Nucleophilic Displacement of 6,8-Dichloro-4-quinazolinone with Ethanolamine

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2- and 4-Quinazolinones have been reported to have a variety of interesting pharmacological properties (1). This has prompted us to prepare for biological testing a number of 4(3*H*)quinazolinones which are substituted at the 3-position as well as in the benzene portion of the molecule. These compounds were prepared either by the addition of a primary amine (2) or by the alkylation of the corresponding quinazolinones which are unsubstituted at the 3-position.

Thus, addition of *d*-amphetamine to 6,8-dichloro-4-quinazolinone (**1**) gave the 3-(phenylpropyl)dichloroquinazolinone (**2a**) in 13% yield, while alkylation of **1**, with diethylaminoethyl chloride, followed by treatment with oxalic acid, furnished the oxalate salt (**2b**) in 32% yield. With ethanolamine, however, not only was the 3-hydroxyethyl derivative (**2c**) obtained in 21% yield, but a second product, in which a chloro group was unexpectedly replaced by ethanolamine, was isolated in 13% yield.

To establish which of the two chloro groups was displaced, the product was catalytically hydrogenated to afford a quinazolinone free of chlorine. The uv and nmr spectra of the reduced product were compared with those of 6-amino-4-quinazolinone (**3**). The results allowed an assignment of structure to the former product.

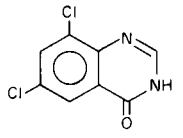
6-Amino-4-quinazolinone (**3**) showed maximal uv absorption of 289-290 nm (ϵ, 12,900). In the nmr spectrum, the 5-H appeared as a doublet at 452 Hz ($J_{5,7} = 2$), the 7-H as a doublet of doublets upfield at 438.5 Hz ($J_{5,7} = 2$, $J_{7,8} = 9$), and the 8-H as a doublet centered at 459.5 Hz ($J_{7,8} = 9$).

The product resulting from dehalogenation absorbed uv maximally at 274.5 nm (ϵ, 11,750). Two of the aromatic protons appeared as doublets and the third as a triplet in the nmr spectrum. All three protons had a coupling constant of 7.5 Hz. One of the doublets was centered at 479 and the other at 485 Hz. The triplet was located at 453.5 Hz. The nmr data are compatible with the presence of three contiguous aromatic protons.

Hence, the structure of the product must be **4b** in which the ethanolamine side chain is attached to C-8. The alternative structure in which this side chain is at C-6 is untenable because the spectral characteristics of the product and those of 6-amino-4-quinazolinone (**3**) were very dissimilar.

In spite of the fact that **4a** was obtained in a yield of only 13%, preferential displacement of the 8-chloro group would be expected to occur because the imino nitrogen, which inductively stabilizes the transition state (3), is nearer to the chloro group at the 8-than to the one at the 6-position.

The high temperature employed in the reaction conceivably facilitated the displacement of the chloro group. Previously, it had been reported that the reaction of 2,4,6- and 2,4,7-trichloroquinazoline with aqueous 2-diethylaminoethylamine at room temperature proceeded to give almost exclusively products in which the chloro group in the azine ring was displaced. Displacement of the chloro group in the benzene ring did not occur to any extent (3,4). Similarly, when 2,6 (or 2,7)-dichloro-4-(β-diethylaminoethyl)aminoquinazoline was reacted with *p*-chloroaniline in boiling acetic acid, reaction occurred only with the 2-chloro group (4).



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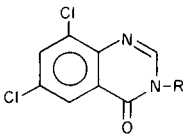
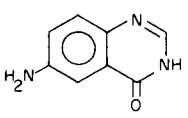


2a R = $-CH(CH_3)-CH_2\phi$
b R = $-CH_2CH_2N(C_2H_5)_2\cdot(CO_2H)_2$
c R = $-CH_2CH_2OH$



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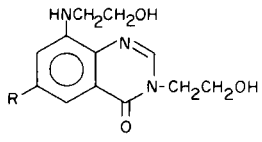

4a R = Cl
b R = H

EXPERIMENTAL (5)

6,8-Dichloro-4-quinazolinone (**1**).

A mixture of 11.0 g. of 3,5-dichloroanthranilic acid and 8 ml. of formamide was thoroughly mixed, kept at 140 ± 5° for 4 hours, and afterward allowed to stand at room temperature for 12 hours. Water was added to the solid mixture. The mixture was stirred. Then the solid was collected by filtration, washed with water, and dried, m.p. > 300°. The analytical sample of **1** was prepared by crystallizing a portion of the solid from ethanol, m.p. > 300°.

Anal. Calcd. for $C_8H_4Cl_2N_2O$: Cl, 32.98; N, 13.03. Found: Cl, 32.91; N, 13.10.

6,8-Dichloro-3-(1-methyl-2-phenylethyl-4-quinazolinone (**2a**).

A mixture of 5.0 g. of 6,8-dichloro-4-quinazolinone (**1**) and 50 ml. of *d*-amphetamine was heated under reflux for 40 hours. Then the reaction mixture was concentrated to a small volume by distillation under reduced pressure. On standing, the residue began to crystallize. Trituration with ether afforded a crystalline product, m.p. 158-159°. Crystallization from ethyl acetate afforded 1.0 g. (13%) of **2a**, m.p. 166.5-167.5°.

Anal. Calcd. for $C_{17}H_{14}Cl_2N_2O$: Cl, 21.28; N, 8.41. Found: Cl, 20.94; N, 8.58.

6,8-Dichloro-3-(2-diethylaminoethyl)-4-quinazolinone Oxalate (**2b**).

A mixture of 3.0 g. of 6,8-dichloro-4-quinazolinone (**1**), 0.8 g. of a 56% dispersion of sodium hydride in mineral oil, and 100 ml. of dimethylsulfoxide was stirred at room temperature in an atmosphere of nitrogen for 1 hour. After the addition of 3 ml. of diethylaminoethyl chloride, the reaction mixture was stirred at room temperature for 6 hours and then allowed to stand at room temperature for 16 hours. The reaction mixture was poured into ice water, and the resultant turbid mixture was extracted with ether. The ether extract was washed with water, dried (sodium sulfate), and evaporated to dryness to afford a viscous brown oil.

The oil was dissolved in 7 ml. of absolute ethanol. To this solution was added a solution of 1.6 g. of oxalic acid in 5 ml. of ethanol whereupon the mixture solidified. The solid mixture was crystallized from ethanol to afford 1.8 g. (32%) of **2b**, m.p. 218.5-219.5°.

Anal. Calcd. for $C_{14}H_{17}Cl_2N_3O \cdot C_2H_2O_4$: Cl, 17.54; N, 10.40. Found: Cl, 17.09; N, 10.11.

6,8-Dichloro-3-(2-hydroxyethyl)-4-quinazolinone (**2c**) and 6-Chloro-8-(2-hydroxyethylamino)-3-(2-hydroxyethyl)-4-quinazolinone (**4a**).

A mixture of 4.0 g. of 6,8-dichloro-4-quinazolinone (**1**) and 75 ml. of monoethanolamine was heated under reflux for 65 hours after which it was concentrated to a small volume by distillation under reduced pressure. The residue was diluted with water to afford a heavy oil which was extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried (sodium sulfate), and evaporated to a small volume on the steam bath and in a stream of nitrogen. The residue was chilled in the refrigerator, after which the resultant solid **4a** was collected, washed with ethyl acetate and ether, and dried: yield 0.68 g. (13%), m.p. 179-180°: λ max (methanol) 278-280 nm (ε, 9,570), 299-301 nm (ε, 6,480): λ min 235-237 nm (ε, 3,150), 295-296 nm (ε, 6,330); λ (potassium bromide): 2.90, 3.05, 3.21, 5.53, 5.68, 6.08, 6.20, 6.38 μ.

Anal. Calcd. for $C_{12}H_{14}ClN_3O_3$: Cl, 12.50; N, 14.82. Found: Cl, 12.31; N, 14.69.

The original mother liquor was further concentrated. The residue was diluted with ether, and the mixture was allowed to stand in the refrigerator overnight to afford 0.98 g. (21%) of the dichloro derivative **2c**, m.p. 98-103°. After crystallization from ethyl acetate-ether it melted at 119-121°.

Anal. Calcd. for $C_{10}H_8Cl_2N_2O_2$: Cl, 27.37; N, 10.82. Found: Cl, 27.35; N, 11.20.

6-Amino-4-quinazolinone (**3**).

This compound was prepared according to the procedure of Baker *et al.* (6): m.p. > 300°; λ max (methanol) 289-290 nm (ε, 12,900); λ min 256 nm (ε, 2,740); λ (potassium bromide): 2.94, 3.03, 3.14, 3.28, 5.97, 6.08 (sh.), 6.20 μ; nmr (perdeuterioacetic acid): 496 (2-H), 459.5 ($J_{7,8}$ = 9, 8-H), 452 ($J_{5,7}$ = 2, 5-H), 438.5 ($J_{7,8}$ = 9, $J_{5,7}$ = 2, 7-H) Hz.

8-(2-Hydroxyethylamino)-3-(2-hydroxyethyl)-4-quinazolinone (**4b**).

A solution of 944 mg. of **4a** in 60 ml. of absolute ethanol was hydrogenated over 100 mg. of 5% palladium on carbon at room temperature and atmospheric pressure. After 2 hours the calculated amount of hydrogen was absorbed. The catalyst was removed by filtration and the filtrate was distilled to dryness under reduced pressure to give a residue which was diluted with a 5% solution of sodium carbonate and extracted with 1-butanol. The extract was distilled to dryness under reduced pressure to afford a semisolid. Trituration of the semisolid with ethyl acetate afforded 616 mg. (74%) of **4b**, m.p. 131-134°. Crystallization from ethyl acetate-ether raised the m.p. to 142-142.5°; λ max (methanol) 274.5 nm (ε 11,750); λ min 228-230.5 nm (ε 2,920); λ (potassium bromide): 3.03, 3.23, 5.17, 5.33, 5.48, 5.61, 6.07, 6.22 μ; nmr (perdeuterioacetic acid); 538 (2-H), 485 ($J_{5,6}$ = 7.5, 5-H), 479 ($J_{6,7}$ = 7.5, 7-H), 453.5 ($J_{5,6}$ = $J_{6,7}$ = 7.5, 6-H), 277 (N-CH_2), 246, 241, 234, 231, 226, 223 Hz.

Anal. Calcd. for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.72; H, 6.25; N, 17.03

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