Benzofurazan Oxide. II. Reactions with Enolate Anions

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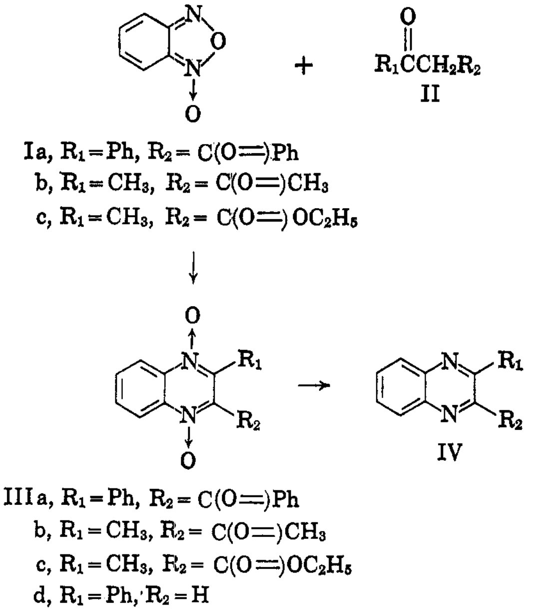
A new synthetic route is described for the preparation of quinoxaline di-N-oxide derivatives from benzofurazan oxide and 1,3-diketones or β-keto esters. A mechanistic interpretation of this reaction is presented.

In a previous paper[1] we reported that benzofurazan oxide (I) reacts readily with enamines to give quinoxaline di-N-oxide derivatives in good yield. The electronic similarity between enamines and enolate anion systems prompted us to investigate the reaction of the latter with benzofurazan oxide. We chose 1,3-diketones and β-keto esters II as model compounds and found that they react directly with I in a basic medium to give substituted quinoxaline di-N-oxides (III).

The reaction of dibenzoylmethane (IIa) with benzofurazan oxide (I) (Scheme I) in triethylamine gave 2-phenyl-3-benzoylquinoxaline di-N-oxide (IIIa) in 38% yield. The structure of this product was established by elemental analysis and its infrared spectrum which displayed bands at 1670 (conjugated carbonyl), 1335 (N-oxide), 770 (*ortho*-substituted phenyl), and 690 cm^{-1} (monosubstituted phenyl). Reduction of IIIa with sodium dithionite gave a product identical (mixture melting point, infrared spectrum) with an authentic sample of 2-phenyl-3-benzoylquinoxaline [IV, R_1 = Ph, R_2 = C(O=)Ph] synthesized from dibenzoylbromomethane and *o*-phenylenediamine.[2]

SCHEME I



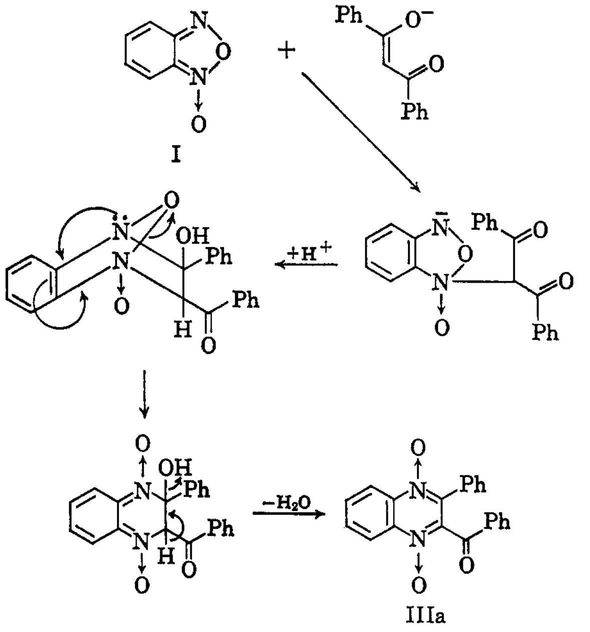
Ia, R_1=Ph, R_2= C(O=)Ph
b, R_1=CH_3, R_2= C(O=)CH_3
c, R_1=CH_3, R_2= C(O=)OC_2H_5

IIIa, R_1=Ph, R_2= C(O=)Ph
b, R_1=CH_3, R_2= C(O=)CH_3
c, R_1=CH_3, R_2= C(O=)OC_2H_5
d, R_1=Ph, R_2=H

Substitution of alcoholic potassium hydroxide for triethylamine in the above reaction gave 2-phenylquinoxaline di-N-oxide (IIId, 90% yield) and not the expected IIIa. Structure IIId was confirmed by an independent synthesis[1] of this compound from benzofurazan oxide and the morpholino derivative of acetophenone. Since dibenzoylmethane is recovered unchanged after treatment with alcoholic potassium hydroxide, it appears that the initial product of the reaction of IIa with benzofurazan oxide in alcoholic potassium hydroxide is IIIa, which then undergoes cleavage by hydroxide ion giving IIId. Support for this view is provided by our finding that alcoholic potassium hydroxide converts IIIa into IIId in excellent yield.

A possible mechanism for the formation of 2-phenyl-3-benzoylquinoxaline di-N-oxide (IIIa) from I and dibenzoylmethane in triethylamine is outlined in Scheme II.[3]

SCHEME II



Acetylacetone (IIb) in triethylamine reacted with I to yield (78%) 2-methyl-3-acetylquinoxaline di-N-oxide (IIIb), the nmr spectrum of which showed singlets at τ 7.55 (3 H) and 7.34 (3 H) and two multiplets centered at 2.24 (2 H) and 1.52 (2 H), respectively. The product showed intense bands in the infrared at 1700 (carbonyl), 1330 (N-oxide), and 770 cm^{-1} (*ortho*-substituted phenyl). These data are consistent with the assigned structure IIIb.

The reaction of ethylacetoacetate (IIc) with I in triethylamine proceeded in the expected manner to give 2-methyl-3-carboethoxyquinoxaline di-N-oxide (IIIc).

The reactions of I with IIb and IIc in alcoholic potassium hydroxide gave intractable mixtures. The failure in these cases to obtain deacylation products corresponding to IIId is not surprising, in view of the

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[1] M. J. Haddadin and C. H. Issidorides, *Tetrahedron Letters*, 3253 (1965).

[2] C. Brandt, G. V. Foerster, and F. Kröhnke, *Ann.*, **688**, 189 (1965).

[3] Although the process may be concerted, the details in this mechanism have been pictured stepwise.

instability[4] to alkali of quinoxaline di-N-oxides with alkyl substituents at positions 2 and 3.

Experimental Section[5]

2-Phenyl-3-benzoylquinoxaline Di-N-oxide (IIIa).—Benzofurazan oxide (I, 3.4 g) and dibenzoylmethane (IIa, 5.6 g) were dissolved in warm triethylamine (25 ml) and allowed to stand at room temperature for 24 hr. The resulting yellow precipitate was thinned with triethylamine and collected by filtration (2.5 g of IIIa). The filtrate was allowed to stand for 30 hr, and a second crop of IIIa was collected (1.1 g). The total yield was 3.6 g (42%). Recrystallization from methanol gave thin yellow needles melting at 234° (90% recovery); infrared spectra: 1670, 1335, 1250, 1090, 900, 870, 770, and 690 cm^{-1}.

Anal. Calcd for $C_{21}H_{14}N_2O_3$: C, 73.67; H, 4.12; N, 8.18. Found: C, 73.88; H, 4.06; N, 8.36.

Reduction of IIIa to 2-Phenyl-3-benzoylquinoxaline (IV).—2-Phenyl-3-benzoylquinoxaline di-N-oxide (IIIa, 0.5 g) was dissolved in hot methanol (150 ml). The solution was cooled to room temperature and concentrated hydrochloric acid was added (1 ml). A solution of sodium dithionite (1 g in 5 ml of warm water) was added slowly to the stirred solution. A black coloration developed and disappeared to give a colorless solution. Water was added (200 ml) and the solution was stirred for 10 min. The resulting yellowish solid was collected, washed with water, and recrystallized from methanol (charcoal treatment) to give shiny prisms melting at 150°, 0.42 g, 92% yield; infrared spectra: 1670, 1018, 925, 770, 740, 715, and 700–690 cm^{-1}. Product IV was identical with a sample of 2-phenyl-3-benzoylquinoxaline prepared by the method of C. Brandt, G. V. Foerster, and F. Kröhnke[2] (mixture melting point and superimposable infrared spectra).

2-Methyl-3-acetylquinoxaline Di-N-oxide (IIIb).—Benzofurazan oxide (I, 5.4 g) and acetylacetone (IIb, 4.5 g) were dissolved in triethylamine (10 ml), and the solution was allowed to stand at room temperature for 18 hr. The yellow precipitate was collected, washed with chilled methanol, and dried to afford 5.45 g of IIIb. The mother liquor, after standing overnight, gave a second crop (1.35 g). The total yield was 6.8 g of IIIb, 78%, mp 152°. Recrystallization from methanol raised the melting point to 153–154°.

The nmr spectrum of product IIIb showed singlets at τ 7.55 (3 H) and 7.34 (3 H) and multiplets centered at 2.24 (2 H) and 1.52 (2 H) in deuterated chloroform with tetramethylsilane (TMS) as internal reference set at 10 (Varian A-60 spectrometer); infrared spectra: 1700, 1510, 1330, 1270, 1100, 1050, 830, and 770 cm^{-1}.

Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.48; H, 4.70; N, 12.33.

2-Methyl-3-carboethoxyquinoxaline Di-N-oxide (IIIc).—A solution of benzofurazan oxide (I, 3.4 g) and ethylacetoacetate (IIc, 3.3 g) in triethylamine (25 ml) yielded IIIc after standing at room temperature for 30 hr. The mother liquor was set aside, and the product was washed with water and recrystallized from acetone–water, giving yellow prisms (1.1 g) melting at 132–133°. Another crop (0.3 g) was obtained from the mother liquor after 18 hr. The total yield was 1.4 g, 22%, mp 132–133°; infrared spectra: 1730, 1510, 1330, 1275, 1240, 1050, 1010–1000, and 770 cm^{-1}.

Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.27; H, 4.74; N, 10.98.

2-Phenylquinoxaline Di-N-oxide (IIId).—To a stirred solution of dibenzoylmethane (IIa, 2.2 g) and benzofurazan oxide (I, 1.5 g) in methanol (50 ml) was added 5% methanolic potassium hydroxide (15 ml). The temperature of the solution rose, and a yellow precipitate appeared within a few minutes. After 2 hr, the product was collected, washed thoroughly with methanol, and dried, giving 2.15 g IIId (91% yield), mp 203–205°. On recrystallization from methanol, bright yellow needles were obtained melting at 205–206° (lit.[6] 202–203°); infrared spectra: 1350, 1240, 1080, 870, 835, 770, 755, and 740 cm^{-1}. Product IIId was identical (mixture melting point, superimposable infrared spectra) with an authentic sample prepared from α-morpholinostyrene and benzofurazan oxide.[1]

Hydrolysis of IIIa to 2-Phenylquinoxaline Di-N-oxide.—2-Phenyl-3-benzoylquinoxaline di-N-oxide (IIIa, 1 g) was suspended in 2% methanolic potassium hydroxide (45 ml). The mixture was heated until the solid dissolved, and then cooled with stirring. The resulting precipitate was collected and washed thoroughly with methanol, yielding 0.65 g (95% yield) of yellow needles melting at 205–206°. The produt was identical with product IIId of the preceeding reaction.

The mother liquor was allowed to stand overnight and filtered. The filtrate was acidified with dilute hydrochloric acid and extracted with ether. The dried ether extract was evaporated to dryness, giving 0.2 g of benzoic acid.

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[4] H. McIlwain, *J. Chem. Soc.*, 322 (1943).

[5] Melting points of most di-N-oxides vary slightly with the rate of heating and are uncorrected. Infrared spectra were run in Nujol mulls on a Perkin-Elmer Model No. 137 spectrophotometer. Analyses were performed by F. Pascher, Bonn, Germany.

[6] J. K. Landquist, *J. Chem. Soc.*, 2822 (1953).