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DEHYDRATION OF HYDROXY-HEMITERPENOID QUINOLINE ALKALOIDS AND SYNTHESIS OF PARAENSIDIMERINES

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ABSTRACT.—The dehydration reaction of ribalinine [**1**] and 3-(2-hydroxy-3-methylbut-3-en-1-yl)-4-hydroxy-1-methyl-2-quinolone [**2**] obtained from platydesminium cation [**3**] has been studied. In the attempts towards this dehydration using mesyl chloride, ribalinine mesylate [**10**] and araliopsine mesylate [**11**] were obtained. *N*-methyl flindersine [**12**] and its furan isomer **9** could be obtained by acid fusion of **1**. Thermal dimerization of *N*-methyl flindersine [**12**] led to paraensidimerines A [**14**], C [**15**], D [**13**], and F [**16**], previously isolated from *Euxylophora paraensis*, along with three new ones, paraensidimerines A′ [**17**], C′ [**18**], and F′ [**19**]. The overall yield of the reaction and the structures of the dimers greatly depended upon the temperature of dimerization. The structures of the new dimers have been established on the basis of their spectral data, mainly ^{1}H nmr and uv.

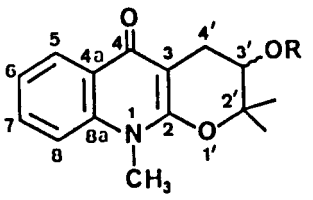
Hydroxy-hemiterpenoid quinoline alkaloids such as linear and angular hydroxyisopropyldihydrofuroquinolones and hydroxy-dimethyldihydropyranoquinolones and linear hydroxyprenylquinolones are widely distributed in plants belonging to the family Rutaceae (1). Dehydration reactions of these various products have not so far been fully studied (2). Nevertheless, these reactions seem interesting from a biomimetic point of view because simultaneous rearrangements of the molecular skeleton can be anticipated. We have, therefore, studied the dehydration reactions of ribalinine [**1**] and 3-(2-hydroxy-3-methylbut-3-en-1-yl)-4-hydroxy-1-methyl-2-quinolone [**2**], for these two compounds can be easily obtained from platydesminium cation [**3**] (3) isolated previously in large amounts from *Araliopsis tabouensis* (4).

Furthermore, in numerous rutaceous plants containing dimethylpyranoquinolone alkaloids, dimeric alkaloids arising from a Diels-Alder reaction are often found (5–12). This dimerization had been previously studied (13) and various vepridimerines had been synthetized, using monomeric veprisine as starting material. Nevertheless, in these experiments, no dimer arising from a hetero Diels-Alder reaction could be observed. Dimerization of *N*-methylflindersine has been studied in order to determine the conditions under which a hetero Diels-Alder reaction could occur, because this mechanism had been postulated as an alternative biogenetic pathway to dimeric alkaloids such as paraensidimerines D and B (8).

RESULTS AND DISCUSSION

Ribalinine [**1**] and 3-(2-hydroxy-3-methylbut-3-en-1-yl)-4-hydroxy-1-methyl-2-quinolone [**2**] were prepared in three steps from platydesminium cation [**3**] according to Grundon's procedure (3,14) through isoplatydesmine [**4**] and the acetates **5** and **6**. When isoplatydesmine [**4**] was treated with Ac_2O and concentrated HCl in refluxing pyridine, the two compounds **5** and **6** were obtained (3). In addition, araliopsine acetate [**7**] was isolated in small amounts from the reaction mixture. The structure of **7** was deduced from its spectral data and confirmed by its alkaline hydrolysis to araliopsine [**8**] identical with an authentic sample (15).

Dehydration of either **2** or **8** using toluene sulfonic acid or mesyl chloride (16) in alkaline solution afforded a complex mixture from which one major product was isolated. Its structure was established as the angular substituted furan **9** on the basis of its spec-



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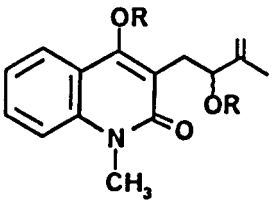
5 R=Ac
10 R=SO_2Me



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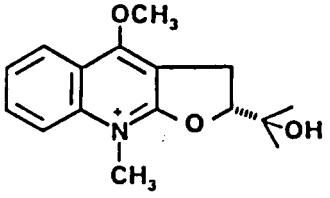
6 R=Ac



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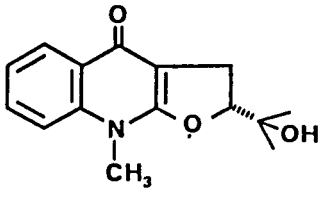

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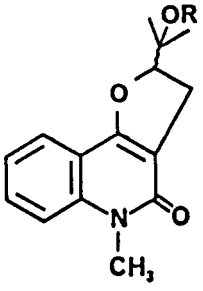
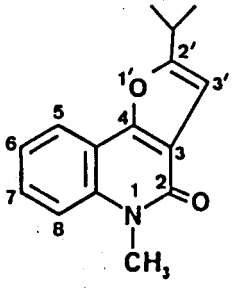


8 R=H
7 R=Ac
11 R=SO_2Me



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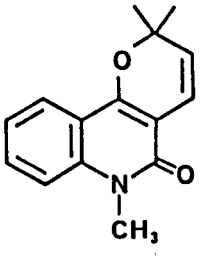

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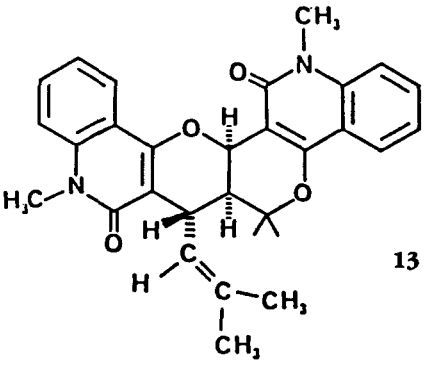
tral data. Of particular interest is its ^{1}H-nmr spectrum, which exhibits the H-5 signal at 7.97 ppm providing unambiguous evidence for an angular structure (14).

Attempts to dehydrate ribalinine [**1**] using mesyl chloride and triethylamine in $CHCl_3$ (16) led in almost quantitative yield to ribalinine mesylate [**10**] which was fully characterized by its spectral data. When the same reaction was carried out in pyridine, the major product was a pyridine adduct, $C_{20}H_{18}N_2O_2$, the structure of which is currently being investigated. In addition, ribalinine mesylate [**10**] and araliopsine mesylate [**11**] could be isolated from the reaction mixture. One-step dehydration of ribalinine [**1**] was carried out by fusion with $KHSO_4$ (17) to give a 40:60 mixture of *N*-methylflindersine [**12**] and its furan isomer **9**.



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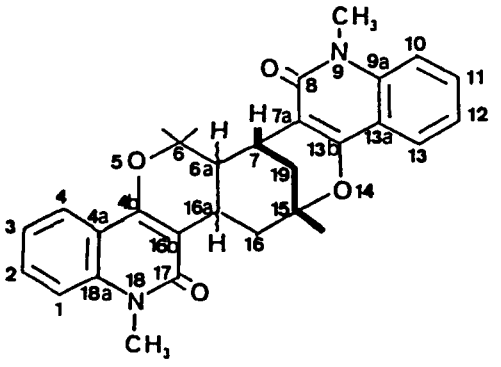
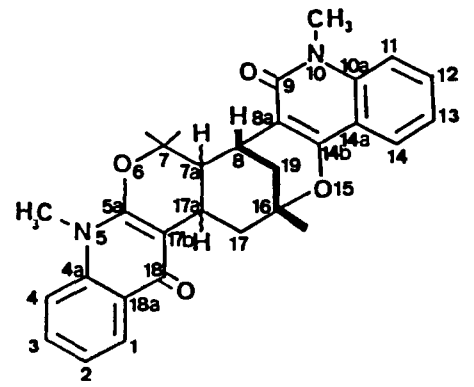


	H6a	H16a
14	α	α
15	α	β
16	β	α



	H7a	H17a
17	α	α
18	α	β
19	β	α

The synthesis of paraensidimerines was achieved by thermal dimerization (13) of *N*-methyflindersine [**12**] (18,19). The starting material was placed in a sealed tube under argon and heated at various temperatures for 24 h. The structures of the dimers obtained in these conditions and the overall yield of the reaction greatly varied with the temperature (see Experimental). Formation of paraensidimerine D [**13**], arising from a hetero Diels-Alder reaction, could be observed only when the reaction was carried out at 105°. Higher reaction temperatures (150 or 210°) led to the formation of classical Diels-Alder adducts, such as paraensidimerines A [**14**], C [**15**], and F [**16**]. In addition, isomeric dimers containing one 4-quinolone unit and one 2-quinolone unit were obtained when the reaction was performed at 150°. The structures of these new dimers, named paraensidimerines A′ [**17**], C′ [**18**], and F′ [**19**], have been determined on the basis of their ^{1}H-nmr spectra compared to those of paraensidimerines A [**14**], C [**15**], and F [**16**] (11). Moreover, the uv spectra of compounds **17–19** were slightly modified

when recorded in acidic medium, in good agreement with the presence of a 4-quinolone unit. Paraensidimerine F′ had been previously obtained by *N*-methylation of geijedimerine isolated from *Geijera balansae* (11).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mp's were taken on a Reichert microscope or a Kofler hot stage. Spectra were recorded on the following apparatus: uv, Unicam SP 800; ir, Beckman 4250 or Perkin Elmer 727B; ms, Nermag R10-10C; ^{1}H nmr, Bruker WP 270 or Perkin Elmer R12; and ^{13}C nmr, Varian XL100 spectrometer with VFT 100 accessory.

DEQUATERNIZATION OF *N*-METHYLPLATYDESMINIUM CATION [**3**].—A solution of **3** (2 g) in dry pyridine (10 ml) was allowed to stand overnight at 80°. The usual workup gave a yellow oil. Repeated cc on Si gel resolved the mixture into isoplatydesmine [**4**] (1.4 g) and unreacted *N*-methyl platydesminium cation [**3**] (100 mg).

ACETYLATION OF ISOPLATYDESMINE [**4**].—Ac_2O (40 ml) and concentrated HCl (2 ml) were added to a solution of **4** (1.3 g) in pyridine (8 ml). The resulting mixture was refluxed for 4 h, after which time the mixture was diluted with H_2O (50 ml) and extracted with $CHCl_3$ (3 × 30 ml). The combined $CHCl_3$ extracts were washed several times with 1 N HCl. Crystallization in Et_2O afforded the diacetate **6** (900 mg), mp 149–150°. The filtrate on further separation on Si gel column yielded ribalinine acetate [**5**] (100 mg) and araliopsine acetate [**7**] (110 mg).

Araliopsine acetate [**7**].—Uv λ MeOH max nm 232, 286, 296, 319, 331; ir ($CHCl_3$) ν max cm^{-1} 3005, 2940, 1730, 1660, 1630, 1600, 1250, 1105; eims *m/z* (%) $[M]^+$ 301 (9), 241 (20), 227 (14), 226 (72), 200 (24), 85 (30), 83 (56), 58 (20), 43 (100); ^{1}H nmr (60 MHz, $CDCl_3$, TMS) δ ppm 7.75–7.10 (4H, m, aromatic protons), 5.26 (1H, t, J = 9 Hz, H-2′), 3.68 (3H, s, N-Me), 3.18 (2H, d, J = 9 Hz, 2H-3′), 1.97 (3H, s, OAc), 1.60, 1.53 (2 × 3H, 2s, *gem*-dimethyl).

HYDROLYSIS OF **5**, **6**, AND **7**.—Methanolic NaOH 0.5 N (12 ml, 150 ml, and 5 ml) was added to MeOH solutions of **5** (60 mg), **6** (800 mg), and **7** (30 mg), respectively. The reaction mixtures were allowed to stand at room temperature for 2 days. The usual workup gave the corresponding alcohols **1** (40 mg), **2** (650 mg), and **8** (24 mg).

DEHYDRATION OF **2** AND **8**.—*p*-Toluene sulfonic acid (100 mg and 500 mg) was added to dry C_6H_6 solutions of **8** (20 mg) and **2** (120 mg), respectively. The reaction mixtures were refluxed with Dean Stark equipment for 20 min, and the residues (15 mg and 100 mg) were purified separately by preparative tlc to yield **9** (5 mg and 30 mg): ir ($CHCl_3$) ν max cm^{-1} 3005, 2985, 1655, 1225, 790, 720; dcims *m/z* $[M+H]^+$ 242; ^{1}H nmr (60 MHz, $CDCl_3$, TMS) δ ppm 7.97 (1H, dd, J = 8 Hz, J' = 2 Hz, H-5), 7.70–7.20 (3H, m, H-6, H-7, H-8), 6.67 (1H, s, H-3′), 3.79 (3H, s, N-Me), 3.14 (1H, septet, J = 6.5 Hz, C*H*Me$_2$, 1.34 [6H, d, J = 6.5 Hz, CH(C*H*$_3$)$_2$].

RIBALININE MESYLATE [**10**].—Freshly distilled triethylamine (1 ml) and methane sulfonyl chloride (0.5 ml) were added to a cold solution of ribalinine [**1**] (130 mg) in $CHCl_3$ (5 ml). The reaction mixture was allowed to stand at 0° while stirring for 3 h. The residue upon cc and preparative tlc afforded ribalinine mesylate [**10**] (45 mg) as a colorless oil, $[\alpha]^{20}$D 0°; ir ν max ($CHCl_3$) 3000, 1610, 1595, 1545, 1470, 1450, 1420, 1360, 1220, 1200, 1100 cm^{-1}; ^{1}H nmr (60 MHz, $CDCl_3$, TMS) δ ppm 8.45 (1H, br d, J = 8 Hz, H-5), 7.2–7.8 (3H, m, aromatic protons), 4.95 (1H, br t, J = 5 Hz, H-3′), 3.70 (3H, s, N-Me), 3.08 (3H, s, S-Me), 2.70–3.40 (2H, m, H-4′), 1.58, 1.50 (2 × 3H, 2s, *gem* dimethyl); ^{13}C nmr ($CDCl_3$, 25.2 MHz, TMS) δ ppm 176.7 (C-4), 153.3 (C-2), 139.3 (C-8a), 131.9 (C-7), 126.6 (C-6), 124.1 (C-4a), 123.0 (C-5), 114.6 (C-8), 94.6 (C-3), 80.3 (C-2′), 75.8 (C-3′), 39.5 (S-Me), 30.3 (N-Me), 24.8 (C-4′), 23.9 and 23.3 (2 × Me).

ACID FUSION OF RIBALININE [**1**].—A homogeneous mixture of a freshly prepared anhydrous $KHSO_4$ (10 g) and ribalinine [**1**] (150 mg) was placed in a long tube and heated in a heating block under reduced pressure (0.2 mm) at 150° for 4 h. The reaction mixture was then dissolved in H_2O and extracted with $CHCl_3$ (3 × 40 ml). The combined $CHCl_3$ extracts were washed (aqueous $NaHCO_3$), dried (anhydrous Na_2SO_4), and evaporated. The residue (60 mg) after preparative tlc [silica, hexanes-EtOAc (85:15)] afforded **9** (15 mg) and **12** (10 mg).

THERMAL DIMERIZATION OF *N*-METHYLFLINDERSINE [**12**].—*N*-Methylflindersine [**12**] (0.50 g) was placed in a sealed tube under argon and heated for 24 h. Cc [silica, hexanes-EtOAc (50:50)] of the reaction mixture yielded paraensidimerine A [**14**] (0.03 g, 6%), paraensidimerine C [**15**] (0.015 g, 3%), paraensidimerine D [**13**] (0.015 g, 3%), and unreacted *N*-methylflindersine [**12**] (0.44 g) when the reaction was performed at 105°. When the reaction was performed at 150°, cc yielded paraensidimerine A [**14**]

(0.075 g, 15%), paraensidimerine C [**15**] (0.03 g, 6%), paraensidimerine F [**16**] (0.025 g, 5%), paraensidimerine A′ [**17**] (0.015 g, 3%), paraensidimerine C′ [**18**] (0.035 g, 7%), paraensidimerine F′ [**19**] (0.030 g, 6%), and unreacted *N*-methylflindersine [**12**] (0.08 g). When the reaction was performed at 210°, cc yielded paraensidimerine A [**14**] (0.09 g, 18%), paraensidimerine C [**15**] (0.09 g, 18%), and paraensidimerine F [**16**] (0.22 g, 44%).

The physical and spectral data of paraensidimerines A, C, D, F, and F′ were identical with those previously published (8–11).

PARAENSIDIMERINE A′ [**17**].—Colorless, amorphous solid: $[\alpha]^{20}D$ 0°; $C_{30}H_{30}N_2O_4$; uv λ max (MeOH) nm 239, 254 (sh), 280 (sh), 306, 318, 330, (MeOH + HCl) 243, 256 (sh), 278 (sh), 290, 298, 314, 329 (sh); eims *m/z* (%) $[M]^+$ 482 (64), 467 (9), 439 (20), 308 (41), 226 (100); ^1H nmr (270 MHz, $CDCl_3$, TMS) δ ppm 8.36 (1H, dd, $J = 8$ Hz, $J' = 2$ Hz, H-1), 8.10 (1H, dd, $J = 8$ Hz, $J' = 2$ Hz, H-14), 7.58–7.23 (6H, m, H-2, H-3, H-4, H-11, H-12, H-13), 3.69 (1H, ddd, $J = 2.5$ Hz, $J' = 2$ Hz, $J'' = 1$ Hz, H-8), 3.68 and 3.65 (2 × 3H, 2s, 2N-Me), 3.38 (1H, ddd, $J = 13$ Hz, $J' = 6$ Hz, $J'' = 2$ Hz, H-17eq), 3.22 (1H, dt, $J = 13$ Hz, $J' = 6$ Hz; H-17a), 2.21 (1H, dd, $J = 6$ Hz, $J' = 1$ Hz, H-7a), 2.15 (1H, dd, $J = 14$ Hz, $J' = 2.5$ Hz, H-19ax), 1.75 (1H, dt, $J = 14$ Hz, $J' = 2$ Hz, H-19eq), 1.62 (1H, t, $J = 13$ Hz, H-17ax), 1.86, 1.61 and 1.53 (3 × 3H, 3s, 3C-Me).

PARAENSIDIMERINE C′ [**18**].—Colorless amorphous solid, $[\alpha]^{20}D$ 0°; $C_{30}H_{30}N_2O_4$; uv λ max (MeOH) nm 240, 267 (sh), 278, 287, 307 (sh), 319, 331 (MeOH + HCl) 245, 266 (sh), 277, 288, 306 (sh), 316, 334 (sh); eims *m/z* (%) $[M]^+$ 482 (5), 439 (1), 308 (1), 295 (2), 294 (2), 281 (2), 256 (2), 227 (4), 226 (30), 44 (100); ^1H nmr (270 MHz, $CDCl_3$, TMS) δ ppm 8.37 (1H, dd, $J = 8$ Hz, $J' = 2$ Hz, H-1), 7.96 (1H, dd, $J = 8$ Hz, $J' = 2$ Hz, H-14), 7.56–7.17 (6H, m, H-2, H-3, H-4, H-11, H-12, H-13), 4.11 (1H, dd, $J = 14$ Hz, $J' = 4$ Hz, H-17eq), 3.70 and 3.62 (2 × 3H, 2s, 2N-Me), 3.22 (1H, q, $J = 3$ Hz, H-8), 2.76 (1H, td, $J = 14$ Hz, $J' = 4$ Hz, H-17a), 2.17 (1H, dd, $J = 13$ Hz, $J' = 3$ Hz, H-19ax), 1.61 (1H, dd, $J = 14$ Hz, $J' = 3$ Hz, H-7a), 1.46 (1H, dd, $J = 13$ Hz, $J' = 3$ Hz, H-19eq), 1.43 (1H, t, $J = 14$ Hz, H-17ax), 1.90, 1.73 and 1.38 (3 × 3H, 3s, 3C-Me).

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