under reduced pressure. The residue was refluxed for 2 hr. with 25 g. of potassium hydroxide in 150 ml. of 1:1 ethanol–water mixture. The bulk of the ethanol was evaporated; the remaining solution was poured into dilute hydrochloric acid and extracted with ether. By filtering off the ethereal suspension, a colorless powder (1.2 g.), m.p. 129°, was isolated showing only infrared absorption bands of a trihydroxy acid: O–H stretching vibrations at 3650, 3450, and 3350 cm.$^{-1}$, COOH vibrations at 1710 and 920 cm.$^{-1}$, other distinctive bands at 1280, 1140, 1090, 1055, and 950 cm.$^{-1}$. The free acid, m.p. 129°, could not be recrystallized unchanged from ethanol but yielded a product, m.p. 113°, which was a mixture of trihydroxy acid and its γ-lactone, as evidenced by a new strong infrared spectral band at 1780 cm.$^{-1}$.

The preparation of copper chelate with cupric acetate in methanol acidified with glacial acetic acid[5] was attempted. The greenish blue powder remained suspended in the ethereal layer.

Anal. Calcd. for $C_{36}H_{70}CuO_{10}$ (726.49): C, 59.52; H, 9.71; Cu, 8.75. Found: C, 58.99; H, 9.24; Cu, 8.65.

DL-*lyxo*- and DL-*ribo*-1,2,3,4-Octadecanetetrols (XVIII and XIX).—A mixture of 2,3,4-trihydroxyoctadecanoic acid and its γ-lactone (1.0 g.) was reduced with lithium aluminum hydride in anhydrous ether in the usual manner. The first crop of crystals (0.2 g.) has been obtained from the ethereal suspension at 20°. One crystallization from ethanol yielded the pure colorless powder, m.p. 120°, to which the DL-*lyxo* configuration was assigned on the basis of its infrared spectrum.

Anal. Calcd. for $C_{18}H_{38}O_4$ (318.48): C, 67.88; H, 12.03. Found: C, 68.01; H, 11.90.

The second isomer (0.3 g.) was isolated from the ethereal filtrate cooled to 0°. Several crystallizations from ethanol gave the colorless DL-*ribo* tetrol, m.p. 98–101° (with sintering at 91°).

Anal. Calcd. for $C_{18}H_{38}O_4$ (318.48): C, 67.88; H, 12.03. Found: C, 67.83; H, 11.80.

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Condensation of Acetals with Cyanoacetic Acid

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Acetals of benzaldehydes containing +M substituents in the ring condense with cyanoacetic acid more slowly than the free aldehydes, whereas *p*-anisaldehyde acetal condenses at a higher rate than the aldehyde. Cyanoacetic acid condenses more rapidly with acetals than ethyl cyanoacetate, but, in the presence of bases, the ester is more reactive. Addition of strong acid lowers the rate of condensation.

Acetals of aromatic aldehydes condense with malonic acid and ethyl hydrogen malonate in the Knoevenagel–Doebner reaction to give the unsaturated acids or esters, respectively. *p*-Tolualdehyde diethyl acetal and cinnamaldehyde diethyl acetal can also be condensed in benzene with ethyl hydrogen malonate in the presence or absence of added catalyst to give the monoethyl esters of the corresponding unsaturated dicarboxylic acids; the aldehyde is not an intermediate in these reactions, since it does not condense under the same conditions.[2]

Further experiments have now shown that in benzene solution benzaldehyde diethyl acetal does not condense with ethyl hydrogen malonate. In the hope that this lack of reactivity of the acetal could be compensated by a greater reactivity of the active methylene compound employed, the reaction of a series of aromatic acetals with cyanoacetic acid has been studied.

The condensations were carried out in tetrahydrofuran or in benzene–dioxane (cyanoacetic acid being only slightly soluble in benzene alone) and in the presence or absence of acidic and basic catalysts.

The influence of substituents in the phenyl ring on the course of the reaction was also studied, the condensations being performed under similar conditions so that the yield could be considered to reflect the reactivity of the acetals (the acetal which did not condense was recovered after the reaction either unchanged or in the form of the corresponding aldehyde). Yields were determined by the isolation of the products. Quantitative estimation of the course of the reaction by physical methods was difficult since competitive reactions were taking place, *e.g.*, esterification of the acids with formation of the aldehydes from the acetals. The results obtained in the absence of catalyst are summarized in Table I.

TABLE I

CONDENSATION OF ACETALS WITH CYANOACETIC ACID

Diethyl acetal of	Yield[a] of acid, % T[b]	B[b]	M.p. of acid, °C.
Benzaldehyde	18	15	185[c]
p-Tolualdehyde	26	20	211[d]
p-Anisaldehyde	35	65	237[d]
m-Nitrobenzaldehyde	10		165
p-Nitrobenzaldehyde	2		209[d]
Cinnamaldehyde	60	40	212[e]
3,4-Dimethoxybenzaldehyde	47	93	204[f]
p-Chlorobenzaldehyde		60	203[g]

[a] After 6-hr. reflux. [b] Solvent used: T, tetrahydrofuran; B, benzene + 10% dioxane. [c] E. Fiquet, *Ann. chim.*, [6]**29,** 472 (1893). [d] E. J. Corey and C. Fraenkel, *J. Am. Chem. Soc.*, **75,** 1168 (1953). [e] G. Wittig, R. Kethur, A. Klein, and R. Wietbrock, *Ber.*, **B69,** 2078 (1936). [f] See footnote *d* and A. Lapworth and J. A. McRae, *J. Chem. Soc.*, **121,** 1699 (1922). [g] R. von Walther and W. Raetze, *J. prakt. Chem.*, [2]**65,** 258 (1902).

It appears that electron-donating groups raise the yield of the α-cyanocinnamic acids formed, whereas electron-attracting groups, like the nitro group, but not the chlorine atom, lower the yield. The results support the view that a dissociation process (1) with formation of a positive charge on the carbon α to the phenyl ring

$$\mathrm{RCH(OEt)_2 + CH_2(CN)COOH \longrightarrow R\overset{+}{C}HOEt + CH_2(CN)COO^- + EtOH} \quad (1)$$

determines the rate of the reaction. The formed ion pair condenses, or gives the free aldehyde which may also undergo the condensation.

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[1] Taken in part from the M.S. thesis of A. Y. M., The Hebrew University, 1960. A preliminary communication was published: *Bull. Res. Council Israel, Sect. A*, **9,** 62 (1960).

[2] J. Klein and E. D. Bergmann, *J. Am. Chem. Soc.*, **79,** 3452 (1957).

TABLE II

Aldehyde or acetal	Moles	Moles of		Solvent	Catalyst, mole	Duration of reaction, hr. (70°)	Yield of condensation products, %
		EC[a]	C[b]				
Benzaldehyde	0.05	0.05		T[c]	0.05 P[d]	8	30 E[e]
Benzaldehyde acetal[f]	0.05	0.05		T	0.05 P	2	8 E
Benzaldehyde	0.05		0.05	T	...	8	18 A[g]
p-Tolualdehyde	0.05	0.05	0.05	T	...	8	7 E, 15 A
p-Tolualdehyde acetal	0.05	0.05	0.05	T	...	8	7 E, 17 A
p-Tolualdehyde	0.05		0.05	T	...	8	30 A
	0.05		0.05	T	0.03 Pi[h]	8	82 A
	0.05	0.05	0.05	T	0.03 Pi	8	44 E, 23 A
	0.05	0.05	0.05	T	0.02 F	8	2 A
p-Tolualdehyde acetal	0.05	0.05	0.05	T	0.03 Pi	8	56 E, 28 A
	0.05	0.05	0.05	T	0.02 F[i]	8	8 A
	0.05	0.05	0.05	B[j]		8	25 A
m-Nitrobenzaldehyde	0.03		0.03	T		8	85 A
	0.02		0.05	T		8	98 A
p-Nitrobenzaldehyde	0.03		0.03	T		8	83 A
	0.02		0.05	T		8	95 A
m-Nitrobenzaldehyde acetal	0.025	0.03	0.03	T		8	15 A
	0.025	0.03	0.03	B	0.05 Pi	8	...
	0.025	0.03	0.03	B	0.01 F	8	...
p-Anisaldehyde	0.05	0.05	0.05	B		2	8 A
	0.05	0.05	0.05	B	0.02 F	2	1 A
	0.05	0.05	0.05	B		8	20 A
	0.05	0.05	0.05	T		8	25 A
	0.05	0.05	0.05	B	0.02 F 0.06 Pi	2	50 E, 40 A
	0.05	0.05	0.05	B	0.08 Pi	2	56 E, 40 A
	0.05	0.05	0.05	EtOH	0.08 Pi	2	40 E, 40 A
	0.05	0.05	0.05	EtOH	NaOH 0.05	2	66 E, 13 A
p-Anisaldehyde acetal	0.05	0.05	0.05	B		8	63 A
	0.05	0.05	0.05	T		8	20 A
	0.05	0.05	0.05	B	0.02 F	8	23 A
	0.05	0.05	0.05	B	0.01 F	2	42 A
	0.05	0.05	0.05	T	0.01 F	2	22 A
	0.05	0.05	0.05	B		2	55 A, 8 E
	0.05	0.05	0.05	B	0.02 F 0.02 Pi	2	50 E, 50 A
	0.05	0.05	0.05	B	0.02 Pi	2	50 E, 50 A
	0.05	0.05	0.05	B	0.07 Pi	2	50 E, 20 A
	0.05	0.05	0.05	T		2	8 E, 20 A
3,4-Dimethoxybenzaldehyde	0.05	...	0.05	B		8	26 A

[a] Ethyl cyanoacetate. [b] Cyanoacetic acid. [c] Tetrahydrofuran. [d] *p*-Nitrobenzoic acid. [e] Unsaturated α-cyano ester. [f] All acetals are diethyl acetals. [g] Unsaturated α-cyano acid. [h] Piperidine. [i] Trifluoroacetic acid. [j] Benzene + 10% dioxane.

The acetal of benzaldehyde yielded only about 6% of ethyl α-cyanocinnamate when condensed in tetrahydrofuran with ethyl cyanoacetate in the presence of *p*-nitrobenzoic acid. The free aldehyde, however, gave under the same conditions a yield of 53%. These results are different from those obtained in the case of ethyl hydrogen malonate. We, therefore, studied the reactivity of the aldehydes under the same conditions as their acetals, as well as the influence of added basic and acidic catalysts.

Competitive reactions between aldehydes or their acetals and equimolar mixtures of cyanoacetic acid and ethyl cyanoacetate were also carried out. The results are summarized in Table II. The yields recorded for the esters are less accurate than those of the acids, particularly in the low-yield cases, since the isolation of esters was carried out by fractional distillation, whereas the acids were isolated by alkaline extraction and acidification. Table II indicates that almost no reaction takes place between the acetals and cyanoacetic acid or its ester in the case of nitrobenzaldehydes; the nitro group would indeed destabilize a positive charge on the carbon atom next to the aromatic ring. The corresponding aldehydes, however, are very reactive. Acetals of benzaldehyde and *p*-tolualdehyde did undergo only limited condensation, much less than the free aldehydes, and it is probable that the reaction of these acetals with cyanoacetic acid proceeds through the intermediary of the aldehydes. This assumption is supported by the rise in yield upon the addition of piperidine and the drop in yield upon addition of trifluoroacetic acid in the condensation of both the aldehyde and the acetal. With *p*-anisaldehyde, however, the acetal gave higher yields than the aldehyde. It may, therefore,· be assumed that from the acetal in the first step of the reaction a carbonium ion is formed, which condenses with cyanoacetic acid before it can decompose to the free aldehyde.

The ratio of acid–ester in the product of the competitive reaction with cyanoacetic acid and its ester was much larger than unity in the absence of catalysts; it was reduced to one or even less when piperidine was added. This result may be attributed to the higher reactivity of enolates as compared to that of enols, and to the slower rate of formation or lower stationary concentration of the enolate of the cyanoacetate anion $(\mathrm{NCCH{=}CO_2})^{-2}$ which has to accommodate two negative charges, and not only one, as in the enolate of ethyl cyanoacetate. In the absence of base, however, the enol of cyanoacetic acid or of its anion reacts faster than the enol of ethyl cyanoacetate. The reason for this is, perhaps, that an ion pair of the enol of cyanoacetate anion and the carbonium ion is formed in the first step of the reaction.

The possibility of thermodynamic and not kinetic product control in the competitive reaction is ruled out, since no exchange[3] is observed when α-cyano-*p*-methoxycinnamic acid or its ester is heated with equimolar amounts of ethyl cyanoacetate and cyanoacetic acid under the conditions of the condensation reaction.

The observed influence of the solvent on the course of the condensation reaction is of interest. Whereas reactions in tetrahydrofuran, which would be expected to assist ionization more effectively than benzene, give, in fact, higher yields of condensation products than in benzene for the less reactive acetals, lower yields were obtained in tetrahydrofuran in the case of the acetal of *p*-anisaldehyde. A possible explanation of this effect is the preferential conversion in more polar solvents of the carbonium ion formed in the first step of the reaction into the less reactive aldehyde.

Addition of trifluoroacetic acid lowered the yields of condensation products. It may be that the strong acid alone is not a good catalyst for the enolization of cyanoacetic acid and that an additional weak base is necessary. Swain[4] has found that acid-catalyzed enolization of ketones proceeds through a reversible, fast protonation of the ketone and that the rate-determining step is the action of a weak base on the protonated species. In our case, when aprotic solvents were used, the concentration of an appropriate base may have a greater influence than the concentration of the acid.[5]

Experimental

Melting and boiling points are uncorrected. Benzene and tetrahydrofuran were dried on sodium and distilled. Dioxane was purified by the method of Fieser.[8]

Preparation of Diethyl Acetals.—The acetals were prepared by method I of ref. 1 yielding ***p*-chlorobenzaldehyde diethyl acetal**, b.p. 108° (3 mm.) (*Anal.* Calcd. for $C_{11}H_{15}ClO_2$: C, 61.5; H, 7.04. Found: C, 61.26; H, 7.15.), ***m*-nitrobenzaldehyde diethyl acetal**, b.p. 181° (23 mm.),[9] and ***p*-nitrobenzaldehyde diethyl acetal**, b.p. 179° (23 mm.).[10]

Condensation in Benzene.—To a solution of 0.05 mole of the acetal in 50 ml. of benzene, a solution of 0.05 mole of cyanoacetic acid in 5 ml. of dioxane was added. The reaction mixture was heated under reflux or kept at the desired temperature for a given time and cooled. The benzene solution was washed with a 10% aqueous sodium carbonate solution and then with water and distilled. The aqueous layer was acidified and the product collected.

Condensation in Tetrahydrofuran.—The working procedure was similar to that in benzene, but dioxane was omitted and tetrahydrofuran was substituted for benzene. Tetrahydrofuran was removed *in vacuo* at the end of the reaction, benzene was added, and the work-up was similar to that after the condensation in benzene. The **α-cyano-*m*-nitrocinnamic acid**, thus formed, had m.p. 265°.

Anal. Calcd. for $C_{10}H_6N_2O_4$: C, 55.0; H, 2.75; N, 12.8. Found: C, 55.3; H, 2.83; N, 12.49.

This acid forms a sparingly soluble sodium salt, and a precipitate appears on treatment of the reaction mixture with aqueous sodium carbonate. This salt can be collected, suspended in water, and acidified to give the acid.

Experiments to Test the Exchange of the Active Methylene Compounds.—A mixture of 5.8 g. of ethyl α-cyano-*p*-methoxycinnamate,[11] 2.8 g. of ethyl cyanoacetate, 3.2 g. of cyanoacetic acid, and 1 ml. of piperidine in 5 ml. of dioxane and 25 ml. of benzene was heated under reflux for 5 hr. The solution was cooled and washed with aqueous sodium carbonate. Distillation gave 5.6 g. of the unsaturated ester, b.p. 150° (0.5 mm.), m.p. 78° (lit.[11] m.p. 85°).

In a similar exchange experiment between α-cyano-*p*-methoxycinnamic acid and ethyl cyanoacetate, all of the starting acid was recovered.

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(4) C. G. Swain, A. J. DiMilo, and J. P. Cordner, *J. Am. Chem. Soc.*, **80**, 5985 (1958); C. G. Swain, E. C. Stivers, J. F. Reuver, Jr., and L. J. Schead, *ibid.*, **80**, 5885 (1958).

(5) A referee suggested that the obtained results, particularly the influence of added acid, can be explained better by assuming that the cyanoacetate anion is the reacting species in the condensation reaction. It is known, however, that bromination of cyanoacetic acid and ethyl cyanoacetate in aqueous solution is much faster than that of sodium cyanoacetate.[6] The assumption that cyanoacetate ion is the reacting species cannot be accommodated with the influence of added base on the acid–ester ratio in the products. The importance of the presence of some weak basic species in the enolization of cyanoacetic acid can be illustrated by the fact that 0.1 *M* solutions of this acid or its ethyl ester did not absorb bromine in dry acetonitrile at 0° during 2 days,[7] whereas in aqueous solution[6] the reaction was too fast to be measured.

(6) H. M. Dawson, R. Sugden, and A. Taylor, *J. Chem. Soc.*, **107**, 1030 (1915).

(7) Our unpublished results.

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