The Knoevenagel Condensation of Malononitrile with Some Cyclic β-Keto-esters. A Correction

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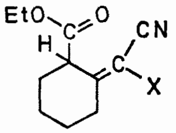
Summary The condensation product of malononitrile with 2-ethoxycarbonylcyclohexanone (I), previously described as (IIIa), is in fact a pyridine derivative (Va).

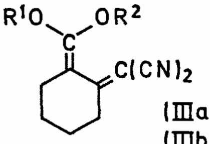
RECENTLY we described the Knoevenagel condensation of malononitrile with 2-ethoxycarbonylcyclohexanone (I).[1] Instead of the expected "normal" reaction product (IIa) we obtained an isomeric compound to which we assigned the structure of a completely enolized ester (IIIa), mainly on basis of the following evidence: whereas the Knoevenagel condensation of cyanoacetic acid ester with (I) yielded the "normal" product (IIb),[2] structure (IIa) was incompatible with the i.r. and n.m.r. spectra of the new compound (strong OH, 3160; very strong CN, 2235 cm^{-1}, suggesting the presence of more than one conjugated cyano-group; no bands between 2235 and 1605 cm^{-1}; no C*H*CO$_2$Et in n.m.r.); the hydrolysis product of (IIIa), formerly described as (IIIb), was a strong organic acid; the structures (IIIa) and (IIIc) were vinylogous to the known dicyanoketen hemiacetals and acetals.[3]

The above mentioned condensations were performed with ammonium acetate–acetic acid as catalyst in benzene–ethanol (1 : 1) as solvent by heating under reflux for more than 24 hr. with continuous water separation (conditions A). When repeating the reaction in benzene *without ethanol* (conditions B), we found the main product (83% yield) to be (IIa) (b.p. 110°/0·05 mm; i.r. (CHCl$_3$): 2235 (CN), 1735 (C=O), 1600 (C=C) cm^{-1}; n.m.r. (CDCl$_3$): C_2H_5O, δ1·28 (t, 3H), 4·23 (q, 2H), CH, 4·00 p.p.m. (br s, 1H); pK_A approx. 10·8), which showed no tendency to enolize. Consequently it became necessary to re-examine the structure of the products formerly assumed to be (IIIa, b, and c).

Spectral and chemical comparison of (IVa) [prepared from (IVb) and diazomethane] and (IVb)[4] with our analogous products, previously described as (IIIc) and (IIIb), and degradation (Scheme)[5] of (IIIa) to (VI),[6] [n.m.r. (CDCl$_3$): δ 6·00 (d, 1H) and δ 7·18 p.p.m. (d, 1H) (*cis* CH:CH), ^3J 6·5 Hz], established the structure of the condensation product of malononitrile with (I) under conditions A to be, in fact, (Va). Likewise, (IIIb) and (IIIc) have to be depicted as (Vb)[7] and (Vc). Compound (IIa) must be considered as an intermediate in the formation of (Va) under conditions A, as it was isolated in more than 80% yield when reaction was stopped after ½ hr. Moreover, (IIa) prepared under conditions B, was converted into (Va) under conditions A in good yield.

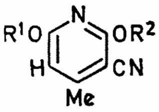


(IIa) X = CN
(IIb) X = CO$_2$Et



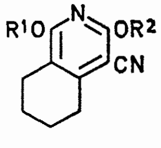
(III)

	R¹	R²
(IIIa)	Et	H
(IIIb)	H	H
(IIIc)	Et	Et

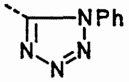


(IV)

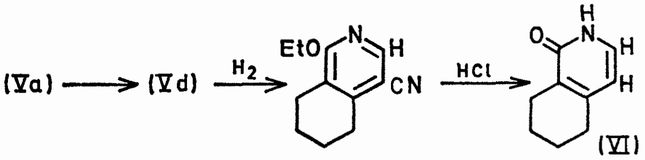
	R¹	R²
(IVa)	Me	Me
(IVb)	H	H



(V)

	R¹	R²
(Va)	Et	H
(Vb)	H	H
(Vc)	Et	Et
(Vd)	Et	

A surprising aspect of the cyclization under conditions A is the retention of the ethoxy-group, for which we could find no precedent in the literature. On the contrary, the Knoevenagel reaction of β-keto-esters and cyanoacetamide furnishes pyridine-2,6-diols.[8] The mechanistic implications of these reactions are being investigated.



SCHEME

Although experimental evidence is still lacking, it is very likely that the condensation product of malononitrile with 1-ethoxycarbonyl-6-methoxy-2-tetralone (conditions A)[1] is also a pyridine derivative. Under the same conditions 2-ethoxycarbonylcyclopentanone yields the "normal" dicyanomethylene condensation product in 70% yield.

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[1] J. L. van der Baan and F. Bickelhaupt, *Chem. Comm.*, 1968, 1661.

[2] (a) N. Itoh, *Chem. and Pharm. Bull.* (*Japan*), 1969, **17**, 206; (b) Own results.

[3] W. J. Middleton and V. A. Engelhardt, *J. Amer. Chem. Soc.*, 1958, **80**, 2788.

[4] J. M. Bobbitt and D. A. Scola, *J. Org. Chem.*, 1960, **25**, 560.

[5] *Cf.* W. J. Musliner and J. W. Gates, jun., *J. Amer. Chem. Soc.*, 1966, **88**, 4271. NaH in DMF with 1 eq. of NaI at 80° during 48 hr. had to be used in the preparation of the tetrazolyl ether (Vd).

[6] T. Kametani and H. Sugahara, *J. Chem. Soc.*, 1964, 3856; (VI) was shown to be identical with the compound described in the literature by comparison of its m.p., u.v., and i.r. spectrum with published data.

[7] U. Basu, *J. Indian Chem. Soc.*, 1931, **8**, 319; (Vb) was identical with an authentic specimen, as shown by mixed m.p. and u.v., i.r., and n.m.r. spectra.

[8] See, *e.g.*, refs. 4 and 7.