

STEREOCHEMISTRY OF THE MICHAEL ADDITION.
AN INTERESTING SOLVENT EFFECT

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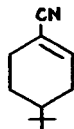
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The Michael Addition has usually been studied under conditions such that the overall stereochemistry observed is probably that resulting from thermodynamic control (1). We report the first systematic study of the stereochemistry of the Michael Addition both under conditions of kinetic and also of thermodynamic control using a conformationally stable system, thus permitting the initial mode of addition of the nucleophile to be established unambiguously.

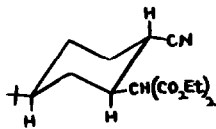
Addition of diethyl malonate to 4-t-butyl-1-cyanocyclohexene (I), m.p. 45-46°, (2) in the presence of sodium ethoxide in ethanol at room temperature for 5 days gave a mixture of two cyanomalonates: (II), m.p. 84.5-85.5°, and (III), m.p. 71.5-72.5°, in the ratio II/III = 5:95. (II) exhibited infrared (2240 (C=N), 1743, 1727 cm⁻¹ (malonate ester) (3)) and n.m.r. (quartet at 5.82 τ ($J = 7$ c.p.s.) (CO₂CH₂CH₃); doublet at 6.48 τ ($J = 12$ c.p.s.) (CH(CO₂Et)₂); broad unsymmetrical two-proton doublet at 7.12 and 7.35 τ (protons β to malonic ester residue at C-2 and CHCN))

spectra consistent with those expected. (III) showed similar absorptions: I.R. (2240, 1750, 1730 cm^{-1}); n.m.r. (quartet at 5.78 τ ($J = 7$ c.p.s.), doublet at 6.43 τ ($J = 11$ c.p.s.); broad multiplet at 7.19 τ). When the addition was carried out in boiling ethanol the ratio II/III changed to 81:11. In addition, an isomeric product $\text{C}_{18}\text{H}_{29}\text{NO}_4$ (IVa), m.p. 44-46°, was formed in small amounts, together with traces of the stereoisomeric acetates resulting from the decarboxylation of II and III, respectively. Base-catalyzed equilibration of II and III indicated that II is the thermodynamically more stable isomer. Similarly, II and III could be decarboxylated with retention of configuration using NaOEt in cold ethanol to the acetates (Va) and (VIa), respectively, Va being the thermodynamically more stable isomer (base catalyzed equilibration). Thus, the nitrile group must be equatorial in II and axial in III (4, 5). Boiling II with 3N HCl gave a single 4-t-butyl-2-carboxymethylcyclohexanecarboxylic acid (Vb), m.p. 180-182°. Similarly, III gave the dicarboxylic acid (VIb), m.p. 211-212°. With 5% aqueous NaOH at 240° for 24 hr. both Vb and VIb gave 70% Vb and 30% VIb.

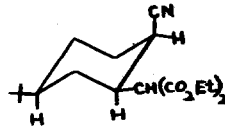
The conformation of the malonate residues in II and III was established unambiguously on the basis of dipole moment determinations. Possible structures are II \rightleftharpoons III and IIa \rightleftharpoons IIIa. The moments calculated (6) for II, IIa, and III (assuming no contribution from the t-butyl group (7)) are 4.96D, while that for IIIa is 1.47D. The values found (8) are 4.95 D for II and 4.17D for III (9), thus establishing the equatorial orientation of the malonate group. Acids Vb and VIb readily form anhydrides, m.p. 58-59° and m.p. 113.5-115°, respectively, that from VIb being formed about



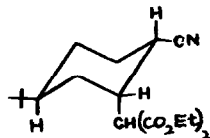
I



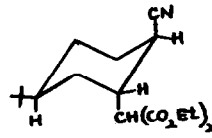
II



III

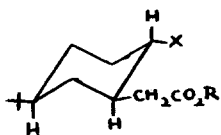


IIa



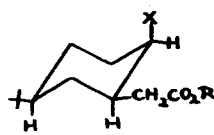
IIIa

twice as fast as that from Vb. This, too, eliminates a diaxial conformation for the functional groups in III.



Va: X = CN; R = Et

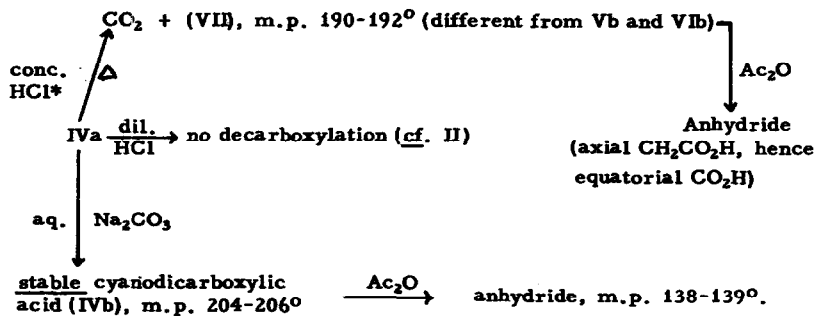
b: X = CO₂H; R = H



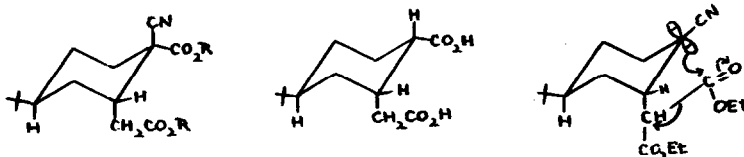
VIa: X = CN; R = Et

b: X = CO₂H; R = H

Compound IVa is not a malonate ester. The characteristic quartet due to $\text{CO}_2\text{CH}_2\text{CH}_3$ in the n.m.r. spectra of malonates is not shown by IVa; instead, two overlapping quartets at 5.72 and 5.89 τ ($J = 7$ c.p.s.) due to two carbethoxyl groups in different environments can be discerned. IVa is an "abnormal addition" product (2b), as is clear from the reactions below.



Assuming a four-centered transition state for the rearrangement (2b), IVa should be formed readily if CO_2Et enters from the equatorial side. The facile formation of an anhydride from IVb confirms the assigned geometry. The dipole moment of IVa (3.13D) indicates that in the axial acetate group, the ester function is oriented away from the ring.



IVa: R = Et
 b: R = H

VII

When the addition is carried out using diethyl sodiomalonate in boiling toluene IVa is the major isomer formed (IVa:II:III = 91:6:3). In dioxan solution IVa again predominates. The product of kinetic control in ethanol is that in which the entering group adopts the equatorial conformation, protonation occurring from the least hindered side (10) to

* Equilibration possible here

give (III). II is the product of thermodynamic control in ethanol. This predominant initial formation of the equatorial isomer may be explained as follows:- in a protic solvent the malonate carbanion is a relatively weak solvated nucleophile so that product development control is observed. In an aprotic solvent the carbanion will be a strong unsolvated nucleophile and the transition state will resemble the ground state, with the nucleophile perpendicular to the plane of the C=C bond. Steric effects will be minimal and one might expect about equal ease of attack from either side. The addition is a reversible process, while the migration of the carbethoxyl group, which should take place readily from the axial side due to the favourable geometry, is not. The predominant formation of IVa is explained by assuming that, in the absence of a proton-donor other than malonic ester itself, the rearrangement is a very fast process so that IVa gradually accumulates. This requires that migration of CO₂Et be faster than that of the active hydrogen from the axial malonate, since no product having an unrearranged axial malonate residue was ever detected.

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REFERENCES

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2. Correct analyzes were obtained for all the new compounds mentioned here. Reaction mixtures were analyzed quantitatively and qualitatively by gas-liquid chromatography.
3. R. A. Abramovitch, Can. J. Chem., 36, 151 (1958).
4. (a) B. Rickborn and F. R. Jensen, J. Org. Chem., 27, 4606 (1962).
(b) N. L. Allinger and W. Szkrybalo, J. Org. Chem., 27, 4601 (1962).
5. The ratio of the molar extinction coefficients of the C=N functions in the infrared was $\epsilon_{II}/\epsilon_{III} = 1.12$. W. Nagata, M. Tokhioka, M. Narisoda, and W. Watanabe (Tetrahedron Letters, 3133 (1964)) report that the ratios of the molar extinction coefficients for equatorial and axial nitrile groups are in the range 1.35 - 1.80. While the ratio obtained here is somewhat lower than this the order is the correct one.
6. The following bond moments were used: diethyl malonate, 2.10D (N. L. Phalnikar, J. Univ. Bombay, 11, 87 (1942); Chem. Abstr., 37, 3310 (1943)); C=N, 3.56D (C. P. Smyth, "Dielectric Constants," Chemical Catalogue Co., Inc., New York, 1931, p. 99); CO₂Et, 1.94D; CH₂CO₂Et, 1.86D (C. P. Smyth, "Dielectric Behaviour and Structure," McGraw-Hill Book Company Inc., New York, 1955).
7. N. L. Allinger, J. Allinger, and N. A. Le Bel, J. Am. Chem. Soc., 82, 2925 (1960).
8. The dipole moments of the compounds in benzene solution were kindly determined by Dr. G. F. Wright.
9. The low value may be due to ring distortion, to different rotational conformers of the malonate group or to the presence of thermally excited states.
10. H. E. Zimmerman and T. W. Cutshall, J. Am. Chem. Soc., 81, 4305 (1959), and references cited therein.