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NATURAL PRODUCT CHEMISTRY, 125.[1] SYNTHESIS OF QUINAZOLINONES RELATED TO THE STRUCTURE PROPOSED FOR ECHINOZOLINONE

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ABSTRACT.—Synthesis of 3-(2-hydroxyethyl)-4(3*H*)-quinazolinone established that the structure of echinozolinone for which this structure has been proposed, has to be revised. Synthesis of 1-(2-hydroxyethyl)-4(1*H*)-quinazolinone exclude the possibility of this structure for echinozolinone.

The quinazolinone alkaloids form a small but important group of naturally occurring bases which have been isolated from a number of different plant families (1,2). Compounds belonging to the class of 4(3*H*)-quinazolinones show an array of biological effects such as antimalarial, hypnotic, anticonvulsant (2), and broncho-dilatory activities (2–4). Although synthetic 3-(2-hydroxyethyl)-4(3*H*)-quinazolinone [**1**] has been known for several decades (5), we were prompted to synthesize it again by the claim that it has been isolated from *Echinops echinatus* (Compositae) as a naturally occurring alkaloid (echinozolinone) for the first time (6).

Because 4(3*H*)-quinazolinones that are not substituted at their 1 or 3 positions react with alkyl halides under basic conditions to give 3-alkyl-4(3*H*)-quinazolinones (2,7), we prepared 3-(2-hydroxyethyl)-4(3*H*)-quinazolinone [**1**] by the treatment of 4(3*H*)-quinazolinone [**3**] with 2-chloroethanol in toluene and aqueous NaOH in the presence of a phase transfer catalyst at 50°. The spectral characteristics of this synthetic quinazolinone **1**, mp 151–152°, were inconsistent with those reported for echinozolinone (6).

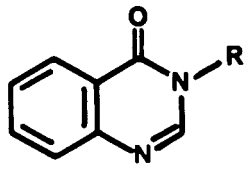
Echinozolinone, thus, is not 3-(2-hydroxyethyl)-4(3*H*)-quinazolinone [**1**], and its structure requires revision. With a view to proposing an alternative structure for this quinazolinone, the synthesis of the hitherto unknown 1-(2-hydroxyethyl)-4(1*H*)-quinazolinone [**2**] was carried out starting with *o*-chlorobenzamide and ethanolamine. The anthranilamide derivative **4**, which was prepared by Ullmann condensation (8) of the above two compounds, was *O*-acetylated and treated with triethylortho formate/Ac_2O (9) to produce the 4(1*H*)-quinazolinone derivative **6**. Deacetylation of the acetate **6** with NaOMe yielded the desired 1-(2-hydroxyethyl)-4(1*H*)-quinazolinone [**2**] (Scheme 1). This product, mp 220–222°, also differed in its spectral properties from those reported for echinozolinone (6).

Because the aromatic region of the ^{1}H nmr of echinozolinone does not show the expected pattern for a quinazolinone system (10) and the signal at δ 3.20, which has been assigned to the CH_2OH group, is unlikely to be due to this group (see Table 1), the alkaloid may not be a quinazolinone. However, the nonavailability of authentic material discouraged us from carrying out further experiments.

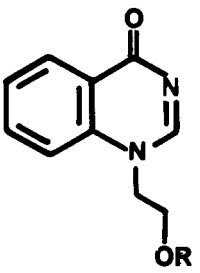
EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Ir spectra were determined on a Pye-Unicam SP 3-200 spectrometer in KBr pellets. ^{1}H-nmr spectra were recorded at 60 MHz and 300 MHz with TMS as internal reference, on Varian 60 A or Bruker WM 300 spectrometer. Mass spectra were obtained on a Varian MAT 44 S instrument at 70

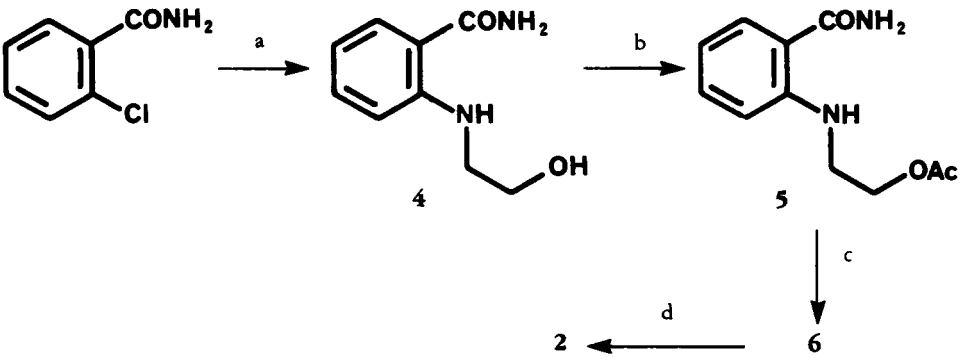
[1]For Part 124, see J. Reisch and G.M.K.B. Gunaherath, *J. Chem. Soc.*, in press.



1 R = CH_2CH_2OH
3 R = H



2 R = H
6 R = Ac



SCHEME 1. Reagents and conditions: (a) $HOCH_2CH_2NH_2$/anhydrous K_2CO_3/Cu/NaI/anhydrous DMF/70°/4 h; (b) Ac_2O/pyridine/room temperature/1 h; (c) $CH(OEt)_3/Ac_2O$/reflux/1.5 h; (d) NaOMe/MeOH/room temperature/1 h.

eV. Si gel 60 F_{254} (pre-coated aluminium sheets; 0.2 mm thickness; Merck 5549) were used for analytical tlc while for preparative work Si gel 60 F_{254} [pre-coated glass plates, 2 mm thickness (Merck 5717) and 0.25 mm thickness (Merck 5715)] were employed. Light petroleum ether had bp 30–40°.

SYNTHESIS OF 3-(2-HYDROXYETHYL)-4(3*H*)-QUINAZOLINONE [**1**].—An aqueous solution of 1 M NaOH (80 ml), 2-chloroethanol (8.0 g), tetrabutylammonium chloride (1.1 g), and a catalytic amount of KI were added to suspension of 4(3*H*)-quinazolinone [**3**] (5.84 g) in toluene (150 ml) and stirred at 50° for 22 h. The reaction mixture was allowed to cool in the refrigerator, and the product formed as colorless needles in the interphase while cooling was collected, washed with H_2O, and dried. This constituted essentially pure 3-(2-hydroxyethyl)-4(3*H*)-quinazolinone [**1**] (3.7 g, 49%): mp 150–152° [lit. (5) 152–153°]; found $[M]^+$ 190.074049, $C_{10}H_{10}N_2O_2$ requires $[M]^+$ 190.074228; ν max 3280, 2940, 2880, 1670, 1620, 1570, 1480, 1450, 1385, 1360, 1350, 1320, 1290, 1255, 1185, 1150, 1110, 1090, 1050, 925, 870, 855, 780, 765, 700 cm^{-1}; ^1H nmr see Table 1; *m/z* (rel. int.) $[M]^+$ 190 (24), 171 (6), 159 (14), 147 (100), 130 (38), 118 (12), 102 (14), 90 (9), 77 (18), 63 (5).

SYNTHESIS OF *N*-(2-HYDROXYETHYL)ANTHRANILAMIDE [**4**].—*o*-Chlorobenzamide (2.0 g) was dissolved in 2-aminoethanol (10 ml), and anhydrous K_2CO_3 (2.0 g), NaI (0.05 g),and Cu powder (0.25 g) were added and heated at 70° for 4 h. The reaction mixture was then filtered; solids were washed with MeOH and evaporated to obtain a viscous liquid, which was subsequently treated with dilute HCl and extracted with EtOAc. The aqueous layer was neutralized with dilute NH_4OH and extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_2, and evaporated to dryness to yield a light brown solid (0.619 g). This was chromatographed over Si gel (eluent CH_2Cl_2 and 2% MeOH in CH_2Cl_2) to yield compound **4**, which on crystallization with $CHCl_3$/light petroleum ether gave colorless needles (0.20 g, 8.6%): mp 115–116°; found C 60.01, H 6.64, N 15.54; $C_9H_{12}N_2O_2$ requires C 59.97, H 6.71, N 15.55%; ν max 3365, 3200, 2960, 2860, 1660, 1615, 1575, 1510, 1455, 1410, 1330, 1300, 1280, 1220, 1165, 1110, 1060, 930, 910, 755, 700, 630 cm^{-1}; ^1H nmr δ (60 MHz, CD_3COCD_3) 8.23–7.66 (1H, brs, OH), 7.48 (1H, dd, J = 8 and 2 Hz, H-6), 7.26 (1H, ddd, J = 9.7 and 2 Hz, H-4), 6.71–6.38 (2H, m, H-3 and H-5), 3.83 (2H, t, J = 6 Hz, -CH_2OH),

TABLE 1. ^{1}H-nmr Data (δ; CD_3OD; 300 MHz) of Echinozolinone, 3-(2-Hydroxyethyl)-4(3*H*)-quinazolinone [**1**], and 1-(2-Hydroxyethyl)-4(1*H*)-quinazolinone [**2**].

Compound	Proton						
	H-2	H-5	H-6	H-7	H-8	-NCH_2	-CH_2OH
Echinozolinone[a] . . .	8.80 s	8.00 d (J = 9 Hz)		7.65–7.40 m		4.12 t (J = 6 Hz)	3.20 t (J = 6 Hz)
1	8.26 s	8.25 dd (J = 8.0 and 1.7 Hz)	7.56 ddd (J = 8.0, 7.3 and 1.0 Hz)	7.83 ddd (J = 8.3, 7.3, and 1.7 Hz)	7.69 dd (J = 8.3 and 1.0 Hz)	4.16 t (J = 5 Hz)	3.85 t (J = 5 Hz)
2	8.45 s	8.26 dd (J = 7.9 and 1.7 Hz)	7.58 ddd (J = 7.9, 7.0 and 0.9 Hz)	7.88 ddd (J = 8.7, 7.0 and 1.7 Hz)	7.74 brd (J = 8.4 Hz)	4.41 t (J = 5 Hz)	3.89 t (J = 5 Hz)

[a]Data recorded at 100 MHz in CD_3OD provided by Dr. P.K. Chaudhuri (6).

3.33 (2H, br t, $J = 6$ Hz, NCH_2); *m/z* (rel. int.) $[M]^+$ 180 (8), 162 (6), 149 (32), 132 (100), 118 (5), 105 (12), 92 (6), 77 (35); found $[M]^+$ 180.089872, $C_9H_{12}N_2O_2$ requires $[M]^+$ 180.089109; *m/z* 132.044152 (100%), C_8H_6NO requires 132.044939.

ACETYLATION OF COMPOUND **4**.—Compound **4** (0.100 g) was dissolved in pyridine (2 ml); Ac_2O (0.5 ml) was added and stirred at room temperature for 1 h. The crystalline solid obtained after evaporation of the solvents under reduced pressure was recrystallized with CH_2Cl_2/light petroleum ether to yield *N*-(2-acetoxyethyl)anthranilamide [**5**] as colorless needles, (0.110 g, 90%): mp 133–135°; found $[M]^+$ 222.100496, $C_{11}H_{14}N_2O_3$ requires $[M]^+$ 222.100435; ν max 3480, 3200, 2960, 1720, 1650, 1620, 1580, 1520, 1460, 1400, 1380, 1320, 1290, 1270, 1250, 1230, 1180, 1160, 1050, 935, 840, 800, 750, 635 cm^{-1}; ^1H nmr δ (60 MHz $CDCl_3$) 7.63–7.16 (2H, m, H-4 and H-6), 6.83–6.46 (2H, m, H-3 and H-5), 4.30 (2H, t, $J = 6$ Hz, CH_2OAc), 3.46 (2H, t, $J = 6$ Hz, NCH_2), 2.10 (3H, s, $OCOCH_2$); *m/z* (rel. int.) 222 (12), 162 (15), 150 (15), 145 (25), 132 (100), 118 (7), 104 (20), 91 (10), 77 (50), 43 (45).

PREPARATION OF 1-(2-ACETOXYETHYL)-4(1*H*)-QUINAZOLINONE [**6**].—Compound **5** (0.070 g) was refluxed in $CH(OEt)_3$-Ac_2O (2:1) (5 ml) for 1.5 h. The complex mixture of products obtained after evaporation of the solvents under reduced pressure was separated by preparative tlc (eluent 2% MeOH in CH_2Cl_2) to yield **6** as a semisolid (0.030 g, 41%): found $[M]^+$ 232.084905, $C_{12}H_{12}N_2O_3$ requires $[M]^+$ 232.084786; ^1H nmr δ (60 MHz $CDCl_3$) 8.41 (1H, dd, $J = 8$ and 2 Hz, H-5), 8.31 (1H, s, H-2), 7.76–7.33 (3H, m, H-6, H-7, and H-8), 4.50 (4H, brs, NCH_2CH_2OAc), 2.08 (3H, s, $OCOCH_3$); *m/z* (rel. int.) $[M]^+$ 232 (34), 172 (38), 145 (66), 132 (100), 117 (8), 104 (18), 90 (14), 77 (68), 63 (14).

DEACETYLATION OF **6** INTO 1-(2-HYDROXYETHYL)-4(1*H*)-QUINAZOLINONE [**2**].—The acetate derivative **6** (0.028 g) was dissolved in dry MeOH (1 ml), a few drops of NaOMe in MeOH (prepared by dissolving Na in MeOH) were added, and the mixture was stirred at room temperature for 1 h. The reaction mixture was chromatographed over preparative tlc using 5% MeOH in CH_2Cl_2 as the eluent, to yield **2** which on crystallization with MeOH gave colorless needles (0.022 g, 96%): mp 220–222°; found C 63.16, H 5.38, N 14.75; $C_{10}H_{10}N_2O_2$ requires C 63.13, H 5.30, N 14.73%; ν max 3400–3180 br, 2980, 1650, 1615, 1550, 1490, 1450, 1415, 1395, 1370, 1290, 1270, 1260, 1250, 1175, 1140, 1090, 1060, 1030, 970, 945, 870, 770, 700 cm^{-1}; ^1H nmr see Table 1; *m/z* (rel. int.) $[M]^+$ 190 (84), 160 (14), 146 (10), 132 (100), 104 (24), 90 (8), 77 (66), 63 (10), 51 (28); found $[M]^+$ 190.074049, $C_{10}H_{10}N_2O_2$ requires $[M]^+$ 190.074222; *m/z* 132.045069 (100%), C_8H_6NO requires 132.044939.

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