18. V. F. Lavrushin and V. G. Tishchenko, Zh. Obshch. Khim., 32, 2262 (1962).
19. L. A. Kutulya, A. E. Shevchenko, and L. A. Terekhina, in: Scintillators and Organic Luminophores [in Russian], Vol. 4, VNIIMonokristallov, Khar'kov (1975), p. 54.
20. S. V. Tsukerman, E. G. Buryakovskaya, Yu. S. Rozum, and V. F. Lavrushin, Zh. Prirodn. Soedin., 8, 453 (1968).

RESEARCH ON IMIDAZO[1,2-a]BENZIMIDAZOLE DERIVATIVES

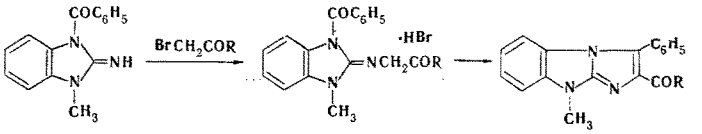
XV.* 2-ACYL-SUBSTITUTED IMIDAZO[1,2-a]BENZIMIDAZOLES

Yu. V. Koshchienko, G. M. Suvorova, and A. M. Simonov

UDC 547.785.5.07

2-Acyl-substituted 3-methyl(phenyl)-9-methylimidazo[1,2-a]benzimidazoles were synthesized by three methods: by the reaction of α-halo ketones with 3-benzoyl-2-imino-1-methylbenzimidazoline, by reaction of acetic anhydride or acetyl bromide with 1-methyl-2-phenacylaminobenzimidazole, and by acylation of 3-substituted imidazo[1,2-a]benzimidazoles. Some of the properties of the resulting 2-acyl-substituted compounds were studied.

The synthesis of 2-acyl-substituted imidazo[1,2-a]benzimidazoles (III) by heating 3-benzoyl-2-imino-1-methylbenzimidazoline (I) with α-halo ketones in dimethylformamide (DMF) at 80-90° for 16-20 h was described in [2].



II a, b — III a, b

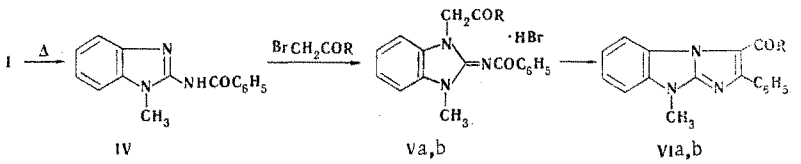
II, III a $R=CH_3$; b $R=C_6H_5$

As shown in the scheme above, the synthesis of 2-acyl derivatives of imidazo[1,2-a]benzimidazole (III) proceeds through a step involving the formation of N-(acylmethyl)imine salts (II). The latter can be obtained by the action of α-halo ketones on imine I in absolute DMF at room temperature. Incorporation of the phenacyl grouping in the imino group was confirmed by conversion of hydrobromide IIb to 1-methyl-2-phenacylaminobenzimidazole (X) by treatment with dilute sodium carbonate solution.

The IR spectra of IIIa and IIIb contain a distinct $\nu_{C=O}$ band at 1619 and 1690 cm^{-1}, respectively. The signals of protons of the $COCH_3$ and $N-CH_3$ groups in the PMR spectrum of 2-acetyl derivative IIIa show up in the form of singlets with identical intensities at 2.1 and 3.77 ppm. The signal of the protons of the N-methyl group of 2-benzoyl derivative IIIb is observed at 3.7 ppm. In addition to the chief reaction products III, their isomers (VI), which hinder purification of the final product, are formed in 5-10% yield. The formation of isomeric 3-acyl derivatives of imidazo[1,2-a]benzimidazole (VI) is due to partial isomerization of imine I [3] to 2-benzamido derivative IV during the reaction; the latter on reaction with α-halo ketones undergoes quaternization at the ring nitrogen atom to give salts V, which are subsequently converted to the previously described [4] VI.

* See [1] for communication XIV.

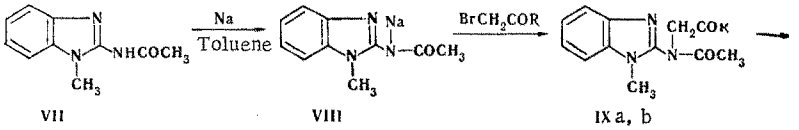
Rostov State University. Scientific-Research Institute of Physical and Organic Chemistry, Rostov-on-Don 344711. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 111-115, January, 1977. Original article submitted May 19, 1976.



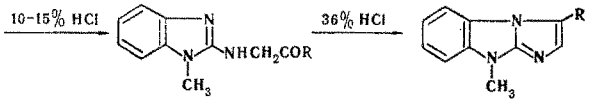
IV Va,b VIa,b

V, VI a $R = CH_3$; b $R = C_6H_5$

In order to obtain 2-acyl derivatives of imidazo[1,2-a]benzimidazole without contamination by the isomeric compounds, we attempted to use benzimidazole derivatives X, which contain an acylmethylamino group in the 2 position, as the starting compound. For the synthesis of the latter, the sodium salt (VIII) of 2-acetamido-1-methylbenzimidazole was subjected to reaction with α-halo ketones, and reaction products IX were subjected to reaction with dilute hydrochloric acid.



VII VIII IX a, b



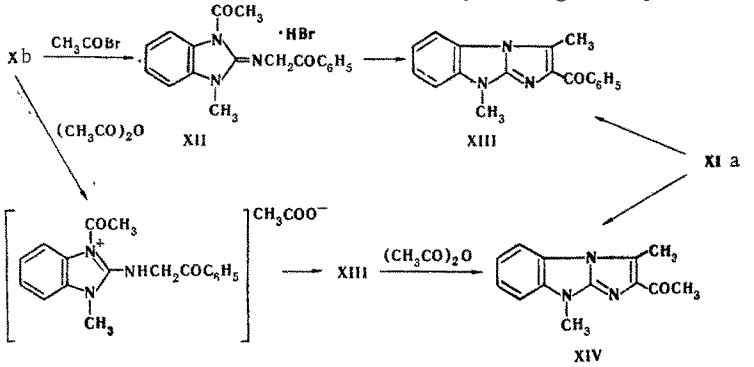
X a, b XI a, b

X, XI a $R = CH_3$; b $R = C_6H_5$

However, in the case of N-acetonyl-substituted IXa closing of the imidazole ring to give 3,9-dimethylimidazo[1,2-a]benzimidazole (XIa) occurs after hydrolysis of the acetyl group; we were unable to isolate the intermediate hydrolysis product 2-acetonylamino-1-methylbenzimidazole (Xa). Hydrolysis of IXb in 15% hydrochloric acid leads to 1-methyl-2-phenacylaminobenzimidazole (Xb); it is converted to 9-methyl-3-phenylimidazo[1,2-a]benzimidazole (XIb) only on prolonged heating in concentrated HCl.

Thus in the process of development of methods for the synthesis of 2-acylmethylamino derivatives of benzimidazole (X) we obtained 3-substituted imidazo[1,2-a]benzimidazoles (XI). The structure of XI was confirmed by the PMR spectral data. Thus the PMR spectrum of 3,9-dimethyl-substituted XIa contains two singlets at 3.6 and 2.2 ppm, which correspond to the signals of the protons of the methyl group in the 3 and 9 positions; the signal of the protons of the methyl group appears as a singlet at δ 3.65 ppm in the spectrum of 3-phenyl derivative XIb.

1-Methyl-2-phenacylaminobenzimidazole (Xb) subsequently undergoes acylation with acetyl bromide;



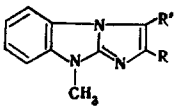
XII XIII XIV

The hydrobromide XII formed in this case is converted to 2-benzoyl-3,9-dimethylimidazo[1,2-a]benzimidazole (XIII) when it is heated in DMF at 80-90° for 20 h.

If acetic acid in the presence of sodium acetate is used instead of acetyl bromide in the reaction with Xb, a mixture of two compounds is obtained after treatment of the reaction mixture with sodium bicarbonate solution. One of them, which is formed in 32% yield, was found to be 2-benzoyl derivative XIII. The second compound (in 40% yield) is 2-acetyl-3,9-dimethylimidazo[1,2-a]benzimidazole (XIV).

The initially formed 2-benzoyl derivative (XIII) evidently undergoes partial transacylation to give XIV on reaction with acetic anhydride.

TABLE 1. 9-Methylimidazo[1,2-a]benzimidazole Derivatives



Compound	R	R′	mp, °C (crystallization solvent)	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
IIIa	$COCH_3$	C_6H_5	152 (octane)	$C_{18}H_{15}N_3O$	74,8	5,4	14,3	74,7	5,2	14,5	58
IIIb	COC_6H_5	C_6H_5	156 (octane)	$C_{23}H_{17}N_3O$	78,3	4,8	12,2	78,6	4,9	12,0	61
XIa	H	CH_3	85 (petroleum ether)	$C_{11}H_{11}N_3$	71,2	6,1	22,5	71,3	6,0	22,7	52
XIb	H	C_6H_5	117—118 (octane)	$C_{16}H_{13}N_3$	77,4	5,3	17,3	77,7	5,3	17,0	51
XIII	COC_6H_5	CH_3	140—142 (acetone)	$C_{18}H_{15}N_3O$	74,9	5,5	14,2	74,7	5,2	14,5	58
XIV	$COCH_3$	CH_3	177 (acetone)	$C_{13}H_{13}N_3O$	69,1	6,1	18,4	68,7	5,8	18,5	80

2-Acyl-substituted XIII and XIV can also be obtained from 3,9-dimethylimidazo[1,2-a]benzimidazole (XIa). Brief heating of the latter with excess acetic anhydride in the presence of sodium acetate gives XIV, whereas XIII is formed by the action of an equimolar amount of benzoyl chloride in the presence of pyridine on XIa.

Attempts to subject 3-phenyl derivative XIb to acylation by means of various acylating agents (acetic anhydride, benzoyl chloride, etc.) did not give positive results.

The 2-acetyl derivatives (IIIa and XIV) of imidazo[1,2-a]benzimidazole are stable with respect to alkalis, but an acetyl group is split out on prolonged heating in dilute hydrochloric acid to give XIa and XIb, respectively. 2-Benzoyl derivatives IIIb and XIII are distinguished by their lower resistance to acid hydrolysis; the benzoyl group is split out even then they are dissolved in dilute hydrochloric acid in the cold.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of carbon tetrachloride solutions were recorded with a Tesla spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard. The PMR spectrum of a chloroform solution of IIIa was also obtained.

2-Acetyl-9-methyl-3-phenylimidazo[1,2-a]benzimidazole (IIIa). A solution of 1.37 g (0.01 mole) of bromoacetone in 3 ml of DMF was added in portions with stirring to a solution of 2.5 g (0.01 mole) of 3-benzoyl-2-imino-1-methylbenzimidazoline (I) in 7 ml of freshly distilled DMF, and the mixture was heated at 80° for 20 h. The solvent was removed by distillation at reduced pressure, and the resinous residue was treated with 3 ml of water. The aqueous mixture was neutralized carefully with 22% ammonium hydroxide and extracted with chloroform. The chloroform was removed by distillation, and the residue was purified with a chromatographic column filled with Al_2O_3 (elution with chloroform, R_f 0.9) to give 1.7 g of IIIa. IR spectrum, cm^{-1}: 1619 (C=O).

2-Benzoyl-9-methyl-3-phenylimidazo[1,2-a]benzimidazole (IIIb). This compound was similarly obtained by the action of phenacyl bromide on imine I, except that the cyclization was carried out at 80° for 16 h. The mixture was carefully neutralized with sodium bicarbonate. Compound IIIb is extremely hygroscopic and has R_f 0.85. IR spectrum, cm^{-1}: 1690 (C=O).

2-(N-Acetyl-N-acetonylamino)-1-methylbenzimidazole (IXa). A solution of 5.1 g (27 mmole) of 2-acetamido-1-methylbenzimidazole (VII) [5] in 80 ml of toluene was added to a suspension of 0.62 g (0.027 g-atom) of finely ground sodium in 50 ml of absolute toluene, and the mixture was refluxed for 4 h. It was then cooled, and a solution of 3.8 g (28 mmole) of bromoacetone in 20 ml of toluene was added with vigorous stirring. The mixture was allowed to stand at room temperature for 1 h, after which it was refluxed for 1 h. One-third the volume of the solvent was removed by distillation at reduced pressure, and the residual solution was filtered. Three volumes of petroleum ether were added to the filtrate, and the resulting precipitate was removed by filtration to give 3.9 g (60%) of colorless crystals with mp 179-180° (from acetone). IR spectrum, cm^{-1}: 1620 (C=O) and 1685 (C=O). Found: C 63.8; H 6.2; N 17.0%. $C_{13}H_{15}N_3O_2$. Calculated: C 63.6; H 6.2; N 17.1%.

2-(N-Acetyl-N-phenacylamino)-1-methylbenzimidazole (IXb). A 0.48-g (0.021 g-atom) sample of finely ground sodium in 30 ml of xylene was added to a solution of 4 g (21 mmole) of VII in 100 ml of absolute xylene, and the mixture was heated at 130° for 4-5 h. It was then cooled, a solution of 4.4 g (22 mmole) of phenacyl bromide in 30 ml of xylene was added, and the mixture was refluxed for 2-3 h. The sodium bromide was

removed by filtration, two-thirds of the volume of the solvent was removed by distillation at reduced pressure, and the product was isolated by the addition of petroleum ether. Workup gave 4.5 g (69%) of colorless crystals with mp 170° (from alcohol). IR spectrum, cm^{-1}: 1679 (C=O, broad band). Found: C 70.0; H 5.3; N 13.8%. $C_{18}H_{17}N_3O_2$. Calculated: C 70.3; H 5.6; N 13.7%.

2-Phenacylamino-1-methylbenzimidazole (Xb). A solution of 0.92 g (0.03 mole) of IXb in 40 ml of 15% hydrochloric acid was refluxed for 5 h, after which it was boiled with activated charcoal. It was then cooled, and the precipitated hydrochloride of Xb was removed by filtration, washed with ice water, and dried at 100° to give 0.63 g (70%) of colorless needles with mp 194-196° (from water). Found: C 63.5; H 5.6; Cl 11.4; N 13.6%. $C_{16}H_{16}ClN_3O$. Calculated: C 63.7; H 5.3; Cl 11.7; N 13.9%. Base Xb was isolated from an aqueous solution of the hydrochloride of Xb by the action of 22% ammonium hydroxide. Workup gave colorless crystals from alcohol with mp 140°. IR spectrum, cm^{-1}: 1683 (C=O) and 3400 (NH). Found: C 72.0; H 5.5; N 15.9%. $C_{16}H_{15}N_3O$. Calculated: C 72.4; H 5.7; N 15.8%.

3,9-Dimethylimidazo[1,2-a]benzimidazole (XIa). A solution of 0.98 g (4 mmole) of IXa in 25 ml of 10% hydrochloric acid was refluxed for 1 h, after which it was cooled and neutralized with 22% ammonium hydroxide. The liberated oil was extracted with chloroform, the solvent was removed by distillation, and the residue was purified chromatographically on Al_2O_3 (elution with ether) to give 0.38 g of XIa.

9-Methyl-3-phenylimidazo[1,2-a]benzimidazole (XIb). A solution of 4.9 g (16 mmole) of IXb in 70 ml of concentrated HCl was refluxed for 4 h, after which it was cooled and treated with an equal volume of water. The mixture was neutralized with 22% ammonium hydroxide, and the precipitated yellowish-white crystals (2.0 g) were removed by filtration.

3-Acetyl-2-phenacylimino-1-methylbenzimidazoline hydrobromide (XII). A 0.5-g (4 mmole) sample of acetyl bromide in 5 ml of acetone was added in portions to a solution of 0.5 g (2 mmole) of Xb in 30 ml of acetone. After 5 min, the resulting precipitate was removed by filtration, washed with acetone and ether, and vacuum dried over P_2O_5 to give 0.61 g (78%) of yellowish-white crystals with mp 214-215°. Found: Br 20.3; N 10.9%. $C_{18}H_{18}BrN_3O_2$. Calculated: Br 20.6; N 10.8%.

2-Acetyl-3,9-dimethylimidazo[1,2-a]benzimidazole (XIV). A 0.16-g (2 mmole) sample of ground anhydrous sodium acetate was added to a solution of 0.18 g (1 mmole) of XIa in 3 ml of acetic anhydride, and the mixture was refluxed for 3.5 h. It was then cooled, diluted with two volumes of water, and neutralized with sodium bicarbonate. The liberated oil was extracted with chloroform, and the chloroform extract was dried with sodium sulfate. The solvent was removed by distillation, and the product was purified with a chromatographic column filled with Al_2O_3 by elution with chloroform–ether (1 : 1) to give 0.18 g of XIV. IR spectrum, cm^{-1}: 1624 (C=O).

2-Benzoyl-3,9-dimethylimidazo[1,2-a]benzimidazole (XIII). A) A mixture of 0.18 g (1 mmole) of XIa and 0.14 g (1 mmole) of benzoyl chloride was dissolved in 1 ml of pyridine, and the mixture was heated at 110-120° for 10 min. It was then cooled, washed with 1 ml of water, and extracted with ether. The ether extract was dried with magnesium sulfate, the ether was removed by distillation, and the residue was crystallized from acetone to give 0.17 g of XIII. IR spectrum, cm^{-1}: 1710 (C=O).

B) A 0.78-g (2 mmole) sample of hydrobromide XII was heated in 5 ml of freshly distilled DMF at 80-90° for 20 h, after which the solvent was removed by distillation, and the residue was triturated with hexane and crystallized from acetone to give 0.3 g (50%) of XIII.

The properties of III, XI, XIII, and XIV are presented in Table 1.

Reaction of 1-Methyl-2-phenacylaminobenzimidazole (Xb) with Acetic Anhydride. A 0.8-g sample of fused sodium acetate was added to a solution of 0.27 g (1 mmole) of Xb in 6 ml of freshly distilled acetic anhydride, and the mixture was poured over ice. The aqueous mixture was neutralized with sodium bicarbonate, during which it was necessary to cool the mixture thoroughly to avoid resinification. The mixture was extracted with chloroform, the solvent was removed by distillation, and the residue was passed through a chromatographic column filled with Al_2O_3. Elution with chloroform–ether (1 : 1) gave fractions with R_f 0.9 and 0.7. The first fraction yielded 0.09 g (32%) of XIII, and the second fraction gave 0.09 g (40%) of XIV.

LITERATURE CITED

1. V. A. Anisimova, N. I. Avdyunina, A. M. Simonov, G. V. Kovalev, and S. M. Gofman, Khim. Geterotsikl. Soedin., No. 12, 1660 (1976).
2. Yu. V. Koshchienko, A. M. Simonov, and G. M. Suvorova, Khim. Geterotsikl. Soedin., No. 1, 140 (1975).
3. B. I. Khristich, G. M. Suvorova, and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 10, 1398 (1974).

4. V. A. Anisimova and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 1, 121 (1976).
5. A. M. Simonov and N. D. Vitkevich, Zh. Obshch. Khim., 30, 590 (1960).

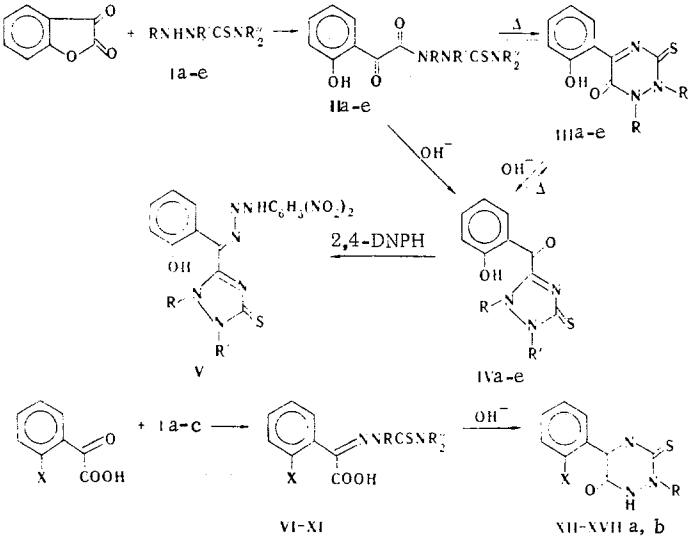
1,2,4-TRIAZINE AND TRIAZOLE DERIVATIVES FROM α-KETO ACIDS AND THIOSEMICARBAZIDES

E. A. Rusakov,* A. B. Tomchin, K. N. Zelenin, A. E. Drabkin, and N. P. Samoilenko

UDC 547.873

Thiosemicarbazides of 2-hydroxyphenylglyoxylic acid, which, depending on the conditions, undergo cyclization to interconvertible 5-(2-hydroxyphenyl)-6-oxo-1,2,4-triazine-3-thiones or (2-hydroxybenzoyl)-Δ^2-1,2,4-triazoline-5-thiones, are formed by the action of thiosemicarbazide and its homologs on coumarindione. The thiosemicarbazones of 2-hydroxyphenylglyoxlyic and other 2-substituted phenylglyoxylic acids undergo cyclization to 6-(2-hydroxyphenyl)-5-oxo-1,2,4-triazine-3-thiones.

The reaction between α-keto acids and thiosemicarbazide derivatives lies at the foundation of several schemes for the synthesis of heterocyclic structures. One of the unexplored pathways may consist in prior condensation at the carboxyl group to give the corresponding thiosemicarbazides of α-keto acids and their subsequent cyclization to 1,2,4-triazine and triazole derivatives. Because of the high activity of the carbonyl group



I a R=R′=R″=H, b R=R″=H, R′=CH_3, c R=R′=H, R″=CH_3, d R=CH_3, R′=R″=H, e R=p-C_4H_9, R′=R″=H; II a R=R′=R″=H, b R=R″=H, R′=CH_3, c R=R′=H, R″=CH_3, d R=CH_3, R′=R″=H, e R=*n*-C_4H_9, R′=R″=H; III a R=R′=H, b R=H, R′=CH_3, d R=CH_3, R′=H, e R=*n*-C_4H_9, R′=H; IV a R=R′=H, e R=n-C_4H_9, R′=H; V R=R′=H; VI X=H, a R′=R″=H, b R′=CH_3, R″=H, c R′=H, R″=CH_3; VII X=OH, a R′=R″=H, b R′=CH_3, R″=H; VIII X=NH_3, a R′=H; IX X=Br, a R′=R″=H, b R′=CH_3, R″=H; X X=NO_2, a R′=R″=H, b R′=CH_3, R″=H, c R′=H, R″=CH_3; XI X=COOH, a R′=R″=H, b R′=CH_3, R″=H, c R′=H, R″=CH_3; XII X=H, a R=H, b R′=CH_3; XIII X=OH, a R′=H, b R′=CH_3; XIV X=NH_2, a R′=H; XV X=Br, b R′=CH_3; XVI X=NO_2, a R′=H, b R′=CH_3; XVII X=COOH, a R′=H, b R′=CH_3

* Deceased.

S. M. Kirov Military Medical Academy, Leningrad. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp, 116-121, January, 1977. Original article submitted May 6, 1976.