Anal. Calcd. N for $C_{15}H_{14}N_2O_5$, 9.27%. Found: 9.18, 9.10%.

3-p-Nitrobenzoylamino-2,4-pentanedione (IV, R = *p*-$NO_2C_6H_4$—). From 5.87 g. (0.04 mole) of 3-amino-2,4-pentanedione hydrochloride and an equivalent amount of *p*-nitrobenzoyl chloride (7.7 g.) the amide was obtained in 92% yield. After crystallization from ethanol it melted 199–200°.

Anal. Calcd. N for $C_{12}H_{12}N_2O_5$: 10.61%. Found: 10.41, 10.45%.

4-Methyl-3-glycylamino-2-pentanone hydrochloride, XIIa. This compound was prepared by an adaptation of the mixed anhydride procedure for preparing amides described by Vaughan and Osato.[27] From 3.78 g. (0.025 mole) 4-methyl-3-amino-2-pentanone hydrochloride and 5.23 g. (0.025 mole) of carbobenzyloxyglycine was obtained 5.6 g. (71% of theory) of an oil which did not crystallize but did give a positive iodoform test. The crude product was subjected to hydrogenolysis with 0.5 g. of A-100 Pd/C catalyst in ethanolic HCl solvent. The product, weighing 3.5 g. (95% of theory) was a viscous hydroscopic oil which refused to crystallize even in vacuum over P_2O_5; it was insoluble in ether, gave a positive iodoform reaction, a positive test for Cl^- ion, and a positive biuret reaction. After several days evidence of decomposition could be observed. Upon benzoylation it formed a solid which, crystallized from benzene, melted 144.5–146°.

Anal. Calcd. for $C_{15}H_{20}N_2O_{30}$: N, 10.14. Found: N, 9.96, 10.18.

4-Phenyl-3-glycylamino-2-butanone hydrochloride, XIIc. From 5.97 g. (0.03 mole) of 4-phenyl-3-amino-2-butanone hydrochloride and 5.85 g. (0.03 mole) of carbobenzyloxyglycine was obtained 8.0 g. (76% of theory) 4-phenyl-3-(carbobenzyloxyglycylamino)-2-butanone, a slightly yellow solid; recrystallized from benzene-ligroin it melted 83.5–84.5°. The crystals gave a positive iodoform reaction.

Anal. Calcd. for $C_{20}H_{22}N_2O_4$: N, 7.91. Found: N, 7.82, 7.90%.

Three and a half grams of the product was subjected to hydrogenolysis with 0.5 g. of A-100 Pd/C catalyst in the presence of ethanolic HCl; the product weighed 2.5 g. (98% of calculated) and melted with decomposition at 141–142°. It was soluble in water but insoluble in ether; it gave a positive iodoform test and a positive test for the Cl^- ion. It discolored readily.

Anal. Calcd. for $C_{12}H_{17}N_2O_2Cl$: N, 10.91. Found: N 10.80, 10.77%.

Alkylation of 3-acetamido-2,4-pentandione. In a 500-ml. three-neck flask equipped with sealed stirrer, reflux condenser, and dropping funnel was placed a cold solution of 400 ml. of absolute ethanol containing 6.6 g. (0.1 mole) of sodium ethoxide and 15.7 g. (0.1 mole) of 3-acetamido-2,4-pentanedione; to the stirred solution was added over the period of an hour 13.6 g. (0.108 mole) of benzyl chloride. Stirring was continued for 4 additional hours, at which time the NaCl had separated and the reaction mixture become neutral to moist litmus. As much as possible of the solvent was removed at reduced pressure on a water bath, and to the residue was added 75 ml. of water. Two layers formed; the mixture was extracted with four 100-ml. portions of ether. Upon evaporation of the ether extracts 10.5 g. of a tan solid remained; upon recrystallization from 40% alcohol, 8.2 g. of 4-phenyl-3-acetamido-2-butanone was obtained. Further crystallization afforded product, m.p. 96.5–97°; reported m.p. 98–100°[23] and 95–95.5°.[28]

CHAPEL HILL, N. C.

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[27] J. Vaughan and R. Osato, *J. Am. Chem. Soc.*, **74**, 676 (1952).

[28] G. H. Cleland and C. Niemann, *J. Am. Chem. Soc.*, **71**, 841 (1949).

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES, WEST POINT, PA.]

Synthetic Antiviral Agents: II. Various Substituted 5-Oxopentanoic and 5-Oxohexanoic Acids and Certain of Their Derivatives[1]

EDWARD J. CRAGOE, JR., A. M. PIETRUSZKIEWICZ, AND C. M. ROBB

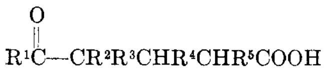
Received January 17, 1958

A number of substituted 5-oxopentanoic and 5-oxohexanoic acids, some of which showed an interesting order of antiviral activity, were prepared by the hydrolysis of the corresponding nitriles. 4,5-Diphenyl-5-oxopentanoic acid was obtained by the interaction of desoxybenzoin and β-propiolactone. 4-(*o*-Chlorophenyl)-4-phenyl-5-oxohexanoic acid was resolved through the cinchonine salt.

The intermediate 5-oxoalkanenitriles containing substituents in the 4 and/or 5 positions were produced by cyanoethylation of the appropriate ketones. 3,4-Diphenyl-5-oxohexanenitrile and 3,4,5-triphenyl-5-oxopentanenitrile were prepared by the action of cinnamonitrile on the appropriate ketone.

4-Phenyl-5-oxohexanamide was synthesized from 1-phenyl-2-propanone and acrylamide. Several derivatives, including three esters, the enol lactone and the corresponding hydroxy lactone of 4,4-diphenyl-5-oxohexanoic acid, are described.

Following the observation of antiviral properties of 4,4-diphenyl-5-oxohexanoic acid and 4-arylalkyl-4-aryl-5-oxohexanoic acids[2] a study of the properties of structurally related compounds was undertaken. There are many portions of the molecule where interesting structural variations could be made. However, it is the intent in this paper to



$$R^1\overset{O}{\overset{\|}{C}}—CR^2R^3CHR^4CHR^5COOH$$

I

restrict the variations in Formula I mainly to examples where one R group is aryl, a second R is aryl, alkyl, or substituted alkyl and a third R is phenyl, methyl, or hydrogen, while the remaining R groups are hydrogen.

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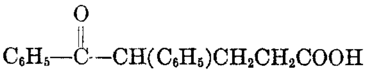
[1] A portion of the material contained in this paper was presented by the first two authors at the First Regional Meeting of the Delaware Valley Sections of the American Chemical Society, Feb. 16, 1956.

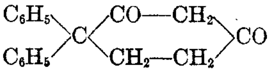
[2] E. J. Cragoe and A. M. Pietruszkiewicz, *J. Org. Chem.*, 22, 1338 (1957).

In general, these 5-oxoalkanoic acids were prepared by the hydrolysis of the corresponding nitriles. One exception to this was the preparation of 4,5-diphenyl-5-oxopentanoic acid (II) by the action of β-propiolactone upon desoxybenzoin in the presence of potassium *tert*-butoxide. The compound



$C_6H_5{-}\overset{O}{\overset{\|}{C}}{-}CH(C_6H_5)CH_2CH_2COOH$

II



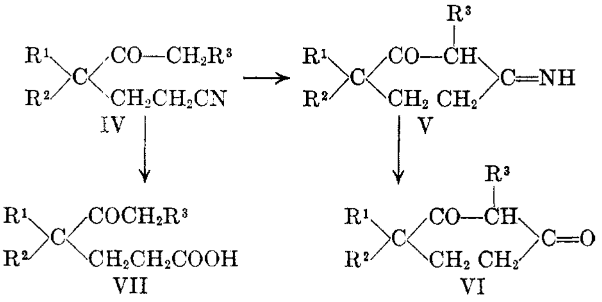
III

obtained by this method is identical with that obtained by the hydrolysis of the nitrile resulting from the monocyanoethylation of desoxybenzoin.[3] The physical properties also checked those reported by Knoevenagel[4] and by Meerwein[5] who had prepared the compound by two other methods.

Although Gresham *et al.*[6] have successfully carboxyethylated such active methylene compounds as acetoacetic ester, malonic ester, and acetylacetone by the use of β-propiolactone, the reaction had been extended to few, if any, ketones of the type considered here.

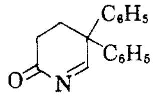
Treatment of 1,1-diphenyl-2-propanone with β-propiolactone in the presence of potassium *tert*-butoxide gave only 4,4-diphenyl-1,3-cyclohexanedione (III). From related 1,1-disubstituted-2-propanones only the corresponding 4,4-disubstituted-1,3-cyclohexanediones were isolated. The reactions leading to cyclic products will be considered in more detail in another paper.

As indicated earlier,[2] hydrolysis of nitriles of the type considered here can be effected in either aqueous alkali or, preferably, by use of a sulfuric acid–acetic acid–water mixture. When the latter method was used with nitriles of type IV, cyclic by-products, V and VI, were isolated in some instances.



In fact, with 4-phenyl-4-(1-naphthylmethyl)-5-oxohexanenitrile and with 5-phenyl-5-(*o*-chlorobenzyl)-6-oxoheptanenitrile, only the cyclic compounds were isolated.

With 5-oxopentanenitriles bearing either hydrogen or an aryl group in the 5-position, obviously cyclic compounds of types V or VI cannot form. However, with 4,4-diphenyl-5-oxopentanenitrile a cyclic compound was formed in 70% yield (which has been tentatively assigned the structure represented by formula VIII) along with 13% of the anticipated 5-oxopentanoic acid. All of these cyclic products are to be considered in another paper.



VIII

The 5-oxopentanoic and 5-oxohexanoic acids containing either one substituent or two dissimilar substituents in the 4-position have only one asymmetric carbon atom and are isolated as the racemic modification. One of the more active members of the series, 4-(*o*-chlorophenyl)-4-phenyl-5-oxohexanoic acid, was resolved through the cinchonine salt.

The hydrolysis of either 2,3- or 3,4-diphenyl-5-oxoalkanenitriles can give rise theoretically to two racemic forms of the corresponding carboxylic acids regardless of whether the nitrile is a pure racemic modification or a mixture. Thus, from the 2,3-diphenyl-5-oxohexanenitrile prepared by the method of Henecka[7] an 82% yield of a mixture of the isomers of the corresponding carboxylic acid was obtained. From this mixture there was isolated a 35% yield of a high melting racemate and 21% of a low melting racemate.

The 3,4-diphenyl-5-oxohexanenitrile used in this study was isolated from the product of the reaction of 1-phenyl-2-propanone with cinnamonitrile. This material had the melting and solubility properties of a pure compound and was assumed to be a pure racemic modification. However, hydrolysis of this material gave a product in 97% yield which appeared to be a mixture of racemates. From this mixture only one racemate was isolated in pure form (29% yield); no attempt was made to isolate another isomer.

$C_6H_5COCH(C_6H_5)CH(C_6H_5)CH_2COOH$

IX

The 3,4,5-triphenyl-5-oxopentanenitrile, prepared by the reaction of desoxybenzoin and cinnamonitrile, had the melting and solubility properties of a pure compound and was assumed to be a pure racemic modification. Hydrolysis of this material gave only one racemic form of the corresponding carboxylic acid (IX). The melting point of this material corresponds to that reported for the higher melting racemate of IX, β-dehydroamaric acid. Klingemann[8] reported obtaining a mixture

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(3) A. D. Campbell and I. D. R. Stevens, *J. Chem. Soc.*, 959 (1956).

(4) E. Knoevenagel, *Ber.*, **21**, 1344 (1888).

(5) H. Meerwein, *J. prakt. Chem.*, [2], **97**, 225 (1918).

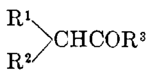
(6) T. L. Gresham, J. E. Jansen, F. W. Shaver, M. R. Fredrick, W. L. Beears, *J. Am. Chem. Soc.*, **73**, 2345 (1951).

(7) H. Henecka, *Ber.*, **82**, 104 (1949).

(8) F. Klingemann, *Ann.*, **275**, 50 (1893).

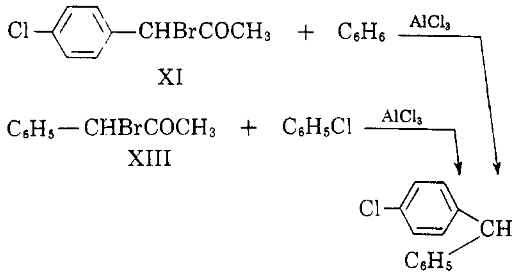
of both the high and low melting isomers by two other methods. The high melting isomer was prepared by Meerwein[5] by two still different processes.

One of the key intermediates for the synthesis of the 5-oxoalkanoic acids are the ketones of type X. These were prepared by one of several methods. Bromination of 1-phenyl-2-propanone followed by


$\mathrm{R^1R^2CHCOR^3}$

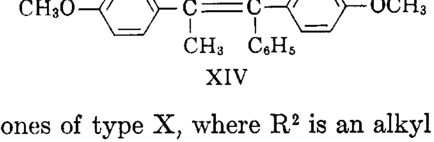
X

a Friedel-Crafts reaction with benzene is known to give 1,1-diphenyl-2-propanone in good yields.[9] Extension of this method produced derivatives containing substituents in the aryl nucleus (R^1 and R^2 = aryl, R^3 = methyl). Interaction of 1-bromo-1-(*p*-chlorophenyl)-2-propanone (XI) with benzene gave 1-phenyl-1-(*p*-chlorophenyl)-2-propanone (XII) in 67% yield. Likewise, the reaction of 1-bromo-1-phenyl-2-propanone (XIII) with chlorobenzene gave a compound in 72% yield whose properties were identical with those of XII. Since the 2,4-dinitrophenylhydrazones prepared from each product showed no mixed melting point depression it appears that XII is produced by either method.



XII

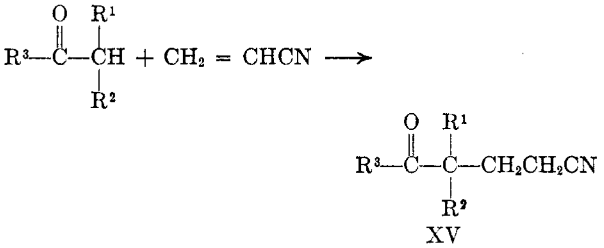
The product of the reaction of XIII with toluene was assumed to be 1-phenyl-1-(*p*-tolyl)-2-propanone. The interaction of XIII with anisole under the same conditions gave a good yield (74%) of a compound that analytical and infrared data indicate to be 1,2-bis(4-methoxyphenyl)-1-phenylpropene (XIV). This reaction is somewhat similar to that reported[10,11] for acetyl chloride and anisole with aluminum chloride which gave 1,1-bis(*p*-methoxyphenyl)ethylene.



XIV

Ketones of type X, where R^2 is an alkyl or substituted alkyl radical and R^1 is aryl, were generally prepared by alkylation methods which have been described previously.[2] Special methods of synthesis were resorted to with some ketones. The details are presented in the experimental section.

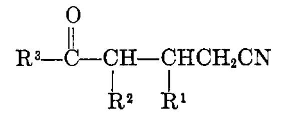
The 5-oxoalkanenitriles of type XV (where R^1 = aryl or alkyl, R^2 = aryl, alkyl, or hydrogen and R^3 = CH_3, or C_2H_5) were usually prepared by cy-



XV

anoethylation of the required ketone by well established procedures.[2,12] The yields were usually quite good. However, with rather hindered ketones, such as, 4-(*o*-chlorophenyl)-3-(*o*-chlorobenzyl)-2-butanone and 1-(*o*-chlorophenyl)-2-phenyl-3-pentanone, the reactions were slow and the yields were poor. With highly hindered ketones, such as, α,α-diphenylacetophenone and 1,2,3-triphenyl-1-propanone no reaction was detected.

With phenylacetaldehyde the basic catalyst (benzyltrimethylammonium hydroxide) promoted violent polymerization; however, diphenylacetaldehyde gave a good yield of 4,4-diphenyl-5-oxopentanenitrile. Although generic claims for cyanoethylated arylalkylcarboxaldehydes are made in two patents[13,14] very few examples are presented.


$\mathrm{R^3{-}CO{-}CH(R^2){-}CH(R^1)CH_2CN}$

XVI

In the present study it was found that two 5-oxoalkanenitriles of type XVI where R^1 is phenyl could be synthesized by the interaction of cinnamonitrile with the appropriate ketone in the presence of a basic catalyst. With 1-phenyl-2-propanone the yield was 58% and with desoxybenzoin the yield was 80%. In the first example apparently two racemates were formed, although only one was obtained in pure form. In the second example only one racemate was found. With 1,2-diphenyl-3-butanone and cinnamonitrile little or no reaction occurred. Although the reaction of cinnamonitrile with compounds containing active methylene groups, such as fluorene, is known,[15] few examples of reactions with ketones of type X have been reported.

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[9] E. M. Schultz, *Org. Syntheses*, **29**, 38 (1949).

[10] L. Gattermann, *Ber.*, **22**, 1129 (1889).

[11] L. Gattermann, R. Ehrhardt, and H. Maisch, *Ber.*, **23**, 1199 (1890).

[12] H. A. Bruson, *Org. Reactions*, **5**, 79 (1949).

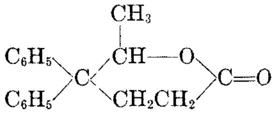
[13] J. F. Walker, U. S. Patent No. **2,409,086**, Oct. 8, 1946.

[14] H. A. Bruson and T. W. Riener, U. S. Patent **2,353,687**, July 18, 1944.

[15] N. Campbell and A. E. S. Fairfull, *J. Chem. Soc.*, 1239 (1949).

The 2,3-diphenyl-5-oxohexanenitrile obtained by the Michael reaction involving benzyl cyanide and benzalacetone according to the procedure of Henecka[7] is doubtless a mixture of racemates. In any event, hydrolysis produced a mixture of two racemic carboxylic acids which have not been previously described.

Two esters, the enol lactone and the *N*-3-dimethylaminopropylamide of 4,4-diphenyl-5-oxohexanoic acid were prepared by methods already described.[2] 4,4-Diphenyl-5-hydroxyhexanoic acid lactone (XVII) was prepared by the reduction of the corresponding keto acid using Raney nickel-aluminum alloy and aqueous sodium hydroxide. Reduction of certain ketones by this method has been described by Papa *et al.*[16]



XVII

$CH_3COCH(C_6H_5)CH_2CH_2CONH_2$
XVIII

4-Phenyl-5-oxohexanamide (XVIII) was produced by the interaction of 1-phenyl-2-propanone and acrylamide in the presence of a catalyst. This reaction appears to be unique since there was no evidence of reaction between acrylamide and either acetone or 1,1-diphenyl-2-propanone.

EXPERIMENTAL[17]

Preparation of intermediates. 1-Phenyl-2-butanone was prepared in 81% yield by treatment of 1-phenyl-2-nitro-1-butene[18] with iron and hydrochloric acid.[19] *1-(o-Chlorophenyl)-2-propanone* was prepared as described earlier.[2] *1-(p-Chlorophenyl)-2-propanone* was prepared from *p*-chlorophenylacetic acid, acetic anhydride, and sodium acetate by a procedure provided by Schultz[20] which is an adaptation of the method of Magidson and Garkusha[21] for the synthesis of 1-phenyl-2-propanone. *2-Methyl-4-chloromethylthiazole* was prepared in 51% yield from 1-thioacetamido-3-chloro-2-propanone by the method of Hooper and Johnson.[22] *Diphenylacetaldehyde* was prepared from hydrobenzoin[23] by the method of Daniloff.[24] *Cinnamonitrile* was prepared by the method of Posner.[25]

The other intermediates were either commercially available or were prepared by well established procedures.

Preparation of the ketones. A. By the Friedel-Crafts method. Examples of 1,1-diaryl-2-propanones prepared from either (1) 1-bromo-1-aryl-2-propanone and benzene or from (2) 1-bromo-1-phenyl-2-propanone and a substituted benzene are presented. The anomalous reaction that occurs with (3) 1-bromo-1-phenyl-2-propanone and anisole is also described.

1. *1-(o-Chlorophenyl)-1-phenyl-2-propanone.* 1-(*o*-Chlorophenyl)-2-propanone (67 g., 0.4 mole) and benzene (250 ml.) were placed in a 1-liter, 3-necked flask equipped with a mechanical stirrer, dropping funnel, and condenser, whose open end was protected with a drying tube. The stirrer was started and bromine (64 g., 0.4 mole) was added over 15 min. The dropping funnel was replaced by a gas inlet tube and dry nitrogen admitted for 3 hr. with stirring.

A second 1-liter flask was equipped like the first one. Aluminum chloride (107.5 g., 0.8 mole) and benzene (250 ml.) were added and the mixture stirred and refluxed. The solution of brominated 1-(*o*-chlorophenyl)-2-propanone was placed in the dropping funnel and added dropwise over a period of 1 hr. The mixture was refluxed for another hour, then cooled and poured into a mixture of crushed ice (800 g.) and concd. hydrochloric acid (150 ml.).

The layers were separated and the aqueous layer extracted with ether (three 100-ml. portions). The combined organic layers were washed with water (100 ml.), 5% sodium hydroxide solution (100 ml.), and finally with water (100 ml.) again.

After drying over sodium sulfate the solvent was removed by distillation and the residue fractionally distilled at reduced pressure. The yield of material boiling at 140–145° at 0.2 mm. was 71.6 g. (74%). Refractionation gave material boiling at 142–146°/0.2 mm., m.p. 55–59°. Recrystallization from hexane and finally from petroleum ether (b.p. 30–60°) gave material melting at 62–67°.

2. *1-(p-Chlorophenyl)-1-phenyl-2-propanone.* 1-Phenyl-2-propanone (111 g., 0.83 mole) and chlorobenzene (600 ml.) were treated with bromine (135 g., 0.84 mole) in the manner described above. This solution was added to a mixture of aluminum chloride (225 g., 1.68 mole) and chlorobenzene (450 ml.). The reaction was carried out and the product isolated in the usual manner. The yield was 146.6 g. (72%), b.p. 150–156°/0.4 mm. Refractionation gave material boiling at 142–147°/0.18 mm.

The 2,4-dinitrophenylhydrazone prepared from this material and from that prepared from the product of brominated 1-(*p*-chlorophenyl)-2-propanone and benzene gave no mixed melting point depression.

3. *1,2-Bis-(p-methoxyphenyl)-1-phenylpropene.* 1-Phenyl-2-propanone (111 g., 0.83 mole) and carbon disulfide (500 g.) were treated with bromine (135 g., 0.84 mole). The solution of brominated material was added to a mixture of anisole (680 ml.) and aluminum chloride (225 g., 1.68 mole). After isolation in the usual manner the product was fractionally distilled. The yield was 204.8 g. (75%), b.p. 195–205°/0.12 mm. Refractionation followed by recrystallization from hexane and then from ethanol gave 133 g., m.p. 93–94°.

Anal. Calcd. for $C_{23}H_{22}O_2$: C, 83.60; H, 6.71; CH_3O, 18.79; mol. wt., 330.4. Found: C, 83.85; H, 6.71; CH_3O, 18.76; mol. wt. (Rast), 311 (ave.).

B. By alkylation of certain ketones: $R^1CH_2COR^3 + R^2X \rightarrow R^1CHR^2COR^3$. An example of a method employing either (1) sodium hydroxide or (2) potassium *tert*-butoxide has already been described.[2]

C. Special methods. The synthesis of *3-(o-chlorobenzyl)-4-(o-chlorophenyl)-2-butanone* was carried out by two methods: (1) by method B-2 with the appropriate reactants and (2) from the required acetoacetic ester derivative. The necessary intermediates required by method 1 and the entire synthetic sequence for method 2 are presented below.

Method 1. Ethyl 2-(o-chlorobenzyl)-3-oxobutanoate was synthesized from acetoacetic ester and *o*-chlorobenzyl chloride

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[16] D. Papa, E. Schwenk, and B. Whitman, *J. Org. Chem.*, **7**, 587 (1942).

[17] All melting and boiling points are uncorrected values unless otherwise specified. Analytical data and specific rotations were supplied by K. B. Streeter and his staff.

[18] H. B. Haas, A. G. Susie, and R. L. Heider, *J. Org. Chem.*, **15**, 8 (1950).

[19] R. V. Heinzelmann, U. S. Patent **2,557,051**, June 12, 1951.

[20] E. M. Schultz, unpublished data.

[21] O. Yu. Magidson and G. A. Garkusha, *J. Gen. Chem.* (*U.S.S.R.*), **11**, 339 (1941).

[22] F. E. Hooper and T. B. Johnson, *J. Am. Chem. Soc.*, **54**, 470 (1934).

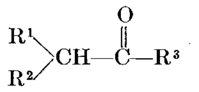
[23] S. Danilow, *Chem. Ber.*, **40**, 2390 (1927).

[24] S. Daniloff and E. Venus-Danilova, *Chem. Ber.*, **59**, 1032 (1926).

[25] T. Posner, *Ann.*, **389**, 1 (1912).

TABLE I

KETONES

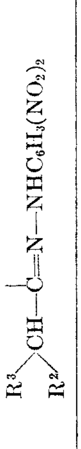


No.	R^1	R^2	R^3	Synthetic Method	Yield, %	B.P., °C./Mm.	Calcd. for	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Halogen Calcd.	Halogen Found
1	Phenyl	Phenyl	Methyl	A-1	70[a]	142–148/2.5							
2	Phenyl	*p*-Tolyl	Methyl	A-2	65	143–148/0.25	$C_{16}H_{16}O$	85.67	85.84	7.19	7.18		
3	Phenyl	*p*-Chlorophenyl	Methyl	A-1	67[b]	142–147/0.2	$C_{15}H_{13}ClO$	73.62	73.77	5.36	5.38	14.49	13.62
				A-2	72				73.21		5.59		14.75
4	Phenyl	*o*-Chlorophenyl	Methyl	A-1	74	142–146/0.2[c]	$C_{15}H_{13}ClO$	73.62	73.44	5.36	5.58		
5	Phenyl	Methyl	Methyl	B-1	77[d]	97–98/10							
6	Phenyl	2-Methyl-4-thiazolylmethyl	Methyl	B-2	83[e]	144–146/0.2	$C_{14}H_{15}NOS$	68.54	68.19	6.16	6.36	(Nitrogen) 5.71	5.69
7	Phenyl	2-Dimethylaminoethyl	Methyl	B-2	25[f]	83–87/0.1							
8	Phenyl	2-(2-Pyridyl)-ethyl	Methyl	[g]	39	154–158/0.1							
9	*o*-Chlorobenzyl	*o*-Chlorobenzyl	Methyl	B-2	29	163–167/0.3	$C_{17}H_{16}Cl_2O$	66.46	66.19	5.25	5.25	23.08	22.71
				C	62[h]								
10	*o*-Biphenylene		Methyl	[i]	19	M.p. 72.5–74.5							
11	Phenyl	1-Naphthylmethyl	Methyl	B-1	53[j]	177–181/0.1	$C_{20}H_{18}O$	87.55	87.51	6.61	6.47		
12	Phenyl	*o*-Chlorobenzyl	Ethyl	B-2	81[k]	169–173/0.2	$C_{17}H_{17}ClO$	74.85	74.64	6.28	6.21	13.00	13.16
13	Phenyl	Phenyl	Phenyl	[l]	78	M.p. 132–134							
14	Phenyl	Benzyl	Phenyl	B-1	82	M.p. 120–121[m]							

[a] M.p. 60–61°. Prepared by the method of Schultz.[9] [b] n_D^{25} 1.5845. [c] M.p. 62–67°. Recrystallized from petroleum ether (b.p. 30–60°). [d] Prepared by the method of Schultz and Bicking.[30] [e] n_D^{25} 1.5673. [f] Prepared by the method of Wilson[31] except that potassium *tert*-butoxide was used in place of sodamide. [g] Prepared by the method of Wilt and Levine[32] who reported a b.p. of 162–164°/2 mm. [h] n_D^{25} 1.5670. [i] There is some confusion in the literature concerning the structure and the proper synthesis of the so-called 9-acetylfluorene. It is assumed that the method of Von and Wagner,[33] which is similar to the one employed here, is valid. They reported m.p. 74.5–75.5°. [j] n_D^{25} 1.6175. [k] n_D^{25} 1.5611. [l] Prepared by the method of Robinson and Mercer.[34] Boyle *et al.*,[35] using another method, reported m.p. 135.5–136.5°. [m] Klingemann,[8] who prepared the compound by another method, reported m.p 120–121°.

TABLE II

KETONE 2,4-DINITROPHENYLHYDRAZONES



No.	R^1	R^2	R^3	M.P., °C.	Recrystallization Solvent	Calcd. for	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	Methyl	Phenyl	*o*-Chlorophenyl	134–135.5	*n*-Propyl alcohol	$C_{21}H_{17}ClN_4O_4$	59.37	59.33	4.03	4.28	13.19	13.11
2	Methyl	Phenyl	*p*-Chlorophenyl	173.5–174[a] 173.5–174[b]	*n*-Propyl alcohol Ethyl acetate and ethanol	$C_{21}H_{17}ClN_4O_4$	59.37	59.59	4.03	3.98	13.19	13.08
3	Methyl	Phenyl	*p*-Tolyl	176–177.5	*n*-Butyl alcohol then ethyl acetate and ethanol	$C_{22}H_{20}N_4O_4$	65.33	65.38	4.98	4.97	13.86	13.83

[a] The ketone was prepared from 1-bromo-1-(*p*-chlorophenyl)-2-propanone, benzene, and aluminum chloride. *Anal.* Calcd.: Cl, 8.35. Found: Cl, 8.36. [b] The ketone was prepared from 1-bromo-1-phenyl-2-propanone, chlorobenzene, and aluminum chloride. *Anal.* Calcd.: Cl, 8.35. Found: Cl, 8.30.

according to the general method of Marvel.[26] The yield was 59%, b.p. 125–129°/0.2 mm., n_D^{25} 1.5106. Falco *et al.*[27] reported a boiling point of 172–185°/48 mm.

Anal. Calcd. for $C_{13}H_{15}ClO_3$: C, 61.30; H, 5.94; Cl, 13.92. Found: C, 61.30; H, 5.96; Cl, 13.95.

4-(o-Chlorophenyl)-2-butanone was prepared by an adaptation of the method which Leuchs *et al.*[28] used in the synthesis of a related compound.

Heating ethyl 2-(*o*-chlorobenzyl)-3-oxobutanoate (69.1 g., 0.27 mole) with acetic acid (280 ml.) and hydriodic acid (280 ml. of 58% material) gave 38 g. (78%) of product boiling at 102–108°/0.3 mm. Refractionation gave material which boiled at 98–102°/0.3 mm., n_D^{25} 1.5272.

Anal. Calcd. for $C_{10}H_{11}ClO$: C, 65.76; H, 6.07; Cl, 19.42. Found: C, 65.96; H, 6.11; Cl, 19.64.

3-(o-Chlorobenzyl)-4-(o-chlorophenyl)-2-butanone was prepared from 4-(*o*-chlorophenyl)-2-butanone and *o*-chlorobenzyl chloride according to method B-2. The yield was 29%.

Method 2. Ethyl 2,2-bis-(o-chlorobenzyl)-3-oxobutanoate was prepared by the application of the general method of Weizmann *et al.*[29] From ethyl acetoacetate (91 g., 0.7 mole), *o*-chlorobenzyl chloride (225.5 g., 1.4 mole), and powdered potassium hydroxide (92.5 g., 1.4 mole of 85% material) in acetal (425 ml.) two products were obtained. The yield of ethyl 2-(*o*-chlorobenzyl)-3-oxobutanoate was 55.6 g. (31%), b.p. 122–127°/0.2 mm. The yield of the disubstituted product was 66.1 g. (25%), b.p. 192–196°/0.2 mm., n_D^{25} 1.5593.

Anal. Calcd. for $C_{20}H_{20}ClO_3$: C, 63.33; H, 5.32. Found: C, 63.80; H, 5.44.

3-(o-Chlorobenzyl)-4-(o-chlorophenyl)-2-butanone was prepared in a manner similar to that described for 4-(*o*-chlorophenyl)-2-butanone. From ethyl 2,2-bis-(*o*-chlorobenzyl)-3-oxobutanoate (34.3 g., 0.09 mole), 58% hydriodic acid (280 ml.), and acetic acid (280 ml.) there was obtained 17.1 g. (62%) of product, b.p. 168–174°/0.3 mm. Further fractionation gave material boiling at 163–167°/0.3 mm.

A summary of the ketone syntheses appears in Table I.

The ketone 2,4-dinitrophenylhydrazones that were prepared are summarized in Table II.

Preparation of 5-oxopentanenitriles, 5-oxohexanenitriles and 5-oxoheptanenitriles. A. From a ketone or aldehyde and acrylonitrile. These syntheses were usually carried out by standard procedures.[2,13] Exceptions to the general methods are pointed out in the notes for Table III.

B. From a ketone and cinnamonitrile. Synthesis by this method is illustrated by the following example: *3,4-Diphenyl-5-oxohexanenitrile.* In a 500-ml., 3-necked flask equipped with a mechanical stirrer, dropping funnel, and thermometer was placed 1-phenyl-2-propanone (40.3 g., 0.3 mole), *tert*-butyl alcohol (125 ml.), and benzyltrimethylammonium hydroxide (6 ml. of 40% aqueous material). The stirrer was started, the solution cooled to 25°, and

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TABLE III

5-OXOPENTANENITRILES, 5-OXOHEXANENITRILES, AND 5-OXOHEPTANENITRILES

No.	Name	Synthetic Method	Yield, %	M.P., °C.	Calcd. for	Analysis					
						Carbon		Hydrogen		Nitrogen	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
1	4,4-Diphenyl-5-oxopentanenitrile	A	74	80–81[a]	$C_{17}H_{15}NO$	81.90	82.21	6.06	6.19	5.62	5.59
2	4,5-Diphenyl-5-oxopentanenitrile	A	58	84–85[b]							
3	3,4,5-Triphenyl-5-oxopentanenitrile	B	80	220–221[c]	$C_{23}H_{19}NO$	84.89	84.72	5.89	5.88	4.30	4.31
4	4,4-Diphenyl-5-oxohexanenitrile	A	77	113–115[d]							
5	4-Phenyl-4-(*p*-tolyl)-5-oxohexanenitrile	A	74	96–97[e]	$C_{19}H_{19}NO$	82.28	82.16	6.90	6.73	5.05	5.06
6	4-(*p*-Chlorophenyl)-4-phenyl-5-oxohexanenitrile	A	67	92–93[f]	$C_{18}H_{16}ClNO$	72.60	72.83	5.42	5.53	4.70	4.71
7	4-(*o*-Chlorophenyl)-4-phenyl-5-oxohexanenitrile	A[g]	70	90.5–92.5[h]	$C_{18}H_{16}ClNO$	72.60	72.63	5.42	5.63	4.70	4.71
8	4-Methyl-4-phenyl-5-oxohexanenitrile	A	83	[i]							
9	4-(2-Methyl-4-thiazolylmethyl)-4-phenyl-5-oxohexanenitrile	A	94	91.5–93.5[j]	$C_{17}H_{18}N_2OS$	68.42	68.33	6.08	6.09	9.39	9.37
10	4-(2-Dimethylaminoethyl)-4-phenyl-5-oxohexanenitrile	A	75	[k]	$C_{16}H_{22}N_2O$	74.38	74.26	8.58	8.58	10.84	10.85
11	4-Phenyl-4-[2-(2-pyridyl)ethyl]-5-oxohexanenitrile	A	69	[l]	$C_{19}H_{20}N_2O$	78.05	77.77	6.90	6.79	9.58	9.51
12	4,4-Di-(*o*-chlorobenzyl)-5-oxohexanenitrile	A[g]	17	[m]	$C_{20}H_{19}Cl_2NO$	66.27	66.56	5.32	5.39	3.89	3.65
13	4-Phenyl-5-oxohexanenitrile	A	81	[n]							
14	9-Acetyl-9-(2-cyanoethyl)fluorene	A[g]	96[o]	88–90	$C_{18}H_{15}NO$	82.73	82.79	5.79	5.93	5.36	5.34
15	3,4-Diphenyl-5-oxohexanenitrile	B	68[p]	146–147.5	$C_{18}H_{17}NO$	82.09	82.06	6.51	6.43	5.32	5.30
16	2,3-Diphenyl-5-oxohexanenitrile	[q]	71								
17	4-(1-Naphthylmethyl)-4-phenyl-5-oxohexanenitrile	A	96[r]	141–143	$C_{23}H_{21}NO$	84.37	84.54	6.46	5.98	4.28	4.26
18	4-(*o*-Chlorobenzyl)-4-phenyl-5-oxoheptanenitrile	A	27	113–115[s]	$C_{20}H_{20}ClNO$	73.72	73.78	6.19	6.06	4.30	4.31

[a] Recrystallized from heptane, then from isopropyl alcohol; b.p. 162–170°/0.08 mm. [b] Recrystallized from ethyl alcohol. Campbell and Stevens[3] report a yield of 90%; m.p. 86.7–87°. [c] Recrystallized from dimethylformamide. [d] B.p. 182–183°/0.4 mm. Schultz[20] who first prepared the compound reported a m.p. of 113.5–114.5°. [e] Recrystallized from heptane and then from isopropyl alcohol; b.p. 168–174°/0.1 mm. [f] Recrystallized from isobutyl alcohol, then from ethanol and finally from heptane. B.p. 183–186°/0.1 mm. *Anal.* Calcd.: Cl, 11.91. Found: Cl, 11.88. [g] The cyanoethylation was carried out using acetonitrile instead of *tert*-butyl alcohol as a solvent. [h] Recrystallized from isopropyl alcohol; b.p. 183–185°/0.05 mm. [i] B.p. 136–140°/0.1 mm.; n_D^{25} 1.5220. This compound was first prepared by Schultz.[20] [j] Recrystallized from isopropyl alcohol; b.p. 196–202°/0.2 mm. [k] B.p. 166–170°/0.1 mm.; n_D^{25} 1.5212. [l] B.p. 195–200°/0.1 mm.; n_D^{25} 1.5612. [m] B.p. 205–210°/0.1 mm. [n] Equimolar quantities of 1-phenyl-2-propanone and acrylonitrile were used. B.p. 136–139°/0.45 mm.; n_D^{25} 1.5165; m.p. of the semicarbazone 163–164.5°. Schultz[20] prepared the compound initially and reported similar physical constants. Bergmann and Szmuszkovicz[36] reported the synthesis using sodium as a catalyst. They report a b.p. of 124–126°/0.1 mm., n_D^{25} 1.4250 (probably a typographical error) and m.p. of the semicarbazone, 163.5–165.5°. Campbell and Stevens[3] report a 64% yield using a 60–70° reaction temperature and record a b.p. of 185–190°/18 mm. [o] Recrystallized from isopropyl alcohol. [p] This is the crude yield of what is apparently a mixture of racemates. The less soluble isomer described here was recrystallized from ethanol, then acetic acid and finally from *n*-propyl alcohol; the yield was 28%. The other racemate was not isolated in pure form. [q] Prepared by the method of Henecka.[7] B.p. 178–182°/0.3 mm. [r] Recrystallized from *n*-propyl alcohol. [s] Recrystallized from isopropyl alcohol. Only one racemate was found.

TABLE IV

5-OXOPENTANOIC ACIDS AND 5-OXOHEXANOIC ACIDS

No.	Name	Synthetic Method	Yield, %	M.P., °C.	Calcd. for	Analysis Carbon Calcd.	Analysis Carbon Found	Analysis Hydrogen Calcd.	Analysis Hydrogen Found
1	4,4-Diphenyl-5-oxopentanoic acid	A	13[a]	96–98	$C_{17}H_{16}O_3$	76.10	76.00	6.01	6.12
2	4,5-Diphenyl-5-oxopentanoic acid	A D	98 19[c]	134–135.5[b]	$C_{17}H_{16}O_3$	76.10	75.58	6.01	5.83
3	3,4,5-Triphenyl-5-oxopentanoic acid	A	59[d]	242–244	$C_{23}H_{20}O_3$	80.21	80.34	5.85	5.81
4	4,4-Diphenyl-5-oxohexanoic acid	A	98[e]	137.5–139					
5	4-Phenyl-4-(*p*-tolyl)-5-oxohexanoic acid	A	97[f]	113–115	$C_{19}H_{20}O_3$	77.00	77.18	6.80	6.90
6	4-(*p*-Chlorophenyl)-4-phenyl-5-oxohexanoic acid	A	89[g]	101.5–103	$C_{18}H_{17}ClO_3$	68.24	68.39	5.41	5.44
7	4-(*o*-Chlorophenyl)-4-phenyl-5-oxohexanoic acid	A	90[h]	132–134	$C_{18}H_{17}ClO_3$	68.24	68.18	5.41	5.64
8	4-Methyl-4-phenyl-5-oxohexanoic acid	A	89	[i]	$C_{13}H_{16}O_3$	70.89	71.11	7.32	7.19
9	4-(2-Methyl-4-thiazolylmethyl)-4-phenyl-5-oxohexanoic acid	B	94[j]	137–138.5	$C_{17}H_{19}NO_3S$	64.33	64.47	6.03	5.93
10	4-(2-Dimethylaminoethyl)-4-phenyl-5-oxohexanoic acid	B	77[k]	185–187	$C_{16}H_{23}NO_3$	69.28	69.47	8.36	8.27
11	4-Phenyl-4-[2-(2-pyridyl)ethyl]-5-oxohexanoic acid	B	88[l]	171.5–173	$C_{19}H_{21}NO_3$	73.29	73.55	6.80	6.61
12	4,4-Di(*o*-chlorobenzyl)-5-oxohexanoic acid	A	100[m]	96–98	$C_{20}H_{20}Cl_2O_3$	63.33	63.58	5.32	5.27
13	4-Phenyl-5-oxohexanoic acid	A	85[n]	43–45	$C_{12}H_{14}O_3$	69.88	69.64	6.84	6.61
14	9-Acetyl-9-(2-carboxyethyl)-fluorene	A	100[o]	172–174	$C_{18}H_{16}O_3$	77.12	76.90	5.75	5.87
15	3,4-Diphenyl-5-oxohexanoic acid	A	97[p]	173–174[b]	$C_{18}H_{18}O_3$	76.57	76.65	6.43	6.46
16	2,3-Diphenyl-5-oxohexanoic acid (α form)	A	[q]	199–201	$C_{18}H_{18}O_3$	76.57	76.56	6.43	6.30
17	2,3-Diphenyl-5-oxohexanoic acid (β form)	A	[r]	167–168.5	$C_{18}H_{18}O_3$	76.57	76.37	6.43	6.19
18	*Levo* 4-(*o*-chlorophenyl)-4-phenyl-5-oxohexanoic acid	C	27	125.5–126.5[b]	$C_{18}H_{17}ClO_3$	68.24	68.19	5.41	5.43
19	*Dextro* 4-(*o*-chlorophenyl)-4-phenyl-5-oxohexanoic acid	C	44	124.5–125.5[b]	$C_{18}H_{17}ClO_3$	68.24	68.54	5.41	5.53

[a] Recrystallized from cyclohexane. A 70% yield of another compound m.p. 173–174.5° was isolated. It is believed to be 5,5-diphenyl-3,4-dihydro-2(5)pyridone. [b] Corrected melting point. [c] Recrystallized from cyclohexane. Campbell and Stevens[3] prepared the compound by hydrolysis of the corresponding nitrile using aqueous potassium hydroxide and report a yield of 90% and a m.p. of 134–135°. Knoevenagel,[4] who prepared the compound by another method, reported a m.p. of 136°. Meerwein,[5] who used still another method, reported a m.p. of 133–134°. [d] Hydrolysis of 25 g. of 3,4,5-triphenyl-5-oxopentanenitrile required refluxing for 7.5 hr. with concd. sulfuric acid (40 ml.), water (50 ml.), and acetic acid (1400 ml.). The product was recrystallized from *n*-butyl alcohol. Only one racemate was found. Klingemann,[8] who prepared the compound by another method, reported a m.p of 240–241°. [e] Recrystallized from an acetic acid–water mixture; b.p. 194–196°/0.08 mm. This compound was first prepared by Schultz.[20] [f] Recrystallized from *n*-heptane and then from acetonitrile. [g] Recrystallized from cyclohexane and then from acetonitrile. *Anal.* Calcd.: Cl, 11.19. Found: Cl, 11.13. [h] Recrystallized from acetonitrile and then from acetic acid–water. [i] B.p. 171–174°/0.1 mm., n_D^{25} 1.5279. [j] Recrystallized from acetonitrile and then from isopropyl alcohol. *Anal.* Calcd.: N, 4.41. Found: N, 4.40. [k] Recrystallized from ethyl acetate and then from acetonitrile. *Anal.* Calcd.: N, 5.05. Found: N, 5.05. [l] Recrystallized from acetonitrile and then from ethanol. *Anal.* Calcd.: N, 4.50. Found: N, 4.54. [m] Recrystallized from heptane. *Anal.* Calcd.: Cl, 18.70. Found: Cl, 18.65. [n] B.p. 145–148°/0.2 mm. Campbell and Stevens[3] reported an 88% yield using an aqueous potassium hydroxide hydrolysis; b.p. 215–220°/18 mm.; m.p. 42°. [o] Recrystallized from acetonitrile. [p] The yield of the mixture of isomers was 97%; however, only the isomer reported here was isolated in pure form. The yield of this pure isomer was 29%. It was recrystallized from carbon tetrachloride and then from acetonitrile and finally from *n*-propyl alcohol. [q] The mixture of racemates was formed in 84% yield from which the high melting racemate (α form) was isolated in 35% yield using acetonitrile as a crystallization solvent. [r] The mixture of racemates was formed in 84% yield. From this the pure low melting racemate (β form) was isolated in 6% yield using ethyl acetate as a crystallization solvent.

cinnamonitrile (38.8 g., 0.3 mole) dissolved in *tert*-butyl alcohol (25 ml.) was added, dropwise, over a period of 30 min. A small temperature rise was noted.

The mixture was stirred and heated at 42–48° for 6 hr. More benzyltrimethylammonium hydroxide solution (1 to 2 ml.) was added every 2 hr. during the heating period so that the *p*H as measured by "Hydrion" paper remained above 10. During the reaction period a solid product slowly separated.

The solution was cooled, neutralized with dilute sulfuric acid, and the solid removed by filtration. The yield was 46 g. (58%), m.p. 141–144°. Recrystallization from alcohol, then from acetic acid, and finally from *n*-propyl alcohol gave material melting at 146–147.5°.

Table III is a summary of the nitrile syntheses.

Preparation of the 5-oxopentanoic and 5-oxohexanoic acids. These compounds were, with one exception, prepared by the hydrolysis of the corresponding nitriles. Two hydrolysis procedures (A and B) are used; the details of the latter one are provided. The procedure (C) employed for the resolution of a racemic modification is given. Also the details of the synthesis from a ketone and β-propiolactone are included.

Table IV consists of a summary of the carboxylic acid syntheses.

A. *Hydrolysis of the nitrile using a sulfuric acid–acetic acid–water mixture.* A description of this method has already been given.[2]

B. *Hydrolysis of the corresponding nitrile using dilute sulfuric acid.* Nitriles which were acid soluble were readily hydrolyzed with 46% (by weight) sulfuric acid.

4-Phenyl-4-[2-(2-pyridyl)ethyl]-5-oxohexanoic acid. 4-Phenyl-4-[2-(2-pyridyl)ethyl]-5-oxohexanenitrile (40 g., 0.137 mole), concd. sulfuric acid (80 ml. of sp. gr. 1.84) and water (160 ml.) were refluxed for 3 hr. The solution was cooled, made strongly alkaline with 40% sodium hydroxide solution, and filtered to remove any insoluble material. The *p*H of the filtrate was adjusted to the point of minimum solubility of the product with dilute hydrochloric acid. The white solid was removed by filtration, washed with water and dried. The yield was 37.7 g. (88%). After recrystallization from acetonitrile, then from ethanol and finally again from acetonitrile, 29.9 g. remained, m.p. 171.5–173°.

C. *Resolution of a racemic 5-oxohexanoic acid. 4-(o-Chlorophenyl)-4-phenyl-5-oxohexanoic acid. Levo form.* Racemic 4-(*o*-chlorophenyl)-4-phenyl-5-oxohexanoic acid (50 g., 0.158 mole) and cinchonine (46.5 g., 0.158 mole) were dissolved in 95% ethanol (250 ml.). The solution was seeded with a few crystals of previously isolated product and refrigerated for 24 hr. The solid that separated (33.1 g.) was filtered off and dried. The mother liquor was concentrated (to 200 ml.) and refrigerated for a week. Another 6.7 g. separated, bringing the total to 39.8 g. The filtrate was concentrated (to 150 ml.), seeded, and refrigerated for a month. Another 2 g. of solid separated. This material was removed by filtration and discarded. The mother liquor was preserved for isolation of the dextro-acid. (This will be referred to as mother liquor I).

The 39.8 g. of combined products were recrystallized from 95% ethanol (250 ml.). After refrigerating for 16 hr. the yield was 28.8 g. After three more recrystallizations from ethanol, 16.1 g. remained, m.p. 171–172°.

Anal. Calcd. for $C_{18}H_{17}ClO_3 \cdot C_{19}H_{22}N_2O$: C, 72.71; H, 6.43; N, 4.58. Found: C, 73.01; H, 6.49; N, 4.54.

The above cinchonine salt (15.85 g., 0.026 mole) was suspended in water and acidified with excess hydrochloric acid. The liberated carboxylic acid was twice extracted with benzene. The combined benzene extracts were washed with water and then twice extracted with an excess of 5% sodium hydroxide solution. The aqueous solution was acidified with hydrochloric acid and extracted with benzene. The benzene solution was washed with water and dried over sodium sulfate.

Evaporation of the benzene gave 8.2 g. of the *levo*-acid. After three recrystallizations from a mixture of benzene (6 ml.) and cyclohexane (75 ml.), 6.93 g. remained; m.p. 125.5–126.5° (corr.). The $[\alpha]_D^{25}$ for a 1% solution in 95% ethanol was −59°.

Dextro form: Mother liquor I, containing the dextro acid-cinchonine salt, was evaporated at reduced pressure. The glasslike product was dissolved in acetonitrile and the insoluble material removed by filtration and discarded. The filtrate was evaporated at reduced pressure and the residue was treated with water and an excess of dilute hydrochloric acid added. The liberated carboxylic acid that separated was extracted twice with benzene. After washing with water, the benzene extract was dried over sodium sulfate.

Evaporation of the benzene gave 28.3 g. of product *A*. Recrystallization of this material from a mixture of cyclohexane (275 ml.) and benzene (60 ml.) gave 16.7 g. of product *B* which is rich in the racemic acid. Recrystallization of *B* from acetonitrile (50 ml.) gave 9.8 g. of nearly pure racemic acid *C*, m.p. 131–132°.

Concentrating and cooling the mother liquors from *B* gave 8.7 g. of *dextro* acid, m.p. 121–122°. Evaporation of the mother liquors from *C* gave 5.2 g. of the same isomer, m.p. 120–122°. These products were combined and twice recrystallized from a mixture of cyclohexane (125 ml.) and benzene (15 ml.). The final yield of *dextro* acid was 11 g., m.p. 124.5–125.5° (corr.). The $[\alpha]_D^{25}$ of a 1% solution in 95% ethanol was +59°.

D. *Interaction of a ketone and β-propiolactone. 4,5-Diphenyl-5-oxopentanoic acid.*[37] In a one-liter, 4-necked flask equipped with a mechanically driven Hershberg stirrer, thermometer, gas inlet tube, and condenser whose open end was protected with a drying tube was placed dry *tert*-butyl alcohol (450 ml.). The flask was flushed with dry nitrogen and potassium (19.5 g., 0.5 mole) added. The mixture was heated and stirred until vigorous reaction occurred, then the reaction was allowed to progress without external heating.

After all the metal had dissolved, desoxybenzoin (98 g., 0.5 mole) was added. An insoluble material immediately separated. The temperature of the stirring mixture was maintained at 40–45° while freshly distilled β-propiolactone (36 g., 0.5 mole) was added over a period of 15 min. The mixture was refluxed for 2 hr. and then the solvent was removed from the viscous product by reduced pressure distillation.

The residue was treated with water (200 ml.) and the aqueous solution extracted with benzene. (About 43% of unreacted desoxybenzoin was recovered from the benzene.) The aqueous solution was acidified with excess hydrochloric acid and the product that separated was extracted with benzene. The benzene extract was washed with water, dried over sodium sulfate, and the solvent removed by reduced pressure distillation.

The semisolid product was recrystallized from a mixture of toluene (200 ml.) and cyclohexane (600 ml.). The yield of white, crystalline product was 25 g. (19%). Two more recrystallizations gave 20 g., m.p. 134.5–135.5° (corr.). This material gave no mixed melting point depression with a sample of material prepared by the hydrolysis of 4,5-diphenyl-5-oxopentanenitrile.

Derivatives of the 5-oxohexanoic acids. Methyl 4,4-diphenyl-5-oxohexanoate. 4,4-Diphenyl-5-oxohexanoic acid (60 g., 0.21 mole) was dissolved in absolute methanol (500 ml.) and concd. sulfuric acid (17 ml.) added. The mixture was refluxed under anhydrous conditions for 5 hr. The solvent was removed by distillation at reduced pressure and the residue dissolved in benzene (200 ml.). The solution was washed with water, then with aqueous sodium bicarbonate and finally dried over sodium sulfate. Fractional distillation gave 49 g. (78%) of product b.p. 160–164°/0.15 mm. Refractionation gave 44.2 g., b.p. 165–170°/0.15 mm., n_D^{25} 1.5625.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.00; H, 6.84.

Ethyl 4,4-diphenyl-5-oxohexanoate was prepared in a manner analogous to that described for the methyl ester. From 4,4-diphenyl-5-oxohexanoic acid (75 g., 0.27 mole), absolute ethanol (450 ml.) and concd. sulfuric acid (16 ml.) there was obtained 69 g. (84%) of product boiling at 175–178°/0.15 mm. Refractionation gave 55.9 g., b.p. 168–170°/0.15 mm.

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.39; H, 7.15. Found: C, 77.35; H, 7.00.

4,4-Diphenyl-5-hydroxy-5-hexenoic acid lactone. 4,4-Diphenyl-5-oxohexanoic acid (42.3 g., 0.15 mole), isopropenyl acetate (45 g., 0.45 mole) and concd. sulfuric acid (3 drops) were placed in a flask equipped with a 12-in. fractionating column connected to a downward condenser. The mixture was heated so that a slow distillation occurred. About 25 ml

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(36) E. D. Bergmann and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **75**, 3226 (1953).

(37) This preparation was carried out by S. C. Bell.

of material boiling at 55–59° distilled in 2.5 hr. The residue was transferred to a Claisen flask and fractionally distilled at reduced pressure. A total of 39 g. (99%) of product boiling at 170–172°/0.05 mm. was collected, m.p. 129–135°. Two recrystallizations from cyclohexane gave 35 g., m.p. 138.5–139.5°.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.71; H, 6.19.

4-Phenyl-5-oxohexanamide. 1-Phenyl-2-propanone (40.3 g., 0.3 mole) was dissolved in *tert*-butyl alcohol (150 ml.) and 40% aqueous benzyltrimethylammonium hydroxide (3 ml.) were placed in a one-liter flask equipped with a mechanical stirrer and dropping funnel. A solution of acrylamide (21.3 g., 0.3 mole) dissolved in *tert*-butyl alcohol (300 ml.) was added, with stirring, over a period of 80 min. The temperature was maintained at 20–25° during the addition by external cooling.

The cooling bath was removed and more benzyltrimethylammonium hydroxide solution (12 ml.) was added. During the next 30 min. the temperature rose to 32°. Addition of a few crystals of product, obtained by evaporation of several drops of reaction mixture, initiated the separation of solid product. After stirring for another 3³/₄ hr. the mixture was neutralized with dilute sulfuric acid and the solid removed by filtration

The product was washed with a little *tert*-butyl alcohol and dried. The yield was 23.7 g. The solvent was removed from the combined mother liquors and washings by reduced pressure distillation. The residue was dissolved in ethyl acetate (200 ml.) and the solution dried over sodium sulfate. Evaporation of the solvent left another 12.5 g. of product, bringing the total to 36.2 g. (59%). Recrystallization first from ethanol and then from water gave material melting at 145.5–147°.

Anal. Calcd. for $C_{12}H_{15}N_2O$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.30; H, 7.45; N, 6.79.

N-(3-Dimethylaminopropyl)-4,4-diphenyl-5-oxohexanamide. 4,4-Diphenyl-5-hydroxy-5-hexenoic acid lactone (13.2 g., 0.05 mole) was placed in a small flask and treated with dry 3-dimethylaminopropylamine (5.6 g., 0.055 mole). The solid partially dissolved with the evolution of heat. The flask was fitted with a reflux condenser whose open end was protected from moisture by means of a drying tube.

The mixture was heated for 15 min. on a steam bath. The resultant solution was treated with petroleum ether (b.p. 30–60°) which caused the product to solidify. The solid was removed by filtration, washed with more petroleum ether, and dried. The yield was 17.7 g. (97%), m.p. 62–65°. One recrystallization from hexane, and then two from petroleum ether gave a product melting at 64–66°.

Anal. Calcd. for $C_{23}H_{30}N_2O_2$: C, 75.37; H, 8.25; N, 7.64. Found: C, 75.30; H, 8.15; N, 7.63.

4,4-Diphenyl-5-hydroxyhexanoic acid lactone. 4,4-Diphenyl-5-oxohexanoic acid (100 g., 0.356 mole) was dissolved in a solution of sodium hydroxide (320 g., 8 mole) and water (2500 ml.). The solution was placed in a 5-liter, 3-necked flask equipped with a mechanical stirrer, reflux condenser, thermometer, and electric heating mantle. The solution was vigorously stirred and, while maintaining the temperature at 88–92°, Raney nickel–aluminum alloy (300 g.) was added, portionwise, over 14 hr.

The mixture was filtered and the filtrate diluted with water (1 liter) and then added slowly to concd. hydrochloric acid (2 liters). The mixture was warmed for a short time and then cooled and the oil removed by decantation. The mother liquor was extracted with ethyl acetate (four 400-ml. portions). The combined extracts and oily product were dried over sodium sulfate and then the solvent removed by reduced pressure distillation.

The residual oil was treated with saturated sodium bicarbonate solution (250 ml.) and the mixture stirred and warmed. After the evolution of gas had ceased the solid that separated was removed by filtration, washed with water, and dried. [Acidification of the filtrate gave 49 g. (49%) of unreacted starting material.] The yield of crude lactone was 42.1 g. (45%), m.p. 117.5–118.5°. Recrystallization from heptane gave 41.9 g., m.p. 118–119°.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.16; H, 6.74.

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[Contribution from the Department of Pharmacology, Medical College of Virginia]

meso and *dl*-2,3-Diaminosuccinic Acids[1]

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Received February 6, 1958

meso and *dl*-2,3-Diaminosuccinic acids have been synthesized by hydrogenolysis of the corresponding bisbenzylamino compounds at room temperature in the presence of Pd-C and hydrogen at atmospheric pressure. The synthesis of *meso-N,N'*-dimethyl-2,3-diaminosuccinic acid was carried out in an analogous manner with platinum oxide or Pd-C (preferably the latter).

As a result of the increased use of hydrazine and its derivatives, biological attention has been focused on a number of its metabolic products.[3,4] Of these, 2,3-diaminosuccinic acid has been implicated in the metabolism of hydrazine through enzymatic reactions which are at present not completely understood. Jacobsohn and Soares[5] considered diaminosuccinic acid to result from addition of hydrazine across the double bond of fumaric acid, but did not state which diastereo or optical isomer was involved. Suzuki, Suzuki, and Egami[6] reported that *E. coli* were capable of carrying out the

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[1] Presented in part at the Southwide Chemical Conference of the American Chemical Society, Memphis, Tenn., Dec. 7, 1956.

[2] Appreciation is expressed for financial aid under National Institutes of Health Grant RG 5337.

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