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The Syntheses of Acronycidine and 4,5,8-Trimethoxyfuro[2,3-*b*]quinoline

Tetsuya Sekiba

Faculty of Chemical Engineering, Toyama Technical College, Hongo, Toyama 930

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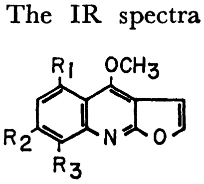
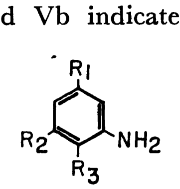
Synopsis. 2,3-Dihydroacronycidine (VIa) was obtained from 2,3,5-trimethoxyaniline by condensation with diethyl *β*-benzyloxyethylmalonate, methylation, debenzylation, and then cyclodehydration. The dehydrogenation of VIa gave acronycidine in relatively high yields.

Acronycidine was isolated from the bark of both *Acronychia baueri*[1] and *Melicope fareana*.[2] Its structure was proposed to be 4,5,7,8-tetramethoxyfuro[2,3-*b*]quinoline (Ia) on the basis of spectral and degradative studies.[3] 4,5,8-Trimethoxyfuro[2,3-*b*]quinoline (Ib) has not yet been found in any natural source, but it is considered useful to synthesize this substance, which may be expected to occur in nature. Govindachari and his co-workers[4] attempted, without success, to synthesize the 2,3-dihydro-derivative of Ia according to the method of Ohta and Mori.[5] They obtained it, therefore, by another route,[6] but never attempted to synthesize Ia. A previous paper[7] reported the successful dehydrogenation of 2,3-dihydrofuroquinoline in dry benzene into furoquinoline with DDQ (2,3-dichloro-5,6-dicyanobenzoquinone).

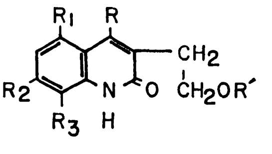
The present paper will describe convenient syntheses of Ia and Ib from 2,3,5-trimethoxyaniline (IIa)[8] and 2,5-dimethoxyaniline (IIb) by a modification of a method previously reported[7] according to Ohta and Mori's method. By careful heating under reduced pressure, the condensation of IIa and IIb and diethyl *β*-benzyloxyethylmalonate without any solvent gave the 4-hydroxy-2-quinolone derivatives (IIIa, b), which were then easily methylated with diazomethane into 4-methoxy compounds (IVa, b). Although the attempted cyclodebenzylation of IVa and IVb with PPA was unsuccessful, the debenzylation of IVa and IVb with hydrogen in the presence of 5% Pd–C gave 3-(*β*-hydroxyethyl)-4-methoxy-2-quinolone derivatives (Va, b). The IR spectra of Va and Vb indicated the presence of a hydroxyl group (*ca.* 3440 cm^{-1}), while the NMR spectra of Va and Vb indicated the absence of the methylene protons and the phenyl protons of the benzyl group, which were present in the spectra of IVa and IVb, and exhibited a signal for one proton (*δ ca.* 3.63 bs ppm) of the hydroxyl group which easily disappeared upon deuterium exchange. The cyclodehydration of Va and Vb with PPE (polyphosphate ester) yielded 2,3-dihydrofuro[2,3-*b*]quinoline derivatives (VIa, b). The structures of VIa and VIb were assigned on the basis of the NMR spectra, which showed signals at *δ ca.* 3.42 t and 4.58 t attributable to two methylene protons of a dihydrofuran-ring system. The dehydrogenation of VIa and VIb by the DDQ method gave furo[2,3-*b*]quinoline derivatives (Ia; acronycidine[1] and Ib; 4,5,8-trimethoxyfuro[2,3-*b*]quinoline). The synthetic acronycidine (Ia) was shown to be identical with a natural specimen by a mixed-melting-point determination and by a comparison of their IR, UV, and NMR spectra* (Table 1).

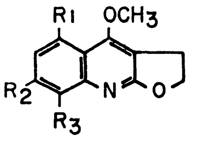


I



II





VI

III, R = OH, R′ = $CH_2C_6H_5$

IV, R = OCH_3, R′ = $CH_2C_6H_5$

V, R = OCH_3, R′ = H

a), $R_1 = R_2 = R_3 = OCH_3$ b), $R_1 = R_3 = OCH_3$, $R_2 = H$

Experimental

3-(2-Benzyloxyethyl)-4-hydroxy-2-quinolones (IIIa,b). A mixture of IIa (4.5 g) or IIb (3.7 g) and diethyl *β*-benzyloxyethylmalonate (7.4 g) was heated under reduced pressure (*ca.* 70 mmHg). The temperature was then raised to 180 °C over a period of 30 min, maintained at that temperature for further 30 min, and then raised and kept at 250 °C for 30 min. The cooled reaction mixture was then dissolved in chloroform. The chloroform solution was treated in a way similar to that used in a previous paper.[7] IIIa: Mp 160—161 °C (colorless needles from ethanol) (yield, 65%). IR (cm^{-1}, Nujol): 3360, 1655. UV: λ_{max}^{EtOH} nm(log ε); 220 (4.80), 238(sh) (4.63), 256 (4.50), 265 (4.50), 311.5 (4.34), 326.5 (4.24). NMR ($CDCl_3$): δ 3.97, 4.01, 4.03 (each 3H, s, $-OC\underline{H}_3$), 3.01, 3.78 (each 2H, t, J=7.0 Hz, $-C\underline{H}_2$), 4.36 (2H, s, $Ph-C\underline{H}_2$), 6.93 (1H, s, $Ar-\underline{H}$), 9.04 (1H, s, $-O\underline{H}$), 9.48 (1H, s, $-N\underline{H}$). Found: C, 65.55; H, 5.97; N, 3.64%. Calcd for $C_{21}H_{23}O_6N$: C, 65.44; H, 6.02; N, 3.63%. IIIb: Mp 138.5—140.5 °C (pale yellow cubes from ethyl acetate) (yield, 40%). IR (cm^{-1}, Nujol): 3220, 1635. UV: λ_{max}^{EtOH} nm(log ε); 210 (4.50), 224 (sh) (4.26), 244 (4.25), 253 (4.31), 262 (4.34), 292 (3.99), 304 (3.94). NMR ($CDCl_3$): δ 3.88, 3.96 (each 3H, s, $-OC\underline{H}_3$), 3.00, 3.71 (each 2H, t, J=7.2 Hz, $-C\underline{H}_2$), 4.56 (2H, s, $Ph-C\underline{H}_2$), 6.25, 6.79 (2H, ABq, J=8.4 Hz, $Ar-\underline{H}$), 9.00 (1H, bs, $-O\underline{H}$), 9.55 (1H, bs, $-N\underline{H}$). Found: C, 67.58; H, 5.94; N, 3.86%. Calcd for $C_{20}H_{21}O_5N$: C, 67.59; H, 5.96; N, 3.94%.

3-(2-Benzyloxyethyl)-4-methoxy-2-quinolones (IVa,b). Diazomethane method: IVa: Mp 135—137 °C (pale yellow plates from ethanol) (yield, 96%). IR (cm^{-1}, Nujol): 1635. UV: λ_{max}^{EtOH} nm(log ε); 212.5 (4.62), 236.5 (4.29), 257.5 (4.34), 265.5 (4.42), 316 (4.19), 325(sh) (4.08). NMR ($CDCl_3$):

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* The UV, IR, NMR spectra, and mp of natural acronycidine were measured in this laboratory.

Table 1. Furo[2,3-*b*]quinolines (Ia,b)

Compound	Mp (°C)	Cryst. form	IR ($\mathrm{cm^{-1}}$) Nujol	Yield (%)	Formula	Analysis (%) Found C H N	Analysis (%) Calcd C H N	UV $\lambda_{\max}^{\mathrm{EtOH}}$	UV nm(log ε)
Ia (Synthetic)	136.5—138.5	Colorless[a] prisms	1620 1505	55	$C_{15}H_{15}O_5N$	62.23 5.18 4.89	62.28 5.23 4.84	256 (4.88)	346 (3.96)
Ia (Natural)	136—137.5		1620 1505					256 (4.88)	346 (3.96)
Ib	110—111.5	Colorless[b] plates	1615 1505	65	$C_{14}H_{13}O_4N$	64.61 4.89 5.46	64.86 5.05 5.40	231 (4.43) 254 (4.61) 277_{sh} (3.81)	311.5_{sh} (3.57) 325_{sh} (3.72) 350 (3.83)

a) from ethanol b) from petroleum benzine.

δ 3.84 (3H, s, $-OC\underline{H}_3$). Found: C, 66.35; H, 6.41; N, 3.45%. Calcd for $C_{22}H_{25}O_6N$: C, 66.15; H, 6.31; N, 3.51%. IVb: Mp 156.5—158.5 °C (colorless plates from ethanol) (yield, 50% (IIIb; 50% recover)). IR ($\mathrm{cm^{-1}}$, Nujol): 1640. UV: $\lambda_{\max}^{\mathrm{EtOH}}$ nm(log ε); 209 (4.70), 244 (4.20), 262(sh) (4.39), 269 (4.40), 300 (4.09), 310 (3.98). NMR ($CDCl_3$): δ 3.78 (3H, s, $-OC\underline{H}_3$). Found: C, 68.06; H, 6.20; N, 3.73%. Calcd for $C_{21}H_{23}O_5N$: C, 68.28; H, 6.28; N, 3.79%.

3-(2-Hydroxyethyl)-4-methoxy-2-quinolones (Va,b). To a hydrogen-saturated solution of Pd-C (5%, 2.0 g) in absolute ethanol, IVa or IVb (5.0 g) was added; the mixture was then stirred for 4 hr at *ca.* 70 °C in an atmosphere of hydrogen. After the catalyst had been filtered off, the filtrate was evaporated under a vacuum. The residue was recrystallized to give Va or Vb. Va: Mp 153—155 °C (colorless prisms from benzene) (yield, 98%). IR ($\mathrm{cm^{-1}}$): 3440, 1610. UV: $\lambda_{\max}^{\mathrm{EtOH}}$ nm(log ε); 217 (4.73), 238(sh) (4.50), 257.5(sh) (4.54), 265.5 (4.60), 316 (4.38), 329.5 (4.29). NMR ($CDCl_3$): δ 3.63 (1H, bs, $-O\underline{H}$). Found: C, 57.98; H, 5.99; N, 4.55%. Calcd for $C_{15}H_{19}O_6N$: C, 58.24; H, 6.19; N, 4.53%. Vb: Mp 157—158.5 °C (colorless needles from ethanol) (yield, 77%). IR ($\mathrm{cm^{-1}}$, Nujol): 3320, 1620. UV: $\lambda_{\max}^{\mathrm{EtOH}}$ nm(log ε); 209 (4.44), 242 (4.12), 265 (4.32), 299 (3.97), 310(sh) (3.89), 338(sh) (3.24). NMR ($CDCl_3$): δ 3.30 (1H, bs, $-O\underline{H}$). Found: C, 58.98; H, 6.20; N, 4.92%. Calcd for $C_{14}H_{17}O_5N$: C, 60.20; H, 6.14; N, 5.02%.

*2,3-Dihydrofuro[2,3-*b*]quinolines (VIa,b).* A mixture of Va or Vb (1.0 g) and PPE (15 g) was heated at 120—130 °C for 2 hr. The cooled mixture was then poured into water, and the insoluble materials were filtered off. The aqueous solution was neutralized with diluted aqueous ammonia. The precipitate was collected, washed with water, and recrystallized to give VIa or VIb. VIa: Mp 191—192 °C (lit,[3] 188.5—190.5 °C) (colorless plates from ethanol) (yield, 70%). IR ($\mathrm{cm^{-1}}$, Nujol): 1620, 1505. UV: $\lambda_{\max}^{\mathrm{EtOH}}$ nm(log ε); 218.5 (4.56), 258.5 (4.70), 308.5 (3.84), 325(sh) (3.74). NMR ($CDCl_3$): δ 3.88, 3.90, 3.93, 3.96 (each 3H, s, $-OC\underline{H}_3$), 4.58, 3.42 (each 2H, t, J=7.8 Hz, α,β-$C\underline{H}_2$), 6.47 (1H, s, Ar-$\underline{H}$). Found: C, 61.79; H, 5.83; N, 4.89%. Calcd for $C_{15}H_{17}O_5N$: C, 61.85; H, 5.88; N, 4.81%. VIb: Mp 149.5—151.5 °C (colorless needles from ethanol) (yield, 78%). IR ($\mathrm{cm^{-1}}$, Nujol): 1620, 1505. UV: $\lambda_{\max}^{\mathrm{EtOH}}$ nm(log ε); 213 (4.46), 259 (4.46), 295 (3.66), 337(sh) (3.50). NMR ($CDCl_3$): δ 3.86, 3.94, 3.98 (each 3H, s, $-OC\underline{H}_3$), 4.63, 3.47 (each 2H, t, J=7.8 Hz, α,β-$C\underline{H}_2$), 6.65, 6.85 (each 1H, ABq, J=7.8 Hz, Ar-$\underline{H}$). Found: C, 64.62; H, 5.81; N, 5.34%. Calcd for $C_{14}H_{15}O_4N$: C, 64.36; H, 5.79; N, 5.36%.

*Furo[2,3-*b*]quinolines (Ia,b).* A mixture of VIa or VIb (1.0 g) and DDQ (1.0 g) in dry benzene (150 ml) was treated by a method similar to that used in a previous paper.[7] The resulting precipitate was collected and recrystallized to give Ia or Ib (Table 1). The mixed melting point of synthetic Ia with a natural specimen was not depressed. Ia: NMR ($CDCl_3$): δ 3.96, 4.02, 4.31 (3H×4, s, $-OC\underline{H}_3$), 6.60 (1H, s, Ar-$\underline{H}$), 7.00, 7.53 (each 1H, d, J=3.0 Hz, Furan-$\underline{H}$). Ib: NMR ($CDCl_3$): δ 3.88, 4.00, 4.28 (each 3H, s, $-OC\underline{H}_3$), 6.70, 6.92 (each 1H, ABq, J=8.4 Hz, Ar-$\underline{H}$), 7.02, 7.60 (each 1H, d, J=2.4 Hz, Furan-$\underline{H}$).

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References

1) F. N. Lahey and W. C. Thomas, *Aust. J. Sci. Res.*, **A2**, 423 (1949).

2) J. R. Price, *ibid.*, **A2**, 249 (1949).

3) F. N. Lahey, J. A. Lamberton, and J. R. Price, *ibid.*, **3A**, 155 (1950).

4) T. R. Govindachari, B. R. Pay, S. Prabhakar, P. S. Santhanam, and V. Sudarsanam, *Indian J. Chem.*, **3**, 71 (1965).

5) T. Ohta and Y. Mori, *Tokyo Yakka Daigaku Kenkyu Nempo*, **10**, 100 (1960); *Chem. Abstr.*, **56**, 4806 (1962).

6) M. F. Grundon and N. J. McCorkindale, *J. Chem. Soc.*, **1957**, 2177.

7) T. Sekiba, This Bulletin, **46**, 577 (1973).

8) H. Richtzenhain and R. Nippus, *Chem. Ber.* **82**, 408 (1949).