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SYNTHESIS OF 2-(3-HYDROXYACETONYL)MALONIC ALDEHYDE AND ITS DERIVATIVES. THEIR REACTIONS WITH 5-AMINOTETRAZOLE

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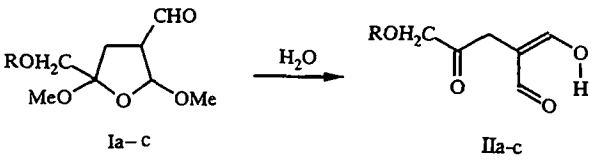
2-(3-Hydroxyacetonyl)malonic aldehyde and its derivatives were prepared for the first time by the hydrolysis of 2-substituted 2,5-dimethoxy-4-formyltetrahydrofuranes. Their interaction with 5-aminotetrazole gave functionally substituted 6-tetrazolo[1,5-a]pyrimidines.

We recently reported on the synthesis and properties of a series of tetrahydrofurane aldehydes, α-substituted β-formyl-2,5-dimethoxytetrahydrofuranes [1]. In a continuation of this study we show that compounds of this can be hydrolyzed to derivatives of malonic aldehyde. For example, 2-hydroxymethyl-4-formyl-2,5-dimethoxytetrahydrofurane and the corresponding methyl ether and acetate (Ia-c) hydrolyzed to give the previously unknown 2-(3-hydroxyacetonyl aldehyde (IIa) and its derivatives (IIb, c) in practically quantitative yield:



Ia–c IIa-c

Ia, IIa R = H; Ib, IIb R = Me; Ic IIc R = MeCO

Compounds II are yellowish oily liquids, unstable on prolonged storage. They are completely enolized in solution according to their ^{1}H NMR spectra. The aldehyde protons are chemically equivalent and appear as a singlet at 8.26-8.42 ppm which is approximately equal to the average of the chemical shifts for olefinic protons and the proton of the formyl group. Similar values were observed for the aldehydic protons of malonic and methylmalonic aldehydes [2]. The methylene protons appear as a singlet at 3.15-3.37 ppm. The IR spectra of compounds II contain strong bands at 1730 cm^{-1} (keto group), 1645 cm^{-1} (CH=O) and 1610 cm^{-1} (C=C), and there is also a broad band with a maximum at 3000 cm^{-1} (C–H). In addition the spectrum of compound IIa contains a hydroxyl absorption at 3350 cm^{-1} while that of compound IIc has an ester absorption at 1745 cm^{-1}.

2-(3-R-hydroxyacetonyl)malonic aldehydes (IIa-c) underwent cyclocondensation with 5-aminotetrazole to give 6-(3-R-hydroxyacetonyl)tetrazolo[1,5-*a*]pyrimidines (IIIa-c) in 51-59% yield. The reaction was carried out by boiling equimolar amounts of the starting materials in 1,4-dioxane.

It might be expected, starting from the structures of the 2-(3-R-hydroxyacetonyl)malonic aldehydes II, which contain 1,3 and 1,4-dicarbonyl units, that the cyclocondensation would be of (4 + 1) type. However that reaction did not occur under these conditions.

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TABLE 1. Characteristics of the 2-(3-R-Hydroxyacetonyl)malonic Aldehydes IIa-c

Compound	Found, %		Molecular formula	Calculated, %		R_f (1:4 methanol–benzene)	IR spectra, ν, cm^{-1}	Mass spectra, *m/z* (I_{rel})
	C	H		C	H			
IIa	49,85	5,62	$C_6H_8O_4$	50,00	5,59	0,23	3350, 3000, 1730, 1645, 1610	126 $[M-H_2O]^+$ (12), 98(5), 83(10), 69(22), 42(100), 39(89)
IIb	53,22	6,32	$C_7H_{10}O_4$	53,16	6,37	0,29	3000, 1730, 1645, 1610	150 $[M-H_2O]^+$ (8)
IIc	51,62	5,38	$C_8H_{10}O_5$	51,61	5,41	0,58	3000, 1745, 1730, 1645, 1610	168 $[M-H_2O]^+$ (8), 158(6), 140(13), 99(45), 43(100), 39(30)

TABLE 2. ^1H and ^{13}C NMR Spectra of 2-(3-R-Hydroxyacetonyl)malonic Aldehydes IIa-c ($CDCl_3$, δ, ppm)

Compound	^1H NMR spectra				^{12}C NMR spectra				
	CHO, s	OH, br s	CH_2, s	CH_2OR	CHO	*tert*-C	CH_2	CO	CH_2OR
IIa*	8,42	—	3,29	4,38 s	183,1	116,5	31,6	210,5	67,4
IIb	8,26	9,8	3,15	4,0 s, 3,43 s	180,4	115,3	31,1	205,8	74,5, 66,4
IIc	8,37	7,7	3,37	4,72 s, 2,11 s	180,1	115,3	32,1	201,0	170,5, 67,8, 20,2

*Spectrum recorded in D_2O. Compound IIa is insoluble in chloroform.

TABLE 3. Characteristics of 2-(3-R-Hydroxacetonyl)tetrazolo[1,5-*a*]pyrimidines IIIa-c

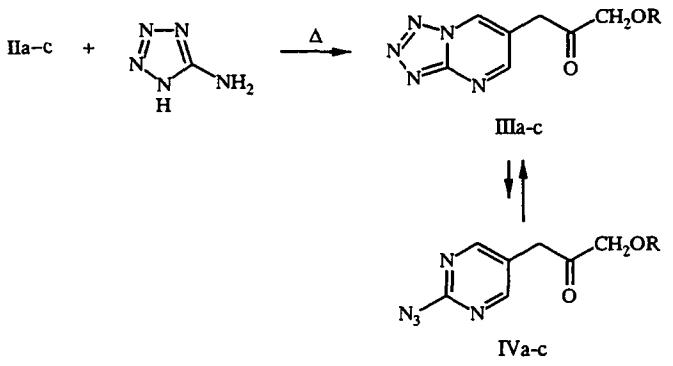
Compound	Molecular formula	(Found, %) (Calculated, %)			mp, °C (from ethanol)	Mass spectra, *m/z* (I_{rel})	Yield, %
		C	H	N			
IIIa	$C_7H_7N_5O_2$	43,55 / 43,53	3,61 / 3,65	36,20 / 36,26	132...133	193 $[M]^+$ (18), 134(22), 107(36), 79(61), 59(18), 53(100), 43(32), 39(59)	51
IIIb	$C_8H_9N_5O_2$	46,35 / 46,38	4,42 / 4,38	33,69 / 33,80	84...85	207 $[M]^+$, 179	52
IIIc	$C_9H_9N_5O_3$	45,91 / 45,96	3,90 / 3,86	29,77 / 29,78	98...99	235 $[M]^+$ (5), 165(30), 134(18), 101(52), 79(39), 73(75), 53(50), 43(100)	59

The ^1H NMR spectra of DMSO-D_6 solutions of the tetrazolo[1,5-*a*]pyrimidines III contained signals of the aromatic protons of the pyrimidine ring at weak field with chemical shifts of 9.0-9.05 and 9.55-9.60 ppm and four bond coupling constants of 2.3 Hz. There was also a low intensity singlet at 8.50-8.54 ppm which related to two chemically equivalent aromatic protons of the 5-substituted 2-azidopyrimidines IV, formed by the reversible rearrangement III ⇄ IV in solution.

The azide-tetrazole rearrangement is characteristic of structures containing a condensed tetrazole ring and is a special case of ring-chain tautomerism [3]. The azide-tetrazole ratio depends on a number of factors: nature of the solvent, temperature, types of substituent in the molecule. The ratio can be estimated from the relative intensities of the corresponding signals of the aromatic protons in the ^1H NMR spectrum. In highly polar aprotic solvents the equilibrium normally shifts strongly towards the tetrazole [4-6]. DMSO-D_6 solutions of compounds III at room temperature contain 7-12% IV. On dilu-

TABLE 4. Spectroscopic Characteristics of 2-(3-R-Hydroxacetonyl)tetrazolo[1,5-*a*]pyrimidines IIIa-c

Compound	^{1}H NMR spectrum (DMSO-D_6), δ, ppm					IR spectrum, ν, cm^{-1}	UV spectrum (in ethanol), λ_{max}, nm (ε)
	5-H, d, J = 2,3 Hz	7-H, d, J = 2,3 Hz	4,6-H, S (in azide IV)	CH_2, S	CH_2OR		
IIIa	9,03	9,55	8,50	4,03	5,4 br.. s, 4,40 s	3350, 1720, 1640, 1500	210(10400), 150(10200), 276(3640)
IIIb	9,05	9,52	8,54	4,22	4,28 s, 3,42 s	1720, 1640, 1500	208(10350), 247(10200), 280(3620)
IIIc	9,00	9,60	8,53	4,98 s	4,14 s, 2,12 s	1740, 1720, 1640, 1500	207(17800), 247(11800), 278(4000)



IIa–IVa R = H; IIb–IVb R = Me; IIc–IVc R = MeCO

tion with deuteroacetone the relative intensity of the signal at 8.5 ppm increased indicating shift of the equilibrium towards the azide IV on decreasing the polarity of the solvent.

The tetrazoles IIIa-c were isolated in pure form. Their IR spectra did not contain a band in the region of 2100-2200 cm^{-1}, characteristic of the azide group.

EXPERIMENTAL

NMR Spectra were recorded with a Bruker AC-200P machine (^{1}H 200.13, ^{13}C 50.32 MHz) with TMS as internal standard. IR Spectra of KBr disks were recorded with a UR-20 spectrometer. Mass spectra were obtained with a Finnigan MAT INCOS-50 machine (70 eV). UV Spectra of ethanolic solutions were recorded with a Specord UV-Vis instrument. The course of reaction and the purity of substances synthesized were monitored by TLC using Silufol UV-254 strips.

The 2,5-dimethoxy-4-formyltetrahydrofurane starting materials Ia-c were prepared as previously described [1].

2-(3-R-Hydroxyacetonyl)malonic Aldehydes (IIa-c). The corresponding 2,5-dimethoxy-4-formyltetrahydrofurane (Ia-c, 10 mmol) was heated in water (5 ml) until the starting material was consumed (TLC). The solvent was then evaporated in vacuum and the residue dehydrated azeotropically with dry benzene to give 96-98% of compound II.

Tetrazolo[1,5-*a*]pyrimidines (IIIa-c). The corresponding malonic aldehyde (II, 5 mmol) and 5-aminotetrazole monohydrate (5 mmol) were boiled in 1,4-dioxane (9 ml) for 2 h. The mixture was cooled, the solvent evaporated in vacuum, and the residue recrystallized from ethanol.

Yields and physicochemical characteristics of the compounds synthesized are given in Tables 1-4.

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