INDOLE DERIVATIVES

XL.* SYNTHESIS OF NEW CONDENSED INDOLE SYSTEMS

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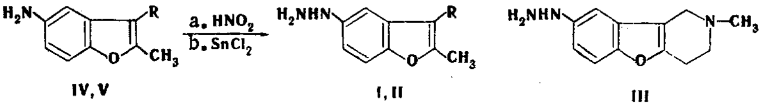
New condensed systems (VII-XVI), the structures of which were confirmed by the PMR spectra, were synthesized by the Fischer reaction of 2-methyl-5-hydrazinofuran, 2,3-dimethyl-5-hydrazinobenzofuran, and 2-methyl-8-hydrazinobenzofuro[3,2-c]pyridine with methyl ethyl ketone, methyl propyl ketone, cyclohexanone, 1-methyl-4-piperidone, and tetrahydro-4-thiopyrone.

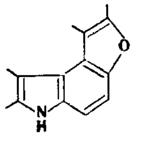
Up to now, hydrazines of the benzofuran series have not been used in the Fischer condensation. In this connection, we undertook the synthesis of previously unknown hydrazinobenzofurans (I-III), the use of which in the Fischer condensation would make it possible to arrive at new heterocyclic, potentially pharmacologically active compounds. It was of simultaneous interest to ascertain the direction of closure of the indole ring during introduction into the reaction of these sorts of heterocyclic hydrazines, which are characterized by nonequivalency of the reaction centers in the ortho positions with respect to the hydrazine group.

Hydrazines I-III were synthesized from 2-methyl-5-aminobenzofuran (IV) [2], 2,3-dimethyl-5-aminobenzofuran (V) [3], and 2-methyl-8-aminobenzofuro[3,2-c]pyridine (VI) [4] by reduction of the corresponding diazonium salts with stannous chloride.

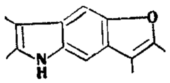


I, IV R=H; II, V $R=CH_3$

Methyl ethyl ketone, methyl propyl ketone, cyclohexanone, 1-methyl-4-piperidone, and tetrahydro-4-thiopyrone were used as the ketone components. The cyclization of the arylhydrazones gave good yields of VII-XVI (Table 1). Their structure corresponds to formula A rather than B, which was proved in the case of IX and X by the PMR spectra (in CCl_4, δ scale, Varian T-60 spectrometer), in which two doublets of the 4-H and 5-H protons appear at ~6.7 and ~7.1 ppm with J ≈ 8-9 Hz.



A



B

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*See [1] for communication XXXIX.

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TABLE 1. New Condensed Indole Systems

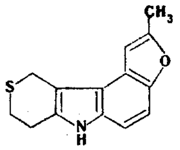
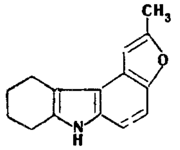
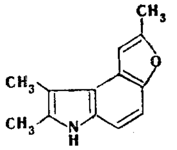
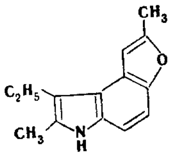
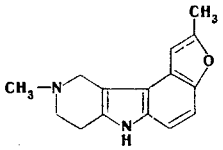
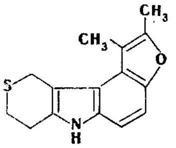
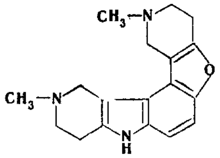
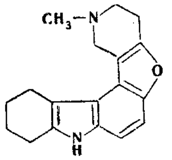
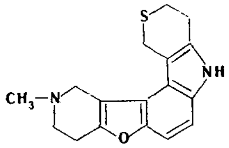
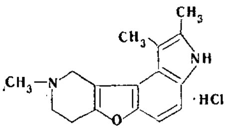
Comp.	Structural formula	Empirical formula	mp, °C	Found, %			Calc. %			Yield, %
				C	H	N	C	H	N	
1	2	3	4	5	6	7	8	9	10	11
VII		$C_{14}H_{13}NOS^a$	188—190[b]	69,0	5,2	5,8	69,0	5,4	5,8	60
VIII		$C_{15}H_{15}NO$	142—143[c]	79,7	6,7	6,6	80,0	6,7	6,2	55
IX		$C_{13}H_{13}NO$	148—149[d]	78,0	6,5	7,3	78,3	6,6	7,0	39
X		$C_{14}H_{15}NO$	132—134[e]	78,8	7,1	6,6	78,8	7,1	6,6	64
XI		$C_{15}H_{16}N_2O^f$	213—215[g]	74,9	6,8	11,7	75,0	6,7	11,7	42
XII		$C_{15}H_{15}NOS^h$	230—232[i]	70,3	6,1	5,6	70,0	5,9	5,4	52
XIII		$C_{18}H_{21}N_3O$	255—257[j]	73,3	7,0	14,2	73,2	7,2	14,2	54
XIV		$C_{18}H_{20}N_2O$	242—244[k]	77,3	7,1	10,1	77,1	7,2	10,0	22

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11
XV		$C_{17}H_{18}N_2OS$[l]	250—252[m]	68,1	6,1	9,5	68,4	6,1	9,4	56
XVI		$C_{16}H_{19}ClN_2O$[n]	290—292[o]			9,6			9,6	52

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[a] Found: S 13.4%. Calculated: S 13.1%. [b] From alcohol and then from hexane–benzene. [c] From alcohol. [d] From heptane–benzene. [e] From heptane. [f] Hydrochloride, mp 245-247° (dec., from absolute alcohol). Found: C 65.1; H 6.3; Cl 12.7%. $C_{15}H_{17}ClN_2O$. Calculated: C 65.4; H 6.2; Cl 12.8%. [g] With decomposition, from alcohol and then from benzene. [h] Found: S 12.3%. Calculated: S 12.4%. [i] From benzene. [j] From absolute alcohol. [k] With decomposition, from absolute alcohol. [l] Found S 11.1%. Calculated: S 10.8%. [m] With decomposition, from methanol–chloroform. [n] Found: Cl 12.3%. Calculated: Cl 12.2%. The base had mp 206-207° (from alcohol). Found: C 75.3; H 7.1; N 11.0%. $C_{16}H_{18}N_2O$. Calculated: C 75.5; H 7.1; N 11.0%. [o] With decomposition, from water.

EXPERIMENTAL

2-Methyl-5-hydrazinobenzofuran (I) Hydrochloride. A 20-g (0.109 mole) sample of the hydrochloride of IV in 77 ml of water and 77 ml of concentrated hydrochloric acid was diazotized at 0 to −2° with a solution of 7.6 g (0.11 mole) of sodium nitrite in 35 ml of water. The reaction mixture was filtered, and a cold solution of 49 g (0.217 mole) of stannous chloride dihydrate in 49 ml of concentrated hydrochloric acid was added with vigorous stirring to the filtrate. The mixture was then stirred for another 15-20 min, and the tin complex was removed by filtration, squeezed out thoroughly, and suspended in 200 ml of water. The cooled and stirred suspension was treated with 40% potassium hydroxide solution until it gave a strongly alkaline reaction. The mass was extracted with ether, and the extract was shaken with magnesium sulfate and filtered. The filtrate was treated with a solution of hydrogen chloride in absolute alcohol, and the precipitated hydrochloride of I was recrystallized from aqueous alcohol to give 14.2 g (64%) of a product with mp 187-188° (dec.). Found: C 54.3; H 5.6; Cl 18.3; N 14.0%. $C_9H_{11}ClN_2O$. Calculated: C 54.4; H 5.6; Cl 17.8; N 14.1%.

2,3-Dimethyl-5-hydrazinobenzofuran (II) Hydrochloride. This compound was similarly obtained in 43% yield from amine V and had mp 179.5-180° (dec., from absolute alcohol). Found: C 56.2; H 6.4; Cl 16.7; N 13.1%. $C_{10}H_{13}ClN_2O$. Calculated: C 56.5; H 6.2; Cl 16.7; N 13.1%.

2-Methyl-8-hydrazino-1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine (III). This compound was similarly obtained in 69% yield from 2-methyl-8-amino-1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine (VI) and had mp 121-122° (from heptane–benzene). Found: C 66.2; H 6.9; N 19.1%. $C_{12}H_{15}N_3O$. Calculated: C 66.3; H 6.9; N 19.3%.

Synthesis of VII-XVI. A. A mixture of 5 mmole of the hydrochloride of I or II and 5.5 mmole of the appropriate ketone in 30 ml of absolute alcohol was refluxed for 20-60 min. The reaction mass was poured into 150 ml of cold water, and the precipitate was separated and washed with water. This method was used to obtain 2-methyl-6,7,8,10-tetrahydrofuro[3,2-e]thiopyrano[4,3-b]indole (VII), 2-methyl-6H-7,8,9,10-tetrahydrofuro[2,3-c]carbazole (VIII), 2,7,8-trimethyl-6H-furo[3,2-e]indole (IX), 2,7-dimethyl-8-ethyl-6H-furo[3,2-e]indole (X), and 1,2-dimethyl-6,7,8,10-tetrahydrofuro[3,2-e]thiopyrano[4,3-b]indole (XII). PMR spectrum of X in CCl_4, δ, ppm: 1.2 (triplet, C_8-C-CH_3); 2.2 (singlet, 7-CH_3); 2.46 (singlet, 2-CH_3); 2.76 (quartet, C_8-CH_2-C); 6.5 (singlet, 1-H); 6.7 (doublet, 5-H); 7.1 (doublet, 4-H).

2,9-Dimethyl-6H-7,8,9,10-tetrahydrofuro[3,2-e]pyrido[4,3-b]indole (XI) was similarly obtained, but the reaction was carried out in a 10% solution of hydrogen chloride in absolute alcohol with treatment of the reaction mixture with aqueous potassium carbonate solution.

B. A 0.01-mole sample of III was refluxed for 10 min with 0.015 mole of the appropriate ketone in 10-15% hydrogen chloride solution, and the mixture was poured into 50 ml of water. The aqueous solution was made alkaline with potassium carbonate solution, and the precipitate was separated. This method was used to synthesize 2,11-dimethyl-8H-1,2,3,4,9,10,11,12-octahydropyrido[3',4':4,5]furo[3,2-e]pyrido[4,3-b]-indole (XIII), 2-methyl-1,2,3,4,9,10,11,12-octahydropyrido[3',4':4,5]furo[2,3-c]carbazole (XIV), and 11-methyl-1,3,4,5,9,10,11,12-octahydropyrido[3',4':4,5]furo[3,2-e]thiopyrano[4,3-b]indole (XV). The hydrochloride of 1,2,9-trimethyl-3H-7,8,9,10-tetrahydropyrido[3',4':4,5]furo[3,2-e]indole (XVI) was similarly obtained without treatment with potassium carbonate.

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4. L. M. Sharkova, N. F. Kucherova, and V. A. Zagorevskii, Khim. Geterotsikl. Soedin., 81 (1972).