Cinnoline Chemistry XIII. 4-Aziridinocinnolines (1)

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Nine substituted 4-aziridinocinnolines have been prepared and subjected to anticancer screening.

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The known anticancer and antileukemic activity of aziridines is well known (4). Thus it appeared of interest to synthesize some 4-aziridinocinnolines for anticancer screening.

From nine known 4-chlorocinnolines, nine aziridinocinnolines have been prepared by allowing the chlorocinnoline to react with a threefold molar excess of aziridine in dry benzene solution in the presence of excess triethylamine. The nitrochlorocinnolines reacted with the greatest ease producing 4-aziridino-6-nitrocinnoline (**8**) in 97% yield and 4-aziridino-8-nitrocinnoline (**9**) in 61% yield. 4-Aziridinocinnoline (**1**) reacted very slowly but was obtained in 64% yield after deducting the 63% of unchanged 4-chlorocinnoline recovered. 4,5-Dichlorocinnoline when allowed to react with aziridine gave 4-aziridino-5-chlorocinnoline (**3**) in 73% yield. 4-Aziridino-8-chlorocinnoline was obtained in a yield of 24%, while the 4-aziridino-6-chloro- (**4**), 4-aziridino-6,7-dichloro- (**6**) and 4-aziridino-6-bromocinnolines (**7**) were each obtained in a yield of 14%. 4-Aziridino-6-fluorocinnoline (**2**) was obtained in a yield of 12%.

The aziridinocinnolines were screened for antitumor activity (5). 4-Aziridino-6-nitrocinnoline (**8**) was active against KB cells in cell culture with a slope of -0.88 and $ED_{50} = 3.6 \times 10^{\circ}$ μg./ml.

EXPERIMENTAL

Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The pmr spectra were recorded on a Varian EM-390 90/MHz spectrometer in the solvent indicated using TMS as the internal standard.

Starting Materials.

The following 4-chlorocinnolines were used as the starting materials: 4-chlorocinnoline (6), 4-chloro-6-fluorocinnoline (7), 4,5-dichlorocinnoline (8), 4,8-dichlorocinnoline (9), 4,6,7-trichlorocinnoline (10), 6-bromo-4-chlorocinnoline (6,11), 4-chloro-6-nitrocinnoline (12) and 4-chloro-8-nitrocinnoline (9).

General Procedure for the Preparation of the 4-Aziridinocinnolines.

The preparation of 4-aziridinocinnoline is described below. A solution containing 6.45 g. (0.15 mole) of aziridine, 30.4 g. (0.3 mole) of triethylamine and 8.0 g. (0.0487 mole) of 4-chlorocinnoline (6) in 100 ml. of dry benzene was heated for about 100 hours at 45-55°. The benzene was removed under reduced pressure to about 20 ml. and the solution was chromatographed on alumina first using benzene, then ether as the eluents. About 5.0 g. of unreacted 4-chlorocinnoline was recovered from the benzene and ether eluates. Elution with ethyl acetate gave, after evaporation, 2.0 g. (64%) of 4-aziridinocinnoline, m.p. 84°.

The analytical and spectral data on 4-aziridinocinnoline and the substituted 4-aziridinocinnolines are recorded in the Table.

In the case of the nitroaziridinocinnolines, the reaction was exothermic and triethylamine hydrochloride separated from the benzene solution. The nitroaziridinocinnolines were recrystallized from benzene. 4,5-Dichlorocinnoline reacted more readily than the other halo-substituted 4-chlorocinnolines under the conditions described for 4-aziridinocinnoline. 4-Aziridino-5-chlorocinnoline was recrystallized from benzene. The other aziridinocinnolines were recrystallized from ethyl acetate.

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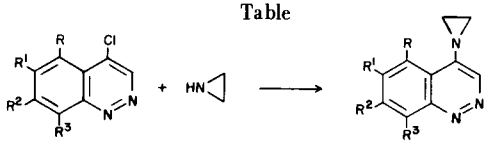
Table



Compound No.	R	R^1	R^2	R^3	M.p. °C	Yield %	Molecular Formula	Analyses: Calcd. (Found) C	H	N	Proton Magnetic Resonance
1	H	H	H	H	84	64	$C_{10}H_9N_3$	70.15 (69.78)	5.29 (5.03)		(a) 8.76 (s, H_3), 8.35-7.93 (m, 4H), 4.97-4.84 (t, 2H), 4.43-4.27 (q, 2H) (b) 9.04 (s, H_3), 8.49-7.79 (m, 4H), 2.56 (s, 4H)
1 picrate					178-181		$C_{10}H_9N_3 \cdot C_6H_3N_3O_7$	48.00 (47.99)	3.02 (2.69)		
2	H	F	H	H	140	12	$C_{10}H_8FN_3$	63.48 (63.01)	4.26 (4.15)		(c) 8.97 (s, H_3), 8.66-7.50 (m, 3H), 2.46 (s, 4H)
3	Cl	H	H	H	152-153	73	$C_{10}H_8ClN_3$	58.39 (58.44)	3.92 (3.77)		(c) 8.97 (s, H_3), 8.43-7.66 (m, 3H), 2.56 (s, 4H)
4	H	Cl	H	H	148 dec.	14	$C_{10}H_8ClN_3$	58.39 (58.62)	3.92 (3.61)	20.43 (20.63)	(c) 9.04 (s, H_3), 8.68-7.78 (m, 3H), 2.60 (s, 4H)
4 picrate					205 dec.		$C_8H_{10}ClN_3 \cdot C_6H_3N_3O_7$	44.19 (44.23)	2.55 (2.39)		
5	H	H	H	Cl	136	24	$C_{10}H_8ClN_3$	58.39 (58.59)	3.92 (3.79)		(c) 9.00 (s, H_3), 8.27-7.58 (m, 3H), 2.45 (s, 4H)
6	H	Cl	Cl	H	169	14	$C_{10}H_7Cl_2N_3$	50.02 (49.93)	2.94 (2.81)	17.50 (17.68)	(c) 8.98 (s, H_3), 8.63 (s, H_8), 8.37 (s, H_5), 2.50 (s, 4H)
7	H	Br	H	H	142	14	$C_{10}H_8BrN_3$	48.02 (48.42)	3.22 (3.47)	16.82 (16.90)	(c) 8.97 (s, H_3), 8.43-7.87 (m, 3H), 2.50 (s, 4H)
8	H	NO_2	H	H	175-177	97	$C_{10}H_8N_4O_2$	55.55 (55.71)	3.73 (3.73)	25.84 (26.20)	(c) 9.22 (s, H_5), 9.13 (s, H_3), 8.65 (d, $H_{7,8}$), 2.47 (s, 4H)
9	H	H	H	NO_2	169-170 dec.	61	$C_{10}H_8N_4O_2$	55.55 (55.68)	3.73 (3.59)	25.84 (25.91)	(c) 9.20 (s, H_3), 8.64-7.81 (m, 3H), 2.63 (s, 4H)

(a) Trifluoroacetic acid. (b) DMSO-d_6. (c) Deuteriochloroform.