Reductive Cleavage of some 3,1,4-Benzoxazones by Sodium Borohydride

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In a continuing investigation of the reduction of heterocyclic systems and functional groups conjugated with heteroaromatic rings by sodium borohydride (2) we have examined the behavior of some 2-substituted 3,1,4-benzoxazones (I) toward this reagent. Several years ago Walker reported that hydrogenolysis of 2-methyl-3,1,4-benzoxazone (Ia) in the presence of palladium catalyst gave 2-acetamidobenzyl alcohol (IIa) in quantitative yield (3). We have found similarly that catalytic hydrogenation of 2-phenyl-3,1,4-benzoxazone (Ib) affords 2-benzamidobenzyl alcohol (IIb). Reduction of the benzoxazone derivative (Ib) by lithium aluminum hydride as described by Witkop, Patrick and Kissman gave the alcohol (IIb) in 84% yield (4). In our work reductions of three benzoxazone derivatives by sodium borohydride in methanol gave mixtures of the corresponding 2-acylamino-benzyl alcohol (II) and *N*-substituted anthranilic acid (*cf.* III). The specific compounds investigated were the 2-methyl- (Ia), 2-phenyl- (Ib), and 2-trifluoromethyl-3,1,4-benzoxazone (Ic). The results are outlined in Table I.

The 3,1,4-benzoxazone ring system, also trivially called an "acylanthranil", is a heterocyclic analog of an anhydride (5). Most reactions with nucleophilic reagents apparently involve attack at the 4-position. For example ammonia or primary amines convert benzoxazones to the corresponding quinazolones (6). We originally sought to correlate the ratio of benzyl alcohol (II) to anthranilic acid (III) with the electronegativity of the substituent at position-2, but the yield data under nearly comparable conditions do not reveal such a simple relationship. In methanol, the reaction of sodium borohydride with 2-phenylbenzoxazone (Ib) gave approximately equal quantities of the amido alcohol (IIb) and the amino acid (IIIb). After this work was completed, a report appeared of the borohydride reduction in absolute ethanol of a compound which was assigned structure Ib on the basis of the fact that *N*-benzyl-anthranilic acid was obtained in 90% yield (7).

Constitutions of the amido alcohols (IIa and IIb) were established by catalytic hydrogenations of the benzoxazones and also by acylation of 2-aminobenzyl alcohol (8). The *N*-substituted anthranilic acids (IIIa and IIb) were independently prepared by alkylation of anthranilic acid. Alternatively the reaction of sodium borohydride with *N*-benzylideneanthranilic acid (IVa) or the cyclic tautomer (IVb) (9) provided another route to *N*-benzylanthranilic acid. Structural assignments for the trifluoromethyl derivatives were made on the basis of analogy, physical properties including solubilities and spectra and elemental analyses.

In contrast to the facile reduction of the benzoxazones, two quinazolone derivatives (V and VI) were unaffected by sodium borohydride in methanol. This results is in accord with the recent report that no reduction of 2-methyl-3-phenyl-4(3*H*)-quinazolone (VII) occurred in methanol, ethanol or tetrahydrofuran with this reagent, but a tetrahydroquinazolone was formed in diglyme at 100° or from the hydrochloride of VII in tetrahydrofuran-diglyme (10).

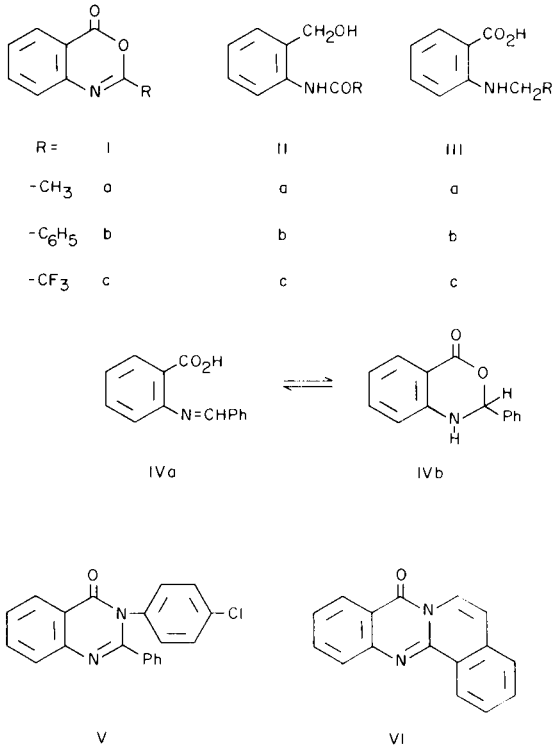

TABLE I

Reduction of some 2-Substituted 3,1,4-Benzoxazones

3,1,4-Benzoxazone (I)	Red. Agent	Product	M.P.	% Yield
R = 2-Methyl	$NaBH_4$	2-Acetamidobenzyl Alcohol (IIa)	114-115°	73
		N-Ethylanthranilic Acid (IIIa)	151-153°	24
R = 2-Phenyl	$NaBH_4$	2-Benzamidobenzyl Alcohol (IIb)	95-96°	50
		N-Benzylanthranilic Acid (IIIb)	175-176°	49
	Pd-C	2-Benzamidobenzyl Alcohol	98-99°	81
R = 2-Trifluoromethyl	$NaBH_4$	2-Trifluoroacetamidobenzyl Alcohol (IIc)	62-63°	74
		N-(2,2,2-Trifluoroethyl)anthranilic Acid (IIIc)	158-159°	22

8*H*-Isoquino[1,2-*b*]-8-quinazolone was prepared by the method of Stephen and Stephen (11) from methyl anthranilate and 1-chloroisoquinoline.

EXPERIMENTAL (12)

The 2-methyl- and 2-phenyl-3,1,4-benzoxazones were prepared by the method in Ref. 6; the reductions with sodium borohydride were carried out the same way as the trifluoromethyl derivative. Alternative syntheses of 2-acetamidobenzyl alcohol (3), *N*-ethylanthranilic acid (13), 2-benzylanthranilic acid (14) are described in the literature, and compounds so prepared were identical with the respective reduction products by melting point and infrared spectral comparisons.

2-Trifluoroacetamidobenzoic Acid.

Anthranilic acid (10 g.) was added in small portions to trifluoroacetic anhydride (30 ml.), and the solution was allowed to reflux 1 hour. After cooling the excess anhydride was evaporated under reduced pressure, and the residual paste was recrystallized from benzene-acetonitrile as colorless needles, 11 g., m.p. 184-185°. The infrared spectrum showed strong absorption bands at 5.85 and 6.05 μ.

Anal. Calcd. for $C_9H_6NO_3F_3$: C, 46.36; H, 2.59; N, 6.00. Found: C, 46.32; H, 2.69; N, 5.92.

2-Trifluoromethyl-3,1,4-benzoxazone (Ic).

A solution of trifluoroacetamidobenzoic acid (2 g.) in acetic anhydride (10 ml.) was boiled in an open container almost to dryness. Extraction of the residue with hot ligroin (b.p. 66-75°) gave a solution which on cooling deposited colorless crystals, 1.2 g., m.p. 53-55°. For analysis the sample was recrystallized from ethyl acetate-ligroin. Significant infrared adsorption bands were found at 5.65 and 6.02 μ.

Anal. Calcd. for $C_9H_4NO_2F_3$: C, 50.24; H, 1.87; N, 6.50. Found: C, 50.39; H, 2.16; N, 6.60.

Reduction of Ic.

To 25 ml. of cold methanol was added sodium borohydride (1 g.). After the reaction had subsided trifluoromethyl-3,1,4-benzoxazone (Ic, 3.0 g.) was added over a 3 minute period. The reaction mixture was allowed to stand 4 hours and diluted with water (50 ml.). The methanol was partly evaporated, and the solid (2.2 g. m.p. 61-62°) was collected by filtration. For analysis the trifluoroacetamidobenzyl alcohol (IIc) was recrystallized from petroleum ether (b.p. 30-60°) and melted at 62-63°.

Anal. Calcd. for $C_9H_8NO_2F_3$: C, 49.32; H, 3.68; N, 6.39. Found: C, 49.10; H, 3.42; N, 6.54.

After removing IIc, the filtrate was acidified with concentrated hydrochloric acid to about *p*H 3, and a crystalline solid (IIIc), 0.66 g., m.p. 151-154°, was obtained. Recrystallization from aqueous methanol raised the m.p. to 158-159°.

Anal. Calcd. for $C_9H_8NO_2F_3$: C, 49.32; H, 3.68; N, 6.39. Found: C, 49.56; H, 3.68; N, 6.45.

N-Benzylanthranilic Acid.

N-Benzylideneanthranilic acid (1.0 g.) (15) in methanol (20 ml.) was treated with sodium borohydride (0.5 g.). After 15 minutes water (100 ml.) was added and the solution was boiled 10 minutes. The cooled solution was acidified with acetic acid, and a colorless solid (0.9 g. m.p. 166-168°) was obtained. A recrystallized sample (m.p. 175-176°) was identical with an authentic specimen of *N*-benzylanthranilic acid (14).

8*H*-Isoquino[1,2-*b*]-8-quinazolone (VI) (16).

Methyl anthranilate (1.50 g.) and 1-chloroisoquinoline (1.65 g.) were heated together in an oil bath. At 150° an orange liquid was first obtained which solidified after 5 minutes and hydrogen chloride was evolved. The reaction mixture was heated to about 210° for 40 minutes and the melt changed to light olive color. The cooled solidified product was granulated and washed with saturated sodium carbonate solution. The organic residue was dissolved in hot pyridine-ethanol (2:1 v/v) and from this solution there was precipitated a pale yellow needle-like crystalline product, 1.6 g., m.p. 171-172°.

Anal. Calcd. for $C_{16}H_{10}N_2O$: C, 78.04; H, 4.09; N, 11.38. Found: C, 78.13; H, 4.23; N, 11.34.

Attempted Reductions of Quinazolones.

2-Phenyl-3-*p*-chlorophenyl-4-quinazolone (1 g., m.p. 155-156°; lit. (17) m.p. 155°) was dissolved in methanol (30 ml.) and sodium borohydride (0.5 g.) was added. After 30 minutes water (50 ml.) was added and the reaction mixture was boiled gently until the volume was 60 ml. The starting compound was recovered completely from the cooled aqueous mixture.

The isoquino[1,2-*b*]quinazolone (VI, 0.5 g.) was allowed to stand over-night in a solution of sodium borohydride (0.2 g.) in methanol (50 ml.) and was recovered unchanged.

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Received July 8, 1968

Nashville, Tennessee 37203