100°C for 1 h, after which it was cooled to precipitate the salt of III. It was removed by filtration, dissolved in methanol, and hydrolyzed with concentrated ammonium hydroxide, as a result of which a yellow precipitate of free base III [0.13 g (35%)], with mp 142-143°C (from methanol), was obtained.

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CONDENSED IMIDAZO-1,2,4-AZINES.

4.* SYNTHESIS OF 1,4-DIHYDROIMIDAZO[1,5-c]-1,2,4-TRIAZINE DERIVATIVES

M. V. Povstyanoi, M. A. Klykov, and N. A. Klyuev

UDC 547.785'873.07

The reaction of 2-methyl-4(5)-nitro- and 2-methyl-4(5)-nitro-5(4)-bromoimidazoles with α-halo ketones was investigated, during which a number of 1-acylmethyl-substituted 2-methyl-4-nitro- and 2-methyl-4-nitro-5-bromoimidazoles were obtained. 1,4-Dihydro derivatives of imidazo[1,5-c]-1,2,4-triazine were synthesized by reaction of the latter with hydrazine and its monosubstituted derivatives. The structures of the 1-acylmethyl-substituted 2-methyl-4-nitro-5-bromoimidazoles and 1,4-dihydro derivatives of imidazo[1,5-c]-1,2,4-triazine were confirmed by their IR, PMR, and mass spectra.

We have previously reported [4] that imidazo[1,2-b]-1,2,4-triazine derivatives luminesce intensely in the UV and blue-violet regions both in the solid state and in solutions. In this connection, it seemed of interest to synthesize other isomeric imidazo-1,2,4-triazines and investigate their luminescence and biological properties.

Prior to our brief communications [3, 5, 6], the heterocyclic 1H-imidazo[1,5-c]-1,2,4-triazine system and its derivatives had not been described. In order to obtain 1-acylmethyl-substituted 2-methyl-4-nitro-5-bromoimidazoles, which are intermediates for the synthesis of derivatives of the two-ring system indicated above, we studied the reaction of 2-methyl-4(5)-nitro- (V) and 2-methyl-4(5)-nitro-5(4)-bromoimidazoles (VI) with α-halo ketones. It

*See [1-3] for Communications 1-3, respectively.

Kherson Branch, M. V. Lomonosov Odessa Technological Institute of the Food Industry, Kherson 325008.

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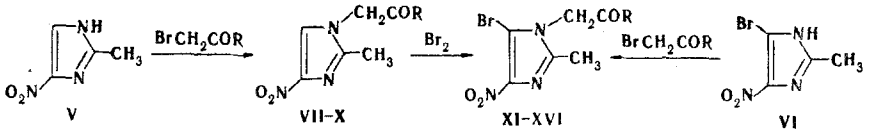
TABLE 1. 1-Acylmethyl-2-methyl-4-nitroimidazoles (VII-X) and 1-Acylmethyl-2-methyl-4-nitro-5-bromoimidazoles (XI-XVI)

Compound	R	mp, °C	IR spectrum, cm^{-1} (CO)	Found, %				Empirical formula	Calculated, %				Yield, %*
				C	H	Br	N		C	H	Br	N	
VII	C_6H_5	212—214	1680	58,8	4,5	—	17,1	$C_{12}H_{11}N_3O_3$	58,8	4,6	—	17,2	88
VIII	C_6H_4Br-*p*	270—271	1685	44,5	3,0	24,9	13,1	$C_{12}H_{10}BrN_3O_3$	44,5	3,1	24,7	13,0	83
IX	C_6H_4Cl-*p*	259—260	1685	51,2	3,5	—	15,2	$C_{12}H_{10}ClN_3O_3$	51,5	3,6	—	15,0	80
X	$C_6H_4NO_2$-*p*	252—253	1710	49,6	3,8	—	19,4	$C_{12}H_{10}N_4O_5$	49,6	3,5	—	19,3	70
XI	CH_3	132—133	1685	32,0	3,0	30,8	15,7	$C_7H_8BrN_3O_3$	32,1	3,1	30,5	16,0	67
XII	C_6H_5	190—191	1690	44,5	3,0	24,3	12,9	$C_{12}H_{10}BrN_3O_3$	44,5	3,1	24,7	13,0	68/84
XIII	$C_6H_4CH_3$-*p*	219—221	1685	45,9	3,6	24,0	12,1	$C_{13}H_{12}BrN_3O_3$	46,2	3,6	23,6	12,4	58/76
XIV	C_6H_4Br-*p*	205—207	1685	35,9	2,4	39,9	10,4	$C_{12}H_9Br_2N_3O_3$	35,7	2,2	39,6	10,4	60/81
XV	C_6H_4Cl-*p*	203—204	1690	40,4	2,4	22,4	11,9	$C_{12}H_9ClBrN_3O_3$	40,2	2,5	22,3	11,7	58/90
XVI	$C_6H_4NO_2$-*p*	222—223	1695	38,8	2,2	21,8	15,1	$C_{12}H_9BrN_4O_5$	39,0	2,4	21,6	15,2	69/80

*The yield for method A is indicated in the numerator, while the yield for method D is indicated in the denominator.

was shown that the reaction proceeds readily in lower alcohols in the presence of a sodium alkoxide and leads to the formation of 1-acylmethyl-2-methyl-4-nitroimidazoles (VII-X) and 1-acylmethyl-2-methyl-4-nitro-5-bromoimidazoles (XI-XVI) (Table 1). Bromination of imidazoles VII-X in aqueous dimethylformamide (DMF) at 40-50°C gave XII and XIV-XVI, which, with respect to their physical constants and IR spectra, are identical to the compounds obtained by alkylation of bromoimidazole VI with α-halo ketones.

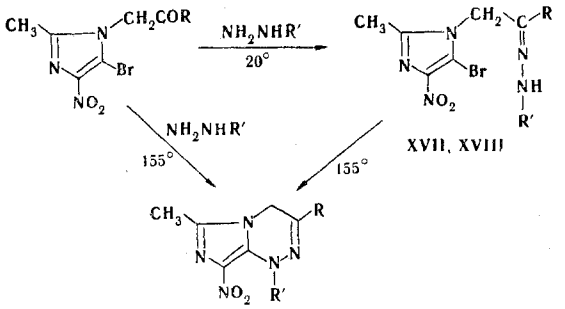


Two isomers, viz., substituted 4-nitroimidazoles (VII-X and XI-XVI) and the corresponding substituted 5-nitroimidazoles, could be formed theoretically in the reaction of imidazoles V and VI with α-halo ketones. We did not isolate substituted 5-nitroimidazoles in any of our experiments, since the process gives 4-nitroimidazole derivatives (VII-XVI). The formation of precisely 1-alkyl-4-nitroimidazoles in the alkylation of 4(5)-nitroimidazoles in an alkaline medium is in agreement with the data in [7, 8].

The PMR spectra of VII-X contain, in addition to the signals of protons of methyl and methylene groups and of a benzene ring, a characteristic lone signal at 8.20 ppm. In order to make a distinct assignment of the signal at 8.20 ppm to the proton in the 5 position of the imidazole ring we recorded the PMR spectra of two pairs of known isomers, viz., 1,2-dimethyl-4-nitroimidazole (I) and 1,2-dimethyl-5-nitroimidazole (II) and 1-(β-hydroxyethyl)-2-methyl-4-nitroimidazole (III) and 1-(β-hydroxyethyl)-2-methyl-5-nitroimidazole (IV). We showed that in the PMR spectra of the 4-nitro isomers (I and III) the proton in the 5 position of the imidazole ring shows up in the form of a distinct singlet at 8.25 ppm, while in the spectra of 5-nitroimidazoles (II, IV) the signal of the proton in the 4 position of the imidazole ring is shifted to stronger field and is observed at 8.00 ppm.

Convincing evidence in favor of the structure of XI-XVI as 4-nitro-5-bromoimidazole derivatives is also afforded by their ready conversion to imidazo[1,5-c]-1,2,4-triazine derivatives. It was established that imidazoles XI-XVI are readily converted to two-ring systems XIX-XXIV by the action of hydrazine hydrate in alcohol solution even under mild temperature conditions (Table 2).

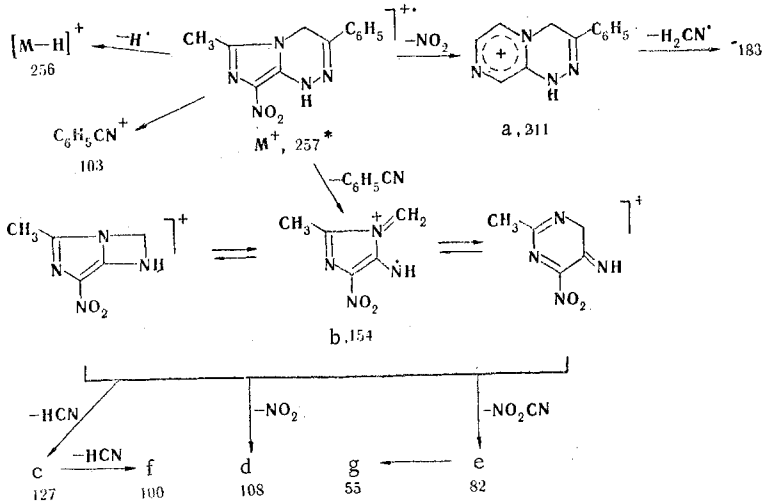
Hydrazones (XVII, XVIII) of the starting 4-nitroimidazolyl ketones were isolated in the reaction of hydrazines with XI-XVI in alcohol at room temperature or upon prolonged refluxing. When XVII and XVIII were refluxed in DMF, they underwent intramolecular splitting out of a molecule of HBr with the formation of a triazine ring to give imidazo[1,5-c]-1,2,4-triazine derivatives. In a preparative respect, in the preparation of imidazo-1,2,4-triazines (XXV-XXXII) it is more convenient to carry out the reaction of ketones XI-XVI with monoalkyl(aryl)hydrazines by heating in high-boiling solvents (butanol and DMF). Under these conditions triazino cyclization of the imidazolyl ketones takes place without isolation of the intermediates.



XIX-XXXII R = Alk, Ar, R' = H, Alk, Ar

In contrast to the spectra of starting XI-XVI, the IR spectra of triazines XVII-XXXII do not contain absorption bands of stretching vibrations of a CO group. The spectra of XIX-XXIV, which contain a free NH group, contain an absorption band at 3180-3310 cm^{-1}. Signals of two protons of a methylene group at 4.9 ppm are observed in the PMR spectra. The protons of the methyl group show up in the form of a distinct singlet at 2.35-2.48 ppm, while the aromatic protons generally give a poorly resolved multiplet at 7.15 ppm.

The splitting out of a nitrogen group that is characteristic for nitroaryl compounds is observed in the dissociative ionization of the molecular ion (M^+) of 1,4-dihydro-3-phenyl-6-methyl-8-nitroimidazo[1,5-c]-1,2,4-triazine (XX). The subsequent fragmentation is due to the elimination of an H_2CN particle from the $[M - NO_2]^+$ ion. It is possible that in this case the imidazole ring undergoes expansion (the a ion). Another fragmentation pathway for M^+ involves the elimination of a PhCN particle from M^+ (the b ion). The latter subsequently loses a number of nitrogen-containing particles of the HCN, NO_2, and NO_2CN type to give fragment ions c-g. The fragmentation of M^+ of XX can be illustrated by the scheme:



Thus we have found a method for the synthesis of imidazo [1,5-c]-1,2,4-triazines that display moderate biological activity and fluoresce less intensely than imidazo[1,2-b]-1,2,4-triazine derivatives.

EXPERIMENTAL

The IR spectra of mineral oil pastes of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions in DMSO were recorded with a Tesla BS-467 spectrometer with hexamethyldisiloxane as the internal standard. The mass spectrum was recorded with a Varian MAT-311 spectrometer with a system for the direct introduction of the samples into the ion source; the ionizing-electron energy was 70 eV, the cathode emission current was 300 μA, the accelerating voltage was 3 kV, and the ionization-chamber temperature was 180°C.

1,2-Dimethyl-4-nitroimidazole (I). This compound was obtained by the method in [9]. PMR spectrum: 3.76 [$CH_{3(1)}$], 2.35 [$CH_{3(2)}$], and 8.25 ppm [$H_{(5)}$].

*The numbers that characterize the ions are the mass-to-charge ratios.

TABLE 2. 1,4-Dihydroimidazo[1,5-c]-1,2,4-triazine Derivatives (XIX-XXXII)

Compound	R	R'	mp, °C	IR spectrum, NH, cm^{-1}	Found, %			Empirical formula	Calc., %			Yield,* %
					C	H	N		C	H	N	
XIX	CH_3	H	248—250	3290	43,3	4,9	36,0	$C_7H_9N_5O_2$	43,1	4,7	35,9	80
XX†	C_6H_5	H	273—275	3310	56,0	4,7	26,8	$C_{12}H_{11}N_5O_2$	55,8	4,7	27,1	94
XXI	$C_6H_4CH_3$-*p*	H	258—260	3270	57,4	4,8	25,8	$C_{13}H_{13}N_5O_2$	57,5	4,8	25,8	83
XXII	C_6H_4Cl-*p*	H	268—270	3280	49,6	3,4	23,9	$C_{12}H_{10}ClN_5O_4$	49,4	3,4	24,0	93
XXIII	C_6H_4Br-*p*	H	279—279,5	3285	42,9	2,9	21,0	$C_{12}H_{10}BrN_5O_2$	42,9	3,0	20,8	83
XXIV	$C_6H_4NO_2$-*p*	H	253—255	3300	47,9	3,6	27,5	$C_{12}H_{10}N_6O_4$	47,7	3,3	27,8	84
XXV	CH_3	$C_6H_4NO_2$-*p*	252—253	—	49,6	4,1	26,6	$C_{13}H_{12}N_6O_4$	49,4	3,8	26,6	78
XXVI	C_6H_5	CH_3	239—240	—	57,6	4,8	26,0	$C_{13}H_{13}N_5O_2$	57,5	4,8	25,8	65/75
XXVII	C_6H_5	C_6H_5	205—206	—	64,9	4,8	21,1	$C_{18}H_{15}N_5O_2$	64,8	4,5	21,0	76/81
XXVIII	C_6H_5	$C_6H_4NO_2$-*p*	235—237	—	57,1	3,8	22,3	$C_{18}H_{14}N_6O_4$	57,1	3,7	22,2	89
XXIX	$C_6H_4CH_3$-*p*	$C_6H_4NO_2$-*p*	280—281	—	58,0	4,1	21,4	$C_{19}H_{16}N_6O_4$	58,2	4,1	21,4	80
XXX	C_6H_4Cl-*p*	$C_6H_4NO_2$-*p*	261—263	—	52,4	3,1	20,4	$C_{18}H_{13}ClN_6O_4$	52,4	3,2	20,4	88
XXXI	C_6H_4Br-*p*	$C_6H_4NO_2$-*p*	269—272	—	47,3	3,0	18,7	$C_{18}H_{13}BrN_6O_4$	47,3	2,9	18,4	93
XXXII	$C_6H_4NO_2$-*p*	$C_6H_4NO_2$-*p*	293—294	—	50,8	3,1	23,2	$C_{18}H_{13}N_7O_6$	51,1	3,1	23,2	88

*The yield for method A is indicated in the numerator, while the yield for method B is indicated in the denominator.

†Mass spectrum of XX, m/e (relative intensity, %): 77 (22.0), 81 (42.1), 101 (9.4), 102 (34.8), 103 (40.8), 104 (24.7), 154 (15.2), 183 (8.4), M^+ = 11.2.

1,2-Dimethyl-5-nitroimidazole (II). This compound was obtained by the method in [10]. PMR spectrum: 3.83 [$CH_{3(1)}$], 2.45 [$CH_{3(2)}$], and 8.00 ppm [$H_{(4)}$].

1-β-Hydroxyethyl-2-methyl-4-nitroimidazole (III). This compound was obtained by the method in [11]. PMR spectrum: 4.40 and 3.85 [$CH_2CH_{2(1)}$], 2.48 [$CH_{3(2)}$], and 8.25 ppm [$H_{(5)}$].

1-β-Hydroxyethyl-2-methyl-5-nitroimidazole (IV). This compound was obtained by the method in [11]. PMR spectrum: 4.40 and 3.73 [$CH_2CH_{2(1)}$], 2.50 [$CH_{3(2)}$], and 8.00 ppm [$H_{(4)}$].

1-Acylmethyl-2-methyl-4-nitroimidazoles (VII-X, Table 1). A 1.37-g (0.01 mole) sample of 2-methyl-4(5)-nitroimidazole and 0.011 mole of the α-bromo ketone were added to a solution of 0.54 g (0.01 mole) of sodium methoxide in 20-30 ml of anhydrous methanol, and the mixture was refluxed for 1-2 h. It was then cooled, and the precipitate was removed by filtration and washed with water. Samples for analysis were crystallized from aqueous DMF.

1-Acylmethyl-2-methyl-4-nitro-5-bromoimidazoles (XI-XVI, Table 1). A) A 2.16-g (0.01 mole) sample of 2-methyl-4(5)-nitro-5(4)-bromoimidazole and 0.011 mole of the α-bromo ketone were added to a solution of 0.68 g (0.01 mole) of sodium ethoxide in 20-30 ml of anhydrous ethanol, and the mixture was refluxed for 1-2 h. It was then cooled, and the precipitate was removed by filtration and washed with water. Samples for analysis were crystallized from aqueous DMF.

B) A 0.015-mole sample of bromine was added to a solution of 0.01 mole of nitroimidazoles VII-X in 100 ml of 50% aqueous DMF, and the mixture was stirred at 45-50°C for 1-1.5 h. It was then cooled, and the resulting precipitate was removed by filtration and washed with water. An additional amount of these substances was isolated by dilution of the mother liquor with water. Compounds XII and XIV-XVI were obtained in 76-90% yields. No melting point depressions were observed for mixtures of these products with the corresponding XII and XIV-XVI obtained by method A, and the PMR spectra of the samples were identical.

1-Phenacyl-2-methyl-4-nitro-5-bromoimidazole Phenylhydrazone (XVII). A solution of 3.2 g (0.01 mole) of imidazole XII and 1.6 g (0.015 mole) of phenylhydrazine in 500 ml of methanol was maintained at room temperature for 3 days, and the resulting precipitate was removed by filtration and washed with methanol to give 2.3 g (54%) of a product with mp 182-184°C (from DMF). Found: C 52.4; H 4.1; Br 18.9; N 16.8%. $C_{18}H_{16}BrN_5O_2$. Calculated: C 52.2; H 3.9; Br 19.3; N 16.9%.

1-Phenacyl-2-methyl-4-nitro-5-bromoimidazole 2,4-Dinitrophenylhydrazone (XVIII). This compound was obtained in the same way as XVII by refluxing in ethanol for 2 h. Workup gave

2.0 g (34%) of a product with mp 231-232°C (from DMF). Found: C 43.1; H 2.8; Br 15.6; N 19.1%. $C_{18}H_{13}BrN_7O_6$. Calculated: C 42.9; H 2.6; Br 15.9; N 19.5%.

1,4-Dihydroimidazo[1,5-c]-1,2,4-triazine Derivatives (XIX-XXXII, Table 2). A) A 0.025-mole sample of 85% hydrazine hydrate was added to a solution of 0.01 mole of imidazoles XI-XVI in 300-500 ml of methanol, and the mixture was stirred at room temperature for 1-2 h. The precipitate was removed by filtration and washed with water. This method was used to obtain triazines XIX-XXIV.

B) A 4.3-g (0.03 mole) sample of methylhydrazine sulfate was added to a solution of 1.2 g (0.03 mole) of sodium hydroxide in a mixture of 10 ml of water and 30 ml of DMF, and the mixture was stirred for 5 min. It was then treated with 3.2 g (0.01 mole) of imidazole XII and refluxed for 2 h. The mixture was cooled and poured into water, and the precipitate was removed by filtration and washed with water to give 2.1 g of triazine XXVI.

C) A mixture of 0.01 mole of imidazoles XI-XVI and 0.03 mole of phenylhydrazine or p-nitrophenylhydrazine in 50-100 ml of DMF was refluxed for 2-3 h, after which it was cooled and poured into water. The resulting precipitate was removed by filtration and washed with water. This method was used to obtain XXV and XXVII-XXXII.

D) A solution of 2.1 g (0.005 mole) of phenylhydrazone XVII in 20 ml of DMF was refluxed for 2 h, after which it was cooled and poured into water. The precipitate was removed by filtration and washed with water. The yield of triazine XXVII was 1.3 g (81%).

The compounds obtained were yellow (XIX-XXIV) or dark-brown (XXV-XXXII) crystalline substances that were only slightly soluble in most organic solvents. They were purified for analysis by crystallization from aqueous DMF.

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