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AZAINDOLE DERIVATIVES.

67.* SYNTHESIS OF N-SUBSTITUTED 1-BENZYL-4-METHYL-5-CYANO-6-AMINO-7-AZAINDOLES

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N-substituted 1-benzyl-4-methyl-5-cyano-6-amino-7-azaindoles have been synthesized from the respective 1-benzyl-4-methyl-5-cyano-6-chloro(and 6-hydroxy)-7-azaindoles. The effect of the 5-cyano group on the oxidation-reduction processes accompanying nucleophilic replacement of chlorine in 6-chloro-7-azaindoles by primary and secondary amines has been considered. 7-Azaindoline compounds were dehydrogenated by chloranil to N-substituted 1-benzyl-4-methyl-5-cyano-6-amino-7-azaindoles.

The selective effect of various 6-amino derivatives of 1-benzyl-7-cyano-azaindoles on central serotoninergic systems has been described in [2]. In order to broaden the study of the antiserotonin effects of isomeric azaindoles it was of interest to obtain the hitherto unknown 6-amino derivatives of 1-benzyl-5-cyano-7-azaindoles (I). The starting material for the synthesis of compounds Ia-g was 1-benzyl-4-methyl-5-cyano-6-chloro-7-azaindoline (II) [1].

We have shown [3, 4] that the nucleophilic replacement of chlorine at position 6 in the 7-azaindoline system is a serious problem. For these reactions in such a system, because of the electron density distribution extremely severe conditions are needed, e.g., 6-chloro-7-azaindolines that do not contain a cyano group react with amines only at temperatures of at least 250°. Under such severe conditions, normal nucleophilic replacement is accompanied by redox processes, so that along with the 6-amino-7-azindolines there are formed the respective 6-amino-7-azaindoles and 7-azaindoles unsubstituted at position 6. The amounts of the latter are determined by the nucleophilicity of the amine and the redox potential of the azoindoline compound [3, 4].

The presence of a cyano group ortho to chlorine in 1-benzyl-6-chloro-7-cyano-5-azaindoline, which is distinguished by a higher redox potential than would be expected, increased the reactivity of the chlorine, and enabled it to undergo nucleophilic substitution by various other amines at lower temperature (180-185°) without the occurrence of redox reactions [2].

An analogous effect of an ortho-cyano group was observed in our case. The chlorine in compound II undergoes nucleophilic substitution with most primary and secondary aliphatic and heterocyclic amines at 180-185° to form N-substituted 1-benzyl-4-methyl-5-cyano-6-amino-7-azaindolines (IIIa-e) in high yield (77-87%). Only in the case of the sterically more hindered di-n-butylamine is the substitution less complete (55%) under these conditions, and about 35% of the starting chloroderivative II is recovered unchanged. With still weaker nucleophiles — aromatic amines of the aniline type — compound II does not react at all, not only at 180-185°, but is recovered practically unchanged even at 250°. Raising the temperature to 280-290° causes significant thermal decomposition of II. However with a stronger nucleophile — viz., hydrazine — II reacts already at 110-120° to form 1-benzyl-4-methyl-5-cyano-6-hydrazino-7-azaindoline (IV).

*For communication 66, see [1].

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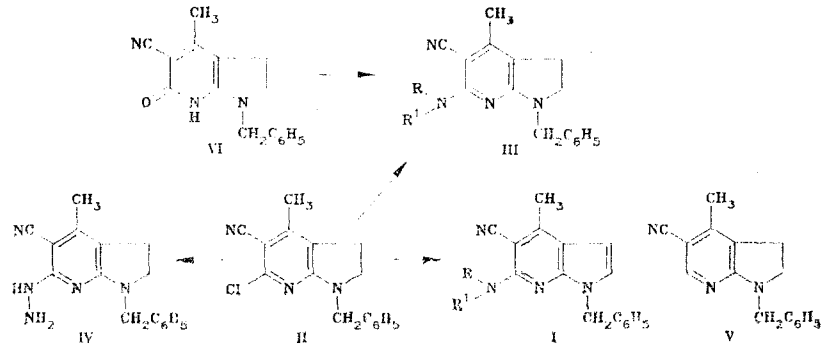

I, III a) RR'N = morpholino; b) RR"N = piperidino; c) RR'N = pyrolidino; d) RR'N = $(C_2H_5)_2N$-; e) RR'N = n-C_4H_9NH; f) RR'N = $(n\text{-}C_4H_9)_2N$_; g) RR'N = $C_6H_5CH_2NH$.

Moreover, in the reaction of chloroazaindoline II with benzylamine the previously noted [5] lower redox potentials of 7-azaindoline compounds as compared with the 5-azindoline analogs caused the formation not of 5-cyano-6-benzylamino-7-azaindoline derivative IIIg, but of the corresponding oxidized compound, viz., 1-benzyl-4-methyl-5-cyano-6-benzylamino-7-azaindole (Ig). In contrast to these previously described redox reactions between a 6-chloro-7-azaindoline without a cyano group and an amine, where along with a 6-amino-7-azaindole an azaindoline compound dehalogenated at position 6 is always obtained [3, 4], in the reaction of compound II (5-cyano-6-chloro-7-azaindoline derivative) with benzylamine not even traces of 1-benzyl-4-methyl-5-cyano-7-azaindoline (V) could be detected in the reaction mixture. The corresponding 6-benzylamino-7-azaindoline IIIg was also entirely absent, but the aminoazaindole Ig was separated in 81% yield. Evidently in this case the redox process is different from that previously observed [3, 4], and needs further intensive study.

In connection with publications on the direct replacement of the oxo group in azine systems by secondary amine residues [6, 7] we studied the analogous reaction as exemplified by the reaction of 1-benzyl-4-methyl-5-cyano-6-hydroxy-7-azaindoline (VI) with piperidine and phosphorus pentoxide. The yield of the 5-cyano-6-piperidino-7-azaindoline compound IIIb was]0%; this is substantially lower than the overall conversion of VI to the aminoitrile IIIb via the corresponding 6-chloro derivative II. The 7-azaindoline compounds IIIa-f were dehydrogenated to the 7-azaindoles IIIa-f by chloranil in boiling xylene in 78-88% yield.

Study of these N-substituted compounds Ia-g* showed that only compound Id shows weak central antiserotonin activity in 50 and 100 mg/kg doses (internal) in mouse tests, reducing the number of head agitations caused by administration of 300 mg/kg of 5-hydroxytryptophane.

The mass spectra of compounds Ia-g and IIIa-f showed molecular ions, the mass numbers of which confirmed the proposed structures. For all these compounds the most characteristic decomposition is the formation of benzyl cation (m/z 91), to which the peak of maximum intensity in the spectra of Ib-f and IIIa, c, e, f corresponds. The other decomposition route of the molecular ions is the stepwise detachment of the RR'N substituent, as a result of which the following ion peaks appear: $[M - CH_2OH]^+$, $[M - C_2H_4OH]^+$, $[M - C_3H_5O]^+$ (Ia, IIIa); $[M - C_2H_5]^+$, $[M - C_4H_7]^+$ (Ib, IIIb); $[M - C_2H_4]^+$, $[M - C_3H_7]^+$ (Ic, IIIc); $[M - CH_3]^+$, $[M - C_2H_5]^+$, $[M - NC_2H_5]^+$ (Id, IIId); $[M - C_3H_7]^+$, $[M - C_4H_9]^+$ (Ie, f, IIIe, f).

The spectra of Ib, c and IIIb, c in which NRR' are pyrolidine and piperidine residues, show ion peaks with m/z 70 and 84 that correspond to fragments of the respective cyclic amines.

The characteristic feature of the decomposition of the azaindoles Ia-f is a certain decrease in the peak intensity of the molecular ions as compared with the respective substituted azaindoline IIIa-f. The increase in peak intensity of benzyl cation observed here causes the $I_M/I_{CH_2C_6H_5}$ ratio to decrease. These data, which are shown in Table 1, show that the N-benzyl group is easier to detach in the azaindole compounds I than in the azaindoline compounds III.

*Carried out in the pharmacology laboratory of the All-Union Scientific-Research Institute for Pharmaceutical Chemistry (Academician M. D. Mashkovskii, manager) by Canad. Med. Sci. N. I. Andreeva, to whom the authors express sincerest thanks).

TABLE 1. N-Substituted 1-Benzyl-4-methyl-5-cyano-6-amino-7-azaindolines and Azaindoles

Compound	mp, °C (solvent)	Found, %			Empirical formula	Calculated, %			IR spectrum, cm^{-1}		UV spectrum, λ_{max}, nm (log ε)	Mass spectrum		Yield, %
		C	H	N		C	H	N	CN	NH		m/z (intensity, %)	$I_M/I_{CH_2C_6H_5}$	
IIIa	136—137 (hexane-benzene)	72,7	6,2	17,0	$C_{20}H_{22}N_4O$	72,3	6,0	16,9	2190	—	335 (0,8), 255 (0,74), 205 (0,79)	334 (100), 303 (21), 289 (17), 277 (34), 276 (21), 91 (62)	162	81
IIIb	85—86 (hexane)	76,0	7,2	17,1	$C_{21}H_{24}N_4$	75,9	7,2	16,9	2190	—	339 (0,75), 312 (0,54), 257 (0,85)	332 (100), 303 (11), 277 (8), 276 (17), 91 (23), 84 (9)	430	87
IIIc	121—122 hexane	75,7	7,0	17,8	$C_{20}H_{22}N_4$	75,5	6,9	17,5	2180	—	347 (0,81), 296 (0,51), 244 (0,74), 240 (0,73)	318 (100), 290 (43), 289 (59), 275 (12), 263 (25), 91 (100), 70 (25)	100	76
IIId	75—76 (hexane)	75,2	7,6	17,8	$C_{20}H_{24}N_4$	75	7,5	17,5	2190	—	346 (0,81), 297 (0,57), 258 (0,80), 240 (0,77)	320 (100), 305 (90), 291 (50), 277 (70), 91 (40)	250	81
IIIд	145—146 hexane benzene	75,0	7,7	17,5	$C_{20}H_{24}N_4$	75,0	7,5	17,5	2180	3350	347 (1,03), 292 (0,47), 247 (0,61)	320 (97), 291 (17), 278 (23), 277 (87), 263 (14), 91 (100)	97	86
III f	39—40*	76,8	7,8	14,6	$C_{24}H_{32}N_4$	76,6	8,5	14,9	2180	—	348 (0,75), 298 (0,51), 259 (0,76)	376 (14), 334 (23), 333 (41), 319 (14), 291 (55), 277 (36), 91 (100)	14	55
Ia	118—119 (hexane)	72,7	6,2	16,8	$C_{20}H_{20}N_4O$	72,3	6,0	16,9	2210	—	334 (0,26), 266 (1,20), 248 (1,27)	332(100), 301 (23), 275 (42), 91 (73)	137	78
Ib	114—115 (hexane)	76,6	6,6	16,9	$C_{21}H_{22}N_4$	76,4	6,7	17,0	2210	—	338 (0,25), 270 (1,11), 248 (1,10)	330 (31), 301 (12), 274 (7), 262 (7), 91 (100), 84 (27)	31	83
Ic	104—105 hexane	76,1	6,4	17,7	$C_{20}H_{20}N_4$	76,0	6,3	17,7	2200	—	358 (0,36), 270 (1,39), 244 (1,05)	316 (90), 287 (72), 273 (8), 261 (14), 91 (100), 77 (31)	90	88
Id	48—49 (hexane)	75,6	7,0	17,5	$C_{20}H_{22}N_4$	75,5	6,9	17,6	2200	—	353 (0,29), 272 (1,28), 244 (1,07)	318 (19), 303 (38), 290 (19), 275 (17), 91 (100)	19	86
Ie	98—99 (hexane)	75,4	6,8	17,6	$C_{20}H_{22}N_4$	75,5	6,9	17,6	2190	3380	349 (0,41), 262 (1,36), 242 (1,08)	318 (25), 289 (17), 275 (60), 262 (13), 91 (100)	25	88
If	60—61*	77,1	8,0	14,9	$C_{24}H_{30}N_4$	77,0	8,0	15,0	2180	—	354 (0,28), 272 (1,05), 244 (0,93)	374 (4), 331 (18), 289 (16), 275 (14), 91 (100)	4	86
I g	186—187	78,4	5,7	15,7	$C_{23}H_{20}N_4$	78,4	5,7	15,9	2200	3380	350 (0,38), 265 (1,01)	352 (100), 275 (11), 261 (20), 106 (22), 91 (65)		81

*Purified by chromatography.

EXPERIMENTAL

Mass spectra were obtained on a Varian MAT-112 instrument with direct introduction of sample into the source. The energy of the ionizing electrons was 70 eV, the temperature of the ionizing chamber was 180°. PMR spectra were obtained on a JNM-4H-100 instrument, with TMS internal standard; IR spectra, on a Perkin-Elmer 457 spectrometer in mineral oil; UV spectra, on a Carl Zeiss (Jena) Specord M-40 spectrophotometer in chloroform.

The properties of compounds Ia-g and IIIa-f are shown in Table 1.

General Synthesis of N-Substituted 1-Benzyl-4-methyl-5-cyano-6-amino-7-azaindolines (IIIa-e). A mixture of 3 g (10.6 mmole) of azaindoline II and 15 ml of amine was heated in a 55 ml steel autoclave for 10 h at 180-185°. The reaction product was treated with 100 ml of water and 30 ml of 50% aqueous potassium hydroxide and extracted with chloroform. The chloroform extract was dried with magnesium sulfate and evaporated in vacuum, and excess amine was removed by addition of toluene and vacuum evaporation. The residue was recrystallized from hexane or a 3:1 hexane—benzene mixture.

1-Benzyl-4-methyl-5-cyano-6-(di-n-butylamino)-7-azaindoline (IIIf) is synthesized as described in the preceding test. After removal of chloroform and excess di-n-butylamine the residue was ground with hexane, and the residue of chloroazaindoline II was filtered off. The material did not depress the melting point of an authentic sample, and has an identical IR spectrum. The hexane filtrate was evaporated and the residue was placed on a column (d 30 mm, h 50 cm) with 100 g of 40/100 μ silica gel. The column was washed with 200 ml of 9:1 hexane—benzene, then with 1.5 liters of 7:3 hexane—benzene which eluted 2.1 g (53%) of azaindoline IIIf; then with 500 ml of 1:1 hexane—benzene which eluted 0.06 g of chlorozazindoline II. Total yield of II, 1.06 g (35.3%).

1-Benzyl-4-methyl-5-cyano-6-hydrazino-7-azaindoline (IV). To a solution of 3 g (11 mmole) of II in 45 ml of butanol at 110-112° was added four 1.1 ml portions of hydrazine hydrate over 1 h. The reaction mixture was stirred at 110-112° for 1 h and cooled to room temperature. The precipitate was filtered off and washed with 40 ml of benzene. There was obtained 1.3 g (44%) of IV. Colorless crystals, mp 256-257° (from methanol). The material was soluble in DMFA and hot alcohols; insoluble in water, acetone, ether. PMR spectrum in DMSO D_6: 2.33 (s, 3H, 4-CH_3); 2.86 (t, 2H, 3-CH_2); 3.44 (t, 2H, 2-CH_2); 4.53 (s, 2H, CH_2-C_6H_5); 4.68 (br. s., 2H, NH_2NH); 7.25-7.35 (m, 5H, $CH_2C_6H_5$); 11.23 ppm (s, 1H, NH_2-NH. Mass spectrum: 279 $[M]^{+\cdot}$ (100); 263 $[M - NH_2]^+$ (9); 202 $[M - Ph]^+$ (45); 91 $[PhCH_2]^+$ (100). Found: C 68.6; H 6.3; N 24.7%: $C_{16}H_{17}N_5$. Calculated: C 68.8; H 6.1; N 25.1%.

1-Benzyl-4-methyl-5-cyano-6-piperidino-7-azaindoline (IIIb). A mixture of 0.4 g (1.5 mmole) of hydroxyazaindoline VI, 0.21 g (1.5 mmole) of phosphorus pentoxide, and 2 ml of piperidine was held for 10 h at 170-180° in a steel autoclave. The reaction product was treated with 50 ml of water and 20 ml of 50% potassium hydroxide solution, and extracted with chloroform. The chloroform extract was dried with magnesium sulfate and evaporated in vacuum. The residue was treated with 40 ml of boiling benzene, and the residue thereof was filtered off to give 0.22 g (55%) of starting VI. The benzene solution was evaporated and the residue was recrystallized from 3:1 hexane—benzene. There was obtained 0.05 g (10%) of IIIb, which did not depress the melting point of an authentic sample obtained by the method described above. R_f values of the two materials were identical in chloroform (0.66) and benzene (0.13).

1-Benzyl-4-methyl-5-cyano-6-benzylamino-7-azaindole (Ig). A mixture of 1.7 g (6 mmole) of compound II and 9 ml of benzylamine was stirred for 10 h at 180-185° in a flask with a reflux condenser. The cooled reaction mixture was treated with 50 ml of water and 20 ml of 50% aqueous potassium hydroxide and extracted with chloroform. The chloroform extract was dried with magnesium sulfate and evaporated in vacuum; excess benzylamine was removed by addition of toluene and evaporation in vacuum. The residue was recrystallized from 1:1 hexane—benzene. There was obtained 1.71 g (81%) of azaindole Ig.

General Method for Synthesizing N-Substituted 1-Benzyl-4-methyl-5-cyano-6-amino-7-azaindoles (Ia-e). A mixture of 6.5 mmole of azaindoline IIIa-f and an equal weight of chloranil in 50 ml of xylene was boiled for 1.5 h. After cooling the xylene solution was washed successively with 150 ml of 10% sodium hydroxide solution and three 150 ml portions of water, dried with magnesium sulfate, and evaporated in vacuum. The residue was recrystallized from hexane.

1-Benzyl-4-methyl-5-cyano-6-(di-n-butylamino)-7-azaindole (If) was synthesized as described in the preceding experiment. The residue after evaporation of xylene was placed on a column (30 mm diameter, 20 cm high) with 90 g of 40/100 μ silica gel. The column was washed with 100 ml of hexane and 300 ml of 9:1 hexane–benzene, and 1.6 g of If was eluted.

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SYNTHESIS AND SOME REACTIONS OF 4-NITRO DERIVATIVES OF IMIDAZO[4,5-c]PYRIDIN-2-ONES

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Imidazo[4,5-c]pyridine and its N-methyl derivatives do not undergo nitration, but the 2-oxo derivatives of these compounds are easily nitrated when heated. Some properties of the resulting 4-nitroimidazo[4,5-c]pyridin-2-ones have been studied.

The introduction of a nitro group into the imidazo[4,5-c]pyridine molecule has not been previously studied. However, work in this direction is of considerable importance in developing the chemistry of this heterocycle.

We have shown that imidazo[4,5-c]pyridine (I) and its 1- and 3-methyl substituted derivatives (II, III) are inert to nitrating mixtures. These compounds do not change when treated with nitric acid or potassium nitrate in concentrated sulfuric acid and high-strength oleum at temperatures up to 200°. The same result was obtained after heating the dinitrate of base I with gaseous sulfur trioxide at 100°. For this reason it was of interest to carry out the nitration of 2-oxo derivatives of compounds I-III, especially because with the analogous substituted imidazo[4,5-b]pyridines the strong activating effect of the oxo group appears in this reaction [1].

Nitration of 1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (IVa) with nitrating mixture proceeds at about 100° to form the mononitro derivative in almost quantitative yield. For example, the PMR spectrum of the product in CF_3COOH solution (Table 1) has two doublets of aromatic protons (8.03 and 8.63 ppm), the spin–spin coupling constants (SSCC) of which, at 6.5 Hz, unambiguously demonstrate their vicinal location; this is possible only in 4-nitro-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (Va). In the spectrum of 7-nitroimidazo[4,5-c]-pyridin-2-one (VI) the pyridine ring protons do not show spin–spin coupling.

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