1,4-Benzoxazines. Conversion to a Benzoxazole and an Indolo[3,2-*b*][1,4]benzoxazine[1]

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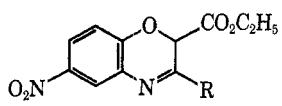
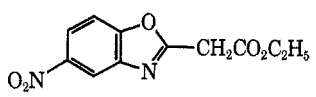
Reaction of 2-carbethoxy-3-methylmercapto-6-nitro-2*H*-1,4-benzoxazine (**1a**) with phenylhydrazine in dimethylformamide led to 2-carbethoxymethyl-5-nitrobenzoxazole (**2**) by reductive ring contraction. Also isolated was 2-carbethoxy-3-phenylazo-6-nitro-2*H*-1,4-benzoxazine (**1c**). When phenylhydrazine *hydrochloride* in benzene–dimethylformamide was used, the expected 2-carbethoxy-3-(β-phenylhydrazino)-6-nitro-2*H*-1,4-benzoxazine (**1b**) was obtained. The latter compound underwent cleavage and cyclization to 11a-carbethoxy-5,11a-dihydro-8-nitroindolo[3,2-*b*][1,4]benzoxazine (**3**) on brief heating with sulfuric acid in acetic acid.

The ring contraction of 3-hydroxy-4-methyl-1,4-benzoxazine to a mixture of dihydroxyindoles[2] and of a 1,4-benzthiazine to a benzthiazole[3] have been reported. Recently, during the treatment of 2-carbethoxy-3-methylmercapto-6-nitro-2*H*-1,4-benzoxazine (**1a**) with phenylhydrazine in dimethylformamide, I observed a ring contraction of **1a** to a benzoxazole. Th emajor product was identified as 2-carbethoxymethyl-5-nitrobenzoxazole (**2**) by the identity of the infrared and nuclear magnetic resonance (nmr) spectra with those of a sample prepared by an unambiguous route.[4] The expected 3-phenylhydrazino compound **1b** was not obtained.



1a, R = SCH_3
b, R = $NHNHC_6H_5$
c, R = $N{=}NC_6H_5$
d, R = OH
e, R = SH



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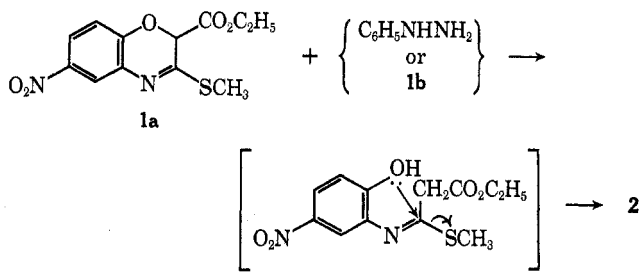
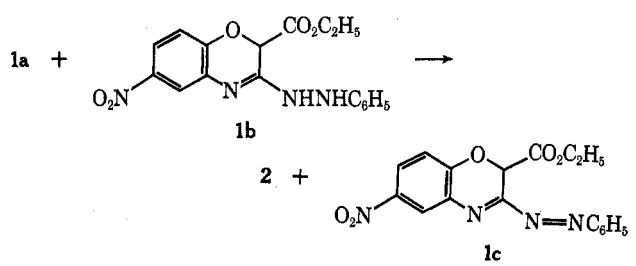
A yellow solid, isolated in low yield, has been assigned the phenylazo structure **1c**. This assignment is based on a peak at *m/e* 354 in the mass spectrum of the compound, assigned to the parent molecular ion; the phenylhydrazine **1b** (*vide infra*) exhibited a parent molecular ion at *m/e* 356. Both **1b** and **1c** gave fragment peaks corresponding to the loss of the nitro and carbethoxy groups. Significantly, however, **1c** gave a fragment peak at *m/e* 277, which has been attributed to the loss of the phenyl group. This fragmentation establishes that a monosubstituted benzene ring is present and is consistent with the presence of a phenylazo group. No corresponding peak was found in the spectrum of the phenylhydrazine **1b**.

The formation of the benzoxazole **2** from the benzoxazine **1a** requires reductive cleavage of the 1,2 bond of **1a**. Although the exact route of the conversion cannot be specified, it appears that phenylhydrazine and/or the hydrazine **1b** may be involved as reductants.

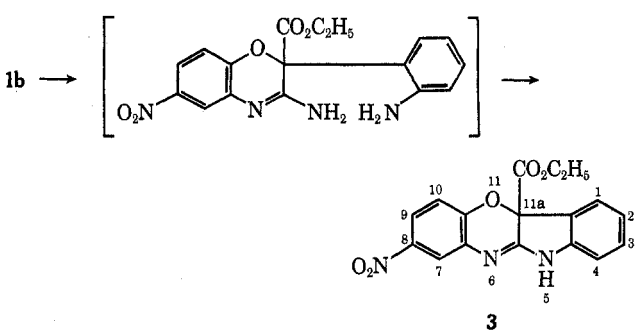
Reduction of ether linkages[5] and nitro groups[6] by phenylhydrazine has been reported. The probable by-



products are nitrogen and benzene.[6] Nmr and gas chromatographic examination of the first cut from a distillation of the reaction mixture indicated the presence of more benzene than could be obtained from a control of phenylhydrazine and dimethylformamide. This suggests that phenylhydrazine is the reductant. On the other hand, the phenylazo compound **1c** and the benzoxazole **2** could arise from reduction of the ether linkage by the hydrazine **1b**.



By using phenylhydrazine *hydrochloride* in benzene–dimethylformamide, the formation of the benzoxazole **2** is avoided and the hydrazine **1b** is obtained. Heating this compound with sulfuric acid in acetic acid resulted in rapid conversion of **1b** to **3**, an example of the previously unknown indolo[3,2-*b*][1,4]benzoxazine ring system. The reaction may be considered to be an example of the *o*-benzidine rearrangement with subse-



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(1) R. W. Hendess, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, Paper No. 78.
(2) (a) J. D. Loudon and J. Ogg, *J. Chem. Soc.*, 739 (1955); (b) E. Kretz, J. M. Muller, and E. Schlittler, *Helv. Chim. Acta*, **38**, 520 (1952).
(3) M. A. T. Rogers and W. A. Sexton, *J. Chem. Soc.*, 1619 (1947).
(4) This compound was prepared by Dr. D. E. Machiele of the Kodak Research Laboratories.
(5) K. J. Clark, *J. Chem. Soc.*, 1511 (1956).
(6) H. Bredereck and H. v. Sehuh, *Chem. Ber.*, **81**, 215 (1948).

quent cyclization or an example of a Fischer indole synthesis from a hydrazidine.

The structure of compound **3** was determined by high-resolution mass spectrometry.[7] The spectrum exhibited a parent molecular ion, determined to be of mass 339.0842 by peak matching. This corresponds to a calculated value of 339.0855 for the empirical formula of $C_{17}H_{13}N_3O_5$. This same formula was arrived at by elemental analysis. As expected for cyclic compounds, the spectrum was relatively uncomplicated, showing fragment ions at *m/e* 266 ($M - CO_2C_2H_5$) and *m/e* 220 [$(M - CO_2C_2H_5) - NO_2$]. Infrared analysis confirmed the presence of the ester function (1750 cm^{-1}). The presence of intense absorption of 745 cm^{-1}, not observed in the spectrum of **1b**, is evidence for the new ortho-substituted benzene ring. The nmr spectrum exhibited only seven aromatic protons, in agreement with this structure.

Experimental Section

2-(α-Carbethoxyacetamido)-4-nitrophenol.—A suspension of 154 g (1.0 mol) of 2-amino-4-nitrophenol in 3 l. of *p*-xylene containing 320 g (2.0 mol) of diethyl malonate was refluxed for 4 hr with a condenser through which steam was being passed. The solution was cooled, and 215 g (80%) of the product was collected, washed with benzene, and dried. Recrystallization from ethyl acetate removed a small amount of insoluble diamide. The compound was used without further purification to prepare compound **1d**.

2-Carbethoxy-3-hydroxy-6-nitro-2*H*-1,4-benzoxazine (1d).—A suspension of 110 g (0.41 mol) of 2-(α-carbethoxyacetamido)-4-nitrophenol in 4 l. of ethyl acetate was heated to reflux to effect solution and then cooled to room temperature. To the resulting solution was added a solution of 33.2 ml (55.4 g, 0.41 mol) of sulfuryl chloride in 800 ml of ethyl acetate. The addition took 2 hr. The solution was stirred an additional 2 hr, filtered, and concentrated to 2.5 l. *in vacuo*. Triethylamine (113 ml, 83 g, 0.82 mol) was added and the solution was refluxed 0.5 hr and then cooled. The precipitated triethylamine hydrochloride was removed, the dark brown filtrate evaporated to dryness, and the residue triturated with methanol to give 40 g (37%) of a light tan solid. Recrystallization from methanol gave an analytical sample, mp 199–200°.

Anal. Calcd for $C_{11}H_{10}N_2O_6$ (266.21): C, 49.6; H, 3.8; N, 10.5. Found: C, 49.6; H, 3.6; N, 10.7.

2-Carbethoxy-3-mercapto-6-nitro-2*H*-1,4-benzoxazine (1e).—A solution of 20 g (0.075 mol) of 2-carbethoxy-3-hydroxy-6-nitro-2*H*-1,4-benzoxazine (**1d**) and 15 g (0.068 mol) of phosphorus pentasulfide in 700 ml of pyridine (dried over sodium hydroxide) was refluxed for 6 hr. The dark brown solution was cooled to 15°, and 3 l. of water was added to precipitate the product which was collected, washed with water, and dried (20 g, 94%). Recrystallization from methanol with charcoal gave yellow needles, mp 169–171°. Further recrystallization gave an analytical sample, mp 172–173°.

Anal. Calcd for $C_{11}H_{10}N_2O_5S$ (282.28): C, 46.8; H, 3.5; N, 9.9; S, 11.4. Found: C, 46.7; H, 3.5; N, 10.0; S, 11.4.

2-Carbethoxy-3-methylmercapto-6-nitro-2*H*-1,4-benzoxazine (1a).—To a suspension of 54.4 g (0.20 mol) of 2-carbethoxy-3-mercapto-6-nitro-2*H*-1,4-benzoxazine (**1e**) in 1 l. of ethanol was added 11.2 g of 85% potassium hydroxide dissolved in 200 ml of ethanol. (This is 0.17 mol based on 85% KOH present; use of 0.20 mol of KOH inhibits crystallization of the product.) After complete solution was obtained, 200 ml of methyl iodide was added and the resulting solution was stirred for 0.5 hr. Concentration to 800 ml *in vacuo*, followed by addition of 1 l. of water, gave 51.8 g of the product as a tan solid. Recrystallization from 1 l. of methanol gave 30 g (51%) of pale yellow crystals, mp 105–107°.

Anal. Calcd for $C_{12}H_{12}N_2O_5S$ (296.31): C, 48.6; H, 4.1; N, 9.4; S, 10.8. Found: C, 48.2; H, 4.0; N, 9.7; S, 11.0.

2-Carbethoxy-3-phenylazo-6-nitro-2*H*-1,4-benzoxazine (1c).—A solution of 12 g (0.04 mol) of 2-carbethoxy-3-methylmercapto-6-nitro-2*H*-1,4-benzoxazine (**1a**) and 4.0 ml (0.041 mol) of phenylhydrazine in 100 ml of dimethylformamide was heated on a steam bath for 3.5 hr and then cooled. Dilution with 100 ml of water gave a yellow solid which was collected, washed with water, dried, and recrystallized from 800 ml of ethanol. The solid (6.0 g) was dissolved in hot acetonitrile; addition of water to the cloud point gave 0.3 g of 2-carbethoxy-3-phenylazo-6-nitro-2*H*-1,4-benzoxazine after cooling. Recrystallization from 15 ml of benzene with charcoal gave bright yellow needles: mp 212–215°; nmr ($CDCl_3$) τ 8.53 (t, J = 7 Hz, 3 H) and 5.51 (q, J = 7 Hz, 2 H) due to the ethyl group, 2.60 (m, 5 H) phenyl group, 2.23 (d, J = 9 Hz, 1 H), 1.60 (m, 1 H), and 1.30 (d, J = 2 Hz, 1 H) the remaining aromatic protons.

Anal. Calcd for $C_{17}H_{14}N_4O_5$ (354.31): C, 57.6; H, 4.0. Found: C, 57.3; H, 3.6.

2-Carbethoxymethyl-5-nitrobenzoxazole (2). A.—The acetonitrile–water filtrate from the isolation of 2-carbethoxy-3-phenylazo-6-nitro-2*H*-1,4-benzoxazine (**1c**) was diluted further with water to give 5.7 g (57%) of 2-carbethoxymethyl-5-nitrobenzoxazole, which was recrystallized from 200 ml of methylcyclohexane with charcoal to give white needles: mp 101–102°; nmr ($CDCl_3$) τ 8.75 (t, J = 7 Hz, 3 H) and 5.77 (q, J = 7 Hz, 2 H) due to the ethyl group, 5.95 (s, 2 H) due to the methylene, and 2.39 (d, J = 9 Hz, 1 H), 1.71 (m, 1 H), and 1.45 (d, J = 2 Hz, 1 H) due to the aromatic protons.

Anal. Calcd for $C_{11}H_{10}N_2O_5$ (250.21): C, 52.8; H, 4.0. Found: C, 52.8; H, 4.0.

B.—A mixture of 16 g (0.10 mol) of 2-amino-4-nitrophenol and 20 g (0.12 mol) of ethyl β,β-dimethoxyacrylate was heated at 70–80° for 1 hr under nitrogen. Upon cooling, the reaction mixture solidified. Recrystallization from methanol gave 19 g (76%) of product, mp 100–102°.

Anal. Found: C, 53.1, H, 4.3.[4]

2-Carbethoxy-3-(β-phenylhydrazino)-6-nitro-2*H*-1,4-benzoxazine (1b).—A slurry of 10 g (0.034 mol) of 2-carbethoxy-3-methylmercapto-6-nitro-2*H*-1,4-benzoxazine (**1a**) and 5.0 g (0.035 mol) of phenylhydrazine hydrochloride (both dried *in vacuo* at 60° for 12 hr) in 1 l. of dry benzene was heated to boiling in an open three-neck flask. While boiling was maintained, 700 ml of dimethylformamide was slowly added. A condenser was placed on the flask and the orange solution was refluxed for 1.5 hr. The solution was cooled, the benzene removed *in vacuo*, and the red dimethylformamide solution poured into 1200 ml of ice and water. The brown solid (10.8 g, 88%) which separated was collected and recrystallized from 800 ml of ethanol. Recrystallization from ethanol gave orange crystals: mp 205–206°; nmr (DMSO-d_6) τ 8.82 (t, J = 7 Hz, 3 H) and 5.78 (q, J = 7 Hz, 2 H) due to the ethyl group, 6.67 (s, 1 H) broad NH, 4.58 (s, 1 H) 2-H, 2.95 (m) and 2.28 (m) 8 aromatic protons, and 1.59 (s, 1 H) a hydrogen-bonded NH.

Anal. Calcd for $C_{17}H_{16}N_4O_5$ (356.33): C, 57.3; H, 4.5; N, 15.7. Found: C, 57.3; H, 4.8; N, 16.2.

11a-Carbethoxy-5,11a-dihydro-8-nitroindolo[3,2-*b*][1,4]benzoxazine (3).—A suspension of 1.0 g (0.0028 mol) of 2-carbethoxy-3-(β-phenylhydrazino)-6-nitro-2*H*-1,4-benzoxazine (**1b**) in 25 ml of acetic acid containing 0.40 ml of concentrated sulfuric acid was heated rapidly to boiling and then boiled for 5 min. The solution was cooled and diluted with 4 vol of water to give 0.8 g (84%) of a yellow solid. Recrystallization from acetonitrile with charcoal gave white crystals: mp 230–231°; nmr (DMSO-d_6) τ 0.5 (t, J = 7 Hz, 3 H) and 5.93 (q, J = 7 Hz, 2 H) due to the ethyl group, and a complex multiplet centered at τ 2.26 of the 7 aromatic protons.

Anal. Calcd for $C_{17}H_{13}N_3O_5$ (339.30): C, 60.2; H, 3.9; N, 12.4. Found: C, 60.2; H, 4.1; N, 12.2.

Registry No.—**1a**, 30135-28-5; **1b**, 30135-29-6; **1c**, 30275-68-4; **1d**, 30135-30-9; **1e**, 30135-31-0; **2**, 30135-32-1; **3**, 30135-33-2.

(7) This structure was first suggested by Mr. D. P. Maier of the Kodak Research Laboratories.