

CONDENSATION REACTIONS OF BENZOYLACETONITRILE*

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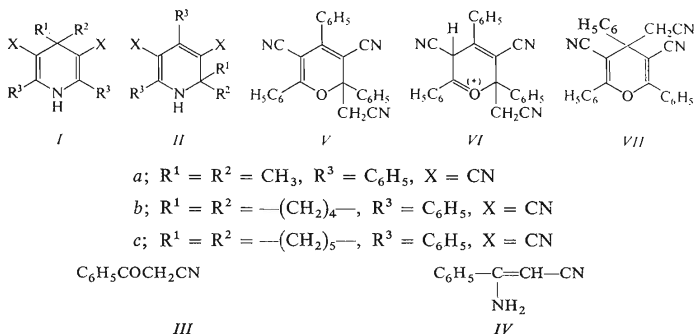
Main products of condensations of acetone, cyclopentanone, and cyclohexanone with benzoyl-acetonitrile (*III*) are 4,4-disubstituted 3,5-dicyano-2,6-diphenyl-1,4-dihydropyridines *Ia–Ic*, which are accompanied by a small amount of 3,5-dicyano-2,4,6-triphenyl-2-cyanomethyl-2*H*-pyrane (*V*). Substance *V* is also formed during the thermal and base-catalysed autocondensations of compound *III*.

Condensation of two molecules of β -dicarbonyl compounds with aldehydes or with ketones in the presence of ammonia or of ammonium salts lead usually¹ to 3,5-difunctional 1,4-dihydropyridine derivatives *I* ($R^1, R^2 = H, \text{alkyl or aryl}$; $R^3 = \text{alkyl or aryl}$; $X = CO_2R, COR \text{ or } CN$).

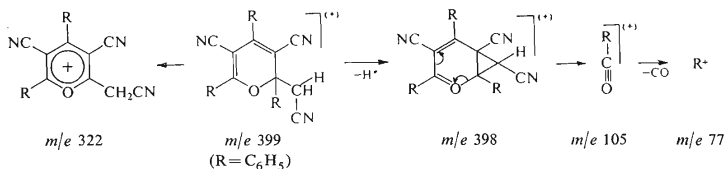
Contrarily, the formation of analogous 1,2-dihydropyridine derivatives of type *II*, the products of "unsymmetrical" condensation, has been reported only recently^{2,3}. While the structure of the product of condensation of two molecules of acetoacetic aldehyde with acetone in the presence of ammonium chloride seems to be well established², the report³ on the formation of substances *IIa–IIc* on heating the corresponding ketone with benzoylacetone (*III*) and ammonium acetate did not seem to us to be convincing for two reasons: 1) The authors did not pay attention to similar physical constants for 1,2-dihydro derivative *II* described by them³ and for 1,4-dihydro isomer *Ia* (ref.⁴). 2) The chemical identity of the reported³ 1,2-dihydro derivatives *IIa–IIc* has not been convincingly proved.

We re-examined the reactions of substance *III* with acetone, cyclopentanone, and with cyclohexanone in the presence of ammonium acetate³ and found that the product obtained is a mixture of bright yellow substance $C_{27}H_{17}N_3O$ and pale yellow 1,4-dihydropyridines *Ia–Ic*, which could be quantitatively separated by chromatography on aluminium oxide. In all cases the corresponding 1,4-dihydro derivative was major product and was proved to be identical with the product of the known^{4,5} condensation of enamionitrile *IV*. Substances *Ia–Ic* exhibit blue fluorescence in UV light and can be detected directly in the reaction mixture by thin-layer chromatography.

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The side product formed is identical with the not yet identified³ by-product of the condensation of the compound *III* with ammonium acetate. Furthermore, we have found that this product is also formed by thermal condensation of ketonitrile *III* in the absence of ketones, and then this compound should be the product of condensation of three molecules of substance *III*. The IR spectrum of this side product indicates that it does not contain OH, NH and C=O bonds; the molecule contains, however, two types of cyano group (2198 and 2222 cm^{-1}) and C=C and C—O bonds (1613 and 1240 cm^{-1}). The ^1H NMR spectrum (100 MHz) of pentadeuteriopyridine solution at 70°C shows signals of fifteen aromatic protons (three multiplets centered at 1.9τ , 2.2τ , and 2.55τ), a singlet at 7.80τ , which we assign to methylenic protons of the —C—CH₂—CN linkage.* We believe that the product has most likely 2*H*-pyrroid structure *V*. The ^1H NMR spectrum of the solution of the compound in concentrated sulphuric acid can be interpreted in accordance with the assumption that we



SCHEMÉ 1

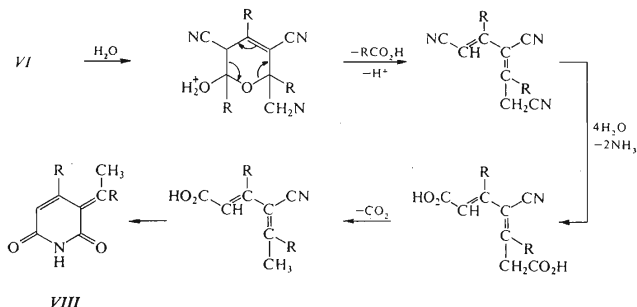
* A solution of ketonitrile *III* in deuteriochloroform shows analogous methylene signal of the —CO—CH₂—CN grouping at 5.93τ .

deal here with one of the protonated forms derived from structure *V*: The spectrum shows the signals of aromatic protons (the multiplet with residence between 2.2τ and 3.2τ), the signal of the methylenic protons is however absent. Instead, there are two singlets at 7.88τ and 8.08τ (with respect to sodium 2,2-dimethyl-2-sila-5-pentan-sulphonate as an internal standard) of the relative intensity 1 : 2, which we assign to the $-\text{CH}-\text{CN}$ methine protons and to the $-\text{C}-\text{CH}_2-\text{CN}$ methylene protons in the ion *VI*.

The mass spectrum of substance *V*, obtained at 70 eV, contains molecular ions at m/e 399 as a base peak and several more intense ions at m/e 398, 322, 105, and 77, the formation of which may be explained by Scheme 1. The UV absorption (λ_{max} 207, 245, and 375 nm, $\epsilon \approx 10^4$) resembles rather the spectra of 2,2,4,6-tetrasubstituted 2*H*-pyranes than those of analogous 4*H*-isomers⁶.

The two additional experiments supported the alternative 2*H*-pyranoid structure *V*. Substance *V* does not react with liquid ammonia at elevated temperature, while 4*H*-pyrane derivatives give under similar conditions corresponding 1,4-dihydropyridine derivatives⁷⁻¹⁰. On heating the compound with concentrated hydrochloric acid in a sealed tube for several hours, hydrolytic destruction of the substance occurs to give benzoic acid and probably 2-(1'-phenylethylidene)-3-phenylglutaconimide (*VIII*), the formation of which is visualized in Scheme 2.

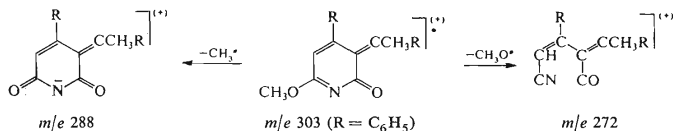
For purposes of identification of the above-mentioned products of the decomposition of compound *V*, their mixture was reacted with diazomethane; the reaction gave methyl benzoate, along with the compound *VIII*, which was isolated as *O*-methyl derivative of structures *IXa* or *IXb*. The ¹H NMR spectrum of this derivative shows two singlets of six methyl protons at 6.58τ and 7.35τ , a singlet corresponding to one $\text{H}-\text{C}=\text{C}$ proton at 2.87τ and a multiplet of ten aromatic protons at $2.3-2.7\tau$ region. The IR spectrum shows the carbonyl absorption at 1728 cm^{-1} and the ultraviolet spectrum exhibits absorption maximum at 244 nm of the $\pi-\pi^*$ type.



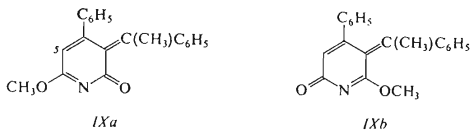
SCHEME 2 ($\text{R} = \text{C}_6\text{H}_5$)

The presence of the methoxy group in substance *IX* is indicated by the mass spectrum. The occurrence of three most abundant ion fragments m/e 303, 288, and 272, detected at 70 eV and interpreted in Scheme 3, is analogous to mass spectrometric fragmentation of the aromatic and heteroaromatic methoxy derivatives^{11,12}.

As seen from the results discussed, ketonitrile *III* undergoes condensation with simple aliphatic ketones, the course of the reaction being analogous to the reaction of enaminonitrile *IV*. Substance *IV* may, no doubt, be an intermediate of this condensation. The autocondensation of substance *III*, proceeding in different way, is likely influenced by greater steric demands of the third component. The incorporation to the heterocyclic ring is easier with product *V* than with its possible isomer *VII*. The remarkable stability of 2*H*-pyranoid derivative *V* is obviously due to the presence of the nitrile groups in positions 3 and 5, analogously to similar 1,2-dihydropyridines^{1,2}.



SCHEME 3



EXPERIMENTAL

Temperature data are uncorrected. Melting points were determined with a Boetius apparatus. IR spectra were recorded with a Perkin-Elmer 325 spectrometer, UV spectra with an Opica-Milano NI 4 CF, instrument, ¹H NMR spectra were taken on a Varian XL-100 spectrometer, and mass spectra on a LKB 9000 instrument (combination gas chromatograph-mass spectrometer, at 70 eV, direct inlet, temperature 250°C).

Autocondensation of Substance *III*

Benzoylacetonitrile *III* (20 g), m.p. 80–81°C (cf.¹³) was melted and heated with stirring at 190 to 200°C for 25 min. After cooling to room temperature, the mixture was ground and washed thrice with 20 ml of an ethanol-ether mixture (1 : 1). Repeated crystallization from toluene afforded 5.2 g (28%) of the yellow derivative *V*, m.p. 305–306°C, the spectral characteristics of which were identical with those reported for the product of the reaction of substance *III* with ammonium acetate³. For C₂₇H₁₇N₃O (399.4) calculated: 81.19% C, 4.29% H, 10.52% H; found: 81.38% C,

4.64% H, 10.19% N. IR spectrum (KBr pellets): 746 and 871 cm^{-1} (?), 1240 cm^{-1} $\nu(\text{C}-\text{O})$, 1337 cm^{-1} $\delta(\text{CH}_2)$, 1613 cm^{-1} $\nu(\text{C}=\text{C})$, 2198 and 2222 cm^{-1} $\nu(\text{C}\equiv\text{N})$. UV spectrum (ethanol): λ_{max} 207, 245, and 375 nm ($\log \epsilon$ 4.55, 4.47, and 4.49). Mass spectrum: m/e (rel. intensity %) 399 (100.0), 398 (23.2), 322 (17.7), 105 (18.4), and 77 (36.1).

Condensation of Ketonitrile III with Ketones

With acetone. A mixture of 2.5 g of substance III, 1.0 g of acetone, and 1.2 g of ammonium acetate was heated at 100°C for 4 h. After cooling, the solidified mixture was washed with 10 ml of a methanol-ether (1 : 1) solution to afford 1.5 g of a yellow material melting at 276–278°C ref.³ records m.p. 282–284°C (which, according to thin layer chromatography on aluminium oxide (activity III, chloroform, detection by UV lamp and by iodine vapours), consisted of substances Ia and V (R_F 0.56 and 0.20, resp.). The mixture (500 mg) was chromatographed on 300 g of aluminium oxide (activity II, chloroform, column length 75 cm, the eluent divided into c. 25 ml-fractions). Fractions 5–14 were evaporated, to give 420 mg of yellowish 1,4-dihydro derivative Ia, m.p. 297–298 (Table I); fractions 19–31 yielded 60 mg of yellow 2H-pyrene derivative V, m.p. 305–306°C.

With cyclopentanone. The reaction mixture obtained analogously, except that 1.5 g of cyclopentanone was used, gave after extraction with 10 ml of acetone 1.4 g of a yellow material which, according to thin layer chromatography, consisted of substances Ib and V (R_F 0.58 and 0.20, resp.). Preparative chromatography of 800 mg of this mixture on a column filled with 300 g of aluminium oxide, carried out as described in the preceding paragraph, yielded 760 mg of 1,4-dihydropyridine derivative Ib, m.p. 286–288 °C (Table I) and 38 mg of 2H-pyrene derivative V, m.p. 305–306°C.

With cyclohexanone. The reaction mixture obtained by heating 1.5 g of compound III, 1.2 g of cyclohexanone, and 0.6 g of ammonium acetate was washed with 20 ml of tetrachloromethane-ether (1 : 1). The yellow product obtained (280 mg, m.p. 224–229°C), consisting of substances Ic and V (by thin layer chromatography, R_F 0.54 and 0.20), was first crystallized from ethanol-benzene (1 : 1), to give 41 mg of pyrene derivative V, m.p. 305–306°C. The filtrate was evaporated under vacuum and chromatographed on 100 g of aluminium oxide (activity II, chloroform) to give 228 mg of 1,4-dihydropyridine derivative Ic, m.p. 234–235°C (Table I).

Condensation of Enaminonitrile IV with Cyclopentanone and with Cyclohexanone

Ethanollic hydrogen chloride (2 ml, 10.4 mmol) was added in portions to a mixture of 2.88 g of enaminonitrile IV (m.p. 86–87°C, cf.⁴), 1.09 g of cyclopentanone, and 15 ml of ethanol, during which addition an exothermic reaction took place. After standing for 3 h the mixture was decomposed with 10 ml of water and the crystalline 1,4-dihydropyridine Ia formed was filtered with suction. By this procedure, 1.25 g (37%) of yellowish crystals, m.p. 286–289°C, were obtained.

In another experiment, 1.4 g of cyclohexanone and 3 ml of acetic acid were added, and the mixture was allowed to stand for 2 days. After diluting with 10 ml of water and washing the product successively with water and ethanol (2 ml), 1.1 g (31%) of substance Ic, m.p. 234–235°C, were obtained. Further data on the products are given in Table I.

Hydrolytic Decomposition of Substance V

A suspension of 2 g substance V in 40 ml of concentrated hydrochloric acid was heated in a sealed tube at 235–250°C for 12 h. The resulting solution was evaporated under vacuum to dryness,

TABLE I

Prepared 4,4-Disubstituted 3,5-Dicyano-2,6-diphenyl-1,4-dihydropyridines Ia—Ic

Compound M.p., °C ^a	Formula (m.w.)	Calc./Found			IR spectrum ^b				UV spectrum λ_{\max} (log ϵ)	
		% C	% H	% N	ν_{NH}	$\nu_{\text{C}\equiv\text{N}}$	$\nu_{\text{C}=\text{C}}$	δ_{NH}	ethanol	aceto- nitrile
Ia 297—298 ^c	C ₂₁ H ₁₇ N ₃ (311.4)	81.00	5.50	13.50	(3 480)	2 195	1 636	1 575	243 (4.34)	240 (4.21)
		81.32	5.65	13.39		3 245			264 (4.27)	260 ^d (4.11)
						3 200				358 (3.68)
Ib 286—288	C ₂₃ H ₁₉ N ₃ (337.4)	81.87	5.68	12.45	(3 430)	2 195	1 635	1 574	241 (4.26)	241 (4.39)
		81.71	5.94	12.70		3 245			263 (4.17)	263 (4.27)
						3 206				358 (3.60)
Ic 235—236 ^c	C ₂₄ H ₂₁ N ₃ (351.5)	82.02	6.02	11.96	(3 430)	2 195	1 606	1 570	244 (4.36)	243 (4.35)
		82.43	6.12	11.90		3 295			258 (4.32)	264 (4.28)
										352 (3.68)

^a Substances were crystallized from ethanol–benzene; ^b KBr pellets; ^c physical constants in reasonable agreement with reported data⁴; ^d inflex; ^e IR characteristics for chloroform solution: 3 411, 3 260, 3 180, 2 200, 1 623, 1 600, and 1 575 cm⁻¹.

and the solid residue was recrystallized from water (activated carbon). The so obtained product (1.32 g, m.p. 78–87°C) was shown by thin layer chromatography (silica Stahl, 3% ethanol in chloroform, detection by Ce(SO₄)₂ in sulphuric acid) to be a mixture of benzoic acid (R_F 0.30) and imide VIII (R_F 0.13). Then the excess ether solution of diazomethane was added and after the reaction subsided (1 h at ambient temperature) the mixture was dried over magnesium sulphate and the solvent was distilled off. Cooling the distillation residue afforded the crystals which were separated by filtration with suction and washed twice with 2 ml of cold light petroleum. Methoxy derivative IX (1.06 g, m.p. 114–117°C) so obtained was repeatedly crystallized from petrol, to give the analytically pure product (0.95 g), m.p. 116–117°C. For C₂₀H₁₇NO₂ (303.4) calculated: 79.19% C, 5.65% H, 4.62% N; found: 79.39% C, 5.72% H, 4.72% N. CH₃O group determination: calculated: 10.23%, found: 10.60%. IR spectrum (chloroform): 1270 cm⁻¹ ν (C—O), 1728 cm⁻¹ ν (C=O). UV spectrum (ethanol): λ_{\max} 244 nm (log ϵ 4.41), inflexes 210 and 279 nm (log ϵ 4.47 and 3.89). Mass spectrum, m/e (rel. int.%): 303 (30.0), 289 (21.4), 288 (100.0), 272 (30.0), 245 (7.4), 244 (7.6), 230 (3.0), 212 (6.8), 115 (7.0), and 77 (3.2). Mother liquors were combined and evaporated, and the residue was distilled under vacuum to give 240 mg of methyl benzoate (b.p. 87–88°C/12 Torr) the identity of which was proved by comparison of its IR and mass spectra with the spectra of an authentic sample.

Attempted Reaction of Substance V with Ammonia

A mixture of 800 mg of substance V and 3 ml of liquid ammonia was heated in a pressure tube at 80–85°C for 5 h. The ammonia was evaporated and the residue was crystallized from toluene, to give 750 mg of starting compound V.

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