RESEARCH ON BENZIMIDAZOLE DERIVATIVES

XLII.* SYNTHESIS AND TRANSFORMATIONS OF AMIDES OF UNSATURATED CARBOXYLIC ACIDS IN SERIES OF 2-AMINO DERIVATIVES OF BENZIMIDAZOLE AND PYRIDINE

P. V. Tkachenko, A. M. Simonov, and I. I. Popov

UDC 547.785.5'857.07:542.953

The acylation of 2-amino derivatives of benzimidazole and pyridine with β-aryl-α, β-unsaturated carboxylic acid chlorides gave the corresponding amides, which were converted to 2-oxo derivatives of pyrimido [1,2-a]benzimidazole and pyridine by the action of bases.

The reactions of 2-aminobenzimidazole [2-4] and 2-aminopyridine [5, 6] with acrylic and acetylenecarboxylic acid esters have been studied in detail; however, the reaction of these amines with unsaturated carboxylic acid chlorides has not been studied adequately. Continuing our research on unsaturated derivatives of 2-aminobenzimidazole [8, 9], we studied the reactions of 2-amino-1-methylbenzylimidazole (I) and 2-aminopyridine (II) with β-aryl-α,β-unsaturated carboxylic acid chlorides (IIIa-c).

It was established that hygroscopic crystalline 2-amino-1-methyl-3-acylbenzimidazolium chlorides (IVa, b) are formed in the reaction of amine I with cinnamoyl (IIIa) and phenylpropiolyl (IIIb) chlorides in dry acetone. When acylium salt IVa is treated with triethylamine in acetonitrile at 10-15°C, it is converted to 2-imino-1-methyl-3-cinnamoylbenzimidazoline (Va),† which is quite stable in the crystalline state but in benzene or chloroform solution undergoes rearrangement to amide VIa in 24 h (see [10]). The latter can be obtained in good yield by direct acylation of amine Ia with acid chloride IIIa in the presence of pyridine or by the action of triethylamine on a suspension of acylium salt IVa in acetonitrile at 20-25°C for 1.5 h. When amide VIa is refluxed in alcohol in the presence of pyridine or triethylamine, it is converted to benzimidazolone VII.

When acylium salt IVb is treated with excess pyridine for 6 h, it undergoes rearrangement through unstable imine IV to phenylpropiolamide VIb, which is cyclized to benzimidazolone VIII under the reaction conditions. In the presence of pyridine, amine Ia is acylated by acid chlorides IIIb,c at −70°C without resinification of the reaction mixture to give amides VIb,c, which undergo cyclization to pyrimidinone VIII under the influence of sodium ethoxide. α-Bromocinnamamide VIc evidently initially undergoes dehydrobromination to give phenylpropiolamide VIb; the latter undergoes partial conversion to pyrimidinone VIII even when it is heated to the point of crystallization from alcohol. The presence of sodium ethoxide in the reaction mixture accelerates intramolecular cyclization appreciably. (See scheme on following page).

The data from the IR spectra of VIa-c indicate an amide structure for these compounds (see [11]). The PMR spectra of VII and VIII contain a four-proton H_{6-9} multiplet at δ 7.3-7.7 ppm; this is in agreement with the pyrimido [1,2-a]benzimidazol-2-one structure (see [2, 7]).‡ The mechanism of the cyclization of derivative VIb to VIII probably includes a step involving addition of the Michael type to the activated C ≡ C bond as a result of attack by the terminal nitrogen atom on the β-carbon atom of the multiple bond (see [8]). The action of

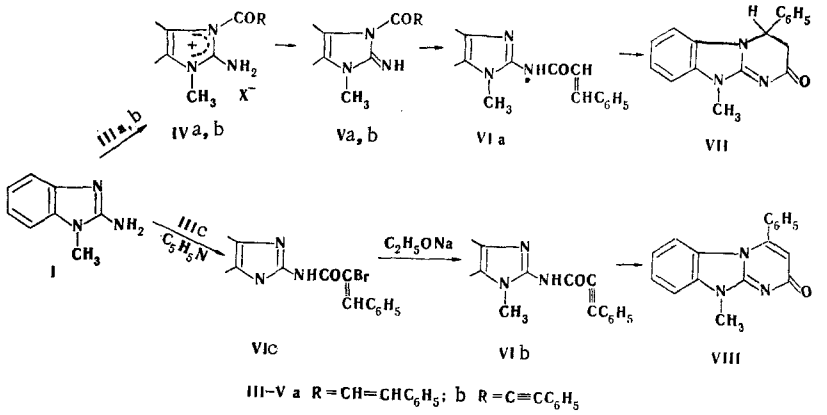
* See [1] for communication XLI.

† Obtained by G. M. Suvorova.

‡ Splitting of the overall aromatic four-proton H_{6-9} multiplet into three-proton (H_{7-9}, δ 7.5-8.0 ppm) and one-proton (H_6 δ 8.5-8.8 ppm) signals would be characteristic for the isomeric pyrimido [1,2-a]benzimidazol-4-one structure [12, 13].

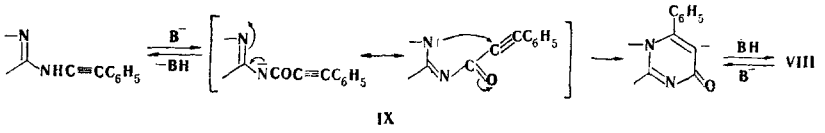
Rostov State University, Rostov-on-Don 344006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 90-93, January, 1978. Original article submitted November 15, 1976.

0009-3122/78/1401-0073$07.50



III–V a R = CH=CHC$_6$H$_5$; b R = C≡CC$_6$H$_5$

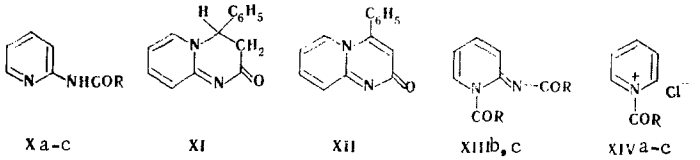
bases on amide VIb evidently leads to the formation of mesomeric anion IX and consequently to an increase in the nucleophilicity of the ring nitrogen atom, as a consequence of which the rate of cycloaddition increases.



IX

The acylation of 2-aminopyridine II with cinnamoyl chloride IIIa in the presence of pyridine proceeds smoothly at −10 to 0°C and leads to amide Xa, which was converted to pyrimidin-2-one XI by refluxing in an alcohol solution of pyridine. The reaction of amine II with acid chlorides IIIb,c in acetone leads to the formation of oily acylium salts; amides, Xb,c, which were converted to 4-phenyl-2H-pyrido[1,2-a]pyrimidin-2-one (XII) by the action of sodium ethoxide in alcohol, are formed in the presence of pyridine at −70°C. Amide Xb can be readily converted to XII also by refluxing in alcohol.

The acylation of amine II with acid chlorides IIIb,c, gives, in addition to amides Xb, c, small amounts of red oily compounds, to which diacylium derivative structures XIIb,c can be assigned on the basis of the IR spectra and the results of elementary analysis. We were unable to synthesize them by acylation of amides Xb, c with acid chlorides IIIb, c because of resinification of the reaction mixture.



X, XIV a R = CH=CHC$_6$H$_5$; X, XIII, XIV b R = C≡CC$_6$H$_5$; c R = CBr=CHC$_6$H$_5$

Amines I and II are acylated most smoothly by acylpyridinium salts XIV, which can be obtained conveniently beforehand from pyridine and the corresponding acid chloride in acetone at −70°C. Acylpyridinium salts XIV are quite stable crystalline compounds, but they are readily hydrolyzed by air moisture, and this makes it difficult to use them.

EXPERIMENTAL

The IR spectra of chloroform solutions of the compounds were recorded with a UR-20 spectrometer. The physical constants, yields, and characteristics of the synthesized compounds are presented in Table 1.

2-Amino-3-acyl-1-methylbenzimidazolium Chlorides (IVa,b). A solution of 0.01 mole of acid chloride IIIa or IIIb in 10 ml of acetone was added with stirring at 10–15°C to a solution of 1.47 g (10 mmole) of I in 20 ml of acetone. After 1 h, the precipitate was removed by filtration, washed with acetone and dry ether, and dried in a vacuum desiccator over calcium chloride to give colorless crystals that are soluble in chloroform and alcohol and are readily hydrolyzed by air moisture.

TABLE 1. Physical Constants and Yields of the Synthesized Compounds

Compound	mp, °C	Found, %			Empirical formula	Calc., %			IR spectrum, cm^{-1}*		Yield, %
		C	H	N		C	H	N	C=O	N—H	
IVa†	150	65,0	5,4	13,6	$C_{17}H_{16}ClN_3O$	65,2	5,1	13,4	1715	—	80
IVb†	170	65,3	4,7	13,6	$C_{17}H_{14}ClN_3O$	65,6	4,5	13,5	1720	—	91
Va	93	73,7	5,1	15,0	$C_{17}H_{15}N_3O$	73,6	5,4	15,2	1700	3374	88
VIa	160	74,0	5,2	14,9	$C_{17}H_{15}N_3O$	73,6	5,4	15,2	1680	3425	71
VIb	117—118	74,3	5,0	15,6	$C_{17}H_{13}N_3O$	74,2	4,7	15,2	1680	3420	88
VIc†	173—174	57,7	4,3	15,2	$C_{17}H_{14}BrN_3O$	57,3	3,9	14,9	1675	3425	76
VII	170—171	73,9	5,7	15,0	$C_{17}H_{15}N_3O$	73,6	5,4	15,2	1625	—	86
VIII	222	74,4	5,1	15,1	$C_{17}H_{13}N_3O$	74,2	4,7	15,2	1615	—	94
Xa	113—115	75,0	5,4	12,3	$C_{14}H_{12}N_2O$	75,0	5,4	12,4	1680	3415	91
Xb	82—83	75,2	4,7	12,3	$C_{14}H_{10}N_2O$	75,6	4,6	12,6	1670	3400	81
Xc†	97—98	55,8	4,0	9,4	$C_{14}H_{11}BrN_2O$	55,5	3,6	9,3	1680	3390	87
XI	140—141	75,4	5,7	12,6	$C_{14}H_{12}N_2O$	75,0	5,4	12,5	1630	—	83
XII	127—129	75,4	4,8	12,8	$C_{14}H_{10}N_2O$	75,6	4,6	12,6	1640	—	57
XIIIb†	156—158	60,6	2,5	12,0	$C_{23}H_{14}N_2O_2 \cdot C_6H_3N_3O_7$	60,2	2,9	12,1	1630, 1700	—	5
		47,3	2,9	9,7							
XIIIb†	144—145				$C_{23}H_{16}Br_2N_2O_2 \times \times C_6H_3N_3O_7$	47,0	2,6	9,5	1650, 1710	—	4

* Bands in the IR spectra: IVa 3373 (ν_{NH_2}) and 1672 (σ_{NH_2}); IVb 3355 (ν_{NH_2}) and 1655 (σ_{NH_2}) IVb and VIb 2210 (C ≡ C); Xb and XIIIb 2200 (C ≡ C).

†Halogen found (calculated) in percent: IVa Cl 11.5 (11.2); IVb Cl 11.5 (11.3); VIc Br 22.1 (22.5); Xc Br 25.9 (26.3); XIIIc Br 21.3 (21.6).

2-Imino-3-cinnamoyl-1-methylbenzimidazoline (Va). A 0.2-g (2 mmole) sample of dry triethylamine was added with vigorous stirring at 10-15°C to a suspension of 0.3 g (10 mmole) of IVa in 15 ml of dry acetonitrile. The resulting bright-yellow crystals of imine Va were removed by filtration, washed with acetonitrile, dried over phosphorus pentoxide, and crystallized from benzene and petroleum ether.

Cinnamic Acid 1-Methyl-2-benzimidazolyl- and 2-Pyridylamides (VIa and Xa). A 3.3 g (20 mmole) sample of acid chloride IIIa was added dropwise with stirring at −10°C to a solution of 2.9 g (20 mmole) of amine I or 1.9 g (20 mmole) of II and 1.6 ml (20 mmole) of pyridine in a mixture of 5 ml of tetrahydrofuran (THF) and 10 ml of acetone, and the mixture was stirred for 40 min. The solvent was then removed by distillation, and 5 ml of water was added to the residue. The resulting precipitate was removed by filtration and washed with water. The products were obtained as colorless needles (from alcohol).

4-Phenyl-3,4-dihydro-2H-pyrimido[1,2-a]benzimidazol-2-one (VII) and 4-Phenyl-3,4-dihydro-2H-pyrido-[1,2-a]pyrimidin-2-one (XI). A solution of 2.7 g (10 mmole) of VIa in 10 ml of ethanol or of 2.1 g (10 mmole) of Xa in 7 ml of ethanol was refluxed for 6-8 h with 1 ml of pyridine, after which the mixture was cooled and poured into 50 ml of water. The precipitate was removed by filtration and crystallized from ethanol to give the products in the form of colorless prisms.

Phenylpropiolic and α-Bromocinnamic Acid 1-Methyl-2-benzimidazolylamides (VIb,c). A solution of 10 mmole of acid chloride IIIb or IIIc in 2 ml of THF was added dropwise at −70°C to a solution of 1.47 g (10 mmole) of amine I and 0.8 ml (10 mmole) of pyridine in 10 ml of dry THF, and the mixture was stirred for 30 min. It was then allowed to stand at room temperature for 3 h, after which it was poured into 30 ml of water. The resulting precipitate was removed by filtration and washed with water. The colorless needles (from alcohol) were soluble in acetone and chloroform.

4-Phenyl-10-methyl-2H-pyrimido[1,2-a]benzimidazol-2-one (VIII). A) A mixture of a solution of 10 mmole of sodium ethoxide in 5 ml of absolute alcohol and 1.9 g (70 mmole) of amide VIb or 1.2 g (35 mmole) of amide VIc was refluxed for 30 min, after which it was cooled, and the resulting precipitate was removed by filtration and washed with alcohol. The product was obtained in 83% yield.

B) A solution of 1.47 g (10 mmole) of I in 10 ml of dry pyridine was added dropwise with stirring at −10°C to a solution of 1.64 g (10 mmole) of acid chloride IIIb in 2 ml of THF, and the mixture was stirred at −10°C for 20 min and allowed to stand at room temperature for 6 h. It was then treated with water (50 ml), and the precipitate was removed by filtration and worked up to give VIII in 94% yield.

Phenylpropiolic and α-Bromocinnamic Acid 2-Pyridylamides (Xb,c). A) A solution of 10 mmole of acid chloride IIIb or IIIc in 2 ml of THF was added dropwise with stirring at −70°C to a solution of 0.94 g (10 mmole)

of amine II in 5 ml of THF and 0.8 ml of pyridine, after which the mixture was stirred for 25 min. The cooling bath was then removed, and the mixture was allowed to stand at room temperature for a certain length of time. It was then poured into 30 ml of water, and the resulting oil was separated and triturated with 20 ml of water. The resulting crystals were dried in a desiccator over phosphorus pentoxide and triturated with 40 ml of ether. They were then removed by filtration to give 1.68 g (76%) of Xb and 2.63 g (87%) of Xc as colorless prisms (from alcohol). The ether extract was evaporated and chromatographed with a column filled with aluminum oxide (elution with ether). The residue contained 0.17 g (4.8%) of XIIb (as a viscous red oil) or 0.2 g (4%) of XIIc (red crystals).

B) A 1.64 g (10 mmole) sample of acid chloride IIIa was added at −70°C to a solution of 0.8 ml (10 mmole) of pyridine in 5 ml of dry acetone, and the precipitated acylpyridinium salt XIVb was removed by filtration and added to a cooled (to −70°C) solution of 0.94 g (10 mmole) of amine II in 3 ml of acetone. The mixture was stirred at −70°C for 20 min and at 0°C for 1 h, after which it was diluted with water and filtered to give 1.8 g (81%) of Xb.

4-Phenyl-2H-pyrido[1,2-a]pyrimidin-2-one (XI). A) A solution of 2.2 g (10 mmole) of amide Xb in 7 ml of alcohol was refluxed for 8 h, after which it was cooled, and the precipitate was removed by filtration and washed with ether. The product was obtained as colorless needles (from alcohol).

B) This compound was also obtained in 73% yield from Xc by the procedure used to obtain VIII (by method A).

LITERATURE CITED

1. P. V. Tkachenko, I. I. Popov, A. M. Simonov, and Yu. V. Medvedev, Khim. Geterotsikl. Soedin., No. 7, 972 (1976).
2. H. Reimlinger, M. A. Peiren, and R. Merenyi, Chem. Ber., 105, 794 (1972).
3. D. W. Dunwell and D. Evans, J. Chem. Soc., Perkin Trans. I, 15, 1588 (1973).
4. H. Ogura, M. Kawano, and T. Iton, Chem. Pharm. Bull. (Tokyo), 21, No. 9, 2019 (1973).
5. G. R. Lappin, J. Org. Chem., 26, 2350 (1961).
6. J. J. Pachter, J. Org. Chem., 26, 4157 (1961).
7. A. W. Chow, D. R. Jakes, B. P. Trotter, N. M. Hall, and J. R. E. Hoover, J. Heterocycl. Chem., 10, 71 (1973).
8. I. I. Popov, P. V. Tkachenko, and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 3, 396 (1975).
9. I. I. Popov, P. V. Tkachenko, and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 4, 523 (1975).
10. B. I. Khristich, A. M. Simonov, and G. M. Suvorova, Khim. Geterotsikl. Soedin., No. 9, 1293 (1973).
11. Yu. N. Sheinker, A. M. Simonov, Yu. M. Yutilov, V. N. Sheinker, and E. I. Perel'shtein, Zh.Org. Khim., No. 6, 917 (1966).
12. E. C. Taylor and A. McKillop, J. Am. Chem. Soc., 87, 1986 (1965).
13. K. Nayarajan, M. D. Nair, and P. M. Pillar, Tetrahedron, 23, 1683 (1967).
14. S. I. Lur'e, Zh.Obshch. Khim., 20, 195 (1950).