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SYNTHESIS OF SUBSTITUTED 3-AMINOSPIRO-4-BUT-2-ENOLIDES

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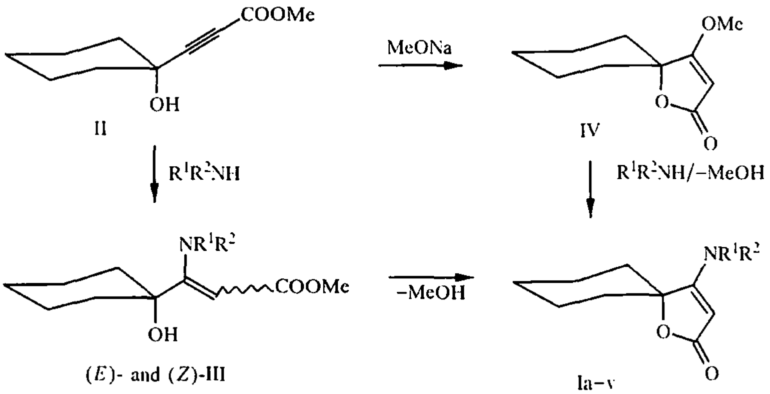
Previously unknown 3-N-alkylamino-, 3-N,N-dialkylamino-4-but-2-enolides containing spirocyclic moiety have been synthesized by nucleophilic addition of amines at the triple bond of methyl ester of β-(1-hydroxycyclohexyl)propiolic acid or by the reaction of amines with the corresponding 3-methoxy-4-but-2-enolide.

3-Substituted 4-but-2-enolides [furan-2(5H)-ones] are of interest as compounds with diverse physiological activities [1,2] and as intermediates in synthesis of natural compounds (tetronic acids, GABA, pheromones) [3-5].

One of the well-known methods for their synthesis is based on cyclization of acyclic compounds obtained on the basis of allenyl- [6] and γ-hydroxyalkynylcarboxylates [7-10].

The objective of the present work was to synthesize a series of 3-amino-4-but-2-enolides I containing spirocyclic moiety, on the basis of methyl ester of β-(1-hydroxycyclohexyl)propiolic acid (II), according to the scheme shown below. This scheme presumes formation of β-aminoacrylic esters III, which immediately undergo ring closure [7].



Ia $R^1R^2 = (CH_2)_4$; b $R^1R^2 = (CH_2CH_2)O$; c $R^1R^2 = (CH_2)_5$; d $R^1R^2 = (CH_2CH_2)_2NMe$; e $R^1R^2 = (CH_2)_6$;
f $R^1R^2 = (CH_2CH_2)_2NCOOEt$; g $R^1R^2 = (CH_2CH_2)_2NCOPh$; h $R^1R^2 = (CH_2CH_2)_2NCHPh_2$; i $R^1 = R^2 = C_3H_7$-*i*;
j $R^1 = R^2$ = cyclohexyl; k–v R^1 = H; k R^2 = cyclopropyl; l R^2 = 2-tetrahydrofuryl; m $R^2 = C_4H_9$-*t*; n R^2 = 2-furfuryl;
o $R^2 = (CH_2)_2NEt_2$; p $R^2 = CH_2C_6H_3Cl_2$-3,4; q $R^2 = CH_2Ph$; r R^2 = (CH)MePh; s $R^2 = (CH_2)_2Ph$;
t $R^2 = CH_2C_6H_4OMe$-4; u $R^2 = CMe_2CH_2CMe_3$; v $R^2 = C_{12}H_{25}$

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TABLE 1. Conditions of Synthesis and Characteristics of 3-N-Alkylamino-, 3-N,N-Dialkylamino-4,4-pentamethylene-4-but-2-enolides Ia-v*

Compound	Empirical formula	Found, % / Calculated, %	mp, °C	Reaction conditions and reaction time	Yield, %
Ia	$C_{13}H_{19}NO_2$	$\frac{6.17}{6.33}$	120-121	A, 2 days	73
Ib	$C_{13}H_{19}NO_3$	$\frac{5.79}{5.90}$	142- 143	A, 6 days	72
Ic	$C_{14}H_{21}NO_2$	$\frac{6.00}{5.95}$	114-115	A, 6 days C, 4 days	67 62
Id	$C_{14}H_{22}N_2O_2$	$\frac{10.81}{11.19}$	156-157	A, 2 days B, 7 h	59 47
Ie	$C_{15}H_{23}NO_2$	$\frac{5.30}{5.62}$	133-134	A, 2 days	53
If	$C_{16}H_{24}N_2O_4$	$\frac{9.01}{9.09}$	169.5-170	A, 6 days	71
Ig	$C_{20}H_{24}N_2O_3$	$\frac{7.67}{8.23}$	265-266	B, 6 h	62
Ih	$C_{26}H_{30}N_2O_2$	$\frac{6.57}{6.96}$	156-157	A, 6 days B, 7 h	64 47
Ii	$C_{15}H_{25}NO_2$	$\frac{5.62}{5.57}$	178-180	C, 10 h	52
Ij	$C_{21}H_{33}NO_2$	—	Oil*[2]	C, 10 h	49
Ik	$C_{12}H_{17}NO_2$	$\frac{6.42}{6.76}$	229.5-230.5	A, 3 days	84
Il	$C_{14}H_{21}NO_3$	$\frac{5.67}{5.57}$	89-90-93	A, 7 days	59
Im	$C_{13}H_{21}NO_2$	$\frac{6.04}{6.27}$	239-240	A, 12 days D, 8 h	46 42
In	$C_{14}H_{17}NO_3$	$\frac{5.51}{5.66}$	170-171	A, 6 days	70
Io	$C_{15}H_{26}N_2O_2$	$\frac{10.29}{10.52}$	97.5- 100	A, 7 days	58
Ip	$C_{16}H_{17}C_{12}NO_2$	$\frac{3.94}{4.29}$	191-192	A, 7 days	65
Iq	$C_{16}H_{19}NO_2$	$\frac{5.35}{5.44}$	176-177	A, 1 day D, 8 h	70 67
Ir	$C_{17}H_{21}NO_2$	$\frac{4.82}{5.16}$	200-201	A, 12 h	58
Is	$C_{17}H_{21}NO_2$	$\frac{4.91}{5.16}$	203- 204	A, 7 days	95
It	$C_{17}H_{21}NO_3$	$\frac{4.54}{4.87}$	214-215	A, 7 days	76
Iu	$C_{17}H_{29}NO_2$	$\frac{5.12}{5.01}$	212-213	A, 7 days	63
Iv	$C_{21}H_{37}NO_2$	$\frac{3.72}{4.18}$	77-78	C, 6 h	43

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* Compounds Ia-f,h are recrystallized from a 2:1 petroleum ether–ethyl acetate mixture; compounds Ig,k,r-u – from ethanol; compounds Ii,n,p,q – from a 1:1 petroleum ether–ethyl acetate mixture; compounds Il,o,v – from hexane.

*[2] According to the PMR spectral data, the sample contains 7-9% of 3-(1-hydroxycyclohexyl)-3-(dicyclohexylamino)acrylic acid methyl ester (IIIj) (singlet from the OCH_3 group at 3.52 ppm).

Compounds I are synthesized under mild conditions by interaction of amines with substituted ester of propiolic acid II in diethyl ether, the molar ratio amine:ester being 1.2-1.4:1 (procedure A). The reaction occurs at room temperature and the reaction time ranges from a few hours to 5-8 days. The substituents on the amine molecules

TABLE 2. UV, IR, and PMR Spectral Characteristics for Synthesized Compounds

Compound	IR spectrum, ν, cm^{-1}			UV spectrum, λ_{max}, nm (ε)	PMR spectrum, δ, ppm, spin-spin coupling constant (*J*), Hz*	
	=C–N	C=O	NH		=CH, s	signals from other protons
1	2	3	4	5	6	7
Ia	1588	1720		270 (18100)	4.41	1.1-2.1 (14H, m, 7CH$_2$); 4.40 (4H, br. s, 2CH$_2$N)
Ib	1596	1716	—	270 (27200)	4.63	1.1-1.9 (10H, m, 5CH$_2$); 3.34 (4H, t, 2CH$_3$N); 3.78 (4H, t, CH$_2$O)
Ic	1590	1720	—	271 (18400)	4.58	1.1-1.9 (16H, m, 8CH$_2$); 3.34 (4H, t, 2CH$_2$N)
Id	1588	1720	—	270 (24600)	4.59	1.2-2.0 (10H, m, 5CH$_2$); 2.24 (3H, s, CH$_3$); 2.38 (4H, t, 2$\underline{CH}_2$NCH$_3$); 3.36 (4H, t, 2CH$_2$NC=)
Ie	1572	1716	—	268 (33500)	4.50	1.1-2.0 (18H, m, 9CH$_2$); 3.38 (4H, t, 2CH$_2$N)
If	1580	1720 1700	—	268 (35700)	4.68	1.26 (3H, t, CH$_3$); 1.2-2.0 (10H, m, 5CH$_2$); 3.32-3.54 [8H, m, (CH$_2$CH$_2$)$_2$N]; 4.09 (2H, q, CH$_2$O)
Ig	1588	1716 1620	—	268 (40000)	4.70	1.2-2.1 (10H, m, 5CH$_2$); 3.3-3.8 [8H, br., m, (CH$_2$CH$_2$)$_2$N]; 7.40 (5H, br. s, C$_6$H$_5$)
Ih	1584	1728		269 (35000)	4.57	1.1-2.0 (10H, m, 5CH$_2$); 2.42 and 3.38 [8H, two br. s, ($\dot{C}$H$_2$CH$_2$)$_2$N]; 4.32 (1H, s, CHN); 7.12-7.55 (10H, m, 2C$_6$H$_5$)
Ii	1576	1716	—	272 (24400)	4.64	1.1-1.9(10H, m, 5CH$_2$); 1.28 (12H, d, 4CH$_3$); 3.92 (2H, m, 2CHN)
Ij	1582	1712		268 (24900)	4.62	1.1-2.0 (30H, m, 15CH$_2$); 3.86 (2H, m, 2CHN)
Ik		1700	3240 3064	257 (34600)	4.50	0.50 and 0.70 (4H, two m, 2CH$_2$); 1.1-1.9 (10H, m, 5CH$_2$); 2.42 (1H, m, CHN); 7.32 (1H, s, NH)
Il	1612	1696	3256 3088	255 (21100)	4.38	1.2-2.0 (14H, m, 7CH$_2$); 3.08 (2H, t, CH$_2$N); 3.18 and 3.31 (2H two q, CH$_2$O); 3.98 (1H, q, CHO); 7.10 (1H, br. s, NH)
Im	1596	1696	3280 3152 3080	256 (15000)	4.46	1.1-1.8 (10H, m, 5CH$_2$); 1.23 (9H, s, 3CH$_3$); 5.90 (1H, br. s, NH)

TABLE 2 (continued)

1	2	3	4	5	6	7
In	1600	1696	3256 3136 3120 3204	256 (29600)	4.47	1.2-1.9 (10H, m, 5CH_2); 4.21 and 4.23 (2H, two s, CH_2N); 6.23, 6.38 and 7.56 (3H, d, *J* = 1.2, d, *J* = 1.2 and t, *J* = 1.2, furyl); 7.50 (1H, s, NH)
Io	1604	1696	3232 3064	256 (17400)	4.31	1.02 (6H, t, 2CH_3); 1.1-1.9 (10H, m, 5CH_2); 2.52 (2H, m, CH_2N); 3.08 (6H, m, 3CH_2N); 6.78 (1H, br. s, NH)
Ip	1608	1700	3272 3080	257 (35000)	4.48	1.1-1.9 (10H, m, 5CH_2); 4.25 and 4.27 (2H, two s CH_2N); 7.20-7.76 (3H, m, C_6H_3); 7.48 (1H, s, NH)
Iq	1600	1696	3256 3120 3112 3104	258 (28200)	4.52	1.1-1.9 (10H, m, 5CH_2); 4.27 and 4.30 (2H, two s, CH_2N); 5.70 (1H, br. s, NH); 7.2-7.4 (5H, m, C_6H_5);
Ir	1600	1698	3272 3112 3056 3008	255 (15400)	4.49	1.1-1.9 (10H, m, 5CH_2); 1.56 (3H, d, CH_3); 4.39 (1H, q, CHN); 5.24 (1H, unresolved d, NH); 7.2-7.4(5H, m, C_6H_5)
Is	1604	1692	3264 3072	258 (27700)	4.34	1.1- 1.9 (10H, m, 5CH_2); 2.84 (2H, t, CH_2Ph); 3.29 (2H, q, CH_2N); 7.08 (1H, br. s, NH); 7.27 (5H, m, C_6H_5)
It	1604	1696	3232 3056	258 (28300)	4.31	1.2-2.0 (10H, m, 5CH_2); 3.39 (3H, s, CH_3O); 4.17 and 4.19 (2H, two s, CH_2N); 6.98 and 7.20 (4H, two d, *J* = 8.6, C_6H_4); 7.50 (1H, br. s, NH)
Iu	1600	1696	3312 3184 3080 3040	260 (14100)	4.68	1.05 (9H, s, 3CH_3); 1.1-1.9 (12H, m, 6CH_2); 1.48 (6H, s, 2CH_3); 4.49 (1H, br. s, NH)
Iv	1604	1700	3280 3080	257 (19100)	4.57	0.89 (3H, t, CH_3); 1.2-1.9 (10H, m, 5CH_2); 1.31 (20H, br. s, 10CH_2); 3.12 (2H, q, CH_2N); 4.62 (1H, br. s, NH)

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* The spin–spin coupling constants for substituents R^1 and R^2 which are not indicated equal to 6.9-7.1 Hz.

(R^1 and R^2) may be varied considerably, which makes it possible to obtain various enaminolactones I in 40% to 80% yields. In this case, change in temperature and the use of different solvents (alcohol, acetone, dioxane) did not lead to a substantial increase in the yield of the target product. In the case of unstable amines, we used their hydrochlorides. Thus compounds Ig,h are synthesized by boiling ester II with the corresponding hydrochlorides in methanol in the presence of sodium acetate (procedure B).

The products Ij,i from sterically hindered amines were obtained by melting the reagents together at 100°C (procedure B).

In addition to the routes of synthesis of enaminolactones I considered above, we also have developed a variant based on nucleophilic substitution of the 3-methoxy group of butenolide IV. Formation of product I probably occurs by Michael addition of amine followed by elimination of methanol [11]. However, the reaction requires vigorous conditions: boiling with two-fold excess of amine in butanol in the presence of triethylamine (procedure D). Under the mentioned conditions, aromatic amines (aniline, 2-aminopyridine) generally do not react. The structures of the synthesized compounds agree well with the results of elemental analysis, and also with PMR, IR, and UV spectral data (see Tables 1 and 2).

In the IR absorption spectra of enaminolactones I, two intense bands are observed – for stretching vibrations of the conjugated carbonyl group in the region of 1690-1720 cm^{-1} and of the enamine moiety in the region of 1570-1610 cm^{-1}. In addition, in the spectra of compounds Ik-v there are characteristic bands of the NH group vibrations in the region of 3080-3260 cm^{-1}.

In the electronic absorption spectra of the synthesized compounds Ia-v, an intense maximum in the region of 257-270 nm is observed, characteristic of the β-aminovinyl carbonyl moiety. In the PMR spectra, there is one-proton singlet signal from the cyclic methine group at δ 4.31-4.68 ppm, and also signals from protons of other moieties whose position, intensity, and multiplicity support structure I for the products.

Thus, using accessible starting reagents, we have developed convenient preparative methods for synthesis of previously unknown N-substituted 3-amino-4,4-pentamethylene-4-but-2-enolides (3-amino-5,5-pentamethylene-furan-2(5H)-ones).

EXPERIMENTAL

The PMR spectra were recorded on Bruker WM-250 (250 MHz) instruments in DMSO-d_6 and $CDCl_3$ (Ia-c,f,i,j,q,r), internal standard TMS. The UV spectra were measured on a Specord UV-vis spectrometer for ethanol solutions. The IR spectra were recorded on a Specord M-80 in KBr pellets. The melting points were determined on a Kofler apparatus. The starting compounds II and IV were synthesized by the well-known procedures [7, 8]. The characteristics of the synthesized compounds I, their synthesis conditions, and the solvents for recrystallization are reported in Table 1. The IR and UV and also the PMR spectral data are presented in Table 2.

Procedures for Synthesis of N-Substituted 3-Amino-4,4-pentamethylene-4-but-2-enolides I. A. The corresponding amine (13-14 mmol) was added to solution of 1.68 g (10 mmol) of ester II in 30 ml of dry diethyl ether. The reaction mixture was allowed to stand at room temperature. The precipitate of product I was filtered, separated, washed on the filter with 2:1 hexane–ethyl acetate mixture, dried in air, and recrystallized.

B. Suspension of ester II (0.84 g, 5 mmol), amine hydrochloride (7 mmol), and anhydrous sodium acetate (7 mmol) in 15 ml of methanol was boiled for the time indicated in Table 1. The reaction mixture was filtered hot to separate the insoluble salts; the precipitate of product I was separated from the filtrate and recrystallized.

C. Mixture of ester II (5 mmol) and amine (7 mmol) was held on a boiling water bath and treated as indicated in procedure A. Then the precipitate was recrystallized.

D. Mixture of lactone IV (5 mmol), amine (10 mmol), and triethylamine (5 mmol) in 15 ml of butanol was boiled and treated as indicated in procedure A. Then the precipitate was recrystallized.

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