Thus, the entering amidomethyl group was found to be *para* to the chlorine and *meta* to the carboxyl group.

A number of derivatives of the 2-chloro-5-aminomethylbenzoic acid were prepared by conventional means and are reported in the Experimental without comment.

EXPERIMENTAL

Condensation of 2-chlorobenzoic acid with N-hydroxymethylacetamide. A mixture of 277.8 g. (1.76 moles) of 2-chlorobenzoic acid and 700 ml. of concd. sulfuric acid was stirred and cooled to 20°. Powdered *N*-hydromethylchloroacetamide[4] (202 g., 1.8 moles) was added over a 30-min. period at 20°. After the reaction mixture was stirred overnight, the solution was poured over ice and allowed to stand for 2 days. The solid was removed, washed with water, dried, and triturated with ether. The solid was removed, m.p. 126–135°. Recrystallization from ethanol gave 300 g. (65%) of 2-chloro-5-(chloroacetylaminomethyl)benzoic acid (I), m.p. 144–146°. Recrystallization from dioxane and then from dimethylformamide raised the melting point to 147–148°.

Anal. Calcd. for $C_{10}H_9Cl_2NO_3$: Cl, 27.06; N, 5.34. Found: Cl, 27.18; N, 5.26.

3-Carboxy-4-chlorobenzylamine hydrochloride (II). A mixture of 118.0 g. (0.45 mole) of 2-chloro-5-(chloroacetylaminomethyl)benzoic acid (I) and 400 ml. of concd. hydrochloric acid was refluxed for 4 hr. After refrigerating overnight, the white solid was collected by filtration, washed with a mixture of ether and acetone, and dried. The 3-carboxy-4-chlorobenzylamine hydrochloride (II) (yield 91 g., 92%) thus obtained melted at 243–244°.

Anal. Calcd. for $C_8H_9Cl_2NO_2$: Cl, 31.93; N, 6.31. Found: Cl, 32.14; N, 6.21.

The free acid was obtained by neutralization with sodium acetate, m.p. 295–297° dec.

Anal. Calcd. for $C_8H_8ClNO_2$: Cl, 19.11; N, 7.54. Found: Cl, 19.41; N, 7.68.

Proof of structure of 5-aminomethyl-2-chlorobenzoic acid. Method A. A mixture of 2.22 g. (0.01 mole) of II from above, 1 g. of sodium bicarbonate, 4 ml. of 40% aqueous formaldehyde and 50 ml. of ethanol was allowed to stand for 1 hr. A 1-g. sample of 5% palladium-on-charcoal was added, and the mixture was hydrogenated at 50° and 35 p.s.i. of hydrogen. The mixture was hydrogenated at 50° and 35 p.s.i. of hydrogen. The mixture was filtered, evaporated, and the residue taken up in 5% sodium hydroxide. This solution was treated with charcoal, filtered, and acidified. The white solid III was recrystallized from water, m.p. 110–112°.[8] The infrared spectra of an authentic specimen of *m*-toluic acid was identical with the preceding acid.

Method B. An intimate mixture of 4 g. of II and 8 g. of soda-lime was heated in a tube and the distillate collected. This distillate yielded *ca.* 0.1 ml. of a liquid amine. A 1-ml. sample of pyridine was added to the liquid followed by a few drops of benzoyl chloride. The mixture was allowed to stand overnight and then worked up to yield a white solid. Recrystallization gave 50 mg. of white crystals, m.p. 140–141°. *N*(4-chlorobenzyl)benzamide is reported to melt at 141°.[9]

Method C. A mixture of 5 g. of II, 6 g. of potassium dichromate, 14 ml. of water, and 8 ml. of concd. sulfuric acid was refluxed 1 hr. Potassium dichromate, 5 g., and 5 ml. of concd. sulfuric acid were added to the reaction and the mixture refluxed 2 hr. The mass was cooled, filtered, and the precipitate washed with water. The solid was recrystallized from dioxane and gave 1.3 g. of white crystals, m.p. 293–295°. 4-Chloroisophthalic acid is reported to melt at 294.5°.[10]

3-Carbomethoxy-4-chlorobenzylamine hydrochloride. A mixture of 22.2 g (0.1 mole) of 3-carboxy-4-chlorobenzylamine hydrochloride and 235 ml. of absolute methanol was refluxed for 3 hr. and simultaneously saturated with hydrogen chloride. The mixture was cooled overnight. The precipitate was collected, washed with ether, and recrystallized from methanol to yield 16.5 g. (70%) of the desired product, m.p. 217–220°.

Anal. Calcd. for $C_9H_{11}Cl_2NO_2$: Cl, 30.04; N, 5.93. Found: Cl, 30.37; N, 6.00.

Methyl 2-chloro-5-(chloroacetylaminomethyl)benzoate. A mixture of 7 g. of 2-chloro-5-(chloroacetylaminomethyl)benzoic acid and 50 ml. of absolute methanol was heated on a steam bath while 1 ml. of concd. sulfuric acid was added dropwise. The solution was refluxed 1 hr., then was allowed to stand overnight, cooled in an ice bath, and filtered. The white solid was recrystallized from ethanol–water mixture, m.p. 83–84°.

Anal. Calcd. for $C_{11}H_{11}Cl_2NO_3$: Cl, 25.68; N, 5.07. Found: Cl, 26.01; N, 5.19.

N-Propyl 3-carboxy-4-chlorobenzylcarbamate. A mixture of 2.22 g. (0.01 mole) of 3-carboxy-4-chlorobenzylamine hydrochloride and 5 ml. of 4*N* sodium hydroxide was cooled in an ice bath. The solution was stirred vigorously and 0.01 mole of *n*-propyl chloroformate and 12.5 ml. of 4*N* sodium hydroxide added simultaneously over a 3-hr. period. The precipitate was discarded and the clear solution acidified with hydrochloric acid. The white solid was collected and recrystallized from ethanol and from chloroform, m.p. 131–133°.

Anal. Calcd. for $C_{12}H_{15}ClNO_4$: Cl, 13.00; N, 5.13. Found: Cl, 13.18; N, 5.30.

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(8) A. Reuter, *Ber.*, **17**, 2028 (1884).

(9) J. von Braun, M. Kuhn, and J. Weismantel, *Ann.*, **449**, 266 (1926).

(10) F. Ullman and J. B. Uzbachion, *Ber.*, **36**, 1799 (1903).

Configurations of the Diastereomeric 4-Benzoyl-2,3-diphenylbutyric Acids and Derivatives[1]

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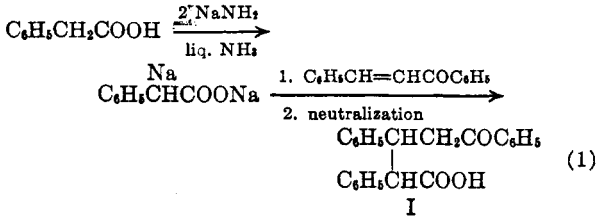
Disodio phenylacetate, prepared from phenylacetic acid and two molecular equivalents of sodium amide in liquid ammonia, has recently[2] been shown to undergo conjugate addition to benzalacetophenone to give keto acid I (Equation 1). Only one isomer of I was isolated from the reaction mixture. It has now been found that both isomers of I are produced in the conjugate addition, and the configurations of these keto acids and their derivatives have been established.

Neutralization of the reaction mixture in liquid ammonia by the addition of solid ammonium

(1) Supported by the National Science Foundation.

(2) C. R. Hauser and M. T. Tetenbaum, *J. Org. Chem.*, **23**, 1146 (1958).



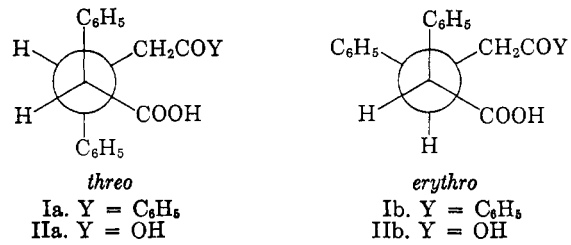
(1)

chloride afforded the high and low melting isomers of I in yields of 41% and 36%, respectively. Similar results were obtained when the ammonia was replaced by ether and the resulting suspension neutralized.

The diastereomeric keto acids I have previously been produced from the conjugate additions of ethyl phenylacetate,[3] methyl phenylacetate,[4,5] and phenylacetonitrile[5,6] to benzalacetophenone followed by hydrolysis of the resulting ester or nitrile. However, the yields or isomer ratios were not reported, and the configurations were not assigned. As the diastereomeric keto acids I can be readily separated (see Experimental), the present procedure affords the most convenient method for the preparation of these acids.

Avery and Jorgensen[5] prepared pure samples of the isomeric keto acids and their esters, and classified the compounds into a high melting and low melting series. They also reported[5] that each keto acid I could be converted to an enol-lactone from which the original acid could be regenerated. The low melting acid formed its enol-lactone rapidly in refluxing acetyl chloride, whereas the high melting isomer afforded its enol-lactone only on prolonged refluxing in the same solvent. We have confirmed these observations although in the latter case the yield was low (6%). A higher yield (25%) of the enol-lactone of the high melting keto acid was obtained with thionyl chloride. We have also found that refluxing acetic anhydride converts the high melting keto acid I to the enol-lactone of the low melting acid (71%).

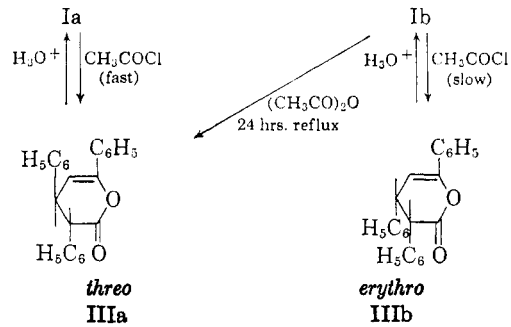
Similar transformations have been observed[7,8] for the isomeric 2,3-diphenylglutaric acids whose configurations are known.[8,9] The *threo* anhydride is obtained from the *threo* diacid IIa with refluxing acetyl chloride and from the *erythro* isomer IIb with refluxing acetic anhydride. An anhydride having the *erythro* configuration has not been reported. By analogy the low melting keto-acid I may be assigned the *threo* configuration Ia and the high-melting isomer the *erythro* configuration Ib. The conversions to the enol-lactones are summarized in Scheme A.



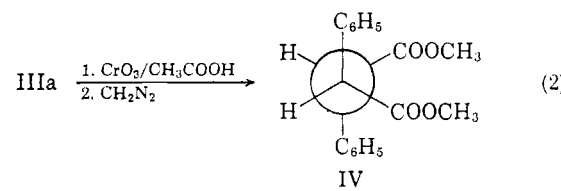
threo Ia. Y = C_6H_5; IIa. Y = OH

erythro Ib. Y = C_6H_5; IIb. Y = OH

SCHEME A



The *threo* configuration for the low melting 4-benzoyl-2,3-diphenylbutyric acid (Ia) was confirmed by oxidation of its enol-lactone (IIIa) to the known racemic 2,3-diphenylsuccinic acid,[10] which was identified as its dimethyl ester IV (Equation 2).



(2)

IV

On the basis of the assignment of the *threo* configuration to the low melting keto-acid Ia the low melting series of Avery and Jorgensen[5] is shown to have the *threo* configuration, and the high melting series the *erythro* configuration. The assignments are summarized in Table I.

TABLE I

CONFIGURATIONS OF DERIVATIVES OF KETO ACIDS Ia AND Ib

Derivative	*threo*, M.P.	*erythro*, M.P.
Acid (I)	186–187°[a]	260–261°
Methyl ester	155°	177–178°
Ethyl ester	100–101°	156°
Enol-lactone (III)	136°	220–222°
Nitrile	—	118°

[a] Melting points as reported by Avery and Jorgensen, ref. 5.

(3) W. Borsche, *Ber.*, **42**, 4496 (1909).
(4) H. Meerwein, *J. prakt. Chem.*, **97**, 272 (1918).
(5) S. Avery and G. C. Jorgensen, *J. Am. Chem. Soc.*, **52**, 3628 (1930).
(6) E. P. Kohler and C. F. H. Allen, *J. Am. Chem. Soc.*, **46**, 1522 (1924).
(7) R. B. Meyer and C. R. Hauser, *J. Org. Chem.*, **26**, 3183 (1961).
(8) S. Avery and W. D. Maclay, *J. Am. Chem. Soc.*, **51**, 2833 (1929).
(9) D. Lednicer and C. R. Hauser, *J. Am. Chem. Soc.*, **80**, 6364 (1958).
(10) G. F. Wright, *J. Am. Chem. Soc.*, **61**, 2106 (1939).

EXPERIMENTAL[11]

4-Benzoyl-2,3-diphenylbutyric acids. I. To a stirred suspension of 0.20 mole of sodium amide in 800 ml. of commercial anhydrous liquid ammonia[12] was added 13.6 g. (0.10 mole) of solid phenylacetic acid. The resulting green solution was stirred for 20 min., and 20.8 g. (0.10 mole) of solid benzalacetophenone was added. The color faded and a dark brown precipitate formed. After stirring for 1 hr., the mixture was neutralized by the addition of solid ammonium chloride (12 g.). The liquid ammonia was evaporated as an equal volume of ether was added. The resulting ethereal suspension was stirred with 300 ml. of 3*N* hydrochloric acid, and the ether was evaporated. Filtration of the remaining aqueous suspension afforded the isomeric keto acids Ia and Ib which were separated by a modification of the procedure of Avery and Jorgensen.[5]

Crystallization of the isomeric acids from glacial acetic acid (800 ml.) afforded 14.2 g. (41%) of *erythro* keto acid Ib, m.p. 258–261°. Recrystallization from glacial acetic acid raised the m.p. to 260–261° (lit.,[5] m.p. 260–261°). The methyl ester, prepared by refluxing the acid with methanol containing sulfuric acid, was crystallized from methanol, m.p. 177–178° (lit.,[5] m.p. 177–178°).

The original acetic acid filtrate was concentrated to 300 ml. and diluted with water at the boiling point until crystals appeared. The solid, which was deposited on cooling, was collected by filtration and was dissolved in 250 ml. of boiling benzene. After filtering to remove a small amount of insoluble material, the solution was cooled and filtered to give 12.4 g. (36%) of *threo* keto acid Ia, m.p. 182–184°. Recrystallization from benzene raised the m.p. to 186–187° (lit.,[5] m.p. 186–187°). The methyl ester, prepared by means of diazomethane, was crystallized from ethanol, m.p. 155–156° (lit.,[5] m.p. 155°).

Similar results were obtained when the ammonia was replaced by ether (without adding ammonium chloride) and ice was added to the ethereal suspension as previously reported.[2] The alkaline aqueous solution was acidified with 3*N* hydrochloric acid and the isomeric keto acids Ia and Ib were crystallized as described above.

threo-Enol-lactone IIIa. A solution of 3.14 g. (9.14 mmoles) of *threo*-keto acid Ia in 20 ml. of acetyl chloride was refluxed for 4 hrs. After cooling, the mixture was poured into 200 ml. of ligroin (b.p. 60–90°) and warmed to remov excess acetyl chloride. On cooling in ice there was obtained 2.45 g. (82%) of the *threo*-enol-lactone IIIa, m.p. 132–136°. Crystallization from glacial acetic acid–ligroin (b.p. 60–90°) afforded 1.85 g. (62%) of *threo*-enol-lactone IIIa, m.p. 138–139° (lit.,[5] m.p. 136°).

erythro-Enol-lactone IIIb. A mixture of 5.0 g. (0.0145 mole) of *erythro*-keto acid Ib and 75 ml. of thionyl chloride was refluxed for 5 hrs., and the excess thionyl chloride was then distilled. The residue was stirred with dilute sodium hydroxide solution and filtered. Crystallization from ethyl acetate afforded 1.2 g. (25%) of *erythro*-enol-lactone IIIb, m.p. 217–220° (lit.,[5] m.p. 220–222°).

When *erythro*-keto acid Ib was refluxed with acetyl chloride as described previously[5] only a 6% yield of the enol-lactone IIIb was obtained.

Epimerization of erythro keto acid Ib *through threo enol-lactone* IIIa. A solution of 2.0 g. (5.8 mmoles) of *erythro*-keto acid Ib in 25 ml. of acetic anhydride was refluxed for 24 hrs. After cooling, the solution was poured into 500 ml. of ligroin (b.p. 60–90°). The crystals which appeared on standing were filtered and discarded (m.p. 147–210°). Concentration of the filtrate to dryness afforded 1.4 g. (71%) of *threo* enol-lactone IIIa, m.p. 130–138°. The crude enol-lactone was dissolved in 20 ml. of glacial acetic acid, and the solution was heated to boiling. To the boiling solution there was added 14 ml. of 50% sulfuric acid, and the mixture was boiled for 5 min. The crude keto acid Ia, which crystallized on cooling, was filtered and recrystallized from benzene to give 1.0 g. (72% on lactone) of *threo* keto acid Ia, m.p. 186–188°. This m.p. was not depressed on admixture with an authentic sample obtained as described above.

Oxidation of threo enol-lactone IIIa. To a stirred solution of 1.6 g. (4.9 mmoles) of *threo*-enol-lactone IIIa in 100 ml. of glacial acetic acid at room temperature there was added during 25 min. a solution of chromium trioxide (1.0 g.) in 25 ml. of acetic acid and 6 ml. of water. The temperature was maintained below 35°. After stirring for 2 hr., 300 ml. of water was added, and the suspension was extracted with ether. The combined organic solutions were distilled under reduced pressure. The residue was dissolved in 50 ml. of ether and added to an ethereal solution of diazomethane. Acetic acid was added to decompose the excess diazomethane, and the solvent was distilled under reduced pressure to give *d,l*-dimethyl-2,3-diphenylsuccinate (0.25 g., 24%), m.p. 171–178°. Crystallization from *n*-propyl alcohol raised the m.p. to 177–178°. The *meso* dimethyl ester is reported[10] to melt at 221–222°. On admixture with the methyl ester of *erythro*-keto acid Ib, m.p. 177–178°, the m.p. was depressed to 152–173°.

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(11) Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected.

(12) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, 8, 122 (1954).

Preparation of Methyl 2-Deoxy-2-sulfamino-α- and β-D-glucopyranoside Sodium Salts

Konoshin Onodera and Tohru Komano

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The presence of sulfamino group in heparin is generally accepted and appears to be in part responsible for the anticoagulant activity of the mucopolysaccharide.[1] Wolfrom, Gibbons, and Huggard[2] reported synthesis of methyl 2-deoxy-2-sulfamino-α-D-glucopyranoside, the β-isomer of which has not yet been reported. In this paper preparation of methyl 2-deoxy-2-sulfamino-α- and β-D-glucopyranoside sodium salts (monohydrates) (XI, XII) is described.

The glycosidation of 2-benzyloxycarbonylamino-2-deoxy-D-glucopyranose (I) was performed by refluxing it in methanol with Amberlite IR 120 (H^+). The product was a mixture of methyl 2-benzyloxycarbonylamino-2-deoxy-α- and β-D-glucopyranosides (II), but we could not separate the isomers at this step. After acetylation of II, with a mixture of pyridine and acetic anhydride, separation and recrystallization of methyl 3,4,6-tri-*O*-acetyl-2-benzyloxycarbonylamino-2-deoxy-α-and β-D-glucopyranosides (III, IV) were effected from ethanol. The β-isomer was more easily crystallizable than the α-isomer. The yield of the mix-

(1) A. B. Foster and A. J. Huggard, *Advances in Carbohydrate Chem.*, 10, 335 (1955), R. W. Jeanloz, *Fed. Proc.*, 17, 1082 (1958).

(2) M. L. Wolfrom, R. A. Gibbons, and A. J. Huggard, *J. Am. Chem. Soc.*, 79, 5043 (1957).