137. *The Kinetics and Mechanism of Carbonyl–Methylene Condensation Reactions. Part XI.* Stereochemistry of the Products.*

By Jacob Zabicky.

A series of condensates of the form $Z{\cdot}C_6H_4{\cdot}CH{:}CXY$ was synthesised where the groups X, Y, Z were suitably varied. Infrared spectra indicate that the aryl group and the smaller of the groups X, Y are *cis* to one other.

In Parts VI—IX [1] of this series the mechanism of the condensation (1) was discussed when Ar was a substituted phenyl group, and X, Y were CN, CO_2Et, or $CO{\cdot}NH_2$. Reaction (1)

$$Ar{\cdot}CHO + CH_2XY \rightleftharpoons Ar{\cdot}CH{:}CXY + H_2O \quad . \; . \; . \; . \; . \; . \; . \; . \quad (1)$$

was carried out in water or 95% ethanol, usually without a catalyst. In this paper we discuss the configuration of the products prepared by standard procedures; the results are used in the following paper to throw light on the mechanism of the reaction.

It was shown by Baker and Howes [2] that ethyl α-cyano-β-*o*-hydroxyphenylacrylate obtained by condensation of salicylaldehyde and ethyl cyanoacetate has the *trans*-configuration (*o*-hydroxyphenyl and ethoxycarbonyl *trans* to one other). They also showed that the *cis*-isomer changes spontaneously on melting into the more stable *trans*-isomer. In this paper we show that the *trans*-form is obtained by condensing ethyl cyanoacetate or cyanoacetamide with a substituted benzaldehyde. The direct demonstration used by Baker and Howes—cyclisation of the acrylic acid to the coumarin—could not be applied to our case, and it was thought feasible to prove the configuration by infrared spectrophotometry, by correlating characteristic absorption bands of three groups.

Table 1 gives frequencies of absorption bands for characteristic stretching modes of the carbon–carbon double bond, the carbon–oxygen double bond, and the carbon–nitrogen triple bond, of a series of products obtained by reaction (1).

(A) *Carbon–Carbon Double-bond Stretching Band.*—Compounds $Z{\cdot}C_6H_4{\cdot}CH{:}C(CN)Y$, with a wide variety of Z and Y groups (I—XXIV), have bands in the same range, *i.e.*, 1582—1629 cm.$^{-1}$. Derivatives of ethyl malonate and malonamide (XXV—XXXVII) have this absorption band in a higher frequency range, *i.e.*, 1637—1681 cm.$^{-1}$ (except XXVI and XXVII). Derivatives of malonamide have the highest frequencies (*ca.* 1667—1681 cm.$^{-1}$), although the exact position of this band is not clearly defined owing to overlapping of the C=O absorption band.

(B) *Carbon–Oxygen Double-bond Absorption Bands.*—In dealing with these bands we divide the compounds IX—XXXVII into two separate groups: the esters (IX—XVI, XXV—XXXII) and the amides (XVII—XXIV, XXXIII—XXXVII).

C=O stretching bands of compounds IX—XVI are at relatively lower frequencies

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* Part X, *Bull. Res. Council Israel*, 1959, **8**, *A*, 179.

[1] Parts VI—IX, *J.*, 1960, 2020—2044.

[2] Baker and Howes, *J.*, 1953, 119.

(1707—1734 cm.$^{-1}$) than those of compounds XXV—XXXII (1724—1747 cm.$^{-1}$); *i.e.*, derivatives of ethyl cyanoacetate have the absorption at lower frequencies than derivatives of ethyl malonate. This trend is reversed for the set of amides studied: derivatives of cyanoacetamide (XVII—XXIV) absorb at higher frequencies (1689—1707 cm.$^{-1}$) than those of malonamide (XXXIII—XXXVII, absorbing at 1667—1681 cm.$^{-1}$).

TABLE 1. *Characteristic absorption bands* [1] [ν (*cm.*$^{-1}$)] *and physical properties of condensates* Z·C_6H_4·CH:CXY.

No.	Z	X	Y	C=C	C=O	C≡N	Synthetic method [2]	M. p.
I [3]	H	CN	CN	1603	—	2255	1	85·5—86°
II [3]	*p*-MeO	,,	,,	1620	—	2255	1	116—117
III [4]	*p*-Me_2N	,,	,,	1629	—	2247	1	183—184
IV [5]	*p*-Me	,,	,,	1594	—	2247	1	128—130
V [3]	*p*-Cl	,,	,,	1596	—	2255	1	160
VI [6]	*p*-Br	,,	,,	1593	—	2255	1	163
VII [7]	*m*-NO_2	,,	,,	1610	—	2260	1	107·5—108
VIII [8]	*p*-NO_2	,,	,,	1596	—	2260	1	159·5—160
IX [9]	H	,,	CO_2Et	1582	1732	2247	2	49·5
X [10]	*p*-MeO	,,	,,	1593	1724	2247	2	83
XI [11]	*p*-Me_2N	,,	,,	1620	1707	2234	2	128
XII [12]	*p*-Me	,,	,,	1607	1732	2242	2	92
XIII [13]	*p*-Cl	,,	,,	1603 1629	1734	2255	2	92
XIV [6]	*p*-Br	,,	,,	1594 1627	1734	2255	2	97·5
XV [14]	*m*-NO_2	,,	,,	1618	1724	2255	1	135
XVI [15]	*p*-NO_2	,,	,,	1607 1627	1733	2255	1	170
XVII [16]	H	,,	CO·NH_2	1603	1699	2247	3	123·5
XVIII [17]	*p*-MeO	,,	,,	1593	1701	2242	3	213
XIX [6]	*p*-Me_2N	,,	,,	1623	1689	2234	1	199—200
XX [6]	*p*-Me	,,	,,	1600	1689	2237	3	159—161
XXI [3]	*p*-Cl	,,	,,	1594	1707	2234	1	208—209
XXII [6]	*p*-Br	,,	,,	1588 1603	1695	2234	1	220—221
XXIII [6]	*m*-NO_2	,,	,,	1620	1701	2255	3	161—163
XXIV [3]	*p*-NO_2	,,	,,	1607	1701	2255	1	236—237
XXV [18]	H	CO_2Et	CO_2Et	1654	1747	—	4	(b. p. 164—165°/6 mm.)
XXVI [19]	*p*-MeO	,,	,,	1620	1740	—	4	(b. p. 180°/11 mm.)
XXVII [20]	*p*-Me_2N	,,	,,	1596	1737	—	2	110—111
XXVIII [21]	*p*-Me	,,	,,	1642	1737	—	4	(b. p. 240°/60 mm.)
XXIX [19]	*p*-Cl	,,	,,	1645	1740	—	4	(b. p. 171—173°/1 mm.)
XXX [6]	*p*-Br	,,	,,	1640	1737	—	4	(b. p. 176°/2 mm.)
XXXI [22]	*m*-NO_2	,,	,,	1637	1724	—	4	74·5
XXXII [23]	*p*-NO_2	,,	,,	1620 1645	1740	—	2	92—92·5
XXXIII [24]	H	CO·NH_2	CO·NH_2	*ca.* 1667	*ca.* 1667	—	3	190—191
XXXIV [6]	*p*-MeO	,,	,,	*ca.* 1678	*ca.* 1678	—	3	206
XXXV [6]	*p*-Br	,,	,,	*ca.* 1667	*ca.* 1667	—	3	217—219
XXXVI [6]	*m*-NO_2	,,	,,	*ca.* 1681	*ca.* 1681	—	5	211
XXXVII [6]	*p*-NO_2	,,	,,	*ca.* 1673	*ca.* 1673	—	5	211

[1] All absorptions are strong. [2] See Experimental part. [3] Part VI, *J.*, 1960, 2020. [4] Sachs and Lewin, *Ber.*, 1902, **35**, 3577. [5] Gal, Fung, and Greenberg, *Cancer Res.*, 1952, **12**, 565. [6] See Table 2. [7] Kaufmann and Jeutter, *Ber.*, 1917, **50**, 523. [8] Hertel and Hoffman, *Z. phys. Chem.*, 1941, **50**, *B*, 390. [9] Carrick, *J. prakt. Chem.*, 1892, **45**, 501. [10] Bechert, *J. prakt. Chem.*, 1894, **50**, 10. [11] Bauer and Seyforth, *Ber.*, 1930, **63**, 2691. [12] Fiquet, *Ann. Chim. Phys.*, 1893, **29**, 479. [13] von Walter and Raetze, *J. prakt. Chem.*, 1902, **65**, 284. [14] Sudborough and Lloyd, *J.*, 1898, **73**, 88. [15] Stuart, *J.*, 1883, **43**, 408. [16] Day and Thorpe, *J.*, 1917, **117**, 1465. [17] Curtis and Day, *J.*, 1923, **123**, 3131. [18] Allen and Spangler, *Org. Synth.*, Coll. Vol. 3, 1955, p. 377. [19] Ogata and Tsuchida, *J. Amer. Chem. Soc.*, 1959, **81**, 2092. [20] Wayne and Cohen, *J.*, 1925, **127**, 459. [21] Pratt and Werble, *J. Amer. Chem. Soc.*, 1950, **72**, 4638. [22] Ruhemann, *J.*, 1903, **83**, 723. [23] Stuart, *J.*, 1885, **47**, 158. [24] Henk, *Ber.*, 1895, **28**, 2256.

(C) *Carbon–Nitrogen Triple-bond Stretching Band.*—The frequency increases almost in the order of increasing electronegativity of the substituent Z on the one hand, and in the order of increasing electronegativity of the substituent Y on the other hand; *i.e.*, derivatives of cyanoacetamide (XVII—XXIV) absorb at 2234—2255 cm.$^{-1}$, those of ethyl cyanoacetate (IX—XVI) absorb at 2234—2255 cm.$^{-1}$, and those of malononitrile (I—VIII) absorb at 2247—2260 cm.$^{-1}$. Some irregularity for the derivatives of cyanoacetamide being neglected, frequencies increase in the following order when the substituent Z is changed: p-Me$_2$N $<$ p-Me $<$ p-MeO $<$ H $<$ p-Cl $<$ p-Br $<$ m-NO$_2$ $<$ p-NO$_2$.

Discussion.—The polarisation of the carbon–oxygen double bond in the esters studied (IX—XVI, XXV—XXXII) is increased by the conjugation of the styrene system with the carbonyl group. It may be expected that the cross-conjugation of a cyano-group with the ethoxycarbonyl group as in compounds IX—XVI will cause a hypsochromic shift in the carbonyl stretching frequencies with respect to those of XXV—XXXII, as the conjugation of the ring with the stronger cyano-group will be preferred; *e.g.*, Felton and Orr[3] found that a change from a 1,1-diethoxycarbonylethylene compound to a 1-cyano-1-ethoxycarbonylethylene compound causes a *hypsochromic* shift in the carbonyl stretching band of about 10 cm.$^{-1}$. In our case the same structural change causes a *bathochromic* shift of 20—30 cm.$^{-1}$.

A model of diethyl benzylidenemalonate shows that it is impossible for it to have a sterically unstrained planar conformation. In order to have two coplanar carbonyl groups with the carbon–carbon double bond and the phenyl group as nearly coplanar as possible, the *cis*-carbonyl group has to be brought near to the phenyl group, with the ethoxy-group projecting out in the opposite direction. This means that either the *cis*-carbonyl group is not coplanar with the remaining *trans*-cinnamic ester system, or the phenyl group is not coplanar with the remaining 1,1-diethoxycarbonylethylene system. In both cases a hypsochromic shift will result with respect to the carbonyl frequency of a completely planar system. A secondary effect is also to be expected as follows: when the carbonyl group that is *cis* to the phenyl group attains its easiest coplanar conformation (directed towards the phenyl group) it will suffer an electrostatic repulsion by the phenyl group, as the normal polarisation of the carbonyl group is $^{+}$C–O^{-}, with the negative end of the dipole near the electron-rich phenyl group.

If we change the *cis*-ethoxycarbonyl group to a cyano-group, the latter is favoured in the conjugation with the styrene system, but we have nevertheless relieved all the steric strain caused by a large group. Therefore the remaining *trans*-carbonyl group will be coplanar with the styrene system and will conjugate better with it, resulting in a bathochromic shift as is actually the case.

The conclusion from the above discussion is that the series of ethyl benzylidenecyanoacetates, IX—XVI, has the so-called *trans*-configuration (cyano-group *cis* to phenyl group). Further evidence for this lies in the experiments by Lohaus,[4] who obtained a mixture of *cis*- and *trans*-ethyl benzylidenecyanoacetate and showed that it was spontaneously converted into one of the isomers; it is to be expected that the *trans*-isomer is the stable one and its reported properties[4] correspond to those of IX.

The carbonyl group of the α-cyano-β-phenylacrylamides, XVII—XXIV, absorb at frequencies, 1689—1701 cm.$^{-1}$, that are lower than those of the carbonyl of the esters. This is to be expected in amides because of the hydrogen-bonding properties of the NH$_2$ group.[5] On the other hand, it is fair to claim that this bonding does not take place to a great extent: derivatives of malonamide, XXXIII—XXXVII, have the same kind of steric hindrance as was described for the model of diethyl benzylidenemalonate; therefore the carbonyl has to absorb at frequencies not lower than those of the derivatives of cyanoacetamide, but benzylidenemalonamides are capable of strong intramolecular

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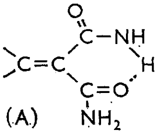
[3] Felton and Orr, *J.*, 1955, 2170.
[4] Lohaus, *Annalen*, 1934, **514**, 137.
[5] Bellamy, "The Infrared Spectra of Complex Molecules," Methuen & Co. Ltd., London, 1956, pp. 175 ff.

hydrogen bonding of the type (A). This, together with the possible intermolecular hydrogen bonding, will cause a bathochromic shift independently of the unfavourable non-planar conformation of the molecule. Strong hydrogen bonding in derivatives of cyanoacetamide would lower the frequencies of the carbonyl absorption to the same range as those of the benzylidene-malonamides. Poorly bonded carbonyl groups of cyanophenylacrylamides of *cis*-configuration are to be expected to absorb at frequencies higher than those found for XVII—XXIV owing to steric hindrance and the unfavourable cross-conjugation of the cyano-group. Therefore it may be concluded that compounds XVII—XXIV have the *trans*-configuration.


(A)

The effect found by changing the group Z on the cyano-group stretching frequencies is as expected: the cyano-group is strongly electronegative and conjugated electron-releasing groups aid its polarisation.

EXPERIMENTAL

Synthesis of compounds in Table 1 was accomplished by the following methods:

Method 1. Equimolecular amounts of aromatic aldehyde and active methylene compound were dissolved in the minimal amount of 95% ethanol. After the addition of a few drops of 10% potassium hydroxide solution the mixture was set aside for an hour. The precipitate was filtered off and purified by repeated recrystallisations from ethanol.

Method 2. A 0·1M-ethanolic solution of both aromatic aldehyde and active methylene compound with a few drops of piperidine was refluxed for 4—6 hr. The solvent was quickly evaporated, and the residue cooled, filtered off, and purified by repeated recrystallisations from ethanol.

Method 3. As method 1, but the reaction mixture was stored for one day at room temperature.

Method 4. A benzene solution of concentration about 3M in both aldehyde and active methylene compound with a few drops of piperidine added was refluxed with azeotropic distillation of water until it was all removed. The mixture was washed with aqueous dilute hydrochloric acid, and the benzene evaporated. If the condensation product was a liquid, it was distilled twice under low pressure; if a solid, it was recrystallised repeatedly from ethanol.

Method 5. Equimolecular amounts of aldehyde and active methylene compound were ground together in a mortar and suspended in aqueous ethanol (3 : 1) with a few drops of 10% potassium hydroxide solution and shaken for 8—10 hr. The precipitate was filtered off and purified by recrystallisations from diluted ethanol (3 : 1).

TABLE 2. *Data on new compounds appearing in Table* 1.

No.*	Aryl subst.	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
					Benzylidenemalononitrile				
VI	*p*-Br	52	51·95	1·7	11·9	$C_{10}H_5BrN_2$	51·5	2·2	12·1
					Ethyl α-cyano-β-phenylacrylate				
XIV	*p*-Br	60	51·6	3·5	4·9	$C_{12}H_{10}BrNO_2$	51·45	3·6	5·0
					α-Cyano-β-phenylacrylamide				
XIX	*p*-NMe$_2$	71	66·8	5·75	20·3	$C_{12}H_{13}N_3O$	67·1	6·1	19·75
XX	*p*-Me	40	71·4	5·4	15·0	$C_{11}H_{10}N_2O$	71·6	4·1	15·3
XXII	*p*-Br	60	48·0	3·0	11·2	$C_{10}H_7BrN_2O$	47·8	2·8	11·2
XXIII	*m*-NO$_2$	10	55·7	3·7	19·6	$C_{10}H_7N_3O_3$	55·3	3·25	19·35
					Ethyl benzylidenemalonate				
XXX	*p*-Br	55	51·1	4·8	—	$C_{14}H_{15}BrO_4$	51·4	4·6	—
					Benzylidenemalonamide				
XXXIV	*p*-MeO	60	60·4	5·7	12·1	$C_{11}H_{12}N_2O_3$	60·0	5·5	12·7
XXV	*p*-Br	45	44·3	3·0	10·4	$C_{10}H_9BrN_2O_2$	44·1	3·4	10·5
XXXVI	*m*-NO$_2$	50	50·8	3·4	17·5	$C_{10}H_9N_3O_4$	51·1	3·8	17·9
XXVII	*p*-NO$_2$	52	51·3	3·5	17·5	$C_{10}H_9N_3O_4$	51·1	3·8	17·9

* No. XIX is orange; the others are colourless.

Data on new compounds synthesised for this investigation are given in Table 2.

Infrared spectra were determined for solids in potassium bromide pellets, and for liquids by placing a thin layer of product between two potassium bromide pellets. A Baird Associates infrared spectrophotometer, equipped with a sodium chloride prism, was used.

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