THE CHEMISTRY OF INDOLE

XII. 2-Aminoindoles and Pyrimidyl[1,2-*a*]indoles*

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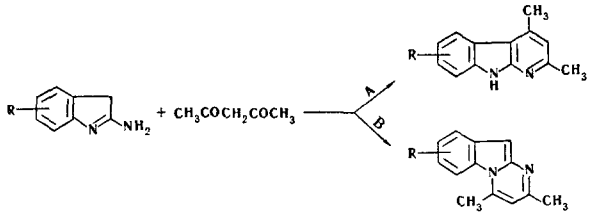
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 6, No. 3, pp. 364–370, 1970

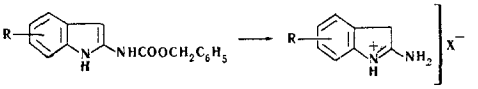
UDC 547.754'.83

The synthesis of 2-aminoindoles substituted in the benzene ring is described. On the basis of a study of the PMR, UV, and IR spectra their salts have been ascribed the structure of indolenine derivatives. A number of pyrimidyl[1,2-*a*]indoles have been obtained from 2-aminoindoles and acetylacetone.

As we have shown previously [1], 2-aminoindoles react smoothly with β-diketones, those substituted on the ring nitrogen forming α-carbolines, and unsubstituted 2-aminoindole forming a new tricyclic system, pyrimidyl[1,2-*a*]-indole. It is possible that in the latter case, if a substituent were present in the benzene ring of 2-aminoindole, its structure and the direction of the reaction with β-diketones (route A or route B) could vary according to the position and nature of the substituent. With this in mind, we have synthesized a series of substituted 2-aminoindoles and have studied the structure of their salts and the product of their cyclization with acetylacetone.



2-Aminoindoles containing methyl and methoxy groups and halogen in the benzene ring were obtained by the debenzylation of the corresponding O-benzyl-N-(indol-2-yl)urethanes [2] and by their hydrogenolysis in the presence of palladium on carbon and a small amount of hydrochloric acid [3]. In the hydrogenolysis of the nitrourethanes, the nitro group is partially reduced, and therefore we removed the benzyl protection from these compounds by heating them in glacial acetic acid saturated with dry hydrogen bromide.



X = Cl, Br

The UV spectrum of the salt of unsubstituted 2-aminoindole is identical with that described in the literature, having an absorption maximum at 257 nm (Fig. 1). The introduction of electron-donating substituents causes a bathochromic shift which is most pronounced in the 6-methoxy compound (273 nm). The protonated ring nitrogen atom in the salts of the 2-aminoindoles acts as a very strong electron acceptor. Halogen substituents in these compounds are electron donors and cause a very slight bathochromic shift. The influence of nitro groups in positions 4 and 6 of the ring is extremely slight (λ_{max} 256 nm). The UV spectrum of 2-amino-7-nitroindole hydrobromide differs from the spectra of the other salts (see Fig. 1). It has absorption maxima at 255 and 347 nm and is similar to the spectrum of O-benzyl-N-(7-nitro-2-indolyl)urethane (λ_{max} 240, 261, and 355 nm). Apparently in this compound, unlike its analog, the partial redistribution of the positive charge within the molecule is possible because of the formation of intramolecular hydrogen bonds.

In the IR spectra of salts of 2-aminoindoles taken in paraffin oil, the NH stretching vibrations are present in the 3410–3130-cm^{-1} region. For unsubstituted 2-aminoindole a broad NH band appears at about 3230 cm^{-1}. Substitution on the ring nitrogen causes a shift of the NH stretching vibrations in the high-frequency direction, 3362 and 3410 cm^{-1} for

*For part XI, see [1].

the N-benzyl- and N-methyl-substituted compounds, respectively. Under the influence of the protonation of the ring nitrogen atom, the IR spectra of the salts of 2-aminoindoles substituted in the benzene ring show a shift in the NH stretching vibrations in the low-frequency direction for all substituents, and only the nitro group causes a shift in the high-frequency direction (for the 4-nitro compound, $\nu_{NH} = 3345$ cm^{-1}). The IR spectra of the salts of 2-aminoindoles in hexachlorobutadiene have a broad band in the 3000–3070-cm^{-1} region that is characteristic for the stretching vibrations of a charged NH^+ group. For 2-amino-7-nitroindole hydrobromide it is still broader and is shifted in the short-wave direction (3100–3220 cm^{-1}). In these circumstances, the NH vibrations are overlapped by the broad band of the NH^+ group. The considerable shift and broadening of the band of the NH vibrations, and also the higher melting point in comparison with the other nitro derivatives, confirm the formation of intromolecular hydrogen bonds in the 7-nitro compounds. Intramolecular hydrogen bonds are also found in other indoles with a nitro group in position 7 [5].

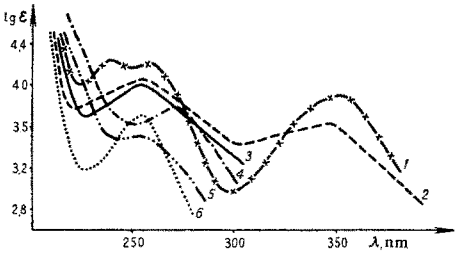
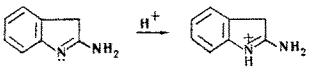


Fig. 1. UV spectra of salts of 2-aminoindoles (in water) and of O-benzyl-N-(7-nitroindol-2-yl)urethane (in methanol, c 10^{-5} M): 1) O-benzyl-N-(indol-2-yl)-urethane, 2) 2-amino-7-nitroindole hydrobromide, 3) 2-amino-4-nitroindole hydrobromide, 4) 2-amino-6-methoxyindole hydrochloride, 5) 2-amino-1-methylindole 6) 2-aminoindole hydrochloride.

The salts of the 2-aminoindoles have a strong absorption band at 1700–1678 cm^{-1} corresponding to the $C{=}N^+$ stretching vibrations, and also several bands in the 1630–1580-cm^{-1} region which are characteristic for the vibrations of an aromatic nucleus (Table 1).

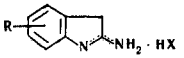
The PMR spectrum of 2-aminoindole hydrochloride in trifluoroacetic acid contains four singlets. The singlet with δ 3.94 corresponds to the CH_2 group in position 3 of the 3H-indole ring, and that with δ 6.98 to four aromatic protons possessing practically identical chemical shifts. The broadened singlets with δ 7.91 and 9.89 having intensities of two and one proton units, respectively, can be ascribed to the amino group and the proton of the ring nitrogen. Consequently, the protonation of 2-aminoindole takes place at the more basic ring nitrogen atom [4] and there is no transformation in the indole structure. The positions of all three protons in the amide system are fixed.



Some deviations in the properties of the nitro derivatives, for example, the UV spectra, require additional investigation. However, the PMR spectrum of 2-amino-7-nitroindole hydrobromide in trifluoroacetic acid indicates that this compound has the indolenine structure, which is shown by the presence of a singlet at δ 4.31, corresponding to a CH_2 group in a five-membered ring. In addition, the spectrum has a singlet with δ 8.68 corresponding to the two protons of the amino group, a doublet with δ 7.91, ascribed to the proton of the benzene ring present in the ortho position with respect to the nitro group ($I_{6-5} = 9.2$ Hz), a doublet with δ 7.58 corresponding to the proton in position 4 ($I_{4-5} = 7.1$ Hz), and a triplet with δ 7.18 corresponding to the proton in position 5 of the indole system. Under the influence of the nitro group, the proton of the ring nitrogen is shifted in the weak-field direction (solvent region). Thus, the introduction of even such a substituent as the nitro group into the benzene ring has practically no influence on the indolenine structure of the 2-aminoindole salts.

We have brought about the reaction of the 2-aminoindoles with acetylacetone, performing it, as in the unsubstituted compound, in pyridine. In all cases, regardless of the nature of the substituent and its position, the reaction products were pyrimidyl[1,2-*a*]indoles, and not α-carbolines (route B) (Table 2). The latter were not detected even by chromatography.

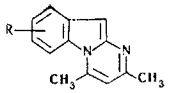
Table 1



R	X	Mp, °C	Empirical formula	Found, %			Calculated, %			UV spectrum, λ_{max}, nm log ϵ	IR spectrum, cm^{-1}			Yield, %
				C	H	N	C	H	N		ν_{NH}	C=N+	vibrations of the aromatic ring	
H	Cl	225—226[1]*								257 (3.71)	3230	1698	1629 1612 1602	77
4-CH_3	Cl	230—231	$C_9H_{10}N_2 \cdot HCl$	59.31 59.44	6.26 6.31		59.18	6.07		259 (3.66)	3205	1693	1623 1609 1601	78
5-CH_3	Cl	221—222	$C_9H_{10}N_2 \cdot HCl$			15.48 15.41			15.33	262 (3.67)	3215	1689	1627 1612 1601	79
6-CH_3	Cl	231—232	$C_9H_{10}N_2 \cdot HCl$	59.31 59.47	6.13 6.29		59.18	6.07		261 (3.69)	3205	1687	1628 1611 1602	74
5-OCH_3	Cl	216—218	$C_9H_{10}N_2O \cdot HCl$			14.45 14.37			14.09	267 (3.69)	3209	1688	1630 1612 1602	72
6-OCH_3	Cl	232—234	$C_9H_{10}N_2O \cdot HCl$			14.67 14.59			14.09	273 (3.78)	3180	1690	1636 1613 1598	69
5-Cl	Cl	229—230	$C_8H_7Cl_2N_2 \cdot HCl$	47.65 47.61	4.07 4.11		47.31	3.97		261 (3.71)	3209	1687	1626 1602 1596	78
6-Cl	Cl	233—234	$C_8H_7Cl_2N_2 \cdot HCl$			14.09 13.96			13.79	261 (3.74)	3196	1687	1623 1602 1598	76
4-Br	Cl	217—218	$C_8H_7BrN_2 \cdot HCl$	39.03 39.31	3.41 3.19	11.65 11.51	38.95	3.26	11.32	257 (3.94)	3220	1687	1623 1604 1591	75
5-Br	Cl	214—215	$C_8H_7BrN_2 \cdot HCl$	39.16 39.21	3.41 3.46		38.95	3.26		258 (3.71)	3220	1689	1623 1604 1592	76
6-Br	Cl	223—223,5	$C_8H_7BrN_2 \cdot HCl$			11.57 11.64			11.32	257 (3.76)	3218	1687	1623 1603 1592	76
4-NO_2	Br	241—242	$C_8H_7N_3O_2 \cdot HBr$			16.51 16.42			16.28	256 (4.02)	3345	1684	1626 1606 1592	66
6-NO_2	Br	236—237	$C_8H_7N_3O_2 \cdot HBr$	37.51 37.64	3.28 3.34		37.23	3.12		256 (4.05)	3350	1684	1626 1606 1592	64
7-NO_2	Br	251—252	$C_8H_7N_3O_2 \cdot HBr$	37.55 37.61	3.41 3.52	16.69 16.52	37.23	3.12	16.28	255 (4.07) 347 (3.67)	3100— 3200	1678	1629 1594 1582	64
1-CH_3	J	262—262[2]*								257 (3.52)	2410	1672	1619 1603 1592	—
1-$CH_2C_6H_5$	Cl	256—259[3]*								259 (3,52)	3362	1682	1611 1606 1587	—

[1]*Literature data [4]: mp 225-226° C. [2]*Literature data [5], mp about 260° C. [3]*Literature data [5]: mp about 260° C.

Table 2



R	Mp, °C	R_f	Empirical formula	Found, %			Calculated, %			λ_{max}, nm (log ε)	Mp of the picrate, °C (from ethanol	Yield, %
				C	H	N	C	H	N			
7-CH_3	93—95	0.34	$C_{14}H_{14}N_2$	80.12 80.14	6.73 6.74		79.97	6.70		227 (4.22), 269 (4.75), 305 (3.72) 320 (3.72), 394 (3.22)	234—235	92
8-CH_3	114—116	0.35	$C_{14}H_{14}N_2$	79.77 79.81	6.72 6.81	13.41 13.44	79.97	6.70	13.33	225 (4.51), 271 (4.78), 319 (7.64), 395 (3.46)	219—220	92
9-CH_3	108—110	0.34	$C_{14}H_{14}N_2$	79.86 79.92	6.87 6.69		79.97	6.70		224 (4.46), 269 (4.69), 305 (3.78), 320 (3.78), 394 (3.26)	205—206	90
8-OCH_3	132—133	0.35	$C_{14}H_{14}N_2O$	74.31 74.11	6.18 6.26	12.45 12.51	74.31	6.24	12.38	228 (4.35), 240 (4.34), 275 (4.58), 290 (4.11), 327 (3.77), 392 (3.66)	206—207	93
9-OCH_3	90—91	0.34	$C_{14}H_{14}N_2O$	74.34 74.47	6.35 6.39		74.31	6.24		233 (4.40), 242 (4.44), 267 (4.60), 294 (4.05), 310 (3.74), 338 (3.30), 390 (3.60)	198—199	94
8-Cl	154—156	0.23	$C_{13}H_{11}ClN_2$	67.92 67.85	5.04 5.01		67.67	4.80		220 (4.35), 262 (4.74), 269 (4.84), 332 (3.95), 415 (3.37)	219—221	93
9-Cl	164—165	0.24	$C_{13}H_{11}ClN_2$	67.56 67.81	4.82 4.91	12.18 12.34	67.67	4.80	12.14	220 (4.42), 261 (4.86), 267 (4.96), 318 (4.06), 418 (3.42)	206—207	91
7-Br	155—156	0.21	$C_{13}H_{11}BrN_2$	56.92 56.99	4.15 4.23		56.74	4.03		266 (4.86), 316 (3.77), 395 (3.42), 425 (3.40)	234—238	88
8-Br	171—172	0.20	$C_{13}H_{11}BrN_2$	56.81 56.83	4.12 4.18		56.74	4.03		217 (4.44), 226 (4.40), 267 (4.91), 318 (3.96), 394 (3.58), 420 (3.49)	226—227	90
9-Br	164—165	0.21	$C_{13}H_{11}BrN_2$	56.90 56.68	4.11 4.15		56.74	4.03		218 (4.40), 225 (4.38), 260 (4.72), 267 (4.81), 318 (3.94), 388 (3.54), 426 (3.46)	218—220	89
7-NO_2	247—248	0.65	$C_{13}H_{11}N_3O_2$	64.73 64.49	4.65 4.72	17.45 17.51	64.72	4.59	17.42	256 (4.83), 310 (3.90), 320 (3.97), 332 (4.03), 434 (3.52)	224—225	91
9-NO_2	238—239	0.65	$C_{13}H_{11}N_3O_2$	64.59 64.51	4.31 4.28		64.72	4.59		255 (4.78), 260 (4.76), 315 (3.81), 330 (3.90), 350 (3.83), 436 (3.51)	217—218	93
10-NO_2	206—207	0.68	$C_{13}H_{11}N_3O_2$	64.59 64.74	4.56 4.58	17.46 17.51	64.72	4.59	17.42	222 (4.82), 273 (4.23), 304 (4.65), 370 (4.18), 428 (3.42)	200—201	64

The pyrimidino[1,2-*a*]indoles obtained are stable to acid hydrolysis and are aromatic compounds, the nucleus of which has a common system of 14 π electrons.

The PMR spectrum of 7-chloro-1,3-dimethylpyrimido[1,2-*a*]indole in trifluoroacetic acid has two singlets in the δ 2.68 and 3.00 regions corresponding to the CH_3 groups in positions 1 and 3. Singlets with δ 6.48 and 6.62 can be ascribed to the protons of the pyrimidine and pyrrole parts of the molecule. A singlet with δ 7.41 we ascribe to the proton in position 6 ($J_{6,8}$ = 1.5 Hz), and two doublets in the δ 7.1 and 7.75 region correspond to the protons in positions 8 and 9 of the ring $J_{8,9}$ = 9.6 Hz). The PMR spectrum of this compound in dimethyl sulfoxide (Fig. 2) gave a sharper resolution of the aromatic multiplet (this is apparently due to the partial protonation of the pyrimido[1,2-*a*]indole molecule in trifluoroacetic acid). Singlets with δ 6.50 and 6.47 correspond to the protons of the pyrimidine and pyrrole rings, a resolved doublet in the δ 7.20 region to the proton in position 8 ($J_{8,9}$ = 10 Hz), and a doublet with δ 8.1 to the proton in position 9. A split singlet with δ 7.78 corresponds to the proton in position 6 of the molecule ($J_{6,8}$ = 2.0 Hz).

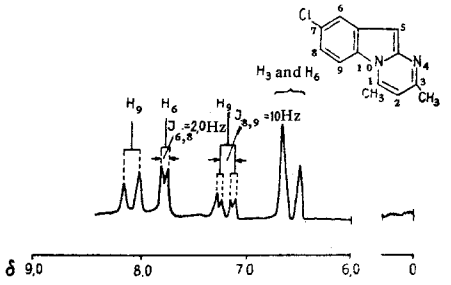


Fig. 2. PMR spectrum of 7-chloro-1,3-pyrimido[1,2-*a*]indole in dimethyl sulfoxide (internal standard: tetramethylsilane) at 80° C.

The UV spectra of almost all the 1,3-dimethylpyrimido[1,2-*a*]indoles (Fig. 3) have a short-wave absorption band λ_{max} 220–242 nm. Only in the 6-bromo and the 6-, 8-, and 9-nitro derivatives, because of a hypsochromic shift, are these bands apparently present in the far UV region. In the spectrum of 1,3-dimethylpyrimido[1,2-*a*]indole, in addition to the first absorption band (at 227 nm) there are three more: at 266 (the strongest), 317, and 400 nm. Methyl and methoxy groups cause a slight bathochromic shift of the second absorption band (267–275 nm), and for the halogen-substituted compounds it is in the 262–269-nm region. A larger hypsochromic shift is found for 1,3-dimethyl-6-nitro- and 1,3-dimethyl-8-nitropyrimido[1,2-*a*]indoles (absorption maxima at 256 and 255 nm, respectively). As a rule, the introduction of substituents into the benzene ring of pyrimidoindole causes a splitting of the short-wave band and also the absorption bands at 267 and 317 nm, particularly for groups capable of mesomeric interaction with the nucleus (methoxy and nitro groups, and halogen atoms). The influence of the substituent has a clear effect on the absorption band present in unsubstituted 1,3-dimethylpyrimido[1,2-*a*]indole at 400 nm. Electron-donating groups cause a hypsochromic shift (λ_{max} 390–395 nm) and electron-accepting groups cause a considerable bathochromic shift of this band (λ_{max} 415–436 nm). The UV spectrum of 9-nitropyrimido[1,2-*a*]indole differs appreciably from the spectra of the other nitro compounds. This is apparently due to the partial deviation of the nitro group from the plane of the ring.

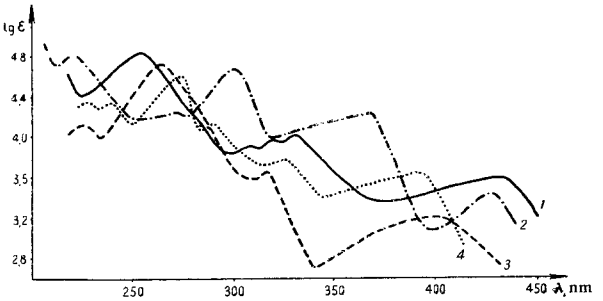


Fig. 3. UV spectra (in methanol) (c 10^{-5} M):
1) 1,3-dimethyl-6-nitropyrimido[1,2-*a*]indole,
2) 1,3-dimethyl-9-nitropyrimido[1,2-*a*]indole,
3) 2,4-dimethylpyrimido[1,2-*a*]indole,
4) 7-methoxy-1,3-dimethylpyrimido[1,2-*a*]indole.

Thus, neither a change in the basicity of the nitrogen atoms associated with the electronic nature of the

substituents in the benzene ring or the spatial restrictions that could appear in the 7-substituted 2-aminoindoles prevent the exclusive formation of a pyrimidine ring in the reaction of 2-aminoindoles with acetylacetone.

EXPERIMENTAL

The UV spectra were taken on an EPS-3 recording ultraviolet spectrophotometer. The IR spectra of the salts of the 2-aminoindoles were taken on a UR-10 instrument. The PMR spectra were recorded by V. A. Budylin (to whom the authors are grateful also for participating in a discussion of the results) on a RS-60 instrument. The purity of the pyrimido[1,2-*a*]indoles was checked by thin-layer chromatography in alumina with benzene as the mobile phase, except for the nitro compounds, for which a benzene–methanol (10 : 1) system was used.

2-Aminoindoles (Table 1). A solution of 0.01 mole of the appropriate O-benzyl-N-(indol-2-yl)urethane [3] in 45 ml of ethanol containing 0.8 ml of conc HCl was shaken in a current of hydrogen with 0.5 g of 50% palladium on carbon. The end of the reaction was established by the disappearance of the spot of the urethane when the reaction mixture was chromatographed in a thin layer of alumina in the benzene–methanol (10 : 1) system (the spots being revealed with iodine vapor). The catalyst was filtered off, the filtrate was evaporated to dryness, the residue was dissolved in hot ethanol, the solution was filtered, and the filtrate was evaporated to dryness. This process was repeated until the residue obtained after the evaporation of the solvent dissolved completely in hot ethanol. This ethanolic solution was treated with 3 volumes of dry ether and, after cooling, the precipitate of the 2-aminoindole salt was filtered off. For analysis it was recrystallized again from ethanol with the addition of ether, or from water with the addition of acetone.

For urethanes containing a nitro group in the benzene ring, a mixture of 0.01 mole with 10 ml of glacial acetic acid saturated with dry hydrogen chloride was stirred at 95–100° C for 20–30 min, cooled to 10° C, and treated with 80 ml of dry ether, and the precipitated 2-aminoindole hydrobromide was filtered off. For analysis, the substance was recrystallized from acetone with the addition of water.

Substituted 1,3-dimethylpyrimido[1,2-*a*]indoles (Table 2). To 0.01 mole of the 2-aminoindole salt were added 2 g (0.02 mole) of freshly distilled acetylacetone and 15 ml of dry pyridine. The mixture was boiled in a current of gas for 2 hr, then cooled and poured into water. The precipitate was filtered off and recrystallized from dilute ethanol or, in the case of the nitro derivatives, from toluene.

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1 April 1968

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