2. N. I. Romanenko, N. A. Klyuev, I. V. Fedulova, B. A. Priimenko, S. N. Garmash, A. Yu. Chervinskii, and A. N. Stepanov, *Khim. Geterotsikl. Soedin.*, No. 8, 1133 (1986).
3. S. N. Garmash, B. A. Priimenko, N. A. Klyuev, N. I. Romanenko, V. A. Golets, and T. A. Kozik, *Khim. Geterotsikl. Soedin.*, No. 4, 534 (1988).
4. A. N. Krasovskii, M. I. Yurchenko, P. M. Kochergin, and I. I. Soroka, *Khim. Geterotsikl. Soedin.*, No. 8, 1121 (1975).
5. N. I. Romanenko, I. V. Fedulova, B. A. Priimenko, B. A. Samura, L. M. Kapkan, A. Yu. Chervinskii, T. M. Pekhtereva, and S. N. Garmash, *Khim-farm. Zh.*, No. 4, 427 (1986).
6. R. Sil'verstein, G. Bassler, and T. Morril, *Spectrometric Identification of Organic Compounds* [Russian translation], Mir, Moscow (1977).
7. J. Heiss, K.-P. Zeller, and W. Voelter, *Org. Mass Spectrom.*, **3**, 181 (1970).
8. N. A. Klyuev, A. N. Krasovskii, A. K. Sheinkman, I. A. Krasovskii, and V. G. Zhil'nikov, *Zh. Org. Khim.*, **17**, 1739 (1981).
9. N. S. Vul'fson, V. G. Zaikin, and A. I. Mikaya, *Mass Spectrometry of Organic Compounds* [in Russian], Khimiya, Moscow (1986), p. 103.
10. M. V. Povstyanoi, P. M. Kochergin, and A. V. Akimov, *Khim. Khim. Tekhnol.*, **18**, 1316 (1975).
11. B. A. Priimenko, N. I. Romanenko, S. N. Garmash, N. A. Klyuev, I. V. Fedulova, N. I. Gnatov, and N. V. Koval', *Ukr. Khim. Zh.*, **51**, 660 (1985).

CYANOACETYLATION OF 6-AMINOURACILS. SYNTHESIS OF 7-AMINOPYRIDO[2,3-d]PYRIMIDINE-2,4,5-TRIONES

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UDC 547.854.4'859.1:542.951.1'953.1

6-Aminouracils and N-substituted derivatives are cyanoacetylated to give 5-cyanoacetyl-6-aminouracils. In the presence of bases these are converted to pyrido[2,3-d]pyrimidine-2,4,5-triones in high yields.

It is known that oxo pyrido[2,3-d]pyrimidines have antitumor activity [1]. With previous work on the acylation of 6-aminouracils and N-substituted derivatives in mind the aim of this study has been the cyanoacetylation of 6-aminouracils and subsequent conversion to trioxopyrido[2,3-d]pyrimidines.

Reaction of 1-methyl or 3-methyl-6-aminouracils Ia, b with cyanoacetic acid in acetic anhydride with pyridine gives the corresponding 5-cyanoacetyl-6-aminouracils IIa, b in high yields. 1-Butyl- (Ih), 1-phenyl- (Ig), and 1,3-disubstituted 6-aminouracils (Ic-f, i-k) are also readily cyanoacetylated without the pyridine. The unsubstituted 6-aminouracil (I*l*) could be converted to the 5-cyanoacetyl derivative (II*l*) only by phosphorus oxychloride in DMF. Evidently the acylation conditions are determined by the differences in electron density on pyrimidine atom $C_{(5)}$, due to the electron-donor substituents on the nitrogen atoms. It follows that the unsubstituted 6-aminouracil demands a more vigorous acylating medium.

Chemicopharmaceutical Science Research Institute, Novokuznetsk 654034. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 971-975, July, 1990. Original article submitted May 7, 1988; revision submitted October 11, 1989.

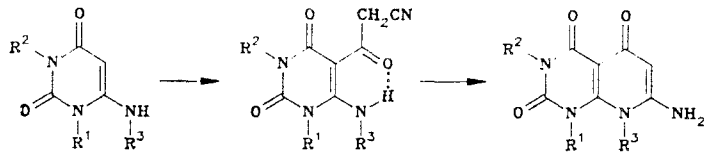
TABLE 1. Compounds Synthesized

Compound	Empirical formula	mp., °C*	IR spectrum, cm^{-1}	PMR spectrum,** δ, ppm	M^+ (I_{rel}, %)	Yield, % (method)
IIb	$C_8H_8N_4O_3$	>300	1613, 1640, 1711, 2245, 3200, 3410	3,16 (3H, s, NCH_3); 4,52 (2H, s, CH_2); 6,70 (1H, s, NH_2); 10,24 (2H, br.s, NHandNH_2)	208 (50)	70
IIc	$C_9H_{10}N_4O_3$	250...251	1611, 1660, 1715, 2260, 3190, 3240	3,10 (3H, s, NCH_3); 3,34 (3H, s, NCH_3); 4,32 (2H, s, CH_2); 8,47 (1H, s, NH_2); 10,67 (1H, s, NH_2)	222 (50)	95
IId	$C_{10}H_{12}N_4O_3$	208...210	1620, 1640, 1720, 2270, 3070, 3310	3,00 (3H, s, NCH_3); 3,92 (2H, q, $\mathbf{CH_2}CH_3$); 1,30 (3H, t, $CH_2\mathbf{CH_3}$); 4,30 (2H, s, CH_2); 8,55 (1H, s, NH_2); 10,84 (1H, s, NH_2)	236 (46)	90
IIe	$C_{10}H_{12}N_4O_3$	115...116	1613, 1640, 1710, 2250, 3200, 3400	3,12 (3H, s, NCH_3); 3,22 (3H, s, NCH_3); 3,50 (3H, s, NCH_3); 4,20 (2H, s, CH_2); 11,40 (1H, br.s, NH)	236 (50)	72
IIf	$C_{21}H_{18}N_4O_3$	200...201	1620, 1640, 1720, 2260, 3650	3,15 (3H, s, NCH_3); 3,50 (2H, d, NCH_3); 4,38 (2H, s, CH_2Ph); 7,04 (2H, m, $CH_2\mathbf{Ph}$); 7,28 (3H, m, $CH_2\mathbf{Ph}$); 7,51 (5H, s, N**Ph**); 10,87 (1H, br. s, NH)	374 (50)	76
IIh	$C_{11}H_{14}N_4O_3$	268...271	1600, 1667, 1733, 2267, 3040, 3153, 3460	0,86 (3H, t, $\mathbf{CH_3}(CH_2)_3$, J=8 Hz); 1,35 (4H, m, $CH_3(\mathbf{CH_2})_3$); 3,81 (2H, t, $CH_3(\mathbf{CH_2})_3$, J=8 Hz); 4,32 (2H, s, $CO\mathbf{CH_2}CN$); 8,50 (2H, s, NH_2); 10,85 (1H, s, NH)	250 (46)	78
IIi	$C_{11}H_{14}N_4O_3$	146...147	1613, 1640, 1707, 2253	3,27 (3H, s, NCH_3); 3,50 (3H, s, NCH_3); 4,24 (2H, s, CH_2); 1,34 (3H, t, $CH_2\mathbf{CH_3}$); 3,52 (2H, q, $\mathbf{CH_2}CH_3$); 10,34 (1H, s, NH)	268 (50)	73
IIj	$C_{15}H_{14}N_4O_3$	183...184	1613, 1649, 1720, 2260, 3100	2,89 (3H, s, NCH_3); 3,20 (3H, s, NCH_3); 4,43 (2H, s, CH_2); 7,31 (5H, m, Ph); 12,44 (1H, s, NH)	298 (50)	92
IIk	$C_{14}H_{12}N_4O_3$	283...285	1613, 1653, 1713, 2260, 3180, 3233, 3427	3,15 (3H, s, NCH_3); 4,37 (2H, s, CH_2); 7,43 (5H, m, Ph); 7,10 (1H, s, NH_2); 10,35 (1H, s, NH_2)	284 (50)	89
IIIa	$C_8H_8N_4O_3$	>300	1650, 1680, 1720, 3250, 3380, 3470	3,10 (3H, s, NCH_3); 5,75 (1H, s, CH)	208 (100)	90 (A)
IIIb	$C_8H_8N_4O_3$	>300	1730, 3270, 3400, 3500	—	208 (100)	95 (B)

IIId	$C_{10}H_{12}N_4O_3$	268...269	3200, 3400	3,51 (3H, s, NCH_3); 6,15 (1H, s, CH); 4,30 (2H, q, CH_2CH_3); 1,30 (3H, b, CH_2CH_3)	236 (100)	98(A,B)
IIIe	$C_{10}H_{12}N_4O_3$	268...269	3200, 3450	3,28 (3H, s, NCH_3); 3,52 (3H, s, NCH_3); 3,72 (3H, s, NCH_3); 6,12 (1H, s, CH)	236 (100)	75 (A)
IIIf	$C_{21}H_{18}N_4O_3$	213...214	1640, 1660, 1670, 3200, 3480	3,10 (3H, s, NCH_3); 4,53 (2H, s, CH_2Ph); 5,16 (1H, s, CH); 6,44 (2H, s, NH_2); 6,92 (2H, m, CH_2Ph); 7,20 (3H, m, CH_2Ph); 7,48 (5H, s, NPh)	374 (100)	70 (A)
IIIg	$C_{13}H_{10}N_4O_3$	300	1647, 1693, 1720, 3180, 3473, 3040, 3240, 3367	5,56 (1H, s, CH); 6,55 (2H, s, NH_2); 7,35 (5H, m, Ph)	270 (100)	95 (A)
IIIh	$C_{11}H_{14}N_4O_3$	209...211	1627, 1667, 1700, 3100, 3200, 3390, 3530	4,00 (2H, t, $(CH_2)_3CH_3$); 1,10...1,70 (4H, m, $(CH_2)_3CH_3$); 0,89 (3H, t, $(CH_2)_3CH_3$); 5,61 (1H, s, CH); 6,68 (2H, s, NH_2)	250 (100)	90 (B)
IIIk	$C_{14}H_{12}N_4O_3$	292...293	1600, 1673, 1707, 3230, 3400	3,20 (3H, s, NCH_3); 5,51 (1H, s, CH); 6,40 (2H, s, NH_2); 7,35 (5H, m, Ph)	284 (100)	93 (A)
IIIl	$C_7H_6N_4O_3$	300	1690, 3200, 3500	—	194 (100)	95 (A)

*Compounds IIb-f, and IIIa, b were recrystallized from acetic acid; IIk, h and IIId, g, h, k from DMF; IIi, j from acetone; IIIe from water; IIIf from butanol; and IIIl by reprecipitation.

**PMR spectra for IIb-e, h, k and IIIg, h, k were recorded in DMSO-D_6; IIf, i in $CDCl_3$; IIk and IIIf in DMF-D_7; and IIIa, d, e in CF_3COOH.



Ia-ℓ IIa-ℓ IIIa-h, k, ℓ

a $R^1=R^3=H$, $R^2=Me$; b $R^1=Me$, $R^2=R^3=H$; c $R^1=R^2=Me$, $R^3=H$; d $R^1=Et$, $R^2=Me$, $R^3=H$; e $R^1=R^2=R^3=Me$; f $R^1=Ph$, $R^2=Me$, $R^3=CH_2Ph$; g $R^1=Ph$, $R^2=R^3=H$; h $R^1=Bu$, $R^2=R^3=H$; i $R^1=R^2=Me$, $R^3=Et$; j $R^1=R^2=Me$, $R^3=Ph$; k $R^1=Ph$, $R^2=Me$, $R^3=H$; ℓ $R^1=R^2=R^3=H$

The absence of the $C_{(5)}$ proton signal in the PMR spectra of IIa-*l* shows that this is the acylation site in the pyrimidine ring. The starting 6-aminouracils Ia-d, g, h, k, *l* show the heterocycle amino group protons as a singlet in the region 6.48-6.81 ppm. By contrast, in IIa-d, g, h, k, *l* these protons are seen as two doublets at 6.80-7.15 and 10-13 ppm. The 6-amino group protons in the 5-cyanoacetyl-6-alkyl(phenyl)aminouracils IIe, f, i, j appear at low field. This is explained by formation of an intramolecular hydrogen bond between an amino group proton and the carbonyl group, forming a stable intermolecular chelate.

Treatment of IIa-*l* with aqueous base or sodium ethylate in anhydrous alcohol causes intramolecular cyclization to the pyrido[2,3-d]pyrimidine-2,4,5-triones IIIa-h, k, *l* [3] in high yields. The IR spectra of IIIa-h, k, *l* show the absence of nitrile stretching bands but the presence of NH_2 stretching at 3350 and 3450 cm^{-1}. The PMR spectra of these compounds show a singlet for the proton at $C_{(6)}$ at 5.14-5.61 ppm and the absence of a signal for the methylene protons of the starting IIa-*l*. Amino-group protons appear as a singlet in the region 6.36-6.88 ppm when DMSO-D_6 is used as the PMR solvent.

EXPERIMENTAL

IR spectra were recorded for KBr tablets using a Specord IR-75 instrument (Table 1). PMR spectra were recorded on a JNM 4-100 using HMDS as internal standard. Mass spectra were taken on a Varian MAT-311A instrument with direct introduction of the sample into the ion source at an ionization energy of 70 eV and chamber temperature of 180°C. Melting points were taken using a Boetius hot stage.

Compounds Ia-*l* were obtained as in [5-7]. Elemental analytical data for C, H, and N agreed with that calculated.

3-Methyl-5-cyanoacetyl-6-aminouracil (IIa, $C_8H_8N_4O_3$). A mixture of Ia (3.53 g, 25 mmoles), cyanoacetic acid (2.55 g, 30 mmoles), acetic anhydride (10 ml), and pyridine (1 ml) was stirred for 3 h at 60-65°C, cooled to 20°C, poured into water (20 ml), and the precipitate filtered, dried, and recrystallized from DMF to give IIa (3.64 g, 70%) with mp >300°C. IR spectrum: 1760 (C=O), 2250 (CN), 3210, 3450 cm^{-1} (NH_2). PMR spectrum (DMSO-D_6): 3.06 (3H, s, CH_3); 4.28 (2H, s, CH_2); 6.28 (1H, s, NH_2); 11.10 ppm (2H, br. s, NH, NH_2). Mass spectrum, m/z*: M^+ 208 (50).

1-Phenyl-5-cyanoacetyl-6-aminouracil (IIg, $C_{13}H_{10}N_4O_3$). Compound Ig (7 g, 34.5 mmoles) was added to a mixture of cyanoacetic acid (6 g, 71 mmoles) and acetic anhydride (21 ml, 243 mmoles) which had been heated to 80°C. The product was held for 1 h at this temperature, cooled to 20°C, diluted with water (20 ml), stirred for 1 h, and the precipitated solid filtered, washed with water and acetone, and dried to give IIg (8.7 g, 93%) with mp 298-299°C (from DMF). IR spectrum: 3050, 3150, 3200, 3433 (NH, NH_2), 1617, 1667, 1740 (C=O), 2273 cm^{-1} (CN). PMR spectrum (DMSO-D_6): 4.36 (2H, s, CH_2); 7.30-7.65 (5H, m, C_6H_5); 7.15 (1H, s, NH_2); 11.12 (1H, s, NH); 10.42 ppm (1H, s, NH_2).

Compounds IIb-k were prepared similarly to IIa and IIg (Table 1).

5-Cyanoacetyl-6-aminouracil (III, $C_7H_6N_4O_3$). Phosphorus oxychloride (1.10 g, 7 mmoles) was added with stirring to a mixture of II (2.54 g, 20 mmoles), cyanoacetic acid (2.13 g, 25 mmoles), and DMF (15 ml) such that the temperature did not exceed 40°C. The reaction mass was held at 50-60°C for 1.5 h, cooled to 20°C, and the precipitate filtered off and dried to give III (3.7 g, 96%) with mp >300°C (from acetic acid). IR spectrum: 1710 (C=O), 2250 (CN), 3200, 3460 cm^{-1} (NH_2). PMR spectrum (DMSO-D_6): 4.42 (2H, s, CH_2); 6.22 (2H, s, NH_2); 10.10 (1H, br.s, NH); 10.80 ppm (1H, br.s, NH). Mass spectrum, m/z: M^+ 194 (50).

1,3-Dimethyl-7-amino-8H-pyrido[2,3-d]pyrimidine-2,4,5-trione (IIIc, $C_9H_{10}N_4O_3$). A. IIc (11.1 g, 50 mmoles) was added with stirring to a solution of sodium (2.3 g, 100 mmoles) in ethanol (100 ml). The product was refluxed for 1 h, cooled to 20°C, neutralized with aqueous acetic acid (3%, 200 ml), and filtered to give a quantitative yield of IIIc (11.1 g) as colorless crystals with mp >300°C (from ethanol). IR spectrum (in Vaseline mull): 3240, 3350, 3450 cm^{-1} (NH, NH_2). PMR spectrum (CF_3COOH): 3.53 (3H, s, CH_3); 3.78 (3H, s, CH_3); 6.15 ppm (1H, s, CH). Mass spectrum, m/z: M^+ 222 (100).

*I_{rel} (% of I_{max}).

B. A mixture of IIc (4.44 g, 200 mmoles) in aqueous sodium hydroxide (40%, 10 ml) was triturated to formation of a homogeneous mass, stirred for 1 h, neutralized with acetic acid (3%, 80 ml), and the precipitate filtered. The product (4.44 g) was identical in all characteristics to compound IIIc obtained by method A.

Pyrido[2,3-d]pyrimidines (IIIa, b, d-h, k, *l*) (Table 1) were obtained by one of the above-mentioned methods.

LITERATURE CITED

1. A. D. Broom, J. L. Shim, and G. L. Anderson, *J. Org. Chem.*, **41**, 1095 (1976).
2. N. M. Smirnova, L. F. Linbert, V. M. Nesterov, and T. S. Safonova, *Khim. Geterotsikl. Soedin.*, No. 4, 537 (1978).
3. N. M. Smirnova, N. M. Cherbantseva, V. M. Nesterob, and T. S. Safonova, USSR Author's Certificate No. 716,279; *Byul. Izobr.*, No. 36, 260 (1987).
4. J. L. Shim, R. Niess, and A. D. Broom, *J. Org. Chem.*, **37**, 578 (1972).
5. V. Papesch, *J. Org. Chem.*, **16**, 1879 (1951).
6. E. Taylor, *J. Org. Chem.*, **30**, 655 (1965).
7. V. M. Nesterov, *Khim. Geterotsikl. Soedin.*, No. 1, 390 (1967).

SYNTHESIS OF HYDROXYISOXAZOLIDINES ON THE SURFACE OF ADSORBENTS

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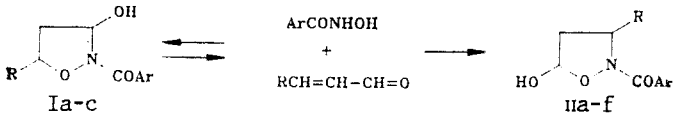
UDC 547.786.1:541.183.2'127

The reaction of arylhydroxamic acids with α, β-unsaturated carbonyl compounds on the surface of adsorbents without a solvent leads, depending on the properties of the adsorbent, to the formation of 2-aroyl-3-hydroxyisoxazolidines and/or 2-aroyl-5-hydroxyisoxazolidines. Reactions on the surface of silica gel and di- and triethylaminoethylcellulose proceed regioselectively.

It has been previously shown [1-4] that the reaction of hydroxamic acids with α, β-unsaturated carbonyl compounds in solution proceeds with the formation of 3- and/or 5-hydroxyisoxazolidines, depending on the character of the substituent in the hydroxamic acid. The aim of our research was to search for methods for the regioselective synthesis of hydroxyisoxazolidines that are independent of the structure of the hydroxamic acid. A new method, viz., reaction on the surface of adsorbents without a solvent [5-8], which makes it possible to increase the selectivity of the process and the yield of the product vis-à-vis shortening of the reaction time, has recently been used successfully for synthetic purposes.

We investigated the reaction of arylhydroxamic acids with α,β-unsaturated carbonyl compounds on the surface of various adsorbents.



Ia-c IIa-f

It has been previously shown [8] that a ratio of the masses of the reagents and the adsorbent (SiO_2) from 1:10 to 1:20 is the optimum ratio for intermolecular condensation reactions, and we therefore selected a charge of 10% for all of the adsor-

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 976-979, July, 1990. Original article submitted December 21, 1988.