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MECHANISM OF CYCLOCONDENSATION OF ISOPRENOID ACYCLIC α,β-ENALS WITH MONOETHYL MALONATE UNDER THE CONDITIONS OF THE KNOEVENAGEL REACTION

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It was shown that the formation of the di- and trisubstituted derivatives of 1.3-cyclohexadiene-1-carboxylic acid during the condensation of 3-methyl-2-butenal, citral, and farnesal with monoethyl malonate in the presence of secondary amines takes place through the enamines corresponding to these aldehydes, which add to the monoesters of the respective alkenylidenemalonic acids (the "normal" products of the Knoevenagel reaction) by a mechanism of [4 + 2]-cycloaddition. The free carboxyl group in the dienophile is required for the spontaneous transformation of the intermediate [4 + 2]-cycloadducts into the derivatives of cyclohexadiene-1-carboxylic acid in which the catalyst of the process (the secondary amine) is regenerated.

Earlier [1] we discovered that mixtures of disubstituted (IIa-c) and trisubstituted (IIIa-c) esters of 1,3-cyclohexadiene-1-carboxylic acid (CHDC) are formed readily under the conditions of the Knoevenagel reaction between monoethyl malonate and 3-methyl-2-butenal ["prenal," (Ia)], citral (Ib), or farnesal (Ic). With the molar ratio [α,β-enals]:[monoethyl malonate] = 2:1 this process becomes predominant. Then we supposed that the derivatives of cyclohexadienecarboxylic acid are formed either by electrocyclic isomerization of hexatrienes of the A'type, which appear during the decarboxylation and dehydration of the initial acyclic bisadducts of the "aldol" type A, or by [4 + 2]-cycloaddition of the dieneamines of type (IV) and (V) corresponding to the enals (Ia-c) to the "normal" Knoevenagel products, i.e., the monoesters of alkenylidenemalonic acids of type (VI), with subsequent elimination of CO_2 and the secondary amine from the cycloadducts of types (VII) and (VIII). In the present communication we give data in favor of the second of these mechanisms (Scheme 1) (see top of following page).

Effect of the Structure of the Catalyst. As we have already observed [2], the condensation of the enals (Ia-c) with monoethyl malonate (MEM) in the presence of tertiary amines does not lead to the formation of derivatives of cyclohexadienecarboxylic acid of types (VII) and (VIII), which only takes place under the influence of secondary amines. This fact makes cyclocondensation through intermediates of the A and A' types unlikely and indicates possible participation of enamines of the (IV) and (V) types in the process.

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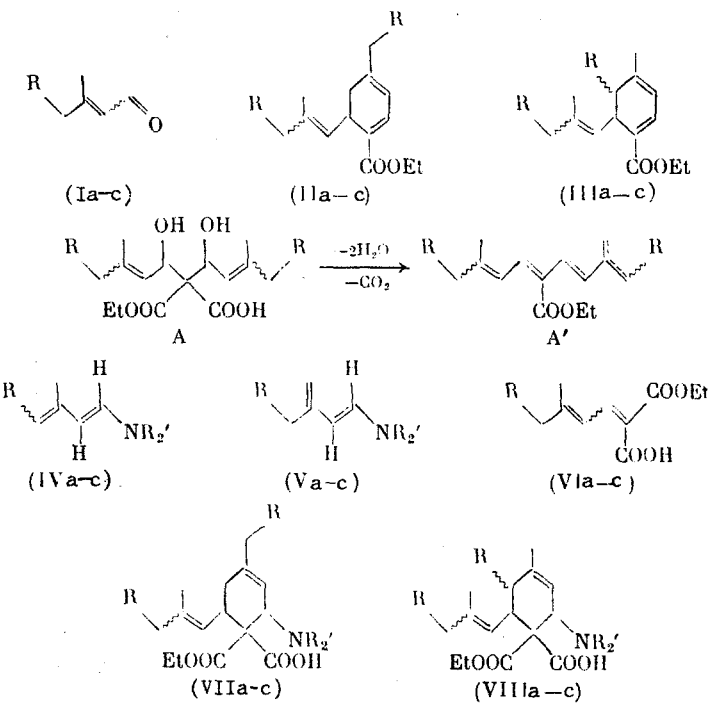
Scheme 1



R = H (Ia), (IIa), (IVa), (VIa), (VIIa); $Me_2C{=}CHCH_2$ (Ib), (IIb), (IVb), (VIb), (VIIb); $Me_2C{=}CH(CH_2)_2C(Me){=}CH{\sim}CH_2$ (Ic), (IIc), (IVc), (VIc), (VIIc).

Effect of the Structure of the Aldehyde. Under the previously described [1] standard conditions of cyclocondensation with monoethyl malonate cinnamaldehyde, 2-methylpropenal, and 3,3-dichloropropenal do not form derivatives of cyclohexadienecarboxylic acid, while crotonaldehyde only gives a small amount of the product, characterized tentatively as ethyl 6-(1'-propenyl)-1,3-cyclohexadiene-1-carboxylate.* Thus, the presence of two CH_3 groups [as in (Ia)] or one CH_3 group and one CH_2 group [as in (Ib, c)] at the β position of the enal is an essential condition for the effective cyclocondensation with monoethyl malonate leading to the derivatives of cyclohexadienecarboxylic acid.

The product from the cyclocondensation of citral (Ib) with monoethyl malonate in the presence of piperidine is a mixture of six isomers, four of which [5,6-cis-E-, 5,6-trans-E-, 5,6-trans-Z-, and 5,6-cis-Z-(IIIb)] belong to structures of type (III) while the other two [E- and Z-(IIb)] belong to structures of type (II) (see [1]). Since this result was obtained with normal citral, which is an equilibrium mixture of the E and Z isomers, in order to reduce the number of components in the obtained mixture of products we decided to use the individual isomers of citral, i.e., geranial E-(Ib) and neral Z-(Ib), obtained by fractional distillation according to [3] in the reactions with monoethyl malonate. However, both E-(Ib) and Z-(Ib) in reaction with monoethyl malonate in the presence of piperidine under the standard conditions were converted into the above-mentioned six-component mixtures of the isomers (IIb) and (IIIb) with almost identical quantitative composition. This result is clearly explained by rapid interconversion E-(Ib) ⇄ Z-(Ib), the rate of which greatly exceeds the rate of the subsequent reactions with monoethyl malonate. In view of the ease of formation of the 1,3-dieneamines from the α,β-enals having "mobile" hydrogen atoms at the γ position [4-7] such interconversion can take place through the dieneamines (IVb) and (Vb).

This is confirmed by the data on the isomerization of pure geranial E-(Ib) and pure neral Z-(Ib) in the presence of catalytic amounts of secondary amines. Thus, after contact

*Determined by TLC on Silufol and UV spectroscopy from the absence of or low intensity of spots having higher R_f values than ethyl alkenylideneacetates of the $X{-}\underset{Y}{C}{=}\underset{Z}{C}{-}CH{=}CH{-}COOEt$ type (where X = Ph, Me, or Cl and Y = H, Me, or Cl), corresponding to these aldehydes and formed under the given conditions [1].

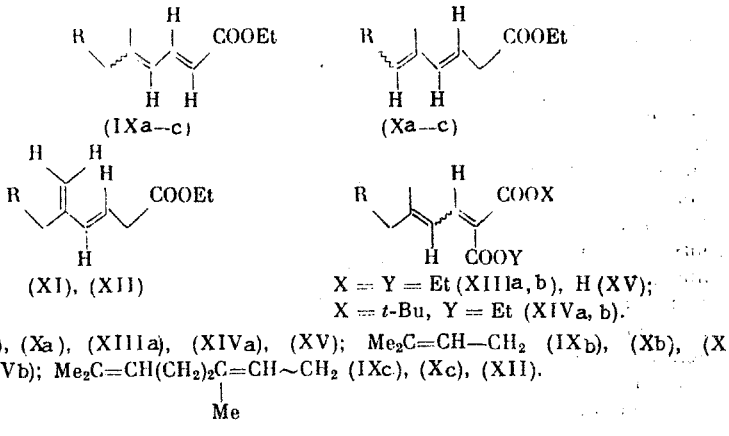
between the aldehyde and 10 mole % of the catalyst (Cat) for 10 min at 20°C the following results were obtained (the data from PMR spectra and GLC):

Aldehyde	Cat	[E-(Ib)]:[Z-(Ib)] in mixture
Geranial E-(Ib)	Piperidine	60:40
Neral Z-(Ib)	Piperidine	60:40
Neral Z-(Ib)	2,2,6,6-Tetramethylpiperidine	56:44
Neral Z-(Ib)	Diisopropylamine	48:52

In order to obtain unambiguous evidence for the formation of the derivatives of cyclohexadienecarboxylic acid of type (II) and (III) from dieneamines of type (IV) and (V) and alkenylidenemalonic esters of type (VI) we synthesized authentic samples of monoethyl prenylidenemalonate (VIa) and citrylidenemalonate (VIb) by the Diels–Alder reaction and compared the composition of the products and (qualitatively) the rate of their reaction with the enamines obtained from prenal (Ia) and citral (Ib), respectively, with the composition of the products and the cyclocondensation rates of (Ia) or (Ib) with monoethyl malonate in the presence of piperidine.

At first we tried to isolate the monoesters (VIa) and (VIb) from the reaction mixtures in the Knoevenagel reaction between the enals (Ia) and (Ib) with monoethyl malonate in the presence of piperidine. It was not possible to do this on account of their rapid transformation into mixtures of ethyl alkenylideneacetates of the "conjugated" (IXa, b) and "deconjugated" type (Xa, b, XI) and into the cyclic compounds (IIb) and (IIIa, b) [2]. However, during the condensation of monoethyl malonate with the less reactive farnesal (Ic) in the presence of 10 mole % of piperidine at 20°C in benzene, after distillation of the latter from the reaction mixture, the PMR spectrum (carbon tetrachloride) of the nonvolatile residue contained signals at δ 6.45 (br. d, J = 12.5 Hz), 7.09 (br. d, J = 12.5 Hz), and 7.88 ppm (d. t, J = 12.5 Hz), which were absent in the spectra both of the initial compounds and of the final products.* The signals at δ 6.45, 7.09, and 7.88 ppm clearly indicate the presence of the initial product from the reaction of (Ic) with monoethyl malonate, i.e., monoethyl farnesylidenemalonate (VIc), in the reaction mixture. After the solution of this residue in benzene had been heated (80°C, 1 h), the PMR spectrum of the obtained product no longer contained signals at δ 6.45, 7.09, and 7.88 ppm, and signals typical of a mixture of farnesylideneacetic ester (IXc), its "deconjugated" isomers (Xc) and (XII), and the cyclic compounds (IIc) and (IIIc), identified and isolated according to [1, 2] (Scheme 2), are observed.

Scheme 2



R = H (IXa), (Xa), (XIIIa), (XIVa), (XV); $Me_2C{=}CH{-}CH_2$ (IXb), (Xb), (XI), (XIIIb), (XIVb); $Me_2C{=}CH(CH_2)_2C(Me){=}CH{\sim}CH_2$ (IXc), (Xc), (XII).

An alternative synthesis of the monoesters (VIa) and (VIb) was realized by two independent methods: a) By partial saponification of diethyl prenylidenemalonate (XIIIa) and citrylidenemalonate (XIIIb) by a water–alcohol solution of alkali (method a, yields 42-46%); b) by the condensation of the enals (Ia) and (Ib) with tert-butyl ethoxycarbonylethanoate ["ethyl tert-butyl malonate" (ETBM)] according to [8] in the presence of piperidine in toluene fol-

*The integral intensities of these signals are in ratios of ~0.5:0.5:1.0. There are analogous signals in the spectra of authentic samples of the monoesters (VIa) and (VIb) (Table 1).

TABLE 1. PMR Spectra of Monoethyl Prenylidenemalonate (VIa) and Citrylidenemalonate (VIb) and Their Related Compounds (deuterochloroform, δ, ppm)

Compound	δ (integral intensity)						
	4-H[a]	3-H[a]	5-CH_3	8-H	10-H_3	9-CH_3	Signals of R in COOR
(VIa)[b]	6,93 br.d (0,45) 7,60 br.d (0,55)	8,42 d (0,45) 8,20 d (0,55)	2,06 s (6H)				1,38 t+1,42 t (total 3H), 4,37 q +4,42 q (total 2H), 10,95 br.s
(XIIIa)	6,22 br.d	7,61 d	1,92 d				1,27 t+1,31 t (total 6H), 4,22 q +4,29 q (total 4H)
(XV)	7,60 br.d	8,60 d	2,37 d				10,6 s (2H)
(VIb)	6,93 br.d[c] (0,45) 7,60 br.d (0,55)	8,48 d>8,42 d[d] (0,45) 8,24 d[d]>8,18 d (0,55)	2,06 d	5,08 m	1,68 s	1,60 s	1,38 t + 1,42 t (total 3H), 4,37 q + 4,42 q (total 2H), 10,95 br.s
(XIIIb)	6,22 br.d	7,48 d+7,52 d	1,95 d	5,02 m	1,68 s	1,60 s	1,28 t + 1,30 t (total 6H), 4,18 q +4,22 q (total 4H)

a) $J_{3,4}$ = 12.5 Hz.
b) For samples synthesized by methods a and b (see the text).
c) In the synthesis of the monoester (VIb) by method b (see the text) the ratio between the same groups of signals was ~63:37.
d) In the synthesis of (VIb) by method a the integral intensity ratio of the signals was ~5:3, by method b ~7:3.

lowed by elimination of 2-methylpropene from the isolated mixed esters (XIVa) and (XIVb) by the action of trifluoroacetic acid (method b, yields 8.5-18%).* The PMR spectra of the monoesters (VIa) and (VIb) show that they are mixtures of the two possible isomers with respect to the Δ^2 bond; the signals from the protons at C^3 and C^4 are double sets of lines, whereas the same signals in the spectra of the diesters (XIIIa) and (XIIIb) and in the spectrum of prenylidenemalonic acid (XV) have the normal multiplicity (Table 1). In the transition from (VIa) to (VIb) the multiplicity of the signals from the proton at C^3 is once again doubled, and this corresponds to the presence of the two possible isomers with respect to the Δ^4 bond in (VIb). The ratio of the isomers with respect to the Δ^2 and Δ^4 bonds for (VIb) varies a little, depending on the method of production (a or b).

The dieneamines (IVa) ($R_2'N = C_5H_{10}N$) and (IVb) ($R_2'N = Et_2N$) were obtained from (Ia) and piperidine or from (Ib) and diethylamine, respectively, by analogy with [4]. The ratio of the isomers (IVb):(Vb), determined by PMR (250 MHz) from the ratio of the integral intensities of the signals from the olefinic protons in the $-CH=CH-N\langle$ ($\delta \sim 6.1-6.3$) and $H_2C=C\langle$ groups (δ 4.45 br. d and 4.60 d, AB system), the signals from the protons in the $N-CH_2$ groups at δ 3.08 d. q for the E/Z isomers of (IVb) and δ (2.68 q for (Vb), and also the signals of the allyl CH_3 groups, amounted to ~96:4 (cf. [6, 7], where the minor isomer was not detected). This nonuniformity in the dieneamine obtained from (Ib) must lead to the formation of the structurally isomeric cycloadducts during its reactions with unsymmetrical dienophiles.

Cycloaddition of Dieneamines to Alkenylidenemalonates. It is known that 1,3-dienamines readily enter into the Diels–Alder reaction with many dienophiles (see the review [9]). In the case of the formation of the derivatives (II) and (III) from the dieneamines (IV) and (V), apart from monoesters (VIa-c), such dienophiles could be the esters of the corresponding alkenylideneacetic acids of type (IX), although their proportion among the products of the Knoevenagel reaction is comparable with the proportions of their $\Delta^{3,5}$ and $\Delta^{3,5(11)}$ or $\Delta^{3,5(15)}$ isomers of type (X-XII) (see [2]). In order to determine the possibility of this the dieneamines (IVa) and (IVb)/(Vb) were held at 20°C for 2-6 days with authentic samples of ethyl prenylideneacetate (IXa) and ethyl citrylideneacetate (IXb), respectively, obtained by the Horner reaction (see [2]), and the reaction products were investigated. Not even traces of the derivatives of cyclohexadienedicarboxylic acid [the esters (IIa) or (IIb) + (IIIb)] were observed here. Thus, the esters (IXa, b) are not the direct precursors of these cyclohexadienes.

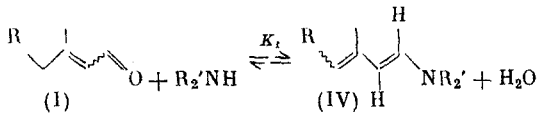
In contrast to this the reaction between the enamine (IVa) and the monoester (VIa) leads after only 5 min to the cyclic diene (IIa) with a 68% yield. Earlier [1] a somewhat smaller yield of the ester (IIa) was obtained after a 40-min reaction of prenal (Ia), monoethyl malonate, and piperidine (in a molar ratio of 2:1:0.2) in boiling toluene. Since the last process is multistage, the intermediate alternatives were examined. In these the initial reaction mixture contained either the diene (IVa) or the dienophile (VIa), while the missing cyclic addend was generated from the remaining components. The (Ia) + (VIa) + piperidine (molar ratios 1:1:0.2) combination at 20°C led after 54 h to the ester (IIa) with a yield of 55%. Such a result probably means that the formation of the dieneamine (IVa) from prenal and piperidine is linked in the general catalytic cycle to the regeneration of the latter during the formation of the cyclohexadiene system (IIa). On the other hand, the (IVa) + monoethyl malonate combination (molar ratio 2:1) in boiling toluene leads after 30 min to (IIa) with a yield of 63%, and this is comparable with the result of the previously investigated [1] three-component cyclocondensation in boiling toluene.

The reaction of the dieneamine obtained from citral and diethylamine, i.e., the mixture [(IVb):(Vb) ~ 96:4, $R_2'N = Et_2N$] with the monoester (VIb) at 20°C leads after 1 h with a 48% yield to a six-component mixture of cyclohexadienecarboxylic acid derivatives, in which (IIb) and (IIIb) are in a ratio of 52:48. Earlier [1] a mixture with similar composition [(IIb):

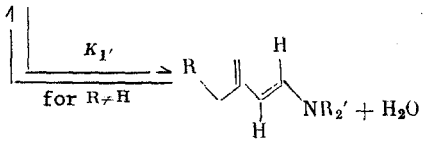
*Attempts to obtain the monoesters (VIa) and (VIb) by the action of lithium iodide or trimethyl silyl iodide on the diesters (XIIIa) and (XIIIb) were unsuccessful.

(IIIb) = 45:55] was obtained with a yield of 85% by boiling (Ib), monoethyl malonate, and piperidine (R_2NH = $C_5H_{10}NH$) in toluene for 40 min.*

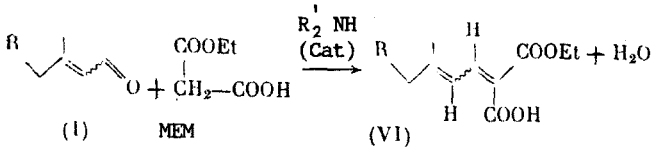
Scheme 3



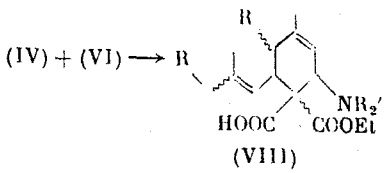
(1)



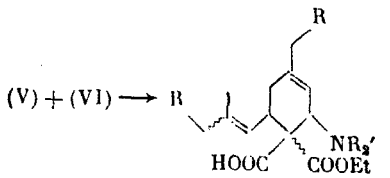
(1')



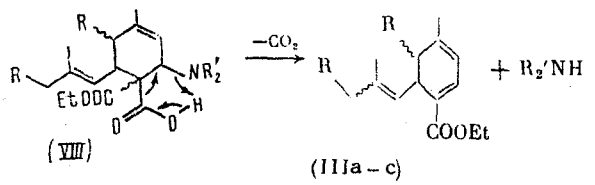
(2)



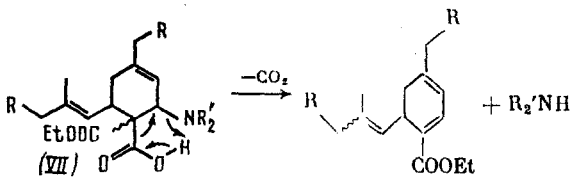
(3)



(3')



(4)



(4')

(IIa–c)

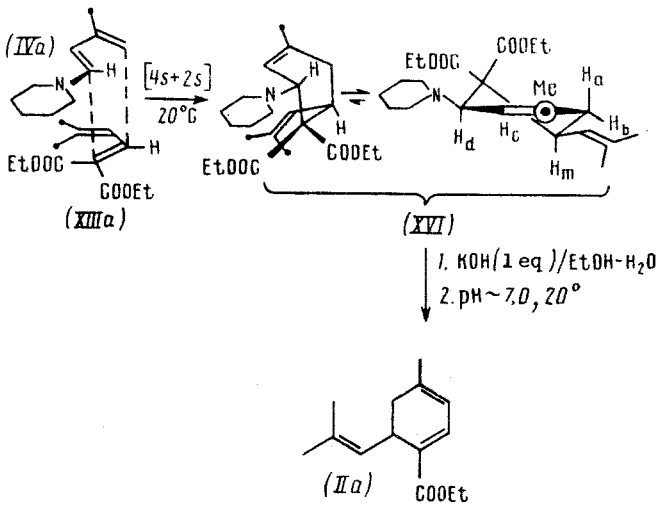
Altogether the obtained data make it possible to propose the following scheme (Scheme 3) for the formation of the cyclic dienes of types (II) and (III) under the conditions of the Knoevenagel reaction between the enals (Ia-c) and monoethyl malonate in the presence of the secondary amines. Stage (2) in this scheme is given in total without details of the possible equilibria; one of the alternatives of stage (2) may be reaction of the dieneamine protonated at the δ position (see [9]) with the monoethyl malonate anion, to which the (IVa) +

*Although the yield in the two-component reaction (20°C, 1 h) is lower than in the three-component cyclocondensation (110°C, 40 min), in the latter case if it is assumed that the rate of the component stages and of the three-component process as a whole is approximately doubled for each 10° the attainment of the same yield at 20°C would require $40 \cdot 2^9$ min or more than 340 h. This is clearly longer than the time required for completion of the two-component reaction between the dieneamine of citral and the monoester (VIb).

monoethyl malonate combination corresponded in our experiments. (For the mechanisms of the Knoevenagel reaction catalyzed by secondary amines, see [10, 11].)

The need for the presence of the free carboxyl group in the dienophile for the easy formation of derivatives of cyclohexadienecarboxylic acid can be seen from the following. In the reaction of the dieneamine (IVa) with diethyl prenylidenemalonate (XIIIa) (20-25°C, 10 days) the cyclic aminodiester (XVI), the structural and stereochemical individuality of which was demonstrated by TLC and PMR spectroscopy, was obtained with a quantitative yield. In the PMR spectrum of the cycloadduct (XVI) the three-proton system at the C^5 and C^6 atoms is characterized by J_{am} = 12 and J_{bm} = 5 Hz, while the interaction of the protons at C^2 and C^3 is characterized by J_{cd} ~ 1 Hz, from which it follows that the dihedral angles are $\varphi_{am} \approx 165 \pm 15°$, $\varphi_{bm} \approx 45 \pm 5°$, and $\varphi_{cd} \approx 80\text{-}90°$. These data agree with the cis-diequatorial arrangement of the substituents at C^2 and C^6, correspondingly to $[4_S + 2_S]$-cycloaddition of (IVa) to the diester (XIIIa) according to the Alder rule. Partial saponification of the aminodiester (XVIa) by an alcohol solution of potassium hydroxide and evaporation of the reaction mixture gave the solid salt of the respective aminodicarboxylic monoester not containing even traces of the diene ester (IIa) (TLC). During neutralization of an aqueous solution of this salt to pH ≈ 7 decarboxylation and deamination with the formation of the ester (IIa) took place readily (Scheme 4).

Scheme 4



Thus, the cyclocondensation of prenal, citral, and farnesal with monoethyl malonate in the presence of secondary amines evidently takes place through the 1,3-dieneamines corresponding to these enals, and they enter into [4 + 2]-cycloaddition with the monoethyl esters of prenylidene-, citrylidene-, and farnesylidenemalonic acid (the "normal" products of the Knoevenagel reaction). As a result of their betaine character the obtained cycloadducts are readily transformed into derivatives of cyclohexadienecarboxylic acid, losing a molecule of CO_2 and returning a molecule of the secondary amine to the catalytic cycle.

The possibility of the production of derivatives of "the hybrid citral–prenal type" on the basis of this mechanism and other Diels–Alder reactions involving acyclic isoprenoid 1,3-dieneamines is reported in the next paper [12].

EXPERIMENTAL

The boiling points of all the obtained compounds were not corrected. The chemical purity and the ratio of the geometric isomers in the reaction products were monitored by GLC on an LKhM-8MD instrument with a stainless steel column (2 m × 3 mm) and a flame-ionization detector (5% of XE-60 stationary phase on Chromaton N-AW-DMCS, additionally silylated by hexamethyldisilazane with nitrogen as mobile phase). The qualitative control of the reaction masses and products was conducted on Silufol plates in the 9:1 hexane–ethyl acetate system. The PMR spectra were recorded on Jeol FX 90Q (90 MHz) and Bruker WM-250 (250 MHz) instruments in deuterochloroform. The IR spectra were recorded in carbon tetrachloride on a Perkin-Elmer 577 instrument. The UV spectra were recorded on a Specord UV-Vis instrument in ethanol. The

mass spectra and the GLC-MS data were obtained on a Varian MAT-311A instrument with a quartz capillary column (25 m × 0.2 mm) with SE-30 as stationary phase (nitrogen, evaporator temperature 290°C, thermostat program from 160°C, 10 deg/min).

3-Methyl-1-(N-piperidino)-1,3-butadiene (IVa). The compound was obtained by analogy with [4] from 8.4 g (0.1 mole) of prenal and 16.8 g (0.2 mole) of piperidine. The yield was 8.6 g (57%); bp 102-103°C (12 mm Hg), n_D^{20} 1.5421. PMR spectrum (δ, ppm): 1.57 m (6H, CH_2 unit), 1.77 s (3H, CH_3), 2.95 m (4H, N–CH_2) 4.5 (1H) and 4.6 m (1H), 5.2 d (1H, J_{AB} = 14.5 Hz), 6.1 d (1H, 1-H, J_{AB} = 14.5 Hz).

Mixture of 3E/Z-3,7-Dimethyl-1-diethylamino-1,3,6-octatriene E/Z-(IVb) and 7-Methyl-3-methylene-1-diethylamino-1,6-octadiene (Vb). The compound was obtained by analogy with [4] from 7.6 g (50 mmoles) of citral and 7.3 g (0.1 mole) of diethylamine. The yield was 7.14 g (71%); bp 85°C (0.2 mm Hg). PMR spectrum (δ, ppm): 1.08 t < 1.12 t (6H, J = 7 Hz, N–$CH_2\underline{CH_3}$), 1.63 br.s < 1.66 br. s + 1.69 br. s (total 6H, 7-CH_3), 1.75 s < 1.81 s (total 3H, 3-CH_3 with E/Z ~ 2:1), 2.68 q [0.16 H, N–CH_2 for (Vb)], 2.69 br. t (2H, J = 7 Hz, 5-H_2), 3.05 < 3.1 q (total 4H, J = 7 Hz, N–CH_2), 4.45 br. d (0.04 H, J_{AB} = 2 Hz, =C(H)H), 4.6 d (0.04 H, J_{AB} = 2 Hz, =C(H)H), 4.81 br. t > 5.06 br. t (total 1H, J = 7 Hz, 4-H), 5.08 < 5.26 d (total 1H, J = 14 Hz, 2-H), 6.16 d < 6.26 d (total 1H, J = 14 Hz, 1-H).

Diethyl Prenylidenemalonate (XIIIa). A 4.2-g sample (50 mmoles) of prenal (Ia) was mixed with 8 g (50 mmoles) of malonic ester in 20 ml of benzene, 0.5 ml (10 mole %) of piperidine was added, and the mixture was left for 12 h. The solvent was evaporated on a rotary evaporator, the residue was distilled under vacuum, and 8.3 g (74%) of the diester (XIIIa) was obtained; bp 85-86°C (0.08 mm Hg), n_D^{22} = 1.5030. The PMR spectrum is given in Table 1. IR spectrum (carbon tetrachloride, ν, cm^{-1}): 1718 s, 1634, 1600.

Diethyl Citrylidenemalonate (XIIIb). The compound was obtained by analogy with (XIIIa) from 7.6 g (50 mmoles) of the citral (Ib). The yield was 7.3 g (~50%); bp 126°C (0.07 mm Hg), n_D^{23} = 1.5085. The PMR spectrum is given in Table 1.

Monoethyl Prenylideneacetate (VIa). a. A 4.52-g sample (20 mmoles) of (XIIIa) was added to a solution of 1.3 g (23 mmoles) of potassium hydroxide in 13 ml of ethanol and 7 ml of water. The mixture was boiled under a reflux condenser for 3 h. The reaction mixture was then evaporated on a rotary evaporator and extracted with ether (2 × 5 ml). The aqueous layer was acidified to pH ~ 6 with hydrochloric acid (1:1) and extracted with ether (3 × 5 ml). The ether extracts were washed with water (2 × 3 ml), dried with sodium sulfate, evaporated on a rotary evaporator, and isolated by chromatography on silica gel with benzene as eluant; R_f ~ 0.3 (6:1 hexane–ethyl acetate). The yield was 1.65 g (42%) of (VIa); n_D^{21} = 1.5117. In addition to (VIa), we isolated 1.2 g (35%) of (XV). (The PMR spectra are given in Table 1.) IR spectrum (carbon tetrachloride, ν, cm^{-1}) for (VIa): 3600-2400, 1740, 1600. UV spectrum (ethanol): λ 284 nm (ε 13,200). Mass spectrum: $[M^+]$ = 198.

b. A 0.94-g sample (5 mmoles) of $CH_2(CO_2Et)CO_2(t\text{-}Bu)$, obtained according to [8], was mixed with 0.42 g (5 mmoles) of the prenal (Ia) in 4 ml of toluene with 0.05 ml of piperidine and boiled under a reflux condenser for 6 h. The ester (XIVa) was isolated by chromatography on silica gel with benzene as eluant. The yield of the crude (XIVa) was 1.2 g (94%). To 1.2 g (~4.7 mmoles) of (XIVa) we added 1.2 ml of trifluoroacetic acid. The mixture was left for 3 h, neutralized with an excess of sodium carbonate solution (to pH ~ 9), and extracted with 2 × 5 ml of ether. The aqueous layer was acidified to pH ~ 6 with hydrochloric acid (1:1) and extracted with ether (2 × 5 ml). The ether layer was dried with sodium sulfate, and (VIa) was isolated by analogy with method a. The yield was 0.08 g (8.4%). The spectral data coincide with the data for (VIa) obtained by method a.

Monoethyl Citrylidenemalonate (VIb). Method a. The compound was obtained by analogy with (VIa) from 3.63 g (12.4 mmoles) of (XIIIb), 0.7 g (12.5 mmoles) of potassium hydroxide in 14 ml of ethanol, and 8 ml of water. The yield of (VIb) was 1.5 g (46%); n_D^{22} 1.5110. The PMR spectrum is given in Table 1. IR spectrum (carbon tetrachloride, ν, cm^{-1}): 3600-2400, 1740, 1610. UV spectrum (ethanol): λ 288 (ε 21,600). Mass spectrum: $[M^+]$ = 266.

Method b. The compound was obtained by analogy with (VIb) from 0.76 g (5 mmoles) of the citral (Ib) after boiling for 14 h. The yield of the crude (XIVb) was 1.25 g (78%). To 0.64 g (~2 mmoles) of (XIVb) we added 0.5 ml of trifluoroacetic acid. The mixture was left for 12 h, and compound (VIb) was isolated by analogy with (VIa). The yield was 0.1 g (~18%). The PMR spectrum is given in the text and in Table 1; $[M^+]$ = 266.

Ethyl 6-(2'-Methyl-1'-propenyl)-4-methyl-1,3-cyclohexadienecarboxylate (IIa). a. A 0.15-g sample (1 mmole) of the dieneamine (IVa) was mixed with 0.2 g (1 mmole) of the monoester (VIa) in 4 ml of benzene. After 5 min the reaction mixture was evaporated on a rotary evaporator, and (IIa) was isolated by chromatography on silica gel with hexane as eluant. The yield was 0.15 g (68%); n_D^{19} = 1.5173.

b. A 0.75-g sample (5 mmoles) of (IVa) was mixed with 0.33 g (2.5 mmoles) of monoethyl malonate in 3 ml of toluene and boiled under a reflux condenser for 30 min. Compound (IIa) was isolated by chromatography on silica gel, and the yield was 0.35 g (63%).

c. A 0.084-g sample (1 mmole) of prenal (Ia) was mixed with 0.2 g (1 mmole) of (VIa) in 4 ml of benzene containing 0.02 ml (20 mole %) of piperidine. The mixture was left at ~20°C for 54 h (monitored by TLC). Compound (IIa) was isolated by chromatography on silica gel with a yield of 0.12 g (55%).

The spectral characteristics for the samples of (IIa) agreed with previously described data [1].

Ethyl 6-(2',6'-Dimethyl-1',5'-heptadienyl)-4-(4'-methyl-3'-pentenyl)-1,3-cyclohexadienecarboxylate (IIb) and 6-(2',6'-Dimethyl-1',5'-heptadienyl)-5-(3'-methyl-2'-butenyl)-4-methyl-1,3-cyclohexadienecarboxylate (IIIb). A 0.2-g sample (~1 mmole) of the citral dieneamine (IVb) + (Vb) was mixed with 0.27 g (~1 mmole) of the monoester (VIb) at ~20°C. After 1 h the benzene was evaporated on a rotary evaporator, and a mixture of the esters (IIb) and (IIIb) was isolated by chromatography on silica gel with hexane as eluant. The yield was 0.17 g (48%); n_D^{21} = 1.5181. UV spectrum (ethanol): λ 310 (ε 12,800). The other spectral characteristics agreed with previously published data [1].

Diethyl 2-Piperidino-6-(2'-methyl-1'-propenyl)-4-methyl-3-cyclohexene-1,1-dicarboxylate (XVI). A 0.15-g sample (1 mmole) of (IVa) was mixed with 0.226 g (1 mmole) of the diester (XIIIa) in 4 ml of benzene and allowed to stand at ~20°C for 10 days. The reaction mixture was then washed with 1 ml of 10% hydrochloric acid and 1 ml of water, which were extracted with 2 ml of ether. To the combined aqueous layer we added a solution of sodium carbonate to pH ~ 7. The product was extracted with ether (2 × 3 ml), and the organic layer was washed with water, dried with sodium sulfate, and evaporated on a rotary evaporator. The yield of (XVI) was 0.37 g (~100%), n_D^{22} 1.4940. PMR spectrum (1.23 t) (6H, OEt + 4H of piperidine), 1.42 m (2H, $N(CH_2)_5$), 1.72 br. s (9H, CH_3), 1.45-1.95 m (2H, J = 5, 12, and 18 Hz), 2.47 and 2.7 m (4H, $N(CH_2)_5$), 3.24 m (1H, J = 5, 10, and 12 Hz), 3.67 br. s (1H, C^2), 4.18 m (4H, OEt), 5.2 br.d (1H, HC=, J = 10 Hz), 5.54 br. s (1H, C^3). IR spectrum: 1755 and 1728 s, 1682.

Ethyl 6-(2'-Methyl-1'-propenyl)-4-methyl-1,3-cyclohexadienecarboxylate (IIa). A 0.135-g sample (0.36 mmole) of the diester (XVI) was added to a solution of 0.02 g (0.36 mmole) of potassium hydroxide in 1 ml of ethanol and boiled for 1 h. The mixture was then evaporated almost to dryness (data from TLC before acidification), acidified with dilute hydrochloric acid (~1:10), and extracted with ether (2 × 3 ml). The ether layer was washed with water and dried with sodium sulfate. The ester (IIa) was isolated by chromatography on silica gel with a yield of ~0.015 g (18.5%). All the spectral characteristics agreed with published data [1].

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ACYCLIC ISOPRENOID 1,3-DIENEAMINES IN THE DIELS–ALDER REACTION

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The dieneamines obtained from 3-methyl-2-butenal and citral (Ia) and (Ib, c) enter into [4 + 2]-cycloaddition with monoethyl citrylidenemalonate (II) and prenylidenemalonate (III), respectively, forming the esters of substituted 1,3-cyclohexadiene-1-carboxylic acids with side chains of the isoprenoid type. The same or analogous cyclohexadiene can be obtained from "citral dieneamine" (Ib, c) and typical dienophiles (methyl acrylate, diethyl fumarate, etc.) in a two-stage path, including the initial production of derivatives of 2-amino-3-cyclohexene-1-carboxylic acid in the Diels–Alder reaction and then elimination of the amino group from the cyclic adducts. The isomeric composition of the mixture of cyclic adducts formed in the reaction of (Ib + Ic) with diethyl fumarate under strictly aprotic conditions correlates with the ratio of the structural isomers with a Δ^3 and $\Delta^{3(9)}$ bond (Ib, c) in the "citral dieneamine." In the reaction of the dieneamine with the less reactive methyl acrylate the obtained mixture of cyclic adducts contains a significantly larger fraction of the isomer corresponding to the minor $\Delta^{3(9)}$ isomer of the dieneamine.

In the previous communication [1] we showed that the alicyclic 1,3-dieneamines obtained from 3-methyl-2-butenal ["prenal (Ia)] and citral [a three-component mixture of the E/Z isomers with the Δ^3 bond E/Z-(Ib) and with the $\Delta^{3(9)}$ bond (Ic), containing ~4% of the latter] react with the monoethyl esters of prenylidenemalonic (III) and citrylidenemalonic (II) acids under mild conditions, forming derivatives of 1,3-cyclohexadiene-1-carboxylic acid (CHDC) with side chains of the isoprenoid type. Since the obtained compounds are structurally similar to certain pharmacologically active compounds of the 4-(norpolyprenyl)benzoic acid type (see the review [2]), we decided to investigate the reactions of the dieneamines (Ia) and (Ib, c) with α,β-unsaturated esters in greater detail.

[4 + 2]-Cycloaddition to Alkenylidenemalonic Esters. The "crossed" [4 + 2]-cycloaddition reaction between the prenal dieneamine (Ia) and citrylidenemalonic monoester (II) and between the citral dieneamine (Ib, c) and the prenylidenemalonic monoester (III) takes place readily at 20-25°C with spontaneous elimination of the amine molecule and CO_2. In the first case ethyl 4-methyl-6-(2',6'-dimethyl-1',5'-heptadienyl)-1,3-cyclohexadiene-1-carboxylate (IV) (a mixture of the 1'E and 1'Z isomers in a ratio of ~5:3) is formed with a yield of 63% after 10 min. In the second case a three-component mixture containing the 5,6-cis and 5,6-trans stereoisomers of the ester (V), corresponding to addition of the E- and Z-dieneamines of structural type (Ib), and the ester (VI), corresponding to addition of the minor dieneamine (Ic), is formed. The overall yield of the esters (V) and (VI) amounts to 55% (20°C, 1 h) or 69% (80°C, 10 min (Scheme 1).

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