Synthesis and Reactions of a New Benzoxadiazocine Structure

P. N. Giraldi, A. Fojanesi, G. P. Tosolini, E. Dradi and W. Logemann

Department of Chemistry, Istituto Carlo Erba per Ricerche Terapeutiche

When treated with ammonia, primary aliphatic amines or hydrazine, 6-chloro-2-chloromethyl-4-phenylquinazoline-3-oxide (**1**) undergoes ring enlargement resulting in the formation of the well-known 2-amino-1,4-benzodiazepine. This paper describes a new type of ring expansion which results when **1** is allowed to react with hydroxylamine.

When an excess of hydroxylamine in alcoholic solution at room temperature was used, a product **2** with the empirical formula $C_{15}H_{12}ClN_3O_2$ was obtained in 45% yield. The infrared spectrum in potassium bromide shows two bands (1650 cm^{-1} and 928 cm^{-1}) corresponding to an oxime group, the presence of which was also confirmed by the bright red coloration which developed when the substance was treated with ferric chloride in aqueous alcohol solution (1).

The IR spectrum in methylene chloride also shows an OH band at 3580 cm^{-1} and an NH band at 3380 cm^{-1}. Compound **2** does not give the reactions which are characteristic for *N*-oxides. Compound **2** was not titratable with titanium trichloride (2) and was not reduced by treatment with phosphorus trichloride (3).

The acetylation of **2** with acetic anhydride only gave compound **3**, the IR spectrum of which in potassium bromide shows two bands ascribable to a monoacetate of an oxime group (1633 cm^{-1}, 915 cm^{-1}) and a NH band at 3290 cm^{-1}. Under similar conditions, the *N*-oxides of the benzodiazepine derivatives exhibit the typical conversion into acetoxy derivatives at position 3 (4). The NMR spectrum of compound **2** shows an AB quartet centered at 4.80 ppm (J = 13.5 cps) produced by the two non equivalent geminal hydrogens. The splitting of the peaks of the two protons at C-3 in **2** was not observed at room temperature in the well-known compounds of general structure **2a** such as nitrazepam (5-7) and more recently 1,4-benzodiazepin-2-one-4-oxide (8). This coupling which is observed in compound **2** arises from a conformer which is stable at room temperature. The interconversion increases as the temperature increases; this quartet collapses into a singlet at 80°.

The absence of an N→O group and the NMR spectrum rules out the benzodiazepine structure **2a** for compound **2**, and suggests instead the benzoxadiazocine cycle **2b** (Chart I).

The acetylated compound **3**, previously described, is consequently the 8-chloro-1,3-dihydro-6-phenyl-2*H*-4,1,5-benzoxadiazocin-2-one-*O*-acetyloxime. The NMR data are consistent with said structure (Chart II). Further proof of the structure **2b** was obtained by a chemical study of some products of hydrolysis. Compound **2b**, when treated with ethanolic 18% hydrochloric acid, reacts as shown in Chart III. The structure of compound **4** was proved by the

Chart I

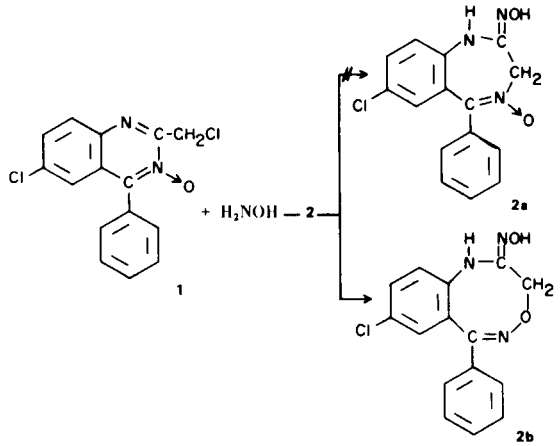


Chart II

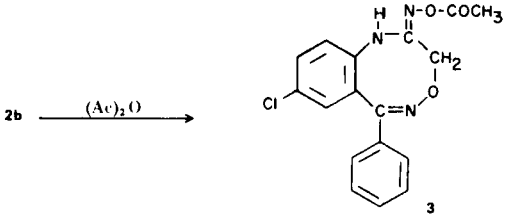
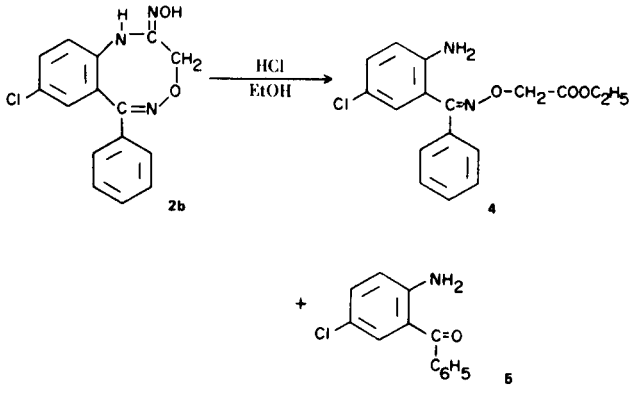


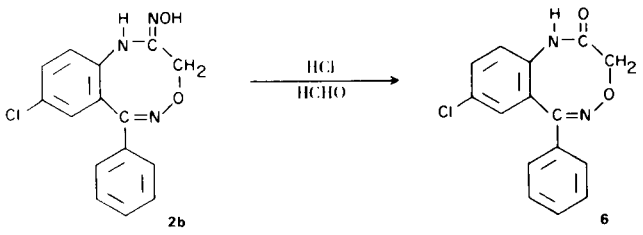
Chart III



infrared spectra as well as by identity with an authentic sample synthesized according to Stempel and co-workers (8). In addition to compound **4**, another product of further hydrolysis, corresponding to formula **5** was obtained.

Compound **2b**, when treated with 2 *N* hydrochloric acid and 40% formaldehyde solution, was converted into compound **6**, identical with the product described by Stempel *et al.* (8) (Chart IV). The identity of the two products was confirmed by IR and NMR spectra.

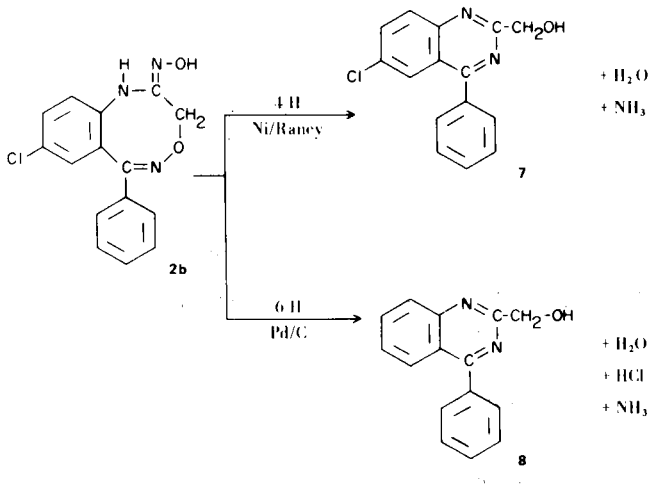
Chart IV



2b **6**

Catalytic hydrogenation of **2b** gave compounds **7** and **8** (Chart V). Assignment of structure **7** was made on the

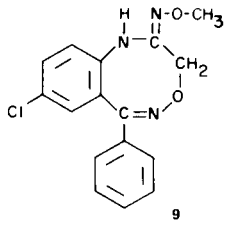
Chart V



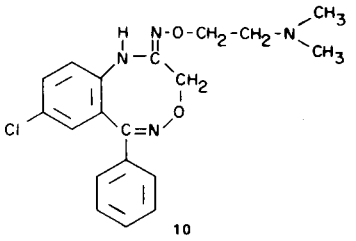
2b **7** **8**

basis of the NMR spectrum which shows a doublet produced by two protons at 4.95 ppm (J = 3.6 cps). This doublet collapses into a singlet after exchange with deuterium oxide. Its acetyl derivative was identical (m.p., TLC, IR, NMR) with the product obtained as described by Sternback *et al.* (9). Hydrogenation follows the same course whether the reaction is carried out at atmospheric pressure or at 4-5 atmospheres. The reaction is also independent of the solvent used (dioxane, ethanol or acetic acid).

Other chemical transformations were also consistent with structure **2b**. The methylation of the oximino group was easily carried out by treatment of **2b** with dimethylsulfate to give **9**; treatment of **2b** with dimethylaminoethyl chloride gave the corresponding aminoalkyl derivative **10**.



9



10

EXPERIMENTAL

Melting points (capillary) are uncorrected. IR spectra were recorded on a Perkin Elmer 125 Spectrophotometer. NMR spectra were determined with a Varian model HA-100 spectrometer, equipped with a variable temperature probe. The chemical shifts (δ) are reported in ppm using TMS as internal standard.

8-Chloro-1,3-dihydro-6-phenyl-2*H*-4,1,5-benzoxadiazocin-2-one Oxime (**2b**).

To 45.4 g. (0.65 mole) of hydroxylamine hydrochloride were added 1300 ml. of 0.5 *N* alcoholic potassium chloride. The suspension was stirred for half an hour and the potassium chloride removed. Ten g. (0.033 mole) of 6-chloro-2-chloromethyl-4-phenylquinazoline-3-oxide (**1**) was added to the solution and the mixture was stirred at room temperature for five hours. Water (5000 ml.) was added and the solid was collected and crystallized from 2-propanol to yield 4.5 g. (45%) of **2b**, m.p. 230-231° dec.; IR (methylene chloride) ν max = 3580, 3380, 1637; (potassium bromide) 1650, 928 cm^{-1}; NMR (DMSO) δ 4.80 (2H, AB quartet, J = 13.5 cps, CH_2), 6.90-7.50 (8H, m, aromatic *H*), 8.14 (1H, broad s, O*H*), 9.92 (1H, broad s, N*H*).

Anal. Calcd. for $C_{15}H_{12}ClN_3O_2$: C, 59.74; H, 4.00; Cl, 11.70; N, 13.90; O, 10.60. Found: C **59.42**; H, 4.06; Cl, 11.75; N, 13.85; O, 10.82.

8-Chloro-1,3-dihydro-6-phenyl-2*H*-4,1,5-benzoxadiazocin-2-one *O*-Acetyloxime (**3**).

To 1.5 g. (0.005 mole) of the oximino derivative **2b** in 10 ml. of glacial acetic acid was added 0.61 g. (0.006 mole) of acetic anhydride and the mixture was stirred at room temperature for four hours. The precipitate was filtered and crystallized from ethanol to yield 1.3 g. (76%) of **3**, m.p. 229-230° dec.; IR (potassium bromide) ν max = 3290, 1633, 1772, 915 cm^{-1}; NMR (DMSO) δ 1.94 (3H, s, $OCOCH_3$), 4.78 (2H, AB quartet, J = 14.5 cps, ring CH_2), 7.0-8.20 (8H, m, aromatic *H*), 8.82 (1H, broad singlet, N*H*).

Anal. Calcd. for $C_{17}H_{14}ClN_3O_3$: C, 59.40; H, 4.10; Cl, 10.30; N, 12.22; O, 13.98. Found: C, 59.48; H, 4.10; Cl, 10.09; N, 12.20; O, 14.16.

8-Chloro-1,3-dihydro-6-phenyl-2*H*-4,1,5-benzoxadiazocin-2-one *O*-Methyloxime (**9**).

To 4.8 g. (0.016 mole) of the oximino derivative **2b** in 64 ml. of dimethyl acetamide was slowly and contemporaneously added

8.8 ml. (0.0176 mole) of 2 *N* sodium hydroxide, diluted with 32 ml. of water, and 2.23 g. (0.0176 mole) of dimethyl sulfate. The mixture was stirred at room temperature overnight and, after dilution with 80 ml. of water, the stirring was continued for two hours. The solid was collected and purified by column chromatography (silica) to yield 1.97 g. (39%) of **9**, m.p. 220-221°; IR (potassium bromide) ν max = 3300, 1624 cm^{-1}; NMR (DMSO) δ 3.62 (3H, s, OCH_3), 4.77 (2H, AB quartet, J = 13.5, ring CH_2), 6.90-7.50 (8H, m, aromatic *H*), 8.34 (1H, broad s, N*H*).

Anal. Calcd. for $C_{16}H_{14}ClN_3O_2$: C, 60.90; H, 4.47; Cl, 11.23; N, 13.32; O, 10.13. Found: C, 61.07; H, 4.50; Cl, 11.36; N, 13.21; O, 10.20.

8-Chloro-1,3-dihydro-6-phenyl-2*H*-4,1,5-benzoxadiazocin-2-one *O*-Dimethylaminoethyl Oxime Hydrochloride (**10**).

To a stirred suspension of 3 g. (0.01 mole) of the oximino derivative **2b** in alcoholic sodium ethoxide [from 0.229 g. (0.01 mole) of sodium and 25 ml. of ethanol] was added 1.45 g. (0.01 mole) of *N,N*-dimethylaminoethyl chloride in alcoholic sodium ethoxide [from 0.229 g. (0.01 mole) of sodium and 25 ml. of ethanol] and the mixture was refluxed for four hours. The sodium chloride was filtered off and the solution, diluted with water, was extracted with chloroform. The organic layer, after drying (calcium chloride) was concentrated and the residue crystallized from acetone, m.p. 181-183°. This product was dissolved in chloroform and saturated with gaseous hydrogen chloride. After dilution with ether the solid was filtered and crystallized from 2-propanol to give 1.43 g. (35%) of **10**, m.p. 210-211° dec.; IR (potassium bromide) ν max = 3240, 2570, 1624 cm^{-1}.

Anal. Calcd. for $C_{19}H_{22}Cl_2N_4O_2$: C, 55.75; H, 5.41; Cl, 17.32; N, 13.68. Found: C, 55.80; H, 5.45; Cl, 17.25; N, 13.59.

2-Hydroxymethyl-4-phenyl-6-chloroquinazoline (**7**).

Three g. (0.01 mole) of the oximino derivative **2b** in 220 ml. of ethanol was hydrogenated, using a Parr apparatus, at room temperature in the presence of 6 g. of Raney Nickel. After filtering, the solution was concentrated and the residue purified by column chromatography (silica) affording 1.32 g. (49%) of **7**, m.p. 129-130°; IR (potassium bromide) ν max = 3435, 1058 cm^{-1}; NMR (deuteriochloroform) δ 3.98 (1H, broad, O*H*), 4.95 (2H, doublet, J = 3.6 cps, CH_2 side chain), 7.40-8.20 (8H, m, aromatic *H*).

Anal. Calcd. for $C_{15}H_{11}ClN_2O$: C, 66.50; H, 4.10; Cl, 13.10; N, 10.36; O.5.93. Found: C, 66.29; H, 4.13; Cl, 13.00; N, 10.26; O, 6.03.

2-Hydroxymethyl-4-phenylquinazoline (**8**).

Three g. (0.01 mole) of the oximino derivative **2b** in 220 ml. of ethanol was hydrogenated, using 6 g. of 5% palladium on carbon, as previously described for the preparation of the compound **7**. The product was crystallized from acetone-water yielding 1.82 g. (76%) of **8**, m.p. 153-155°.

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76; O, 6.71. Found: C, 75.43; H, 6.00; N, 11.63; O, 6.63.

Ethyl *N*-(2-Amino-5-chlorodiphenylmethylene)aminoxy Acetate (*syn* Isomer) (**4**).

Three tenths g. (0.001 mole) of the oximino derivative **2b** was suspended in 10 ml. of 10% alcoholic hydrogen chloride and warmed on a steam bath overnight. Concentration gave a residue from which was chromatographically isolated a product with chemical and physico-chemical properties (m.p., TLC, IR, DSC) identical with an authentic sample of **4** (8).

Anal. Calcd. for $C_{17}H_{18}Cl_2N_2O_3$: C, 55.29; H, 4.91; Cl, 19.20; N, 7.59; O, 13.00. Found: C, 54.81; H, 4.96; Cl, 19.37; N, 7.60; O, 13.20.

8-Chloro-1,3-dihydro-6-phenyl-2*H*-4,1,5-benzoxadiazocin-2-one (**6**).

To 2 g. (0.00663 mole) of the oximino derivative **2b** was added 10 ml. of 40% formaldehyde and 5 ml. of *N* hydrochloric acid and the mixture was warmed on a steam bath for three hours. After dilution with water and extraction with chloroform, the organic layer was concentrated. The oil residue which solidified on standing was purified by column chromatography (silica) giving 1.66 g. (84%) of **6**, m.p. 192-194°.

Anal. Calcd. for $C_{15}H_{11}ClN_2O_2$: C, 62.83; H, 3.87; Cl, 12.36; N, 9.77; O. 11.16. Found: C, 62.90; H, 3.98; Cl, 11.44; N, 9.69; O, 11.33.

Acknowledgments.

The authors wish to thank Dr. E. Pella for the microanalysis and Messrs. C. E. Confalonieri and G. Longo for their technical assistance.

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Received September 9, 1970 Milan, Italy