10. G. A. Golubeva, Yu. N. Portnov, A. N. Kost, and L. A. Sviridova, Khim. Geterotsikl. Soedin., No. 1, 118 (1971).
11. G. A. Golubeva, L. A. Sviridova, N. Yu. Lebedenko, and A. N. Kost, Khim. Geterotsikl. Soedin., No. 4, 547 (1973).
12. Houben-Weyl, Methoden der organischen Chemie, Vol. 9, Georg Thieme Verlag, Stuttgart.
13. A. N. Kost, A. V. Dovgilevich, and L. A. Sviridova, Zh. Org. Khim., 16, (1980).

REACTION OF 1,4-DIAZINES WITH INDOLES IN THE PRESENCE OF ACYLATING AGENTS*

A. K. Sheinkman, Kh. Ya. Lopatinskaya, N. A. Klyuev, and Zh. K. Torosyan

UDC 547.759.2'863:542.951.1

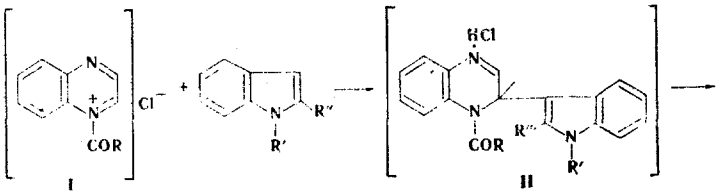
2,3-Diindolyl-1,4-diacyl-1,2,3,4-tetrahydropyrazines and 2,3-diindolyl-1,2,3,4-tetrahydroquinoxalines with acyl residues attached to one or both nitrogen heteroatoms were obtained by the reaction of pyrazines and quinoxalines with indole and 1-methyl- and 2-methylindoles in the presence of acyl chlorides or acetic anhydride.

In the reaction of monoazines and acylating agents with indoles the latter undergo hetarylation by the intermediately formed N-acyl azinium cations [3].

It seemed extremely tempting to attempt to extend this reaction also to 1,4-diazines, since the participation of these N-heteroaromatic systems, which are the least basic diazines [4], in hetarylation would imply the possibility of its extension to other diazines. One example of such a reaction with the participation of a phthalazine with a basicity that is higher by a factor of five than the basicities of 1,4-diazines is known [5]. This reaction involves the formation of Reissert compounds by the reaction of phthalazine with potassium cyanide in the presence of benzoyl chloride.

We first attempted to preparatively synthesize N-acyl salts of 1,4-diazines by the reaction of pyrazine and quinoxaline with acylating agents. It was found that the N-acyl salts of these N-heteroaromatic systems are not formed either under the conditions for the preparation of N-acylpyridinium chlorides [6] or under the conditions described for the preparation of stable N-acylimmonium [7] and N-acylazolium [8] stibnates. However, we obtained hetarylation products, viz., 1-acyl-2,3-diindolyl-1,2,3,4-tetrahydroquinoxalines (III) and 1,4-diazyl-2,3-diindolyl-1,2,3,4-tetrahydropyrazines (IV), in the reaction of pyrazine and quinoxaline with indoles in the presence of acyl halides.

Nevertheless, the process evidently takes place through the intermediate formation of N-acyl salts I, which attack the indoles electrophilically to give monosubstituted adducts II, as described for N-alkylquinoxalinium salts [9]. However, in our case when an oxidizing

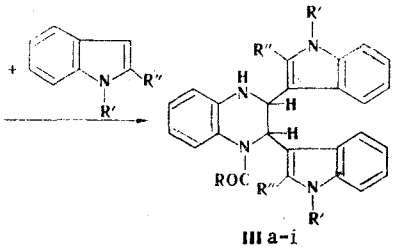


I II

*See [1, 2] for our preliminary communications.

Donetsk State University, Donetsk 340055. Dnepropetrovsk Construction-Engineering Institute, Dnepropetrovsk 320631. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 234-238, February, 1980. Original article submitted March 19, 1979.

 0009-3122/80/1602-0174$07.50

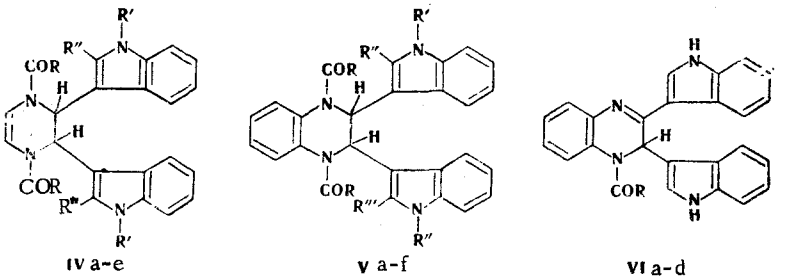


III a-i

III a R=R′=CH$_3$, R″=H; b R=C$_6$H$_5$, R′=R″=H; c R=C$_6$H$_5$, R′=CH$_3$, R″=H; d R=C$_6$H$_5$, R′=H, R″=CH$_3$; e R=2-thienyl, R′=R″=H; f R=*o*-CH$_3$—C$_6$H$_4$, R′=R″=H; g R=*o*-CH$_3$OC$_6$H$_4$, R′=R″=H; h R=*p*-Cl—C$_6$H$_4$, R′=R″=H; i R=*p*-NO$_2$—C$_6$H$_4$, R′=R″=H

agent is absent, one does not observe aromatization of II but rather addition of a second molecule of the indole to the $-\overset{+}{N}H=CH- \longleftrightarrow -NH-\overset{+}{C}H-$ bond.

In the case of pyrazine 1,4-diacyl derivatives IV are formed under the same conditions, evidently as a consequence of acylation of the monosubstituted 1,2-dihydropyrazines with the subsequent addition to them of a second molecule of the indole or as a consequence of participation of 1,4-diacylpyrazinium salts in the reaction. This possibility, although it is less likely, cannot be excluded, since 1,4-dialkylpyrazinium salts are known [10]. It should be noted that the impossibility of the preparative synthesis of N-monoacyl and N,N′-diacyl salts of 1,4-diazines by no means indicate that these salts cannot be formed as intermediates in the reaction and in situ attack the π-surplus indole ring. Instances of this sort are known in a number of other N-heteroaromatic systems [11]. We obtained 1,4-diacetyl derivatives IV, V, and VI in all cases in the reaction of pyrazine and quinoxaline with indoles in acetic anhydride.



IV a-e V a-f VI a-d

IV a R=CH$_3$, R′=R″=H; b R=R″=CH$_3$, R′=H; c R=R′=CH$_3$, R″=H; d R=C$_6$H$_5$, R′=R″=H; e R=*p*-NO$_2$—C$_6$H$_4$, R′=R″=H; f R=2-thienyl R′=R″=H; V a R=R′=CH$_3$, R″=R‴=H; b R=R′=R″=CH$_3$, R‴=H; c R=R′=R‴=CH$_3$, R″=H; d R=CH$_3$, R′=C$_6$H$_5$, R″=R‴=H; e R=CH$_3$, R′=*p*-NO$_2$—C$_6$H$_4$, R″=R‴=H; f R=CH$_3$, R′=*p*-Cl—C$_6$H$_4$, R″=R‴=H; VI a R=CH$_3$; b R=C$_6$H$_5$; c R=*o*-CH$_3$—C$_6$H$_4$; d R=*o*-CH$_3$O—C$_6$H$_4$

Compounds V are readily obtained by acylation of monoacyl derivatives III, which are formed directly in the hetarylation reaction, and this confirms their structure. 1,2-Dihydro derivatives VI are formed in the dehydrogenation of III with chloranil. In contrast to monoacyl derivatives III, 1,4-diacyl derivatives of 1,2,3,4-tetrahydropyrazine (IV) and quinoxaline (V) cannot be dehydrogenated, and this may also serve as an additional confirmation of their structure.

The IR spectra of III-VI contain intense absorption bands at 1640-1670 cm^{-1}, which are characteristic for the carbonyl group of anilides; the band at 3400 cm^{-1} belongs to the absorption of the NH group of the tetrahydroquinoxaline ring in III (this band is absent in the spectra of their dehydrogenation products VI) and of the NH group of the indole ring at 3490 cm^{-1}.

Signals at 1.86 (q, CH_3CO, J_{2,CH_3} = 1.08 Hz, J_{6,CH_3} = 1.28), 3.47 (s, N—CH_3; this signal is absent in the spectrum of IVc), 5.81 (d, 2-H), 6.42 (d, 6-H), 7.18 (m, benzene ring protons), and 7.76 ppm (s, indole α-H) are observed in the PMR spectrum of IVa. The assignment of the signals was made on the basis of a comparison with the spectrum of IVc and the ratio of the number of protons for these signals (3:3:1:1:4:1). The splitting of the signal of the CH_3CO group to give a quartet (for IVa, c) is due to coupling with the 2-H and 6-H protons of the pyrazine ring. The shift of the signal of the 2-H proton to stronger field as compared with the signal of the 6-H proton is due to sp^3 hybridization of the C_2 atom.

TABLE 1. Characteristics of the Compounds Obtained

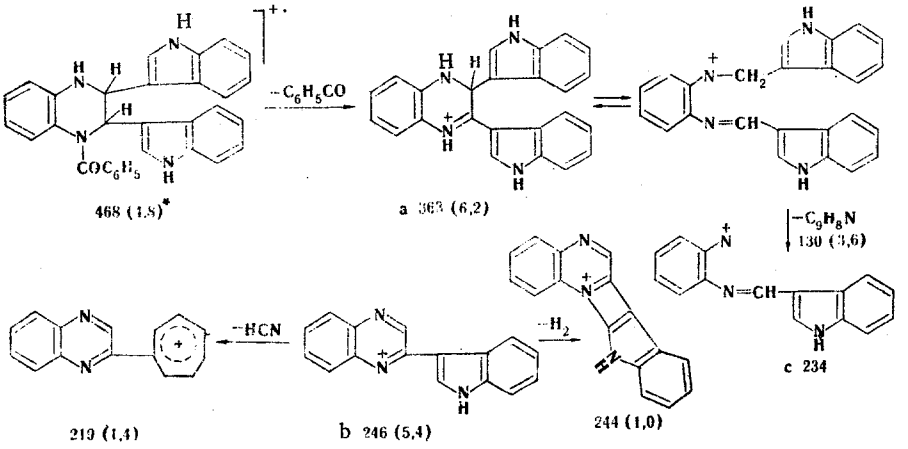
Compound	mp, °C	Found				Empirical formula	Calc.				R_f	Yield, %
		C, %	H, %	N, %	M		C, %	H, %	N, %	M		
IIIa	299—300[a]	77,1	6,6	11,0	437	$C_{28}H_{26}N_4O$	77,5	6,0	12,9	437,289	0.64	69
IIIb	300—301[a]	79,2	5,2	11,9	468	$C_{31}H_{24}N_4O$	79,5	5,2	11,9	468,19	0,36	41
IIIc	285—287[a]	79,9	5,4	11,4	496	$C_{33}H_{28}N_4O$	79,8	8,5	11,3	469,59	0,45	39
IIId	250—252[a]	79,5	5,5	11,6	496	$C_{33}H_{24}N_4O$	79,8	5,7	11,3	469,59	0,30	42
IIIe	288—289[b]	71,0	5,0	13,4	424	$C_{25}H_{20}N_4O$	70,7	4,7	13,2	424,51	0,45	35
IIIf	318—320[c]	79,6	5,6	11,6	482	$C_{32}H_{26}N_4O$	80,5	5,8	11,1	482,57	0,30	45
IIIg	327—329[a]	76,8	5,7	10,9	499	$C_{32}H_{27}N_4O_2$	76,9	5,4	11,2	499,57	0,45	49
IIIh	320—321[d]	74,3	5,0	11,0	502	$C_{31}H_{23}N_4OCl$	74,0	4,6	11,4	502,69	0,43	43
IIIi	293—294[b]	72,3	4,7	13,9	513	$C_{31}H_{23}N_5O_3$	72,5	4,5	13,7	513,54	0,44	53
IVa	320—322[a]	73,1	5,2	13,9	398	$C_{24}H_{22}N_4O_2$	72,3	5,5	14,0	398,45	0,76	49
IVb	308—310[c]	73,5	5,9	13,2	426	$C_{26}H_{26}N_4O_2$	73,2	6,1	13,1	426,50	0,65	50
IVc	268—270[e]	77,9	6,7	12,7	426	$C_{26}H_{26}N_4O_2$	73,2	6,1	13,1	426,50	0,45	54
IVd	203—205[f]	77,9	4,8	10,6	522	$C_{34}H_{26}N_4O_2$	78,1	5,0	10,7	522,58	0,37	45
IVe	220—221[f]	66,5	3,7	13,4	612	$C_{34}H_{24}N_4O_2$	66,7	3,9	13,7	612,59	0,42	42
IVf	195—197[f]	67,2	4,0	10,6	534	$C_{30}H_{22}N_4O_2$	67,4	4,1	10,5	534,14	0,45	63
Va	342—344[a]	75,0	5,6	12,9	448	$C_{28}H_{24}N_4O_2$	74,9	5,4	12,5	448,51	0,31	48
Vb	272—273[a]	75,2	6,1	12,0	476	$C_{30}H_{28}N_4O_2$	75,6	5,9	11,7	476,56	0,44	50
Vc	295—296[c]	75,9	6,0	12,2	476	$C_{30}H_{28}N_4O_2$	75,6	5,9	11,7	476,56	0,40	26
Vd	285—286[g]	77,2	5,5	11,2	510	$C_{33}H_{26}N_4O_2$	77,6	5,1	10,9	510.58	0,32	85
Ve	190—193[g]	73,0	4,0	12,9	555	$C_{33}H_{25}N_5O_4$	71,3	4,0	12,6	555,58	0,25	90
Vf	254—255[b]	72,4	4,8	10,0	545	$C_{33}H_{25}N_4O_2Cl$	72,7	4,6	10.2	545,07	0,56	93
VIa	189—190[h]	77,3	4,4	13,6	402	$C_{26}H_{18}N_4O$	77,5	4,5	13.9	402,44	0,45	80
VIb	184—185[h]	79,6	4,5	12,2	466	$C_{31}H_{22}N_4O$	79,8	4,7	12,0	466,53	0,30	80
VIc	179—180[h]	79,7	4,8	11,9	480	$C_{32}H_{24}N_4O$	79,9	5,0	11,6	480,56	0,31	95
VId	187—188[f]	77,6	5,1	10,9	496	$C_{32}H_{24}N_4O_2$	77,4	4,9	11,3	496,56	0,32	90

[a]From DMF. [b]From acetone. [c]From dioxane. [d]From dioxane—water. [e]From n-butanol. [f]From ethanol. [g]From acetic acid. [h]From methanol.

The spectrum of IIIa contains a singlet at 5.82 ppm and a complex multiplet centered at 7.18 ppm. The ratio of the integral intensities (2:19) confirms the proposed structure.

The high-resolution mass spectra confirmed the empirical compositions of the molecular ions and most of the fragment ions of III-VI.

In the first step of the fragmentation of the M^+ ions of these compounds the labile amide bond is cleaved to give $(M - COR)^+$ and $(COR)^+$ ion peaks. Successive elimination of two COR groups from M^+ is observed in the case of 1,4-diacyl derivatives of quinoxaline or pyrazines IV and V. The fragmentation of the molecular ions of III-VI can be illustrated thoroughly in the case of IIIb (Table 2):



All of the processes indicated above were also observed in the mass spectra of III-VI (Table 3). One should note the unusual behavior upon electron impact of III, cleavage of the pyrazine ring, which leads to the appearance of an ion peak at 258* of the 1,2-di(3-indolyl) ethylene structure. The appearance of ion peaks at 142 in the mass spectra of VI constitutes

*The m/e values are given here and subsequently for the ion peaks in the mass spectra.

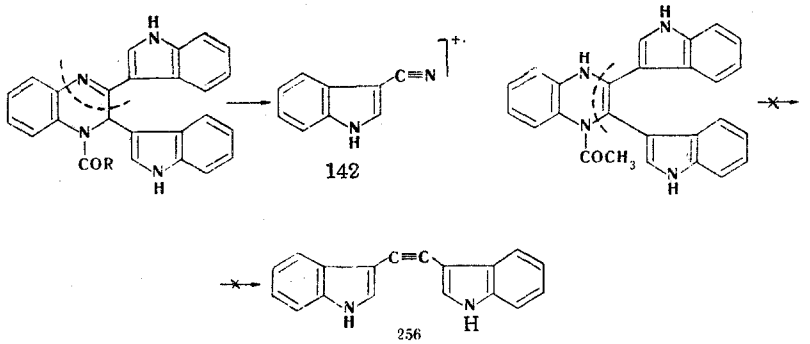
TABLE 2. Elementary Compositions of the Ions in the Mass Spectrum of IIIb

Empirical formula (arbitrary designation of the ion)	Mass No.	
	calc.	determined
$C_{31}H_{24}N_4O$ (M^+)	468,19511	468,1952
$C_{24}H_{19}N_4$ (a)	363,16105	363,1611
$C_{18}H_{12}N_3$ (b)	246,10317	246,10320
$C_{15}H_{12}N_3$ (c)	234,10317	234,10319
C_9H_8N	130,06571	130,06573
C_8H_7N	117,05789	117,05791

TABLE 3. Mass Spectra of III-VI (Intensities in Percent of the Maximum Ion Peak)

Ion peak	IIIg		IIIf		IVd		VIb		VIc		VId	
	I	*m/e*	*I*	*m/e*	*I*	*m/e*	*I*	*m/e*	*I*	*m/e*	*I*	*m/e*
M^+	40,1	498	9,0	482	22,2	522	22,3	466	12,5	480	3,0	496
$[M-2COR]^+$ (A)	38,2	363	25,5	363	4,1	417	100,0	361	99,4	361	71,8	361
$[M-2COR]^+$	—	—	—	—	3,1	312	—	—	—	—	—	—
$[M-In]^+$	—	—	—	—	4,1	406	5,2	349	—	353	—	379
$[A-In]^+$	11,2	247	34,6	247	4,5	301	11,0	245	26,5	245	12,4	245
$[(M-2COR)-In]^+$	—	—	—	—	6,1	196	—	—	—	—	—	—
$[(A-In)-H]^+$ (B)	58,0	246	100,0	246	4,6	300	28,9	244	64,8	244	31,8	244
$[(A-In)-2H]^+$	17,7	245	63,4	245	—	299	4,3	243	9,9	243	5,0	243
$[(A-In)-3H]^+$	6,2	244	21,6	244	8,3	298	—	—	—	—	—	—
$[(A-In)-HCN]^+$	3,0	220	16,8	220	7,4	275	7,2	218	27,6	218	11,0	218
$[B\ HCN]^+$	15,3	219	78,8	219	8,2	274	3,6	217	13,0	217	6,0	217
$[(B\ HCN)-H]^+$	8,7	218	36,0	218	3,0	273	—	—	—	—	—	—
$(In-CH=CH-In)^+$	3,0	258	3,4	258	71,0	258	—	—	—	—	—	—
$(COR)^+$	100	135	32,4	119	100,0	105	24,6	105	100,0	119	100,0	135
In^+	17,9	117	7,7	117	7,3	117	3,0	117	7,9	117	3,0	117
$(In-H)^+$	4,5	116	3,5	116	4,0	116	3,0	116	13,0	116	4,6	116

evidence in favor of our proposed 1,2-dihydro derivative structure, since in the case of the 1,4-dihydro derivatives the formation of this ion is impossible, and ions at 256 of the 1,2-di(3-indolyl)acetylene structure should appear:



Thus the set of spectral data and some of the chemical transformations enable us to assign structures III-VI to the compounds obtained.

EXPERIMENTAL

The IR spectra of Nujol suspensions and chloroform solutions of the compounds were recorded with a UR-20 spectrometer. Chromatography in a loose thin layer of Al_2O_3 (activity II) and preparative separation were carried out by elution with acetone–hexane systems (1:2 and 2:1). The PMR spectra of CF_3COOH solutions were recorded with a Tesla BS-487-C spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard. The mass spectra were

recorded with a Varian Mat-311 spectrometer with a system for direct introduction of the samples into the ion source at an ionizing-electron energy of 70 eV, a cathode emission current of 300 μA, an accelerating voltage of 3 kV, and an ionization-chamber temperature of 180°C. The high-resolution mass spectra were obtained with the same apparatus under the same conditions for $M/\Delta M = 15000$ with polyphosphoric acid as the standard.

Typical Method for the Hetarylation of Indoles with 1,4-Diazines in the Presence of Acyl Halides. A mixture of 0.02 mole of pyrazine or quinoxaline, 0.02 mole of the acyl halide, and 0.02 mole of indole in 40 ml of dry benzene (or chloroform) was maintained at room temperature with constant stirring for 5 h. The precipitate was removed by filtration, washed three times with small portions of methanol, and recrystallized from a suitable solvent (Table 1).

1,Acetyl-4-acyl-1,2,-di(3-indolyl)-1,2,3,4-tetrahydroquinoxalines (V). These compounds were obtained by refluxing 0.005 mole of monoacyl derivative III in 20 ml of acetic anhydride until a precipitate formed. The latter was removed by filtration, washed with methanol, and recrystallized (Table 1).

1,4-Diacetyl-2,3,-di(3-indolyl)-1,2,3,4-tetrahydropyrazines (IVa-c) and -quinoxalines (Va-c). These compounds were obtained by refluxing 0.02 mole of indole and 0.01 mole of pyrazine or quinoxaline in 30 ml of acetic anhydride for 4 h. The acetic anhydride was removed by vacuum distillation, and the residue was washed with water and recrystallized (Table 1).

1-Acyl-2,3-di(3-indolyl)-1,2-dihydroquinoxalines (VI). These compounds were obtained by refluxing 0.001 mole of the corresponding tetrahydro derivative III in 40 ml of alcohol with 0.015 mole of chloranil for 4-5 h until starting derivative III dissolved completely. The alcohol was removed by vacuum distillation until the original volume was halved, and the residue was treated with alkali. The precipitate was removed by filtration, washed with water, and recrystallized (Table 1).

LITERATURE CITED

1. A. K. Sheinkman, Kh. Ya. Lopatinskaya, and N. A. Klyuev, Khim. Geterotsikl. Soedin., No. 11, 1569 (1977).
2. Kh. Ya. Lopatinskaya, A. I. Kolodin, and A. K. Sheinkman, Khim. Geterotsikl. Soedin., No. 2, 273 (1978).
3. A. K. Sheinkman, Khim. Geterotsikl. Soedin., No. 1, 3 (1974).
4. A. Albert, in: Physical Methods in the Chemistry of Heterocyclic Compounds, A. R. Katritzky (ed.), Academic Press (1963).
5. D. Bhattacharjee and F. Popp, Heterocycles, 6, 1905 (1977).
6. A. K. Sheinkman, S. A. Portnova, Yu. N. Sheinker, and A. N. Kost, Dokl. Akad. Nauk SSSR, 157, 1416 (1964).
7. A. K. Sheinkman, E. N. Nelin, A. I. Kostin, and V. P. Marshtupa, Zh. Org. Khim., 14, 1289 (1978).
8. T. V. Stupnikova, A. I. Serdyuk, E. Portsel', and A. K. Sheinkman, Dokl. Akad. Nauk Ukr. SSR, Ser. B, No. 1, 45 (1977).
9. O. N. Chupakhin, E. O. Sidorov, and I. Ya. Postovskii, Khim. Geterotsikl. Soedin., No. 10, 1433 (1975).
10. I. Curphey, J. Am. Chem. Soc., 87, 2063 (1965).
11. A. K. Sheinkman, S. I. Suminov, and A. N. Kost, Usp. Khim., 42, 1415 (1973).