SYNTHESIS OF 3-METHYL-5-(HETARYL)-2,4-PENTADIENOIC ACIDS FROM ALDEHYDES

K. I. Kuchkova

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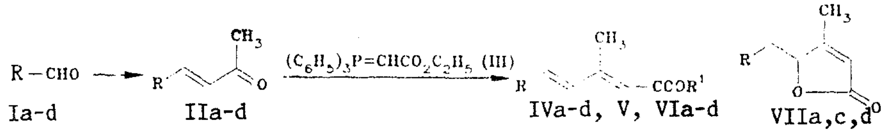
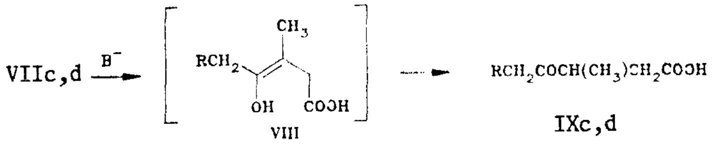
Reaction of 4-(2-, 3-, 4-pyridyl, or 2-quinolyl)but-3-en-2-ones with carbethoxymethylenetriphenylphosphorane and subsequent hydrolysis gives 3-methyl-5-(2-, 3-, 4-pyridyl, or 2-quinolyl)-2,4-pentadienoic acids and also 3-methyl-4-(2-, 4-pyridyl-, or 2-quinolylmethyl)but-2-en-4-olides as products of cyclization of the corresponding pentadienoic acids.

We have previously synthesized E,E-3-methyl-5-(3-indolyl)-2,4-pentadienoic acid V. At low concentration in a series of green crops this has high antitranspirational activity comparable to abscisic acid which is a natural regulator of water balance in plants [1]. In a search for novel organic compounds with similar activity we have synthesized the pentadienoic acids VIa-d containing a pyridine or quinoline ring. The α,β-unsaturated ketones IIa-d were prepared from the aldehydes Ia-d according to [2] and used in a Wittig condensation with carbethoxymethylenetriphenylphosphorane III to give a mixture of the Z,E- and E,E-isomers of the ethyl 2,4-pentadienoates IVa-d. Hydrolysis with KOH gave the acids VIa-d. In the case of IVb the corresponding, stable Z,E- and E,E-isomeric acids of VIb were separated.



I, II, IV, VII: a) R = 2-pyridyl, b) 3-pyridyl, c) 4-pyridyl, d) 2-quinolyl; V, R = 3-indolyl; VI, $R^1 = C_2H_5$; V, VI, R^1 = H.

Only the E,E-isomers of the acids were stable when prepared from the ethyl esters IVa,c,d, which contain the 2- or 4-pyridyl or 2-quinolyl side chains. Although the Z,E-isomers were formed upon ester hydrolysis they were only stable in the solid state. In solution during crystallization they were almost completely converted to the γ-lactones VIIa,c,d by an intramolecular addition to the activated double bond. Treatment of lactones VIIc,d with sodium ethylate gave the ketoacids IXc,d.



The configuration of the isomeric esters IVa-d and acids VIa-d were determined from PMR spectral data which has shown that, for E,E-isomers of 3-methyl-2,4-pentadienoic acids when compared with the Z,E-isomers, there is a characteristic low field shift of the methylene group and 2-H proton signals [3]. The IR spectra of the synthesized pentadienoic acids and esters show absorption bands for the Z,E-isomers at 970-990 cm^{-1} and the E,E-isomers at 960-970 cm^{-1} in agreement with [3]. The spectra of acids VIa-d also contain absorptions at 1590-1600 and 1620-1630 cm^{-1} (C=C) and 1680-1700 cm^{-1} (COOH) and for VIa-d and IXc,d broad bands at 1870-1900 and 2400-2500 cm^{-1} which are specific for pyridine carboxylic acids. The mass spectra of VIIc,d and IXc,d supported the assigned structures. The scheme shows the basic mode of mass spectrometric decomposition of these substances as seen in the lactone VIIc and keto acid IXc (see Scheme 1).

EXPERIMENTAL

Infra-red spectra were recorded on a Specord-75 instrument for Vaseline mulls, NMR spectra on a Tesla-467 (60 MHz) instrument with TMS or HMDS internal standard, and mass spectra on an MK-1320 instrument with direct introduction of the sample into the ion source and ionization energy of 70 eV. The melting points were determined

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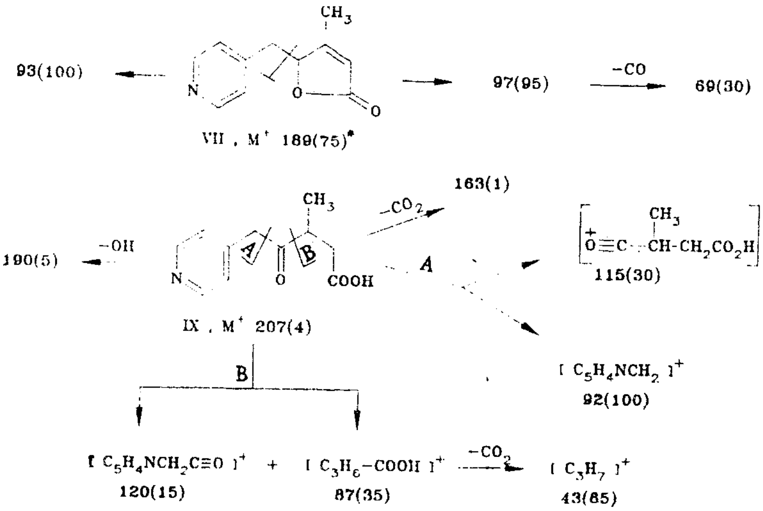
Chemistry Institute, Academy of Science of the Moldavian SSR, Kishinev 277028. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 653-656, May, 1991. Original article submitted August 11, 1989.

Scheme 1



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*m/z value (I_{rel}, %).

on a Boetius microstage. Monitoring of the reactions and the product purities was performed by TLC on Silufol plates with chloroform—methanol 19:1 (A) or 9:1 (B) solvents and visualization with iodine vapor. Column chromatography was carried out on L 100/160 grade silica gel.

Elemental analytical data for C, H, Cl, and N agreed with that calculated.

Ethyl 3-Methyl-5-hetaryl-2,4-pentadienoate (IVa-c, $C_{13}H_{15}NO_2$; IVd, $C_{17}H_{17}NO_2$). A mixture of ketone IIa-d (25 mmoles) and phosphorane III (28 mmoles) was heated for 40-60 min in an inert atmosphere at 100-145°C, cooled, and dissolved in a small volume of ether. Crystals of triphenylphosphine oxide separated on cooling and were filtered off. After distillation of ether the residue was chromatographed on a silica gel column using benzene—ether (4:1) to give the Z,E- and E,E-isomers IVa-d in 50-70% yield as the individual isomers or as a mixture. The viscous liquid or low-melting colorless crystals had IR bands at 1700 cm^{-1} and PMR signals at 1.27-1.30 (3H, t, CH_3) and 4.17-4.20 ppm (2H, q, CH_2); Z,E-isomer: 2.10-2.17 (3H, s, 3-CH_3) and 5.80-5.83 (1H, s, 2-H); E,E-isomer: 2.40 and 5.93-5.97 ppm, respectively.

E,E-3-Methyl-5-(2-pyridyl-2,4-pentadienoic Acid (E,E-VIa, $C_{11}H_{11}NO_2$). A solution of the E,E-ester IVa (0.8 g, 3.7 mmoles) in potassium hydroxide (20%, 15 ml in methanol) was held at room temperature for 24 h, diluted with water (20 ml), and the methanol distilled off in vacuo. The solution was neutralized with acetic acid and the precipitate filtered off, washed with water, and recrystallized from methanol to give colorless crystals (0.37 g, 53%) with mp 171-172°C and R_f 0.36 (A) (Table 1).

TABLE 1. PMR Spectra of the Synthesized Compounds*

Compound	Solvent	Chemical shift, ppm
Z.E-VIa	DMSO-D_6	2,10 (3H,s , CH_3); 5,83 (1H. s, 2-H)
E,E-VIa	DMSO-D_6	2,40 (3H, s, CH_3); 6,08 (1H,s, 2-H)
Z,E-VIb	CD_3OD	2,16 (3H, s, CH_3); 5,86 (1H, s, 2-H)
E,E-VIb	CD_3OD	2,36 (3H, s, CH_3); 6,00 (1H, s, 2-H)
E,E-VIc	CF_3COOH	2,50 (3H, s , CH_3); 6,36 (1H, s , 2-H)
Z,E-VId	DMSO-D_6	2,06 (3H, s , CH_3); 5,66 (1H, s, 2-H)
E.E-VId	DMSO-D_6	2,38 (3H, s, CH_3); 6,08 (1H, s, 2-H)
VIIa	CCl_4	2,07 (3Hs , CH_3); 2,70 . . . 3,43 (2H, m, CH_2); 5,20 (1H, t, 4-H); 5,58 (1H, s, 2-H)
VIIc	$(CD_3)_2CO$	2,17 (3H,s, CH_3; 2,67 . . . 3,57 (2H, m. CH_2); 5,27 (1H, t, 4-H); 5,80 (1H,s, 2-H)
VIId	$CDCl_3$	2,10 (3H s, CH_3; 2,91 . . . 3,65 (2H, m, CH_2); 5,40 (1H, t, 4-H); 5,65 (1H, s, 2-H)
IXc	CF_3COOH	0,92 (3H, d. $J=6$ Hz, CH_3); 1,94 (1H, m, 3-H); 2,41 . . . 2,84 (2H, m , 2-H); 4,04 (2H, s 5-H)
IX d	CF_3COOH	0,95 (3H, d, $J=6$Hz., CH_3); 2,37 (1H, m, 3-H); 2,43 . . . 2,83 (2H, m. 2-H); 4,30 (2Hs., 5-H)

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*The table does not show the signals for the protons of the pyridine or quinoline rings or of the $C_{(4)}$—$C_{(5)}$ double bond in VIa-d.

Z,E-3-Methyl-5-(2-pyridyl)-2,4-pentadienoic Acid (Z,E-VIa, $C_{11}H_{11}NO_2$). Treatment of Z,E-IVa (1.2 g, 5.5 mmoles) with 10% KOH solution in methanol as described for E,E-IVa gave a crystalline precipitate (0.64 g, 61%) with mp 106-107°C and R_f 0.33 (A). Recrystallization from $CHCl_3$ gave 0.12 g (11%) with mp 108-109°C.

3-Methyl-4-(2-pyridylmethyl)but-2-en-4-olide (VIIa, $C_{11}H_{11}NO_2$). The mother liquor after recrystallization of the Z,E-acid VIa was distilled, the residue dissolved in ether, and filtered through a silica gel layer. Lactone VIIa was obtained as a viscous liquid (0.4 g, 38% based on IVa) with n_D^{20} 1.4523, R_f 0.60 (A). IR spectrum (film): 1630 (C=C), 1740 cm^{-1} (γ-lactone).

Hydrochloride ($C_{11}H_{11}NO_2 \cdot HCl$). Colorless crystals, mp 144-145°C (from alcohol). IR spectrum: 1740 (γ-lactone), 1980, 2050, 2450 cm^{-1} ($C=\overset{+}{N}-H$).

3-Methyl-5-(3-pyridyl)-2,4-pentadienoic Acid ($C_{11}H_{11}NO_2$, Z,E-VIb and E,E-VIb). A. A solution of ester IVb (6.6 g, 30 mmoles as a mixture of isomers) and 10% KOH in methanol (165 ml) was held at room temperature for 24 h and worked up as described for acid E,E-VIa. The product was neutralized, extracted with ethyl acetate (5 x 200 ml), dried (Na_2SO_4), and evaporated in vacuo to 50-100 ml. Crystals of VIb (as a mixture of Z,E- and E,E-isomers) were filtered off (3.16 g, 55%). Recrystallization from methanol gave initially 1.5 g of the Z,E-isomer with mp 199-200°C and R_f 0.66 (B). Evaporation of the mother liquor gave crystals of the E,E-isomer (1.20 g) with mp 149-150°C and R_f 0.63 (B).

B. A mixture of ketone IIb (1 g, 6.8 mmoles) and phosphorane III (2.6 g, 7.5 mmoles) was heated under nitrogen for 1 h at 125°C and then worked up as described in the general method for IVa-d. After evaporation of ether the residue was treated with 10% KOH solution in 90% ethanol (40 ml), refluxed for 1 h, poured into water (400 ml), and extracted with ether. The aqueous-base solution was neutralized with acetic acid and again extracted with ether (5 x 100 ml). The ether extract was dried (Na_2SO_4 and distilled to give a crystalline residue (0.98 g, 76%). Recrystallization from methanol gave the Z,E- (0.23 g) and E,E-isomers (0.22 g) of VIb.

E,E-Methyl-5-(4-pyridyl)-2,4-pentadienoic Acid (E,E-VIc, $C_{11}H_{11}NO_2$). Ten percent KOH in 90% alcohol (11 ml) was added to ester IVc (mixture of Z,E- and E,E-isomers, 2.58 g, 11.9 mmoles) and refluxed in an inert atmosphere for 0.5 h, the ethanol evaporated in vacuo, and the residue treated with water (11 ml) and neutralized with acetic acid. The precipitate was filtered off and washed with water to give the Z,E- and E,E-isomers of VIc (1.7 g, 75%) which were recrystallized from methanol to give crystals of the acid E,E-VIc (0.39 g, 17%) with mp 241-242°C and R_f 0.45 (B).

3-Methyl-4-(4-pyridylmethyl)but-2-en-4-olide (VIIc, $C_{11}H_{11}NO_2$). The mother liquor after recrystallization of the mixture of isomers of VIc was evaporated and the residue recrystallized from CCl_4 to give colorless crystals (0.93 g, 41% based on IVc) with mp 88-89°C, R_f 0.80 (B), and IR spectrum: 1630 (C=C), 1740, 1760 cm^{-1} (d) (γ-lactone).

Hydrochloride ($C_{11}H_{11}NO_2 \cdot HCl$). Colorless crystals, mp 161-162°C (from alcohol), and IR spectrum: 1740 (γ-lactone), 1830, 1970, 2060, 2570 cm^{-1} (C=N—H).

Z,E-3-Methyl-5-(2-quinolyl)-2,4-pentadienoic Acid (Z,E-VId, $C_{15}H_{13}NO_2$). A mixture mixture of Z,E-IVd (2.3 g, 8.6 mmoles) and 10% KOH in methanol (69 ml) was stirred for 2 h, poured into water (700 ml), and extracted with ether. The aqueous layer was acidified with acetic acid and the precipitate filtered off, and washed with water to give Z,E-VId (1.74 g, 84%) as colorless crystals with mp 113-114°C.

E,E-3-Methyl-5-(2-quinolyl)-2,4-pentadienoic Acid (E,E-VId, $C_{15}H_{13}NO_2$). A mixture of E,E-IVd (1.58 g, 5.9 mmoles) and 10% KOH solution in methanol (48 ml) was stirred for 2 h and the precipitated potassium salt of acid E,E-VId filtered off, and washed with a little water to give crystals (0.61 g) with mp >350°C. They were dissolved in water (20 ml), acidified with acetic acid, and the precipitate filtered off, washed with water, and recrystallized from methanol to give E,E-VId (0.49 g, 35%) as colorless crystals with mp 200-201°C and R_f 0.44 (A).

Additional E,E-VId was obtained from the mother liquor after removal of the potassium salt. The filtrate was diluted with water (0.5 liter), extracted with ether, acidified with acetic acid, and extracted with ethyl acetate. The ethyl acetate was dried (Na_2SO_4) and distilled and the residue recrystallized from methanol to give crystals (0.37 g) with mp 200°C. Overall yield 0.86 g (61%).

3-Methyl-4-(2-quinolylmethyl)but-2-en-4-olide (VIId, $C_{15}H_{13}NO_2$) was obtained by recrystallization of Z,E-VId acid from ethanol in 70-80% yield as colorless crystals with mp 109-110°C and R_f 0.77 (A). IR spectrum: 1640 (C=C), 1735, 1750 cm^{-1} (γ-lactone). Mass spectrum, m/z (I_{rel}, %): M^+ 239 (100), 142 (70), 128 (15), 97 (30), 69 (22).

Hydrochloride ($C_{15}H_{13}NO_2 \cdot HCl$). Colorless crystals, mp 156-157°C (from isopropanol). IR spectrum: 1760, 1785 (γ-lactone), 1960, 2280, 2500 cm^{-1} ($C=\overset{+}{N}-H$).

3-Methyl-4-oxo-5-(4-pyridyl)pentanoic Acid (IXc, $C_{11}H_{13}NO_3$). Sodium (0.25 g, 10 mmoles) was added portionwise to lactone VIIc (0.78 g, 4.1 mmoles) in absolute alcohol (8 ml), refluxed for 1 h, and the alcohol distilled off in vacuo. The residue was treated with water (4 ml), neutralized with acetic acid, extracted with ether, and dried (Na_2SO_4). Distillation of solvent gave a residue (0.76 g) which was recrystallized from acetone to give acid IXc (0.22 g, 26%) as colorless crystals with mp 151-152°C and R_f 0.52 (B). IR spectrum (KBr): 1415, 1870, 2450 (COOH), 1715 cm^{-1} (C=O).

3-Methyl-4-oxo-5-(2-quinolyl)pentanoic Acid (IXd, $C_{15}H_{15}NO_3$) was obtained similarly in 40% yield from lactone VIId by refluxing for 15 min. Yellow crystals, mp 150-151°C (from alcohol) and R_f 0.58 (A). IR spectrum (KBr): 1420, 1900, 2500 (COOH), 1720 cm^{-1} (C=O). Mass spectrum, m/z (I_{rel}, %): M^+ 257 (26), 239 (8), 212 (10), 170 (95), 143 (100), 129 (18), 115 (46), 87 (15), 43 (15).

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SYNTHESIS OF 1-SUBSTITUTED-3,3-DIMETHYL-3,4-DIHYDROISOQUINOLINES

B. B. Aleksandrov, M. Yu. Dormidontov, V. S. Shklyaev, and Yu. V. Shklyaev

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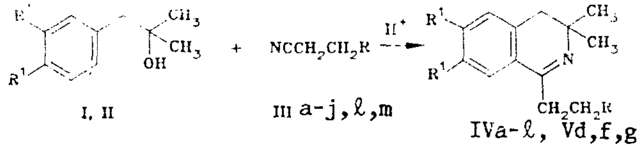
The Ritter reaction between β-substituted propionitriles and dimethylbenzylcarbinols gives 3,3-dimethyl-3,4-dihydroisoquinolines containing substituents in the 1-position corresponding to those in the starting nitrile.

The Ritter reaction has been successfully used for synthesizing 3,4-dihydroisoquinolines and other heterocyclic systems [1]. Certain rules are known which govern the course of the cyclization [2]. Comparatively little work has been reported on the preparation of 3,4-dihydroisoquinolines containing 1-substituted alkyl derivatives, however. These derivatives can be valuable in preparing condensed polycyclics having the isoquinoline fragment and also alkaloids of the isoquinoline series.

We have synthesized novel compounds of this type using the Ritter reaction between the carbinols I or II and β-substituted propionitriles III



I, IV: R^1 = H; II, V: R^1 = OCH_3; III-V: R) *a* = piperidino, b = morpholino, c = NHC_6H_5; d = $N(C_2H_5)_2$, e = cyclohexylamino, f = $O(CH_2)_2N(C_2H_5)_2$, g = OCH_3, h = SC_4H_9, i = SC_3H_7-iso, j = $OCH_2CF_2CHF_2$, k = 2-(3,3-dimethyl-3,4-dihydroisoquinol-1-yl)ethylthio, *l* = NHC_6H_4Br-p; III: m = SCH_2CH_2CN.

The synthesized compounds IVa-j,*l* and Vd,f,g were characterized as their salts VIa-j,*l* and VId,f,g, respectively (Table 1). The PMR spectral data for the bases are given in Table 2.

The reaction yields depend on the nature of the atom bonded to the β-carbon of the 1-alkyl substituent. Thus IVa-e and Vd having nitrogen in the side chain were obtained in yields of 93-68%, IVf,g and Vf,g with an oxygen atom 79-60%, and IVh,i with sulfur 50-22%. This is probably due to the protonation of the nitrogen and oxygen atoms under Ritter conditions (concentrated H_2SO_4) which increases the electrophilic character of the carbimmonium ions formed, thus facilitating the closing of the heterocycle.

The structures of IVa-*l* and Vd,f,g were confirmed by IR and PMR spectroscopy which show them to be 3,4-dihydroisoquinolines with an azo-methine double bond. All of the compounds show IR absorption bands at 1650-1640 cm^{-1} and the absence of a band at 3500-3100 which would characterize an NH enamine form [3].

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