Synthesis of 1,2,3,4,4a,5-Hexahydropyrido-[1′,2′:4,5][1,4]oxazino[2,3-*b*]quinoxaline Derivatives

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Reactions of 2,3-dichloroquinoxalines with 2-(hydroxymethyl)piperidine resulted in a series of 1,2,3,4,4a,5-hexahydropyrido[1′,2′:4,5][1,4]oxazino[2,3-*b*]quinoxaline derivatives. The structures of the products were confirmed by nmr and x-ray crystallography.

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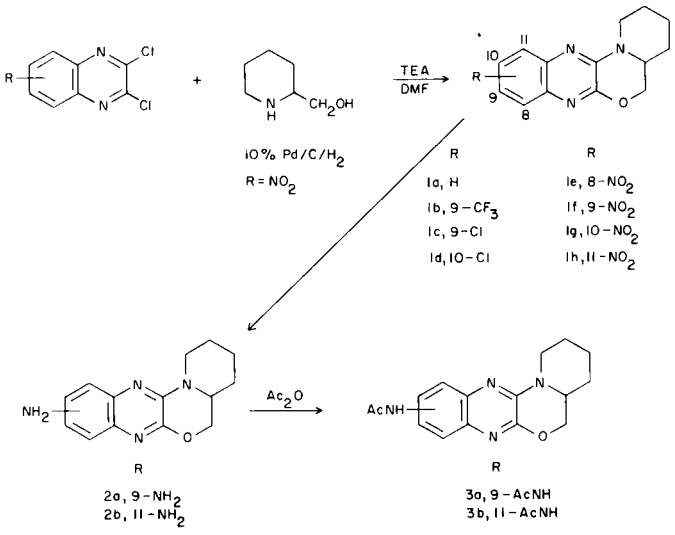
As part of an investigation into the reactions of 2,3-dichloroquinoxalines, we have prepared a series of 1,2,3,4,4a,5-hexahydropyrido[1′,2′:4,5][1,4]oxazino[2,3-*b*]-quinoxaline derivatives. As this polycyclic ring system appears to be unknown in the literature, we wish to report on the synthesis and properties of these compounds.

When 2,3-dichloroquinoxalines were heated with 2-(hydroxymethyl)piperidine in the presence of triethylamine as acid binder and dimethylformamide as solvent, derivatives of 1,2,3,4,4a,5-hexahydropyrido[1′,2′:4,5][1,4]-oxazino[2,3-*b*]quinoxaline were obtained (Scheme I and Table I). Reactions in which R was chloro or nitro resulted in two isomeric products, which were isolated in pure form by a combination of recrystallization and chromatography (see Experimental Section). The correct structure of one isomer (**1d, 1g, 1h**) of each pair was determined by x-ray crystallography (1) and the structure of the second isomer (**1c,1e,1f**) was assigned accordingly. The structure of the 9-trifluoromethyl derivative (**1b**) was also determined by x-ray crystallography. Nmr determinations were in agreement with the assigned structures.

The 9-amino (**2a**) and 11-amino (**2b**) derivatives were prepared by catalytic reduction of the corresponding nitro compounds and were converted to the 9-acetamido (**3a**) and 11-acetamido (**3b**) derivatives by reaction with acetic anhydride.

Scheme I



EXPERIMENTAL

The preparation of the compounds is described below using general procedures where possible. Physical constants, yields and analytical values are reported in Table I. Melting points were taken using a Mel-Temp apparatus with open capillaries and are uncorrected. The nmr spectra were recorded on a Varian HA-100 spectrometer with tetramethylsilane as the internal reference.

Procedure A. 1,2,3,4,4a,5-Hexahydropyrido[1′,2′:4,5][1,4]oxazino[2,3-*b*]-quinoxaline (**1a**) and 1,2,3,4,4a,5-Hexahydro-9-(trifluoromethyl)pyrido-[1′,2′:4,5][1,4]oxazino[2,3-*b*]quinoxaline (**1b**).

A mixture of 0.1 mole of the 2,3-dichloroquinoxaline, 13.8 g. (0.12 mole) of 2-(hydroxymethyl)piperidine, 40 ml. of triethylamine and 200 ml. of dimethylformamide was heated on the steam bath for 44 hours and diluted with 400 ml. of water. The crystalline product was filtered, washed with water and air dried. The crude product was dissolved in methylene chloride, passed through magnesium silicate, recovered, and recrystallized from ethyl acetate; nmr of **1a** (deuteriodimethylsulfoxide): δ 1-2 (6H, m, $CH_2CH_2CH_2$), 2.72 (1H, t, H-1, J = 12 Hz), 3.48 (1H, m, H-4a), 4.16 (1H, dd, H-5, J = 8,11 Hz), 4.46 (1H, dd, H-5′, J = 4,11 Hz), 4.74 (1H, d, H-1′, J = 12 Hz), 7.2-7.7 (4H, m, H-8,9,10,11); nmr of **1b** (deuteriodimethylsulfoxide): δ 1-2 (6H, m, $CH_2CH_2CH_2$), 2.81 (1H, t, H-1, J = 12 Hz), 3.60 (1H, m, H-4a), 4.25 (1H, dd, H-5, J = 8,11 Hz), 4.55 (1H, dd, H-5′, J = 4,11 Hz), 4.75 (1H, d, H-1′, J = 13 Hz), 7.68 (2H, d, H-10,11, J = 1,2 Hz), 7.85 (1H, t, H-8, J = 1,2 Hz).

Procedure B. 9-Chloro-1,2,3,4,4a,5-hexahydropyrido[1′,2′:4,5][1,4]oxazino[2,3-*b*]quinoxaline (**1c**) and 10-Chloro-1,2,3,4,4a,5-hexahydropyrido-[1′,2′:4,5][1,4]oxazino[2,3-*b*]quinoxaline (**1d**).

2,3,6-Trichloroquinoxaline (23.3 g., 0.1 mole), 11.5 g. (0.1 mole) of 2-(hydroxymethyl)piperidine, 40 ml. of triethylamine and 400 ml. of dimethylformamide was stirred at room temperature for 4 hours and then heated on the steam bath for 48 hours. Water (500 ml.) was added dropwise, and the precipitate was filtered off, washed with water and air dried. The crude product (21.0 g.) was dissolved in methylene chloride, passed through magnesium silicate, recovered and recrystallized from ethyl acetate for 10.2 g., m.p. 139-143°. Recrystallization twice from ethanol resulted in pure **1d**, m.p. 150-152°. Recoveries and fractional cyrstallization from the mother liquors resulted in a 33% yield of **1d** plus a 15% yield of **1c**, m.p. 107-109°; nmr of **1c** (deuteriodimethylsulfoxide): δ 1-2 (6H, m, $CH_2CH_2CH_2$), 2.74 (1H, t, H-1, J = 12 Hz), 3.50 (1H, m, H-4a), 4.16 (1H, dd, H-5, J = 8,12 Hz), 4.48 (1H, dd, H-5′, J = 4,12 Hz), 4.70 (1H, d, H-1′, J = 13 Hz), 7.1-7.6 (3H, m, H-8,10,11); nmr of **1d** (deuteriodimethylsulfoxide): δ 1-2 (6H, m, $CH_2CH_2CH_2$), 2.76 (1H, t, H-1, J = 12 Hz), 3.52 (1H, m, H-4a), 4.16 (1H, dd, H-5, J = 8,12 Hz), 4.48 (1H, dd, H-5′, J = 4,12 Hz), 4.70 (1H, d, H-1′, J = 13 Hz), 7.26 (1H, dd, H-9, J = 2,9 Hz), 7.50 (2H, m, H-8,11).

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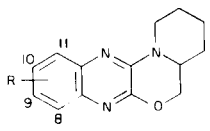
Table I

1,2,3,4,4a,5-Hexahydropyrido[1′,2′:4,5]oxazino[2,3-*b*]quinoxalines



Compound	R	Procedure	M.p., °C	Yield, %	Molecular Formula		C	H	N
1a	H	A	141-143	71	$C_{14}H_{15}N_3O$	Calcd.	69.69	6.27	17.42
						Found	69.69	6.25	17.30
1b	9-CF_3	A	155-157	40 (a)	$C_{15}H_{14}F_3N_3O$	Calcd.	58.25	4.57	13.58
						Found	58.59	4.68	13.69
1c	9-Cl	B	107-109	15 (b)	$C_{14}H_{14}ClN_3O$ (c)	Calcd.	60.98	5.12	15.24
						Found	61.34	5.32	15.43
1d	10-Cl	B	150-152	33 (b)	$C_{14}H_{14}ClN_3O$ (d)	Calcd.	60.98	5.12	15.24
						Found	61.15	5.17	15.41
1e	8-NO_2	C	205-207	(e)	$C_{14}H_{14}N_4O_3$	Calcd.	58.73	4.93	19.57
						Found	58.33	4.96	19.51
1f	9-NO_2	D	151-154	53	$C_{14}H_{14}N_4O_3$	Calcd.	58.73	4.93	19.57
						Found	58.87	5.06	19.49
1g	10-NO_2	D	237-242	(e)	$C_{14}H_{14}N_4O_3$	Calcd.	58.73	4.93	19.57
						Found	58.32	5.05	19.29
1h	11-NO_2	C	182-184	23	$C_{14}H_{14}N_4O_3$	Calcd.	58.73	4.93	19.57
						Found	58.79	4.99	19.35
2a	9-NH_2	E	229-232	92	$C_{14}H_{16}N_4O$	Calcd.	65.60	6.29	21.86
						Found	65.77	6.42	22.18
2b	11-NH_2	E	207-209	80	$C_{14}H_{16}N_4O$	Calcd.	65.60	6.29	21.86
						Found	65.76	6.38	22.07
3a	9-AcNH	F	245-247	57	$C_{16}H_{18}N_4O_2$	Calcd.	64.41	6.08	18.76
						Found	64.29	5.99	18.55
3b	11-AcNH	F	257-261	90	$C_{16}H_{18}N_4O_2$	Calcd.	64.41	6.08	18.76
						Found	64.49	6.29	18.62

(a) Calcd. for fluorine: 18.43. Found: 18.36. (b) 76% crude yield of mixed isomers. (c) Calcd. for chlorine: 12.86. Found: 13.11. (d) Calcd. for chlorine: 12.86. Found: 12.90. (e) Minor product from chromatography.

Procedure C. 1,2,3,4,4a,5-Hexahydro-8-nitropyrido[1′,2′:4,5][1,4]oxazino-[2,3-*b*]quinoxaline (**1e**) and 1,2,3,4,4a,5-Hexahydro-11-nitropyrido[1′,2′:4,5][1,4]oxazino[2,3-*b*]quinoxaline (**1h**).

A mixture of 24.4 g. (0.1 mole) of 2,3-dichloro-5-nitroquinoxaline (2), 12.4 ml. (0.1 mole) of 2-(hydroxymethyl)piperidine, 40 ml. of triethylamine and 400 ml. of dimethylformamide was stirred for 4 hours and then heated on the steam bath for 48 hours. The reaction mixture was diluted with 600 ml. of water, cooled overnight and filtered. The crude product was dissolved in methylene chloride, passed through magnesium silicate and recovered (19.8 g.). Recrystallization twice from ethyl acetate resulted in pure **1h**. Recoveries gave mixtures difficult to purify. The second isomer (**1e**) was obtained by a combination of partition chromatography using a heptane, methanol, diatomaceous earth system and thick plate chromatography; nmr of **1e** (deuteriodimethylsulfoxide): δ 1-2 (6H, m, $CH_2CH_2CH_2$), 2.81 (1H, t, H-1, J = 12 Hz), 3.60 (H, m, H-4a), 4.26 (1H, dd, H-5, J = 8,11 Hz), 4.55 (1H, dd, H-5′, J = 4,11 Hz), 4.71 (1H, d, H-1′, J = 12 Hz), 7.53 (1H, m, H-10), 7.80 (2H, m, H-9,11); nmr of **1h** (deuteriodimethylsulfoxide): δ 1-2 (6H, m, $CH_2CH_2CH_2$), 2.80 (1H, t, H-1, J = 13 Hz), 3.64 (1H, m, H-4a), 4.26 (1H, dd, H-5, J = 8,12 Hz), 4.60 (1H, dd, H-5′, J = 4,12 Hz), 4.72 (1H, d, H-1′, J = 13 Hz), 7.40 (1H, dd, H-9, J = 8,10 Hz), 7.84 (2H, m, H-8,10).

Procedure D. 1,2,3,4,4a,5-Hexahydro-9-nitropyrido[1′,2′:4,5][1,4]oxazino-[2,3-*b*]quinoxaline (**1f**) and 1,2,3,4,4a,5-Hexahydro-10-nitropyrido[1′,2′:4,5][1,4]oxazino[2,3-*b*]quinoxaline (**1g**).

2,3-Dichloro-6-nitroquinoxaline (2) (36.6 g., 0.15 mole), 17.3 g. (0.15 mole) of 2-(hydroxymethyl)piperidine, 60 ml. of triethylamine and 500 ml. of dimethylformamide were stirred for 4 hours, heated on the steam bath for 48 hours, diluted with 700 ml. of water and cooled overnight. The water was decanted and the residue was taken up in methylene chloride, washed once with water and passed through magnesium silicate. The solution was concentrated to remove the solvent and the oil was dissolved in ethyl acetate and cooled. The crystals were filtered off and recrystallized from ethyl acetate for pure **1f**, 7.6 g. (18%), m.p. 151-154°. The filtrate from the first precipitate was concentrated to remove the solvent and triturated with ether for a second fraction, 10.5 g., m.p. 138-143°. This was boiled with the mother liquor from the above pure **1f** and an insoluble portion, 0.43 g., m.p. 226-229°, of impure **1g** was obtained. When the filtrate was cooled, 5.9 g. (14%) of **1f** m.p. 150-154°, was obtained. Additional fractional recrystallization increased the total yield to 53%. Pure **1g**, 0.3 g., m.p. 237-242° was obtained by partition chromatography of mother liquors using a heptane, methyl cellosolve, diatomaceous earth system; nmr of **1f** (deuteriodimethylsulfoxide): δ 1-2 (6H, m, $CH_2CH_2CH_2$), 2.84 (1H, t, H-1, J = 12 Hz), 3.64 (1H, m, H-4a), 4.24 (1H, dd, H-5, J = 8,12 Hz), 4.54 (H, dd, H-5′, J = 4,12 Hz), 4.81 (1H, d, H-1′, J = 13 Hz), 7.56 (1H, d, H-11, J = 9 Hz), 8.10 (1H, dd, H-10, J = 2,9 Hz), 8.25 (1H, d, H-8, J = 2 Hz); nmr of **1g** (deuteriodimethylsulfoxide): δ 1-2 (6H, m, $CH_2CH_2CH_2$), 2.82 (1H, t, H-1, J = 12 Hz), 3.64 (1H, m, H-4a), 4.24 (1H, dd, H-5, J = 8,12 Hz), 4.56 (1H, dd, H-5′, J = 4,12 Hz), 4.72 (1H, d, H-1′, J = 13 Hz), 7.68 (1H, d, H-8, J = 9 Hz), 8.04 (1H, dd, H-9, J = 2,9 Hz), 8.25 (1H, d, H-11, J = 2 Hz).

Procedure E. 9-Amino-1,2,3,4,4a,5-hexahydropyrido[1′,2′:4,5[[1,4]oxazino[2,3-*b*]quinoxaline (**2a**) and 11-Amino-1,2,3,4,4a,5-hexahydropyrido-[1′,2′:4,5][1,4]oxazino[2,3-*b*]quinoxaline (**2b**).

The nitro derivative (5.72 g., 0.02 mole), 200 ml. of dioxane and 1.5 g. of palladium-on-carbon catalyst was shaken in a Parr hydrogenator under about 3 atmospheres of hydrogen pressure until reduction was complete. The catalyst was filtered off and the mother liquor was concentrated to remove the solvent. The crystalline residue was washed onto a filter with ether. A sample was recrystallized from ethanol for microanalysis.

Procedure F. *N*-(1,2,3,4,4a,5-Hexahydropyrido[1′,2′:4,5][1,4]oxazino-[2,3-*b*]quinoxalin-9-yl)acetamide (**3a**) and *N*-(1,2,3,4,4a,5-Hexahydropyrido-[1′,2′:4,5][1,4]oxazino[2,3-*b*]quinoxalin-11-yl)acetamide (**3b**).

When the amide (**2a,2b**) was mixed with about 3 parts of acetic anhydride, an exothermic reaction occurred. The reaction mixture was allowed to stand for 4-6 hours, diluted with ether and filtered. The product was purified by recrystallization from ethanol.

2,3-Dichloro-6-trifluoromethylquinoxaline.

A mixture of 23.0 g. (0.1 mole) of 6-trifluoromethyl-2,3-quinoxalinediol (3) 50 g. of phosphorus pentachloride, and 6 ml. of phosphorus oxychloride was carefully heated to reflux temperature and held for 4 hours. The solution was allowed to cool, poured into ice water and filtered. The crude product was extracted into methylene chloride, washed with water, dried over magnesium sulfate and concentrated. The residue was triturated with hexane and filtered. The 2,3-dichloro-6-trifluoromethylquinoxaline melted at 81-83°.

Anal. Calcd. for $C_9H_3Cl_2F_3N_2$: C, 40.49; H, 1.14; Cl, 26.56; F. 21.35; N, 10.50. Found: C, 40.34; H, 1.19; Cl, 26.54; F, 20.91; N, 10.52.

REFERENCES AND NOTES

(1) X-ray crystallography was determined by Dr. F. M. Lovell and N. A. Perkinson.

(2) H. I. X. Mager and W. Berendo, *Rec. Trav. Chim.*, **78**, 5 (1959).

(3) R. L. St. Clair, T. D. Thibault, German Offen, 2,459,453 (1975); *Chem. Abstr.*, **83**, 164237X (1975).