ELECTROPHILIC SUBSTITUTION REACTIONS OF ACYLATED 2-AMINOINDOLE DERIVATIVES

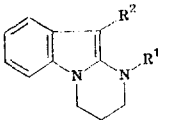
E. S. Besidskii, G. A. Golubeva, and L. A. Sviridova

UDC 547.757'853.5.04:
542.944.4'951.1'958.1

The bromination, nitration, and acylation reactions of various acyl derivatives belonging to the 2-aminoindole series of compounds have been investigated. It has been found that substitution occurs both at the β-carbon atom as well as at the 5- and 6-positions of the benzene ring. The ratio of reaction products depends upon the nature of the electrophile as well as on the degree of substitution of the 2-aminoindole.

The literature contains many reports concerning the electrophilic substitution reactions of indole compounds [1], although very few of these deal with the substitution reactions of 2-aminoindole derivatives. We recently demonstrated that, in the case of basic aminoindoles lacking other functional groups, electrophilic substitution occurs at the 3-position, whereas in the protonated forms containing the amidinium cation substitution occurs at the 5-position [2].

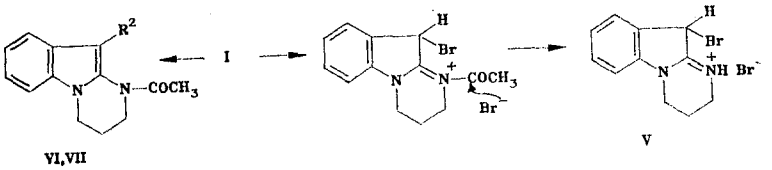
We have now studied the nitration, bromination, and acylation reactions of the acylated tetrahydropryimido[1,2-a]indole derivatives I-IV, which may be thought of as cyclic analogs of 2-aminoindoles. The basic forms of these materials are relatively stable, which greatly simplifies their use as substrates.



I–IV

I, III, IV R^1=$COCH_3$; II, III R^2=CHO; IV R^2=CH_3

We have found that bromination, nitration, and acylation of aminoindole I all occur at the 3-position* (to give compounds V-VII). In contrast to the other substitution reactions, bromination is accompanied by deacylation of the nitrogen atom, apparently as a result of nucleophilic attack by a Br^- anion on the activated carbonyl group of the intermediate amidinium ion. The resulting hydrobromide salt V gives a very labile, easily decomposed base [2].



VI,VII V

VI R^2=NO_2; VII R^2=$COCH_3$

It is known that electrophilic substitution reactions of basic 3-acylindoles are nonselective, and that along with 5- and 6-substituted 3-acylindoles, other products, resulting from unco-attack at the 3-position, followed by elimination of the acyl group, are also formed [3-5]. In the case of the reactions of compound II, we have established that unco-attack is the dominating pathway for both bromination and nitration reactions in the 3-acyl-2-aminoind-

*Here and elsewhere, the indole numbering system is used.

M. V. Lomonosov Moscow State University, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 941-945, July, 1985. Original article submitted June 30, 1984.

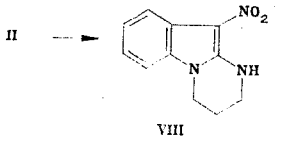
 0009-3122/85/2107-0782$09.50

TABLE 1. Properties of the Indoles I-IV and of Other Individual Compounds V-VIII, XI, XIV, and XV

Compound	mp, °C	PMR spectrum, δ, ppm	Found, %		Molecular formula	Calc., %		Yield, %
			C(N)	H(Br)		C(N)	H(Br)	
I	129	2,6 (3H, s, CH_3); 6,4 (1H, s, 3-H)	72,4	6,3	$C_{13}H_{14}N_2O$	72,9	6,5	60
II	167	7,85 (1H, s, NH); 9,72 (1H, s, CHO)	72,2	5,9	$C_{12}H_{12}N_2O$	72,0	6,0	75
III	158	2,34 (3H, s, CH_3); 7,25—7,4 (3H, m, 5-H—7-H); 8,15—8,3 (1H, m, 4-H); 9,95 (1H, d, CHO)	69,7	6,3	$C_{14}H_{14}N_2O_2$	69,4	5,8	55
IV	97	2,25 (3H, s, CH_3); 2,4 (3H, s, CH_3)	73,7	7,1	$C_{14}H_{16}N_2O$	73,7	7,0	60
V	222 (dec)	7,1—7,9 (4H, m, Ar); 9,4 (1H, s, NH)	(8,2)	(48,2)	$C_{11}H_{12}Br_2N_2$	(8,4)	(48,2)	68*
VI	156	2,3 (3H, s, CH_3); 7,2—7,5 (3H, m, 5-H—7-H); 8,2—8,4 (1H, m, 4-H)	59,9	5,1	$C_{13}H_{13}N_3O_3$	60,2	5,0	26*
VII	115	2,2 (3H, s, CH_3); 2,56 (3H, s, CH_3)	70,6	6,3	$C_{15}H_{16}N_2O_2$	70,3	6,2	61
VIII	242	7,2—7,35 (3H, m, 5-H—7-H); 7,8—8,0 (1H, m, 4-H), 8,8 (1H, s, NH)	60,6	5,6	$C_{11}H_{11}N_3O_2$	60,8	5,1	48
XI	196	2,26 (3H, s, CH_3); 7,2—8,2 (3H, Ar), 9,82 (1H, s, CHO)	52,9	4,4	$C_{14}H_{13}BrNO_2$	52,3	4,1	65
XIV	231	2,62 (3H, s, CH_3); 7,95 (1H, s, NH), 9,88 (1H, c, CHO)	69,9	6,1	$C_{14}H_{14}N_2O_2$	69,4	5,8	13
XV	208	5,47 (1H, d, $=CH_2$; $J=2$ Hz); 5,73 (1H, d, $=CH_2$); 7,92 (1H, s, NH); 9,86 (1H, s, CHO)	—	—	—	—	—	25

*The yield of compound V is given for the bromination of indole II, and the yield of compound VI is that for the nitration of indole I.

ole series; the 3-substituted 3-aminoindoles (compounds V and VIII) are formed, respectively.



VIII

The PMR spectra of compounds V and VIII do not contain the aldehydic proton signal, but do exhibit multiplets corresponding to four aromatic protons. The 4-H proton signal in the spectrum of the nitroindole VIII appears at very weak field ($\Delta\delta$ = 0.6 ppm) relative to the group of signals for the remaining aromatic protons, apparently due to its position close to the electron-withdrawing nitro group (see Table 1). For the diacylaminoindole III, unco-attack is less favored, due to the lower electron density at the 3-position. Thus, in the case of nitration of compound III, an equimolar mixture of the 5- and 6-nitro derivatives* (IX) is formed in 41% yield along with 32% of the unco-substituted product (VI); bromination, on the other hand, occurs exclusively on the benzene ring, and an equimolar mixture of the 5- and 6-brominated derivatives† (X) is formed in 92% yield.

Acylation of 3-acylindoles under Friedel-Crafts type conditions (using a CH_3COCl—$AlCl_3$ complex) occurs under mild conditions (at room temperature in CH_2Cl_2) to give a mixture of the 5-, 6-, and 7-acetylsubstituted derivatives, with the 5-isomer predominating [7]. Acylation of the acylaminoindoles I, II, and IV, on the other hand, could be achieved only after prolonged heating (10 h) with an excess of acylating complex in dichloroethane. Indole III, containing two acyl substituent groups, could not be acylated at all under these conditions, and was isolated unchanged from the reaction mixture. The lower reactivity of the indoles I-

*The 3-nitro derivative VI was separated chromatographically from the mixture of the 5- and 6-substituted isomers IX.

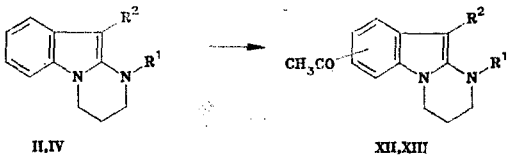
†The 5-bromo isomer XI was synthesized independently via another method [6], which allowed us to assign the signals due to the 6-isomer in the PMR spectrum of the mixture (X).

TABLE 2. Properties of Substitution Product Mixtures Obtained from Indoles I-IV

Isomeric mixtures	PMR spectrum, δ, ppm (J, Hz)						Yield, %
	5-isomer			6-isomer			
	4-H,d (J_1)	6-H,d,d	7-H,d (J_2)	4-H, d (J_2)	5-H, d,d	7-H,d (J_1)	
X*	8,15 (1,8)	7,25	7,15 (8,5)	7,96 (7,8)	7,3	7,56 (2,0)	82
XII*	8,2 (1,8)	7,74	7,04 (8,2)	7,58 (8,0)	7,8	7,72 (2,0)	84
XIII	8,25 (2,1)	8,17	7,02 (8,6)	7,54 (8,4)	7,06	8,2 (2,0)	35
XVII	8,2 (1,8)	7,88	7,23 (8,2)	7,53 (8,4)	7,76	7,92 (1,8)	12

*The PMR spectrum of the isolated 5-isomer is presented in Table 1 (compounds XI and XIV).

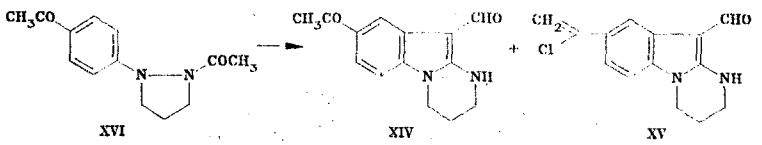
IV, which are stronger bases, may be ascribed to the formation of stable complexes with aluminum chloride, which are then inert toward further reaction. As noted before, acylation of indole I results in substitution at the C(3) carbon atom to generate compound VII. Acylation of indoles II and IV gives a mixture of the 5- and 6-isomers, namely compounds XII and XIII, in almost equal amounts (5:6 and 4:3, respectively, according to PMR analysis) (see Table 2); these compounds could not be separated into the individual components:



II,IV XII,XIII

XII R^2=CHO; XIII R^1=$COCH_3$, R^2=CH_3

The 5-acetyl derivative XIV was prepared independently via a modified Kost reaction [8]. We would like to point out that the rearrangement of 1-acyl-2-arylpyrazolines containing electron-withdrawing substituents in the benzene ring to give indoles has not been demonstrated before. In fact, the reaction proceeded to give a mixture of compounds XIV and XV, with the former compound predominating; the isomeric products were separated by preparative chromatography. The PMR spectra of compounds XIV and XV contain singlet peaks for the NH and CHO protons, and an ABC signal pattern for the three aromatic protons. In place of the methyl group signal at 2.62 ppm, which is found in compound XIV, the PMR spectrum of indole XV contains absorptions due to interacting vinyl protons (doublets at 5.47 and 5.73 ppm, with a coupling constant of 2 Hz).



XVI XIV XV

Bromination of indole IV led to a complex mixture of products; no identifiable compounds could be isolated from this mixture. Nitration of this same compound could be accomplished under selected conditions to yield a mixture of the 5- and 6-nitroderivatives XVII, albeit in low yield (12%) (see Table 2); most of the starting material was converted to resinous material under these conditions.

Our experiments have established that 2-acylaminoindole derivatives undergo electrophilic substitution reactions at the 3-position, just as was observed in the case of 2-aminoindoles. For 3-acyl-2-aminoindoles bromination and nitration are characterized by predominant unco- attack, accompanied by deacylation; the importance of this pathway decreases as the electron density at the 3-position of the indole ring is lowered, for instance upon introduction of a second electron-withdrawing group. Friedel–Crafts type acylation of 3-substituted 2-aminoindoles occurs on the benzene ring of the indole nucleus (at the 5- and 6-positions).

EXPERIMENTAL

The reactions were monitored and the purities of the reaction products were assayed by TLC on Silufol using the eluent system benzene–methyl ethyl ketone–methanol, 10:5:1. This solvent mixture was also employed to purify the products via column chromatography on Silpearl grade silica gel as the support material. PMR spectra were recorded on Tesla BS-497 and WP200SY spectrophotometers at an operating frequency of 200 MHz using solutions in $CDCl_3$ or DMSO versus TMS as internal standard. In all of the experiments the course of the reaction was controlled by first measuring the PMR spectrum of the impure reaction mixture followed by that of the purified product sample.

Bromination. A solution of 10 mmole of indole I-IV in chloroform at 0°C was treated with 0.1 ml (20 mmole) of bromine; the reaction mixture was maintained at room temperature for several hours and then the precipitate was filtered and washed with chloroform.

Nitration. A solution containing 2 mmole of nitronium fluoroborate in acetonitrile at 0°C was treated with 4 mmole of pyridine, followed by 1.5 mmole of indole I-IV; after several minutes the mixture was poured onto ice water, extracted with chloroform, washed with water, and dried. The volatile solvent and other components were evaporated under vacuum, and the residue was purified by column chromatography.

Acylation. A solution of indole I-IV in absolute dichloroethane at 0•C was treated with a three- to fivefold excess of aluminum chloride, mixed 10-20 min at 20°, and then refluxed for 10 h. The reaction mixture was decomposed with ice water, aqueous base was added (with cooling) until all of the insoluble aluminum hydroxide hydrate had dissolved, and then the organic layer was separated and the aqueous layer was extracted with another portion of chloroform. The combined organic extracts were dried, concentrated in vacuo, and the residue was purified by column chromatography.

Indolization of 1-Acetyl-2-(p-acetylphenyl)pyrazolidine (XVI). A solution of 200 mg (0.86 mmole) of pyrazolidine XVI [9] in 5 ml of dry DMF at 0°C was treated with 0.157 ml (1.72 mmole) of $POCl_3$; the mixture was then heated for 3 h at 100-120°C. The reaction mixture was poured into 20 ml of water, neutralized to pH 9 with 10% NaOH solution, and extracted with chloroform (2 × 15 ml); the residue remaining after solvent evaporation was subjected to column chromatography using methyl ethyl ketone. Yield 27 mg (13%) of indole XIV (R_f 0.25), and 56 mg (25%) of indole XV (R_f 0.4).

The properties of the products as well as of the starting materials, which were synthesized according to known methods [8, 10-12], are recorded in Tables 1 and 2.

LITERATURE CITED

1. V. A. Budilin, L. G. Yudin, and A. N. Kost, Khim. Geterotsikl. Khim., No. 9, 1181 (1980).
2. G. A. Golubeva, E. S. Besidskii, L. A. Sviridova, N. V. Postavnaya, and Yu. G. Bundel', Khim. Geterotsikl. Khim., No. 7, 946 (1985).
3. L. G. Yudin, A. I. Pavlyuchenko, V. A. Budilin, V. A. Mishkin, and A. N. Kost, Khim. Geterotsikl. Khim., No. 11, 1506 (1971).
4. G. Berti, A. Da Settimo, and O. Livi, Tetrahedron, 20, 1397 (1964).
5. A. Da Settimo, E. Namipieri, J. Org. Chem., 35, 2546 (1970).
6. G. A. Golbeva, Yu. N. Portnov, A. N. Kost, L. I. Borisova, and A. K. Trukhmanov, Khim. Geterotsikl. Khim., No. 10, 1377 (1978).
7. T. Hino, Y. Torisawa, and M. Nakagaw, Chem. Pharm. Bull., 30, 2349 (1982).
8. B. I. Gorin, G. A. Golubeva, L. A. Sviridova, A. V. Dovgilevich, and Yu. G. Bundel', Khim. Geterotsikl. Khim., No. 3, 397 (1983).
9. B. I. Gorin, G. A. Golubeva, L. A. Sviridova, and Yu. G. Bundel', Vestn. MSU, Ser. 2, Khimiya, 24, 389 (1983).
10. Yu. N. Portnov, G. A. Golubeva, and A. N. Kost, Khim. Geterotsikl. Khim., No. 1, 61 (1972).
11. Yu. N. Portnov, G. A. Golubeva, A. N. Kost, and V. S. Bolkov, Khim. Geterotsikl. Khim., No. 5, 647 (1973).
12. B. I. Gorin, G. A. Golubeva, E. S. Besidskii, L. A. Sviridova, and Yu. G. Bundel', Khim. Geterotsikl. Khim., No. 5, 1630 (1983).