UNSATURATED HYDANTOIN DERIVATIVES

XI.* SYNTHESIS AND REARRANGEMENT OF SOME ETHYL ESTERS OF α-SUBSTITUTED HYDANTOIN-$\Delta^{5,\alpha}$-ACETIC ACIDS

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UDC 547.783.07:542.422.25.4.6

α-Substituted (CH_3, C_6H_5, OCH_3, OC_6H_5, Cl, and F) hydantoin-$\Delta^{5,\alpha}$-acetates were obtained from diethyl oxaloacetates and urea, and their 3-methyl derivatives were obtained from N-methylurea or by methylation of the nitrogen-unsubstituted hydantoins with diazomethane; the α-nitro derivative was obtained by nitration of unsubstituted ethyl hydantoin-$\Delta^{5,\alpha}$-acetate with nitric acid in acetic acid, and ethyl hydantoin-$\Delta^{5,\alpha}$-glycolate was obtained from hydantoin and diethyl oxalate. All of the synthesized hydantoin-$\Delta^{5,\alpha}$-acetates, except for the α-nitro and α-hydroxy derivatives, are converted to the corresponding 3- and 5-substituted orotic acids.

Up until now the rearrangement of hydantoin-$\Delta^{5,\alpha}$-acetic acids and their esters to the corresponding orotic acids by the action of aqueous solutions of alkalis has been used only to obtain orotic acid itself [2] and its 3- and 5-alkyl and phenyl derivatives [3-8] and also to synthesize orotic acid with a ^{14}C-labeled carboxyl group [9]. We attempted to use this reaction for the preparation of orotic acids containing various functional groups (NO_2, Cl, F, OAlk, and OAr) in the 5 position of the pyrimidine ring. For this, ethyl hydantoin- and 3-methylhydantoin-$\Delta^{5,\alpha}$-acetates IX-XX (Table 2) were obtained by condensation of urea with the appropriate substituted oxaloacetates (II-VIII, Table 1). The starting β-keto esters were synthesized by condensation of substituted acetates with diethyl oxalate (the condensing agents were sodium hydride, sodium metal, or sodium ethoxide). α-Diethylaminodiethyl oxaloacetate (I) was similarly obtained from

* See [1] for communication X.

TABLE 1. Substituted Diethyl Oxaloacetates (I-VIII)

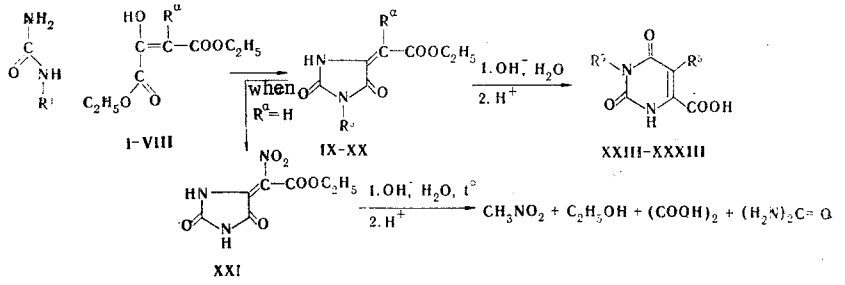
Compound	R	mp, °C (mm)	n_D^{22}	Empirical formula	Found, % C	Found, % H	Calc., % C	Calc., % H
I	NEt_2[a]	—	—	$C_{11}H_{21}NO_5$[b]	55,7	8,3	55,6	8,1
II	OPh	110 (1)	1,5015	$C_{14}H_{16}O_6$	59,7	5,8	60,0	5,8
III	OMe	85 (0,8)	1,4345	$C_9H_{14}O_{16}$	43,4	6,4	49,5	6,5
IV	Ph	97 (1)	1,4880	$C_{14}H_{16}O_5$	63,9	6,0	63,7	6,0
V	Me	117 (12)	1,4316	$C_9H_{14}O_5$	53,6	7,0	53,5	6,9
VI	H	100 (3)	1,4425	$C_8H_{12}O_5$	48,7	6,5	48,5	6,4
VII	F	95 (2)	1,4210	$C_8H_{11}FO_5$[c]	46,7	5,6	46,6	5,4
VIII	Cl	109 (1)	1,4447	$C_8H_{11}ClO_5$[d]	43,4	5,0	43,2	5,0

[a] Mp 92°.
[b] Found, %: N 5.6. Calculated, %: N 5.4.
[c] Found, %: F 9.2. Calculated, %: F 9.2.
[d] Found, %: Cl 15.8. Calculated, %: Cl 16.0.

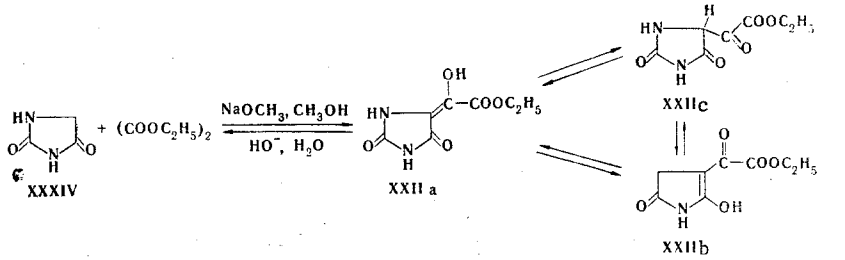
Lensovet Leningrad Technologic Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1527-1535, November, 1974. Original article submitted June 21, 1973; revision submitted December 10, 1973.

N,N-diethylglycine ethyl ester and diethyl oxalate. Its structure was proved by its PMR spectrum (CCl_4 solution), in which signals of two equivalent NC_2H_5 groups [quartet centered at 4.00 ppm (δ), $-2-NCH_2$, J = 8.8 Hz, and triplet near 1.65 ppm, $-2-CCH_3$, J = 8.1 Hz], two different $COOC_2H_5$ groups (doublet of quartets near 4.65 ppm, $-2-OCH_2$, J = 5.0 Hz, two triplets near 1.70 ppm, $-2-CCH_3$, J = 5.0 Hz), and a signal of a hydroxyl proton (~10.0 ppm) are observed. The number of signals, their position, and the intensity ratio constitute evidence that in CCl_4 solution this ester exists practically entirely in the enol form. The conclusion regarding the correctness of the structure of ester I is confirmed by the similarity of the UV spectra of its anion and the spectra of the anions of the oxaloacetate and diethyl α-oxalylpropionate, by the similarity between the IR spectrum and the spectra of other oxaloacetates, and by the appearance in them of bands corresponding to the vibrations of C–N bonds (1215, 700 cm^{-1}). Unfortunately, the condensation of diethyl α-diethylaminooxaloacetate with urea in glacial acetic acid in a stream of anhydrous hydrogen chloride at 100-120° gives a mixture of several products, which we were unable to separate.

3-Methylhydantoin-$\Delta^{5,\alpha}$-acetates (X, XII, and XVIII-XX) are obtained either from N-methylurea and α-substituted oxaloacetates or by methylation of hydantoin-$\Delta^{5,\alpha}$-acetates with diazomethane (an equimolar amount) in ether, dioxane, or methanol.



Ethyl hydantoin-$\Delta^{5,\alpha}$-nitroacetate (XXI) was obtained by nitration of unsubstituted acetate IX with a mixture of nitric (sp.gr. 1.55) and glacial acetic acids at 45-50°. Products of the destruction of the starting material and of product XXI appear in the reaction mixture at higher temperatures. The structure of the compound obtained was proved by the UV, IR, and PMR spectra. Signals of protons of $COOC_2H_5$ groups (1.32 ppm, t, CCH_3; 4.42 ppm, q, OCH_2) and a broad signal of two protons of NH groups of the hydantoin ring centered at 10.70 ppm (the signal-intensity ratio in hexadeuteroacetone is 3 : 2 : 2) are observed in the PMR spectrum of product XXI, and the signal of the methylidyne proton of the starting material at 4.5-6.0 ppm is absent. The electronic spectra of XXI are similar to the spectra of other hydantoin-$\Delta^{5,\alpha}$-acetates (Table 1), and the observed shifts of the absorption bands with respect to their position in the spectrum of IX are due to the effect of the nitro group. Just as in the spectra of other similar hydantoins [10] (Fig. 1), bands of stretching vibrations of the $C^2=O$ and $C^4=O$ and $COOC_2H_5$ groups and the exocyclic $C^5=C^\alpha$ bond are observed in the IR spectrum of crystalline hydantoin XXI, and new bands (1562, 1355 cm^{-1}) due to the stretching vibrations of the nitro group, which are absent in the spectra of the other two compounds, appear. Thus nitro derivative XXI is actually formed in the nitration of hydantoin IX under relatively mild conditions.



Insofar as we know, this is the first example of electrophilic reactions of hydantoin-$\Delta^{5,\alpha}$-acetic acids that proceed with the participation of the exocyclic portion of the molecule.

Ethyl hydantoin-$\Delta^{5,\alpha}$-glycolate (XXII) was obtained by condensation of hydantoin with diethyl oxalate in methanol at 20-25° in the presence of $NaOCH_3$ [10], but it differs considerably in its spectral characteristics from the other substituted hydantoins (IX-XXI) (Table 2 and Figs. 2 and 3). The reason for this is the ability of glycolate XXII, in constrast to IX-XXI, to undergo keto–enol tautomerism to give three tautomers – "β-diketone" XXIIc and two "monoenols" XXIIa,b. Each of the enols can probably exist in the form of two three-dimensional isomers. Enol forms XXIIa,b are primarily stabilized in dioxane, dimethyl

TABLE 2. Physical Constants and UV Spectra of 3- and 5-Substituted 5-Carbethoxymethylidenehydantoins (IX-XXII)

Compound	R^3	R^α	mp[a], °C	R_f [b]			pK_a [c]	UV spectrum [d]				Empirical formula	Found, %			Calc., %		
				A	Б	B		nonionized compounds		anions			C	H	N	C	H	N
								λ_{max}	ε	λ_{max}	ε							
IX	H	H	185	0,87	0,52	—	7,62	231 294	10050 17000	256 305	14300 9300	$C_7H_8N_2O_4$	45,8	4,5	15,0	45,6	4,3	15,2
X	Me	H	134	—	—	0,60	—	248 300	11200 11900	253 357	7900 12400	$C_8H_{10}N_2O_4$	48,1	5,0	14,5	48,5	5,0	14,2
XI	H	Me	178	0,95	0,71	—	8,36	236 304	7850 18250	262 309	16500 12750	$C_8H_{10}N_2O_4$	48,8	5,0	14,2	48,5	5,0	14,2
XII	Me	Me	106	—	—	0,90	—	252 308	9150 14700	258 360	6550 10800	$C_9H_{12}N_2O_4$	50,4	5,8	13,3	50,9	5,7	13,1
XIII		OMe	222	0,88	0,48	—	8,50	232 310	6350 12750	270 320	9600 7650	$C_8H_{10}N_2O_5$	44,7	4,8	13,2	44,8	4,7	13,1
XIV		Ph	189	0,95	0,68	—	7,67	238 306	7050 12500	268 321	12850 8900	$C_{13}H_{12}N_2O_4$	60,0	5,0	10,6	60,0	4,6	10,8
XV	H	OPh	260	0,93	0,56	—	8,58	238 306	7050 12500	268 321	12850 8300	$C_{13}H_{12}N_2O_5$	56,7	4,6	10,0	56,5	4,3	10,2
XVI		F	212	0,81	0,30	—	7,22	235 300	6100 14500	264 302	14500 10100	$C_7H_7FN_2O_4$	42,1	3,6	13,8	41,6	3,5	13,8
XVII		Cl	210	0,84	0,40	—	7,25	240 312	5100 14100	269 318	12450 9600	$C_7H_7ClN_2O_4$	39,0	3,4	13,1	38,4	3,2	12,8
XVIII	Me	Ph	128	—	—	—	—	255 300	11900 11700	260 370	17300 11300	$C_{14}H_{14}N_2O_4$	61,2	5,3	10,3	61,3	5,2	10,2
XIX	Me	OPh	181	—	—	—	—	260 305	11300 12000	265 370	15000 11100	$C_{14}H_{14}N_2O_5$	57,8	5,1	9,5	57,9	4,9	9,6
XX	Ph	H	193	—	—	0,82	—	285	13250	275 357	7000 11250	$C_{13}H_{12}N_2O_4$	60,2	4,8	10,8	60,0	4,6	10,8
XXI	H	NO_2	143	0,90	—	—	5,76	240 335	14960 15960	275 360	14000 4790	$C_7H_7N_3O_6$	37,3	3,5	18,4	36.7	3.1	18,3
XXII	H	OH	212	0,73	—	—	—	322	3000	316	10500	$C_7H_8N_2O_5$	42,1	3,8	13,8	42,0	4,0	14,0

[a] Compounds IX-XX were recrystallized from alcohol.

[b] Obtained by paper chromatography (Watmann No. 1) with butanol–acetic acid–water (5 : 2 : 3) (A) and in a thin layer of Al_2O_3 with the following solvent systems: propanol–water (8 : 2) (B) and acetone–hexane (1 : 1) (C).

[c] The pK_a values were refined in comparison with the results of the research by extrapolation of the optical density at λ_{analyt} to zero time.

[d] These are the spectra of solutions of the nonionized compounds in water (pH 2-4), the anions of IX, XI, XIII-XVII, XXI, and XXII in water (pH 10-12), and of the anions of X, XII, and XVIII-XX in a 0.05 N methanol solution of sodium methoxide.

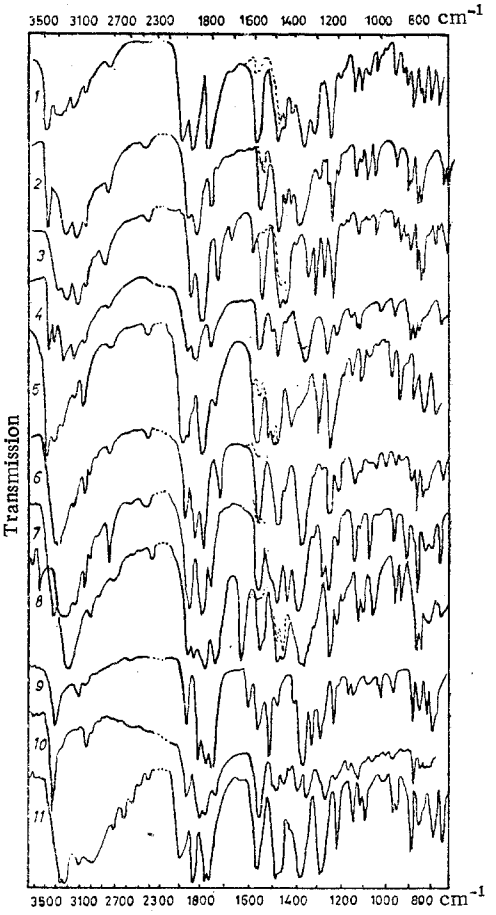


Fig. 1. IR spectra of suspension of crystalline samples of α-substituted (R) hydantoin-$\Delta^{5,\alpha}$-acetates in mineral oil (700-1900 cm^{-1}) and perfluorinated mineral oil (1900-3650 and the dash line in the 1300-1900 cm^{-1} region). The concentrations of the substances in films for recording of the spectra at 1900-3650 cm^{-1} are considerably higher than in samples for recording of the spectra below 1900 cm^{-1}: R = Ph (1), OMe (2), OPh (3), Me (4), OH (5), Cl (6), F (7), NO_2 (8), 3-PH (9), 3-Me (10), and H (11).

sulfoxide (DMSO), and methanol solutions. Proof of this is furnished by the high intensity of the bands in the UV spectra of these solutions (Fig. 2), which is close to the intensity of the corresponding bands in the spectra of ethyl hydantoin-$\Delta^{5,\alpha}$-methoxyacetate (XIII), which models the structure of enol XXIIa. The IR spectra (Fig. 3) of these solutions of glycolate XXII, methoxyacetate XIII, and unsubstituted IX are similar, and one can consequently speak of predominance of tautomer XXIIa in the glycolate solutions. Only signals of the "labile" protons of the NH and OH, methylene (multiplet of overlapped quartets), and methyl (triplet) groups are observed in the PMR spectra of solutions of this substance in dioxane, deuteroacetone, DMSO, and d_6-DMSO, and the signal of the methylidyne proton of tautomer XXIIc is absent. The IR spectra (Fig. 3) make it possible to assume that the enol forms also predominate in the crystalline state. The tautomeric equilibrium is shifted to favor the "diketone" in aqueous solutions. This is confirmed by the sharp reduction in the absorption intensity near 318-320 nm in the UV spectrum (Fig. 2) with ε 10,000 to 2000 2 to 3 min after dissolving the substances; this cannot be explained by rapid hydrolysis of the hydantoin. According to the results of thin-layer chromatography (TLC), only glycolate XXII is retained in the time that is adequate for recording the spectrum, and, in addition, the spectrum of a dioxane solution of a sample of the hydantoin prepared by evaporation of an aqueous solution of it to dryness in vacuo is identical to the spectrum of a solution of the substance that was not treated with water. Unfortunately, the IR spectra of aqueous solutions of the glycolate cannot be recorded because of its low solubility in water.

In aqueous alkali solutions 5-carbethoxymethylidenehydantoins IX, XI, XIII-XVII, and XXI, except for 3-substituted X, XII, XVIII-XX and α-hydroxy derivative XXII, are ionized by stripping of a proton from the nitrogen atom in the 3 position of the hydantoin ring [10]. The pK_a values of these compounds correlate satisfactorily with the McDaniel–Brown σ_p constants [Eq. (1)] (or the Taft σ^0 constants). Glycolate XXII is not included in the correlation because of the fact that the anion of this compound is formed by stripping of a proton from C^5 (or from the hydroxyl groups of the enols, which are present in small amounts in the solution). This is also confirmed by the considerable difference in the UV spectrum of the anion of this substance and the spectra of the anions of hydantoins IX, XI, XIII-XVII, and XXI (Table 1 and Fig. 2).

$$pK_a = (7.72 \pm 0.06) - (2.61 \pm 0.20)\sigma_p$$
$$n = 8,\ r = 0.985,\ s = 0.178.\ \tau = 2.36 \qquad (1)$$

Like IX-XII and XVI, α-phenyl- (XIV), α-phenoxy- (XI), α-methoxy- (XIII), and α-chlorohydantoin-$\Delta^{5,\alpha}$-acetates (XVII) and their N-methyl derivatives are rearranged by the action of aqueous solutions of alkalis to the corresponding orotic acids (XXIII-XXXIII) (Table 3). In this case, the yields of orotic acid decrease somewhat as the electron-acceptor properties of the substituents increase. The structures of the orotic acids obtained were proved by their UV and IR spectra, which differ considerably from the spectra of the starting compounds (see Tables 2 and 3 and Figs. 1 and 4). The changes in the UV spectra of alkaline solutions of hydantoin-$\Delta^{5,\alpha}$-acetates observed during the rearrangement are very characteristic: the intensity of the long-wave band initially falls gradually (at different rates for the different compounds), while the intensity of the short-wave band remains practically unchanged for a certain time (it sometimes

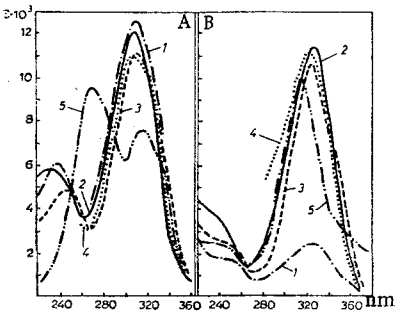


Fig. 2

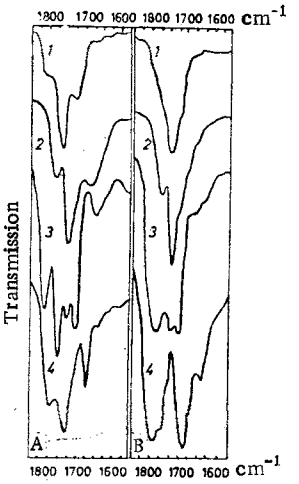


Fig. 3

Fig. 2. UV spectra of solutions of α-methoxy- (A) and α-hydroxyethylhydantoin-$\Delta^{5,\alpha}$-acetates (B) in water at pH 1-3 (1), 13 (2), dioxane (3), dimethyl sulfoxide (4), and methanol (5).

Fig. 3. IR spectra of solutions of α-methoxy- (A) and α-hydroxyethylhydantoin-$\Delta^{5,\alpha}$-acetates (B) in methanol (1), DMSO (2), and dioxane (3) and of crystalline samples (suspensions in perfluorinated mineral oil) (4).

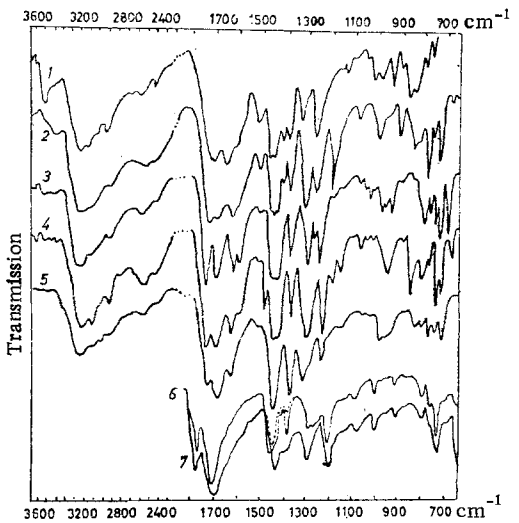


Fig. 4. IR spectra of crystalline samples (see the caption to Fig. 1) of the products of rearrangement of substituted ethyl hydantoin-$\Delta^{5,\alpha}$-acetates – orotic acid (1), 5-methyl- (2), 5-phenyl (3), 5-phenoxy- (4), and 5-methoxy-(5) orotic acids – of the product of hydrolysis (0.1-2 N KOH, 25-95°) of ethyl hydantoin-$\Delta^{5,\alpha}$-glycolate (6), and of hydantoin (7).

increases slightly), after which the intensity of the short-wave band begins to fall; as a result, the spectra is transformed to the spectrum of the anion of the corresponding orotic acid. This is explained by the fact that the carbethoxymethylidenehydantoins are hydrolyzed during the reaction to the corresponding carboxymethylidenehydantoins, and both of these compounds are rearranged simultaneously to the orotic acid. If one assumed that the intensities of the long-wave maximum in the spectra of the ester and the acid are identical (which was established in the case of XI and XVIII), the rate of change of the intensity of this band reflects the overall rate of hydrolysis of the ester to the corresponding acid and rearrangement of each of them to the orotic acid. The intensity of the short-wave maximum in the spectra of hydantoin-$\Delta^{5,\alpha}$-acetic acids is higher than in the spectra of their ethyl esters, and the induction period, during which the intensity of this band does not change, is related to hydrolysis of the ester to the acid, whereas the rate of decrease in the intensity coincides with the rearrangement of pure 5-carboxymethylidenehydantoin to orotic acid. The differences in the IR spectra of the carbethoxymethylidenehydantoins and the corresponding orotic acids or their esters are also extremely characteristic (compare Figs. 1 and 4). However, the noted difference cannot, unfortunately, be used for observance of the course of the reaction because of strong absorption of the medium in the most interesting region of the spectrum (1400-1800 cm^{-1}, vibrations of ionized carbonyl groups and C–N and C=C bonds).

Hydantoin-$\Delta^{5,\alpha}$-glycolic acid ester (XII) decomposes quite rapidly in aqueous alkali solutions to give ethanol, oxalic acid, and hydantoin (Fig. 4). 5-Hydroxyorotic acid cannot be detected in solution in this

TABLE 3. 3- and 5-Substituted Orotic Acids (XXIII-XXXIII)

Compound	R^3	R^5	Reac. time,[a] h·min	mp[b], °C	R_f[c]	UV spectrum[d] neutral compounds λ_{max}	UV spectrum[d] neutral compounds ε	UV spectrum[d] dianions λ_{max}	UV spectrum[d] dianions ε	Empirical formula	Found, % C	Found, % H	Found, % N	Calc., % C	Calc., % H	Calc., % N	Yield, %
XXIII	H	H	0,50	330	0,35	280	7600	286	6000	$C_5H_4N_2O_4$	38,6	2,5	18,0	38,5	2,6	17,9	70
XXIV		Me	2,50	327 (dec.)	0,33	292	7700	292	8000	$C_6H_6N_2O_4$	42,2	3,9	16,4	42,4	3,5	16,5	75
XXV		Ph	3,0	335 (dec.)	0,36	278	8900	286	11300	$C_{11}H_8N_2O_4$	56,4	3,7	12,3	56,9	3,4	12,1	78
XXVI		OPh	4,0	283 (dec.)	0,37	278	14400	295	15800	$C_{11}H_8N_2O_5$	53,0	3,5	11,5	53,2	3,2	11,3	70
XXVII		OMe	5,0	270 (dec.)	0,41					$C_6H_6N_2O_5$	38,6	3,4	14,9	38,7	3,2	15,1	68
XXVIII		F	0,50	252 (dec.)	0,48	282	7600	285	6600	$C_5H_3FN_2O_3$[e]	34,8	2,0	16,2	34,5	1,7	16,1	55
XXIX		Cl	0,50	323 (dec.)	0,27	280	14600	298	17900	$C_5H_3ClN_2O_3$[f]	31,4	1,7	14,6	31,5	1,6	14,7	60
XXX		NO_2	0,50	230 (dec.)	0,25	290	19000	345	36000	$C_5H_3N_3O_6$	29,4	1,8	20,5	29,9	1,5	20,9	15
XXXI	Me	H	0,20	325 (dec.)	0,49	279	6800	298	7500	$C_6H_6N_2O_4$	42,5	3,8	16,4	42,4	3,5	16,5	90
XXXII	Me	Me	0,50	287 (dec.)	0,63	284	4900	290	7700	$C_7H_8N_2O_4$	45,8	4,4	15.0	45,6	4,3	15,2	88
XXXIII	Ph	H	0,50	278 (dec.)	0,54					$C_{11}H_8N_2O_4$	56,6	3,6	12,2	56,9	3,4	12,1	98

[a]The reaction times and yields of products with respect to the above-described method are presented.
[b]Compounds XXIII-XXXIII were recrystallized from water or alcohol.
[c]Obtained from paper chromatograms, $C_4H_9OH-CH_3COOH-H_2O$ (5 : 2 : 3).
[d]In water at the appropriate pH values.
[e]Found, %: F 10.5. Calculated, %: F 10.9.
[f]Found, %: Cl 18.5. Calculated, %: Cl 18.6.

case. α-Nitroacetate XXI reacts with aqueous alkalis at 20-30° to give a small amount of 5-nitroorotic acid (≥ 15%, calculated from the intensity of the absorption band of the dianion of nitroorotic acid; see Table 3), nitromethane, and ethanol. 5-Nitroorotic acid is not formed when solutions of hydantoin XXI in aqueous alkalis are heated, and approximately equal amounts of nitromethane and ethanol are found after acidification of the hydrolyzate by means of gas–liquid chromatography (GLC). 5-Nitroorotic acid is stable under similar conditions and, according to the UV spectra, does not change over a considerably longer time than is necessary for complete decomposition of hydantoin XXI. In addition, we were unable to detect the formation of glycine in the reaction of nitro derivative XXI with alkalis by chromatography (development with ninhydrin). Consequently, the hydrolysis of this compound does not proceed with cleavage of the molecule to hydantoin and nitroglyoxylic acid. Thus it can be assumed that hydration or hydroxylation of the exocyclic C=C bond of the intermediates in the hydrolysis plays a substantial role during treatment of hydantoin XXI with aqueous alkali. One cannot exclude the possibility that this is also the reason for the decrease in the yields of orotic acids in the rearrangement of carbethoxymethylidenehydantoins with electron-acceptor substituents as their electron-acceptor properties increase.

EXPERIMENTAL*

The UV spectra of 10^{-4}-10^{-5} M solutions of the substances were recorded with an SF-4A spectrophotometer. The IR spectra of suspensions of the crystalline substances in mineral oil or perfluorinated mineral oil were recorded with an IKS-14A spectrometer with NaCl and LiF prisims, while the spectra of solutions of the substances were recorded in CaF_2 cuvettes. The PMR spectra of ~20% solutions of the compounds were recorded with a Perkin-Elmer R-12 spectrometer with hexamethyldisiloxane as the internal standard. The pK_a values were determined spectrophotometrically with allowance for hydrolysis of the starting esters (extrapolation to zero time, SF-4A spectrophotometer, phosphate buffer solutions). The potentiometric measurements were made with an LPM-60M potentiometer with glass and silver chloride electrodes.

Substituted diethyl oxaloacetates I-VIII were obtained by reaction of the appropriate acetate with diethyl oxalate in absolute ether, benzene, or toluene at 10-25° (the condensing agents were sodium hydride or sodium methoxide or ethoxide prepared from strictly equimolar amounts of NaH and absolute alcohol).

Diethyl α-Diethylaminooxaloacetate (I). A 0.168-mole sample of absolute ethanol was added dropwise with vigorous stirring to 0.168 mole of sodium hydride in 60 ml of absolute ether, and 0.168 mole of ethyl α-diethylaminoacetate [7] was added with stirring to the resulting suspension of sodium ethoxide. The resulting transparent slightly yellowish solution was stirred at 20-25°; after 9 h, the solution began to become turbid, and a voluminous amorphous precipitate crystallized rapidly. The mixture was allowed to stand overnight, after which it was acidified to pH 2-3 with 10% HCl, the ether layer was separated, and the aqueous layer was neutralized to pH 7 with potassium carbonate. The product was extracted with ether (six 50-ml portions). The ether extract was dried with potassium carbonate and evaporated to give 30 g of a crystalline product. The latter was recrystallized from alcohol or vacuum sublimed to give 23.2 g (53.5%) of a colorless crystalline substance (Table 2).

Ethyl Hydantoin-$\Delta^{5,\alpha}$-acetates (IX-XX). An intense stream of anhydrous hydrogen chloride was bubbled with vigorous stirring into a heated (to 100°) mixture of equimolecular amounts of urea, substituted oxaloacetate, and glacial acetic acid. The reaction mass initially became homogeneous, after which a precipitate gradually formed. A very viscous pasty mixture formed at the end of the reaction. The precipitate was removed by filtration and recrystallized. The yields and physical constants of the products are presented in Table 1.

Ethyl Hydantoin-$\Delta^{5,\alpha}$-nitroacetate (XXI). A 4.4-g sample of fuming nitric acid (sp. gr. 1.5) was added slowly at 15-20° to a stirred suspension of 0.03 mole of ethyl hydantoin-$\Delta^{5,\alpha}$-acetate IX in 10 ml of glacial acetic acid. The mixture was gradually heated to 35-40° and held at this temperature until the starting material had dissolved completely. The solution was then heated additionally at 45° for 30 min, after which it was cooled to 0-5° for 1-2 h. The resulting crystalline product was removed by filtration, washed with a small amount of cold acetic acid, and dried in a vacuum desiccator over solid KOH. It was then recrystallized from anhydrous benzene.

Ethyl Hydantoin-$\Delta^{5,\alpha}$-glycolate (XXII). A 0.1-mole sample of hydantoin and 0.1 mole of freshly distilled diethyl oxaloacetate were added with stirring to a solution of 0.2 mole of sodium methoxide in 75 ml

*With the participation of V. D. Yakovleva.

of methanol, after which the mixture was stirred at 20-25° for 10-12 h and maintained at this temperature for another 12 h. It was then cooled and acidified to pH 2-3 with 10% HCl, and the resulting colorless crystalline product was removed by filtration, recrystallized, and vacuum dried at 100°.

3- and 5-Substituted Orotic Acids (XXIII-XXXIII) (see Table 3). A solution of 0.05 mole of substituted 5-hydantoin-$\Delta^{5,\alpha}$-acetic acid or its ester in 20-50 ml of 0.5-2 M KOH was heated at 100° for the time indicated in Table 3 (established from the disappearance of the spot of the starting hydantoin and the corresponding acid on paper or thin-layer chromatograms). The mixture was then cooled and acidified to pH 1 with concentrated hydrochloric acid, and the precipitated orotic acid was removed by filtration and recrystallized.

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