Spirans XVIII (1). *gem*-Dialkyl and Spirotetrahydrocarbazoles (2)

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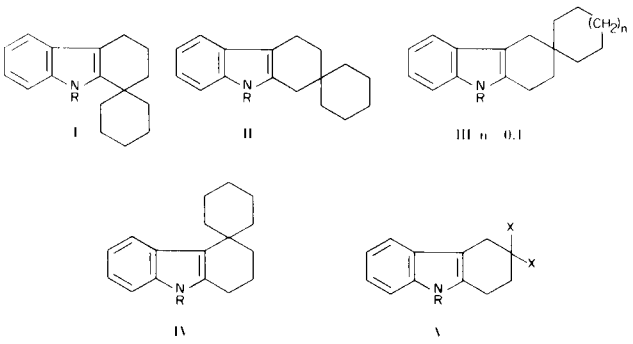
The reactions of 4,4-dialkylcyclohexanones, spiro[4.5]decan-8-one and various spiro[5.5]-undecanones with phenylhydrazines to produce corresponding 3,3-dialkyltetrahydro and spiro (cycloalkyl 1,n′)-1′,2′,3′,4′-tetrahydrocarbazoles (n = 1, 2 or 3) by the Fischer indole synthesis were examined. Structural assignment of the one isomeric product derived from spiro[5.5]-undecan-2-one was obtained on the basis of pmr spectra.

In a continuing investigation in tetrahydrocarbazoles (3) directed toward biologically active substances we have now examined the reactions of various *gem*-substituted cyclic ketones in a modified Fischer indole synthesis (4). The products obtained contain a number of unique ring systems, mainly I, II, and III.



The reactions of 4,4-dimethylcyclohexanone (5a) and 4,4-diethylcyclohexanone (5b) proceeded normally with phenylhydrazine or 1-methyl-1-phenylhydrazine to yield the corresponding 3,3-dialkyltetrahydrocarbazoles, V (X = CH_3; C_2H_5). In a like manner spiro[4.5]decan-8-one (6), spiro[5.5]undecan-3-one (7) and 9-methylspiro[5.5]-undecan-3-one (6) gave the ring system III.

Spiro[5.5]undecan-1-one (8), a somewhat hindered ketone afforded I in excellent yield. In the same reaction of spiro[5.5]undecan-2-one (9,10) two isomeric ring systems (II and IV) were possible. However, one product was isolated in very good yield whose pmr spectra was compatible only with structure II.

Comparison of pmr spectra of 1,1 (I, R = H) and 3,3 (III, R = H) substituted tetrahydrocarbazoles with the spectrum of the tetrahydrocarbazole obtained from spiro[5.5]undecan-2-one indicated that this tetrahydrocarbazole was substituted in the 2,2 (II, R = H) position rather than 4,4 (IV, R = H) position on the basis of the number of allylic protons present: 1,1 (deuteriochloroform) δ 1.53, S, 10; 1.78, m, 4; 2.63, m, 2; 7.15, m, 3; and 7.50, m, 2. 3,3 (deuteriochloroform) δ 1.44, s, 10; 1.68, t, 2, (J = 6 Hz); 2.50, broad S, 4; 7.10, m, 4; 7.33, broad singlet, 1. 2,2 (deuteriochloroform) δ 1.43, S, 10; 1.66, t, 2 (J = 6 Hz); 2.37, broad singlet, 2; 2.63, triplet, 2 (J = 6 Hz); 7.13, m, 4; and 7.43, broad singlet, 1.

The 3,3-dialkyltetrahydrocarbazoles and the 1,1′; 1,2′; and 1,3′ spirotetrahydrocarbazoles (R = H) were converted to *N*-substituted derivatives with various dialkylaminoalkyl chlorides by means of sodium hydride employing dimethylformamide as a solvent. All compounds prepared are listed in Table I with appropriate data.

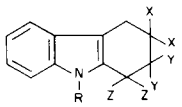
Many of the compounds listed in Table I have been assayed against tissue cultures of human cancer cells (lymphoma, breast and prostate) for their antineoplastic activity. Compounds in which the R substituent on the nitrogen was either hydrogen or methyl did not possess any significant activity. Compounds 2, 3, 13 and 15 showed activities at less than 10 gamma per ml., with compound 2 showing toxic degeneration in the cultured cells at 1 gamma per ml. This compound had an acute toxicity of approximately 200 mg./kg. These compounds, a different class of spirans, are less active than some previously reported spirans (11) in which the nitrogen is part of the alicyclic ring containing the spiro carbon atom. However, they still possess some high order of activity.

EXPERIMENTAL

All melting points were determined on a Thomas-Hoover capillary type melting apparatus and are corrected. All compounds corresponded in structure to their infrared spectra. Microanalyses

TABLE I

gem-Dialkyl and Spirotetrahydrocarbazoles



	X X	Y Y	Z Z	R	M.p. or B.p. °C	Empirical Formula	Analyses Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1.	–C–C(C)–C–	H H	H H	H	133-134	$C_{17}H_{21}N$	85.31	85.26	8.84	8.91	5.85	6.03
2.	–C–C(C)–C–	H H	H H	$(CH_2)_2N(C_2H_5)_2$ (a)	170-180 0.05	$C_{23}H_{34}N_2$	81.60	81.78	10.12	10.24	8.27	8.18
3.	–C–C(C)–C–	H H	H H	$(CH_2)_3N(CH_3)_2$ (b)	168-175 0.05	$C_{22}H_{32}N_2$	81.43	81.64	9.94	10.12	8.63	8.44
4.	–C–C(C–C)–C–	H H	H H	H	163-165	$C_{18}H_{23}N$	85.32	85.02	9.15	9.17	5.53	5.41
5.	–C–C(–)–C–	H H	H H	H	97-98	$C_{16}H_{19}N$	85.28	85.42	8.50	8.43	6.22	6.18
6.	CH_3CH_3	H H	H H	H	107-108	$C_{14}H_{17}N$	84.37	84.27	8.60	8.63	7.03	7.26
7.	CH_3CH_3	H H	H H	$(CH_2)_2N(C_2H_5)_2$ (c)	136-140 0.03	$C_{20}H_{30}N_2$	80.48	80.35	10.13	10.31	9.39	9.19
8.	CH_3CH_3	H H	H H	$(CH_2)_3N(CH_3)_2$ (d)	135-138 0.03	$C_{19}H_{28}N_2$	80.23	80.24	9.92	10.06	9.85	9.61
9.	C_2H_5 C_2H_5	H H	H H	H	87-88	$C_{16}H_{21}N$	84.53	84.81	9.31	9.45	6.16	6.19
10.	C_2H_5 C_2H_5	H H	H H	CH_3	66-67	$C_{17}H_{23}N$	84.59	84.81	9.61	9.80	5.80	5.54
11.	C_2H_5 C_2H_5	H H	H H	$(CH_2)_3N(CH_3)_2$ (e)	155-157 0.04	$C_{21}H_{32}N_2$	80.71	80.86	10.32	10.51	8.96	8.83
12.	H H	H H	–C–C(C)–C–	H	132-133	$C_{17}H_{21}N$	85.31	85.39	8.84	9.06	5.85	5.85

TABLE I (continued)

	X X		Y Y	Z Z	R	M.p. or B.p. °C		Empirical Formula	Analyses Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
13.	H	H	H H		$(CH_2)_3N(CH_3)_2$ (f)	163-173	0.06	$C_{22}H_{32}N_2$	81.43	81.42	9.94	10.09	8.63	8.43
14.	H	H		H H	H	118-119		$C_{17}H_{21}N$	85.31	85.50	8.84	8.92	5.85	6.16
15.	H	H		H H	$(CH_2)_3N(CH_3)_2$ (g)	164-170	0.03	$C_{22}H_{32}N_2$	81.43	81.63	9.94	9.97	8.63	8.62

(a) Hydrochloride, m.p., °C 201-202. *Anal.* Calcd. for $C_{23}H_{35}ClN_2$; Cl, 9.44. Found: Cl, 9.59. (b) Hydrochloride, m.p., °C 201-202. *Anal.* Calcd. for $C_{22}H_{33}ClN_2$: Cl, 9.82. Found: Cl, 9.62. (c) Maleate, m.p., °C 191-192. *Anal.* Calcd. for $C_{24}H_{34}N_2O_4$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.56; H, 8.33; N, 6.98. (d) Maleate, m.p., °C 175-176. *Anal.* Calcd. for $C_{23}H_{32}N_2O_4$: C, 68.97; H, 8.05; N, 6.99. Found: C, 69.23; H, 8.10; N, 6.92. (e) Hydrochloride, m.p., °C 173-174. *Anal.* Calcd. for $C_{21}H_{33}ClN_2$: Cl, 10.16. Found: Cl, 10.37. (f) Hydrochloride, m.p., °C 238-240. *Anal.* Calcd. for $C_{22}H_{33}ClN_2$: Cl, 9.82. Found: Cl, 9.70. (g) Hydrochloride, m.p., °C 182-183. *Anal.* Calcd. for $C_{22}H_{33}ClN_2$: Cl, 9.82. Found: Cl, 9.82.

Woodside, New York. Proton magnetic resonance spectra were taken on a Varion A-60 spectrometer in deuteriochloroform with tetramethylsilane as an internal reference. The following abbreviations are used in reporting pmr data: s = singlet, t = triplet, m = multiplet. All reactions proceeded in 70-95% yields. Representative ones are given.

(1) *N*-Methyl-3,3-diethyltetrahydrocarbazole V (X = C_2H_5; R = CH_3).

To 6.2 g. (0.04 mole) of 4,4-diethylcyclohexanone dissolved in 30 ml. of acetic acid and heated to reflux was added slowly 5.38 g. (0.04 mole + 10% excess) of 1-methyl-1-phenylhydrazine. After refluxing for 3 hours the mixture was allowed to cool and 30 ml. of acetic acid was added.

The mixture was kept at 20° overnight and filtered. The product was washed with a small volume of acetic acid and dried. One recrystallization from methanol yielded 4.7 g. white needles. The mother liquor was diluted with water and filtered. Additional material was obtained which on recrystallization from methanol gave 4.5 g., a total of 9.2 g. (95%).

(2) Spiro(cyclohexane 1,3′)-1′,2′,3′,4′-tetrahydrocarbazole. III (n = 1, R = H).

To spiro[5.5]undecan-3-one, 5.0 g. (0.03 mole) dissolved in 40 ml. of acetic acid, 3.56 g. (0.03 mole + 10% excess) phenylhydrazine was added in one portion. The mixture was refluxed for 3 hours, allowed to cool and poured into 500 ml. of 5% hydrochloric acid. The product was filtered and washed with dilute acetic acid. One recrystallization from ethanol yielded 6.4 g. (89%), m.p. 133-134°.

(3) *N*-(3-Dimethylaminopropyl)spiro(cyclohexane 1,3′)-1′,2′,3′,4′,-tetrahydrocarbazole. III [n = 1, R = $(CH_2)_3N(CH_3)_2$]

Sodium hydride 2.4 g. (50% in mineral oil) was suspended by stirring in 50 ml. of dimethylformamide. To this was added a solution of 12.0 g. (0.05 mole) of III (n = 1, R = H) dissolved in 100 ml. of dimethylformamide. After stirring for an hour the mixture was heated 50-60° while 7.3 g. (0.06 mole) of dimethylaminopropyl chloride was added. The temperature was raised to 90-100° and maintained for 4 hours. The reaction mixture was allowed to cool, poured into 600 ml. of ice-water and was acidified with concentrated hydrochloric acid. The solution was extracted with ether to remove nonbasic components and the aqueous acid fraction was made basic with 20% sodium hydroxide. The oily layer was extracted with ether, washed with saline and dried over anhydrous sodium sulfate. Following the removal of the ether the resulting oil was vacuum distilled, b.p. 168-175° (0.05 mm), 11.36 g. (70%).

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