SYNTHESIS AND SOME DERIVATIVES OF 2-CYANO-1, 3-CYCL OHEXANEDIONES

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Of the cyclic 2-cyano-1, 3-diketones the 2-cyano-4-cyclopentene-1, 3-dione derivatives are known [1], including 1,3-indandione [1,2]. The 2-cyano-1-cycloalkanones belonging predominantly to the cyclohexane series are known more extensively. Their methods of synthesis reduce mainly to the following: 1) reaction of alkali metal cyanides with α -halocycloalkanones [3]; 2) hydrolysis of the 1-amino-2-cyanocycloalkenes that are obtained by the cyclization of α , ω -dinitriles employing the Thorp-Ziegler method [4], or by the reaction of halo cyanides [5] or organic cyanates [6] with enaminocycloalkanes; 3) cleavage by strong bases of the cycloalkan[1, 2-d] isoxazoles that are obtained by the reaction of NH₂OH with α -formylcycloalkanones [7]. However, a limitation of these methods is the use of either difficultly available or highly poisonous compounds, or else the low overall yield of the final product.

A method for the preparation and some of the properties of the previously unknown 2-cyano-1, 3-cyclohexanediones (III) is discussed in the present communication. Similar to the 2-alkyl-1, 3-cyclo-alkanediones, these compounds can find use in the total synthesis of steroids by known schemes [8], and also in the synthesis of various condensed heterocycles [9, 10].

We selected the anilides (I) as the starting materials, which are easily obtained in good yield by the reaction of the ethyl ester of N-phenylformimidic acid and the appropriate cyclic β -diketones [11,13]. With the expectation of accomplishing the transenamination reaction for the (I) compounds, which reaction is characteristic [12, 14] for enaminodiketones, these compounds were treated further with NH₂OH in either methanol or ether. Here in the cases of (Ib and c) we isolated and characterized the unstable hydroxyamino-diketones (IIb and c), the structure of which follows mainly from the physicochemical analysis data. In particular, the NMR spectra (in DMSO-d₆) testify to the presence of two protons that rapidly exchange with deuterium and one olefinic proton: δ 8.09 ppm for (IIb) and 8.24 ppm for (IIc). The choice of one of several possible tautomeric forms in favor of the enaminodiketones (II) was made on the basis of analyzing the spectra of the methylene protons of the ring. For example, in the case of (IIb), the same as in the starting anilide (Ib) [15], the spectrum has the form of a slightly broadened four-proton single signal at δ 2.28 ppm, which evidently testifies in support of the more symmetrical (cf. [16]) enaminodicarbonyl form and the absence of a substantial contribution by the hydroxyimino tautomer containing an enolized keto group. Besides this, the data of the IR spectra indicate the presence of a stable intramolecular hydrogen bond of the chealate type in compounds (IIb and c).

We also obtained enaminodiketone (IIb) by an independent route from 2-formyldimedon [17] and NH_2OH . Undoubtedly, the use of the readily available and stable anilides (I) as the starting products: (Scheme 1), instead of the unstable and difficultly available [17] 2-formyl-1, 3-cyclohexanediones, greatly simplifies the synthesis of the desired diketo cyanides (III). Their availability is increased by the ease with which the hydroxylamino derivatives (II) are dehydrated. It could be postulated in advance that this dehydration will lead either to the intermediate 4-oxo-4, 5, 6, 7-tetrahydrobenz[1, 2-d]-isoxazoles [18] or directly to the nitriles (III). As it proved, the latter are the sole reaction products independent of the reaction conditions: thermal dehydration (method A), dehydration in the presence of acids (method B), or under the influence of acetic anhydride (method C). Bases can also catalyze the dehydration. Thus, the treatment of the dihydroresorcinol anilide (Ia) with a slight excess of NH_2OH makes it possible to accomplish the one-step synthesis of cyanide (IIIa) in good yield, without isolating the unstable intermediate hydroxyamine (IIa). The exclusive formation of the diketonitriles (III) is probably associated with their more favorable energy characteristics (especially the ionized form) when compared with the benzisoxazoles, which were not detected in a single case.

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Scheme 1

The cyanodiketones (III) are colorless crystalline compounds, which are completely enolized in the solid state ($\nu_{C=O}$ 1620-1640, $\nu_{C=N}$ 2230-2240 cm⁻¹), with a definite intermolecular association. The diketo form is detected in nonpolar media; for example, the IR spectrum of (IIIb) in CHCl₃ has the bands of $\nu_{C=O}$ at 1720 and 1740 cm⁻¹. This same diketo cyanide (IIIb) is a strong acid ($p_{K_{aH,O}}$ 3.0), and is completely dissociated in 10⁻⁴ M alcohol solution, as is evidenced by the same UV absorption of the alcohol solution, irrespective of whether they are neutral or contain either acid or base. The NMR spectra of the cyanides (III) (in CD₃COCD₃) contain the signals of the protons of all of the structural elements of the corresponding molecules in the expected regions, in which connection the enolic proton, which easily undergoes deuterium exchange, is located in the 7.0-7.5 ppm region. The existence of the symmetrical enolized structures of (III) in solution also follows from the equivalence of the methylene protons at C₄ and C₆, which are detected for example, in the spectrum of the dimedon derivative (IIIb) as a narrow singlet at 2.38 ppm. The structure of the (III) compounds was corroborated by the data of the chemical study. The known [19] carbamido-dimedon (VII) was obtained when diketonitrile (IIIb) is heated with H₂SO₄; the refluxing of the cyanodiketones (III) in orthoformic ester leads, the same as in the series of the 1,3-cyclohexandiones [20], to the formation of the ethers of enols (IV), which are easily hydrolyzed to the starting products (III). Besides this, by refluxing hydroxyamine (IID). The structure of the obtained compounds was confirmed by the data of the NMR spectra, and also by those of the IR spectra, which contain three characteristic bands; $\nu_{C=C}$ 1575-1585, $\nu_{C=O}$ 1655-1670 and $\nu_{C=N}$ 2220-2230 cm⁻¹.

The vinylog cyanoethers (IV), being polyfunctional compounds, represent independent synthetic interest [10]. We studied their behavior in the reactions with various nucleophiles. In particular, the treatment of the (IV) ethers with amines gave the corresponding α -cyano- β -aminovinyl ketones (Va-i) in high yields (Table 1). The direct enamination of the cyanodiketones (III) is very difficult in view of the stability of the formed intermediate ammonium salts; for example, the benzylammonium salt (VI) could not be converted to the enaminoketone (Vd). The structure of the vinylog amides (V) is confirmed by the data of the IR spectra (see Table 1), which contain a characteristic set of bands in the 1520-1630 and 2200-2210 cm⁻¹ regions. Besides this, compounds (Vb-d), in contrast to the related 3-amino-2-acetyl-2-cyclohexen-1ones [21], have distinct absorption in the 3100-3300 cm⁻¹ region, which testifies to the presence of unassociated NH groups in these molecules. The latter additionally follows from the NMR spectra of enamines (Vc and d), which possess (cf. [22]) a broad signal at ~6.9 ppm from the NH proton, which is found in spin -spin coupling with the protons of the adjacent methylene group. Finally, the transoid enaminoketo chromophore, present in the (V) molecules, appears in the UV spectra (see Table 1) as an intense band at ~300 nm (cf. [21]), which exhibits bathochromic shift in the series of tertiary enaminoketones (Vf-h) with increase in the size of the heterocycle.

EXPERIMENTAL METHOD

The melting points were determined on a Kofler block. The IR spectra as KBr pellets were measured on a UR-10 instrument, while the UV spectra of the alcohol solutions were measured on a recording Unicam SP-700 spectrophotometer. The NMR spectra were taken on a Varian DA-60 spectrometer using HMDS as the internal standard.

<u>2-Cyano-1, 3-cyclohexanedione (IIIa)</u>. A solution of 7 g of anilide (Ia) [12,13] and 1.6 g of NH₂OH in 0.8 liter of absolute ether was allowed to stand for a week at ~20°, after which the obtained precipitate was recrystallized from THF. We obtained 2.2 g (50%) of nitrile (IIIa) with mp 208.5-210° (sublimes). C 61.09; H 5.16; N 10.05%. C₇H₇NO₂. Infrared spectrum (ν , cm⁻¹): 1590, 1635, 1660, 2240, 2800-3200. Ultraviolet spectrum (λ_{max} , nm): 236 (ϵ 6940); 273 (ϵ 15400).

	а Шт(в)	'max,	236 (5700) 238 (5700)	226 (6570) 226 (6570)	228 (5920) 228 (5920) 288 (24500)	232 (4950)	232 (7800) 232 (7800)	237 (5500) 237 (5500)	237 (5500) 302 (21200)	237 (5100) 306 (27000)	236 (8300) 300 (24300)
	v, cm ⁻¹		1537, 1630, 2200	1540, 1600, 1629, 33200, 33200, 332000, 33200, 33200, 33200, 33200, 332000, 332000, 33200, 33200, 33200, 332000, 332000, 332000, 332000, 332000, 332000, 332000, 332000, 332000, 332000, 332000, 332000, 332000, 3320000, 3320000000000	1545, 1590, 1620, 2200, 3400, 3270	1519, 1552, 1595,	1543, 1588, 1610,	1540, 1625, 2203	1535, 1630, 2200	1555, 1630, 2200	1542, 1625, 2205
	Calculated, %	N	14,73	17,06	12,72	11,02	10,14	13,72	12,83	12,06	10,52
		н	7,42	7,37	9,15	7,13	10, 21	7,90	8,31	8,68	6,81
		U	69,44	65,83	70,87	75,56	73,86	70,56	71,52	72,38	76,66
	Empirical formula		$C_{11}H_{14}N_{2}O$	$C_9H_{12}N_2O$	$C_{13}H_{20}N_2O$	$\mathrm{C_{16}H_{18}N_{2}O}$	$C_{17}H_{28}N_2O$	$C_{12} H_{16} N_2 O$	$C_{13}H_{18}N_2O$	$\mathrm{C}_{14}\mathrm{H}_{20}\mathrm{N}_{2}\mathrm{O}$	$C_{17}H_{18}N_{2}O$
	Found, η_0	z	14,90	17,12	12,79	11,12	10, 12	13,58	12,92	11,91	10,31
		н	7,64	7,30	9,07	7,01	10,06	7,98	8,34	8,73	6,98
		ບ ບ	69,64	66,10	70,83	75,42	73,67	70,30	71,80	72,54	76,46
	Mp, °C (solvent)		145,5—146 (THF)	242—243 (EtOH)	122,5—123 (PhH)	220-221 (PhH)	128—129(THF	170-171,5 (PhH)	216-217 (THF	165-166 (PhH $165-166$ (PhH	233-234 (THF - hexane)
	Yield, %		87	85	67	95	90	95	95	60	67
	R ² , R ³		(CH ₂) ₄	Н, Н	H, n-Bu	H, CH ₂ Ph	<i>n</i> -Bu, <i>n</i> -Bu	-(CH ₂) ₃ -	(CH ₂) ₄	-(CH ₂) ₅ -	$-(CH_2)_{4}-$
	R1		н	Me	Me	Me	Me	Me	Me	Me	Ч
	24		н	Me	Me	Me	Me	Me	Me	Me	н
	Com-	punod	(Va)	(dV)	(Vc)	(bV)	(Ve)	(Vf)	(Vg)	(dV)	(Vi)

TABLE 1. 3-Amino-2-cyano-2-cyclohexen-1-ones (V)

2-Hydroxyaminomethylene-5, 5-dimethyl-1, 3cyclohexanedione (IIb). A solution of 5 g of anilide (Ib) [13] and 2.9 g of NH₂OH · HCl in 120 ml of MeOH was treated with an equivalent (based on the HCl) amount of 10% NaOH solution and then allowed to stand for 3 days at ~20°. Then the reaction mixture was concentrated in vacuo to 1/4 of the starting volume, diluted with 100 ml of water, extracted with ether (to remove the formed aniline) and then acidified with 15% HCl solution to pH 1-2 and extracted with CHCl₃. After the usual workup and recrystallization of the product from THF we obtained 3.1 g (80%) of hydroxyamine (IIb) as colorless plates with mp 134-135° (decompn.) C 58.89; H 7.23; N 7.49%. C₉H₁₃NO₃. Infrared spectrum (ν , cm⁻¹): 1570, 1650, 3120-3220.

A solution of 3.0 g of 2-formyldimedon [17] and 1.25 g of NH₂OH ·HCl in 30 ml of MeOH was treated with an equivalent (based on the HCl) amount of 10% NaOH solution and allowed to stand for 3 days at ~20°. Then the mixture was diluted in half with water, acidified with 15% HCl solution to pH 1-2, and extracted with CHCl₃. After the usual workup we obtained 2.6 g (80%) of hydroxyamine (IIb) with mp 134-135° (decompn.) (from THF), which was identical with the above described sample.

 $\frac{2-\text{Hydroxyaminomethylene-5-phenyl-1, 3-cyclo-}}{\text{hexanedione (IIc)}. To a solution of anilide (Ic) [13] in 60 ml of MeOH was added a solution of 0.48 g of NH₂OH in 5 ml of water (obtained by the neutralization of 0.8 g of the hydrochloride with 10% NaOH solution), after which the mixture was refluxed for 2.5 h, allowed to stand at ~20° for 12 h, and then it was diluted in half with water, extracted with ether, acidified with 15% HCl solution to pH 1-2, and extracted with CHCl₃. After the usual workup and recrystallization of the product from THF we obtained 0.7 g (85%) of hydroxyamine (IIc) as colorless plates with mp 138-139°. C67.43; H 5.52; N 6.38%. C₁₃H₁₃NO₃. Infrared spectrum(<math>\nu$, cm⁻¹): 1560, 1590, 1648, 3050-3140.

2-Cyano-5, 5-dimethyl-1, 3-cyclohexanedione (IIIb). Method A. Using a water-jet pump, 3.1 g of hydroxyamine (IIb) was heated at 140° (in the bath) for 1-2 min sufficient to solidify the initially formed melt, and then it was cooled rapidly and the product was recrystallized from THF. We obtained 2.5 g (90%) of nitrile (IIIb) with mp 220-222° (sublimes). C 65.13; H 6.86; N 8.52%. C₉H₁₁NO₂. Infrared spectrum (ν , cm⁻¹): 1590, 1653, 2235, 2800-3200. Ultraviolet spectrum (λ_{max} ,nm): 232 (ϵ 7560); 270 (ϵ 20500).

Method B. A solution of 1.2 g of hydroxyamine (IIb) in 20 ml of benzene was heated in the presence of a catalytic amount of TsOH until water failed to collect in the Dean-Stark trap, after which the mixture was evaporated in vacuo and the residue was recrystallized from THF. We obtained 0.8 g (75%) of nitrile (IIIb) with mp 220-222° (sublimes), which was identical with the above described sample.

Method C. A solution of 1.0 g of hydroxyamine (IIb) in 5 ml of Ac_2O was refluxed for 1 h, after which it was evaporated in vacuo, and the residue was treated with hexane and recrystallized from THF. We obtained 0.7 g (80%) of nitrile (IIIb) with mp 220-222° (sublimes), which was identical with the above described sample.

2-Cyano-5-phenyl-1,3-cyclohexanedione (IIIc). Using method B, hydroxyamine (IIc) was converted in 50% yield to nitrile (IIIc), which was obtained as colorless plates with mp 221-222° (sublimes) (from THF). C 73.03; H 5.15; N 6.51%. $C_{13}H_{11}NO_2$. Infrared spectrum (ν , cm⁻¹): 1540, 1620, 1655, 2229, 2800-3200.

Benzylamine Salt of 2-Cyano-5, 5-dimethyl-1, 3-cyclohexanedione (VI). A solution of 0.6 g of cyanodiketone (IIIb) and 0.4 ml of benzene was refluxed for 30 min, evaporated in vacuo, and the residue was recrystallized from THF. We obtained 0.85 g (85%) of salt (VI) as colorless needles with mp 193.5-194.5°. C 70.36; H 7.55; N 10.35%. $C_{16}H_{20}N_2O_2$. Infrared spectrum (ν , cm⁻¹): 1510, 1595, 1628, 1664, 2194, 2600-3200. Ultraviolet spectrum (λ_{max} ,nm): 232 (ϵ 8200); 272 (ϵ 224400).

<u>Hydrolysis of Nitrile (IIIb)</u>. A solution of 0.5 g of (IIIb) in 10 ml of conc. H_2SO_4 was heated at 50-60° for 1 h, poured into ice water, and the obtained precipitate was recrystallized from ether. We obtained 0.35 g (60%) of amide (VII) with mp 144-145°, which failed to depress the mixed melting point with an authentic sample of (VII) [19].

<u>2-Cyano-3-ethoxy-2-cyclohexen-1-one (IVa)</u>. Cyanodiketone (IIIa) (0.5 g) was dissolved in 8 ml of boiling $HC(OEt)_3$, refluxed for another 15-20 min, evaporated in vacuo, and the residue was recrystallized from THF. We obtained 0.4 g (65%) of ether (IVa) as colorless prisms with mp 125-126°. C 65.26; H 6.61; N 8.29%. $C_9H_{11}NO_2$. Infrared spectrum (ν , cm⁻¹): 1585; 1668; 2232.

In a similar manner, from cyanide (IIIb) we obtained an 80% yield of 2-cyano-3-ethoxy-5,5-dimethyl-2-cyclohexen-1-one (IVb) with mp 156-157° (from THF). C 68.02; H 7,79; N 7.48%. $C_{11}H_{15}NO_2$. Infrared spectrum (ν , cm⁻¹): 1582, 1666, 2225. Ultraviolet spectrum (λ_{max} , nm): 270 (ϵ 15900).

The refluxing of a solution of 1.1 g of hydroxyamine (IIIb) in 10 ml of orthoester for 1.5 h gave 0.92 g (80%) of ether (IVb) with mp 156-157° (from THF), which was identical with the above described sample.

Similar to (IIIa and b), cyanodiketone (IIIc) was converted in ~80% yield to 2-cyano-3-ethoxy-5-phenyl 2-cyclohexen-1-one (IVc) with mp 156.5-157.5° (from THF). C 74.89; H 6.46; N 5.57%. C₁₅H₁₅NO₂. Infrared spectrum (ν , cm⁻¹): 1576, 1655, 2219. Ultraviolet spectrum (λ_{max} , nm): 269 (ϵ 14900).

<u>Hydrolysis of Ether (IVb)</u>. To a solution of 0.3 g of (IVb) in 10 ml of MeOH was added 0.5 ml of conc. HCl, after which the mixture was refluxed for 1 h, evaporated in vacuo, and the residue was recrystallized from THF. We obtained 0.24 g (~95%) of diketo cyanide (IIIb) with mp 220-222° (sublimes), which was identical with an authentic sample.

The synthesis of the 3-amino-2-cyano-2-cyclohexen-1-ones (V) listed in Table 1 was accomplished by treating either alcohol or benzene solutions of the appropriate (IV) ethers with amines as described in [21].

CONCLUSIONS

1. A method was developed for the synthesis of 2-cyano-1,3-cyclohexanediones by the transenamination of the readily available 2-phenylaminomethylene-1,3-cyclohexanediones with hydroxylamine and subsequent dehydration of the intermediate 2-hydroxyaminomethylene derivatives.

2. The ethers of the enols of the 2-cyano-1,3-cyclohexanediones were obtained and a study was made of their reaction with amines.

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