two 300 ml. portions of chloroform. The combined extracts were concentrated to a sirup and distilled, b.p. 127–128°/0.008 mm. The product has recrystallized from ligroin to give 43 g. (40%) of plates, m.p. 80.8–81.3°; $[\alpha]_D^{20}$ −41.65° (c 10, U.S.P. $CHCl_3$).

Anal. Calcd. for $C_{18}H_{26}O_6$: C, 63.88; H, 7.74. Found: C, 64.15; H, 7.80.

1,2-O-Isopropylidene-3,5-di-O-methyl-D-glucofuranose (VII). A solution of 25 g. of VI in 50 ml. of ethyl acetate was treated with hydrogen in the presence of palladium charcoal catalyst. After filtering off the catalyst, the filtrate was concentrated to a sirup and distilled under reduced pressure, b.p. 89–90°/0.011 mm., to give a nearly quantitative yield of sirup which did not crystallize on standing for several months. It formed a crystalline *p*-phenylazobenzoate which was recrystallized from ligroin, m.p. 93.2–93.5°.

Anal. Calcd. for *p*-phenylazobenzoyl: 45.83. Found: 45.64.

3,5-Di-O-methyl-D-glucofuranose (VIII). A solution of 6.5 g. of VII in 70 ml. of acetone and 96 ml. of water containing 5 ml. of concentrated hydrochloric acid was refluxed for 2 hr. The solution was neutralized as in the preparation of V and concentrated under reduced pressure to yield 13 g. of a sirup $[\alpha]_D^{20}$ −20.1° (c 1.37, H_2O).

Anal. Calcd. for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 46.11; H, 7.74.

2,3,5,6-Tetra-O-methyl-D-glucose. A solution of 15 g. of VI in 150 ml. of methanol containing 0.5% hydrogen chloride was refluxed for 3 hr. The solution was neutralized with silver carbonate, treated with charcoal, and filtered. The filtrate was shaken for 15 hr. under a hydrogen atmosphere in the presence of a palladium charcoal catalyst. After filtering off the catalyst and concentrating the filtrate to a sirup the residue was methylated with 68 ml. of methyl sulfate and 114 g. of 50% sodium hydroxide. The product was extracted with 400 ml. of chloroform and the chloroform distilled. The residue was refluxed for 5 hr. in a solution of 70 ml. of acetone, 70 ml. of water, and 5 ml. of concentrated hydrochloric acid. The solution was neutralized with sodium bicarbonate, filtered, and evaporated under reduced pressure. The sirupy residue was extracted with ether and the extract concentrated under reduced pressure to a sirup. $[\alpha]_D^{20}$ −30.0° (c 1.06, U.S.P. $CHCl_3$).

The product, *2,3,5,6-tetra-O-methyl-D-glucose* was oxidized with bromine to the 2,3,5,6-tetra-*O*-methyl-D-gluconic acid from which the phenylhydrazide was prepared, m.p. 135–135.5° (lit.[7,11,12] 136°).

Anal. Calcd. for $C_{16}H_{26}O_6N_2$: N, 8.18. Found: N, 8.05.

Methyl 2,3,5-tri-O-methyl-β-D-glucofuranoside (IX). A solution of 30 g. of VI in 300 ml. of methanol containing 0.5% hydrogen chloride was refluxed for 3 hr. The solution was neutralized with silver carbonate, concentrated, and the crude product methylated with 100 ml. of methyl sulfate and 170 ml. of 50% sodium hydroxide as described in the preparation of VI except that the methylation was started at 10° and then raised to 50°. The sirup produced was distilled and the product (25 g.) dissolved in ethyl acetate and shaken in a hydrogen atmosphere with palladium charcoal for 15 hr. After filtration and concentration to a sirup the residue was distilled, b.p. 81–84°/0.01 mm. The product crystallized on standing and was recrystallized from ligroin, b.p. 60–70°, m.p. 74–75°; $[\alpha]_D^{20}$ −69.7° (c 1.8; H_2O).

Anal. Calcd. for $C_{10}H_{20}O_6$: C, 50.87; H, 8.47. Found: C, 50.81; H, 8.48.

2,3,5-Tri-O-methyl-D-glucose (X). A solution of IX in 60 ml. of water and 5 ml. of hydrochloric acid was refluxed for 5 hr. The solution was neutralized as described in the preparation of V and concentrated to a sirup. The product was a hydroscopic liquid $[\alpha]_D^{20}$ −13.4 (c 2.14, H_2O).

Anal. Calcd. for $C_9H_{18}O_6$: C, 48.67; H, 8.10. Found: C, 48.75; H, 8.04.

Compound X was oxidized as described by Smith[1] and the 2,3,5-tri-*O*-methyl-D-gluconic acid identified by the preparation of its phenylhydrazide, m.p. 156–156.5° (lit,[1,2] 156°, 156–157°).

Anal. Calcd. for $C_{15}H_{24}O_6N_2$: N, 8.53. Found: N, 8.45.

DETROIT 2, MICH.

(11) W. N. Haworth and S. Peat, *J. Chem. Soc.*, 129, 3094 (1926).

(12) W. N. Haworth and C. W. Long, *J. Chem. Soc.*, 544 (1927).

[CONTRIBUTION FROM THE MERCK SHARP AND DOHME RESEARCH LABORATORIES)

Synthetic Antiviral Agents. I. 4-Arylmethyl-4-aryl-5-oxohexanoic Acids and Certain of Their Derivatives*,[1]

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Received July 29, 1957

A number of 4-arylmethyl-4-aryl-5-oxohexanoic acids were prepared by the following series of reactions: Various arylacetones were condensed with certain arylmethyl halides to give the corresponding 3,4-diphenyl-2-butanones. Cyanoethylation produced the 4-arylmethyl-4-aryl-5-oxohexanenitriles which upon hydrolysis yielded the corresponding 4-arylmethyl-4-aryl-5-oxohexanoic acids.

Several of the 4-arylmethyl-4-aryl-5-oxohexanoic acids were resolved through the brucine salts. Derivatives of some of the hexanoic acids were prepared. Among the derivatives were esters, amides, and enol-lactones. Many of the compounds described have been found to have antiviral activity against certain influenza viruses.

Interest in this group of compounds began with an observation by the virologists associated with this organization that 4,4-diphenyl-5-oxohexanoic acid markedly inhibited the multiplication of PR8 influenza virus in the allantoic cavity of the chicken embryo as measured by hemagglutinin production. This effect was also observed when the mouse served as the host and activity was measured by inhibition of lung lesions or by hemagglutinin formation. In the investigation that followed strong

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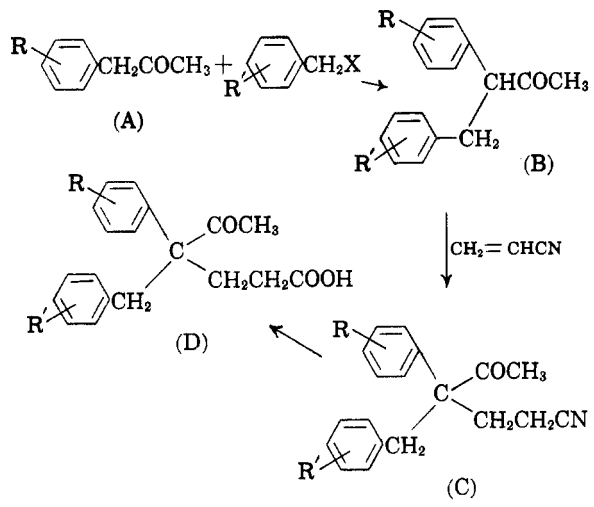
* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) A portion of the material contained in this paper was presented by the authors at the First Regional Meeting of the Delaware Valley Sections of the AMERICAN CHEMICAL SOCIETY, Feb. 16, 1956.

antiviral activity was noted in certain 4-arylmethyl-4-aryl-5-oxohexanoic acids. Therefore a number of the members of this series of compounds and their derivatives were prepared for studying as antiviral agents.

The synthetic procedure consisted of the following four steps: Preparation of phenylacetones (A) which, in turn, were alkylated with certain arylmethyl halides to give substituted 3,4-diphenyl-2-butanones (B). Cyanoethylation produced 4-arylmethyl-4-aryl-5-oxohexanenitriles (C) which upon hydrolysis yielded the corresponding 4-arylmethyl-4-aryl-5-oxohexanoic acids (D). In some instances the racemic hexanoic acids were resolved in order to obtain one or both of the two antipodes.



This synthetic method is essentially that employed by Campbell and Fairfull[2] who prepared a few 4-alkyl-4-aryl-5-oxohexanoic acids. Similar methods were used by Schultz[3] of these laboratories to prepare 4,4-diphenyl-5-oxohexanoic acid and 4-benzyl-4-phenyl-5-oxohexanoic acid.

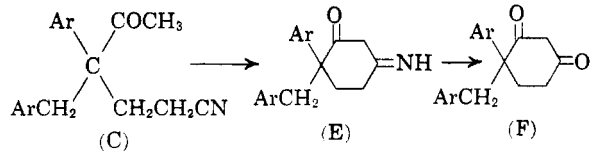
The substituted 3,4-diphenyl-2-butanones (B) were prepared by the reaction of a phenylacetone with an arylmethyl halide. It has been reported[4] that phenylacetone itself can be alkylated with certain alkyl halides using sodium hydroxide as a condensing agent. Corrigan[5] of these laboratories had found that the polymerization of phenylacetone and the hydrolysis of the alkyl halide contributed to a decreased yield when the reaction was carried out by adding the alkyl halide to a mixture of the ketone and sodium hydroxide. He had found that these side reactions could be avoided to a considerable extent by employing elevated temperatures and adding the phenylacetone and alkyl halide simultaneously to the alkali. When this technique was applied to the present study the yields were markedly higher. The yield of 4-(*o*-chlorophenyl)-3-phenyl-2-butanone resulting from phenylacetone and *o*-chlorobenzyl chloride was increased from 51% to 79%.

This alkylation is readily carried out using potassium *tert*-butoxide in *tert*-butyl alcohol as the condensing agent. Although few comparative data are available the yields appear to be a little higher when this agent is employed, especially if either reactant is sterically inhibited. The only specific example where a compound was prepared by both methods was in the synthesis of 4-(*o*-bromophenyl)-3-phenyl-2-butanone which was produced in 79% yield by the sodium hydroxide method and in 84% yield by the potassium *tert*-butoxide method. A summary of the preparations is presented in Table I.

Cyanoethylation of the ketones was carried out by the usual procedures outlined by Bruson.[6] Each of the cyanoethylations presented in Table II was carried out in *tert*-butyl alcohol at temperatures of 25° to 45° except for two reactions. Acetonitrile was employed as a solvent in these two instances. This solvent was used with 4-(2,6-dichlorophenyl)-3-phenyl-2-butanone since it will tolerate the elevated reaction temperature required to obtain the maximum yield. It was used with 4-(*m*-cyanophenyl)-3-phenyl-2-butanone in order to provide better solvent properties. The steric problems presented by 4-phenyl-3-(*o*-chlorophenyl)-2-butanone, 4-(2,6-dichlorophenyl)-3-phenyl-2-butanone, and 3,4-bis-(*o*-chlorophenyl)-2-butanone undoubtedly account for the lower yields obtained with these ketones.

The hydrolysis of the 4,4-disubstituted-5-oxohexanenitriles to the corresponding carboxylic acids was effected by refluxing a short time with a mixture of acetic acid, sulfuric acid, and water. This method appeared to be superior to the use of aqueous alkali which Campbell[2] employed. The yields are generally good as indicated in Table III.

By either hydrolysis method by-products were formed, although smaller quantities of these substances appeared to arise when the acid hydrolysis method was employed. The most troublesome by-products were the 4-arylmethyl-4-aryl-1,3-cyclohexanediones (F) and, in some cases, the intermediate 4-arylmethyl-4-aryl-3-oxocyclohexanimines (E). The strongly acidic nature and the solubility characteristics of the cyclohexanediones made them difficult to separate from the carboxylic acids. These by-products will be discussed in a later paper.



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

(3) E. M. Schultz, unpublished data.

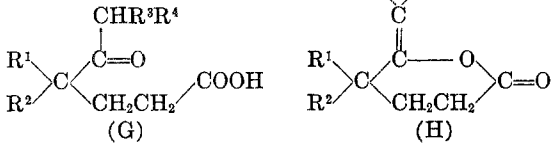
(4) E. M. Schultz, J. B. Bicking, S. Mickey, and F. S. Crossley, *J. Am. Chem. Soc.*, 75, 1072 (1953).

(5) J. R. Corrigan, unpublished data.

(6) H. A. Bruson, *Org. Reactions*, 5, 79 (1949).

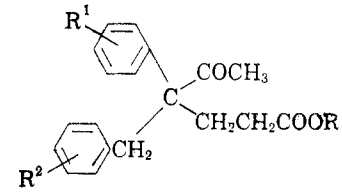
Since each of the carboxylic acids prepared possesses an asymmetric carbon atom, the product that was isolated in each instance was the racemic modification. It was considered possible that the biological activity resided in one of the two antipodes. Therefore, one of the more active racemates, 4-(*o*-chlorobenzyl)-4-phenyl-5-oxohexanoic acid, was resolved so that the two pure antipodes might be studied biologically. The resolution was quite simple since the solubility of the brucine salt of the *levo* acid in methanol was considerably less than that of the *dextro* acid. It was found that the *levo* antipode possessed most, if not all of the antiviral activity as measured by most tests.

Two more resolutions were carried out. In each instance the *levo* form was the more readily isolated since it gave the less soluble brucine salt. Furthermore, this isomer was the more attractive biologically as deduced from the earlier experience. Therefore, only with the *levo* form was an effort made to obtain high optical purity. With one compound no attempt was made to isolate the *dextro* isomer and with the other compound no attempt was made to purify the crude *dextro* isomer. A summary of data concerning the resolutions appears in Table IV.



Vorlander and Knotzsch[7] reported that 5-oxohexanoic acid (G, where R^1, R^2, R^3, and R^4=H) was converted to the corresponding enol-lactone (H) by boiling acetic anhydride. However, Campbell and Fairfull[8] found that 4-ethyl-4-phenyl-5-oxohexanoic acid (G, where R^1 = ethyl, R^2= phenyl, and R^3= R^4= H) was unaltered by boiling acetic anhydride. The latter authors also found that 4-phenyl-6-methyl-5-oxoheptanoic acid (G, where R^1= phenyl, R^2= H, and R^3= R^4= methyl) was unchanged either by boiling acetic anhydride or by heating with a mixture of sirupy phosphoric acid and phosphorus pentoxide.

In the present work it was found that the 4-arylmethyl-4-aryl-5-oxohexanoic acids were also unaltered by the action of boiling acetic anhydride. However, it was found that isopropenyl acetate[8] produced the enol-lactones (H) in good yields. Both the DL and *levo*-4-(*o*-chlorobenzyl)-4-phenyl-5-hydroxy-5-hexenoic acid lactones were prepared by this method. These enol-lactones served as useful intermediates for the preparation of derivatives of the acids. They are particularly advantageous in obtaining the more complex or difficultly accessible esters and amides.



I

Esters of type *I* are readily produced from the corresponding acid (D) when R is derived from a simple alcohol. Refluxing 4-benzyl-4-phenyl-5-oxohexanoic acid or *levo*-4-(*o*-chlorobenzyl)-4-phenyl-5-oxohexanoic acid with methanol and a little concd. sulfuric acid produced the corresponding methyl esters in excellent yields. More complex esters, such as 2-dimethylaminoethyl 4-(*o*-chlorobenzyl)-4-phenyl-5-oxohexanoate or the corresponding *levo* isomer, were prepared by the interaction of the required enol-lactone (H) with 2-dimethylaminoethanol.

levo-4-(*o*-Chlorobenzyl)-4-phenyl-5-oxohexanamide was prepared by the action of ammonia on either *levo*-methyl 4-(*o*-chlorobenzyl)-4-phenyl-5-oxohexanoate or *levo*-4-(*o*-chlorobenzyl)-4-phenyl-5-hydroxy-5-hexenoic acid lactone. Only the synthesis by the former method is described in the Experimental section although the two methods appear to be equally acceptable.

Like many other methyl ketones the 4-arylmethyl-4-aryl-5-oxohexanoic acids will react under the conditions of the Mannich reaction to produce the expected product. Thus 4-(*o*-chlorobenzyl)-4-phenyl-5-oxo-7-dimethylaminoheptanoic acid was prepared from dimethylamine, paraformaldehyde, and the appropriate 5-oxohexanoic acid.

Because of its structural relationship to the series of compounds under study, 4-(*m*-carboxyphenyl)-3-phenyl-2-butanone was prepared for comparison of the biological activity; its preparation is described in the Experimental.

Many of the 4-benzyl-4-phenyl-5-oxohexanoic acids and their derivatives were found to have antiviral activity against the influenza virus. This effect has been noted in several hosts as measured by several criteria. One compound, *levo*-4-(*o*-chlorobenzyl)-4-phenyl-5-oxohexanoic acid has been assigned the generic name caprochlorone. This compound has received a considerable amount of detailed study as an antiviral agent, some of which has already been reported by Liu and his colleagues.[9,10] The nature of the substituents on the

(7) D. Vorlander and A. Knotzsch, *Ann.*, **294**, 317 (1897).

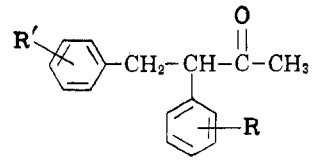
(8) G. H. Hagemeyer and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949).

(9) O. C. Liu, R. G. Malsberger, J. L. Carter, A. N. DeSanctis, F. P. Wiener, B. Hampil, *Bacteriological Proceedings of the Society of American Bacteriologists*, Houston, Tex., page 69, M18 (1956).

(10) O. C. Liu, R. G. Malsberger, J. L. Carter, A. N. DeSanctis, F. P. Wiener, B. Hampil, *Bacteriological Proceedings of the Society of American Bacteriologists*, Houston, Tex., page 69, M19 (1956).

TABLE I

PREPARATION OF 3,4-DIPHENYL-2-BUTANONES



R	R′	% Yield	Condensing Agent	B.P. °C./Mm. or M.P. (°C.)	Calcd. for	Analysis C Calcd.	C Found	H Calcd.	H Found	Halogen Calcd.	Halogen Found
H	H	62	NaOH	122–124/0.3 25.5–28.5	$C_{16}H_{16}O$[a]						
H	2-F	82[b]	Potassium *tert*-butoxide	145–149/0.25 28–28.5	$C_{16}H_{15}FO$	79.31	79.10	6.24	6.15	...	...
H	2-Cl	79[c]	NaOH	153–159/2.3	$C_{16}H_{15}ClO$	74.27	74.47	5.84	5.72	13.70	13.44
H	3-Cl	75[d]	Potassium *tert*-butoxide	157–160/0.2	$C_{16}H_{15}ClO$	74.27	74.27	5.84	5.99	...	...
H	4-Cl	46	NaOH	160–165/0.2 79–80[e]	$C_{16}H_{15}ClO$	74.27	74.39	5.84	5.71	13.70	13.48
H	2,4-Cl_2	48	NaOH	155–162/0.2 69–70[f]	$C_{16}H_{14}Cl_2O$	65.54	65.41	4.81	4.79	24.19	24.02
H	3,4-Cl_2	65[g]	NaOH	178–182/0.1	$C_{16}H_{14}Cl_2O$	65.54	65.52	4.81	4.88	24.19	23.99
H	2,6-Cl_2	82	Potassium *tert*-butoxide	160–165/0.1 68–70[h]	$C_{16}H_{14}Cl_2O$	65.54	65.50	4.81	4.98	24.19	24.12
H	2-Br	84[i]	Potassium *tert*-butoxide	166–170/0.1	$C_{16}H_{15}BrO$	63.38	63.27	4.99	4.99	26.36	26.39
		79	NaOH								
H	2-CH_3	63	NaOH	142–146/0.15	$C_{17}H_{18}O$	85.67	85.54	7.61	7.64	...	...
H	3-CH_3	59[j]	NaOH	132–136/0.2	$C_{17}H_{18}O$	85.67	85.58	7.61	7.55	...	...
H	2-CH_3O	77[k]	Potassium *tert*-butoxide	150–154/0.2	$C_{17}H_{18}O_2$	80.28	79.92	7.13	7.12	...	...
H	3-CN	82	Potassium *tert*-butoxide	180–186/0.2 67–69[l]	$C_{17}H_{15}NO$	81.90	81.72	6.06	6.05[m]	...	...
2-Cl	H	93[n]	Potassium *tert*-butoxide	150–155/0.3	$C_{16}H_{15}ClO$	74.27	74.10	5.84	6.05	13.70	13.64
2-Cl	2-Cl	78[o]	Potassium *tert*-butoxide	161–165/0.1	$C_{16}H_{14}Cl_2O$	65.54	65.59	4.81	4.98	24.19	24.00

[a] Reported by Schultz *et al.*[3] [b] n_D^{25} 1.5455. [c] n_D^{25} 1.5678. [d] n_D^{25} 1.5679. [e] Recrystallized from hexane then ethanol. [f] Recrystallized from ethanol. [g] n_D^{25} 1.5779. [h] Recrystallized from hexane. [i] n_D^{25} 1.5839. [j] n_D^{25} 1.5555. [k] n_D^{25} 1.5657. [l] Recrystallized from methanol. [m] Calcd. for N: 5.62; found: 5.60. [n] n_D^{25} 1.5682. [o] n_D^{25} 1.5762.

benzyl, phenyl, or carboxyl groups greatly influences the antiviral activity of the compound. A paper dealing with the relationship of the structure to the activity of these compounds is planned for the future.

EXPERIMENTAL[11]

A. Preparation of intermediates: o-Methoxybenzyl alcohol, n_D^{25} 1.5428, was prepared in 59% yield by the catalytic hydrogenation of *o*-methoxybenzaldehyde using Adams catalyst according to a procedure similar to that employed by Carothers[12] for the synthesis of the *p*-isomer. *o-Methoxybenzyl chloride*, b.p. 110–114°/14 mm., was prepared in 57% yield by the action of hydrogen chloride on *o*-methoxybenzyl alcohol.[13] *o-Fluorobenzyl chloride*, b.p. 172–175°/760 mm. n_D^{25} 1.5148, was prepared in 73% yield by the chlorination of *o*-fluorotoluene.[14] *m-Chlorobenzyl chloride*, b.p. 219–222°, n_D^{25} 1.5556, was prepared in 37% yield by chlorination of *m*-chlorotoluene.[15] *m-Cyanobenzyl bromide*, m.p. 92.5–93.5°, was prepared in 35% yield by the bromination of *m*-tolunitrile.[16] *2,6-Dichlorobenzyl chloride*, b.p. 117–119°/14 mm., was prepared in 73% yield by the chlorination of 2,6-dichlorotoluene.[17] *o-Bromobenzyl bromide*, b.p. 129–130°/16 mm., was prepared in 73% yield by the bromination of *o*-bromotoluene.[18] *1-(o-Chlorophenyl)-2-nitro-1-propene*, m.p. 38–41°, was prepared in 62% yield by the method of Schales.[19] *1-(o-Chlorophenyl)-2-propanone*, b.p. 94–97°/2 mm., n_D^{25} 1.5340, was prepared by the iron and hydrochloric acid reduction of 1-(*o*-chlorophenyl)-2-nitro-1-propene. Johns and Burch[20] had previously prepared it by another method. The

(11) All melting and boiling points recorded are uncorrected values unless otherwise specified. Analytical data and specific rotations were supplied by K. B. Streeter and his staff.

(12) W. H. Carothers and R. Adams, *J. Am. Chem. Soc.*, **46**, 1675 (1924).

(13) R. L. Shriner and C. J. Hull, *J. Org. Chem.*, **10**, 228 (1945).

(14) G. Schiemann and H. G. Baumgarten, *Ber.*, **70**, 1416 (1937).

(15) G. M. Bennett and B. Jones, *J. Chem. Soc.*, 1815 (1935).

(16) J. von Braun and H. Reich, *Ann.*, **445**, 225 (1925).

(17) P. R. Austin and J. R. Johnson, *J. Am. Chem. Soc.*, **54**, 647 (1932).

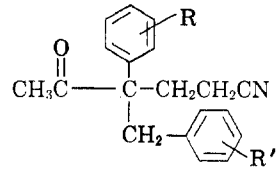
(18) J. Kenner and J. Wilson, *J. Chem. Soc.*, 1108 (1927).

(19) O. Schales and H. A. Graefe, *J. Am. Chem. Soc.*, **74**, 4486 (1952).

(20) I. B. Johns and J. M. Burch, *J. Am. Chem. Soc.*, **60**, 919 (1938).

TABLE II

4-ARYLMETHYL-4-ARYL-5-OXOHEXANENITRILES



R	R'	Yield, %	Product B.P. °C./Mm. or M.P., °C.	Recryst. Solvent	Reaction[a] Temp., °C.	Calcd. for	Analysis: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
H	H	95	127.5–129	Ethyl alcohol	25	$C_{19}H_{19}ON$[b]						
H	2-F	95	123.5–125.5	*n*-Propyl alcohol	40	$C_{19}H_{18}FNO$	77.26	77.28	6.14	6.07	4.74	4.72
H	2-Cl	92	106–108	Isopropyl alcohol	25	$C_{19}H_{18}ClNO$	73.19	73.10	5.82	5.77	4.49	4.47
H	3-Cl	81	220–225/0.4 53.5–55.5[c]	...	40	$C_{19}H_{18}ClNO$	73.19	73.09	5.82	5.70	4.49	4.50
H	4-Cl	80	197–203/0.2 86–88	Isopropyl alcohol	40	$C_{19}H_{18}ClNO$	73.19	73.19	5.82	5.90	4.49	4.47
H	2,4-Cl_2	79	215–220/0.5 89–91	Isopropyl alcohol	25	$C_{19}H_{17}Cl_2NO$	65.90	65.95	4.95	4.91	4.05	4.02
H	3,4-Cl_2	87	105–107	Isopropyl alcohol	40	$C_{19}H_{17}Cl_2NO$	65.90	66.15	4.95	4.77	4.05	4.03
H	2,6-Cl_2	31	205–212/0.4 97.5–99.5	Isopropyl alcohol	82[d]	$C_{19}H_{17}Cl_2NO$	65.90	65.76	4.95	5.09	4.05	4.05
H	2-Br	85	114–115	Isopropyl alcohol	45	$C_{19}H_{18}BrNO$	64.05	64.16	5.09	5.11	3.93	3.92
H	2-CH_3	89	88–90	Isopropyl alcohol	40	$C_{20}H_{21}NO$	82.44	82.39	7.26	7.48	4.81	4.81
H	3-CH_3	87	94.5–96	Isopropyl alcohol	40	$C_{20}H_{21}NO$	82.44	82.42	7.26	7.22	4.81	4.81
H	2-CH_3O	83	110–111	Isopropyl alcohol	42	$C_{20}H_{21}NO_2$	78.14	78.30	6.89	6.90	4.56	4.56
H	3-CN	83	227–235/0.05 86–88	Ethanol	40[d]	$C_{20}H_{18}N_2O$	79.44	79.46	6.00	6.19	9.27	9.23
2-Cl	H	30	200–212/0.2 124–126	Isopropyl alcohol	45	$C_{19}H_{18}ClNO$	73.19	73.15	5.82	5.56	4.49	4.50
2-Cl	2-Cl	16	195–200/0.1	...	45	$C_{19}H_{17}Cl_2NO$	65.90	66.03	4.95	4.82	4.05	4.05

[a] All reactions carried out in *tert*-butyl alcohol unless otherwise specified. [b] Compound reported by Schultz.[3] [c] M.p. of the product which solidified after distillation. No attempt was made to recrystallize it. [d] Acetonitrile was used as a reaction solvent.

remaining intermediates were either made by well described methods or they were commercially available.

B. Preparation of 3,4-diphenyl-2-butanones. These ketones were prepared by condensing an arylacetone with an arylmethyl halide using either sodium hydroxide or potassium *tert*-butoxide as a condensing agent. An example of each method is presented. A summary of each of the syntheses appears in Table I.

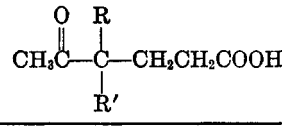
4-(o-Chlorophenyl)-3-phenyl-2-butanone. Flake sodium hydroxide (Bakers purified) (89 g., *ca.* 2 moles) was placed in a 1-liter 4-necked, round-bottomed flask equipped with a mechanical stirrer, dropping funnel, thermometer, and reflux condenser protected from moisture with a drying tube. Phenylacetone (Mathesons' practical grade) (201.5 g., 1.5 moles) and *o*-chlorobenzyl chloride (Eastman Kodak) (282 g., 1.75 moles) were thoroughly mixed and approximately 100 ml. of the mixture added to the reaction vessel with vigorous stirring. The reaction mixture was heated on a steam bath to 70° and the remaining ketone-halide mixture added dropwise at a rapid rate while no heat was applied. The temperature rose to 90–95° and then remained constant for about 15 min. After this time it was necessary to heat the mixture with a steam bath to maintain a temperature of 90–100°. The total addition time was 35 min.

After the addition was complete, the mixture was stirred and heated on the steam bath for a total of 9 hr. The mixture was then cooled and treated with water (200 ml.) and benzene (200 ml.). Concd. hydrochloric acid (50 ml.) was added to acidify the mixture. The mixture was shaken and the layers separated. The aqueous layer was washed with benzene (50 ml.). The combined organic layers were dried over anhydrous sodium sulfate. Fractional distillation gave 308 g. (79%) of material boiling at 145–150° at 1.5 mm. Refractionation gave a 90–93% recovery of material boiling at 155–159° at 2.3 mm.

4-(o-Bromophenyl)-3-phenyl-2-butanone. Potassium (31.6 g., 0.81 mole) was added to sodium-dried *tert*-butyl alcohol (700 ml.) in a 2-liter 4-necked, round-bottomed flask fitted with a mechanically driven Hershberg stirrer, dropping funnel, thermometer, and reflux condenser protected with a soda-lime drying tube. The potassium was dissolved rapidly by heating the solvent until the potassium melted and then violently agitating the mixture. After cooling, phenylacetone (108.8 g., 0.86 mole) was added within a period of a few minutes. *o*-Bromobenzyl bromide (214.5 g., 0.81 mole) was dissolved in dry benzene (100 ml.) and the solution added dropwise with stirring over 40 min. while the temperature was maintained at 35–40° by cooling when necessary. The

TABLE III

4-ARYLMETHYL-4-ARYL-5-OXOHEXANOIC ACIDS



R	R′	Yield, %	M.P., °C.	Calcd. for	Analysis: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Halogen Calcd.	Halogen Found
Phenyl	Benzyl[a]	87[b]	143–144.5	$C_{19}H_{20}O_3$						
Phenyl	*o*-Fluorobenzyl	96[c]	165–167	$C_{19}H_{19}FO_3$	72.59	72.45	6.09	5.80	...	...
Phenyl	*o*-Chlorobenzyl	97[d]	132–134	$C_{19}H_{19}ClO_3$	68.98	69.20	5.79	5.64	10.72	10.23
Phenyl	*m*-Chlorobenzyl	97[c]	119–121	$C_{19}H_{19}ClO_3$	68.98	69.29	5.79	5.51	10.72	10.76
Phenyl	*p*-Chlorobenzyl	96[c]	131–132.5	$C_{19}H_{19}ClO_3$	68.98	69.14	5.79	5.51	10.72	10.48
Phenyl	2,4-Dichlorobenzyl	94[e]	147–148.5	$C_{19}H_{18}Cl_2O_3$	62.48	62.80	4.97	4.87	19.42	19.33
Phenyl	3,4-Dichlorobenzyl	94[f]	117.5–119	$C_{19}H_{18}Cl_2O_3$	62.48	62.72	4.97	4.99	19.42	19.27
Phenyl	2,6-Dichlorobenzyl	91[g]	164.5–166	$C_{19}H_{18}Cl_2O_3$	62.48	62.69	4.97	5.24	19.42	19.43
Phenyl	*o*-Bromobenzyl	96[c]	122–123.5	$C_{19}H_{19}BrO_3$	60.81	60.89	5.10	5.04	21.30	21.15
Phenyl	*o*-Methylbenzyl	77[h]	115–117	$C_{20}H_{22}O_3$	77.39	77.88	7.14	7.05	...	...
Phenyl	*m*-Methylbenzyl	81[i]	122.5–124	$C_{20}H_{22}O_3$	77.39	77.61	7.14	7.26	...	...
Phenyl	*o*-Methoxybenzyl	74[j]	110–113	$C_{20}H_{22}O_4$	73.60	73.91	6.79	6.58	...	...
Phenyl	*m*-Carboxybenzyl[k]	95[l]	239–241	$C_{20}H_{20}O_5$	70.57	70.55	5.92	6.13	...	...
o-Chlorophenyl	Benzyl	69[c]	185–187	$C_{19}H_{19}ClO_3$	68.98	68.92	5.79	5.57	10.72	10.76
o-Chlorophenyl	*o*-Chlorobenzyl	82[c]	179.5–181.5	$C_{19}H_{18}Cl_2O_3$	62.48	62.42	4.97	4.95	19.42	19.33

[a] Prepared by E. M. Schultz[3] by alkaline hydrolysis of the nitrile. [b] Recrystallized from isopropyl alcohol. [c] Recrystallized from acetonitrile. [d] Recrystallized from acetic acid–water then acetonitrile. [e] Recrystallized from acetonitrile then toluene. [f] Recrystallized from cyclohexane then carbon tetrachloride. [g] Recrystallized from toluene, acetic acid, then ethyl acetate. [h] Recrystallized from benzene-hexane then acetic acid–water. [i] Recrystallized from cyclohexane then ethyl acetate–cyclohexane. [j] Recrystallized from benzene-hexane, toluene-heptane, then acetic acid–water. [k] Prepared by the hydrolysis of 4-phenyl-4-(*m*-cyanophenyl)-5-oxohexanenitrile. [l] Recrystallized from acetic acid then *n*-butyl alcohol.

reaction mixture was stirred for an additional 10 min. and then refluxed for 2 hr.

The solvents were distilled off at reduced pressure and the residue treated with benzene (200 ml.) and water (200 ml.). The two layers were separated and the aqueous layer extracted with benzene (50 ml.). The combined organic layers were dried over anhydrous sodium sulfate and the solvent distilled. Fractional distillation of the residue at reduced pressure gave 205 g. (84%) of product, b.p. 164–170° at 0.1 mm. Refractionation gave material b.p. 166–170° at 0.1 mm.

C. Preparation of 4-arylmethyl-4-aryl-5-oxohexanenitriles. The nitriles of this type were prepared by cyanoethylation of the corresponding 3,4-diphenyl-2-butanones. A typical example follows and a summary of all the preparations appears in Table II.

4-(o-Chlorobenzyl)-4-phenyl-5-oxohexanenitrile. 4-(*o*-Chlorophenyl)-3-phenyl-2-butanone (456 g., 1.76 moles) was dissolved in *tert*-butyl alcohol (Eastman Kodak) (1200 ml.) in a flask fitted with a mechanical stirrer and dropping funnel. A solution of 40% aqueous benzyltrimethylammonium hydroxide (Eastman) (20 ml.) was added to the solution and acrylonitrile (Eastman) (112 g., 2.12 moles) added dropwise with stirring. The solution was externally cooled so that the temperature remained below 30°.

After the addition was complete stirring was continued at room temperature for 2 hr. and then for 1 hr. at 38–45°. A check was made at periodic intervals to be sure the solution remained alkaline throughout the reaction. (If a neutral or weakly alkaline reaction was observed, more catalyst was added.) The solution was neutralized with sulfuric acid and the solid which had separated during the reaction was removed by filtration. The dry product weighed 491 g. (90%), m.p. 103–106°. Recrystallization from isopropyl alcohol (1500 ml.) gave 467 g., m.p. 104.5–107°. A second recrystallization gave material melting at 106–108°.

D. Preparation of 4-arylmethyl-4-aryl-5-oxohexanoic acids. These compounds were all prepared by hydrolysis of the corresponding nitriles. Essentially the same procedure was employed in all instances. An example is described in detail and Table III summarizes all of the syntheses which were carried out.

Four of the acids were resolved. Again similar procedures were used in each instance. An example of the resolution procedure is presented along with a summary (Table IV) of all of the preparations.

DL-*4-(o-Chlorobenzyl)-4-phenyl-5-oxohexanoic acid.* 4-(*o*-Chlorobenzyl)-4-phenyl-5-oxohexanenitrile (412.5 g., 1.32 moles) was suspended in a mixture of concd. sulfuric acid (450 ml.), glacial acetic acid (2 liters), and water (600 ml.). Upon heating to boiling the solid dissolved. The mixture was refluxed for 1.25 hr.

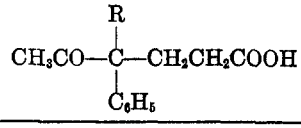
After this time a sample of the reaction mixture was completely soluble when made alkaline with sodium hydroxide. The mixture was poured, with stirring, into cold water (8 l.). An oil separated which solidified upon stirring. The solid was separated by filtration, washed with water, dried, and pulverized. The yield was 415 g. (97%), m. p. 106–125°. Material at this stage may contain as much as 10% 4-(*o*-chlorobenzyl)-4-phenyl-1,3-cyclohexanedione. One recrystallization from acetonitrile (830 ml.) gave 354 g., m.p. 124–130°. Several more recrystallizations from acetic acid–water and/or acetonitrile gave material melting at 132–134°.

levo-4-(o-Chlorobenzyl)-4-phenyl-5-oxohexanoic acid. A mixture of DL-4-(*o*-chlorobenzyl)-4-phenyl-5-oxohexanoic acid (354.4 g., 1.07 moles) and brucine (422.6 g., 1.07 moles) were dissolved in boiling methanol (975 ml.). The solution was cooled and seeded with a few crystals of the product. After 24 hr. at room temperature followed by 24 hr. at 5° the white solid that separated was removed by filtration and dried. The yield was 351 g. (91% of one antipode), m.p. 97–101°. (The mother liquors were saved for recovery of the *dextro* antipode.)

One recrystallization from methanol gave 300 g., m.p. 100–102°. A second recrystallization gave 289 g. (74%), m.p. 100–102°. Analysis of the brucine salt indicated it to be

TABLE IV

RESOLUTION OF 4-ARYLMETHYL-4-ARYL-5-OXOHEXANOIC ACIDS



R	Yield, %[a]	M.P.	Antipode	Specific Rotation[b]	Calcd. for	Analysis: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
o-Fluorobenzyl[c]	58	121–121.5	levo[d]	−137.6[e]	$C_{19}H_{19}FO_3$	72.59	72.26	6.09	6.05
o-Chlorobenzyl[f]	70	110–111	levo	−143.1	$C_{19}H_{19}ClO_3$	68.98	69.04	5.79	5.75
o-Chlorobenzyl[g]	63	109–110	dextro	+142.0	$C_{19}H_{19}ClO_3$	68.98	69.11	5.79	6.04
o-Bromobenzyl[h]	57	85.5–87.5	levo	−118.5	$C_{19}H_{19}BrO_3$	60.81	60.96	5.10	5.40
o-Bromobenzyl[i]	50	77–84	dextro	+106.6	$C_{19}H_{19}BrO_3$	...	...	..	..

[a] Calculated on the basis that 100% is the theoretical yield for each antipode. [b] Specific rotation of a 2% solution in 95% ethanol at 25°. [c] The brucine salt was recrystallized from an isopropyl alcohol–water mixture and the free acid from cyclohexane. [d] No attempt was made to isolate or purify the dextro antipode. [e] A 3% solution was used in this case. [f] The brucine salt was recrystallized from methanol; the free acid from heptane. [g] Recrystallized from acetonitrile then from heptane. [h] The brucine salt was recrystallized from methanol; the free acid was recrystallized from cyclohexane. [i] No attempt was made to obtain this antipode in pure form.

solvated. Adjusting for solvation by calculation, the specific rotation of the brucine salt is −87.9° for a 2% solution in 95% ethanol at 25°.

The *levo*-acid-brucine salt was treated with dilute hydrochloric acid (1500 ml., 1*N* concn.) and then extracted twice with benzene (500 ml. portions). The combined benzene extracts were dried over sodium sulfate and the solvent removed by distillation at reduced pressure. The yield of dry solid residue was 120 g. (70%), m.p. 106–109°. Recrystallization from heptane gave 118.5 g., m.p. 109–110°. Several more recrystallizations from either acetic acid–water or heptane gave material melting at 110–111°, $[\alpha]_D^{25}$ −143.1° for a 2% solution in 95% ethanol.

dextro-4-(o-Chlorobenzyl)-4-phenyl-5-oxohexanoic acid. The mother liquors from the initial crystallization of the *levo*-acid-brucine salt were evaporated to dryness to give a viscous liquid residue. This crude brucine salt was treated by a procedure similar to that described for the *levo*-acid-brucine salt. The crude *dextro*-acid generated in this manner was dissolved in a small volume of acetonitrile (about 1 ml. per g.) and the solution refrigerated. The material which separated was the racemic acid (*ca.* 15%). Evaporation of the solvent gave the *dextro*-acid (63%), m.p. 97–101°. Recrystallization, first from a small volume of acetonitrile, then several times from heptane gave material melting at 109–110°, $[\alpha]_D^{25}$ +142° for a 2% solution in 95% ethanol.

Preparation of derivatives of 4-arylmethyl-4-aryl-5-oxohexanoic acids. Methyl 4-benzyl-4-phenyl-5-oxohexanoate. A mixture of 4-benzyl-4-phenyl-5-oxohexanoic acid (50 g., 0.169 mole), absolute methanol (200 ml.) and concd. sulfuric acid (14 ml.) was refluxed under anhydrous conditions for 7.5 hr. The mixture was poured into ice water. An oil separated which soon solidified. The solid was dissolved in ether and the solution washed with water, then with aqueous sodium bicarbonate and finally with water. After drying over sodium sulfate the solvent was removed by evaporation. The residue consisted of 52 g. (99%) of white crystalline solid, m.p. 89–90°. The ester obtained by this method is quite pure and does not require further purification.[21]

levo-Methyl 4-(o-chlorobenzyl)-4-phenyl-5-oxohexanoate. levo-4-(*o*-Chlorobenzyl)-4-phenyl-5-oxohexanoic acid (100 g., 0.3 mole) was dissolved in a mixture of absolute methanol (400 ml.) and concd. sulfuric acid (16 ml.) and the mixture refluxed for 7 hr. The mixture was concentrated to 200 ml. at reduced pressure then poured into water (350 ml.) and extracted four times with toluene (350 ml. total).

(21) E. M. Schultz[3] reported a melting point of 88.5–90°.

The combined toluene extracts were washed with water (50 ml.), then with saturated sodium bicarbonate (50 ml.) and finally with water (25 ml.). After drying over sodium sulfate the solvent was removed by distillation and the residue fractionally distilled *in vacuo*. A total of 90.4 g. (87%) was collected, b.p. 187–192°/0.2 mm. Refractionation gave material boiling at 194–199°/0.2 mm., n_D^{25} 1.5621. The $[\alpha]_D^{25}$ of a 4% solution in 95% ethanol was −117.6°.

Anal. Calcd. for $C_{20}H_{21}ClO_3$: C, 69.66; H, 6.14; Cl, 10.28. Found: C, 69.78; H, 6.14; Cl, 10.18.

4-(o-Chlorobenzyl)-4-phenyl-5-hydroxy-5-hexenoic acid lactone. 4-(*o*-Chlorobenzyl)-4-phenyl-5-oxohexanoic acid (82.7 g., 0.25 mole), isopropenyl acetate (75.1 g., 0.75 mole) and concd. sulfuric acid (3 drops) were placed in a flask equipped with an 18 in. fractionating column attached to a downward condenser. The mixture was heated with an electric heating mantle so that a slow distillation occurred. About 40 ml. of material (mostly acetone) boiling at 55–59° was collected in 2.5 hr.

The residue was transferred to a Claisen flask and fractionally distilled *in vacuo*. A total of 66 g. (85% of material, b.p. 196–204° at 0.1 mm., m.p. 126–132°, was obtained. Recrystallization first from toluene, then from cyclohexane gave material melting at 134.5–136°.

Anal. Calcd. for $C_{19}H_{17}ClO_2$: C, 72.96; H, 5.48. Found: C, 72.78; H, 5.47.

levo-4-(o-Chlorobenzyl)-4-phenyl-5-hydroxy-5-hexenoic acid lactone. levo-4-(*o*-Chlorobenzyl)-4-phenyl-5-oxohexanoic acid (125 g., 0.378 mole) was dissolved in isopropenyl acetate (151 g., 1.5 moles) and concd. sulfuric acid (5 drops) was added. The mixture was heated as described for the racemic material for 7 hr. The volatile components were distilled off at reduced pressure and the residue was treated with hexane to give 84 g., of white solid, m.p. 100–106°. Recrystallization from heptane gave 62.2 g., m.p. 112–113°. The combined mother liquors from the two recrystallizations were evaporated to dryness and the residue was fractionally distilled *in vacuo* to give 42.6 g., b.p. 205–215°/0.2 mm. This material was treated with isopropenyl acetate (60 g., 0.6 mole) and concd. sulfuric acid (3 drops). The mixture was heated as before for 4 hr. Fractional distillation of the product gave 40.6 g., b.p. 200–210°/0.2 mm., m.p. 106–110°. Recrystallization from heptane gave 33.5 g., m.p. 111.5–113°.

The total yield was 95.7 g. (81%). A final recrystallization from heptane gave material melting at 113–113.5°. The $[\alpha]_D^{25}$ for a 3% solution in dry toluene was −382.2°.

Anal. Calcd. for $C_{19}H_{17}ClO_2$: C, 72.96; H, 5.48. Found: C, 72.96; H, 5.36.

2-Dimethylaminoethyl 4-(o-chlorobenzyl)-4-phenyl-5-oxohexanoate hydrobromide. 4-(*o*-Chlorobenzyl)-4-phenyl-5-hydroxy-5-hexenoic acid lactone (36.1 g., 0.115 mole) was dissolved in dry 2-dimethylaminoethanol (89 g., 1 mole) and the mixture was heated at 95° under anhydrous conditions. After a few minutes at this temperature the mixture was refluxed for 2 hr. The excess amine was removed by distillation at reduced pressure and the residue was dissolved in benzene (250 ml.).

The solution was washed with water twice and then dried over sodium sulfate. The benzene was removed by distillation and the residue dissolved in cyclohexane (150 ml.) and dry hydrogen bromide was introduced into the solution until precipitation no longer occurred. Addition of benzene (50 ml.) caused the conversion of the gummy product to a white solid, 48.2 g. (87%), m.p. 144–148°. Two recrystallizations from isopropyl alcohol gave 41.7 g., m.p. 149–151°.

Anal. Calcd. for $C_{23}H_{29}BrClNO_3$: C, 57.20; H, 6.05; N, 2.90; Br, 16.55. Found: C, 56.95; H, 6.35; N, 2.90; Br, 16.59.

levo-2-Dimethylaminoethyl 4-(o-chlorobenzyl)-4-phenyl-5-oxohexanoate hydrobromide. levo-4-(*o*-Chlorobenzyl)-4-phenyl-5-oxohexanoic acid lactone (37.5 g., 0.12 mole) and freshly distilled dry 2-dimethylaminoethanol (107 g., 1.2 moles) were refluxed for 2 hr. and the product isolated as described for the racemic modification. The free base was dissolved in isopropyl alcohol and treated with hydrogen bromide gas to give 52.6 g. (90%) of the hydrobromide salt. Two recrystallizations from isopropyl alcohol gave 46.5 g. of pure material, m.p. 149.5–151.5°. The $[\alpha]_D^{26}$ of a 1% water solution was −37.7°.

Anal. Calcd. for $C_{23}H_{29}BrClNO_3$: C, 57.20; H, 6.05; N, 2.90; Br, 16.55. Found: C, 57.65; H, 5.98; N, 2.86; Br, 16.49.

4-(o-Chlorobenzyl)-4-phenyl-5-oxo-7-dimethylaminoheptanoic acid hydrochloride. 4-(*o*-Chlorobenzyl)-4-phenyl-5-oxohexanoic acid (66.2 g., 0.2 mole), dimethylamine hydrochloride (16.3 g., 0.2 mole), and paraformaldehyde (6.6 g., 0.22 mole) were intimately mixed and placed in a one-liter flask fitted with a Claisen head and receiver. The system was evacuated by means of a water aspirator and the mixture heated at 140° using a metal bath.

The solids melted and vigorous bubbling occurred for a few minutes. After heating at 135–145° for 30 min. the mixture was cooled and the resulting sirup was digested with butanone. After cooling the solid that had formed was removed by filtration and dried. The yield was 48.6 g. (57%), m.p. 123–139°. Two recrystallizations from isopropyl alcohol gave 29.2 g. of pure material, m.p. 165–167°.

Anal. Calcd. for $C_{22}H_{27}Cl_2NO_3$: C, 62.26; H, 6.41; N, 3.30; Cl, 16.69. Found: C, 62.73; H, 6.17; N, 3.25; Cl, 16.93.

levo-4-(o-Chlorobenzyl)-4-phenyl-5-oxohexanamide. Ammonia gas (31 g., 1.8 moles) was dissolved in 2-methoxyethanol (200 ml.) at −40°. *levo*-Methyl 4-(*o*-chlorobenzyl)-4-phenyl-5-oxohexanoate (25 g., 0.073 mole) was dissolved in 2-methoxyethanol (50 ml.) and the solution cooled to −40°. The two solutions were united in an autoclave and heated at 100° for 4 hr. After standing at room temperature for 48 hr. the solvent was removed by distillation at reduced pressure.

The residue was dissolved in benzene (150 ml.) and washed with saturated sodium bicarbonate solution (25 ml.) and then with water (25 ml.). The benzene solution was dried over sodium sulfate and the solvent was removed by distillation. Treatment of the residue with a mixture of benzene and hexane gave a solid. The yield was 14.7 g. (64%), m.p. 58–69°. After one recrystallization from a mixture of benzene and hexane and two recrystallizations from benzene, 8.1 g. remained, m.p. 81–83°.

Anal. Calcd. for $C_{19}H_{20}ClNO_2$: C, 69.19; H, 6.11; N, 4.25; Cl, 10.75. Found: C, 69.97; H, 6.22; N, 4.16; Cl, 10.38.

4-(m-Carboxyphenyl)-3-phenyl-2-butanone. 4-(*m*-Cyanophenyl-3-phenyl-2-butanone (25 g., 0.1 mole) was suspended in a mixture of glacial acetic acid (150 ml.), water (70 ml.), and concd. sulfuric acid (50 ml.). The mixture was refluxed for 2 hr. and then cooled and poured into water (2 l.). The oil that separated was extracted with ethyl acetate. The ethyl acetate extract was evaporated to dryness and the residue treated with an excess of aqueous potassium hydroxide solution. The solution was extracted with a little benzene to remove a small amount of insoluble material.

The aqueous solution was acidified with hydrochloric acid. The oil which separated initially solidified upon standing. The product was removed by filtration and dried. The yield was 18.6 g. (70%), m.p. 86–90°. Two recrystallizations from cyclohexane gave pure material (15.1 g.), m.p. 87–89°.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.35; H, 6.01.

WEST POINT, PA.

[CONTRIBUTION FROM THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

Further Studies with the Bacitracin Polypeptides*

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The fractionation of bacitracin by countercurrent distribution has been reinvestigated from the standpoint of obtaining a product with the highest antibiotic activity. Evidence has been given that the decrease in antibiotic activity at lower *p*H may be associated with a change in the optical activity of at least one of the amino acid residues, probably the isoleucine residue forming part of the thiazoline ring. This is a transformation apparently not related to that occurring at higher *p*H which leads to the F type of peptide.

Preliminary data for the characterization of bacitracin B have been given. These include amino acid analyses, ultimate analyses, determination of the amino groups capable of reacting with the Sanger reagent, and antibiotic activity.

The bacitracin polypeptides[1] comprise an interesting family of naturally occurring antibiotics with unique structures. None of them has been brought to a crystalline state as yet, although the major features of a structural formula for bacitracin A, the most abundant member of the family, appear to have been established. Formula 1 derived in this laboratory[1,2] and independently in England by

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

** Fellow of the National Science Foundation.

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(2) J. R. Weisiger, W. Hausmann, and L. C. Craig, *J. Am. Chem. Soc.*, 77, 3123 (1955).