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SYNTHESIS AND REACTIONS OF ESTERS OF 3-CYANO-2-OXO-5,6-TRI(TETRA)METHYLENE-1,2-DIHYDROISONICOTINIC AND 2-AMINO-3-ETHOXYCARBONYL-5,6-TRI(TETRA)-METHYLENEISONICOTINIC ACIDS

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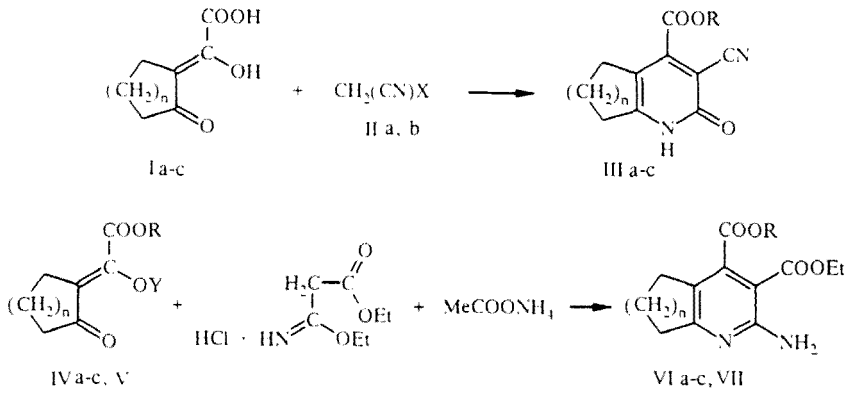
Esters of 3-cyano-2-oxo-5,6-tri(tetra)-methylene-1,2-dihydroisonicotinic and 2-amino-3-ethoxycarbonyl-5,6-tri(tetra)methyleneisonicotinic acids have been obtained by the reaction of 2-oxocyclopentyl(hexyl)glyoxylic acid esters with malonic acid derivatives. Boiling the esters containing a tetramethylene ring with 75% sulfuric acid gave hydrolysis of the ester and cyano groups to carboxyl with subsequent decarboxylation at the 3 position and the formation of 2-oxo-5,6-tetramethylene-1,2-dihydroisonicotinic acid (2-oxo-1,2,5,6,7,8-hexahydroquinoline-4-carboxylic acid).

Derivatives of 3-cyano-2-oxo-5,6-tri(tetra)methylene-1,2-dihydroisonicotinic acids are of interest as starting materials for the synthesis of potentially biologically active compounds [1, 2].

The aim of the present work was to extend the routes of synthesis of these derivatives, and of esters of 2-amino-3-ethoxycarbonyl-5,6-tri(tetra)methyleneisonicotinic acid which are closely related to them, to investigate their properties, and their reaction with acids and ammonia, which have not been studied previously.

It has been shown that the esters of 2-oxocyclopentyl- and 2-oxocyclohexylglyoxylic acid (Ia-c) readily react with malononitrile (IIa) in dioxane at 50°C under conditions of the Michael reaction with the formation of esters of substituted 2-oxo-1,2-dihydroisonicotinic acids (IIIa-c) (see Scheme 1 and Table 1). Compound (IIIb) was also synthesized from cyanoacetamide (IIb) and the methyl ester of 2-oxocyclohexylglyoxylic acid (Ib) on boiling in ethanol. The structures of the products obtained were confirmed by data of PMR and IR spectra (see Experimental section and Table 2).

Scheme 1



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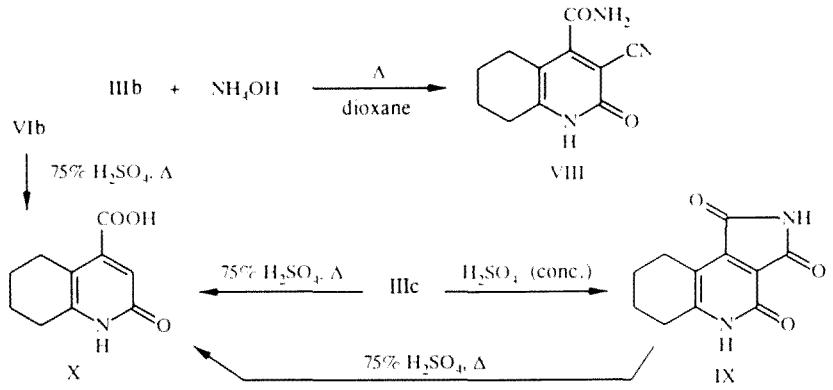

I, III a n = 1, R = Pr-*i*, b n = 2, R = Me, c n = 2, R = Pr-*i*; II a X = CN, b X = $CONH_2$; IV a-c Y = Na; IV, VI a n = 1, R = Pr-*i*, b n = 2, R = Pr-*i*, c n = 2, R = Me; V, VII n = 2, R = Y = H

The sodium salts of esters of 2-oxocyclopentyl(hexyl)glyoxylic acids (IVa-c) and 2-oxocyclohexylglyoxylic acid (V) undergo a Michael reaction with iminomalonic ester hydrochloride and ammonium acetate in alcohol. Esters of substituted isonicotinic acids (VIa-c) or a substituted isonicotinic acid (2-amino-3-ethoxycarbonyl-5,6,7,8-tetra-hydroquinoline-4-carboxylic acid) (VII) are formed respectively. This reaction was not successful between the methyl ester of 2-oxocyclohexylglyoxylic acid, acetylacetic acid anilide, and ammonium acetate, or with cyanoacetic acid ethyl ester or piperidide, probably due to the reduced reactivity of these compounds.

The ester group of the methyl ester (IIIb) underwent aminolysis on boiling in dioxane with a twofold excess of aqueous ammonia with the formation of 3-cyano-2-oxo-5,6-tetramethylene-1,2-dihydroisonicotinic acid amide (3-cyano-2-oxo-1,2,5,6,7,8-hexahydroquinoline-4-carboxamide) (VIII). The nitrile group in the methyl ester (IIIb) was hydrated to amide by the action of concentrated sulfuric acid and underwent intramolecular cyclization with the neighboring ester group with the formation of 1,3,4-trioxo-1,2,6,7,8,9-hexahydro-3H-pyrrolo[2,4-c]quinoline (IX). The analogous intramolecular cyclization was not effected under the conditions of the Radzishevsky reaction [boiling the initial ester (IIIb) with sodium hydroxide in the presence of 10% hydrogen peroxide in ethanol (50 ml) at 100°C], probably due to steric hindrance at the nitrile group. Compound (IX) dissolved readily in alkali.

On boiling the 3-cyanoester (IIIc) in 75% sulfuric acid hydrolysis of the ester and nitrile groups to carboxyl occurred with subsequent decarboxylation at position 3 and the formation of 2-oxo-1,2,5,6,7,8-hexahydroquinoline-4-carboxylic acid (X), previously synthesized by other methods [1]. Under the same conditions the diester (VIb) and compound (IX), containing a pyrrolidinedione fragment, are readily hydrolyzed and decarboxylated, as a result of which acid (X) is also obtained in both cases.

EXPERIMENTAL

The IR spectra were taken on UR 20 and Specord instruments (as Nujol mulls), and PMR spectra on a RYa 2310 spectrometer (60 MHz), the internal standard being HMDS. TLC was effected on Silufol UV 254 plates.

Elemental analysis data for C, H, and N for the compounds synthesized corresponded with calculated values (Table 1).

Esters of 3-Cyano-2-oxo-5,6-tri(tetra)methylene-1,2-dihydroisonicotinic Acids (IIIa-c). A. A solution of ester (Ia-c) (0.1 mole), malononitrile (IIa) (6.6 g, 0.1 mole), and piperidine (0.5 ml) in dioxane (70 ml) was maintained at 50°C for 2 h. The product (IIIa-c) which separated was filtered off and crystallized from ethanol.

B. A solution of ester (Ib) (18.4 g, 0.1 mole), the cyanoacetamide (IIb) (8.4 g, 0.1 mole), and piperidine (0.5 ml) in ethanol (75 ml) was boiled for 1 h. After cooling, the reaction mixture was diluted with water, then acidified with 10% sulfuric acid. The product (IIIb) which separated was filtered off, dried, and crystallized from ethanol. Yield was 17.1 g (74%). IR spectrum: 1630-1660 (CO), 1710-1730 (CO, COOAlk), 2220-2230 (CN), 3290-3310 cm^{-1} (NH).

A mixed melting point for samples of (IIIb) obtained by methods A and B gave no depression of melting point.

Esters of 2-Amino-3-ethoxycarbonyl-5,6-tri(tetra)methyleneisonicotinic Acids (VIa-c). A solution of the sodium salt of (IVa-c) (0.1 mole), iminomalonic ester hydrochloride (19.5 g, 0.1 mole), and ammonium acetate (7.7 g, 0.1 mole) in

TABLE 1. Characteristics of Compounds Synthesized

Compound	Empirical formula	mp, °C	Found, % / Calculated, %			R_f*	Yield, %
			C	H	N		
IIIa	$C_{13}H_{14}N_2O_3$	121...123	63.21 63.41	5.38 5.69	11.09 11.38	0.86	45
IIIb	$C_{12}H_{12}N_2O_3$	215...217	62.23 62.07	5.12 5.17	12.18 12.07	0.91	56†
IIIc	$C_{14}H_{16}N_2O_3$	211...213	64.43 64.62	6.29 6.15	10.46 10.77	0.85	64
VIa	$C_{15}H_{20}N_2O_4$	69...71	61.39 61.64	6.64 6.85	9.34 9.59	0.84	72
VIb	$C_{16}H_{22}N_2O_4$	98...100	62.41 62.75	7.03 7.19	9.14 9.15	0.81	83
VIc	$C_{14}H_{18}N_2O_4$	101...103	65.07 65.12	6.84 6.98	10.71 10.85	0.75	73
VII	$C_{13}H_{16}N_2O_4$	233 (decomp.)	61.22 61.42	6.01 6.30	11.00 11.02	0.97	51
VIII	$C_{11}H_{11}N_3O_2$	227...228	60.67 60.83	5.13 5.07	19.37 19.35	0.77	90
IX	$C_{11}H_{10}N_2O_3$	320...321	60.42 60.55	4.37 4.59	12.66 12.84	0.28	79
X	$C_{10}H_{10}NO_3$	293...296	62.33 62.50	5.08 5.21	14.39 14.58	0.54	50†

*Solvent system: butanol–benzene, 1:1.

†Yield of method A.

TABLE 2. PMR Spectra of Compounds (IIIa-c), (VIa-c), (VII), (VIII), and (X)*

Compound	Chemical shifts, δ, ppm			
	5- and 7-CH_2, m (4H) or 5- and 8-CH_2, m (4H)	6-CH_2, m or 6- and 7-CH_2, m	1-NH, s or 2-CNH_2, br s	Other protons (R, COOEt, $CONH_2$)
IIIa	2.70...3.13	1.90...2.30 (2H)	7.16 (1H)	5.00...5.40 m (CH), 1.30 b ($2CH_3$)
IIIb	2.57...3.03	1.50...1.87 (4H)	7.76 (1H)	3.80 s (CH_3)
IIIc	2.17...2.80	1.50...2.00 (4H)	13.03 (1H)	4.06...4.47 m (CH), 1.25 d ($2CH_3$)
VIa	2.47...2.93	1.81...2.23 (2H)	6.33 (2H)	4.87...5.27 m (CH), 1.25 d ($2CH_3$), 3.93...4.40 m (CH_2), 1.18 d (CH_3)
VIb	2.47...2.93	1.80...2.13 (4H)	6.30 (2H)	4.15...4.26 m (CH), 1.26 t ($2CH_3$), 3.40...4.18 m (CH_2), 1.23 d (CH_3)
VIc	2.18...2.73	1.46...1.83 (4H)	6.93 (2H)	3.77 s (CH_3), 4.03...4.40 m (CH_2), 1.21 t (CH_3)
VII	2.17...2.66	1.41...1.81 (4H)	6.80 (2H)	3.87...4.30 m (CH_2), 1.15 t (CH_3)
VIII	2.33...2.93	1.43...1.90 (4H)	12.46 (1H)	5.16 br. s. ($CONH_2$)
X	2.40...2.90	1.60...2.10 (4H)	5.83 (1H)	6.50 s (CH)

*The spectra of compounds (IIIa-c) and (VIa, b) were taken in $CDCl_3$, and of compounds (VIc), (VII), (VIII), and (X) in DMSO-D_6.

ethanol (150 ml) was boiled for 2 h. The cooled reaction mixture was poured into water, and neutralized with 10% ammonia solution until the medium was alkaline. The precipitated solid product (VIa-c) was filtered off and crystallized from ethanol. The IR spectra of the products (VIa-c) contained characteristic absorption bands in the ranges: 1670-1680, 1720-1740, (CO, COOAlk), 3270-3290, 3480-3500 cm^{-1} (NH_2).

2-Amino-3-ethoxycarbonyl-5,6,7,8-tetrahydroquinoline-4-carboxylic Acid (VII). A solution of 2-oxocyclohexylglyoxylic acid (V) (16.6 g, 0.1 mole), iminomalonic ester hydrochloride (19.5 g, 0.1 mole), and ammonium acetate (7.7 g,

0.1 mole) in 75% ethanol (150 ml) was boiled for 2 h. After cooling, the precipitated solid product (VII) was filtered off, dried, and crystallized from DMF. IR spectrum: 1660 (CO, COOEt), 1740 (CO, COOH), 3260, 3400 cm^{-1} (NH_2).

3-Cyano-2-oxo-1,2,5,6,7,8-hexahydroquinoline-4-carboxylic Acid Amide (VIII). A solution of the methyl ester (IIIb) (2.32 g, 0.01 mole) in dioxane (45 ml) containing 30% aqueous ammonia solution (5 ml) was boiled for 2 h. After cooling and acidifying the medium to neutral, a precipitate of the product (VIII) separated, and was crystallized from ethanol. IR spectrum: 1640 (CO), 1710 (CO, $CONH_2$), 2230 (CN), 3240, 3340, 3410 cm^{-1} (NH and NH_2).

1,3,4-Trioxo-1,2,6,7,8,9-hexahydro-3H-pyrrolo[3,4-c]quinoline (IX). A solution of compound (IIIc) (2.6 g: 0.01 mole) in concentrated H_2SO_4 (40 ml) was maintained at 100°C for 6 h. The cooled reaction mixture was poured into ice–water, the separated product (IX) was filtered off, dried, and crystallized from DMF. IR spectrum: 1650, 1730, 1760 (CO), 3140, 3216 cm^{-1} (NH). PMR spectrum (DMSO-D_6): 1.47-1.77 (4H, t, 7- and 8-CH_2), 2.30-2.70 (4H, t, 6- and 9-CH_2), 7.83 (1H, s, 5-NH), 10.90 ppm (1H, s, 2-NH).

2-Oxo-1,2,5,6,7,8-hexahydroquinoline-4-carboxylic Acid (X). A. A solution of ester (IIIc) (26.0 g, 0.1 mole) in 75% H_2SO_4 (150 ml) was boiled for 5 h. The cooled reaction mixture was poured into cold water (250 ml) and filtered. A 10% aqueous NaOH solution was added to the filtrate until the medium was weakly acidic, the precipitated solid product (X) was filtered off, dried, and crystallized from DMF.

B. The product (X) (1.95 g, 64%) was obtained from the diester (VIc) (3.06 g, 0.01 mole) by the method described above.

C. Product (X) (0.98 g, 43%) was obtained similarly from the tetrahydropyrroloquinoline (IX) (2.18 g: 0.01 mole). Mixed melting points of the samples of compound (X) obtained by methods A-C gave no depression of melting point.

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