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NEW *BALFOURODENDRON* 4-QUINOLONE ALKALOIDS[1]

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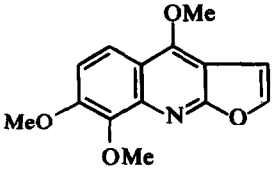
Abstract—New tertiary alkaloids with a 4-quinolone skeleton, (±)-ribalinine (**3b**), (−)-ribalinidine (**3c**), (±) and (+)-ribaline (**2b**), have been obtained from *Balfourodendron riedelianum*. During isolation, **3c** and **3b** were found together with the quaternary alkaloidal fraction. The structure elucidations were in part based on spectrometric data. Furthermore, **2b** and **3c** were chemically correlated with the known ribalinium whilst the structure of **3b** was confirmed by total synthesis. The configuration of **3c** is *S* as determined by the Horeau's method.

Previous publications[2-4] report a number of alkaloids in the trunk-bark of *Balfourodendron riedelianum* (Engler) Engler (Rutaceae). Most of them are tertiary bases, more commonly furoquinoline alkaloids that typically occur in Rutaceae (e.g. skimmianine, **1**). Other tertiary alkaloids are representatives of dihydrofuro- (balfourodine, **2a**), dihydropyrano-4-quinolones (isobalfourodine, **3a**); 2-phenyl-1-methyl-4-quinolone and the acridone alkaloid named evoxanthine.

Furthermore, two quaternary alkaloids, O^4-methylbalfourodinium (**4a**) and ribalinium (**4b**) were characterized.



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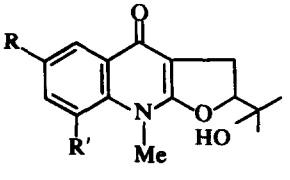
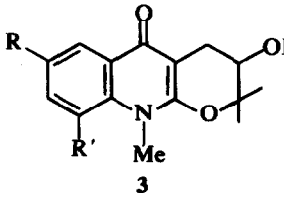


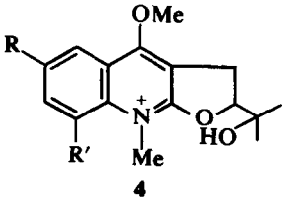
	R	R'
a	H	OMe
b	OH	H
c	OMe	H

2



	R	R'
a	H	OMe
b	H	H
c	OH	H
d	OMe	H

3



	R	R'
a	H	OMe
b	OH	H
c	OMe	H

4

The present paper[5] deals with other tertiary bases, structurally related to the ones mentioned; two of them are dihydropyrano-4-quinolones ((±)-ribalinine **3b** and (−)-ribalinidine **3c**) and the others, dihydrofuro-4-quinolone derivatives ((±)- and (+)-ribaline **2b**).

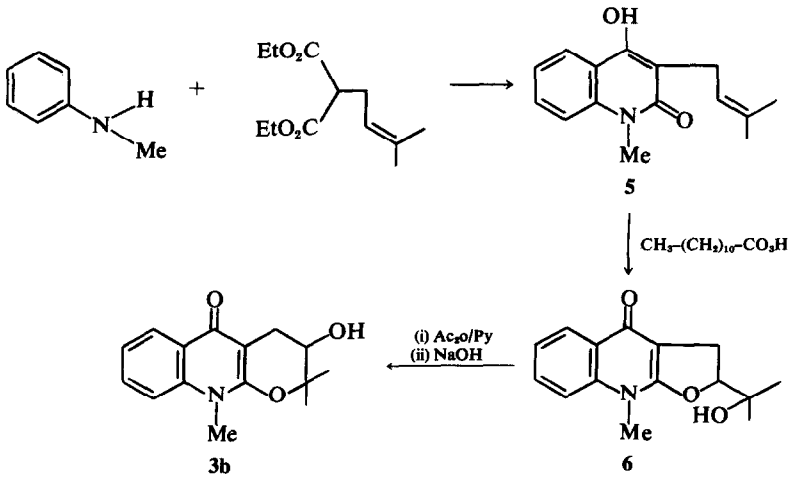
Applying the usual procedure for the extraction and fractionation of alkaloids, ribalinine (**3b**) was obtained from the mixture of tertiary bases extracted with chloroform at pH 11. The other alkaloids (**2b** and **3c**) were not extracted but subsequently precipitated as reineckates together with the quaternary compounds; this peculiar behaviour is ascribed to their phenolic character (partially ionized at pH 11) and very low solubility in chloroform.

The ribalinine (**3b**) and ribalinidine (**3c**) structures were essentially deduced from the spectroscopic data of these bases and derivatives.

Furthermore, the total synthesis of (**3b**), patterned on that described for isobalfourodine[2,7] was carried out (Scheme 1); this provided an independent proof of its structure. In connection with NMR studies compound (**3b**) has already been synthetized using another reaction sequence.[6]

The discussions leading to the above conclusions[5] are not repeated and only the experimental details are given.

The formulation **3c** for ribalinidine has been con-



SCHEME 1. Synthesis of (±)-ribalinine (**3b**)

firmed by two analogous chemical correlations (Scheme 2) with the quaternary ribalinium (**4b**) chloride of known structure.[4]

In the first step the ribalinium (**4b**) or its O^7-methyl derivative (**4c**) were degraded to the corresponding dihydrofuro-4-quinolone (**2b** or **2c**) by heating with pyridine.[4]

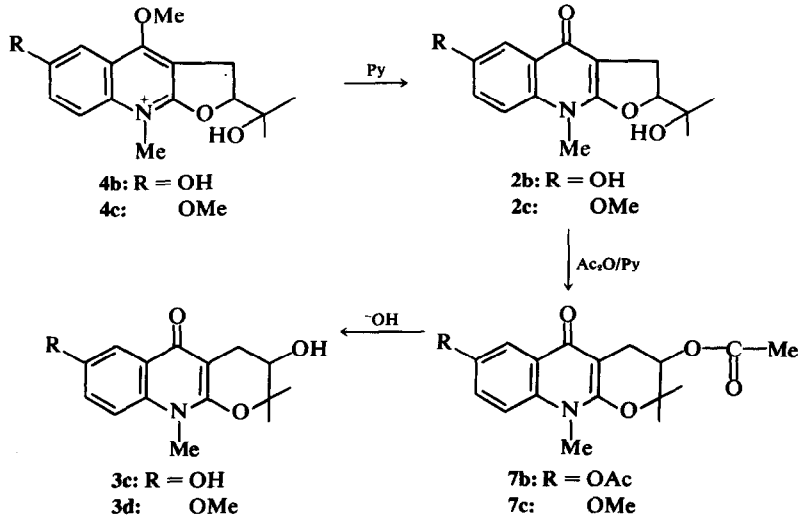
Compound **2b** was obtained as *dextro* and racemic forms (see later). The latter was isomerized to the dihydropyrano-4-quinolone (**7b**) which upon hydrolysis gave (±)-ribalinidine (**3c**). Similarly, (+)-(**2c**) provided the (+) and (±)-monoacetyl-derivative (**7c**) and was subsequently hydrolysed to (−) and (±)-O^7-methylribalinidine (**3d**) respectively.

The isomerization and hydrolysis steps were performed according to the analogous conversion of balfourodine (**2a**) into isobalfourodine (**3a**).[2]

The asymmetric C atom (3-C) of (−)-ribalinidine (**3c**) possesses the *S*-configuration based on Horeau's method applied to (−)-O^7-methyl-ribalinidine (**3d**).

The alkaloid (±)-ribaline (**2b**) shows UV absorption (Fig 1) in neutral and basic media indicative of a phenolic character; the spectrum in neutral medium and the changes by acidification support the presence of a 2-alkoxy-4-quinolone system. This is also consistent with the IR bands in the 1650–1470 cm^{-1} region.[2,8]

The same molecular composition ($C_{15}H_{17}NO_4$) and the strong spectral similarities of (**2b**) with (−)-ribalinidine (**3c**) together with the co-occurrence



SCHEME 2. Correlations of ribalinium (**4b**), ribaline (**2b**) and ribalinidine (**3c**)

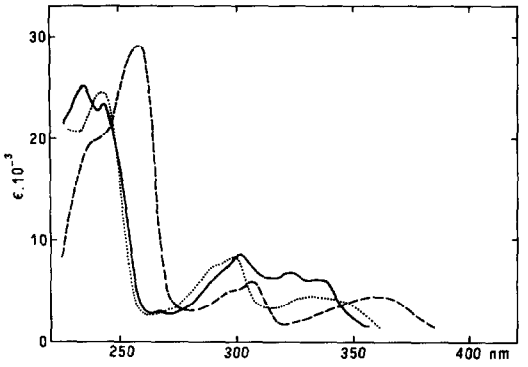


Fig 1. UV spectra of (±)-ribaline (**2b**) in alcohol 50°: —— neutral; ---- 0·01 N NaOH; ···· 0·3 N HCl.

with ribalinium (**4b**) suggest formula (**2b**) as a working hypothesis.

This structure results from a chemical correlation (Scheme 2) with (+)-ribalinium (**4b**). The latter, by dequaternization with pyridine furnishes a racemic tertiary base characterized as such and as its picrate salt, and identical with natural (±)-ribaline (**2b**).

The structure of this dequaternization product is based on its preparation and, conclusively, from its methylation with diazomethane to the known[4] **2c**.

The ribalinium (**4b**) dequaternization (at 115°) unlike that of **4c** (at 80°)[4] occurs with significant racemization. In addition to the above racemic base it was isolated as the *dextro* form, which is identical with the natural (+)-ribaline (**2b**) described.

As shown in the Scheme 2, ribaline (**2b**) is an intermediate in the partial synthesis of ribalinidine (**3c**) starting from ribalinium (**4b**).

Ribaline (**2b**) and ribalinidine (**3c**) were detected or isolated in numerous extractions of different samples of plant material. Furthermore, several control experiments were performed to prove that these tertiary bases are not artifacts. Thus, these alkaloids were detected or isolated by extractions and subsequent work-up without heating and avoiding any alkalinization step. On the other hand, ribalinium (**4b**) and ribaline (**2b**) remain unaltered when pyridine was added to their methanolic solutions and kept two days at 20°.

EXPERIMENTAL

The m.ps, taken in sealed capillaries, were not corrected; the evaporations were carried out at reduced pressure. R_F values refer to paper chromatograms using methyl ethyl ketone saturated with water and addition of 5% MeOH; the spots were detected by UV fluorescence and by a modified Dragendorff reagent.[9] The UV spectra were measured with 50% alcohol as solvent; NMR values are given as δ (ppm) downfield from internal TMS; the mass spectra were run by direct insertion technique.

The microanalyses were performed in the Dr. A. Bernhardt (Germany) and Dr. B. B. de Deferrari (Buenos Aires) laboratories.

Isolation of alkaloids

The fractionation of crude quaternary alkaloids (6 g) extracted from the trunk bark (1 K) of *B. riedelianum* was detailed in a previous paper. With methyl ethyl ketone saturated with water and 5% MeOH, 190 tubes were collected; fractions 105–170 contained the alkaloid **4b**.[4]

The fractions 31–62 (0·63 g) showing two alkaloidal spots (R_F 0·75 and 0·85) were now used for the isolation. Further amounts of the same material resulted from several Soxhlet extractions and fractionated as described.[3,4]

The material from fractions 31–62 was passed through a column of neutral alumina (activity II, 10 g) using abs EtOH–$CHCl_3$ (4:1). The eluted alkaloids (0·57 g) were fractionated by heating with H_2O (3 × 4 ml) and then cooling in the refrigerator giving an insoluble (0·32 g; main spot R_F 0·85, UV fluorescence greyish blue) and a soluble portion (0·25 g; main spot R_F 0·75, UV fluorescence greenish blue).

*(−)-Ribalinidine (**3c**).* The water-insoluble material was crystallized several times from abs EtOH providing pure (−)-ribalinidine (0·22 g), R_F 0·85; it gives only one spot on paper electrophoresis at pH 3 but does not move at pH 8; m.p. 257–258° (dec); $[\alpha]_D^{20°}$ -15° (*c*, 1·0 in MeOH); λ_{max} nm (log ε): 220 sh (4·31), 235 (4·48), 245 sh (4·43), 301 (3·88), 331 (3·87), 346 (3·81); λ_{min} 266 (3·09), 310 (3·66), 341 (3·80); in 0·3 N HCl λ_{max} 220 (4·34), 243 (4·48), 301 (3·90), 342 (3·64); λ_{min} 225 (4·32), 262 (3·10), 316 (3·42); in 0·01 N NaOH λ_{max} 240 sh (4·41), 256 (3·52), 296 (3·63), 300 sh (3·64), 307 (3·70); λ_{min} 277 (4·43), 320 (2·14); ν_{max} (KBr; 1650–1470 cm^{-1} region): 1610, 1578, 1558, 1520, 1470; in Nujol, broad bands at 3340 and 3200 cm^{-1}; NMR (60 MHz, F_3CCO_2H) δ: 1·66 and 1·83 (s, 3H each, *gem*-diMe), 3·38 (d, 2H, 4-CH_2), 4·18 (s, 3H, N—CH_3), 4·48 (t, 1H, 3-CH), 7·86–8·06 (m, 3H, aromatic H). (Found: C, 65·22; H, 6·24; N, 5·23; O, 23·41; OCH_3, 0·12; N—CH_3, 6·40; C—CH_3, 5·48; active H, 0·67; M^+ at *m/e* 275. $C_{15}H_{17}NO_4$ requires: C, 65·24; H, 6·22; N, 5·09; O, 23·25; one OCH_3, 11·26; one N—CH_3, 5·46; one C—CH_3, 5·46; two active H, 0·70%; mol. wt. 275).

(±) and (+)-Ribaline (**2b**). The water-soluble alkaloidal fraction was chromatographed on a silica gel column using $CHCl_3$ with increasing amounts of MeOH. The eluates giving on paper chromatography a single spot with greenish blue UV fluorescence (R_F 0·75) were made up and evaporated to dryness (0·15 g); the residue dissolved in alcohol (4·5 ml) with addition of picric acid (0·20 g in 2 ml alcohol). The crude picrate (0·12 g) was crystallized several times from alcohol furnishing (±)-ribaline picrate (30 mg), constant m.p. 223–224° (dec).

The picrate (25 mg) was converted into the free base using a column of neutral alumina (activity II, 4·5 g) and $CHCl_3$-abs EtOH mixtures (1:4 to 1:9) as eluants. By recrystallizations from MeOH the (±)-ribaline (13 mg) gave m.p. 259–260° (dec); optically inactive in the range 700–350 nm (*c* 0·28 in MeOH); UV (Fig 1) λ_{max} nm (log ε): 235 (4·37), 245 (4·34), 304 (3·90), 325 (3·80), 339 (3·71); λ_{min} 241 (4·32), 262 (2·99), 316 (3·74), 331 (3·69); in 0·3 N HCl λ_{max} 241 (4·41), 289 sh (3·92), 298 (3·95), 330 (3·70); λ_{min} 232 (4·36), 259 (3·54), 310 (3·59); in 0·01 N NaOH λ_{max} 238 sh (4·30), 257 (4·47), 295 sh (3·70), 307 (3·77); λ_{min} 274 (3·42), 319 (3·14); IR (KBr; 1650–

1470 cm^{-1} region) ν_{max}: 1618, 1580, 1558, 1545, 1519, 1470. (Found: M^+ at *m/e* 275·1168. $C_{15}H_{17}NO_4$ requires: mol. wt. 275·1158).

The mother liquor from the first crystallization of the crude picrate was passed through a column of resin Dowex-2 chloride. The eluted material dissolved in H_2O with addition of aq $Mg(ClO_4)_2$; the precipitated salt was crystallized from H_2O giving (+)-ribaline perchlorate (40 mg), constant m.p. 224–225° (dec); $[\alpha]_D^{27}+68°$ (*c*, 0·29 in alcohol).

This salt was converted, using alumina, into the free base as described for the racemic compound. (+)-Ribaline, crystallized from MeOH, showed no definite m.p. which usually started about 210° (dec); $[\alpha]_D^{25°}+86°$ (*c*, 0·44 in MeOH); UV (neutral, acid and basic media) and chromatographic mobility coincident with those of (±)-ribaline; the IR spectrum (KBr) displays the pattern of a 4-quinolone system[2,8] and it is slightly different with that of the racemic form; a comparison in solution was difficult due to their very low solubility; in the narrow useful region using Me_2SO (1650–1500 cm^{-1}) their absorptions were coincident.

The natural (±) and (+)-ribaline (**2b**) and their salts were identical with the samples prepared from **4b** (see later).

(±)-*Ribalinine* (**3b**). The tertiary alkaloidal fraction from the trunk bark (2 K) of *B. riedelianum*, afforded 6 known bases when chromatographed on alumina.[3] The material (0·60 g) of the last tubes from the column eluted with $CHCl_3$-abs EtOH (4:1 to 1:9), EtOH 95° and 75°, was now further fractionated by absorption columns of alumina (neutral, activity II) and silica gel.

The eluates were analysed by UV absorption; the fractions with λ_{max} 237, 314 and 326 nm were combined and crystallized from abs EtOH giving (±)-ribalinine (80 mg), constant m.p. 233–234° (dec), optically inactive between 700–370 nm (*c*, 2·90 in MeOH); UV in neutral and 0·01 N NaOH λ_{max} nm (log ϵ): 237 (4·34), 314 (3·83), 326 (3·78); λ_{min} 223 (4·10), 263 (3·11), 321 (3·74); in 0·3 N HCl λ_{max} 236 (4·41), 300 (3·82); λ_{min} 223 (4·16), 256 (2·94); IR (KBr; 1650–1470 cm^{-1} region) ν_{max}: 1618, 1603, 1570, 1527, 1502, 1470; in Nujol, hydroxyl band at 3170 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ: 1·37 and 1·53 (s, 3H each, *gem*-di-Me), 2·94 (d, 2H, J = 4·5 Hz, 4-CH_2), 3·58 (s, 3H, N—CH_3), 3·92 (t, 2H, 3-CH and OH), 7·43 (m, 3H, aromatic H), 8·36 (q, 1H, 6—CH). (Found: C, 69·66; H, 6·66; N, 5·80; N—CH_3, 4·57; OCH_3, 0·00; M^+ at *m/e* 259. $C_{15}H_{17}NO_3$ requires: C, 69·48; H, 6·61; N, 5·40; one N—CH_3, 5·79%; mol. wt. 259).

(±)-Ribalinine dissolved in anhydrous pyridine-Ac_2O was kept 48 hr at room temp. Partition between $CHCl_3$ and $NaHCO_3$ aq followed by evaporation of the organic phase gave an oil which solidified with hexane; IR in Nujol, ester band at 1746 cm^{-1} and no OH absorption; NMR (60 MHz, $CDCl_3$) δ: 2·02 (s, 3H, CH_3-CO), 5·12 (t, 1H, 3—CH).

Control isolation experiments

(a) The above quaternary alkaloidal fraction was obtained after separation of tertiary bases at pH 11.[3,4] In an experiment, the alkalinization step was excluded and the tertiary bases were extracted at pH 5. Working as above, the presence of **3c** and **2b** was shown by paper chromatography; furthermore, **3c** was isolated and identified by m.p. and mixed m.p., IR (KBr) and UV (neutral, acid and alkaline media) spectra.

(b) A sample of the plant material (100–200 g) was extracted with several portions of alcohol or MeOH shaking at room temp; the combined extracts were processed following essentially the above directions but performing all operations below 30°.

The quaternary alkaloidal fraction provided the following compounds: **4b**[4] crystallized from MeOH–EtOAc and identified by paper chromatography, m.p. and mixed m.p.; (±)-**2b** isolated as picrate which was identified by m.p., mixed m.p. and IR (KBr) absorption; (+)-**2b** separated by crystallization from MeOH, identical with a pure sample according to its IR (KBr) spectrum. Besides, the presence of **3c** was ascertained by paper chromatography although it could not be isolated due to its low concentration in admixture with ribaline.

(c) To a solution of (±)-**2b** or **4b** (10^{-5} mole) in MeOH (1·5 ml), pyridine (10^{-4} mole) was added and allowed to stand 2 days at 20°. The soln was acidified with 6 N HCl and examined by paper chromatography and electrophoresis and compared with pure specimens of the starting alkaloids and **3c**; for the detection of the spots the very sensitive UV light fluorescence was used. Both alkaloids, **2b** and **4b**, were found unchanged.

(−)-*Ribalinidine* (**3c**) *derivatives*

O^7-*Methylribalinidine* (**3d**). To an ice-cold soln of (−)-**3c** (0·5 mmole) in MeOH (18 ml) an ethereal soln of diazomethane (1·5 mmole) was added six times at intervals of 12 hr; after removal of the ether *in vacuo*, the excess diazomethane was decomposed with AcOH. The residue obtained by evaporation was taken up with $CHCl_3$ (18 ml) which was washed with 1 N NaOH aq (3 × 6 ml), H_2O (2 × 3 ml), then dried ($MgSO_4$) and evaporated to dryness.

Crystallization from abs EtOH furnished **3d** in 65% yield; m.p. 232–233° (dec); $[\alpha]_D^{14°}-20°$ (*c*, 0·5 in MeOH); UV in neutral or 0·01 N NaOH λ_{max} nm (log ϵ): 220 sh (4·41), 235 (4·57), 245 (4·56), 302 (3·98), 327 (3·97), 345 (3·93); λ_{min} 242 (4·53), 265 (3·22), 309 (3·78), 335 (3·89); in 0·3 N HCl λ_{max} 223 (4·50), 244 (4·67), 301 (4·02), 332 (3·78), 345 (3·76); λ_{min} 230 (4·49), 262 (3·34), 314 (3·64), 337 (3·76); IR (Nujol; 1650–1470 cm^{-1} region) ν_{max}: 1608, 1575, 1550, 1508, 1470; broad hydroxyl band at 3180 cm^{-1}; NMR (60 MHz, F_3CCO_2H) δ: 1·62 and 1·78 (s, 3H each, *gem*-di-Me), 3·30 (d, 2H, 4-CH_2), 4·01 and 4·10 (s, 3H each, N—CH_3 and O—CH_3), 4·43 (t, 1H, 3-CH), 7·7–8·1 (m, 3H, aromatic H). (Found: C, 66·15; H, 6·82; N, 4·65; M^+ at *m/e* 289. $C_{16}H_{19}NO_4$ requires: C, 66·42; H, 6·62; N, 4·84%; mol. wt. 289).

Other methylations using MeI or SO_4Me_2 and Na_2CO_3 in MeOH, afforded **3d** in lower yields.

(−)-O^7-Methylribalinidine (**3d**) was subjected to the Horeau's method.[10] Applying essentially literature directions[11] (−)-α-phenylbutyric acid was obtained, pure according to its NMR spectrum; $[\alpha]_D$-9·4° (*c*, 6·6 in C_6H_6), optical yield 29%. A duplicate experiment gave coincident data.

O^3,O^7-*Diacetylribalinidine* (**7b**). (−)-Ribalinidine (**3c**; 0·1 mmole) was dissolved in anhydrous pyridine (1 ml), Ac_2O (0·5 ml) added and the soln kept protected from humidity at 25° for a week. The soln was diluted with $CHCl_3$ (8 ml), washed with saturated $NaHCO_3$ aq (16 ml) and H_2O (2 × 3 ml).

The dried ($MgSO_4$) extract was evaporated to give the crude diester which was crystallized from acetone furnishing (**7b**); 38% yield; m.p. 203–204°; IR (Nujol) ν_{max}: 1750 and 1730 (phenolic and alcoholic ester resp.), 1635, 1610, 1595, 1555, 1510 cm^{-1} (4-quinolone system);

no hydroxyl absorption; NMR (60 MHz, $CDCl_3$) δ: 1·38 and 1·43 (s, 3H each, *gem*-di-Me), 2·02 (s, 3H, 3–OAc), 2·30 (s, 3H, 7–OAc), 2·90 (d, 2H, 4–CH_2), 3·68 (s, 3H, N—CH_3), 5·13 (t, 1H, 3–CH), 7·4 (m, 2H, 8– and 9–CH), 8·03 (q, 1H, J = 1·0 and 2·5 Hz, 6–CH); in F_3CCO_2H, the 3–CH signal at δ 5·54. (Found: N, 3·68. $C_{19}H_{21}NO_6$ requires: N, 3·90%).

A solution of **7b** (8 mg) in MeOH (1 ml) and 0·5 N NaOH aq (1 ml) was left 2 days at room temp. The MeOH was evaporated without heating and after addition of 2 N NH_4Cl aq, a crystalline ppt was obtained. Crystallization from abs EtOH gave **3c** identified by mixed m.p. and IR (KBr) absorption.

O^7-*Acetylribalinidine* (**7a**). A solution of (−)-**3c**; (0·3 mmole) in anhydrous pyridine (2 ml) and Ac_2O (1 ml) was allowed to stand 2 days at room temp with exclusion of moisture. The crude product, obtained as described for the diacetyl derivative, was extracted with boiling acetone (0·8 and 0·4 ml).

The acetone extract furnished **7b** (23 mg) identified by IR (Nujol) and NMR ($CDCl_3$) spectra.

The insoluble material was crystallized from abs EtOH giving **7a**; 33% yield; m.p. 240–242° (dec); IR (Nujol) ν_{max}: 3185 (broad, OH), 1752 (phenolic ester), 1622, 1600, 1578, 1545, 1500 cm^{-1} (4-quinolone system); NMR (60 MHz, $CDCl_3$) δ: 1·33 and 1·47 (s, 3H each, *gem*-di-Me), 2·27 (s, 3H, 7–OAc), 2·83 (d, 2H, 4–CH_2), 3·10 (broad, 1H, 3–COH; at 60° shifted to lower field), 3·47 (s, 3H, N—CH_3), 3·80 (t, 1H, 3–CH), 7·1 (m, 2H, 8– and 9–CH), 7·80 (m, 1H, 6–CH). (Found: N, 4·72. $C_{17}H_{19}NO_5$ requires: N, 4·41%).

O^7-*Methylribalinidine* (**3d**) *from ribalinium* (**4b**). The quaternary alkaloid **4b** was converted to **4c** and this degraded to the corresponding **2c**.[4]

(±) *and* (+) *Compound* (**7c**). Following a method applied to a similar compound,[2] **2c** (1 mmole) in anhydrous pyridine (1·5 ml) and Ac_2O (6 ml) was heated 3 hr at 125° protecting from humidity. Then, $CHCl_3$ (30 ml) and H_2O (20 ml) were added, the organic phase washed with H_2O (3 × 3 ml) was dried ($MgSO_4$) and evaporated to dryness. The residue (325 mg) was fractionated by crystallization from MeCN (3 ml) furnishing two products.

The separated crystalline compound (125 mg; 38% yield) was further purified from the same solvent giving racemic **7c**, m.p. 228–229° (dec); optically inactive in the range 700–370 nm (*c*, 3·26 in MeOH); UV λ_{max} nm (log ε): 220 (4·41), 235 (4·58), 245 (4·57), 288 sh (3·80), 300 (3·97), 315 sh (3·82), 328 (3·99), 342 (3·95); λ_{min} 224 (4·40), 241 (4·55), 266 (3·26), 308 (3·75), 336 (3·91); in 0·3 N HCl λ_{max} 224 sh (4·43), 244 (4·71), 288 sh (3·92), 299 (4·04), 332 (3·79); λ_{min} 263 (2·57), 314 (3·56); IR (Nujol) ν_{max}: 1745 (ester), 1620, 1595, 1562, 1515 cm^{-1} (4-quinolone system); no hydroxyl absorption; NMR (60 MHz, F_3CCO_2H) δ: 1·60 and 1·70 (s, 3H each, *gem*-di-Me), 2·20 (s, 3H, 3–OAc), 3·36 (d, 2H, 4–CH_2), 4·03 and 4·16 (s, 3H each, N—CH_3 and O—CH_3), 5·50 (t, 1H, 3–CH), 7·8 (m, 3H, aromatic H). (Found: C, 65·46; H, 6·47; N, 4·41; M^+ at *m/e* 331. $C_{18}H_{21}NO_5$ requires: C, 65·24; H, 6·39; N, 4·23%; mol. wt. 331).

The soluble material from the fractionation with MeCN, was purified through the picrate prepared with picric acid in C_6H_6 solution. Upon crystallization from alcohol the pure picrate of *dextro*-**7c**, m.p. 187–188°, was obtained in 42% yield. (Found: C, 51·29; H, 4·60; N, 10·14. $C_{18}H_{21}NO_5 \cdot C_6H_3N_3O_7$ requires: C, 51·43; H, 4·31; N, 10·00%).

A suspension of this picrate (14 mg) in C_6H_6 (4 ml) and saturated $NaHCO_3$ aq (2 ml) was stirred for 1 hr. The organic layer was washed with $NaHCO_3$ aq (2 × 0·25 ml), dried ($MgSO_4$) and evaporated to dryness. Crystallization from EtOAc-diisopropyl ether gave the free base *dextro*-**7c**, with wide m.p. range (56–75°); $[\alpha]_D^{25°}$ + 5°, $[\alpha]_{370}$ − 13° (*c*, 0·83 in MeOH). It showed coincident IR ($CHBr_3$) absorption with that of racemic-**7c**.

(−) *and* (±)-O^7-*Methylribalinidine* (**3d**). A solution of *dextro*-**7c** (0·5 mmole) in 25 ml of 0·25 N NaOH in MeOH-H_2O (1:1) was kept 24 hr at room temp. The MeOH was distilled off without heating and after dilution with H_2O, the mixture was extracted with $CHCl_3$; the latter was washed (H_2O), dried ($MgSO_4$) and filtered through a column of alumina (neutral, activity II; 2·5 g). The filtrate was evaporated and crystallized from abs EtOH to constant m.p. 235-236° (dec); 50% yield; $[\alpha]_D^{14°}$ − 20° (*c*, 0·5 in MeOH). (Found: C, 66·22; H, 6·92; N, 4·92. $C_{16}H_{19}NO_4$ requires: C, 66·42; H, 6·62; N, 4·84%). It was identical with (−)-**3d** (prepared by methylation of natural ribalinidine, see above) according to mixed m.p., optical rotations and IR (Nujol) spectra.

Similarly, the hydrolysis of the racemic-**7c** led to (±)-O^7-methylribalinidine, m.p. 235–236° (dec), 76% yield. (Found: C, 66·37; H, 6·54; N, 4·92. $C_{16}H_{19}NO_4$ requires: C, 66·42; H, 6·62; N, 4·84%). The IR ($CHBr_3$), UV (neutral and 0·3 N HCl) and NMR (trifluoracetic acid) spectra were coincident with those of the (−)-**3d** from (−)-**3c**.

(±) *and* (+)-*Ribaline* (**2b**) *and* (±)-*ribalinidine* (**3c**) *from ribalinium* (**4b**)

(a) A soln of (+)-**4b**[4] (0·003 mole) in anhyd pyridine (55 ml) was heated at 115° during 12 hr. In another experiment run at 80° **4b** was partially dissolved and it reacted incompletely.

The mixture was evaporated and the residue chromatographed through a column of cellulose powder (100 g; Whatman CF 11) using methyl ethyl ketone sat with H_2O plus 5% MeOH. The eluates with R_F 0·75 were combined (0·85 g), dissolved in alcohol (25 ml) and mixed with picric acid (1·3 g) in alcohol (5 ml). The crude picrate was worked up as detailed above under the isolation of natural (±) and (+)-**2b**.

The (±)-ribaline picrate (18% yield) gave constant m.p. 223–224° (dec). (Found: C, 50·12; H, 4·25; N, 11·43. $C_{15}H_{17}NO_4 \cdot C_6H_3N_3O_7$ requires: C, 50·00; H, 4·00; N, 11·11%). It was identical (mixture m.p. and IR in KBr) with the picrate of natural (±)-**2b**. The picrate (114 mg) was converted into the free base (±)-ribaline (36 mg), m.p. 259–260° (dec); optically inactive between 700–350 nm (c, 0·27 in MeOH); M^+ at *m/e* 275·1157 ($C_{15}H_{17}NO_4$ requires: mol. wt. 275·1158). Mixture m.p. with (−)-ribalinidine (**3c**; m.p. 257–258°) showed strong depression. The identification with natural (±)-**2b** was run by paper chromatography, mixture m.p. and coincidence of the UV (neutral, basic and acid media) and IR (KBr) curves.

The free base (16 mg) in MeOH (4 ml) was treated at 0° with excess ethereal diazomethane to give (±)-**2c**, m.p. 226–227° (dec) from alcohol, that showed coincident R_F value, UV and IR (KBr) spectra with those of (+)-**2c** described earlier.[4]

The mother liquor from the first crystallization of the above crude picrate was passed through Dowex-2 chloride resin followed by crystallizations from abs EtOH to give (+)-ribaline hydrochloride; m.p. 222–223° (dec); M^+ at *m/e* 275·1162 (the free base, $C_{15}H_{17}NO_4$

requires: mol. wt. 275·1158). (Found: Cl^-, 6·23. $(C_{15}H_{17}NO_4)_2 \cdot HCl$ requires: Cl, 6·04%).

This hydrochloride was transformed into the perchlorate using $Mg(ClO_4)_2$ aq; crystallizations from H_2O gave constant m.p. 225–226° (dec); $[\alpha]_D^{26°} + 68°$ (*c*, 0·30 in alcohol). It was identical with the perchlorate of natural (+)-**2b** according to mixed m.p., ORD and IR (KBr) curves. The free base prepared from this perchlorate was crystallized from MeOH; $[\alpha]_D^{30°} + 85°$ (*c*, 0·31 in MeOH); M^+ at *m/e* 275·1143 ($C_{15}H_{17}NO_4$ requires: mol. wt. 275·1158). The identity with natural (+)-**2b** was shown by paper and TLC and coincident UV (neutral, basic and acid media), IR (KBr) and ORD curves.

(b) (±)-Ribaline prepared in (a) (59 mg), anhyd pyridine (0·3 ml) and Ac_2O (0·3 ml) were heated at 125° for 3 hr. The mixture was partitioned between $CHCl_3$ (6 ml) and H_2O (6 ml); the organic layer was washed with sat $NaHCO_3$ aq (8 × 5 ml) until alkaline reaction in the aqueous phase, dried ($MgSO_4$) and evaporated. The IR (Nujol) of the residue was identical with that of **7b**.

The crude diacetyl compound dissolved in MeOH (4 ml) and 1 N NaOH aq (2 ml) was kept at 35° during 12 hr; after removal of MeOH *in vacuo*, NH_4Cl (4 mmole) was added. Crystallization of the ppt from abs EtOH gave (±)-ribalinidine (32 mg), m.p. 256–257° (dec), showing IR (KBr) spectrum superimposable with that of natural (−)-**3c**.

Synthesis of (±)-*ribalinine* (**3b**)

4-Hydroxy-1-methyl-3-(3'-methyl-but-2'-enyl)-2-quinolone (**5**). Previous steps were performed following literature directions as such or slightly modified. Isoprene with HBr in AcOH gave 3,3-dimethylallyl bromide,[12] b.p. 57–60°/60 Torr, 70% yield; NMR (CCl_4) δ: 1·75 and 1·80 (two C—CH_3), 3·93 (d, J = 8·5 Hz, —CH_2—), 5·52 (t, J = 8·7 Hz, =CH—).

This bromide (0·15 mole) in diisopropyl ether (20 ml) was added to diethyl sodiomalonate (0·15 mole) in alcohol (80 ml) and the mixture refluxed 1 hr.[13] After filtration, the solvents were removed (60°/110 Torr), the residue diluted with CCl_4 (30 ml) and magnetically stirred twice with conc NH_3 aq (2 × 12 ml) for 1 hr.[14] The organic phase was washed with H_2O, dried and evaporated (60°/10 Torr) to give crude diethyl 3-methyl-but-2-enylmalonate; 71% yield; its NMR was identical with that of the rectified product, b.p. 126°/11 Torr, δ (CCl_4): 1·25 and 4·10 (t, 6H and q, 4H resp, two CH_3—CH_2), 1·65 and 1·68 (6H, two C—CH_3), 2·47 (t, 2H, —CH_2—), 3·13 (t, 1H, O=C—CH), 4·98 (t, 1H, =CH—).

The above crude malonate ester (0·025 mole) was dissolved in boiling Dowtherm (110 ml; previously[5] the diphenyl ether was used) and then N-methylaniline (0·02 mole) added dropwise (30 min). After refluxing 1·5 hr more, the cooled solution was diluted with hexane (50 ml) and extracted with 1 N NaOH aq (3 × 25 ml). Acidification of the aqueous phase with AcOH (ice bath) furnished a ppt (2·1 g) which was extracted with hot EtOAc (12 ml). From the extract, after heating with charcoal and concentration, crude **5** crystallised and was purified from the same solvent, constant m.p. 162–163°; 6% yield; NMR (60 MHz, $CDCl_3$) δ: 1·77 and 1·83 (two C—CH_3), 3·55 (d, J = 7·5 Hz, —CH_2—), 3·73 (s, N—CH_3), 5·38 (t, J = 7·5 Hz, =CH), 7·40 (m, 6—, 7— and 8—CH), 8·05 (splitted d, J = 8 Hz, 5—CH); M^+ at *m/e* 243·1259 ($C_{15}H_{17}NO_2$ requires: mol. wt. 243·1259).

After our preliminary communication,[5] other authors[15] used the same reaction to prepare **5** giving a very different m.p. (216°), but no further characterization data. More recently[16] **5** was obtained with m.p. 156–159° applying another reaction.

2-(1'-Hydroxy-1'-methyl-ethyl)-9-methyl-4-oxo-2,3,4,9-tetrahydro-furo [2, 3-b] *quinoline* (**6**).[6] A solution of **5** (2 mmole) and peroxylauric acid (70% purity; 2·3 mmole) in $CHCl_3$ (8 ml) was left 3 days at room temp; extractions with 2 N HCl aq (6 × 15 ml) were basified (Na_2CO_3) and extracted with $CHCl_3$ (6 × 25 ml); the latter, washed with H_2O and dried, was evaporated and the residue crystallized from MeOH-diisopropyl ether giving **6**, constant m.p. 208–210° (dec); 47% yield; NMR (60 MHz, 20°, Me_2SO-d_6) δ: 1·15 and 1·24 (two C—CH_3), 3·02 (d, J = 8 Hz, —CH_2—), 3·70 (s, N—CH_3), 4·83 (t, J = 8 Hz, 2—CH), 7·50 (m, 6—, 7— and 8—CH), 8·15 (splitted d, J = 8 Hz, 5—CH); M^+ at *m/e* 259 ($C_{15}H_{17}NO_3$ requires: mol. wt. 259).

(±)-*Ribalinine* (**3b**). Compound **6** (0·14 mmole) in pyridine (0·25 ml) and Ac_2O (0·75 ml) were heated protecting from humidity 3 hr at 125° and the soln was evaporated *in vacuo*. The residue was dissolved in $CHCl_3$ (6 ml), the latter washed with sat $NaHCO_3$ aq and dried. Removal of the solvent gave the crude (±)-ribalinine acetate (oily, 35 mg) with ester band (Nujol) at 1750 cm^{-1}; it was saponified keeping its solution in 0·25 N NaOH (14 ml) in MeOH—H_2O (1 : 1) during 2 days at ambient temp.

After removal of the MeOH (without heating) the mixture was extracted with CH_2Cl_2 (10 × 5 ml); the dried extract was evaporated and the residue crystallized from abs EtOH to give (±)-ribalinine (yield 53%), constant m.p. 233–234° (dec); M^+ at *m/e* 259·1213 ($C_{15}H_{17}NO_3$ requires: mol. wt. 259·1208.

The identity of this compound with natural (±)-**3b** was proved by mixed m.p. and coincidence of the UV (neutral and acid media) and IR (KBr) absorptions.

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