SYNTHESIS OF ESTERS OF δ-AMINOPENTADIENE-CARBOXYLIC ACIDS

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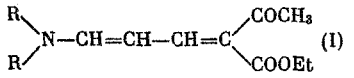
UDC 542.91:547.315:547.466.5'26

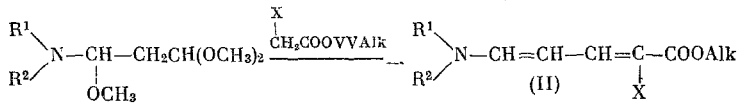
The δ-aminoketo esters



(I)

previously synthesized by us, were found to have a number of interesting properties: an easy conversion to N-substituted pyridone derivatives [1], and a rapid (on the NMR time scale) rotation around the α,β double bond under the equilibrium conditions for the geometric isomers, with a retardation of the rotation around the C–N bond [2]. For a further study of the observed phenomena we synthesized the δ-amino acid esters (II), which contain electron-acceptor substituents in the α-position (Table 1).

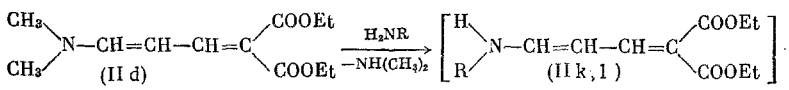
Several examples are known where compounds of the (II) type have been synthesized by the condensation of 3-dimethylaminoacrolein acetal (III) with compounds that contain an active methylene group [3]. The yield of (II) is increased by 20% when 1, 1, 3-trimethoxy-3-dialkylaminopropanes (IV) are used, the synthesis of which is simpler than that of (III). We obtained the (IV) compounds by the action of methanolic CH_3ONa solution on the adducts of the 3-dialkylaminoacrolein with dimethyl sulfate. Compounds of the



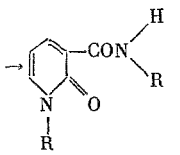
$R^1 = R^2 = CH_3$ (IVa); $R^1R^2 = -(CH_2)_5$ (IVb); X = COOAlk, NO_2, CN, $CONH_2$

(II) type, with an ethylenimino group in the δ-position, the conjugation effect of which with an activated double bond is substantially weaker than in the case of a dialkylamino group [4], were of undoubted interest.

We developed a method for the synthesis of the previously unknown 3-ethyleniminoacrolein and 3-ethylenimino-3-phenylacrolein, but we were unable to obtain the corresponding trimethoxypropanes or acetals from them. In order to synthesize diesters (IIk, l), which contain a secondary amino group, we subjected (IId) to transamination with primary amines; here the 1-alkyl-3-carbamoyl-2-pyridones (VI) were obtained in good yields as the result of the intramolecular cyclization of (IIk, l) and the amination of the carbethoxy group. A decrease in the amount of amine gave 40% of the starting (IId) and 60% of the



(II d) (II k, l)

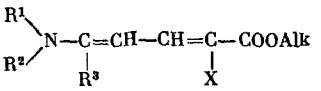


R = C_4H_9 (VIa), $CH_2C_6H_5$ (VIb)

1-alkyl-3-carbethoxy-2-pyridone.

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 9, pp. 2008-2012, September, 1973. Original article submitted March 2, 1973.

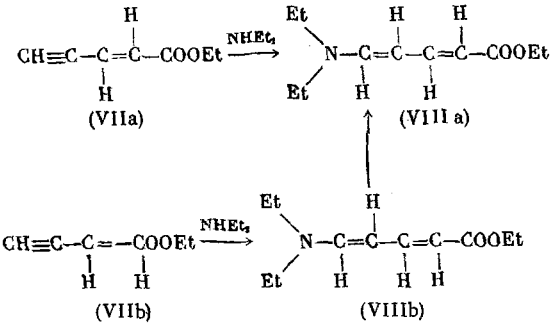
TABLE 1



Compound	Alk	X	R^1	R^2	R^3	Yield, %	mp, °C	Ultraviolet spectrum		Found/Calculated, %		
								λ_{max}, nm	ε	C	H	N
(IIa)	CH_3	NO_2	CH_3	CH_3	H	55	114–115	245	5500	48,01 47,99	6,19 6,04	13,54 13,99
								303	12300			
								417	41500			
(IIb)*	CH_3	$COOCH_3$	CH_2	CH_3	H	57	105–106	235	7000			
								374	57400			
(IIc)	CH_3	$COOCH_3$	—	$(CH_2)_5$	H	52	62–63†	238	7170	61,71 61,64	7,70 7,56	5,75 5,54
								379	40700			
(IId)	C_2H_5	$COOC_2H_5$	CH_3	CH_3	H	56	55–56‡	235	6500	59,50 59,73	7,94 7,94	5,71 5,81
								374	59800			
(IIe)	C_2H_5	CN	CH_3	CH_3	H	90	128–129	224	8000	61,56 61,83	7,28 7,27	14,08 14,42
								378	64500			
(IIf)*	CH_3	CN	CH_2	CH_3	H	78	156–157	223	10100			
								386	60000			
(IIg)	CH_3	NH_2CO	CH_3	CH_3	H	15	160–161	236	9900	54,48 54,53	7,08 7,12	14,22 14,18
								382	62200			
(IIh)	C_2H_5	NH_2CO	CH_3	CH_3	H	20	170–172	234	10200	56,82 56,59	7,46 7,76	13,43 13,20
								250	6600			
								380	65500			
(IIi)	CH_3	NO_2	C_2H_5	C_2H_5	C_6H_5	90	108–109	250	6600	63,20 63,14	6,64 6,62	9,37 9,21
								310	8700			
								440	50200			

*The melting points of (IIb) and (IIf) correspond to the data given in [3].
†bp 180-183° (0.5 mm).
‡bp 137-139° (0.1 cm).

The esters of the unsubstituted δ-aminopentadienecarboxylic acids were synthesized previously [5] by the addition of amines to the ester of 2-penten-4-ynoic acid (VII). In the present paper we studied the stereochemistry of the addition of diethylamine to (VIIa) and (VIIb) directly in the NMR ampul as described in [2].



The trans-isomer (VIIIa) is formed immediately when diethylamine is added to the trans-ester (VIIa) at 20° in CCl_4 (or C_6H_{12}), i.e., the configuration of the α,β double bond is retained in the kinetic reaction product, whereas when diethylamine is added to vinylacetylenic ketones and keto esters the kinetic products are the cis-isomers at this bond independent of its configuration in the starting compounds [2]. The observed differences are well explained by the reaction scheme [2] proposed by us for the latter case. The absence of a carbonyl group in the (VII) esters hinders the formation of the intermediate enol, in which electron transfer to a 6-membered ring occurs, which leads to the cis-isomer.

The addition of diethylamine to the cis-ester (VIIb) leads to a compound that differs from (VIIIa) in its NMR spectrum, which in CCl_4 at 20° is completely isomerized to the trans-isomer (VIIIa) in 20 days. On the basis of the data of the IR, UV, and mass spectra, and also of TLC, it may be assumed that the formed compound in its structure is identical with (VIIIa), and is its isomer. However, on the basis of these data and the NMR data (due to the complexity of the spectrum of the protons at the double bonds they were not identified) we were unable to determine the configuration of the double bonds. But the result of

adding diethylamine to the trans-ester (VIIa) makes it possible to assume that the formed compound is the cis-isomer at the α,β double bond (VIIIb).

EXPERIMENTAL

The NMR spectra (δ, ppm) were taken on a DA-60-IL instrument; the internal standard was HMDS. The starting (V) compounds were obtained: as described in [6] when X = NO_2 and Alk = CH_3, as described in [7] when X = $CONH_2$ and Alk = CH_3 (mp 37°), and as described in [8] when X = $CONH_2$ and Alk = C_2H_5.

1,1,3-Trimethoxy-3-dimethylaminopropane (IVa). A mixture of 9.9 g (0.1 M) of 3-dimethylaminoacrolein and 12.6 g (0.1 M) of dimethyl sulfate was heated at 70° for 3 h. With stirring and cooling to 2-5°, the sirupy quaternary salt was gradually added to 2.3 g of Na in 30 ml of absolute MeOH, after which the reaction mixture was stirred at 20° for 1 h. The obtained precipitate was separated and washed with absolute ether. Distillation gave 9.2 g (52%) of (IVa) with bp 79-82° (18 mm); n_D^{20} 1.4280. NMR spectrum of (IVa) (δ, ppm): 1.58 (CH_2); 2.17 ($(CH_3)_2N$); 3.15 $(OCH_3)_2$; 3.22 (OCH_3); 3.68 (1 CH); 4.31 (3CH); $J_{2,1} = J_{2,3} = 6$ Hz. The spectrum has additional signals that belong to (III), the amount of which is 20% (δ, ppm): 2.58 ($(CH_3)_2N$); 3.15 $(OCH_3)_2$; 4.04 (2CH); 4.71 (1CH); 6.15 (3CH); $J_{2,3} = 14$ Hz, $J_{3,1} = 1$ Hz, $J_{2,1} = 6$ Hz.

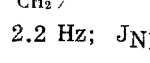
Compound (IVb) was obtained in a similar manner. The application of the above described method to 3-diethylamino-3-phenylpropenal (XII) gave its acetal.

3-Ethyleniminoacrolein. With stirring, to 30 ml of absolute MeOH at 0° were simultaneously added, in 20 min, solutions of 0.5 ml of ethylenimine in 25 ml of MeOH and 0.6 ml of propargylaldehyde in 20 ml of absolute MeOH. After holding at 20° for 15 min the mixture was evaporated in vacuo at 30-35°. The residue (1.1 g) was a clear mobile oil with n_D^{20} 1.5450 and λ_{max} (in EtOH) 275 nm, and, based on the NMR spectrum, is the pure trans-isomer (CD_3OD, δ, ppm): 2.08 (CH_2-CH_2); 5.6 (2CH); 7.51 (3CH); 9.24 (1CH); $J_{1,2} = 8$ Hz, $J_{2,3} = 13$ Hz. Complete tarring occurred when ethylenimine was added to propargylaldehyde in benzene.

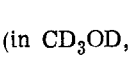
The distillation of (VIII) in vacuo is accompanied by substantial tarring.

3-Ethylenimino-3-phenylacrolein. To 10 ml of absolute MeOH at 0° were simultaneously added 0.85 ml of ethylenimine in 10 ml of absolute MeOH and 2.13 g of phenylpropargylaldehyde in 10 ml of absolute MeOH in 1 h; the mixture was refluxed for 1 h and then evaporated in vacuo. We obtained 1.8 g of an oil with λmax (in EtOH) 295 nm, which, based on the NMR spectrum, represents (IX) as a mixture of the cis- and trans-isomers (1:3) (CD_3OD, δ, ppm): 2.06 and 2.24 (CH_2-CH_2); 5.64 and 5.70 (2CH); 7.34 (C_6H_5); 9.24 and 10.05 (1CH); $J_{1,2} = 8$ Hz.

Esters (IIa-h). Equimolar amounts of (IV) and (V) were mixed in alcohol solution at <25° and allowed to stand for a day at 20°. Compounds (IIa, b, e, f, g, h) were isolated by cooling (an additional amount can be obtained by chromatographing the mother liquor on SiO_2), while compounds (IIc, d) were isolated by vacuum-distillation; (IIi) was obtained in a similar manner from acetal (XII). When subjected to TLC (SiO_2) the (II) compounds give one yellow spot, which is visible without development; system = 2:3 acetone–hexane; for (IIg, h), system = 12:6:1 acetone–chloroform–ethanol. In view of the easy transesterification that occurs during reaction it is necessary to use the alcohol that corresponds to the OAlk in (V).

N-Butyl-3-butylaminocarbamoyl-2-pyridone (VIa). A mixture of 0.75 g (0.0035 M) of (IId) and 1 ml (0.01 M) of butylamine was allowed to stand for 2 days at 20°, after which it was evaporated, and the residue was chromatographed on SiO_2 (elution with a 1:2 acetone–hexane mixture). We obtained 0.7 g (80%) of (VIa) with bp 180-182° (0.1 mm); n_D^{20} 1.5340; λ_{max} (in C_2H_5OH) 236 nm (ε 5650); 330 nm (ε 8800). Found: C 67.01; H 9.01; N 10.81%. $C_{14}H_{22}N_2O_2$. Calculated: C 67.17; H 8.86; N 11.19%. NMR spectrum (in CCl_4, δ, ppm): 0.97 (CH_3); 3.33  ; 3.97 (NCH_2); 6.27 (5CH); 7.58 (4CH); 8.32 (6CH); 9.65 (NH); $J_{4,5} = 7$ Hz; $J_{5,6} = 7$ Hz; $J_{4,6} = 2.2$ Hz; $J_{NHCH_2} = 7$ Hz; $J_{CH_2CH_2N} = 7$ Hz.

N-Benzyl-3-benzylaminocarbamoyl-2-pyridone (VIb). A mixture of 0.35 g (0.003 M) of (IId) and 0.6 ml (0.045 M) of benzylamine was heated for 30 min at 120-140°. Then the mixture was cooled, ether was added, and we separated 0.48 g (52%) of (VIb) with mp 95-96° (from absolute MeOH); λ_{max} (in alcohol) 238 nm (ε 6500); 333 nm (ε 9450). In the IR spectrum, ν 3230 cm^{-1} (NH). Found: N 8.64%, $C_{20}H_{18}N_2O_2$.

Calculated: N 8.80%. NMR spectrum (in CD_3OD, δ, ppm): 5.13 (NCH_2); 4.50 (); 6.40 (5CH); 7.83 (4CH); 8.38 (6CH); 7.23 (C_6H_5); $J_{4,5}$ = 7 Hz; $J_{5,6}$ = 7 Hz; $J_{4,6}$ = 2 Hz.

Esters (VIIa) and (VIIb). The esters were obtained as described in [9, 10]. NMR spectrum (δ, ppm) of (VIIa): 1.2 (CH_3); 3.27 (5CH); 4.08 (CH_2); 6.13 (2CH); 6.62 (3CH); $J_{CH_3CH_2}$ = 7 Hz; $J_{3,5}$ = 2 Hz; $J_{2,3}$ = 16.5 Hz; (VIIb) (in CCl_4): 1.27 (CH_3); 3.44 (5CH); 4.13 (CH_2); 5.75-6.25 (2CH and 3CH); $J_{CH_3CH_2}$ = 7 Hz; $J_{3,5}$ = 1.5 Hz; $J_{2,3}$ = 11 Hz.

Esters (VIIIa) and (VIIIb). The esters were obtained by the addition of Et_2NH to (VIIa) and (VIIb). When subjected to TLC (SiO_2, 1:2 acetone–hexane), compounds (VIIIa), mp 26-28° (from ether), and (VIIIb) (oil) give one yellow spot with R_f 0.5; λ_{max} of (VIIIa) and (VIIIb) (in CCl_4) 340 nm. Infrared spectrum in CCl_4 (ν, cm^{-1}): (VIIIa) = a band at 1600 and a small shoulder at 1620 (C = C), and 1702 (COOEt); (VIIIb) = bands of equal intensity at 1590 and 1612 (C = C), and 1695 (COOEt). The mass spectra of (VIIIa) and (VIIIb) are identical, but M-1/M = 0.35 (VIIIa) and 0.03 (VIIIb). The NMR spectrum of (VIIIa) is given in [2].

CONCLUSIONS

We synthesized some esters of δ-aminopentadienecarboxylic acids, which had an electron-acceptor substituent in the α-position, and also some N-alkyl-3-carbamoyl-2-pyridones.

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