SYNTHESIS OF MELINEURINE AND EVELLERINE

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ABSTRACT.—Melineurine (**2**) was synthetized by condensation of 7-hydroxy-4-methoxyfuro|2,3b|quinoline (**1**) with 1-bromo-3-methyl-2 butene. Epoxidation of **2** by mCPBA followed by acidic hydrolysis gave evellerine **4**.

Three alkaloids with a 7-prenyloxy-4-methoxyfuro|2,3b|quinoline skeleton are known natural compounds: the olefin melineurine (**2**) recently isolated from *Melicope lasioneura* (Baill.) Guillaumin (1); the corresponding epoxide **3** isolated from *Evodia zanthoxyloides* F. Muell. (2); and the diol evellerine (**4**) obtained from *Evodia elleryana* F. Muell. (3). In a continuation of our studies on the rutaceous alkaloids, we now wish to report here their first synthesis.

RESULTS AND DISCUSSION

Condensation of 7-hydroxy-4 methoxyfuro|2,3b|quinoline (**1**) (1, 3, 4, 5) with 1-bromo-3-methyl-2-butene (6) yielded a mixture of three products easily separated by column chromatography: melineurine (**2**), identical with the natural product (1); 7-(3-methyl-2-buten-1-oxy)-8-(3-methyl-2-butenyl)-4-methoxyfuro|2,3b|quinoline (**5**); and 7-(3-methyl-2-buten-1-oxy)-1-(3-methyl-2-butenyl)-furo|2,3b|-4-quinolone (**6**). An optimal yield of melineurine was obtained when the reaction was carried out at room temperature for 2 hours with an excess of alkylating reagent. A longer reaction time and/or an increase of the temperature led only to the formation of compounds **5** and **6**.

Epoxidation of melineurine (**2**) with *m*-chloroperbenzoic acid in dichloromethane gave the epoxide **3** in 95% yield. Subsequent acidic hydrolysis of **3** (2) yielded the corresponding diol, evellerine (**4**).

EXPERIMENTAL[1]

CONDENSATION OF 7-HYDROXY-4-METHOXYFURO|2,3b|QUINOLINE **1** WITH 1-BROMO-3-METHYL-2-BUTENE: COMPOUNDS **2**, **5** AND **6**.—To a solution of **1** (0.86 g) in dry acetone (15 ml) containing potassium carbonate (2 g) and potassium iodide (2 g) was added 1-bromo-3-methyl-2-butene (2 ml). The reaction mixture was stirred at rt (20°) for 30 minutes. The saline precipitate was then filtered off and the acetone solution evaporated. Column chromatography of the residue (silica gel, eluent: chloroform) gave, successively, **5** (0.32 g, yield: 23%), melineurine (**2**) (0.46 g, yield: 41%), and **6** (0.19 g, yield: 14%).

5: mp: 118–119°; uv: λ EtOH max nm: 252, 307(sh), 319, 332, 345; ir (KBr): ν max cm^{-1}: 2980, 2915, 2860, 1630, 1610, 1585, 1365, 1260, 1095, 995, 985, 790, 735; ms: *m/z* (%): 351(M^+)(20), 283(16), 282(64), 268(15), 266(6), 252(28), 240(100), 228(20), 225(8), 186(7); nmr (80 MHz, $CDCl_3$, TMS): δ=7.97 (1H, d, *J*=9Hz, H-5); 7.40 (1H, d, *J*=3Hz, H-α), 7.08 (1H, d, *J*=9Hz, H-6), 6.86 (1H, d, *J*=3Hz, H-β), 5.41 (2H, m, 2C*H*=CMe_2), 4.63 (2H, d, *J*=7Hz, O-CH_2-CH=CMe_2), 4.29 (3H, s, O-Me), 3.96 (2H, d, *J*=7Hz, Ar-CH_2-CH=CMe_2), 1.89, 177, 1.75 and 1.65 (4 x 3H, 4s, 2CMe_2).

2: mp: 99–100° identical with the natural product (1) (tlc, mp, mmp, uv, ir, ms, nmr).

6: mp: 148–149°; uv: λ EtOH max nm: 230, 255(sh), 263, 291(sh), 307(sh), 324; ir (KBr): ν max cm^{-1}: 3150, 3100, 2970, 2930, 2910, 1630, 1615, 1595, 1535, 1510, 1485, 1275, 1250, 1210, 1190, 1005, 975, 840, 815, 780, 745, 700; ms: *m/z* (%): 337(M^+)(13), 269(2), 202(13), 201(100), 172(4); nmr (80 MHz, $CDCl_3$, TMS): δ=8.36 (1H, d, *J*=9Hz, H-5), 7.14 (1H, d, *J*=3Hz, H-α), 6.93 (1H, d, *J*=3Hz, H-β), 6.84 (1H, dd, *J*=9Hz, *J'*=2Hz, H-6), 6.74 (1H, d, *J*=2Hz, H-8), 5.45 (1H, t, *J*=7Hz, O-CH_2-C*H*-CMe_2), 5.19 (1H, t, *J*=7Hz, N-CH_2-C*H*=CMe_2), 4.82 (2H, d, *J*=7Hz, N-CH_2-CH=CMe_2), 4.55 (2H, d, *J*=7Hz, O-CH_2-CH=CMe_2), 1.89, 1.77, 1.75 and 1.74 (4 x 3H, 4s, 2CMe_2).

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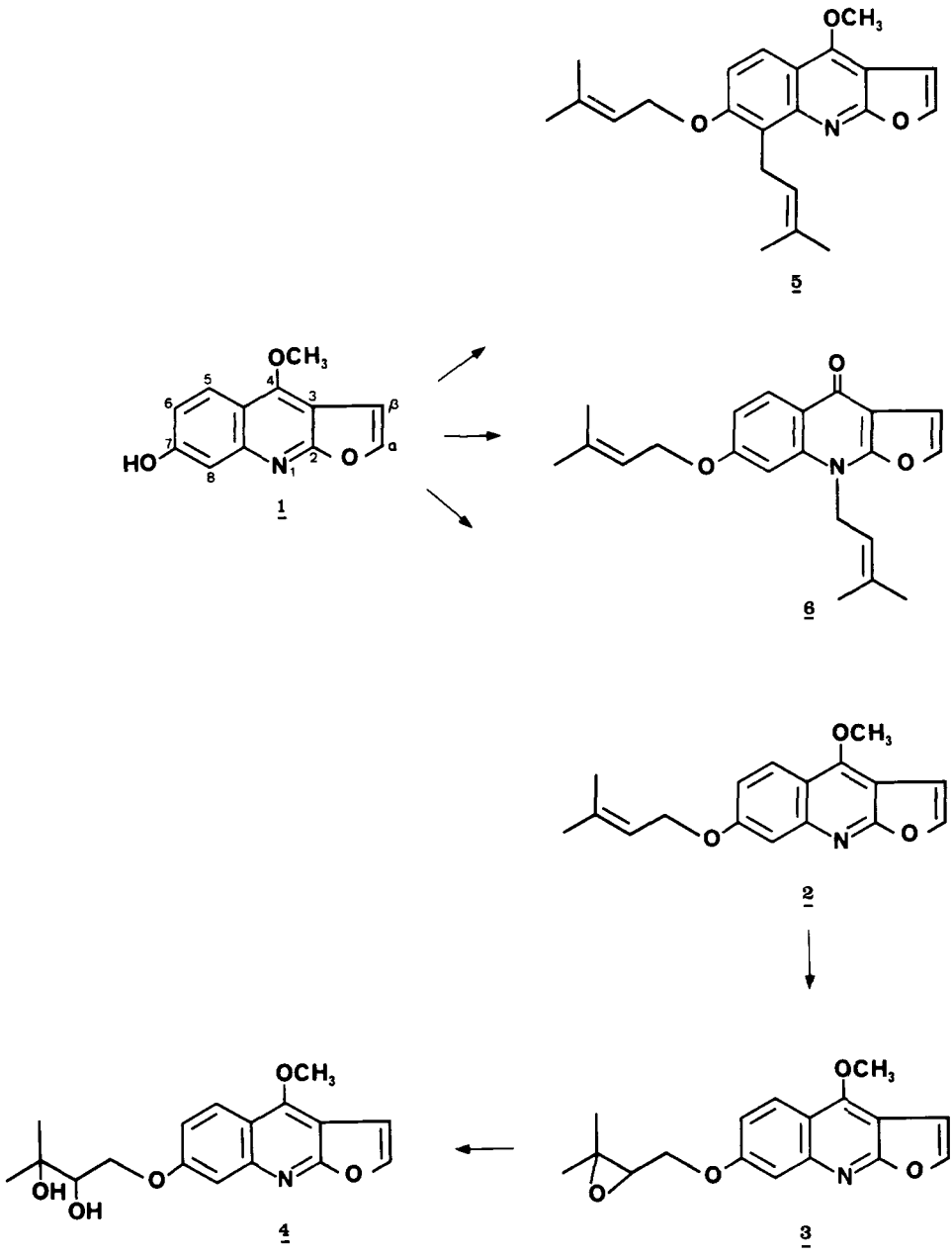
[1]Proton nmr spectra were recorded on a Bruker WP 80 spectrometer. Mass spectra were run on a VG Micromass 70 70 F instrument. Ir spectra were obtained on a Beckman 4250 and uv spectra on an Unicam SP 800 spectrophotometer. Melting points were measured with a Reichert microscope and are uncorrected.



EPOXIDATION OF **2**: EPOXIDE **3**.—A solution of **2** (0.12 g) and m-CPBA (0.30 g) in dichloromethane (4 ml) was stirred at rt (20°) for 24 hours. The reaction mixture was then washed with 5% aqueous sodium bicarbonate, and the dichloromethane was evaporated. Column chromatography of the obtained residue (silica gel, eluent: toluene-ethyl acetate 8:2) gave **3** (0.12 g, yield: 95%).

3: mp: 146–147°; uv and nmr data identical with those described in ref. (2); ir (KBr): ν max cm^{-1}: 2970, 2930, 1625, 1590, 1450, 1430, 1370, 1245, 1170, 1090, 1035, 965, 865, 745, 715; ms: *m/z* (%): 300(12), 299(M^+)(59), 240(3), 228(15), 216(23), 215(100), 200(24), 186(5), 172(8).

ACIDIC HYDROLYSIS OF **3**: EVELLERINE (**4**).—A solution of **3** (0.10 g) in 10% aqueous oxalic acid (10 ml) was refluxed for 30 minutes. After cooling, the reaction mixture was alkalized and extracted with ethyl acetate. Evellerine (**4**) crystallized from the ethyl acetate extract upon concentration (0.08 g, yield: 76%).

4: mp: 153–154°; uv and ms data identical with those published in ref. (3); ir (KBr): ν max cm^{-1}: 3400, 2970, 1630, 1585, 1455, 1375, 1270, 1180, 1095, 995, 880, 775, 745, 715; nmr (80 MHz, $CDCl_3$, TMS): δ=8.04 (1H, d, J=9Hz, H-5), 7.54 (1H, d, 7=3Hz, H-α), 7.29 (1H, d, J=2Hz,

H-8), 7.02 (1H, dd, J=9Hz, J'=2Hz, H-6), 6.95 (1H, d, J=3Hz, H-β), 4.36 (3H, s, O-Me), 4.35-3.90 (3H, m, $CHOH$-CH_2-OH), 3.33 (2H, broad s, D_2O exch., 2OH), 1.36 and 1.34 (2 x 3H, 2s, CMe_2).

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