporphine **12** could not be isolated but underwent air oxidation to the corresponding oxoaporphine during work-up.

The fifth alkaloid was a new orange-red base, imerubrine, m.p. 183–185°. Its high resolution mass spectrum indicates the molecular composition $C_{20}H_{17}NO_5$, making imerubrine an isomer of imenine. Its NMR spectrum reveals the presence of four methoxyls (δ 3·92, 4·04, 4·10 and 4·14); the remainder of the spectrum consists only of five aromatic proton signals: a singlet at δ 7·98, a pair of doublets (2H, J = 11 Hz) at δ 6·65 and δ 7·80 and a pair of doublets (2H, J = 6 Hz) at δ 7·53 and δ 8·43. These signals correspond to one isolated proton and two pairs of ortho protons. The small ortho coupling constant of 6 Hz is consistent with the assignment of the δ 8·43 and δ 7·53 signals to pyridine-ring protons at C-2 and C-3, respectively, since the same value of J is found for the corresponding proton pair in models **2**, **3** and **4**. The chemical shifts observed for these protons are quite different from those (δ 8·14, 8·89) of the oxoaporphine **4**, but very similar to those of **2** and **3** (δ 7·57, 8·65 and 7·63, 8·59 respectively), suggesting an azafluoranthene-type structure for imerubrine. In addition, imerubrine shows strong CO absorption at 6·35μ, a position quite different from that (6·03μ) observed in the oxoaporphine model **4**. Since the companion alkaloids **2**, **3** and **4** all have a 1,2,3-trimethoxy substitution pattern, the same pattern seems likely in imerubrine. Indeed, the OMe signals of imerubrine correspond almost exactly to those of rufescine (**3**), the lowest field OMe in both compounds being assignable to the lower ring. The tentative structure **13** is suggested for imerubrine on the basis of the spectroscopic data, although several other possibilities, especially the novel 10-oxoaporphine structure **13a**, cannot be excluded at present. A definitive solution of this problem by an X-ray crystallographic analysis is in progress.

The sixth alkaloid was a new orange base, m.p. 235–238° (dec). Its high resolution mass spectrum indicates the molecular formula $C_{18}H_{15}NO_4$, and its NMR spectrum reveals the presence of three OMe's at δ 4·04, 4·08, and

*We thank Professor Bick for making the comparison of **4** with an authentic sample.



4·10. Since this alkaloid is converted by diazomethane to rufescine (3), we have named it norrufescine. Since norrufescine gives a positive coupling reaction with *p*-nitrobenzenediazonium chloride, it must contain a phenolic function having a free *ortho* or *para* position. Thus, the phenolic function must be present in the lower ring, permitting the assignment of structure **14** to norrufescine.

EXPERIMENTAL

All m.ps were determined in open tubes using a Thomas–Hoover Uni-melt apparatus and are uncorrected. UV-visible spectra were measured in 95% EtOH with a Perkin–Elmer Model 202 spectrophotometer. IR spectra were recorded in KBr with a Perkin–Elmer Model 137 spectrophotometer. Mass spectra were determined using Perkin–Elmer Model 270B and Varian MS-9 instruments. The NMR spectra were obtained in $CDCl_3$ (except as noted) using Varian A-60A, HA-100 and XL-100 instruments; chemical shifts are reported as ppm (δ) downfield from TMS. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana.

Isolation of the tertiary bases. Stems of *Abuta rufescens* were collected on Itacoatiara Road, Manaus, Brazil, in January 1965. Stems of *Abuta imene* were collected at the same location in March 1965. Voucher specimens of *A. rufescens* (herbarium number 5367) and *A. imene* (herbarium number 15793) are on file at the Instituto Nacional de Pesquisas da Amazonia. The same method was used for isolation of alkaloids from both *Abuta* species; a detailed procedure is given for *A. rufescens*.

Ground stems of *A. rufescens* (19 kg) were extracted by percolation with EtOH. Concentration of the extract afforded a dark gum (1·5 kg). A portion (100 g) of this was triturated with ether (1000 ml) and the insoluble residue (61 g) removed by filtration. The ether soln was extracted with 5% NaOH and then 3 times with 4 N HCl. The combined aqueous acid extracts were neutralized with conc NH_4OH and extracted 3 x with $CHCl_3$. Drying ($MgSO_4$) and evaporation of the $CHCl_3$ extract afforded the crude nonphenolic alkaloids (455 mg).

Separation of the non-phenolic alkaloids was accomplished by chromatography on preparative plates of neutral alumina using four consecutive elutions with $CHCl_3$. The principal bands were separated by inspection under visible and long wavelength UV light: (band number, R_f (multiple), visible color) 1, 0·09, orange red; 2, 0·26, light orange; 3, 0·51, dark orange; 4, 0·71, yellow; 5, 0·82, yellow. Fractions were extracted with MeOH and the residues from evaporation reextracted with $CHCl_3$ to remove alumina. Crystallization afforded pure alkaloids as follows.

Band 1 gave imerubrine (8 mg), orange red needles, m.p. 183–185° (MeOH–ether): IR 6·35μ; λ_{max} 250 nm (log ϵ 4·48), 267 (4·52), 295 (4·40), 350 (4·35), 372 sh (4·20), 394 (4·11), 450 (3·93); NMR δ 3·92, 4·04, 4·10, 4·14 (all 3H, s), 6·65, 7·80 (both 1H, d, J = 10 Hz), 7·98 (1H, s), 7·53, 8·43 (both 1H, d, J = 6 Hz); high resolution mass spectrum *m/e* calcd. for $C_{20}H_{17}NO_5$ 351·1105, found 351·1098.

Band 2 gave imenine **1**, (74 mg), yellow needles, m.p. 206–207° (MeOH): IR 6·06 μ; λ_{max} 240 nm (log ϵ 4·30), 275 (4·38), 335

(3·71), 345 (3·71), 434 (4·03); NMR δ 4·02, 4·07, 4·12, 4·22 (all 3H, s), 7·35–7·80 and 8·56 (3H, m), 8·57 (1H, s), 9·12 (pair of doublets, J = 8 and 2 Hz); *m/e* 351.

Band 3 gave homomoschatoline **4**, (81 mg), orange–yellow needles (MeOH), m.p. 186–188°: IR 6·03 μ; λ_{max} 242 (log ϵ 4·01), 280 (4·08), 310 sh (3·65), 435 (3·71); NMR δ 4·05, 4·08, 4·17 (all 3H, s), 7·4–7·8 (2H, m), 8·14, 8·89 (both 1H, d, J = 6 Hz), 8·50 (pair of doublets, J = 8 and 2 Hz), 9·03 (pair of doublets, J = 8 and 1·5 Hz); *m/e* 321.

Band 4 gave imeluteine **2**, (10 mg), yellow prisms, m.p. 146–147° (isopropyl ether–MeOH): IR 6·35 μ; λ_{max} 233 nm (log ϵ 4·48), 253 (4·49), 288 (4·43), 317 (3·75), 365 sh (3·72), 380 (3·85), 400 sh (3·72); NMR δ 3·94, 4·02, 4·08, 4·10, 4·17 (all 3H, s), 6·91, 7·60 (both 1H, d, J = 8 Hz), 7·57, 8·65 (both 1H, d, J = 6 Hz); high resolution MS calcd. for $C_{20}H_{19}NO_5$ 353·1262, found 353·1235.

Band 5 was purified by another chromatography as before and afforded rufescine **3** (8 mg), bright yellow needle-shaped prisms, m.p. 88–90° (hexane–ether): IR 6·15, 6·31 μ; λ_{max} 247 (log ϵ 4·52), 285 sh (4·31), 295 (4·34), 304 (4·29), 315 sh (3·84), 356 (3·65), 373 (3·78), 400 sh (3·32); NMR δ 3·94, 4·05, 4·11, 4·13 (all 3H, s), 7·63, 8·59 (both 1H, d, J = 6 Hz), 6·96 (1H, pair of doublets, J = 8 and 2 Hz), 7·68 (1H, d, J = 2 Hz), 7·82 (1H, d, J = 8 Hz); high resolution MS calcd. for $C_{19}H_{17}NO_4$ 323·1157, found 323·1135.

Norrufescine was obtained by workup of the aqueous NaOH extract of the crude ether soluble material. The extract was acidified to pH 2 with HCl and extracted with ether to remove non-basic material. Neutralization of the aqueous phase with concentrated NH_4OH, extraction with $CHCl_3$, drying ($MgSO_4$) and evaporation of the organic layer gave a dark gum (565 mg). On standing with a small volume of $CHCl_3$ this material yielded crystals which were filtered and recrystallized from MeOH, affording pure norrufescine (66 mg), orange–yellow plates, m.p. 235–238° (dec): IR 3–4 (broad), 6·21, 6·31 μ; λ_{max} 225 nm (sh) (log ϵ 3·56), 248 (3·83), 303 (3·68); 315 (sh) (3·36), 374 (2·87); after addition of NaOH 230 (sh) (3·64), 245 (3·77), 317 (3·85), 382 (2·60), 495 (2·30); NMR ($CDCl_3$ plus a drop of $(CD_3)_2SO$) δ 4·04, 4·08, 4·10 (all 3H, s), 7·59, 8·52 (both 1H, d, J = 6 Hz), 6·90 (1H, pair of doublets, J = 8 and 2 Hz), 7·53 (1H, d, J = 2 Hz), 7·71 (1H, d, J = 8 Hz); high resolution MS calcd. for $C_{18}H_{15}NO_4$ 309·1001, found 309·0991.

Treatment of norrufescine (22 mg) with diazomethane (from 1 g N-nitrosomethylurea) overnight in 1:1 MeOH–ether (100 ml) afforded, after workup and crystallization (diisopropyl ether–hexane) rufescine (9 mg) m.p. 85–87°, identical by IR with the natural base. A coupling reaction of norrufescine with *p*-nitrobenzenediazonium chloride in aqueous soln afforded a green–purple coloration; a comparison test on rufescine was negative.

Alkylation of **7** *and hydrolysis of* **8**. To a stirred mixture of the Reissert compound **7**[13] (1·050 g), *o*-nitrobenzyl chloride (684 mg), NaI (20 mg), and dry benzene (100 ml) was added portionwise 57% NaH in mineral oil (168 mg) at 0–5°. After stirring for 7·5 hr in the presence of N_2 at room temp, NH_4Cl (200 mg) was added to the mixture, followed by a soln of Triton B (8 ml, 30% methanolic soln) in abs MeOH (30 ml). The mixture was allowed to stir for 20 hr at room temp. Benzene (100 ml) and water (50 ml) were added to the mixture, and the organic layer was separated, washed with water, and dried (K_2CO_3). Workup as usual gave a brownish syrup, which was chromatographed (silica gel) by PTLC using $CHCl_3$–Et_2O (1:2) as developer to give the following compounds. Compound **9** (682 mg, 59%) was obtained from the more polar zone as pale yellow needles, m.p. 145–146° ($CHCl_3$–hexane); IR 6·75, 7·35 μ (NO_2): NMR δ 8·36 (1H, d, J = 6·0 Hz, C_3–H), 8·25–7·25 (4H, m, aromatic), 7·81 (1H, d, J = 6·0 Hz, C_4–H), 7·20 (1H, s, C_8–H), 4·94 (2H, s, CH_2), 4·04, 4·01, 3·95 (each 3H, $3 \times OCH_3$), 7·20 (1H, s, C_8–H), 4·94 (2H, s, CH_2), 4·04, 4·01, 3·95 (each 3H, $3 \times OCH_3$); λ_{max} 243 nm (log ϵ 4·60), 325 (sh) (3·60); 336 (3·64) (Found: C, 64·49; H, 4·97; N, 7·85. $C_{19}H_{18}N_2O_5$ requires: C, 64·40; H, 5·12; N, 7·91%).

The less polar zone yielded **10**, (270 mg, 37%) as colorless needles, m.p. 119–120° (Et_2O): IR 4·45 μ (CN): NMR δ 8·64 (1H, d, J = 6·0 Hz, C_3–H), 8·11 (1H, d, J = 6·0 Hz, C_4–H), 7·37 (1H, s, C_8–H), 4·12 (6H, s, $2 \times OCH_3$), 4·08 (3H, s, OCH_3): λ_{max} 255 nm (log ϵ 4·46), 353 (3·63) (Found: C, 64·07; H, 4·72; N, 11·51. $C_{13}H_{12}N_2O_3$ requires: C, 63·92; H, 4·95; N, 11·47%).

Hydrogenation of **9** *and Pschorr reaction of* **11**. The nitro compound **9** (200 mg) was dissolved in THF (30 ml) and hydrogenated for 20 hr in the presence of Raney Ni (W-2) at atmo press. The catalyst was filtered off and solvent was removed. The pale green residue was dissolved in Et_2O and Et_2O saturated with gaseous HCl was added to afford the hydrochloride of **11** (192 mg) as a colorless powder which was used directly in the next synthetic step.

The preceding hydrochloride (185 mg) was dissolved in MeOH (15 ml) and 2 N H_2SO_4 (1·4 ml), and diazotized with 10% $NaNO_2$ (0·9 ml) at 0–5°. After stirring for 25 min at 0–5°, Cu (50 mg) was added to the mixture. After stirring for an additional 20 min at 0–5°, the mixture was gradually heated to 40° and allowed to stir for 1·5 hr at 40–45°. After basification with NH_4OH and extraction with $CHCl_3$, the usual workup gave a brownish gum, which was purified by PTLC (silica gel) using benzene–Me_2CO (1:1) as developer to afford **4** (48 mg, 27%) as yellow needles, m.p. 185–186° ($CHCl_3$–n–hexane).

Its IR spectrum (KBr) was superimposable upon that of natural homomoschatoline and a mixture m.p. (184–186°) showed no depression. In addition, the NMR spectra of both samples were identical.

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