β-DIKETONES WITH HETEROCYCLIC GROUPINGS

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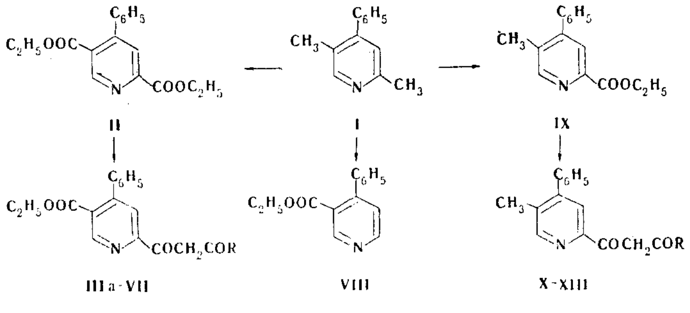
New β-diketones containing pyridine, thiophene, and furan rings were synthesized. Data characterizing their structures are presented.

The special reactivity of β-diketones and their practical value continue to attract the attention of investigators. Among this group of compounds, an as yet limited number of this sort of β-diketone, in which the carbonyl grouping is bonded to the heteroring, are known. However, a study of such compounds, in particular the elucidation of the effect of the heteroring on their keto–enol tautomerization,* is of theoretical interest. In order to synthesize some β-diketones containing a substituted pyridine grouping, we used 2,5-dicarbethoxy-4-phenylpyridine (II), which was obtained from the accessible 2,5-dimethyl-4-phenylpyridine (I) [1]. Compound II was subjected to ester condensation with methyl aryl ketones in the presence of sodium amide in ether. The condensation proceeds only at the α-carbethoxy group. This trend in the reaction is due to the distribution of electron density in the pyridine ring, a consequence of which is a different degree of weakening of the electron density on the carbon atoms of the carbethoxy groups in the α and β' positions. The following β-diketones were obtained: 1-phenyl- (IIIa), p-methoxyphenyl- (IV), m,p-dimethoxyphenyl- (V), 2-thienyl- (VI), 2-furyl- (VII), and 3-(4-phenyl-5-carbethoxy-2-pyridyl)-1,3-propanediones.

To experimentally verify this trend of the condensation reaction, we carried out the following syntheses. Ester VIII was obtained from I by oxidation to 4-phenylisocinchomeronic acid, partial decarboxylation of the acid, and esterification of the resulting 4-phenylnicotinic acid. Condensation of VIII with acetophenone and α-acetylthiophene did not occur under various conditions. Using known methods, we synthesized ethyl 5-methyl-4-phenylpicolinate (IX) [2] from I, the condensation of which with the appropriate methyl aryl ketones gave the following β-diketones: 1-phenyl- (X), p-methoxyphenyl- (XI), 2-thienyl- (XII), 2-furyl- (XIII), and 3-(5-methyl-4-phenyl-2-pyridyl)-1,3-propanediones.

1-Phenyl-3-(4-phenyl-5-carboxy-2-pyridyl)-1,3-propanedione (IIIb) was isolated along with IIIa in the condensation of II with acetophenone. The products were separated by chromatography on silica gel. The esterification of IIIb gave IIIa, which in turn was hydrolyzed to acid IIIb. Thermal hydrolysis of IIIb gave 4-phenylpyridine.



IIIa, X $R = C_6H_5$; IV, XI $R = p\text{-}CH_3OC_6H_4$; V $R = m, p\text{-}(CH_3O)_2C_6H_3$; VI, XII $R = \alpha\text{-}C_4H_3S$;
VII, XIII $R = \alpha\text{-}C_4H_3O$

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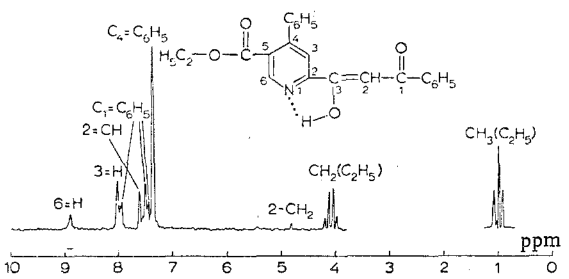


Fig. 1. PMR spectrum of β-diketone IIIa in acetone (at 100 MHz).

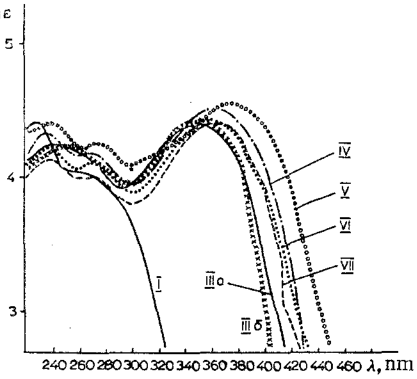


Fig. 2. UV spectra of β-diketones IIIa-VII.

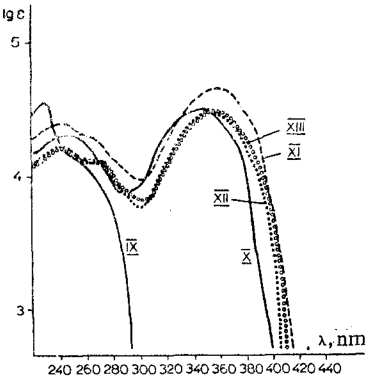
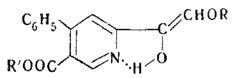


Fig. 3. UV spectra of β-diketones X-XIII.

β-Diketones III-VII and X-XIII are crystalline yellow substances. Information regarding their structures was obtained from spectral analysis and from some of their properties. They do not form picrates. In the case of VI, it was shown that this pyridine base forms a hydrochloride, but it decomposes readily on heating in alcohol. The weakening of the basic properties of these pyridine systems is due to the formation of a chelate complex with a rather strong intramolecular hydrogen bond between the enol hydroxyl group and the nitrogen of the pyridine ring.

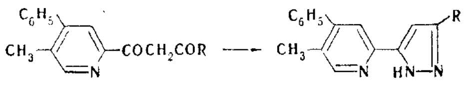


Bands corresponding to the hydroxyl group at 2500-3600 cm^{-1} are absent in the IR spectra of all of the investigated β-diketones (III-VII and X-XIII), while there is a group of intense, very broad overlapping bands at 1538-1638 cm^{-1}; this is characteristic for β-diketones in which the enol form predominates [3]. The absorption band at 1700-1732 cm^{-1} in the IR spectra of IIIa and IV-VII corresponds to an ester grouping.

Signals of olefin protons of the enol form at δ ~ 7.5 ppm are observed in the PMR spectra (Table 2 and Fig. 1) of III, VI, VII, X, XII, and XIII (in acetone, partial weakening of the enolization), while signals of the methylene group of the ketone form lie at ~4.8 ppm. Measurement of the integral intensity of the signal of the methylene group made it possible to make an approximate estimate of the concentration of the ketone form in the ketone ⇌ enol equilibrium mixture: 4% for IIIa, 7.5% for IIIb, 7.5% for VI, 6% for VII, 5% for X, 15% for XII, and 17% for XIII. The spectra of IV and V (dissolved in carbon tetrachloride) do not contain the signal of protons of a methylene group; this attests to practically complete enolization of these compounds. The signal of an OH group is absent in the PMR spectra of all of the β-diketones obtained (in CCl_4 and acetone); this can be explained by the formation of an intramolecular hydrogen bond between the enol hydroxyl group and the nitrogen of the pyridine ring.

Similar conclusions can also be drawn from the UV spectra (Figs. 2 and 3). They have two characteristic maxima at ~240 and ~360 nm. The presence of a very intense (log ε ≥ 4) long-wave band with λ_{max} ~ 360 nm should be considered to be the most characteristic feature of the UV spectra of the investigated β-diketones; this band is evidence that the enol predominates. Only two bands with maxima at about 230 and 260 nm should be present in the UV spectra in the case of the keto form.

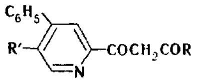
3-Phenyl- (XIV) and α-thienyl- (XV) 5-(5-methyl-4-phenyl-2-pyridyl)pyrazoles were obtained from β-diketones X and XII and hydrazine hydrate.



X, XII   XIV, XV

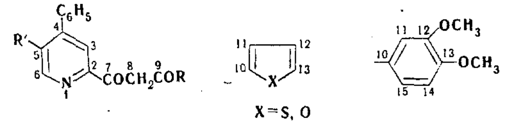
X, XIV R = C_6H_5;   XII, XV R = α-C_6H_3S

TABLE 1. 1-Aryl-, α-Thienyl-, and α-Furyl-3-[5-carbethoxy(methyl)-4-phenyl-2-pyridyl]-1,3-propanediones



Comp.	R	R′	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
IV	p-$CH_3OC_6H_4$	$COOC_2H_5$	124—125	$C_{24}H_{21}NO_5$	71,3	5,1	3,4	71,5	5,2	3,5	32,2
V	m,p-$(CH_3O)_2C_6H_3$	$COOC_2H_5$	118—120	$C_{25}H_{23}NO_6$	69,9	5,1	3,2	69,3	5,3	3,2	10
VI	α-C_4H_3S	$COOC_2H_5$	108—110	$C_{21}H_{17}NO_4S$			3,5			3,7	34,2
VII	α-C_4H_3O	$COOC_2H_5$	137—138	$C_{21}H_{17}NO_5$	69,4	4,9	3,6	69,5	4,7	3,9	60,5
X	C_6H_5	CH_3	127—128,5	$C_{21}H_{17}NO_2$	79,7	5,6	4,6	80,0	5,4	4,5	59,7
XI	p-$CH_3OC_6H_4$	CH_3	182—183	$C_{22}H_{19}NO_3$	75,0	6,1	3,9	76,6	5,5	4,0	7,0
XII	α-C_4H_3S	CH_3	144—145	$C_{19}H_{15}NO_2S$	70,9	4,9	4,2	71,0	4,7	4,4	67,7
XIII	α-C_4H_3O	CH_3	145—146	$C_{19}H_{15}NO_3$	74,4	4,7	4,9	74,7	4,9	4,6	59,4

TABLE 2. Chemical Shifts (δ, ppm), Multiplicity, and Coupling Constants (J, Hz)[a] of the Investigated β-Diketones



R′=$COOC_2H_5$ (IIIa—VIII), COOH (IIIb), CH_3 (X—XIII);
R=C_6H_5 (IIIa, X), p-$CH_3OC_6H_4$ (IV), m,p-$(CH_3O)_2C_6H_3$ (V);
α=C_4H_3S (VI, XII), α=C_4H_3O (VII, XIII).

Comp.	3-H	4-C_6H_5[b]	C_5—R	6-H	8-H (enol)	8-H (ketone)	C_9—R[b]
IIIa	8,08; s	7,42; s	4,10 (q, 8), 1,00 (t, 8) ($COOC_2H_5$)	8,97; s	7,66; s	4,84; s	7,50—8,10; m (C_6H_5)
IIIb[c]	8,07; s	7,44; s		9,03; s	7,68; s	4,85; s	7,50—8,10; m (C_6H_5)
IV	8,08; s	7,37; s	4,11 (q, 8), 1,01 (t, 8) ($COOC_2H_5$)	8,93; s	7,53; s		8,04 (d, 8,8); 6,91 (d, 8) (C_6H_4); 3,85; s (C_{13}—OCH_3)
V	8,07; s	7,36; s	4,12 (q, 8), 1,03 (t, 8) ($COOC_2H_5$)	8,92; s	7,50; s		7,8—6,7; m (C_6H_3); 3,88; s; and 3,90, s (OCH_3) at C_{12} and C_{13}
VI	7,99; s	7,42; s	4,09 (q, 8), 1,00 (t, 8) ($COOC_2H_5$)	8,94; s	7,47; s	4,80; s	7,99 (C_{13}—H or C_{11}—H overlaps with the C_3—H signal); 7,89 (q, 1,4) (C_{11}—H or C_{13}—H); 7,22 (q, 4,5) (C_{12}—H)
VII	8,06; s	7,46; s	4,17 (q, 8), 1,08 (m, 8) ($COOC_2H_5$)	8,99; s	7,48; s	4,73; s	7,90 (bs) (C_{11}—H at C_{13}—H); 7,42 (C_{11}—H or C_{13}—H); 6,75 (q, 1,5) (C_{12}—H)
X	7,91; s	7,40; s	2,31, s (CH_3)	8,57; s	7,61; s	4,76; s	7,5—8,1; m(C_6H_5)
XII[d]	7,86; s	7,44; s		8,59; s	7,44	4,76; s	8,00 (q, 1,4) (C_{13}—H or C_{11}—H); 7,87 (q, 1,5) (C_{11}—H or C_{13}—H); 7,25 (q, 4,5) (C_{12}—H)
XIII[d]	7,92; s	7,47; s		8,63; s	7,47	4,81; s	8,02; d (C_{11}—H or C_{13}—H); 7,90 (C_{11}—H or C_{13}—H); 7,27 (m, 4) (C_{12}—H)

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[a] Abbreviations: s is singlet, d is doublet, t is triplet, q is quartet, m is multiplet, and bs is broad singlet. [b] The protons of the phenyl group attached to C_4 in the investigated compounds give a signal that is almost a singlet, while those of the phenyl group attached to C_9 give a complex multiplet. [c] The spectrum of IIIb was recorded within the 0-10 ppm range, and the proton of the carboxyl group was not observed in this case. [d] The signal of the CH_3 group is masked by the signal of the solvent.

EXPERIMENTAL

The IR spectra were obtained with a UR-20 spectrophotometer. The samples were in the form of mineral oil pastes and KBr pellets. The UV spectra of alcohol solutions were measured with an SF-4a spectrophotometer. The PMR spectra of IIIa, IIIb, VI, VII, XII, and XIII in acetone, of X in deuteroacetone, and of IV and V in CCl_4 were measured with a Varian HA-100D spectrometer. The internal standard in the case of IIIa, IIIb, IV, V, VII, and XIII was tetramethylsilane, while hexamethyldisiloxane was used for VI, X, and XII.

Condensation of 2,5-Dicarbethoxy-4-phenylpyridine (II) with Acetophenone. A solution of 2.4 g (0.02 mole) of acetophenone in 10 ml of ether and a solution of 3 g (0.01 mole) of II in 50 ml of ether were added successively to sodium amide (obtained from 2 g of sodium) and 50 ml of ether, and the mixture was refluxed for 4 h and poured into a mixture of 50 g of ice and 14 ml of acetic acid. The products were extracted with ether (three 50-ml portions), and the extract was dried with sodium sulfate. The ether was removed by distillation, and the residue (1.1 g) was separated with a chromatographic column filled with KSK No. 2 silica gel with elution by ethyl acetate–heptane (1 : 2). Initially, 0.84 g (22.5%) of IIIa was separated as bright-yellow needles with mp 131-132° (from alcohol) and R_f 0.55 (with the same system). Found,%: C 74.2; H 4.7; N 3.3. $C_{23}H_{19}NO_4$. Calculated,%: C 73.9; H 5.1; N 3.7. After this, 0.2 g (7%) of IIIb was separated as yellow crystals with mp 228-230° (dec., from alcohol) and R_f 0.25. Found,%: C 73.5; H 4.0; N 4.1. $C_{21}H_{15}NO_4$. Calculated,%: C 73.2; H 4.2; N 4.1.

A similar method was used to obtain IV-VII and X-XIII (Table 1). A 0.35-g (1 mmole) sample of IIIb was esterified with ethanol in a stream of dry hydrogen chloride. The reaction products were isolated by chromatography as described above to give 0.11 g (30%) of IIIa and 0.1 g of IIIb. Acid hydrolysis of 0.5 g (1.3 mmole) of IIIa gave 0.08 g of IIIb and 0.28 g of IIIa.

A mixture of 0.5 g (1.45 mmole) of IIIb and 20 ml of water was heated at 250° for 3 h in an autoclave. The reaction products were extracted with ether and dried with sodium sulfate. The ether was removed by distillation, and the residue gave 0.2 g (38%) of the picrate of 4-phenylpyridine with mp 197-198° (from alcohol) [4]. Found,%: N 14.5. $C_{11}H_9N \cdot C_6H_3N_3O_7$. Calculated,%: N 14.6.

4-Phenyl-3-carbethoxypyridine (VIII). A mixture of 15 g (0.06 mole) of 4-phenylisocinchomeronic acid and 300 ml of water was heated in an autoclave at 190° for 3 h. The solid was dried and then refluxed for 4 h in 350 ml of ethanol in a stream of dry hydrogen chloride. The alcohol was removed by distillation, 150 ml of water was added, and the mixture was treated with sodium carbonate until it was alkaline. The ether extract yielded 6.9 g (49%) of VIII with mp 51-52° (from heptane–ethyl acetate). Found,%: C 73.8; H 5.5; N 5.9. $C_{14}H_{13}NO_2$. Calculated,%: C 74.0; H 5.7; N 6.2.

5-Methyl-4-phenyl-2-carbethoxypyridine (IX). A mixture of 32 g (0.175 mole) of I and 32 g (0.3 mole) of selenium dioxide was refluxed in 350 ml of pyridine for 5 h. The selenium was removed by filtration, and the solvent was removed by distillation. The residue was treated with 200 ml of water, and the mixture was refluxed. It was then cooled, and the water was decanted. The residue was dried and refluxed with 250 ml of heptane. Cooling of the hexane solution to −5° precipitated crystals. The extraction was repeated five times to give 17.5 g (61.5%, based on the I consumed in the reaction) of 5-methyl-4-phenyl-2-carboxypyridine with mp 154-155° (from acetone). Found,%: C 73.4; H 5.3; N 6.4. $C_{13}H_{11}NO_2$. Calculated,%: C 73.3; H 5.2; N 6.6. The picrate of IX had mp 173.5-175° (from alcohol). Found,%: N 12.6. $C_{13}H_{11}NO_2 \cdot C_6H_3N_3O_7$. Calculated,%: N 12.7. Removal of the heptane from the mother liquor by distillation gave 7.6 g of I.

A 5-g (0.025 mole) sample of the isolated acid was heated for 6 h with 5 g of thionyl chloride. The excess thionyl chloride was then removed by distillation, 20 ml of ethanol was added to the residue, and the mixture was refluxed for 2 h. The alcohol was removed by distillation, and sodium carbonate solution was added to the residue until it was alkaline. The reaction products were extracted with ether and crystallized from heptane to give 4.7 g (85%) of IX with mp 50-51°. Found,%: C 74.6; H 6.5; N 5.5. $C_{15}H_{15}NO_2$. Calculated,%: C 75.0; H 6.1; N 5.7.

3-Phenyl- (XIV) and α-Thienyl-5-(5-methyl-4-phenyl-2-pyridyl)pyrazole (XV). A 0.3-g (1 mmole) sample of X and 0.5 ml of hydrazine hydrate was refluxed in 8 ml of alcohol for 2 h. The alcohol and hydrazine hydrate were removed by distillation, and the residue was crystallized from 50% alcohol to give 0.11 g (37%) of XIV as colorless crystals with mp 179-180° and R_f 0.37 [KSK No. 2 silica gel, ethyl acetate–heptane (1 : 2)]. Found,%: C 81.1; H 5.4; N 13.0. $C_{21}H_{17}N_3$. Calculated,%: C 81.1; H 5.5; N 13.5.

Compound XV, with mp 200-201° and R_f 0.25 (in the same system), was similarly obtained from XII in 34% yield. Found,%: C 71.8; H 4.6; N 13.2. $C_{19}H_{15}N_3S$. Calculated,%: C 72.0; H 4.7; N 13.3.

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