

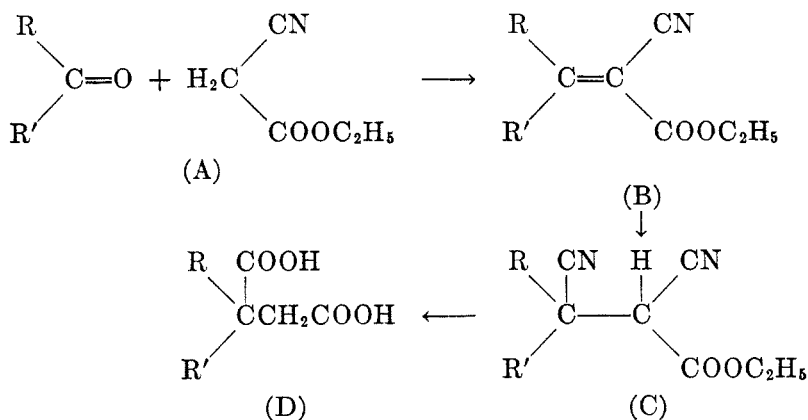
THE SYNTHESIS OF α,α -DISUBSTITUTED SUCCINIC ACIDS
FROM ETHYL ALKYLIDENECYANOACETATES

E. J. CRAGOE, JR., CHARLES M. ROBB, AND JAMES M. SPRAGUE

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A number of investigators have prepared α -substituted succinic acids by the addition of hydrogen cyanide to alkylidenecyanoacetates (or alkylidenemalonates) followed by hydrolysis of the resulting nitrile. In the early work very few examples of α,α -disubstituted succinic acids appear, largely because the alkylidene compounds derived from ketones were difficultly accessible. The more recent studies of Cope and his associates (1, 2) have extended the number of alkylidenecyanoacetates that may be prepared from ketones by the Knoevenagel reaction.

The present paper reports further improvements in the application of the Knoevenagel reaction to ketones with ethyl cyanoacetate and describes the conversion of a variety of the alkylidene compounds (B) to α,α -disubstituted succinic acids (D).



The condensation of cyanoacetic acid and its esters with simple ketones has been reported by a number of the earlier investigators. In general, the usual conditions of the Knoevenagel reaction, employing basic catalysts such as piperidine, diethylamine or other amines, were effective. Cope (1) found more recently that with simple ketones better yields could be obtained using catalysts such as acetamide or the acetate salts of amines such as piperidine, diethylamine or ammonia. The maximum yield was obtained when the reaction was carried out in the presence of acetic acid and an inert, water-insoluble solvent that aided in the removal of water by distillation. In a later paper, Cope and associates (2) describe the condensation of cyanoacetic ester with a variety of ketones including aliphatic, alicyclic or mixed aromatic-aliphatic types. Furthermore, they were able to obtain reaction with benzophenone, the first example of the condensation

of an aromatic ketone with a cyanoacetate. Heretofore, the Knoevenagel reaction with diaryl ketones had been unsuccessful, in fact, it was said to be impossible according to the proposed mechanism (3).

When we attempted to prepare ethyl alkylidencyanoacetates from higher molecular weight dialkyl and aryl alkyl ketones or diaryl ketones by the available methods, poor yields were encountered in many cases. Particular difficulty was met in the case of substituted diaryl ketones. Using benzophenone as a prototype, a study was made of the effect of catalyst, solvent, time, and temperature on the yield obtained in the Knoevenagel reaction. Ethyl cyanoacetate, benzophenone, acetic acid, and toluene were refluxed in the presence of various catalysts, with the continuous removal of water under the conditions described by Cope (2).

TABLE I
EFFECT OF CATALYST
 $(C_6H_5)_2CO + H_2C(CN)COOC_2H_5 \rightarrow (C_6H_5)_2C=C(CN)COOC_2H_5$

CATALYST	REACTION TIME, HOURS	YIELD, %
None	8	0
Sodium acetate	2	0
Ammonium sulfate	2	0
Piperidine	4	0
Triethylamine	3	0
Acetamide	2	0
Heptamide	2	0
Ethylenediamine	15	18
Ammonium acetate	8	42

Ethyl cyanoacetate (0.6 mole), benzophenone (0.5 mole), acetic acid (0.5 mole), toluene (100 ml.), and catalyst (0.1 mole) were refluxed under the conditions of Cope's (2) method B. Where no product was obtained, no water separated.

From Table I it appears that of the previously recommended catalysts, only ethylenediamine and ammonium acetate gave any product and only the latter gave a good yield. In contrast to Cope's (1) observation in the case of simple aliphatic ketones, acetamide was not a catalyst for benzophenone.

Several different solvents have been reported useful in aiding the removal of water by distillation from the reaction mixture; among these are toluene (4), benzene (1, 2), and chloroform (5). In the present study, using benzophenone as the ketone and ammonium acetate as the catalyst, the solvent was varied. Benzene, cyclohexane, toluene, and xylene were investigated. In general, the reaction rate, as indicated by the formation of water, increased and the yield of alkylidene ester decreased with an increase in the boiling point of the solvent. However, it is difficult to compare the results, because at higher temperatures ammonium acetate dehydrates more rapidly to acetamide, which is not a catalyst for the reaction. In reactions where the condensation is very slow, it is obvious

that the catalyst will have completely decomposed long before the reaction is complete. In order to get a better comparison of the solvents it was necessary to add the ammonium acetate catalyst in small portions at frequent intervals until further addition gave no more reaction. The effect of the portionwise addition of catalyst when benzene was used as a solvent is illustrated in Table II. With a single addition only 66% yield was obtained while multiple addition gave yields as high as 84%. Using the multiple addition technique the effect of solvent was determined as recorded in Table II.

These data obtained with benzophenone, and those obtained with other ketones using benzene and toluene (*cf.* Table III), indicate that benzene is the best solvent. When the ammonium acetate catalyst was added portionwise at short intervals, with benzene as a solvent, the optimum yields were obtained. Under these conditions, ketones such as benzophenone, that previously gave

TABLE II
EFFECT OF SOLVENT

SOLVENT	AMMONIUM ACETATE		TOTAL TIME, HOURS	YIELD, %
	Total, G.	Number of Additions		
Cyclohexane	19	11	50	30
Benzene	7.7	1	18	66
Benzene	10	4	42.5	84
Benzene	20	14	32	80
Toluene	16	8	13.5	42
Xylene	20	10	8.5	35

Ethyl cyanoacetate (0.6 mole), benzophenone (0.5 mole), acetic acid (0.4 mole), and the solvent (100 ml.) were refluxed and the ammonium acetate catalyst added either all at once or in divided, equal portions at regular intervals until no more reaction occurred.

moderate yields, gave excellent yields (increased from 66% to 84%). Ketones that gave poor yields, such as 2,4'-dichlorobenzophenone or phenyl 2-thienyl ketone, now gave moderate yields. Furthermore, ketones said to be completely unreactive (2) such as camphor and pinacolone have yielded reasonable quantities of the ethyl alkylidenecyanoacetate derivative, 37% and 13% respectively. Recently, Cope and Field (7) have successfully used our method in condensing 2-allyl-1-indanone with ethyl cyanoacetate.

In general, the reactions proceeded without the formation of significant quantities of by-products. In a few cases of relatively inert ketones, *i.e.* those requiring a long reaction time and large quantities of catalyst, considerable amounts of high-boiling, polymeric materials were formed. In the case of 4,4'-dichlorobenzophenone, a 13% yield of the amide, $(p\text{-Cl-C}_6\text{H}_4)_2\text{C}=\text{C}(\text{CN})\text{CONH}_2$, was isolated in addition to 43.5% of the expected ethyl di-(*p*-chlorophenyl)methylidenecyanoacetate. With *o*-hydroxyhexanophenone, the product isolated was not ethyl 1-(*o*-hydroxyphenyl)hexylidenecyanoacetate but a cyclized product, 3-cy-

TABLE III
ETHYL ALKYLIDENECYANOACETATES
RR'CO (A) + H₂C(CN)COOC₂H₅ → RR'C=C(CN)COOC₂H₅ (B)

NUMBER	KETONE (A)	METHOD	REAC- TION TIME, HRS.	YIELD, %	B.P., °C.	MM.	ETHYL ALKYLIDENECYANOACETATE (B)			
							M.P., °C. (uncor.)	²³ #D	FORMULA	N Calcd Found
I	Diamyl	B1	11	70 ^a	136-138	1	—	—	—	—
II	Dinonyl	B2	3.5	47	184-185	2	—	C ₂₁ H ₄₃ NO ₂	3.71	3.69
		A2	32.5	79						
III	Phenyl methyl	A2	46	71 ^b	134-135	2	—	—	—	—
IV	Phenyl ethyl	B1	3	41	138-140	2	—	—	—	—
		A1	32	78 ^c						
V	Phenyl amyl	B3	3	39	161-163	2	—	—	—	—
		A1	32	87 ^d						
VI	Phenyl heptyl	B2	4.5	52	170-177	0.08	—	C ₁₉ H ₃₅ NO ₂	4.68	4.78
		A1	42	86						
VII	Phenyl hendecyl	B2	6	22	182-185	2	—	C ₂₃ H ₃₉ NO ₂	3.94	4.02
		A1	24	68						
VIII	Phenyl 2-cyclohexylethyl	B2	4	52	174-177	1	—	C ₂₁ H ₃₅ NO ₂	4.50	4.51
		A1	32.5	75						
IX	Phenyl 5-cyclohexylpentyl	B2	6.5	29	190-195	0.1	—	C ₂₃ H ₃₇ NO ₂	3.96	3.83
		A1	26.5	67						
X	<i>p</i> -Butylphenyl hexyl	B2	4	14	180-185	1	—	C ₂₃ H ₃₇ NO ₂	4.10	4.09
		A1	52	34 ^e						
XI	<i>p</i> -Hydroxyphenyl ethyl	A1	45	45	185-188	0.1	92-93.5 ^f	C ₁₄ H ₁₅ NO ₃	5.71	5.72
XII	<i>o</i> -Hydroxyphenyl pentyl	B3	11	28 ^g	188-190	0.4	94-95	^g	—	—
		A1	80	64						
XIII	Di-(<i>β</i> -phenethyl)	B2	4	68	184-187	0.1	—	C ₂₃ H ₃₃ NO ₂	4.20	4.20
		A1	10	73						
XIV	Diphenyl	B4	13.5	41.7	175-182	1	95-97	—	—	—
		A1	42.5	84 ^h						
XV	Phenyl <i>p</i> -chlorophenyl	A1	42.5	81.7	160-180	0.15	110-111 ⁱ	C ₁₉ H ₁₇ ClNO ₂	4.49	4.45

XVI	Di-(<i>p</i> -chlorophenyl)	B3	6.5	31.5 43.5 (56.5) ⁱ	185-192	0.13	88-89 ^k	—	C ₁₈ H ₁₃ Cl ₂ NO ₂	4.05	4.05
XVII	<i>o</i> -Chlorophenyl <i>p</i> -chlorophenyl	B3 A1	6.3	4.3 46	190-195	0.18	105-106 ^m	—	C ₁₈ H ₁₃ Cl ₂ NO ₂	4.05	4.01
XVIII	Phenyl <i>p</i> -methoxyphenyl	A1	32	75	187	0.075	—	"	C ₁₉ H ₁₇ NO ₃ ^p	4.56	4.37
XIX	Phenyl 2-thienyl	B3 A1	5 47	8.8 53	185-188	2	77-78 ^q	—	C ₁₆ H ₁₃ NO ₂ S ^q	4.94	4.93
XX	Fluorenone	A1	22	87	194-196	0.09	58-60	—	C ₁₈ H ₁₃ NO ₂ ^r	5.09	5.09
XXI	Camphor	A2	69	37	121-122	0.05	86-87 ^s	—	C ₁₅ H ₂₁ NO ₂ ^t	5.66	5.67
XXII	Pinacolone	A2	80.5	13.2	127-130	12	—	1.4680	C ₁₁ H ₁₇ NO ₂ ^u	7.17	7.19

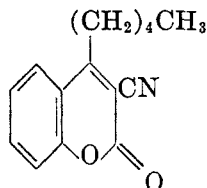
^a Cope (2) reports 87% yield using benzene as a solvent. ^b Cope (2) reports 69% yield. ^c Cope (2) reports 73% yield. ^d Cope (2) reports 75% yield. ^e A very small run was made in this case, thus the yield recorded may not be an accurate value. ^f The distilled material was purified by recrystallization from aqueous methanol, then hexane. *Anal.* Calc'd: C, 68.55; H, 6.17. Found: C, 68.74; H, 6.23. ^g The product is not the expected cyanoester but appears to be the cyclized derivative 3-cyano-4-pentylcoumarin. The distilled material was purified by recrystallization from hexane. *Anal.* Calc'd for C₁₅H₁₃NO₂: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.84; H, 5.92; N, 5.75. ^h Cope (2) reports 66% yield. The distilled material can be further purified by recrystallization from *n*-heptane. ⁱ The distilled material was recrystallized first from ethanol, then from *n*-hexane. ^j In addition to 43.5% of the alkylidenecyanoacetic ester, there was isolated 13% of a substance which appeared to be the corresponding amide (*p*-ClC₆H₄)₂C=C(CN)CONH₂, m.p. 189-191°. *Anal.* Calc'd for C₁₆H₁₀Cl₂N₂O: C, 60.59; H, 3.18; N, 8.83. Found: C, 60.41; H, 3.01; N, 8.81. ^k The product was purified by distillation followed by recrystallization from heptane. ^l The distilled material was purified by recrystallization from ethanol. ^m This material is too viscous at 25° for refractive index determination. ⁿ Purification of the distilled product was effected by recrystallization from cyclohexane. *Anal.* Calc'd: C, 67.82; H, 4.63. Found: C, 67.92; H, 4.69. ^o Calc'd: C, 78.52; H, 4.76. Found: C, 78.49; H, 4.84. ^p The distilled product was purified by repeated recrystallizations from ethanol-water. ^q Calc'd: C, 72.84; H, 8.56. Found: C, 72.99; H, 8.66. ^r Calc'd: C, 67.66; H, 8.78. Found: C, 67.35; H, 8.75.

TABLE IV
 α, α -DISUBSTITUTED SUCCINIC ACIDS AND ANHYDRIDES
 $RR'C=C(CN)COOC_2H_5 \rightarrow RR'C(CN)CH(CN)COOC_2H_5 \rightarrow HOOCRR'CH_2COOH \rightarrow COCRR'CH_2CO$
(E)

(B)	R	R'	YIELD, %		B.P., °C	MM.	M.P., °C (uncorr.)	n_D^{25}	FORMULA	ANALYSES					
			Acid (D)	Anh. (E)						Calc'd		Found			
										C	H	C	H		
I	<i>n</i> -Amyl	<i>n</i> -Amyl	—	63	134-135	1.5	—	1.4537	C ₁₄ H ₂₂ O ₃	69.96	10.07	69.91	10.14		
II	<i>n</i> -Nonyl	<i>n</i> -Nonyl	—	41	186-192	1	—	1.4625	C ₂₂ H ₄₀ O ₃	74.95	11.44	75.19	11.76		
IV	Phenyl	Ethyl	77 ^a	—	—	—	149-150	—	C ₁₃ H ₁₄ O ₄	64.85	6.35	65.02	6.51		
V	Phenyl	<i>n</i> -Amyl	—	65	162	1	—	1.5159	C ₁₃ H ₁₈ O ₃	73.15	7.37	73.11	7.47		
VI	Phenyl	<i>n</i> -Heptyl	—	56	170-172	2	—	1.5081	C ₁₇ H ₂₂ O ₃	74.42	8.08	74.43	8.18		
VII	Phenyl	<i>n</i> -Hendecyl	—	48	193-196	1-2	—	1.5010	C ₂₁ H ₃₀ O ₃	76.32	9.15	76.36	9.37		
VIII	Phenyl	2-Cyclohexylethyl	—	52	185-188	1-2	—	1.5301	C ₁₈ H ₂₂ O ₃	75.49	7.74	75.47	7.82		
IX	Phenyl	5-Cyclohexylpentyl	—	45	210	1-2	—	1.5210	C ₂₁ H ₂₈ O ₃	76.79	8.59	76.78	8.86		
X	<i>p</i> -(<i>n</i> -Butyl)phenyl	<i>n</i> -Hexyl	—	54	178-180	1-2	95-98 ^b	1.5055 ^c	C ₂₀ H ₂₈ O ₃	75.91	8.92	75.85	9.02		
XIV	Phenyl	Phenyl ^d	80	—	—	—	175 ^d	—	C ₁₄ H ₁₄ O ₄	71.10	5.22	71.13	5.34		
XIII	2-Phenethyl	2-Phenethyl	16	—	—	—	155-156 ^f	—	C ₂₀ H ₂₂ O ₄	73.60	6.80	73.75	6.85		
XV	Phenyl	<i>p</i> -Chlorophenyl	82	—	—	—	187-188 ^f	—	C ₁₄ H ₁₃ ClO ₄ ^e	63.06	4.30	63.19	4.48		
XVII	<i>p</i> -Chlorophenyl	<i>o</i> -Chlorophenyl	47	—	—	—	195-196 ^f	—	C ₁₆ H ₁₂ Cl ₂ O ₄ ^h	56.66	3.56	56.70	3.72		
XVI	<i>p</i> -Chlorophenyl	<i>p</i> -Chlorophenyl	76	—	—	—	188-189 ^f	—	C ₁₆ H ₁₂ Cl ₂ O ₄ ⁱ	56.66	3.56	56.88	3.73		

^a Purification was carried out by recrystallization from water. ^b This material solidified only after long standing. ^c The refractive index was taken on the supercooled liquid. ^d α, α -Diphenylsuccinic acid, prepared by another method, has been reported by Salmon-Legagneur (15). He reported that with slow heating it melted at 170° with the formation of the anhydride, while in a preheated bath the minimum instantaneous m.p. was 197-199°. The sample prepared in the present work melted at 175° when placed in a bath preheated to 165° and heated at a rate of 1° per 10 sec. In a bath held at 175° it melted in 70 to 75 sec. ^e α, α -Diphenylsuccinic anhydride, m.p. 90.5-91.5° was prepared by warming the corresponding acid with thionyl chloride; yield, 95%. ^f *Anal.* Calc'd for C₁₆H₁₂O₄: C, 76.18; H, 4.80%. Found: C, 76.43; H, 5.01%. Salmon-Legagneur (15) reported the synthesis of this compound by the action of acetyl chloride on the succinic acid, m.p., 90-91°. ^g Purification of this compound was effected by recrystallization from a mixture of acetic acid and water. ^h *Anal.* Calc'd: Cl, 11.64. Found: Cl, 11.52. ⁱ *Anal.* Calc'd: Cl, 20.91. Found: Cl, 20.68. ^j *Anal.* Calc'd: Cl, 20.91. Found: Cl, 20.60.

ano-4-pentylcoumarin (XII). No product was isolated when the reaction was carried out with xanthone; when anthrone was used no nitrogenous product was isolated.



(XII)

In 1896 Bredt and Kallen (8) reported the synthesis of α -monosubstituted succinic acids by a method involving the hydrolysis of the hydrogen cyanide addition product of ethyl alkylidenemalonates. Shortly thereafter Lapworth (9) showed that alkylidenecyanoacetic acid salts could be used in a similar manner to give substituted succinic acids. Higson and Thorpe (10) found the reaction to be more generally applicable when the sodium derivative of ethyl cyanoacetate was condensed with cyanohydrins of aldehydes or ketones followed by conversion to the dicyano derivative and finally hydrolysis to the succinic acid. Later Lapworth (11, 12) improved his method by employing the alkylidenecyanoacetic ester rather than the salt. Other than α,α -dimethyl- (10), α -methyl- α -ethyl- (10), α,α -diethyl- (13), α,α -diphenyl- (14) and α,α -pentamethylene-succinic acids (11), few α,α -disubstituted succinic acids have been reported in the earlier literature. More recently Birch and Robinson (4) have synthesized α -methyl- α -hexylsuccinic acid and Ray and Bhattacharyya (14) have prepared α -ethyl- α -decylsuccinic acid by a combination of the methods of Cope (2) and Lapworth (9, 11, 12).

In the present work the conversion of the ethyl alkylidenecyanoacetates (B) to the ethyl β,β -disubstituted- α,β -dicyanopropionates (C) by Lapworth's method was rapid and nearly quantitative. Earlier experience in these laboratories¹ had shown that the hydrolysis of these dicyano derivatives using hydrochloric acid [according to Lapworth (9)] or sulfuric acid [described by Ray and Bhattacharyya (14)] often gave unsatisfactory results. Much better results were obtained using the method of Birch and Robinson (4) who employed a mixture of sulfuric acid, acetic acid, and water. However, even under these conditions, products were obtained which contained nitrogenous impurities, probably the succinamic acid derivatives. When the acid hydrolysis was followed by an alkaline hydrolysis, pure succinic acids resulted. Since in many cases, the α,α -disubstituted succinic acids were oils, it was found convenient to convert them to the corresponding anhydrides which then could be purified by distillation (*cf.* Table IV).

¹ The early work in these laboratories on the preparation of ethyl diphenylmethylenecyanoacetate and its conversion to α,α -diphenylsuccinic acid was carried out by Floyd Todd.

EXPERIMENTAL²

Ethyl alkylidenecyanoacetates. For comparative purposes, two different methods and several variations of each method were employed in the synthesis of the ethyl alkylidenecyanoacetates. These methods may be summarized as follows: Method A—benzene as a solvent, (A-1) multiple addition of ammonium acetate catalyst, (A-2) increased quantities of ethyl cyanoacetate, solvents, and catalyst for slowly reacting ketones. Method B—toluene as a solvent and ammonium acetate added in (B-1) one portion, (B-2) two portions, (B-3) three portions, and (B-4) multiple portions. A summary of the runs made by these methods appears in Table III.

Method A-1. Ethyl cyanoacetate (135.7 g., 1.2 moles), the ketone (1.0 mole), acetic acid (48 g., 0.8 mole), and benzene (200 ml.) were placed in a flask attached to a modified Dean and Stark (2, 6) constant water-separator. The mixture was vigorously refluxed and the ammonium acetate catalyst (19–62 g., 0.25–0.8 mole) added in small portions (4-g. portions for the rapid reactions and 3-g. portions for the slow reactions) at 3–4-hour intervals. Before each addition of catalyst, the water layer was removed from the separator. The reaction was considered to be complete when the rate of water formation reached a small constant value following each addition of catalyst. Usually acetamide crystallized from the aqueous phase. Care was taken to avoid excessive quantities of catalyst (*i.e.*, 1–2 moles). When this precaution was not observed considerable polymeric material was produced. Heating was continued for several hours after the last addition of catalyst. The total reaction time varied from 10–92 hours. The mixture was allowed to cool, washed with water (three 300-ml. portions), and dried over sodium sulfate. The solvent was removed by distillation and the residue fractionated; both operations were carried out at reduced pressure. In the case of a solid product further purification was carried out by recrystallization from an appropriate solvent.

Method A-2. Ethyl cyanoacetate (226.2 g., 2.0 mole), the ketone (1.0 mole), glacial acetic acid (96 g., 1.6 mole), benzene (400 ml.), and ammonium acetate (57.8–92.5 g., 0.75–1.2 moles) were allowed to react as in Method A-1. The catalyst was again added portionwise. This modification was especially advantageous with very inert ketones which requires long reaction times and large quantities of catalyst.

Method B-1. Ethyl cyanoacetate (135.7 g., 1.2 moles), the ketone (1.0 mole), acetic acid (48 g., 0.8 mole), and toluene (200 ml.) were allowed to react using the same apparatus as for Method A-1. The ammonium acetate (15.4 g., 0.2 mole) was added in one portion and refluxing continued until one hour after water ceased to separate. The product was isolated as in Method A-1.

Method B-2. The reaction was carried out as in Method B-1 except the ammonium acetate (19–27 g., 0.25–0.35 mole) was added in two equal portions; the second portion was added as soon as water ceased to separate following the initial addition.

Method B-3. The reaction was carried out the same as Method B-2 except the catalyst (19–58 g., 0.25–0.75 mole) was added in three portions.

Method B-4. The reaction was carried out as in B-1 except that a portion (approximately 4 g.) of catalyst (38.5 g., 0.5 mole) was added whenever the water ceased to separate.

Ethyl α,β -dicyano- β,β -disubstituted propionates. All of the ethyl alkylidenecyanoacetates (B) were converted to the ethyl α,β -dicyano- β,β -disubstituted propionates (C) in a similar fashion. A typical example is described below. In general, the products were viscous oils that failed to crystallize, therefore they were not purified and identified but used directly in the hydrolysis step (D).

Ethyl α,β -dicyano- β,β -diphenylpropionate. Ethyl diphenylmethylenecyanoacetate (118.5 g., 0.428 mole) was dissolved in warm ethanol (180 ml.) and treated with a solution of potassium cyanide (58.5 g., 0.9 mole) in water (180 ml.). The clear yellow solution that resulted

² Microanalyses by Mr. K. B. Streeter, Mrs. Thelma Buchanan, Miss Ruth Lynch, and Miss Joyce Pyett.

was heated on a steam-bath, with stirring for fifteen minutes. The solution was cooled and acidified with excess concentrated hydrochloric acid. The product separated, nearly quantitatively, as a viscous oil which solidified on cooling overnight. Recrystallization from aqueous ethanol gave 116.5 g. (90%) of white crystals, m.p. 89–91°.

Anal. Calc'd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21.

Found: C, 74.94; H, 5.29; N, 9.20.

α, α -Disubstituted succinic acids. The succinic acids were prepared in a manner similar to that described for α, α -diphenylsuccinic acid. In the cases where the products were oils they were converted to the anhydrides and purified in that form (*C.f.* Table IV).

α, α -Diphenylsuccinic acid. Ethyl α, β -dicyano- β, β -diphenylpropionate (116.3 g., 0.382 mole) was added to a solution of sulfuric acid (475 g.), glacial acetic acid (380 g.), and water (95 ml.) and the mixture heated gently until the initial vigorous evolution of carbon dioxide subsided. Then the solution was refluxed for twelve hours, cooled, and poured onto ice (1 kgm.). The oil that separated soon solidified. After removing by filtration and washing with water, the solid was refluxed for 72 hours with 20% potassium hydroxide (350 ml.). After cooling, the solution was treated with decolorizing carbon and filtered. The filtrate was made acid to Congo Red paper with concentrated hydrochloric acid. The oil that separated solidified on stirring. The solid was removed by filtration, washed with water, and dried; yield, 100 g. (97%). The crude material was recrystallized twice from a mixture of acetic acid and water. The yield of pure material was 82.4 g. (80%), m.p. 175° (see Note^d, Table IV).

α, α -Disubstituted succinic anhydrides. The succinic anhydrides were all prepared in a manner similar to that described for α -phenyl- α -(2-cyclohexylethyl)succinic anhydride. Table IV gives a summary of the results.

α -Phenyl- α -(2-cyclohexylethyl)succinic anhydride. Ethyl 1-phenyl-3-cyclohexylpropylidenedecyanoacetate (61 g., 0.196 mole) was dissolved in ethanol (80 ml.) and treated with a solution of potassium cyanide (25.5 g., 0.392 mole) in water (80 ml.). The orange solution was heated, with stirring, on a steam-bath for fifteen minutes, then cooled, diluted with water (100 ml.), and acidified with excess concentrated hydrochloric acid. The oily layer was extracted with benzene (three 75-ml. portions) and the combined extracts washed with water. The benzene was removed by distillation at reduced pressure. The residual oil (66 g., 99%) was ethyl 2,3-dicyano-5-cyclohexyl-3-phenylpentanoate. This material was added to a solution composed of concentrated sulfuric acid (248 g.), glacial acetic acid (262 g.), and water (50 ml.). The mixture was refluxed for 15 hours and then poured onto crushed ice (640 g.). The oily layer was removed by extraction with benzene (three 100-ml. portions). The benzene was removed from the combined extracts at reduced pressure. The residual oil was treated with 20% potassium hydroxide (185 ml.) and the resulting solution refluxed for 72 hours. After cooling, the solution was treated with decolorizing carbon, filtered, and the filtrate acidified with excess hydrochloric acid. The oily succinic acid derivative was removed by extraction with benzene (three 100-ml. portions), the extract washed with water, and dried over magnesium sulfate. After removal of the benzene by distillation at reduced pressure, a waxy solid remained; yield, 59.6 g. (94%), m.p. 100–110°.

The crude α -phenyl- α -(2-cyclohexylethyl)succinic acid was refluxed with acetyl chloride (75 ml.) for two hours. The excess acetyl chloride was removed by distillation and the residue fractionated under reduced pressure. The yield of material boiling at 184–188° at 1–2 mm. was 30.4 g. (54%). Refractionation gave 29.3 g. (52%) of material boiling at 185–188° at 1–2 mm.

SUMMARY

Ammonium acetate was found to be a satisfactory catalyst for the Knoevenagel reaction involving diaryl ketones and certain hindered ketones with ethyl cyanocetate. The yields of ethyl alkylidenedecyanoacetates were improved by the portionwise addition of catalyst at frequent intervals.

Camphor and pinacolone, ketones that failed to react under conditions used previously, gave the corresponding alkylidene derivative.

A variety of the ethyl alkylidenecyanoacetates were converted to the corresponding α,α -disubstituted succinic acids by the addition of hydrogen cyanide followed by hydrolysis. Many of the succinic acids were converted to the corresponding α,α -disubstituted succinic anhydrides.

GLENOLDEN, PA.

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