INVESTIGATION OF THE ALKYLATION OF NITROAZOLES WITH α-HALOKETONES BY ^{13}C, ^{15}N, and ^{14}N NMR

V. V. Semenov, B. I. Ugrak, S. A. Shevelev,
M. I. Kanishchev,* A. T. Baryshnikov,
and A. A. Fainzil'berg

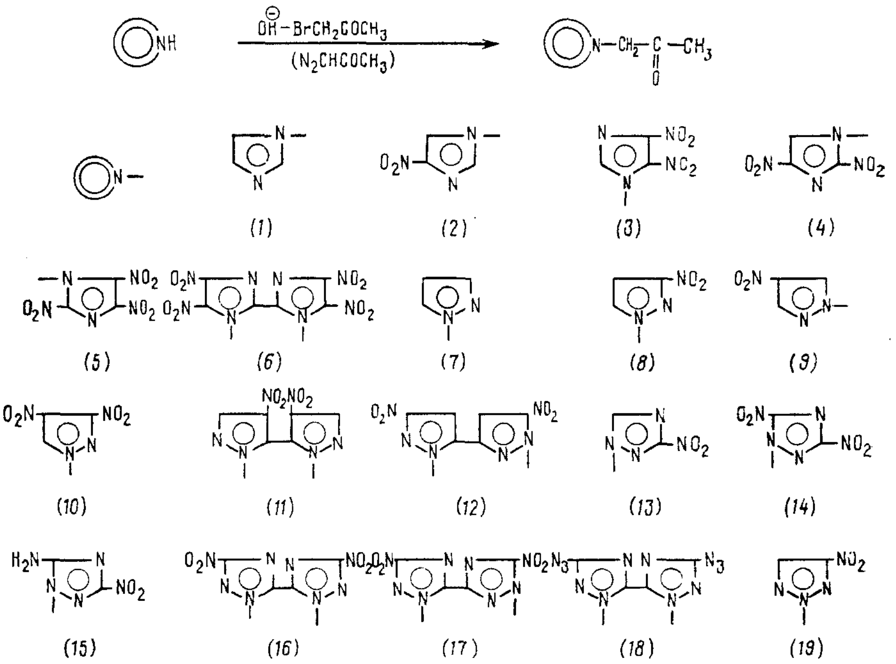
UDC 543.422.25:66.095.253:547.77

General methods have been worked out for the alkylation of nitroazoles with bromoacetone, bromoacetophenone, and diazoacetone in homogeneous media and by phase-transfer catalysis. The structures of the N-acetonylazoles were established by ^{13}C, ^{15}N, and ^{14}N high-resolution NMR spectroscopy.

Nitroazoles with a carbonyl function in the substituents provide convenient synthons for the synthesis of polycyclic compounds having biological activity [1-3]. These structures are most simply obtained by alkylating nitro-NH-azoles with α-haloketones.

Such reactions have previously been examined in only a few cases [4-6], and there have been no literature reports of the use of high-resolution NMR spectroscopy (especially ^{15}N) which is essential for the correct assignment of the positions of the substituents in the heterocycle.

Most of the N-acetonylazoles obtained were prepared by alkylating the anions of the appropriate azoles with bromoacetone in aqueous acetone. As will be seen from Table 1, the reaction is undergone by azoles which differ wisely in the basicity of the anions, their NH-acidity values ranging over some ten orders of magnitude. The conditions required for the reaction to proceed depend on the pK$_a$ value of the heterocycle (scheme 1, Table 1).

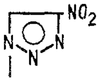


---

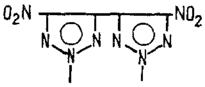
*Deceased.

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 8, pp. 1827-1837, August, 1990. Original article submitted July 24, 1989.

0568-5230/90/3908-1658$12.50


(20)

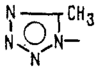

(21)

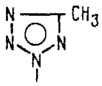

(22)

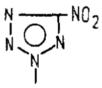

(23)

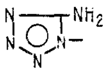

(24)

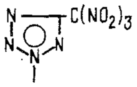

(25)

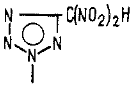

(26)


(27)

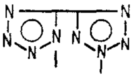

(28)

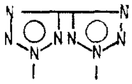

(29)

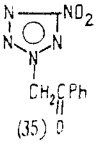

(30)


(31)


(32)

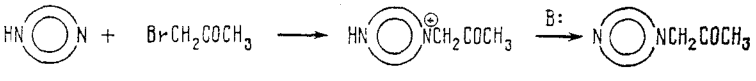

(33)

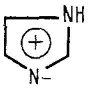

(34)

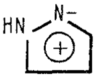

(35)

Azoles with pK_a values of 3-6 (tetrazole, 5-methyltetrazole, 3-nitro-1,2,4-triazole, 4-nitro-1,2,3-triazole, 4,5- and 2,4-dinitroimidazole) are alkylated by bromoacetone in high yield in a homogeneous acetone–water medium over 24 h at 20°C. With the more basic 4-nitroimidazole and 4-nitropyrazole anions (pK_a = 9.3 and 9.7), the reaction proceeds with evolution of heat, and is complete within a few hours.

In the case of the highly basic imidazole and pyrazole anions (pK_a = 14.5 and 14.2), which decompose α-halocarbonyl compounds, the required ketones can only be obtained by quaternization via hydrobromides (1) and (7) followed by treatment with base:



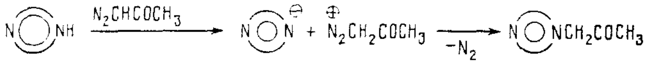

(1)


(7)

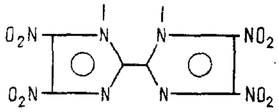
The weakly nucleophilic anions of fully nitrated and bicyclic azoles (nitrotetrazole, dinitro-1,2,4- and 1,2,3-triazoles, bicyclic nitro-1,2,4- and 1,2,3-triazoles, and bitetrazolyl) are alkylated in acceptable yields only at 60-70°C.

This method, however fails even in strongly polar solvents (DMF and DMSO) to give ketones derived from 2,4,5-trinitroimidazole and bis(4,5-dinitroimidazol-2-yl), since in the final structures (5) and (6) the nitro groups are extremely readily replaced by the nucleophilic reagents present in the reaction mixture (Br^- and H_2O).

In such cases, alkylation requires the use of diazoacetone. As a result of the high NH-acidity of the nitroazoles, the diazoacetone is readily protonated, and reacts rapidly with the heterocyclic anion:




(5)


(6)

Efficient methods for the alkylation of weakly nucleophilic nitroazoles by α-bromoketones involving phase-transfer catalysis have been developed by us (for the use of phase-transfer catalysis for the alkylation of azoles, see [8]). The phase transfer catalyst used

TABLE 1. Conditions for Synthesis, and Constants of N-Acetonylazoles

Compound	Method of synthesis* (solvent)	Yield, %	Reaction conditions		Mp, °C (solvent for cryst.)	IR spectrum, ν, cm^{-1} (KBr)		pK$_a$† of starting azole
			T, °C	time, h		CO	NO_2	
(1), HBr	A (acetone)	80	20	20	101 (*i*-PrOH)	1730 1740		14,5
(2)	A (H_2O+acetone)	87	20	5	164 (H_2O)	1720	1330 1550	9,35
(3)	»	67	20	24	95 (H_2O)	1732	1342 1540 1567	3,37
(4)	»	87	20	24	133 (DCE)	1730	1334 1350 1553	2.85
(5)	B (ether)	50	20	3	Oil	1748	1326 1559 1572	−5,59
(6)	»	61	20	3	230 ($(CH_3)_2CO$)	1735	1360 1548 1572	−4.26 −5,63
(7), HBr	A (CH_3OH)	40	20	20	Oil	1742		14,2
(8)	A (H_2O – acetone)	50	20	20	125 (DCE)	1722	1305 1504	9,81
(9)	»	56	20	20	90 (DCE)	1722	1305 1535	9,67
(10)	»	52	20	20	120 (DCE)	1740	1342 1538	5,48
(11)	C (H_2O – DCE)	45	20	10	190	1728	1340 1362 1538	
(12)	»	15	20	12	168	1720 1730	1326 1350 1639	
(13)	A (H_2O – acetone)	85	20	16	101 (DCE)	1735	1310 1558	6.05
(14)	»	56	20	144	136 ($CHCl_3$)	1735	1322 1350 1522	−0.66
(15)‡							1577	
(16)	A (H_2O – acetone)	57	70	5	280 (CH_3OH)	1738	1319 1340 1365 1560	3,30
	C (H_2O – DCE)	66	30	7				5,35
(17)	»	18	30	7	158	1730	1322 1346 1364 1563 1585	3.30
	»	24	30	7				5,35
(18)	A (H_2O – acetone)	18	20	18	158–160	1737	2146 (N_3)	6,87 10,26
(19)	»	37	20	48	112–114 (DCE)	1735	1363 1535	4,80
(20)	»	42	20	48	119–120 (ether+EA)	1735	1360 1540	4.80
(21)	»	65	60	10–12	64 (CH_3OH)	1736	1344 1368 1565	
(22)	»	42	20+60	20+3	198 ($CHCl_3$+ +$(CH_3)_2CO$)	1740	1362 1545	
(23)	»	23	20+60	20+3	188–189 ($CHCl_3$+ +$(CH_3)_2CO$)	1738	1358 1542 1550	
(24)	»	23	20	16	87–88 (DCE)	1738		4.86
(25)	»	23	20	16	55–57 (distillation)	1732		4.86

TABLE 1 (continued)

Compound	Method of synthesis* (solvent)	Yield, %	Reaction conditions		Mp, °C (solvent for cryst.)	IR spectrum, ν, cm^{-1} (KBr)		pK_a† of starting azole
			T, °C	time, h		CO	NO_2	
(26)	»	44	20	16	98.5–99.5 (benzene)	1729		5,50
(27)	»	23,5	20	16	69–70 (H_2O)	1729		5,50
(28)	»	75	70–80	15	98–99 (CH_3OH)	1732	1316 1340 1578	–0,83
(29)	»	55	20	15	215 (H_2O+acetone)	1730		6,03
(30)	»	68	20	15	94–95 (CH_3OH+H_2O)	1735	1280 1590 1600	0,5
(31)							1620	
(32) **					106.5–107,5 (CH_3OH+H_2O)	1735	1260 1580 1610	
(33)	A (H_2O +acetone)	5	65–70	16				1,41 4,25
(34)	»	29	60–70	16				1,41 4,25
(35)	»	39	60–70	16	224–226 (CH_3OH)	1729		1,41 4,25
(36)	C (H_2O – DCE)	60	50–60	10	130 (DCE)	1698	1315 1345 1575	–0.83

---

*A — alkylation with bromoacetone in a homogeneous medium; B — alkylation with diazomethane; C — phase-transfer catalyzed alkylation with bromoacetone.

†Lit. values [4, 7].

‡Compound (15) was presented by M. S. Pevzner and T. P. Kofman (Lensovet Leningrad Institute of Technology).

**Obtained by denitrating (30).

was tetrabutylammonium bromide. As is shown by the reactions of nitrotetrazole with bromoacetophenone, and of bis(3-nitro-1,2,4-triazol-5-yl) and bis(4-nitropyrazol-3-yl) with bromoacetone in dichloroethane—water, the reaction times are much shorter than when the alkylation is carried out under homogeneous conditions. The structures of the N-acetonylazoles were proved by ^{1}H, ^{13}C, ^{15}N, and ^{14}N NMR spectroscopy (Table 2). The ^{1}H NMR spectra, while showing the presence of protons in the molecule, failed to give full structural information. The structures of the products were established by their ^{13}C, ^{14}N, and ^{15}N NMR spectra. The presence in the azole molecules of one or two nitro groups resulted in broadening of the $^{13}C–NO_2$ groups. The ^{13}C NMR spectra were therefore recorded with heteronuclear triple resonance (observation of the ^{13}C nuclei with wide-band decoupling from protons, and selective decoupling from the nuclei of the $^{14}NNO_2$ groups). This enabled a narrow signal for the ^{13}C atom attached to the nitro group to be obtained after a relatively small number of accumulations, and the remote $^{13}C–^{1}H$ coupling constant of the carbon attached to the nitro-group to be measured.

The structures of the N-acetonylazoles were shown by the chemical shifts of the ^{13}C carbons of the azole ring and the CH_2 groups, and the coupling constants of the methylene protons with the nearest ring carbon atom. The ^{13}C chemical shifts were in broad agreement with the few data for N-substituted azoles to be found in the literature [9-12]. The vicinal coupling constants of the methylene protons with C^5 of the azole ring range from 2.2 to 2.4 Hz, whereas the $^{4}J_{^{13}C-^{1}H}$ values are less than 1 Hz, and are not always seen. The analogous vicinal coupling constant reported in [13] was 2.5 Hz.

The structures of the isomeric 1- and 2-acetonyl-1,2,3-triazoles and tetrazoles were also proved by the ^{13}C chemical shifts of the methylene group, as in [14]: The signal for the 2-isomer is seen at lower field than that for the 1-isomer.

TABLE 2. ^1H, ^{13}C, and ^{15}N NMR Chemical Shifts, ppm (coupling constants $^{13}C-^1H$ and $^{15}N-^1H$, Hz) for N-Acetonylazoles in DMSO-d_6

Compound	^1H NMR	^{13}C NMR	^{15}N NMR
(1)	2,23 s – CH_3 5,50 s – CH_2 7,69 d (1,4) – H^4, H^5 9,00 t (1,4) – H_2	27,04 q (128,2) – CH_3 57,69 t (145,4) – CH_2 199,96 q.t (6.2; 4,2) – CO 123,16 d.d.t ($^1J_{C-H}$ = 203,8; $^2J_{C^5-H^4}$ = 12,2; $^2J_{C^4-H^5}$ = 5,4; $^3J_{C^5-HCH_2}$ = 3,9)—$C^5(C^4)$. 137,68 d.t.t ($^1J_{C-H}$ = 224,0; $^3J_{C^3-H^{4,5}}$ = 5,2; $^3J_{C^2-HCH_2}$ = 3,9) —C^2	
(2)	2,21 s – CH_3 5,19 s – CH_2 7,69 d (1,3) – H^2 8,21 d (1,3) – H^5	26,8 q (128,2) – CH_3 56,4 t (145,4) – CH_2 200,9 q.t (6,2; 4,2) – CO 122,60 d.d.t (202,2; 3,4; 3,8) – C^5 138,20 d.d.t (217,3; 8,1; 4,0) – C^2 146,80 d.d ($^2J_{C^4-H^5}$ = 6,4; $^3J_{C^4-H^2}$ = 13,2)—C^4	—18,3 s—4-NO_2, —126,7 d ($^2J_{N^3-H^2}$ = =12,1)—N^3, —208,0 d.d.t ($^2J_{N^1-H^2}$ = = 8,2, $^2J_{N^1-H^5}$ = 3,0; 2,3)—N^1
(3)	2,25 s – CH_3 5,50 s – CH_2 7.78 s – H^2	26. 50 q (128,5) – CH_3 59,30 t (145,2) – CH_2 199.50 q.t (6,0; 4.1) – CO 129.90 d.t (5,0; 3,2) – C 137.20 d.t (224,8; 4,3) – C^2	–24,0 s – 4-NO_2 –32,60 s – 5-NO_2 130,70 d (12,4) – N_3 –130,70 d (12,4) – N^3 213,50 d.t (7,8; 1,3) – N^1
(4)	2,26 s – CH_3 5,65 s – CH_2 8,26 s – H^5	140.90 d (12.3) – C^4 26.80 q (128,5) – CH_3 59.3 t (145,2) – CH_2 199,60 q.t (6,2; 4,2) – CO	–22,70 s – 4-NO_2 –31,10 s – 2-NO_2 –129,7 s – N^3 213,10 t (1,9) – N^1
(5)	2,47 – CH_3 5,69 – CH_2		
(6)	2,42 s – CH_3 5,89 s – CH_2	27,01 q (128,8) – CH_3 58.00 t (146.5) – CH_2 198,60 q.t (6,2; 41) – CO 132,38 t (3,7) – C^2 133.81 t (3,4) – C^5 139,89 s – C^4	–27,60 s (165) – 4-NO_2 * –35,00 s (54) – 5-NO_2 *
(7)	2,00 s – CH_3 5,00 – CH_2 6.23 t (3,0) – H^4 7,41 d (3,0) – H^3 7,59 d (3,0) – H^5	26.60 q (127.6) – CH_3 60,30 t.s (139.6) – CH_2 202,00 q.t (6.1; 4.2) – CO 131,20 d.m (187.1) – C^5 105,50 d.d.d (175,7; $^2J_{C^4-H^3}$ =8,3; $^2J_{C^4-H^5}$ = 5,5) — C^4 139,00 d.d.d (184,0; $^2J_{C^3-H^4}$ = =5,5; $^3J_{C^3-H^5}$ = 8,3) — C^3	–68,90 m – N^2 –169.70 m – N^1
(8)	2,33 s – CH_3 5.31 s – CH_2 6,93 d (3,0) – H^4 7,81 d (3,0) – H^5	26,80 q (128.5) – CH_3 64.60 t (141,5) – CH_2 200,81 q.t (6.3; 4,4) – CO 102.80 d.d (187,5; 8,9) – C^4 135.30 d.d.t (195,7; 7,9; 3,1) – C^5 155,28 d.d ($^2J_{C^3-H^4}$ = 2,0; $^3J_{C^3-H^5}$ = 9,2) — C^3	–20,40 s – 3-NO_2 –76,20 tr (2,6) – N^2 –174,00 tr (2,2) – N^1
(9)	2,19 s – CH_3 5,30 s – CH_2 8.76 – H^5 8,20 s – H^3	26,30 q (128,4) – CH_3 60.80 t (144.2) – CH_2 200,1 q.t (6,1; 4,3) – CO 131,1 d.t (198,8; 2,8) – C^5 134,6 d.d ($^2J_{C^4-H^5}$ = 4,0; $^2J_{C^4-H^3}$ = 5,6) — C^4	–18,80 s – 4-NO_2 —69,70 d.t ($^2J_{N^2-H^3}$ = =13,6; $^3J_{N^2-H}CH_2$ = =2,3)—N^2 —174,00 d.t ($^3J_{N^1-H^5}$ = =10,2; $^2J_{N^1-H}CH_2$ = =1,7)—N^1
(10)	2.30 s – CH_3 5,46 s – CH_2 8,74 s – H^5	134,8 d (197,0) – C^3 26.80 q (128.4) – CH_3 62,21 t (144.3) – CH_2 199,82 q.t (6.2; 4,3) – CO 126,40 d (5,2) – C^4 135.04 d.t (204,4; 3,2) – C^5 147.06 d (8,1) – C^3	–26.7 – 4-NO_2 –26.8 – 3-NO_2 –78,10 t (2,7) – N^2 –181,00 t (2.5) – N^1
(11)	2.22 s – CH_3 5,30 s – CH_2 8,92 s – H^5	26,96 q (128,2) – CH_3 61,34 t (141,6) – CH_2 200,20 q.t (6,0; 4.2) – CO 133.06 d.t (201,4; 3,5) – C^5 133,60 d (4,8) – C^4 136,91 d (6,1) – C^3	

TABLE 2 (continued)

Compound	^{1}H NMR	^{13}C NMR	^{15}N NMR
(12)	2,10 s; 2,35 s – CH$_3$; CH$_3'$ 5,27 s; 5,38 s – CH$_2$; CH$_2'$ 9,00 s – H^5 8,50 s – H$^{3'}$		
(13)	2,29 s – CH$_3$ 5,54 s – CH$_2$ 8,54 s – H^5	26,90 q (128,5) – CH$_3$ 59,20 t (143,2) – CH$_2$ 199,8 q.t (6,0; 4,0) – CO 147,90 d.t (221,0; 2,8) – C^5 161,90 d (13,3) – C^3	−26,6 s – 3-NO$_2$ −84,15 t (2,4) – N^2 −135,90 d (12,4) – N^4 −166,31 d.t (10,8; 1,4) – N^1
(14)	2,37 s – CH$_3$ 5,60 s – CH$_2$	28,00 q (128,0) – CH$_3$ 63,70 t (145,0) – CH$_2$ 199,60 q.t (6,2; 4,1) – CO 152,10 t (2,5) – C^5 158,50 s – C^3	−31,21 s – 3-NO$_2$ −35,90 s – 5-NO$_2$ −75,42 t (2,5) – N^2 −141,41 s – N^4 −172,90 t (2,1) – N^1
(15)	2,16 s – CH$_3$ 5,05 s – CH$_2$ 6,95 s – H$_2$	26.79 q (128,3) – CH$_3$ 56,59 t (141,3) – CH$_2$ 200,47 q.t (5,8; 4,0) – CO 157.27 t (2.8) – C^5 159,59 s – C^3	−23,91 s – 3-N$_2$O$_2$ —99,47 t ($^3J_{N^2-H}$CH$_2$= =2,5)—N^2 −177,83 s – N^4 —204,30 t ($^2J_{N^1-H}$CH$_2$ = =1,3)—N^1 —324,16 t ($^1J_{N-H}$ = =87,0)—NH$_2$
(16)	2.46 – CH$_3$ 5,92 – CH$_2$	26,90 q (130,0) – CH$_3$ 61,00 t (147,0) – CH$_2$ 198,80 q.t (6,0; 4,2) – CO 142,90 t (2,8) – C^5 160,20 s – C^3	
(17)	2,41 s – CH$_3'$ 5,88 s – CH$_2'$ 2,41 s – CH$_3$ 5,91 s – CH$_2$	26,93 q (129.0) – CH$_3$; 26,93 q (129,0) – CH$_3'$ 61.10 t (147,0) – CH$_2$; 61,94 t (153,0) – CH$_2'$ 146.64 t (2.6) – C^5. 148,06 s – C$^{5'}$ 161.14 s – C^3; 152,69 t (2,6) – C$^{3'}$ 199.59 q.t (6,3; 4.3) – CO; 199,0 q.t (6,2; 4,1) – CO$'$	−28,20 s – 3-NO$_2$; −34,76 – 3$'$-NO$_2$ −79.24 t (2,3 – N^2; −68.39 t (2,3) – N$^{1'}$ −133.80 s – N^4; −136,68 s – N$^{4'}$ −168.83 t (1,6) -N^1. −172,36 t (1,9) – N$^{2'}$
(19)	2,34 s – CH$_3$ 5.67 s – CH$_2$ 8,50 s – H^5	27,00 q. (128.5) – CH$_3$ 64.41 t (143.3) – CH$_2$ 200.08 q.t (6.2; 4.4) – CO 131.71 d (206,2) – C^5 153.62 d (8.6) – C^4	−25.70 s – 4-NO$_2$ −39,20 d.t (12.3; 2,3) – N^1 −53.30 t (2,4) – N^3 −131,00 d.t (9,9; 1,8) – N^2
(20)	2.37 s – CH$_3$ 5.72 s – CH$_2$ 8,86 s – H^5	26,91 q (129,4) – CH$_3$ 59.30 t (144,0) – CH$_2$ 199,50 q. t (6,1; 4,3) – CO 126.02 d.t (208,7; 7; 2,5) – C^5 152,90 d (6.8) – C^4	−24,70 s – 4-NO$_2$ −16,30 t (2.2) – N^2 −36,80 s – N^3 −135,81 t (1,7) – N^1
(21)	2.38 s – CH$_3$ 5.86 s – CH$_2$	27,10 q (129.3) – CH$_3$ 66.40 t (145.3) – CH$_2$ 198,40 q.t (6,0; 4,2) – CO 145,30 s – C^4; C^5	−32.50 s – 4-NO$_2$; 5-NO$_2$ −46,20 t (2,1) – N^2; N^3 −140.70 t (1,9) – N^1
(22)	2,40 s – CH$_3$ 5,83 s – CH$_2$	26.90 q (128,5) – CH$_3$ 65.10 t (145.2) – CH$_2$ 199,4 q.t (6,0; 4,2) – CO 131.20 s – C^5 150,90 s – C^4	- 27,50 s – 4-NO$_2$ −35,80 t (2,2) – N^1 −50.30 t (2,4) – N^3 −131,52 (1,6) – N^2
(23)	2.38 s – CH$_3$ 5.91 s – CH$_2$ 2,26 s – CH$_3'$ 5.74 s – CH$_2'$	26,80 q (128,5) – CH$_3$; 65,10 t (146.1) – CH$_2$ 199.47 q.t (6,3; 4.0) – CO 127.90 s – C^5 151,60 s – C^4 26.60 q (129,5 – CH$_3'$; 58,60 t (146.1) – CH$_2'$ 198.76 q. t (6.2; 4.1) – CO$'$, 124,4 t (2,8) – C$^{5'}$; 150,9 s – C$^{4'}$	−39,50 t (2,3) – N^1 −130.20 t (1,9) – N^2 −50,00 t (2,3) – N^3 −16,10 t (2,1) – N$^{2'}$ −37,3 s N$^{3'}$ −134,7 t (1,5) – N$^{1'}$
(24)	2,98 s – CH$_3$ 5.42 s – CH$_2$ 8.82 s – H^5	26.90 q (128,2) – CH$_3$ 56.12 t (145.9) – CH$_2$ 199.93 q.t (6,1; 4.2) – CO 144,80 d.t (219,7; 2,5) – C^5	+10.10 s – N^3 −12,11 t (2.1) – N^2 −52.00 d (11,9) – N^4 −152,21 d.t (8,4; 1,7) – N^1
(25)	2.17 s – CH$_3$ 5.60 s – CH$_2$ 8.62 s – H^5	27.90 q (130,0) – CH$_3$ 61.90 t (144.0) – CH$_2$ 200.20 q.t (6.3; 4.1) – CO 154.20 d (216,0) – C^5	+0,77 t (1,9) – N^3 −46,60 d (12,6) – N^4 −72,76 d.t (14,5; 2,0) – N^1 −103.61 d.t (6,7; 1,6) – N^2

TABLE 2 (continued)

Compound	^1H NMR	^{13}C NMR	^{15}N NMR
(26)	2,25 s – CH_3 5,23 s – CH_2 2,36 s – 5-CH_3	9.90 q (132,0) – CH_3 28,60 q (129,0) – CH_3 58.60 t (142.0) – CH_2 199,60 q.t (6,1; 4,1) – CO 154,90 q.t (7,3; 2,5) – C^5	
(27)	2,12 s – CH_3 5,42 s – CH_2 2,40 s – 5-CH_3	12,10 q (132,0) – 5-CH_3 28,40 q (130,0) – CH_3 62,00 t (147.0) – CH_2 200,00 q.t (6,0; 4,2) – CO 164,50 q (7,1) – C^5	
(28)	2,37 s – CH_3 5,98 s – CH_2	27,00 q (129,0) – CH_3 62,70 t (144.0) – CH_2 198,20 q.t (6,3; 4,0) – CO 166,00 s – C^5	+8,70 t (1,9) – N^3 –33,80 s – 5-NO_2 –53,70 s – N^4 –75,10 t (2,1) – N^1 –99,20 t (1,5) – N^2
(29)	2,16 s – CH_3 5,25 s – CH_2	27,24 q (128,20) – CH_3 54.32 t (141,30) – CH_2 200,63 q.t (6,1; 4.0) – CO 155,99 t (2,2) – C^5	+1,49 s – N^3 –22,67 t (2,0) – N^2 –100.02 s – N^4 –182,8 t (1,5) – N^1 –333,95 s – NH_2
(30)	2,40 s – CH_3 6,16 – CH_2	27,18 q (128,8) – CH_3 63.31 t (145.8) – CH_2 197.93 q. t (5,9; 4,0) – CO 122,13 s – $C(NO_2)_3$ 152,99 s – C^5	+9,90 t (1,9) – N^3 –35,25 s – $C(NO_2)_3$ –39.29 s – N^4 –61,25 t (2.3) – N^1 –94,80 t (1,6) – N^2
(31)	2.18 s – CH_3 5.82 s – CH_2 8,70 s – $C(NO_2)_2H$	27,22 q (129.4) – CH_3 62.57 t (144.6) – CH_2 104,46 d (178,0) – $C(NO_2)_2H$ 155,00 s – C^5 198,63 q.t (6,2; 4,5) – CO	
(32)	2.35 s – CH_3 6,06 s – CH_2	27,00 q (129,2) – CH_3 58,00 t (145,4) – CH_2 198,90 q.t (6,1; 4,2) – CO 142,60 t (2,8) – C^5	
(33)	2,35 s – CH_3 2.35 s – CH_3' 6,13 s – CH_2' 6,00 s – CH_2	26,79 q (129,5) – CH_3'; 26.74 q (129,0) – CH_3 61,50 t (145,0) – CH_2'; 57,51 t (145,1) – CH_2 152,66 s – $C^{5'}$; 145,16 t (2, 3) – C^5 198.48 q.t (6,3; 4.5) – CO'; 198,90 q.t (6,2; 4,0) – CO	+5,23 t (2,1)—$N^{3'}$ † —71,49 t (2,1)—N^1 † —98,69 t (1,7)—$N^{2'}$ † —6,15 t (1,8)—N^2 †
(34)	2,35 s – CH_3 6,10 s – CH_2	26,79 q (129,4) – CH_3 61,18 t (145,2) – CH_2 198,64 q.t (6,3; 4,4) – CO 155,00 t ($^4J_{C^5-H}CH_2 = 0,6$) — C^5	+5,26 t (1,8)—N^3 † —72,92 t (2,1)—N^1 † —99,80 t (1,6)—N^2 †
(35)		60,72 t (145,6) – CH_2 166.15 s – C^5 189,77 t (4,2) – CO 128,46; 128,98; 133,35; 134,74 – C_6H_5	–152,96 t (1,5) – N^1 † –33,48 s – 5-NO_2 +10,34 t (1,9) – N^3 –52,40 s – N^4 –73,81 t (2,1) – N^1 –99,05 t (1,8) – N^2

---

*Values obtained from ^{14}N spectrum.

†Values obtained by the INEPT method.

The ^{15}N and ^{14}N NMR spectra also provide information on the structure of the azoles. The ^{15}N chemical shifts of the ring nitrogens in N-acetonylazoles are comparable with those in N-methylazoles [15]. The signals for the NO_2 groups were assigned by comparing the chemical shifts of the N-acetonylazoles with the literature values [16, 17], and also by using the ^{14}N spectra, in which the breadth of the signal for the NO_2 group at half-height is 40-200 Hz.

The ^{15}N—^1H coupling constants between the ring nitrogens and hydrogen through two and three bonds in a number of known compounds also provide information on the disposition of the CH_2COCH_3 group in the ring. The geminal coupling constants for hydrogen with "pyrrole-type" nitrogens ranges up to 10.8 Hz, and with "pyridine-type" nitrogens from 11.9 to 14.5 Hz. The vicinal coupling constants for hydrogen with a "pyrrole-type" nitrogen are from 6.7 to 10.2 Hz, and with a "pyridine-type" nitrogen they are less than 1 Hz, or are not seen.

The coupling constants between the methylene protons and the ring atoms N^1 ($^2J_{^{15}N-^1H}$) and N^2 ($^3J_{^{15}N-^1H}$) are 1.3-2.7 Hz.

Although two isomers are required for proof of structure using the ^{13}C spectra, in the case of the ^{15}N spectra one isomer is sufficient. In substituted tetrazoles, the chemical shifts of the ^{15}N-substituted nitrogen are of the order of −150 ppm for the 1-isomer and −100 ppm for the 2-isomer. For example, the ^{15}N NMR spectrum of compound (29) shows unambiguously that the acetonyl group is attached to N^2, since the chemical shift of the substituted N^2 atom is only −94.80 ppm, and there are in addition three coupling constants for the methylene protons with N^1, N^2, and N^3.

The spectral data given in Table 2 show that in most of the compounds the acetonyl group is located at the nitrogen with the smallest number of nitro groups in the ortho position (scheme 1).

This general rule may not, however, hold if other bulky electron-acceptor groups are present in the azole in addition to nitro groups. For instance, with bicyclic nitroazoles further isomers are formed in which the nitro group and the acetonyl group are ortho-located, as in (17) and (23).

In the case of bitetrazolyl, all three possible isomers (32), (33), and (34) are formed, in accordance with the influence of the substituent in the 5-position in tetrazoles on the course of alkylation [6].

EXPERIMENTAL

A solution of bromoacetone in dichloroethane was obtained from the pilot plant of the Kristall Scientific Production Organization, prepared by reacting bromine with acetone in the presence of potassium chlorate in the system DCE—water.

PMR spectra were obtained on a Bruker WM-250, operating frequency 250.13 MHz, and ^{13}C, ^{14}N, and ^{15}N spectra on a Bruker AM-300 at frequencies of 75.47, 21.68, and 30.42 MHz respectively relative to TMS (^{13}C) and $CH_3{}^{15}NO_2$ (^{14}N, ^{15}N). High-field shifts in the ^{14}N and ^{15}N spectra are given with a minus sign. The $^{13}C-^1H$ and $^{15}N-^1H$ coupling constants were measured to an accuracy of 0.5-0.05 Hz, depending on the purpose of the measurement.

^{13}C NMR spectra were obtained with and without decoupling from protons, and the ^{15}N spectra without decoupling from protons. The ^{13}C and ^{15}N NMR spectra were obtained by the INEPT method [18], utilizing selective transfer of polarization from one proton and simultaneous selective suppression of coupling with the other proton [19].

General Method of Preparation of N-Acetonylazoles. Method A. Equimolar amounts (0.1 mole) of the azole and potassium (or sodium) hydroxide were dissolved in 20 ml of water or a solvent, 0.1-0.12 mole of bromoacetone in 20 ml of solvent added, and the mixture stirred under the conditions given in Table 1. The ketones obtained were in general insoluble in water, and were isolated in the crystalline state by evaporation of the solvent from the aqueous mixture, and filtration. In other cases, the reaction mixture was either evaporated to dryness and extracted with a low-boiling solvent (acetone, chloroform, or benzene), or poured into water (for solutions in DMF) and the products which separated filtered off.

Preparation of (28) without Isolation of 5-Nitrotetrazole. To a solution of 30.8 g of potassium nitrite (or 25 g of sodium nitrite) (0.36 mole) in 160 ml of water was added at 60-70°C dropwise a solution of 10.3 g (0.1 mole) of 5-aminotetrazole monohydrate in 160 ml of 1.5% sulfuric acid warmed to 50°C. There was then added 0.6 ml of sulfuric acid (d = 1.83) over 5-7 min, and the mixture stirred at 80°C for 2 h. The mixture was then evaporated in a rotary evaporator until inorganic solid began to separate (approximately to 200 ml), cooled, neutralized with sodium bicarbonate, diluted with 600 ml of acetone, and filtered from the solid. To the resulting 5-nitrotetrazole salt solution was added 12 ml (0.15 mole) of bromoacetone, and the mixture kept at 70°C for 15-16 h. The acetone was removed in a rotary evaporator, and the solid which separated was filtered off, washed with water and ether, and dried in air to give 12.32 g of (28) (75% on aminotetrazole).

Method B. Preparation of (5) and (6). To a solution (or suspension) of 2.0 mmoles of 2,4,5-trinitroimidazole or bis(4,5-dinitrodiimidazol-2-yl) in 30-40 ml of dry ether was added dropwise at room temperature over a few minutes an equimolar amount of diazoacetone in 5 ml of ether. The mixture was kept for 3 h at room temperature, and the solvent removed to give (5) or (6).

Method C. 1. Preparation of Isomeric Ketones (16) and (17). To a solution of 24.8 g (0.62 mole) of sodium hydroxide in 170 ml of water were added 70 g (0.31 mole) of bis(3-nitro-1,2,4-triazol-5-yl), 2 g of sodium carbonate, and 1.7 g of tetrabutylammonium bromide, and the mixture stirred until a yellow solid separated (10 min). A solution of bromoacetone in dichloroethane was then added, and the mixture stirred vigorously at 30-35°C for 7-8 h. The resulting nearly colorless solid was washed with water and dichloroethane, and air-dried to give 69 g (66%) of (16).

The organic layer was separated from the mother liquors, washed with 2 × 200 ml of water, and evaporated. The resulting oil was diluted twice with methanol, a little water added (until crystallization commenced), and cooled. The solid which separated was filtered off and air-dried to give 25 g (24%) of (17).

2. Preparation of (35). To a solution of 0.033 mole of 5-nitrotetrazole in 100 ml of water [see preparation of (28)] were added a solution of bromoacetone in 60 ml of dichloroethane and 0.9 g of tetrabutylammonium bromide in 5 ml of water. The reaction mixture was heated at 50-60°C with vigorous stirring for 10 h, the dichloroethane layer separated and evaporated, and the residue stirred with a few milliliters of ether. The crystals which separated were filtered off to give 4.5 g of (35).

LITERATURE CITED

1. T. P. Kofman and M. S. Pevzner, Khim. Geterotsikl. Soedin., No. 10, 1403 (1981).
2. G. I. Migachev and V. A. Danilenko, Khim. Geterotsikl. Soedin., No. 7, 867 (1982).
3. J. H. Boyer, the C-Nitro Derivatives of Five-Membered N- and N,O-Heterocycles, VCH Publishers Inc., Florida (1986).
4. F. Einberg, J. Org. Chem., 35, 3978 (1970).
5. V. V. Semenov, V. S. Bogdanov, B. S. Él'yanov, L. G. Mel'nikova, S. A. Shevelev, V. M. Zhulin, and A. A. Fainzil'berg, Khim. Geterotsikl. Soedin., No. 8, 1118 (1982).
6. M. B. Shcherbinin, L. G. Bazanov, and I. V. Tselinskii, Zh. Org. Khim., 18, No. 2, 463 (1982).
7. K. Schofield, M. Grimmett, and B. Keene, Heteroaromatic Nitrogen Compounds — The Azoles, Cambridge Univ. Press (1976), p. 419.
8. G. I. Koldobskii, V. A. Ostrovskii, and T. F. Osipova, Khim. Geterotsikl. Soedin., No. 11, 1443 (1983).
9. C. Newton, D. Ollis, M. Podmore, and D. Wright, J. Chem. Soc., Perkin Trans. 1, No. 1, 63 (1984).
10. P. Cabildo, R. M. Claramunt, and J. Elguero, Org. Magn. Reson., 22, No. 9, 603 (1984).
11. A. McKillop, D. E. Wright, M. L. Podmore, and R. K. Chambers, Tetrahedron, 39, No. 22, 3797 (1983).
12. K. Nagarajan, V. Sudarsanam, P. Parthasarathy, et al., Indian J. Chem., 21B, No. 11, 1006 (1982).
13. G. Biagi, O. Levi, A. Settimo, et al., J. Farm. Sci., 40, No. 2, 73 (1985).
14. R. Butler, T. McEvoy, F. Scott, and J. Tobin, Can. J. Chem., 55, No. 9, 1564 (1977).
15. D. Wofford, D. Forkey, and J. Russell, J. Org. Chem., 47, No. 26, 5132 (1982).
16. E. Lippmaa, M. Magi, S. S. Novikov, et al., Org. Magn. Reson., 4, No. 1, 153 (1972).
17. V. A. Petrosyan, M. E. Niyazymbetov, M. S. Pevzner, and B. I. Ugrak, Izv. Akad. Nauk SSSR, Ser. Khim., No. 7, 1643 (1988).
18. G. A. Morris and R. Freeman, J. Am. Chem. Soc., 101, 760 (1979).
19. K. G. R. Pachler and P. L. Wessels, J. Magn. Reson., No. 12, 377 (1973).