KNOEVENAGEL CONDENSATION PRODUCTS FROM SOME CYCLIC KETONES

STRUCTURE AND STEREOCHEMISTRY

G. JONES and (in part) W. J. RAE Department of Chemistry, University of Keele, Keele, Staffordshire, England

(Received 29 April 1966)

Abstract—NMR spectra are used to determine the stereochemistry of the Knoevenagel condensation products of type I. Corrected structures are given for the products of condensation between ethyl cyanoacetate and isatin, indan-1-one, or indan-2-one; and between α -tetralone and cyano-acetamide.

SOME modifications of the Knoevenagel condensation show a high degree of stereospecificity. The Verley-Doebner modification is a good example¹ though here the stereospecificity is probably due to the decarboxylation stage. Other modifications, notably those involving cyanoacetic esters, are reported to give mixtures of isomers.² Since a knowledge of the stereochemistry of the products may throw light on the mechanism of the condensation or on the nature of the intermediates we report here a method which can assist in determination of the stereochemistry of condensation products of type I. We also give corrected structures for some reported condensation products.



Our attention was drawn to the problem through a consideration of the reported condensation between isatin and ethyl cyanoacetate.^{3a} Equimolar amounts of these reagents condense in the presence of piperidine to give the normal product II which is red in colour. It was also reported that a ratio of ethyl cyanoacetate to isatin of 2:1 led to formation of a colourless product $C_{18}H_{17}N_3O_6$, assigned structure III (with one

³⁰ M. Yokoyama, J. Chem. Soc. Japan 57, 251 (1936); ^b Chem. Abstr. 30, 5204 (1936) gives



for the structure of the bis-condensation product.

¹ See, for examples; K. Sisido, M. Kawanisi, T. Morimoto, A. Saito and N. Hukue, J. Org. Chem. 27, 4073 (1962); L. Crombie, A. H. A. Krasinski and M. Manzoor-I-Khoda, J. Chem. Soc. 4970, (1963); R. H. Jaeger and R. Robinson, Tetrahedron 14, 321 (1961).

⁸ W. S. Johnson, H. C. E. Johnson and A. Petersen, J. Amer. Chem. Soc. **68**, 1927 (1946); A. Foucaud, Bull. Soc. Chim. Fr. 125 (1964); N. N. Saha, B. K. Ganguly and P. M. C. Dutta, J. Amer. Chem. Soc. **81**, 3672 (1959).

molecule of water of crystallization).^{3b} Since such a formula implied the unlikely condensation between a molecule of ethyl cyanoacetate and a lactam carbonyl group we prepared II and III to examine the NMR spectra, anticipating that the biscondensation product would have formula IV—the normal product formed by Michael addition of a second molecule of ethyl cyanoacetate to II. The crude product from condensation of two equivalents of ethyl cyanoacetate with one of isatin was pale green but attempts to recrystallize the product led to formation of red materials, m.p. $\sim 200^\circ$, shown to be identical with the mono-condensation product (II). Once it was realised that an extremely easy retro-Michael reaction was occurring, it was possible to recrystallize the bis-condensation product from alcohol containing a trace of acid, and to obtain a colourless material, agreeing in m.p. with that reported by Yokoyama.^{3a} The NMR spectrum⁴ in trifluoroacetic acid (TFA) showed a single proton at 9.6 ppm (amide NH), a four proton multiplet between 7.2 and 7.9 ppm (aromatic H), a sharp two-proton singlet at 5.1 ppm $(CH(CN)CO_2C_2H_5)_2$, methylene quartet at 4.36 ppm (4 protons) and methyl triplet at 1.4 ppm (6 protons) due to the two ethyl groups of the ester. This spectrum is in exact agreement with that expected for the structure IV which is therefore correct for the bis-condensation product.

More interesting, however, was the NMR spectrum of the mono-condensation product (II), also in TFA. In the aromatic region the spectrum showed a group of three protons at 7.30 ppm and a one-proton doublet at 8.35 ppm (J = 7 c/s) approximately 1 ppm down-field from the other three. From a model it is clear that either the cyanide group or the ester carbonyl in the structures IIa and IIb would lie across the ortho proton (H^A) in a de-shielding position. Since it seemed likely that the electron withdrawing groups used to activate a methylene group towards Knoevenagel condensations would cause differing de-shielding effects, a number of products of general type I were examined to see if their stereochemistry could be established by this method. The results are shown in Table 1.



All NMR shifts are expressed as ppm from TMS as internal standard.

Cyclic ketone	Active methylene component	Product	Ortho-proton shift ^a and solvent ^b
1-Indanone	Malononitrile	VII ⁵	0·85 (A) 0·80 (C)
	Ethyl cyanoacetate	VIII ⁶	1·0 (C) 1·15 (B)
	Methyl cyanoacetate	IX	1·2 (A, B)
α-Tetralone	Malononitrile	X ⁷⁴	0·9 (A) 0·8 (C)
	Cyano-acetamide	XVII ⁸	0·6 (C) 0·7 (A)
2,3-Benzsuberone	Malononitrile	XI ²	None
Fluorenone	Malononitrile	XII [®]	0·7 (D)
	Cyano-acetamide	XIII [®]	0·4, 0·85 (C)
	Ethyl cyanoacetate	XIV ¹⁰	0·5, 0·85 (C); 0·6, 1·05 (B)
Isatin	Malononitrile	V ¹¹	0·75 (D)
	Ethyl cyanoacetate	IIb ²⁴	1·05 (C)
	Diethyl malonate	VI	1·05 (B) 1·05 (C)
4-Keto-1,2,3,4-tetrahydro-1- methylquinoline	Malononitrile	XV ¹⁸	0·8 (C)

TABLE 1

^a Measured in ppm from the centre of the three proton aromatic multiplet.

 $^{\flat}$ A = CDCl₃; B = CCl₄; C = CF₃CO₃H; D = CCl₃FCO₃H.

The first observation from Table 1 is that in the cases where a nitrile group provides the de-shielding (in the condensation products derived from malononitrile) the ortho proton shift is remarkably constant, varying only from 0.7 to 0.9 ppm (Since many of the condensation products are insoluble in any non-protonating solvent, it is fortunate that change of solvent makes little difference to the size of the down-field shift.) The absence of any ortho-proton shift in the case of compound XI is in accord with the known buckling of the seven-membered ring which removes the carbonyl group of benzsuberone from conjugation with the benzene ring.¹³ Since the downfield shift for the ortho-proton in the original condensation product of isatin and ethyl cyanoacetate lies well outside the range obtained for nitrile groups, it seems likely that the compound has structure IIb, and this is confirmed by a comparison with the shift obtained for compound VI, obtained by condensation of isatin and diethyl malonate in the presence of piperidine (attempts to prepare the di-ester VI by treatment of cyano-ester IIb with ethanol and sulphuric acid, as described by Yokoyama^{3a} gave an isomer of IIb, shown by its IR and NMR spectra to be 3-cyano-4-carbethoxycarbostyril (XVI). Similarly follows the suggestion that 1-indanone condenses with ethyl or methyl cyanoacetate in the sense shown in formulae VIII and IX with the

- ⁵ D. M. W. Anderson, F. Bell and J. L. Duncan, J. Chem. Soc. 4705 (1961).
- ⁶ C. K. Ingold and J. F. Thorpe, J. Chem. Soc. 115, 150 (1919).
- ⁷ Kindly supplied by Professor E. Campaigne; ^a D. T. Mowry, J. Amer. Chem. Soc. 67, 1050 (1945); ^b E. E. Campaigne, R. Subramanya and D. R. Maulding, J. Org. Chem. 27, 4428 (1962).
- ⁸ A. Foucaud, H. Person and A. Robert, Bull. Soc. Chim. Fr. 1873 (1964). Specimens kindly supplied by Professor A. Foucaud.
- * R. Schenck and H. Finken, Liebigs Ann. 462, 271 (1928).
- ¹⁰ E. J. Cragoe, Jr., L. M. Robb and J. M. Sprague, J. Org. Chem. 15, 388 (1950).
- ¹¹ W. Walter, Ber. Dtsch. Chem. Ges. 35, 1321 (1902).
- ¹⁸ P. I. Ittyerah and F. G. Mann, J. Chem. Soc. 3179 (1956). Kindly supplied by Dr. F. G. Mann.
- ¹³ G. D. Hedden and W. G. Brown, J. Amer. Chem. Soc. 75, 3744 (1953); E. A. Braude and F. Sondheimer, J. Chem. Soc. 3754 (1955).

ester groups adjacent to the benzene ring. Conversely, from the condensations involving fluorenone it would be assumed that the amide group gave rise to a shift of only 0.4 ppm and this in turn suggests that one of the isomeric condensation products (see below) from α -tetralone and cyanoacetamide (XVII) is correctly formulated with the cyano group adjacent to the benzene ring. Most notable of all, in all cases where stereoisomers might be expected a *single* condensation product was in fact obtained, so that in the limited cases examined the Knoevenagel condensation with derivatives of cyanoacetic acid seems to show a high degree of stereospecificity.

However, there are in the literature some cases where mixtures of isomers are reported as products in condensations between α -tetralone and derivatives of cyanoacetic acid. While some of these are probably mixtures containing exo- and endocyclic double bonds² one was directly attributed⁸ to geometrical isomerism about an exo-cyclic double bond. As this reaction (between α -tetralone and cyano-acetamide) seemed to provide a test case for the use of the ortho-proton shift the NMR spectra of specimens supplied by Professor Foucaud were examined. The isomer of m.p. 145° formulated as XVII, had the expected displacement of the ortho-proton (0.7 ppm downfield) though the magnitude of the shift was less than that in compound X, but it is felt that this isomer is probably correctly represented by formula XVII. On the other hand, the isomer of m.p. 165°, formulated as XVIII, was shown quite clearly to be the positional isomer, XIX. The spectrum showed a six proton multiplet around 7.4 ppm (4 aromatic protons and NH₂), a one proton triplet at 6.7 ppm (ethylenic H) a sharp singlet at 5.15 ppm (CH(CN)CONH₂) and a multiplet between 2.5 and 3.1 ppm equivalent to four protons (C3 and C4 methylenes).



Finally, it has been reported⁶ that indan-1-one and indan-2-one condense with ethyl cyanoacetate to give the indene derivatives XX and XXI respectively.

Since the working-up procedure used by Ingold and Thorpe involved treatment of the crude condensation products with sodium hydroxide it seemed possible that an initially-obtained mixture was isomerized to the more stable isomer; the crude product from the condensation of indan-1-one with ethyl cyanoacetate was therefore examined by NMR spectroscopy. Rather surprisingly, the crude product showed a single aromatic proton well downfield from the other three, and no evidence of any olefinic proton such as would be expected for compound XX. Recrystallization of the condensation product from carbon tetrachloride gave a good yield of a compound with the same m.p. as that reported by Ingold and Thorpe (the same material was obtained, though in poorer yield, by following the previously reported working-up conditions). The NMR spectrum showed two two-proton multiplets centred at 3.1 and 3.5 ppm with no evidence of any olefinic proton, in agreement with formula VIII; the methyl ester obtained from methyl cyanoacetate and indan-1-one similarly had structure IX. Thus the condensation-elimination proceeds exclusively to form the exo-cyclic double bond, in contrast to the corresponding six-membered ketone (α -tetralone) where a mixture of endo- and exo-cyclic double bond isomers is formed.² Attempted equilibration of the esters VIII and IX with sodium alkoxide in the appropriate alcohol gave no isolatable isomers of type XX.

However, when the ethyl ester VIII was dissolved in ethanol and treated with sodium ethoxide and then methyl iodide the indene derivative XXII was obtained. The NMR spectrum of XXII in CCl₄ showed an ethylenic proton at 6.7 ppm as a broad triplet and a methylene doublet (J = 2 c/s) at 3.45 ppm, with a sharp methyl singlet at 2.0 ppm.

Similar results were obtained from the condensation of 2-indanone with methyl or ethyl cyanoacetate. The crude condensation mixture contained mainly the esters XXIII and XXIV; extra peaks in the NMR spectra of the crude condensation mixtures could be assigned to 'anhydro bis- β -hydrindone' known⁶ to be formed as a byproduct by self-condensation of indan-2-one. The two esters XXIII and XXIV when purified showed NMR peaks (CDCl_s) due to two non-equivalent methylene groups as multiplets centred at 4.25 and 4.4 ppm, leaving no doubt as to the exocyclic nature of the double bond. Again, attempted equilibration with alcholic alkoxide gave no evidence of isomerization to the indenes of type XXI. Methylation of the esters XXIII and XXIV gave the methylated indenes XXV and XXVI. The ester group in compound XXVI is reported⁶ to be easily removed, for example, by sodium ethoxide at 15°, to give nitrile XXVII. However, we had some difficulty in removing the ester group completely from either compound XXV or XXVI. When the ester XXVI was boiled with sodium ethoxide in ethanol a mixture was obtained; from the NMR spectrum the mixture appears to be of nitriles XXVII and XXVIII, but we have been unable to separate the nitriles by column chromatography.

EXPERIMENTAL

NMR spectra (Perkin-Elmer 60 Mc); IR spectra (Perkin-Elmer 221 or 257 spectrophotometer). M.ps (Kofler hot-stage) are uncorrected. The purity of all compounds was checked by GPC using 1% SE-30 on Gaschrom P (10' column).

Diethyl isatinylidene malonate (VI). Isatin (3 g) and diethyl malonate (3.5 g) were dissolved in 95% EtOH (100 ml); a few drops piperidine were added and the soln boiled for 3 hr. The cooled soln was poured into water (500 ml) and the orange solid filtered off (2 g). Recrystallized from aqueous EtOH as orange prisms, the malonate (VI) had m.p. 126°, (Found: C, 62.7; H, 5.25; N, 5.0. $C_{18}H_{18}NO_{5}$ requires: C, 62.3; H, 5.25; N, 4.85%.) ν_{max}^{COl4} 1740, 1720, 1610, 1235 cm⁻¹.

Ethyl 3-cyanocarbostyril-4-carboxylate (XVI). A soln of ethyl isatinylidenecyanoacetate (IIb) in absolute EtOH containing 10% conc H₃SO₄ was boiled for 6 hr; cooled, poured into water and the

precipitated solid filtered off. Recrystallization from EtOH gave yellow prisms m.p. 228-230°. (Found: C, 64.5; H, 4.15; N, 11.7. $C_{13}H_{10}N_{2}O_{3}$ requires: C, 64.45; H, 4.16; N, 11.57%) ν_{max}^{0014} 2235, 1739, 1680 cm⁻¹.

Isatinylidene malononitrile (V). The nitrile (V) precipitated when a soln of isatin and malono nitrile in absolute EtOH was treated with a drop of piperidine. Recrystallized from EtOH as red needles, V had m.p. 239° (Reported¹³ m.p. 235°).

Methyl 1-indanylidenecyanoacetate (IX). A mixture of 1-indanone (9.5 g), methyl cyanoacetate (8 g) and piperidine (3.2 g) was kept at 35-40° for 45 hr. The cooled mixture was filtered, the solid condensation product washed with alcohol and dried (4 g). Recrystallization from 95% EtOH gave colourless prisms, m.p. 145.5°. (Found: C, 72.9; H, 5.35; N, 6.65. C₁₈H₁₁NO₂ requires: C, 73.22; H, 5.20; N, 6.57%) $\nu_{0.04}^{0.04}$ 2200, 1718 cm⁻¹.

Methyl 2-indanylidenecyanoacetate (XXIII). A mixture of 2-indanone (26 g) and methyl cyanoacetate (22 g) was treated with 40 drops diethylamine, keeping the mixture at 18°. After 2 days at 0° a first crop of 20 g crude condensation product was obtained. Recrystallization from CCl₄ gave colourless prisms, m.p. 131°. (Found: C, 72·95; H, 5·15; N, 6·4. C₁₃H₁₁NO₃ requires: C, 73·22; H, 5·20; N, 6·57%). $\nu_{0Cl_4}^{OCl_4}$ 2215, 1732, 1290 cm⁻¹.

Methyl 2-cyano-2-(2-indenyl)propionate (XXV). To a soln of XXIII (6.4 g) and Na (0.65 g) in MeOH (100 ml) was added MeI (7 g). The mixture was boiled (1 hr) and then concentrated. Addition of water gave a solid; filtration and recrystallization from MeOH gave the *methylated ester* (XXV) as colourless prisms, m.p. 85–86°. Recrystallization from petrol (40–60 b.p.) gave m.p. 88–89°. (Found: C, 74.15; H, 5.65; N, 6.2. $C_{14}H_{13}NO_3$ requires: C, 74.99; H, 5.77; N, 6.16%.) γ_{max}^{Ol14} 1754, 1235 cm⁻¹.