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SYNTHESIS OF SOME PYRROLO[3,4-b]QUINOXALINE 4,9-DIOXIDES

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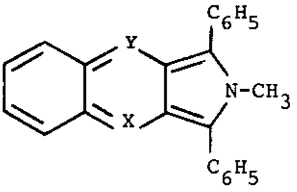
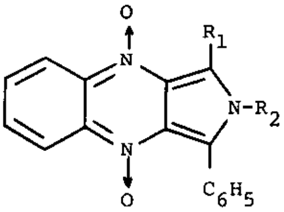
Abstract - The syntheses of a number of derivatives of the, hitherto, unknown pyrrolo[3,4-b]quinoxaline 4,9-dioxides are reported.

In previous reports, we described the syntheses of 1,3-diphenyl-2-methylbenzo[f]isoindole (1a), 1,3-diphenyl-2-methylpyrrolo[3,4-b]quinoline (1b), and 1,3-diphenyl-2-methylpyrrolo[3,4-b]quinoxaline (1c)[1a,b]. With the exception of 2-methylpyrrolo[3,4-b]quinoxaline 4-oxide[2], apparently, no N-oxides of the pyrrolo[3,4-b]quinoxaline system are known. We report a simple method for the synthesis of a number of pyrrolo[3,4-b]quinoxaline 4,9-dioxides (2).



1a, X = Y = CH
1b, X = CH, Y = N
1c, X = Y = N



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The key intermediates in these syntheses were 2-benzoyl-3-bromomethylquinoxaline 1,4-dioxide (5), and 2-benzoyl-3-bromobenzylquinoxaline 1,4-dioxide (6) which were prepared by the addition of bromine (ethyl acetate) to 2-benzoyl-3-methylquinoxaline 1,4-dioxide (3) and to 2-benzoyl-3-benzylquinoxaline 1,4-dioxide (4) in ethyl acetate at reflux temperature[3]. We found that this method is superior to other methods in which the bromination was carried out in chloroform or carbon tetrachloride as solvents.

The various pyrrolo[3,4-b]quinoxaline 4,9-dioxides (table) were prepared by the treatment of the proper bromoquinoxaline, 5 or 6, with the respective primary amines in hot solutions of methanol or 1-propanol. Products 2a-e crystallized out of the reaction mixture and were purified further by thick layer chromatography (TLC). Pyrrolo[3,4-b]quinoxalines 2f-i were extracted from the reaction mixture and purified by TLC. p-Nitroaniline did not react with either 5 or 6 under the above reaction conditions. The yields of 2b-e and 2f-i increased considerably with the increasing electron-releasing properties of the p-substituents of the aromatic amines. Furthermore, the reactions of 6 with amines 7 (R_2 = C_6H_5, p-$CH_3C_6H_4$, p-$CH_3OC_6H_4$, p-BrC_6H_4) to give pyrrolo[3,4-b]quinoxalines 2f-i were rather slow in boiling methanol, however, the rates of these reactions and their yields were improved by using boiling 1-propanol as a solvent. The relatively low reactivity of 6 compared with that of 5 could be partly due to the extra phenyl group in 6.

The structures of pyrrolo[3,4-b]quinoxaline 4,9-dioxides 2a-i, the color of which ranged between violet and indigo-blue, were established by spectroscopic methods (table).

The mass spectra of products 2e, 2f, and 2h displayed a significant mass unit of 105 $(C_6H_5CO)^+$ with intensities of 98%, 30%, and 22% respectively. The formation of a strong benzoyl ion in the mass spectra of 2-phenylisatogen[4] and 2-phenylbenzimidazole 1-oxide[5] has been reported recently, and an oxaziridine intermediate has been postulated to explain the oxygen migration.

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Experimental[7]

2-Benzoyl-3-bromomethylquinoxaline 1,4-dioxide (5)

2-Benzoyl-3-methylquinoxaline 1,4-dioxide (3, 2.8 g, 0.01 mol)[6] was dissolved in ethyl acetate (140 ml). The solution was heated at reflux temperature during which a bromine solution in ethyl acetate (1.6 g, 0.01 mol Br_2 in 20 ml) was added dropwise. The solution was heated for 4 hr after which the solvent was evaporated and the product (5) was collected, 2.4 g (65%) m.p. 177-8°. The analytical sample was purified by TLC and recrystallized from methanol, m.p. 179-80°. I.R. (cm^{-1}): 3060, 1665, 1590, 1505, 1450, 1340, 1275, 1260, 1040, 945, 910, 830, 795, 770, 675, and 655.

Elemental analysis calculated for $C_{16}H_{10}N_2O_3Br$: C, 53.50; H, 3.09; N, 7.80; Br, 22.25. Found: C, 53.70; H, 3.10; N, 7.93; Br, 22.33.

2-Benzoyl-3-bromobenzylquinoxaline 1,4-dioxide (6)

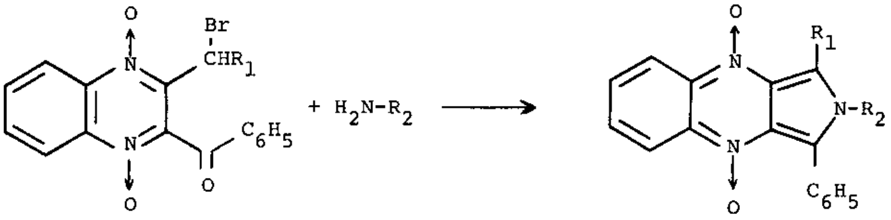
The same procedure used for the preparation of 5 was followed. 2-Benzoyl-3-benzylquinoxaline 1,4-dioxide[1b] (4, 3.56 g, 0.01 mol, in 60 ml ethyl acetate). Bromine (1.6 g, 0.01 mol, in 20 ml ethyl acetate). The reaction time was 2.5 hr. Yield of 6 was 3.4 g (78%), m.p. 157-9°. The analytical sample was purified by TLC and recrystallized from methanol, m.p. 164-6°. I.R. (cm^{-1}): 3060, 2940, 1665, 1590, 1440, 1345, 1330, 1290, 1230, 1045, 945, 770, 715, 680, and 660.

Elemental analysis calculated for $C_{22}H_{15}N_2O_3Br$: C, 60.70; H, 3.47; N, 6.43; Br, 18.36. Found: C, 60.48; H, 3.45; N, 6.51; Br, 18.74.

Preparation of pyrrolo[3,4-b]quinoxaline 4,9-dioxides. General procedure

The specific amine 7 (1.2 mmol) was added to either a methanolic solution of 2-benzyl-3-bromomethylquinoxaline 1,4-dioxide (5, 0.5 mmol, 15 ml methanol) or to a 1-propanol solution of 2-benzyl-3-bromobenzylquinoxaline 1,4-dioxide (6, 0.5 mmol; 15 ml 1-propanol). The solution was heated at reflux temperature for 10 min., and upon cooling, products 2a-e crystallized out of solution whereas products 2f-i were isolated after the evaporation of the solvent and purification by thick layer chromatography. Further purification of all the products was achieved by recrystallization from methanol or methanol-chloroform, or by thick layer chromatography (silica gel, $CHCl_3$, C_6H_6, CH_3OH 100-1).

Table



5, $R_1 = H$ 7 2
6, $R_1 = C_6H_5$

2a $R_1 = H$, $R_2 = CH_3$. M.p. 171-3°C. Yield 10%. IR (cm^{-1}) 3140, 1480, 1380 1350, 1330, 1085, 800, 770, 735, 710, 670. Nmr (δ) 3.9 (s, 3H), 7.55 (m, 7H), 7.65 (s, 1H), 8.44 (m, 2H).

2b $R_1 = H$, $R_2 = C_6H_5$. M.p. 165-7°C. Yield 35%. IR (cm^{-1}) 3090, 1590, 1490, 1480, 1370, 1345, 1320, 1240, 1090, 780, 750, 725, 695. Nmr (δ) 7.4 (s, 5H), 7.5 (s, 5H), 7.74 (m, 2H), 8.28 (s, 1H), 8.4 (m, 2H).

2c $R_1 = H$, $R_2 = C_6H_4$-CH_3-p. M.p. 137-9°C. Yield 83%. IR (cm^{-1}) 3100, 1515, 1475, 1370, 1345, 1320, 1305, 1245, 1090, 830, 775, 760, 700. Nmr (δ) 2.32 (s, 3H), 7.04 (s, 4H), 7.22 (s, 5H), 7.42 (m, 2H), 7.8 (s, 1H, 8.4 (m, 2H).

2d $R_1 = H$, $R_2 = C_6H_4$-OCH_3-p. M.p. 182-4°C. Yield 65%. IR (cm^{-1}) 3130, 3090, 1605, 1510, 1475, 1370, 1345, 1320, 1300, 1250, 1180, 1090, 1080, 1030, 775, 755, 705, 680. Nmr (δ) 3.8 (s, 3H), 7.1 (m, 9H), 7.5 (m, 2H), 7.82 (s, 1H), 8.4 (m, 2H).

2e $R_1 = H$, $R_2 = C_6H_4$-Br-p. M.p. 188-9°C. Yield 38%. IR (cm^{-1}) 3090, 1490, 1470, 1360, 1340, 1310, 1090, 1080, 1060, 1010, 760, 745, 725. Nmr (δ) 7.44 (m, 11H), 8.08 (s, 1H), 8.66 (m, 2H). Mass spec. m/e (relative intensity) 433 (M^+, 15), 431 (17), 417 (16), 415 (18), 277 (14), 261 (100), 260 (9), 258 (11), 218 (8), 205 (41), 173 (16), 171 (18), 157 (8), 155 (8), 129 (14), 105 (98), 102 (17), 90 (11), 77 (76).

2f $R_1 = C_6H_5$, $R_2 = C_6H_5$. M.p. 189-91°C. Yield 15%. IR (cm^{-1}) 3060, 1500, 1480, 1400, 1350, 1315, 1230, 1090, 820, 780, 735, 710, 690. Nmr (δ) 7.2 (m, 15H), 7.5 (m, 2H), 8.4 (m, 2H). Mass spec. m/e (relative intensity) 429 (M^+, 8), 413 (48), 412 (6), 397 (54), 396 (12), 322 (8), 308 (4), 292 (7), 198 (7), 181 (16), 180 (100), 165 (8), 105 (30), 77 (61).

2g $R_1 = C_6H_5$, $R_2 = C_6H_4\text{-}CH_3\text{-}p$. M.p. 212-3°C. Yield 18%. IR (cm^{-1}) 3060, 1510, 1470, 1450, 1400, 1350, 1305, 1225, 1180, 1085, 1030, 840, 810, 770, 745, 705. Nmr (δ) 2.2 (s, 3H), 6.85 (s, 4H), 7.22 (s, 10H), 7.55 (m, 2H), 8.4 (m, 2H).

2h $R_1 = C_6H_5$, $R_2 = C_6H_4\text{-}OCH_3\text{-}p$. M.p. 223-5°C. Yield 26%. IR (cm^{-1}) 3060, 1510, 1470, 1450, 1400, 1350, 1315, 1300, 1260, 1225, 1090, 1025, 845, 775, 770, 750, 705. Mass spec. m/e (relative intensity) 459 (M^+, 18), 443 (64), 427 (52), 350 (5), 338 (4), 322 (9), 295 (3), 294 (4), 210 (100), 195 (4), 167 (4), 105 (22), 92 (10), 77 (28).

2i $R_1 = C_6H_5$, $R_2 = C_6H_4\text{-}Br\text{-}p$. M.p. 206-8°C. Yield 4%. IR (cm^{-1}) 3080, 1480, 1470, 1340, 1305, 1220, 1185, 1165, 1110, 840, 800, 765, 740, 735, 690. Nmr (δ) 6.84 (d, 2H), 7.35 (m, 14H), 7.5 (m, 4H), 8.4 (m, 2H).

Elemental Analysis

Compound		Calculated				Found			
	Formula	C	H	N	Br	C	H	N	Br
2a	$C_{17}H_{13}N_3O_2$	70.09	4.50	14.43	-	69.59	4.54	14.20	-
2b	$C_{22}H_{15}N_3O_2 \cdot H_2O$	71.15	4.61	11.32	-	70.33	4.70	10.80	-
2c	$C_{23}H_{17}N_3O_2 \cdot H_2O$	71.69	4.97	10.90	-	72.17	4.86	10.72	-
2d	$C_{23}H_{17}N_3O_3$	72.05	4.47	10.96	-	71.65	4.49	10.80	-
2e	$C_{22}H_{14}N_3O_2Br$	61.12	3.26	9.72	18.49	61.00	3.31	9.72	18.74
2f	$C_{28}H_{19}N_3O_2$	78.30	4.46	9.78	-	78.36	4.58	9.55	-
2g	$C_{29}H_{21}N_3O_2 \cdot CH_3OH$	75.77	5.30	8.84	-	75.01	5.08	8.84	-
2h	$C_{29}H_{21}N_3O_3$	75.80	4.61	9.15	-	74.93	4.45	9.06	-
2i	$C_{28}H_{18}N_3O_2Br$	66.15	3.57	8.26	15.72	66.03	3.70	8.33	15.86

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7. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded as potassium bromide disks using Perkin-Elmer grating infrared spectrometer models 257 and 621. Proton nmr spectra were taken on a Varian T60 spectrometer in deuterated chloroform with tetramethylsilane as internal reference. Mass spectra were determined on a AEI 902 spectrometer. Silica gel Merck 60 PF_{254} was used in thick layer chromatography. Elemental analyses were performed by E. Pascher, West Germany.

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