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SYNTHESIS OF HETEROCYCLES ON THE BASIS OF IMINOTETRAHYDROCARBAZOLES.

1. 3-BENZYL-8-METHYL-2-OXO-2,3,3a,4,5,6-HEXAHYDRO-1H-PYRAZINO[3,2,1-j,k]-CARBAZOLE

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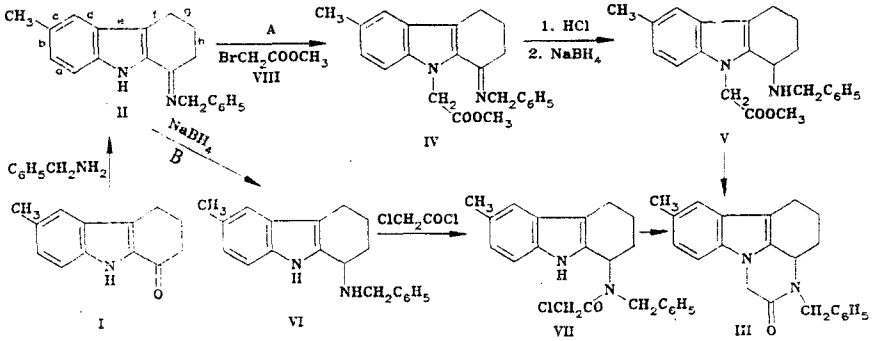
The reaction of 6-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole and benzylamine gave 1-benzylimino-6-methyl-1,2,3,4-tetrahydrocarbazole, which was converted by two methods to a pyrazinocarbazole derivative. The promising character of the use of iminotetrahydrocarbazoles for the synthesis of more complex heterocyclic systems was thereby demonstrated.

6-Methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (I) is an intermediate in the manufacture of the antidepressant pirazidol [1]. The chemical transformations of ketone I were described in [2-4], but the reactions with primary amines were not studied. We have established that 1-benzylimino-6-methyl-1,2,3,4-tetrahydrocarbazole (II) is formed in high yield when a mixture of ketone I and benzylamine in xylene is refluxed.

3-Benzyl-8-methyl-2-oxo-2,3,3a,4,5,6-hexahydro-1H-pyrazino[3,2,1-j,k]carbazole (III) was synthesized via two pathways on the basis of iminocarbazole II.

Pathway A includes alkylation, reduction, and cyclization steps, and the overall yield of pyrazinocarbazole III is 43% based on iminocarbazole II. Pathway B includes reduction, acylation, and cyclization steps, and the overall yield is 42%. It is appropriate to note that an attempt to obtain a 2-oxopyrazino[3,2,1-j,k]carbazole derivative via a different scheme [5] (not through the iminotetrahydrocarbazole) was unsuccessful.



Iminocarbazole II was alkylated with methyl bromoacetate (VIII) in benzene—50% aqueous NaOH solution in the presence of tetrabutylammonium bromide. The optimum time of the pro-

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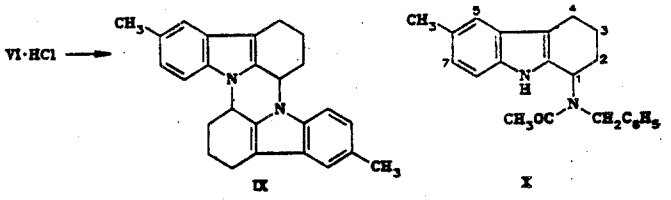
cess was 1 h. When the reaction time was increased, the yield of alkylated iminocarbazole IV decreased, evidently as a consequence of hydrolysis of the product; nevertheless, the use of solid alkali (instead of a 50% solution) did not increase but rather decreased the yield of IV, evidently as a consequence of slowing down the alkylation reaction. When we used methyl chloroacetate in place of the more active brominated ester VIII we did not obtain IV at all; the only product isolated in this experiment was ketone I in 20% yield.

Iminocarbazole IV in ethanol at 20°C did not react with sodium borohydride, but its hydrochloride was readily reduced under these conditions to give aminocarbazole V. Pyrazinocarbazole III was obtained by thermolysis of aminocarbazole V in refluxing xylene.

In contrast to alkylated iminocarbazole IV, starting iminocarbazole II, even in the base form, reacted rapidly with sodium borohydride. The aminocarbazole (VI) obtained as a result of the reduction was converted, without purification, to amide VII, which, under the influence of alkali in the presence of an interphase-transfer catalyst, underwent cyclization to pyrazinocarbazole III; in this case also the use of solid alkali (instead of a 50% solution) did not lead to an increase in the yield of the desired product III.

Oily aminocarbazole VI was characterized in the form of the crystalline hydrochloride. However, the chemical stability of the hydrochloride is significantly lower than the stability of the free base VI. Thus when an alcohol solution of the salt was refluxed, it underwent complete decomposition in 1 h; one of the decomposition products could be isolated and identified as diindolophenazine IX. Compound IX has not been described, but its demethylated homolog is known [6].



The maximum peak in the mass spectra of hexahydropyrazinocarbazoles corresponds to the $[M - C_2H_4]^+$ ion radical [7]. The maximum peak in the mass spectrum of IX is the peak with m/z 310, which corresponds to the detachment of two C_2H_4 molecules from the molecular ion; this constitutes evidence that the carbazole fragments in the IX molecule are not connected.

In the PMR spectra of III and V-VII the diastereotopic geminal protons of the benzyl groups are observed in the form of an AB quadruplet. Not only the chemical shifts but also the J_{gem} constants of the benzyl protons change when the benzylamino groups are acylated. Acetamide X was obtained to determine the parameters of the signals of the benzyl groups more precisely.

EXPERIMENTAL

The mass spectra were recorded with a Varian MAT-112 spectrometer with direct introduction of the samples into the ion source; the temperature of the ionization chamber was 180-200°C, and the ionizing-electron energy was 70 eV. The IR spectra of suspensions of the compounds in mineral oil were recorded with a Perkin-Elmer 457 spectrometer. The PMR spectra of solutions in $CDCl_3$ were obtained with a Varian XL-200 spectrometer with tetramethylsilane (TMS) as the internal standard.

1-Benzylimino-6-methyl-1,2,3,4-tetrahydrocarbazole (II). A mixture of 40 g (0.2 mole) of ketone I, 42 g (0.39 mole) of benzylamine, and 90 ml of xylene was refluxed for 3 h in a flask equipped with a Dean-Stark adapter. The xylene was evaporated in vacuo, and the residue was dissolved in 100 ml of boiling ethanol. The solution was filtered, and the filtrate was cooled, during which iminocarbazole II crystallized out. The substance retained ethanol, for the removal of which it was necessary to dry it for a long time in vacuo over phosphorus pentoxide. The yield was 52.8 g (91%). PMR spectrum: 4.72,* 2.86 (2H, t, J = 6.0 Hz, 4-H); 2.66 (2H, broad t, J = 6.4 Hz, 2-H); 2.43 (3H, s, CH_3); 2.10 ppm (2H, m, 3-H). Mass spectrum, m/z (%): 288 (100) M^+, 211 (11) $[M - C_6H_5]^+$, 197 (28) $[M - CH_2C_6H_5]^+$, 184 (12), 183 (12) $[M - NCH_2C_6H_5]^+$, 182 (15). The hydrochloride had mp 217-221°C (from ethanol). Found: C 74.0; H 6.5; Cl 11.0; N 9.0%. $C_{20}H_{20}N_2 \cdot HCl$. Calculated: C 73.9; H 6.5; Cl 10.9; N 8.6%.

*The signal of the benzyl protons; see Table 1.

TABLE 1. Characteristics of the Tetrahydrocarbazole Derivatives

Compound	T_{mp}, °C (solvent)	IR spectrum, ν, cm^{-1}		PMR spectrum ($C_6H_5CH_2$)		Found, %			Empirical formula	Calculated, %			Yield, %
		C=O	NH	δ, ppm	J, Hz	C	H	N (Cl)		C	H	N (Cl)	
II	98—100 (hexane)	—	3130 3260	4,72 (2H, s)	—	83,5	7,2	10,0	$C_{20}H_{20}N_2$	83,3	7,0	9,7	91
III	178—180 (THF)	1655	—	5,18 (1H, d); 4,57 (1H, d)	15,5	80,4	6,9	8,6	$C_{22}H_{22}N_2O$	80,0	6,7	8,5	85, 52
IV	132—134 (2-propanol)	1755	—	4,66 (2H, s)	—	76,5	6,6	7,5	$C_{23}H_{24}N_2O_2$	76,6	6,7	7,8	78
V	121—125 (ethanol)	1750	3320	4,08 (1H, d); 3,68 (1H, d)	13,0	76,4	7,0	7,6	$C_{23}H_{26}N_2O_2$	76,2	7,2	7,7	66
VI · HCl	170 (dec)(ethanol)	—	3250	3,95 (1H, d); 3,81 (1H, d)*	13,1*	73,6	6,9	8,3 (10,9)	$C_{20}H_{22}N_2 \cdot HCl$	73,5	7,1	8,6 (10,8)	79
VII	183—184 (dioxane)	1640	3260	4,60 (1H, d); 4,35 (1H, d)	18,0	72,1	6,4	7,5 (9,6)	$C_{22}H_{23}ClN_2O$	72,0	6,3	7,6 (9,6)	81
X	252—255 (DMF)	1625	3170	4,49 (1H, d); 4,27 (1H, d)	18,4	79,7	7,3	8,3	$C_{22}H_{24}N_2O$	79,5	7,3	8,4	86

*The spectrum of base VI.

1-Benzylimino-6-methyl-9-carbomethoxymethyl-1,2,3,4-tetrahydrocarbazole (IV). A solution of 40 g of NaOH in 40 ml of water was added to a solution of 28.8 g (0.1 mole) of iminocarbazole II and 5.7 g of tetrabutylammonium bromide in 190 ml of benzene, after which the mixture was cooled, and a solution of 24.9 g (0.16 mole) of methyl bromacetate (VIII) in 100 ml of benzene was added in the course of 5 min at 12°C. Cooling was then discontinued, and the mass was stirred vigorously at 25°C for 1 h. It was then cooled again and neutralized gradually at 10-12°C with 47 ml of glacial acetic acid. Benzene (70 ml) and 100 ml of water were added, and the organic layer was separated, washed with water, dried with magnesium sulfate, and evaporated. The oily residue was treated with 150 ml of methanol, during which imine IV crystallized out immediately. The yield was 28.2 g (78%). PMR spectrum: 5.44 (2H, s, CH_2CO); 4.66,* 3.52 (3H, s, OCH_3); 2.90 (2H, t, J = 6 Hz, 4-H); 2.68 (2H, broad t, J = 6 Hz, 2-H), 2.44 (3H, d, J = 0.9 Hz, 6-CH_3); 2.08 ppm (2H, m, 3-H). Mass spectrum, m/z (%): 360 (100) M^+, 328 (78) $[M - CH_3OH]^+$, 301 (55) $[M - COOCH_3]^+$, 287 (36) $[M - CH_2COCH_3]^+$, 269 (11) $[M - CH_2C_6H_5]^+$. The hydrochloride had mp 150-153°C (dec.) and was obtained in the form of bright-yellow plates (from a mixture of methanol with ether). Found: C 69.6; H 6.3; Cl 8.7; N 6.8%. $C_{23}H_{24}N_2O_2 \cdot HCl$. Calculated: C 69.6; H 6.4; Cl 8.9; N 7.0%.

1-Benzylamino-6-methyl-9-carbomethoxymethyl-1,2,3,4-tetrahydrocarbazole (V). A 1-N solution of hydrogen chloride in methanol was added at 2-3°C to a suspension of 25.4 g (70 mmole) of imine IV in 250 ml of methanol, after which the solution was filtered, the methanol was removed by vacuum distillation, and the residue was triturated in dry benzene. The solid material was removed by filtration. This material, which was the hydrochloride of imine IV (27.6 g), was suspended in 640 ml of absolute ethanol, 2.7 g (71 mmole) of sodium borohydride was added to the suspension at 5-8°C, and the mass was stirred for 4 h at 22°C. The ethanol was removed by vacuum distillation, and the residue was dissolved in 400 ml of benzene. The solution was washed with dilute acetic acid (4 ml of the acid in 250 ml of water) and then with water and dried with magnesium sulfate. The benzene was removed by vacuum distillation, and the residue was treated with methanol. The yield was 16.9 g (66%). Mass spectrum, m/z (%): 362 (7) M^+, 255 (100) $[M - C_6H_5CH_2NH_2]^+$, 196 (60) $[M - C_6H_5CH_2NH_2, - COOCH_3]^+$.

Hydrochloride of 1-Benzylamino-6-methyl-1,2,3,4-tetrahydrocarbazole (VI). A 4.5-g (0.12 mole) sample of sodium borohydride was added gradually at no higher than 20°C to a solution of 55.3 g (0.19 mole) of iminocarbazole II in 300 ml of absolute ethanol, and the resulting suspension was stirred at 20°C for 4 h. Dilute (1:1) hydrochloric acid was added at no higher than 15°C to the resulting solution up to pH 4-5, after which the mixture was stirred for 1 h, and the salt of amine VI was then removed by filtration. The yield was 49.6 g (79%). Mass spectrum, m/z (%): 290 (7) M^+, 183 (100) $[M - C_6H_5CH_2NH_2]^+$, 182 (100), 167 (40).

N-Benzyl-N-(6-methyl-1,2,3,4-tetrahydro-1-carbazolyl)chloroacetamide (VII). A solution of 33.4 g (116 mmole) of iminocarbazole II in 170 ml of ethanol was reduced with 2.2 g (58 mmole) of sodium borohydride as described in the preceding experiment, after which the ethanol was removed by vacuum distillation, and the residue was dissolved in 230 ml of benzene. The solution was washed with water and dried with magnesium sulfate, and the benzene was removed by distillation. The resulting aminocarbazole VI (a viscous, clear, light-brown oil) was dissolved in 300 ml of absolute toluene, 16 ml of triethylamine was added to the solution, the mixture was cooled to −5°C to −2°C, and a solution of 13 g (116 mmole) of chloroacetyl chloride in 100 ml of absolute toluene was added gradually. Cooling was then discontinued, and the mass was stirred at 20°C for 2 h and filtered. The precipitate was washed with ether to remove toluene residues, removed from the filter, and triturated in water to remove the triethylamine hydrochloride. The yield of product with mp 175-180°C was 34.6 g (81%).

N-Benzyl-N-(6-methyl-1,2,3,4-tetrahydro-1-carbazolyl)acetamide (X). A 3.5-ml sample of triethylamine and 2 g (25 mmole) of acetyl chloride were added successively at 10°C to a solution of 7.3 g (25 mmole) of aminocarbazole VI in 90 ml of absolute toluene, and the resulting suspension was stirred at 20°C for 1 h and filtered. The precipitate was treated as described in the preceding experiment. The yield was 7.2 g (87%).

3-Benzyl-6-methyl-2-oxo-2,3,3a,4,5,6-hexahydro-1H-pyrazine[3,2,1-j,k]carbazole (III). A) A solution of 16 g (44 mmole) of aminocarbazole V in 150 ml of xylene was refluxed for 5 h, after which 50 ml of xylene was removed by distillation, and the concentrate was cooled, during which pyrazinocarbazole III crystallized out. The yield of product with mp 178-180°C was 12.4 g (85%). Mass spectrum, m/z (%): 330 (100) M^+, 302 (88) $[M - C_2H_4]^+$, 239 (35) $[M - CH_2C_6H_5]^+$, 211 (100) $[M - CH_2C_6H_5 - C_2H_4]^+$.

*The signal of the benzyl protons; see Table 1.

B) A 3.2-g sample of tetrabutylammonium bromide and 72 g of 50% aqueous NaOH solution were added to a suspension of 34.6 g (94 mmole) of amide VII (mp 175-180°C) in 450 ml of benzene, and the mass was heated with vigorous stirring at 65°C in the course of 30 min. The resulting solution was cooled, diluted with 350 ml of benzene, and washed successively with water and dilute acetic acid to pH 7. The benzene extract was dried with magnesium sulfate, the benzene was removed by vacuum distillation, and the residue was treated with 150 ml of ethanol. The pyrazinocarbazole III was removed by filtration. The yield of product with mp 175-179°C was 23.7 g. Crystallization from 180 ml of tetrahydrofuran gave 16.3 g (52%) of III with mp 178-180°C. The IR spectrum was identical to the spectrum of the sample obtained in experiment A.

5,13-Dimethyl-1,2,3,8a,9,10,11,16a-octahydrodiindolo[3,2,1-d,e:3',2',1'-k,l]phenazine (IX). A solution of 8.3 g (25 mmole) of the salt of amine VI in 100 ml of ethanol was refluxed for 1 h, after which the precipitate was removed by filtration to give 1.3 g (28%) of diindolophenazine IX. The product was crystallized from toluene and decomposed without melting at 265°C. Mass spectrum, m/z (%): 366 (70) M^+, 338 (85) $[M - C_2H_4]^+$, 310 (100) $[M - 2C_2H_4]^+$, and 183 (40). Found: C 85.5; H 7.1; N 7.6%. $C_{26}H_{26}N_2$. Calculated: C 85.2; H 7.1; N 7.6%.

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