quite pure even after two distillations and was unsuitable for our work.[4] Therefore no satisfactory method was available for the preparation of the dimethyl ester. This compound could be conveniently prepared (75% yield) by transesterification[10] of ethyl methyl β-oxoadipate by refluxing its methanolic solution with a trace of sodium methoxide, or in a better yield (89%) by treating the methanolic solution with 1.05 g. atom of sodium methoxide at room temperature. Treatment of the latter solution, containing the sodio derivative, *in situ* with methyl iodide gave dimethyl α-methyl-β-oxoadipate in 83% yield.

EXPERIMENTAL

Diethyl β-oxoadipate. To magnesium ethoxide, prepared from 16.5 g. of magnesium and 94.6 ml. of absolute ethanol and suspended in 200 ml. of dry ether, was added a solution of 87 g. of ethyl acetoacetate in 100 ml. of dry ether followed by a solution of 109 g. of β-ethoxycarbonylpropionyl chloride in 100 ml. of dry ether.[8] The crude α-acetyl ester weighing 154 g. was dissolved in 300 ml. of dry ether and cooled to 0°, and a stream of dry ammonia was passed through it for 40 min.[6] The yield of diethyl β-oxoadipate was 86 g. (60%); b.p. 119–120°/1.5 mm. (reported 122–126° at 0.5 mm.[7]).

Ethyl methyl β-oxoadipate, b.p. 115–117°/1.5 mm. (reported b.p. 90°/0.06 mm. and 148–150°/12 mm.[8]) was similarly prepared in about the same yield.

Dimethyl β-oxoadipate. (i) To a solution of sodium methoxide, prepared from 0.35 g. of sodium and 100 g. of absolute methanol, was added ethyl methyl β-oxoadipate (20 g.), and the mixture was refluxed for 20 hr. The cooled product was taken up in ether, washed repeatedly with saturated ammonium sulfate solution, and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was distilled to yield 14 g. (75%) of dimethyl β-oxoadipate; b.p. 125–126°/3 mm. (reported b.p. 122°/0.5 mm.[1] and 125–126°/3 mm.[5b]).

(ii) Ethyl methyl β-oxoadipate (20 g.) was added to a solution of sodium methoxide, from 2.4 g. of sodium and absolute methanol (120 g.), and allowed to stand at room temperature for 5 hr. It was then acidified with glacial acetic acid and most of the alcohol removed on a water bath under reduced pressure, the residue was taken up in ether and washed with sodium bicarbonate solution and water. After drying, the solvent was removed and the residue distilled, b.p. 125–126°/3 mm., yield 16.7 g. (89%).

Dimethyl α-methyl-β-oxoadipate. To a solution of sodium methoxide, from 3.63 g. of sodium and absolute methanol (180 ml.), was added ethyl methyl β-oxoadipate (30.3 g.) and left for 2 hr. at room temperature. Methyl iodide (19 g.) was added, and after 1 hr. at room temperature it was refluxed for 2 hr. A fresh quantity of methyl iodide (12 g.) was then added and the refluxing continued for 2 hr. Most of the alcohol was removed under reduced pressure, the residue taken up in ether and washed with water. The solvent was removed after drying and the residue distilled to yield 25.2 g. (83%) of dimethyl α-methyl-β-oxoadipate, b.p. 135–136°/3 mm.

Anal. Calcd. for $C_9H_{14}O_5$: C, 53.46; H, 6.93. Found: C, 53.03; H, 6.91.

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[10] T. Peters, *Ann.*, **257**, 353 (1890).

Synthesis of *p*-Benzoylmandelic Acid

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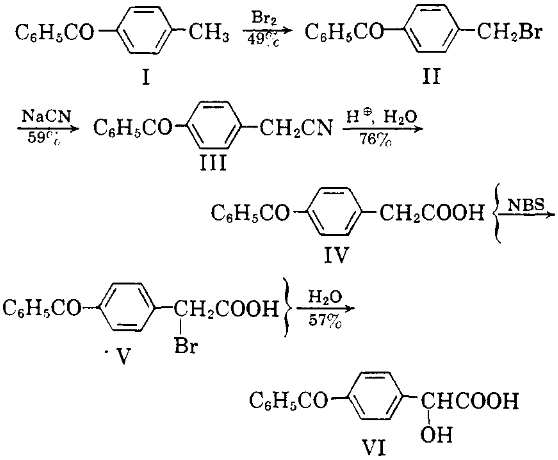
In connection with a problem in the field of asymmetric synthesis we have been interested in the synthesis and resolution of *p*-benzoylmandelic acid (VI). Over the past several years we have developed several alternative syntheses for this substance. The purpose of the present note is to discuss these syntheses, to evaluate them and to describe several new compounds encountered in their development.

The first of these syntheses,[1] with yields given for each step, is shown in Chart I, where the overall yield of *p*-benzoylmandelic acid (VI) from *p*-methylbenzophenone (I) is 12.5%. In the preparation of *p*-benzoylbenzyl bromide (II) by bromination of I we obtained a sample of II having m.p. 112.5°. This bromide has been reported by Bourcet[2] to have m.p. 96.6°. The melting point discrepancy may be due to polymorphism, since this phenomenon has been observed with *p*-methylbenzophenone (I) itself.[3]

Chart I



Since the development of the synthesis in Chart I Zelinski[4] has reported the preparation of our intermediate *p*-benzoylphenylacetic acid (IV) by an alternative method. We have employed Zelinski's procedure in the preparation of *p*-benzoylmandelic acid according to the sequence given in Chart II, where the yields from VIII to IV are those reported by Zelinski. The overall yield

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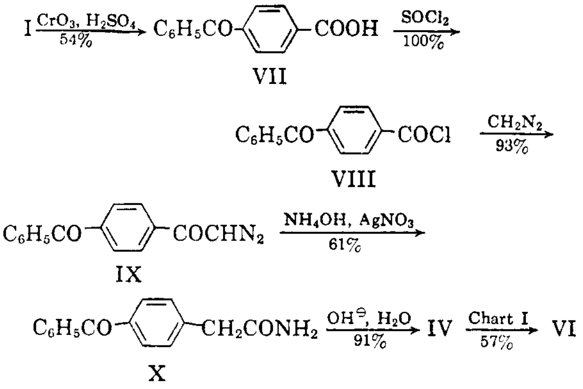
[1] J. A. Zderic, M. S. thesis, Stanford University (1952).

[2] P. Bourcet, *Bull. soc. chim.*, **1**, 946 (1896).

[3] K. Schaum, K. Schaeling, and F. Klausing, *Ann.*, **411**, 188 (1916).

[4] R. P. Zelinski, B. W. Turnquest, and E. C. Martin, *J. Am. Chem. Soc.*, **73**, 5521 (1951).

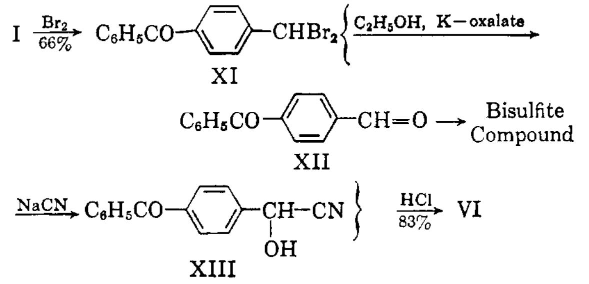
Chart II



of 15.9% in Chart II represents a slight improvement over that obtained by the reactions sequence in Chart I.[5]

In our hands, the most satisfactory synthesis of *p*-benzoylmandelic acid from *p*-methylbenzophenone has been that indicated in Chart III, where the overall yield of VI from I was about 55%.[6]

Chart III



Again, in the preparation of the dibromide XI from I, the melting point of the product (105.5–107.5°) was considerably higher than that (86.8°) reported by Bourcet,[7] perhaps again because of polymorphism.

EXPERIMENTAL

p-Benzoylbenzyl bromide (II). *p*-Methylbenzophenone (300 g.) was placed in a 2-l., three necked flask equipped with a sealed stirrer, dropping funnel and reflux condenser, then melted at 150°. While maintaining this temperature, the dropwise addition of bromine (244.2 g.) was undertaken. When addition was complete and the evolution of hydrogen bromide had ceased, the melt was poured into water and the resulting solid was filtered and recrystallized from ethanol, affording 203 g. (49%) of white crystals, m.p. 112.5°. Since this melting point did not agree with the 96.6° value reported by Bourcet,[2] the compound was analyzed.

Anal. Calcd. for $C_{14}H_{11}OBr$: C, 61.11; H, 4.03; Br, 29.05. Found: C, 61.03, 61.21; H, 4.11, 4.19; Br, 29.28, 29.32.

p-Benzoylphenylacetonitrile (III). *p*-Benzoylbenzyl bromide (16.2 g.) was dissolved in dioxane (100 ml.) and the solution was treated with a solution of sodium cyanide (35 g.) in water (100 ml.). The mixture was heated under reflux for 2 hr., during which time the organic product appeared as a separate layer. The cooled reaction mixture was extracted with benzene and the extracts were washed with water, then dried over anhydrous sodium sulfate. The residue resulting on solvent removal was distilled *in vacuo* and a fraction (7.7 g.; 59%) boiling at 204° (1 mm.) was collected. This distillate was crystallized from petroleum ether (b.p. 80–110°) to give a white solid, m.p. 64°.

Anal. Calcd. for $C_{15}H_{11}ON$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.27, 81.36; H, 5.06, 5.11; N, 6.21, 6.32.

p-Benzoylphenylacetic acid (IV). *p*-Benzoylphenylacetonitrile (10 g.) was dissolved in a mixture containing 80 ml. each of water, acetic acid and sulfuric acid. The solution was heated under reflux for 48 hr., cooled and extracted with ether. The extracts were washed with water and sodium carbonate solution, then discarded. The alkaline layer was acidified and extracted with benzene. The extract was stripped of solvent, leaving 13.7 g. of an oil which crystallized slowly. Recrystallization from ether afforded 8.3 g. (76%) of the desired acid. The m.p. of the product was 111°, and a mixed melting point with an authentic sample, m.p. 112°, was undepressed. (We are indebted to Dr. R. P. Zelinski for furnishing the authentic sample.)

Ethyl p-benzoylphenylacetate. Impure *p*-benzoylphenylacetic acid (11 g.) was dissolved in ethanol (175 ml.) containing sulfuric acid (2 ml.) and the mixture was heated under reflux overnight, then reduced to a volume of 50 ml. by vacuum distillation and neutralized with aqueous sodium hydroxide. The solution was extracted with ether and the extracts were clarified by filtration through Norit. Solvent removal yielded 9.5 g. of an oil which was distilled, affording 6.3 g. (51%) of clear oil, b.p. 176–178° (0.5 mm.), which rapidly crystallized. Recrystallization from ligroin yielded white crystals, m.p. 61–63°.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.68, 75.69; H, 5.98, 6.04.

α-Bromo-p-benzoylphenylacetic acid (V). A mixture of *p*-benzoylphenylacetic acid (0.5 g.) and *N*-bromosuccinimide (0.37 g.) in carbon tetrachloride (5 ml.) was heated under reflux for 3 days, then extracted with water and finally with aqueous sodium bicarbonate solution. The alkaline solution was acidified and the resulting oil extracted into ether. Solvent removal yielded an oil which slowly crystallized from a mixture of benzene and ligroin, m.p. 131–133°. Recrystallization failed to raise the melting point.

Anal. Calcd. for $C_{15}H_{11}O_3Br$: C, 56.44; H, 3.47; Br, 25.04. Found: C, 56.17, 56.35; H, 3.38, 3.44; Br, 24.78.

p-Benzoylmandelic acid (VI). A solution of *p*-benzoylphenylacetic acid (17.36 g.) *N*-bromosuccinimide (12.98 g.) and benzoyl peroxide (0.5 g.) in carbon tetrachloride (300 ml.) was heated under reflux for 48 hr. After cooling, the solution was extracted with saturated aqueous sodium carbonate and the alkaline extract was heated for 25 min. on the steam bath. Acidification with nitric acid caused the precipitation of 10.6 g. (57%) of crude acid, m.p. 169°. Recrystallization from dilute acetone yielded 8 g. of white crystals, m.p. 177–178°.

Anal. Calcd. for $C_{15}H_{12}O_4$: C, 70.31; H, 4.72; Neutral equivalent, 256. Found: C, 69.87, 69.88; H, 4.85, 4.68; Neutral equivalent, 259.

p-(Dibromomethyl)benzophenone (XI). *p*-Methylbenzophenone (100 g.) was placed in a 500-ml., three necked flask equipped with a condenser, a mercury sealed stirrer and a dropping funnel reaching below the surface of the flask contents. The ketone was melted, held at a temperature of 120°, and stirred vigorously under illumination of a 300-watt unfrosted lamp bulb. Half of the total quantity of bromine (179.5 g.) was added over a period of approximately 8 hr., the rate of addition being regulated to prevent free bromine from collecting in the condenser. During the second half of the addition the reaction temperature was raised to 170–175°. After another 8 hr. addition was com-

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(5) E. Wertheim, *J. Am. Chem. Soc.*, 55, 2541 (1933); Wertheim reports a yield of 65%.

(6) Mother Mary J. Kubitschek, Ph.D. thesis, Stanford University (1958).

(7) P. Bourcet, *Bull. soc. chim.*, [3], 15, 446 (1896).

plete and the mixture was heated and stirred for an additional hour, then cooled and the contents dissolved in 2 l. of hot 2-propanol. The solution was filtered twice through Norit, then chilled, yielding 119.3 g. (66%) of colorless, shining platelets, m.p. 101–104°. This material was employed in the hydrolysis reaction below. Two additional recrystallizations from 2-propanol raised the melting point to a constant value of 105.5–107.5°. Since the melting point reported by Bourcet[7] for *p*-(dibromomethyl)benzophenone was 86.8°, the substance obtained was analyzed. A mixed melting point with the above *p*-benzoylbenzyl bromide (II), m.p. 112.5°, showed a marked depression, 84–98°.

Anal. Calcd. for $C_{14}H_{10}OBr_2$: C, 47.49; H, 2.85. Found: C, 47.52, 47.70; H, 2.88, 2.94.

p-Benzoylbenzaldehyde (XII). Hydrolysis of the above *p*-(dibromomethyl)benzophenone to *p*-benzoylbenzaldehyde was accomplished in two ways, the first employing sulfuric acid as the hydrolyzing agent and the second employing potassium oxalate in ethanol and water. The second method was found to give more reproducible results and is reported below. The aldehyde obtained by either procedure was contaminated with unchanged dibromide as well as *p*-benzoylbenzoic acid. Accordingly the product was isolated through its bisulfite addition compound, which was washed free of contaminants by means of ether, procedure preventing autooxidation of the aldehyde, which seemed to take place quite readily.

p-(Dibromomethyl)benzophenone (57.8 g.), potassium oxalate (31.0 g.), ethanol (400 ml.) and water (130 ml.) were heated under reflux for a period of 50 hr., after which the ethanol was distilled until the residue became heavily clouded with yellow oil, which solidified on cooling and stirring. The product was filtered, washed twice with water and then stirred into a saturated solution of sodium bisulfite. The resulting bisulfite addition compound was filtered, washed with ether until white and then dried. It weighed 42.1 g. (82%) and melted over a wide range from approximately 170 to 190°.

p-Benzoylmandelonitrile (XIII). The bisulfite addition compound prepared from 65 g. of *p*-(dibromomethyl)-benzophenone was placed in a beaker with water (200 ml.). The mixture was stirred while slowly adding a solution of sodium cyanide (9 g.) in water (50 ml.). Toward the end of the addition the last of the bisulfite addition compound had dissolved, and crystallization commenced. The white product was filtered, washed with water and dried. The crude product had m.p. 90–98°. A sample, recrystallized four times from toluene, had m.p. 105.5–107°.

Anal. Calcd. for $C_{15}H_{11}O_2N$: C, 75.93; H, 4.67. Found: C, 75.62, 75.44; H, 4.80, 4.81.

p-Benzoylmandelic acid (VI). The crude, moist *p*-benzoylmandelonitrile was immediately placed in a large evaporating dish containing concentrated hydrochloric acid (300 ml.). The covered mixture was allowed to stand overnight, during which time a heavy amber syrup settled. The mixture was heated on the steam bath for 30 min., whereupon the syrup dissolved and glistening, colorless crystals separated. The cooled *p*-benzoylmandelic acid was filtered, washed with water and dried, 38.7 g. (82%), m.p. 169–175°. One recrystallization from glacial acetic acid raised the m.p. to 176–179°, undepressed on admixture with the above sample of the same compound.

O-Acetyl-p-benzoylmandelic acid. p-Benzoylmandelic acid (4.446 g.) in acetyl chloride (20 ml.) was heated under reflux until a clear solution was obtained. The excess acetyl chloride was distilled *in vacuo*, and the residue crystallized on prolonged standing *in vacuo* at room temperature. The crude product weighed 4.68 g. (91%), m.p. 110–116°. Two recrystallizations from 1:1 benzene-ligroin raised the m.p. to a constant value of 135–136.5°.

Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.43, 68.56; H, 4.89, 4.81.

Methyl O-acetyl-p-benzoylmandelate. A solution of diazomethane in anhydrous ether was added dropwise with stirring to a solution of *O*-acetyl-*p*-benzoylmandelic acid (3.7 g.) in anhydrous ether until the yellow color of the diazomethane just persisted. Solvent evaporation yielded 3.9 g. of glistening white crystals. After one recrystallization from 2-propanol the product weighed 3.47 g. (89.7%) and had m.p. 80–82°.

Anal. Calcd. for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.46, 69.36; H, 5.29, 5.34.

Methyl p-benzoylmandelate. p-Benzoylmandelic acid (2.00 g.) was converted to its methyl ester using diazomethane in the manner described above. The crude product (1.91 g.; 89.9%), m.p. 107–109°, was purified by three recrystallizations from 2-propanol, m.p. 110–110.5°.

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.99; H, 4.86.

Attempted Resolution of p-Benzoylmandelic Acid. Attempts to resolve *p*-benzoylmandelic acid using strychnine, brucine, cinchonine, nicotine and the α-phenylethylamines led to samples of amine salts which, on decomposition, gave acid samples, recrystallization of which yielded fractions of variable optical activity, indicating that resolution was incomplete. Our attempts to resolve this acid were thus only partially successful.

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Reaction of Chloromethyl Ether with Primary Amines

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The reaction of primary and secondary amines with chloromethyl ether (I) is reported[1] to give the alkylmethoxymethylamine derivatives. Several examples for the reaction of secondary amines are reported[1] whereas only one example of the reaction of a primary amine, namely allylamine, has been mentioned.[1]

In our attempt to prepare allylmethoxymethylamine (II) by the reaction of chloromethyl ether with allylamine, we have isolated instead of the expected product (II) 1,3,5-triallylhexahydro-*s*-triazine (III), which is probably formed by the trimerization of allylazomethine IV (R = $-CH_2-CH{=}CH_2$) an intermediate, produced from the initial product II by loss of methanol. This elimination is not surprising in view of the strong nucleophilic property of the amino group in the initial reaction product, allylmethoxymethylamine (II). The trimerization of IV is consistent with the fact that aliphatic aldimines, especially those from primary amines, trimerize rapidly, as evidenced by cryoscopic data.[2]

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(1) F. E. Merck, German Patent **273,323** (1914); *Chem. Zentr.*, **1914 I**, 1718; *Frdl.*, **12**, 761.

(2) F. Klager, F. Kircher, and M. Block, *Ann.*, **547**, 23 (1941) in *The Chemistry of Heterocyclic Compounds, s-Triazine and Derivatives* by E. M. Smolin and L. Rapoport, Interscience, New York, 1959, p. 476.