The ease with which *o*-chlorophenylbenzoylacetylene reacts with methyl alcohol in the presence of bases explains the fact that acetylenic ketones are not among the products obtained when α,β-dibromo ketones are treated with alcoholic solutions of bases.

Experimental

α-Bromo-*o*-chlorobenzalacetophenone, IV.—In the earlier paper[1] IV was prepared by the action of an alcoholic solution of anhydrous potassium acetate on the dibromide. Two other methods of preparation are herein described. Method A is particularly significant since α,β-dibromo ketones are not generally pyrolyzed to give α-bromo unsaturated ketones as the chief product.

A. By the Pyrolysis of the Dibromide.—Five grams of *o*-chlorobenzalacetophenone dibromide was heated for one and one-half hours at 170°, the evolution of hydrogen bromide practically ceasing after one hour. The liquid was allowed to cool and then taken up in ether. The washed and dried ether solution gave 2.7 g. of α-bromo-*o*-chlorobenzalacetophenone melting at 59°, a yield of 75%. The residual material consisted of about 0.5 g. of unchanged dibromide and an oil which has not as yet given solid products.

B. By the Action of Pyridine on the Dibromide.—A solution of 15.5 g. of the dibromide in 25 cc. of pyridine was refluxed for thirty minutes. By the usual manipulations, 6.2 g. of IV was obtained, a yield of 50%. The residual oil has not crystallized.

***o*-Chlorophenylbenzoylacetylene, I.**—A solution of 5 g. of α-bromo-*o*-chlorobenzalacetophenone in 15 cc. of acetone (free of methyl alcohol) and a solution of 1.3 g. of potassium hydroxide in 15 cc. of water were mixed and the mixture was refluxed for one hour. The cooled solution was diluted with 200 cc. of water and extracted with ether. The ether solution, red in color, gave 2.8 g. of the acetylenic ketone. Separation of the acetylenic ketone and the residual, viscous oil is extremely difficult since there is little difference in solubility. The yield of acetylenic ketone is therefore higher than is indicated by the above description.

o-Chlorophenylbenzoylacetylene is very soluble in ether but only sparingly soluble in petroleum ether. It crystallizes as long colorless needles and melts at 94°.

Anal. Calcd. for $C_{15}H_9OCl$: C, 74.8; H, 3.77. Found: C, 74.9, 74.6, 74.7; H, 3.81, 3.78, 3.74.

Conversion of I into *o*-Chlorodibenzoylmethane, II.—A solution of one gram of the acetylenic ketone in 15 cc. of concentrated sulfuric acid was left at room temperature for forty-eight hours and then poured into iced water. The ether extract gave a quantitative yield of the copper salt of the diketone when shaken with saturated cupric acetate solution. The diketone was recovered from the copper salt and identified by comparison with a known sample.

Conversion of I into β-Methoxy-*o*-chlorobenzalacetophenone, III.—One gram of the acetylenic ketone was dissolved in a solution of one gram of potassium hydroxide in 30 cc. of methyl alcohol. After standing for five hours at room temperature, β-methoxy-*o*-chlorobenzalacetophenone had crystallized from the solution. All of the material was poured into iced water. The ether extract gave 1.1 g. of β-methoxy-*o*-chlorobenzalacetophenone melting at 114°, practically a quantitative yield.

The Action of Potassium Hydroxide on I.—An absolute ether solution of 0.5 g. of the acetylenic ketone was left in contact with 2 g. of potassium hydroxide pellets for twelve hours. The acetylenic ketone was recovered.

The Action of Bases on IV. A. Solid Potassium Hydroxide.—A mixture of 3.35 g. of the bromo ketone and 1.4 g. of potassium hydroxide pellets reacted vigorously when heated on the water-bath for a few minutes. The resulting solid cake was cooled and then treated with water and ether. Acidification of the water layer gave the calculated quantity of benzoic acid, assuming complete cleavage.

B. Solid Sodium Carbonate.—Procedure A was followed, substituting 4 g. of anhydrous sodium carbonate for the potassium hydroxide. The bromo ketone was recovered.

C. Aqueous Potassium Hydroxide.—Three grams of the bromo ketone was added to a solution of 15 g. of potassium hydroxide in 100 cc. of water and the mixture was refluxed for two and one-half hours. The bromo ketone was unchanged.

D. Solid Potassium Hydroxide and Ether.—An absolute ether solution of 5 g. of the bromo ketone was left in contact with 5 g. of potassium hydroxide pellets for twenty-four hours. The bromo ketone did not react.

Summary

The preparation of *o*-chlorophenylbenzoylacetylene from α-bromo-*o*-chlorobenzalacetophenone is reported.

EXETER, NEW HAMPSHIRE RECEIVED JULY 29, 1946

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Extension of the Modified Stobbe Condensation. Acid-Catalyzed Decomposition of the Products and a Lacto–Enoic Tautomerism[1]

BY WILLIAM S. JOHNSON, JACK W. PETERSEN[2] AND WILLIAM P. SCHNEIDER[3]

In previous work[4,5,6] it was demonstrated that in the Stobbe condensation of ketones with diethyl succinate the use of potassium *t*-butoxide in *t*-butyl alcohol generally gave higher yields and purer products during shorter reaction periods than were obtained by the classical procedure with sodium ethoxide. Applications of the modified procedure to three additional ketones, benzophenone, acetophenone and propiophenone are reported herewith as well as an account of the acid-catalyzed decarbethoxylation of the products.

Benzophenone is an especially suitable ketone for the study of the Stobbe condensation because the resulting half-ester (I), in contrast to that derived from a ketone like acetophenone, has neither stereo nor structural isomers, and is a homogeneous crystalline material lending itself

(1) This work was assisted in part by a grant from the Wisconsin Alumni Research Foundation.

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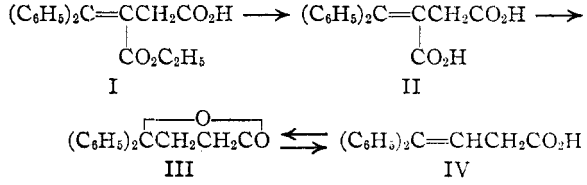
(4) Johnson, Goldman and Schneider, THIS JOURNAL, **67**, 1357 (1945).

(5) W. S. Johnson, H. C. E. Johnson and Petersen, *ibid.*, **67**, 1360 (1945).

(6) Johnson and Petersen, *ibid.*, **67**, 1366 (1945).

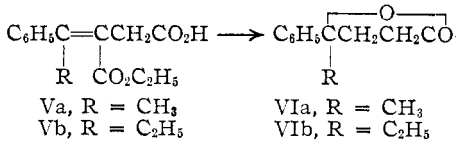
well to a study of the decarbethoxylation reaction, because both of the products, III and IV, are also crystalline with characteristic melting points. Under the best conditions, benzophenone heated thirty minutes with 1.1 moles of potassium *t*-butoxide and 1.5 moles of diethyl succinate per mole of ketone gave the almost colorless crystalline half-ester I in 90% yield. In contrast the sodium ethoxide-catalyzed condensation is reported to give the half-ester in 58–62% yield after several days.[7] No appreciable ester exchange to form the half *t*-butyl ester was observed, and the small neutral fraction consisted largely of unchanged benzophenone. Increasing the proportion of catalyst and prolonging the heating lowered the yield and purity of the half-ester, and the neutral fraction contained benzhydrol presumably arising from a Meerwein–Ponndorf type of reduction of the ketone by the potassium ethoxide produced in the condensation. No detectable reduction occurred when di-*t*-butyl was used instead of diethyl succinate,[8] but the rate of condensation appeared to be slower and optimum yields (80%) were obtained only after one hour of heating.



The decarbethoxylation of the half-ester I may be effected with a boiling mixture of hydrochloric and acetic acid but the process is slow, requiring about sixty hours for completion, probably because a large proportion of the hydrogen chloride is volatilized (see below). A boiling mixture composed of two volumes of 48% hydrobromic acid, three of acetic acid and one of water retained the hydrogen bromide, and effected complete decarbethoxylation of the half-ester I in five hours, yielding an easily separable mixture of γ,γ-diphenylvinylacetic acid, IV, and γ,γ-diphenylbutyrolactone, III, formed in the ratio of about 7 to 3. Approximately the same ratio of products was obtained from the dibasic acid II, the rate of decarboxylation, however, being more rapid (90% complete in two hours), which suggests that the hydrolysis is the rate controlling step in the decarbethoxylation of the half-ester I. Prolonged heating of the reaction mixture did not change the ratio of products; indeed the mixture containing 33% of the lactone was obtained on heating either pure III or IV in the acid and represents the true tautomerism, IV ⇆ III. Such behavior represents a case of what has been termed by Linstead and his collaborators[9] a "lacto-enoic tautomerism," hitherto recognized as a general phenomenon only with δ-lactones. In the present communication three examples of acid-catalyzed γ-lacto-enoic tautomerism are described.

The reactions described above constitute an excellent method for preparing γ,γ-diphenylvinylacetic acid which has been obtained previously from less readily accessible materials.[10] The lactone III is also easily prepared, since it was found that the unsaturated acid IV was lactonized in 95% yield by the action of concentrated sulfuric acid at room temperature for fifteen minutes.

The behavior of acetophenone and propiophenone in the modified Stobbe condensation resembled that of 2-acetylnaphthalene previously described.[4] The resulting half-esters, produced in almost quantitative yields, were obtained as pale yellow oils which undoubtedly consisted of mixtures of the various bond- and stereo-isomers, such as were previously obtained by the sodium ethoxide-catalyzed condensation.[11,12] The itaconic acid structure only is shown in formulas Va and Vb. Decarbethoxylation of the half-esters with the hydrobromic–acetic acid mixture gave the lactones VIa and VIb in 85 and 81% over-all yields from the ketones.[13]



If the acetophenone, the propiophenone and the 2-acetylnaphthalene[4] derivatives undergo a lacto-enoic tautomerism, either the lactone predominates in the equilibrium, or tautomerism is very slow and the lactone is the primary product of decarboxylation as in the cases described below.

Previous communications[5,6] noted that in the decarbethoxylation of VIIa and XIa the ratio of lactone to unsaturated acid, particularly in the phenanthrene series, varied with conditions. Further examination at different acid concentrations, namely, with acetic acid, concentrated hydrochloric acid and water in the proportions by volume of 7 to 3.5 to 5 (reagent A) and of 10 to 2.3 to 3 (reagent B),[14] has revealed an acid-catalyzed lacto-enoic tautomerism, IX ⇆ X and XIII ⇆ XIV. With either reagent in the

(7) Stobbe, *Ann.*, **308**, 89 (1899). The crude itaconic acid II, however, was obtained by Stobbe in 90% yield from a dark oily product of condensation under more vigorous conditions. Using this procedure, we have been unable to reproduce this yield.

(8) Observation made by Chester E. Davis.

(9) Linstead and Rydon, *J. Chem. Soc.*, 580 (1933); Boorman and Linstead, *ibid.*, 258 (1935).

(10) Borsche, Kettner, Gillies, Kuhn and Manteuffel, *Ann.*, **526**, 1 (1936).

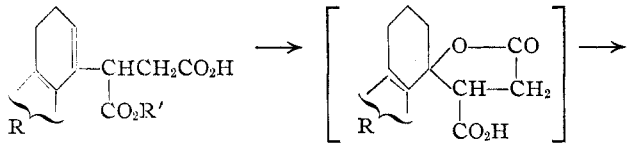
(11) Stobbe, *ibid.*, **308**, 114 (1899).

(12) Stobbe and Niedenzu, *ibid.*, **321**, 94 (1902).

(13) Both of these lactones have been prepared previously either in poor or in unspecified yields by the reaction of a Grignard reagent with a keto ester: (a) Grignard, *Compt. rend.*, **135**, 627 (1902); (b) Trivedi and Nargund, *J. Univ. Bombay*, **10**, Pt. 3, 102 (1941) [*C. A.*, **36**, 3801 (1942)].

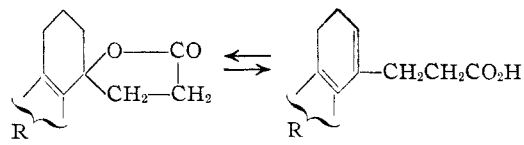
(14) Reagent B was developed from a 10 to 5 to 1 mixture which was used in earlier work (ref. 6) but was found to lose hydrogen chloride on boiling until the composition reached that of reagent B.

naphthalene series the concentration of unsaturated acid X at equilibrium was about 60%; in the phenanthrene series the value was 60–70% of XIV with reagent B and 90–95% with A.



VIIa, R = benzo, R′ = C_2H_5
VIIb, R = benzo, R′ = H
XIa, R = 1,2-naphtho, R′ = C_2H_5
XIb, R = 1,2-naphtho, R′ = H

VIII, R = benzo
XII, R = 1,2-naphtho



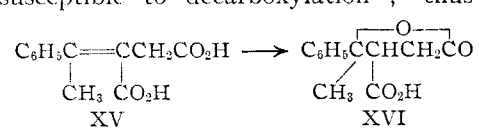
IX, R = benzo
XIII, R = 1,2-naphtho

X, R = benzo
XIV, R = 1,2-naphtho

The decarboxylation of the polycyclic and most strikingly the phenanthrene compounds, unlike diphenylitaconic acid, proceeded more rapidly than the lacto-enoic tautomerism of the products; so that it was possible to stop the treatment before equilibrium was reached, whereupon the lactones were always isolated in higher proportions than found at equilibrium, with as much as 70% of XIII being obtained in a medium yielding only 30–40% of the lactone at equilibrium. These observations suggest that the lactones IX and XIII are the primary products of the decarboxylation step, and that the unsaturated acids are formed *via* the lacto-enoic tautomerism.

The dicarboxylic acids VIIb and XIb, like diphenylitaconic acid, decarboxylated more rapidly than the corresponding half-esters; with reagent B, XIb was almost completely decarboxylated in one-half hour, yielding 67% of lactone XIII, whereas the half-ester required about four hours.

The conclusion that the lactones IX and XIII are the precursors of the unsaturated acids suggests that the decarboxylation process may proceed through cyclization of the dibasic to intermediary paraconic acids VIII and XII which in turn lose carbon dioxide forming the lactones. Although no such intermediates were isolated in the present work, it is known that itaconic acids are cyclized to paraconic acids by mineral acid,[15] the methylphenylitaconic acid XV thus being converted into the methylphenylparaconic acid XVI.[16] Paraconic acids, moreover, are known to be susceptible to decarboxylation[17]; thus the substance XVI was observed by Stobbe[16] to lose carbon dioxide on heating with sulfuric acid. The product, although isolated in low yield, appeared to have lactonic properties and was undoubtedly γ-methyl-γ-phenylbutyrolactone, VIa, the formation of which from Va (see above), thus, possibly proceeds *via* the paraconic acid XVI.



XV XVI

The direct decarboxylation of the itaconic acids, analogous to that of cinnamic acids, represents an alternate possible mechanism, for even with the alkylidene pyrotartaric acid structure predominating, the itaconic acid is potentially available by a three-carbon tautomerism, or from the paraconic acid through a lacto-enoic tautomerism; thus the formation of VIa from XVI (see above) could conceivably proceed through the itaconicacid XV. The itaconic acid mechanism, however, is incompatible with the appearance of the lactone, rather than the unsaturated acid, as the primary product of decarboxylation, and, although the mechanism has not been ascertained for those reactions wherein the rate of equilibration between the lactone and the unsaturated acid is faster than that of decarboxylation, the existing evidence appears to favor the paraconic acid mechanism.

Experimental Part[18]

The Potassium *t*-Butoxide-Catalyzed Condensation of Benzophenone, (a) with Diethyl Succinate.—To a cooled solution of 2.15 g. (0.055 mole) of potassium in 45 cc. of dry *t*-butyl alcohol was added 9.11 g. (0.05 mole) of benzophenone and 13.05 g. (0.075 mole) of diethyl succinate. The system was evacuated, filled with nitrogen, and protected from the atmosphere by a mercury trap. The mixture was allowed to reflux gently for thirty minutes, and after cooling was acidified with dilute hydrochloric acid. The *t*-butyl alcohol was removed at reduced pressure, water was added and the residue was extracted with ether. The ether solution was washed several times with 2% sodium hydroxide solution. Acidification of these alkaline solutions afforded 13.94 g. (90% yield) of almost colorless, crystalline β-carbethoxy-γ,γ-diphenylvinylacetic acid (I), m. p. 119–123° (not clear until 125°). A single recrystallization from benzene–petroleum ether (b. p. 60–68°) afforded practically pure half-ester, m. p. 125–126° (reported,[7] 124.5–125.5°). The neutral fraction was saponified with 45% potassium hydroxide to remove diethyl succinate. The unsaponifiable material solidified on cooling and seeding with benzophenone; weight 0.67 g. Crystallization from petroleum ether (b. p. 40–60°) gave material, m. p. 48–49°, undepressed on admixture with benzophenone.

In one experiment in which 4.0 g. of potassium, 12.5 g. of benzophenone and 11.9 g. of diethyl succinate were used, and the heating period was twelve hours, the yield of crude half-ester was 17.02 g. (80%), m. p. 85–108°. From the neutral fraction a total of 1.3 g. of benzhydrol, m. p. 64–65°, was isolated. The melting point was not depressed on admixture with an authentic specimen.

(b) **With Di-*t*-butyl Succinate.**[19]—A solution of 1.0 g. of potassium in 25 cc. of *t*-butyl alcohol was treated with 3.92 g. of benzophenone and 8.02 g. of di-*t*-butyl succinate[20]

(15) Fittig, Geissler and Frost, *Ann.*, **226**, 365 (1884).
(16) Stobbe, *ibid.*, **282**, 280 (1894).
(17) Richter-Anschutz, "Organic Chemistry," Nordemann Publishing Co., Inc., New York, N. Y., Vol. I, p. 612 (1934).
(18) All melting points are corrected.
(19) Carried out by Chester E. Davis.
(20) Prepared according to Backer and Homan, *Rec. trav. chim.*, **58**, 1048 (1939), from succinoyl chloride obtained by the method of Ruggli and Maeder, *Helv. Chim. Acta*, **26**, 1476 (1943).

(m. p. 35–37°) in 10 cc. of *t*-butyl alcohol. The general procedure described under *a* above was followed. When a heating period of one hour was used, the yield of colorless crystalline **β-carbo-*t*-butoxy-γ,γ-diphenylvinylacetic acid** after trituration with petroleum ether was 5.2 g., m. p. 164.5–165.5°. From the mother liquors an additional 0.65 g. of material melting at 143–153° was obtained making the total yield 80%. A sample purified for analysis by recrystallization from petroleum ether (b. p. 90–100°) was obtained as colorless blades, m. p. 167–168°.

Anal. Calcd. for $C_{21}H_{22}O_4$: C, 74.53; H, 6.55; N.E., 338.4. Found: C, 74.33; H, 6.76; N.E., 339.7.

When the heating period was reduced to one-half hour, the yield of half-ester was 63%. After twelve hours of heating the yield was 77%. No benzhydrol could be found in the neutral fractions, only benzophenone being isolated.

Decarbethoxylation of β-Carbethoxy-γ,γ-diphenylvinylacetic Acid.—A solution of 1.00 g. of the half-ester I (m. p. 120–124°) in 15 cc. of acetic acid, 10 cc. of 48% hydrobromic acid and 5 cc. of water was boiled under reflux until no more gas was being evolved (five hours). The solvent mixture was removed under reduced pressure, water was added and the residue extracted with ether. γ,γ-Diphenylvinylacetic acid (IV) was extracted from the ether solution with 5% potassium carbonate solution.[21] Acidification of the carbonate washings gave 0.56 g. (73% yield) of the acid IV, m. p. 115–116°. A sample purified by recrystallization from dilute alcohol melted at 117.5–118.5° (reported m. p. 114–115°[10]). The ether solution was washed with saturated salt solution and dried over anhydrous sodium sulfate. Evaporation yielded 0.25 g. of crude γ,γ-diphenylbutyrolactone, m. p. 82–87°, which after recrystallization from benzene–petroleum ether (b. p. 60–68°) amounted to 0.17 g. (22% yield); m. p. 90–91°. A sample was distilled at reduced pressure, b. p. 225–228° (14 mm.), and recrystallized as above; m. p. 90–91° (reported,[10] 92–93°).

Lactonization of γ,γ-Diphenylvinylacetic Acid.—A solution of 1.00 g. of the acid in 15 cc. of cold concentrated sulfuric acid was allowed to stand at room temperature for fifteen minutes, poured onto ice, and extracted with ether. The ether layer was washed with 5% potassium carbonate solution, dried over anhydrous sodium sulfate, and evaporated to give 0.95 g. (95% yield) of crystalline γ,γ-diphenylbutyrolactone, m. p. 87–90°.

γ-Methyl-γ-phenylbutyrolactone (VIa).—A mixture of 18.0 g. of acetophenone and 39.1 g. of diethyl succinate was added to a refluxing solution of 6.45 g. of potassium in 140 cc. of *t*-butyl alcohol. The heating was carried out in an atmosphere of nitrogen for forty minutes. The light orange solution was chilled, 14 cc. of concentrated hydrochloric acid in 100 cc. of water was added, and the *t*-butyl alcohol was removed at reduced pressure. The product was worked up in the customary way, and the oily half-ester (about 38 g.) was dissolved in 135 cc. of acetic acid, 90 cc. of 48% hydrobromic acid, and 45 cc. of water. After refluxing for seventeen hours, the solution was concentrated at reduced pressure, and the residue was extracted with ether. The acidic material which was separated from the ether solution by washing with saturated sodium bicarbonate solution, amounted to 14.73 g. of partially crystalline material. This was retreated with 68 cc. of acetic acid, 45 cc. of 48% hydrobromic acid and 22 cc. of water for twenty hours, and worked up as above. The acidic material remaining after this treatment amounted to only 0.81 g. of brown gummy material.[22]

The combined ether solutions of neutral material were washed with saturated salt solution and dried over anhydrous sodium sulfate. The residue obtained on evaporation of the ether was distilled and the fraction boiling at 140–145° (5 mm.) amounted to 22.41 g. (85% over-all yield) of almost colorless lactone. The reported boiling point is 145–147° (5 mm.),[13b] and 168–170° (16 mm.).[13a] A sample was redistilled at 117° (0.05 mm.); $n^{20}D$ 1.5315 (reported, $n^{32.5}D$ 1.5273[13b] and $n^{17.4}D$ 1.5300[13a]).

One gram of the lactone was warmed with 2% potassium hydroxide until solution was complete. Acidification gave 0.95 g. of γ-hydroxy-γ-phenylvaleric acid, m. p. 100–103°. After recrystallization from benzene–petroleum ether (b. p. 60–68°) the m. p. was 104–106° (reported,[13b] 106°).

γ-Ethyl-γ-phenylbutyrolactone (VIb).—The condensation was carried out as described in the preceding experiment, using 6.45 g. of potassium in 140 cc. of *t*-butyl alcohol, 20.10 g. of propiophenone and 39.1 g. of diethyl succinate. The oily half-ester (about 39 g.) decarbethoxylated even more slowly than that derived from acetophenone[22] and, after boiling with 135 cc. of acetic acid, 90 cc. of 48% hydrobromic acid and 45 cc. of water for eighteen hours, left considerable acidic material which, after two retreatments with proportionate amounts of reagents, amounted to 0.94 g. Distillation of the neutral products, isolated as before, gave 23.22 g. (82% yield) of lactone; b. p. 160–165° at 7 mm. (reported,[13b] 160° at 10 mm.). Redistillation gave material with the b. p. 135° (0.05 mm.); $n^{20}D$ 1.5283.

General Method of Decarboxylation.—The reaction mixture indicated in the table was charged into a round bottom flask attached by a ground glass joint to a small coil condenser which was connected with a 100-cc. mercury-filled gas buret through a three-way stopcock designed for evacuating and filling the system with nitrogen. Except for the diphenylitaconic acid experiments, the reaction mixture was heated (bath at 140°) in an atmosphere of nitrogen with the apparatus vented until condensing vapors reached the condenser coils, whereupon the rate of decarboxylation was determined by periodically ascertaining the gas then collected in the buret. When decarboxylation was rapid, some gas escaped during preliminary heating, but a minimum of 90% of the available gas was invariably collected. The mixture was finally concentrated at reduced pressure, treated with water and extracted with ether. The unsaturated acid was separated by extraction with dilute alkali (sodium carbonate, sodium bicarbonate and dilute ammonium hydroxide being used respectively for IV, X and XIV). Evaporation of the dried (over anhydrous potassium carbonate) ether solution gave the lactone, which was further purified in the case of XIII by trituration with hot (40–60°) petroleum ether, and in the case of IX by evaporative distillation at 0.05 mm.

Interpretation of Data.—In certain of the decarboxylation experiments, some of the hydrogen chloride was removed along with the evolving carbon dioxide resulting in a decrease in the rate of the equilibration step, an effect which was particularly noticeable in the dihydrophenanthrylsuccinic acid series. The results with the polycyclic compounds are further complicated in that the acids X and XIV both slowly undergo a secondary (irreversible) change, probably a disproportionation,[23] which resulted in a raising of the melting point of X and a lowering of that of XIV. Prolonged heating gave impure acidic fractions which on recrystallization gave a poor recovery of pure material; thus it was not possible to obtain the equilibration point with certainty in the dihydrophenanthrylsuccinic acid series with reagent B. An additional problem was encountered in the decarboxylations of XIa and XIb with reagent A in which the reactants and products were not completely soluble. The abnormally rapid rate at which the crude half-ester XIa (m. p. 142–148°) decarbethoxylated to give high yields of the unsaturated acid XIV may possibly be attributable to a higher solubility of the im-

(21) The acid IV is extracted only slowly with 5% sodium bicarbonate solution. A preliminary washing with this reagent affords a convenient means of separating small amounts of γ,γ-diphenylitaconic acid which is readily soluble and is sometimes present if decarboxylation is incomplete.

(22) Some studies now being carried out by A. Russell Jones on the decarbethoxylation of the Stobbe condensation product from methyl *p*-tolyl ketone indicate that the rate of reaction can be markedly increased by using a mixture containing a higher concentration of hydrobromic acid. Such a procedure might make it possible to reduce the reaction time in the present case.

(23) The susceptibility of X to disproportionation has already been noted (ref. 5).

TABLE I

SUMMARY OF DECARBOXYLATION AND EQUILIBRATION EXPERIMENTS

Substance treated	Amount, moles	Reagent[a]	Heating period, hours	Decarboxylation time,[b] hours	Lactone	% Yield	M. p., ° C.	Acid	% Yield	M. p., ° C.
Diphenylitaconic Acid Series										
II[c]	0.00354	C	1.5	2	III	30	87–90	IV	66	109–113[d]
II[c]	.00354	C	2	2	III	31	87–90	IV	62	111–115
II[c]	.00354	C	9	2	III	32	87–89.5	IV	65	111.5–116
II[c]	.00354	C	24	2	III	32	87.5–89.5	IV	66	110.5–115.5
III[e]	.00354	C	5	...	III	33	89–90	IV	63	111–115.5
IV[f]	.00354	C	5	...	III	33	87.5–89	IV	65	110–115
Dihydronaphthylsuccinic Acid Series										
VIIa[g]	.00183	A	4	4	IX	33	58–62	X	62	103–105
VIIa[g]	.00183	A	17	4	IX	30	42–53	X	62	102–109
VIIa[g]	.00183	A	24	4	IX	26	Oily	X	65	105–120[h]
VIIb[i]	.00183	A	0.5	0.5	IX	41	58–63	X	52	99–103
VIIb[i]	.00183	A	3	0.5	IX	35	55–60	X	60	98–103
IX[j]	.00183	A	2	...	IX	35	58–62	X	57	101–102
X[k]	.00183	A	2	...	IX	27	55–60	X	65	104–106
VIIa[g]	.00183	B	3.5	3.5	IX	33	57–61	X	63	99–101
VIIb[i]	.00183	B	0.5	0.5	IX	46	59–62	X	46	102–103
VIIb[i]	.00183	B	3.5	0.5	IX	27	55–58	X	65	98–101
IX[j]	.00183	B	2	...	IX	35	57–61	X	60	106–107
X[k]	.00183	B	2	...	IX	32	58–62	X	57	108–109
Dihydrophenanthrylsuccinic Acid Series										
XIa[l]	.00154	A	3.5	3.5	XIII	67	122–125	XIV	28, 21[m]	158–164, 176–179[m]
XIa[l]	.00154	A	24	3.5	XIII	10	110–120	XIV	85, 54[m]	148–160,[h] 169–173[m]
XIb[n]	.00154	A	0.4	0.5	XIII	62	123–125	XIV	32, 18[m]	150–167,[d] 175–178[m]
XIb[n]	.00154	A	3.5	0.5	XIII	40	124–126	XIV	55, 41[m]	165–173, 176–179[m]
XIa[o]	.00154	A	2	3.5	XIII	16	123–125	XIV	78	173–178
XIII[p]	.00154	A	1.5	...	XIII	4	118–122	XIV	95	181–183
XIV[q]	.00154	A	1.5	...	XIII	5	119–122	XIV	91	178–181
XIa[l]	.00154	B	4	4	XIII	70	125–126	XIV	23, 16[m]	155–167, 176–178[m]
XIb[n]	.00154	B	0.5	0.5	XIII	67	123–125	XIV	28, 21[m]	156–167, 176–178[m]
XIb[n]	.00154	B	4	0.5	XIII	39	125–126	XIV	53, 41[m]	170–176, 178–180[m]
XIII[p]	.00154	B	3	...	XIII	38	123–126	XIV	56, 49[m]	164–166, 180–183[m]
XIV[q]	.00154	B	3	...	XIII	22	125–126	XIV	76, 67[m]	176–178, 176–178[m]

[a] A: 3.5 cc. of acetic acid, 1.75 cc. of concentrated hydrochloric acid and 2.5 cc. of water. B: 5.0 cc. of acetic acid, 1.15 cc. of concentrated hydrochloric acid and 1.5 cc. of water. C: 15 cc. of acetic acid, 10 cc. of 48% hydrobromic acid and 5 cc. of water. [b] Approximate time required for liberation of 90–95% of theoretical amount of carbon dioxide. [c] Prepared by saponification of I; purified by one recrystallization from dilute alcohol; m. p. 172–173° (dec.). [d] Since decarboxylation was incomplete this product probably contained some starting material. [e] Purified by distillation and recrystallization as described above; m. p. 90–91°. [f] M. p. 117.5–118.5°. [g] Prepared as described in ref. 5; purified by recrystallization from dilute methanol; m. p. 89–90°. [h] Probably partly disproportionated (see "interpretation of data"). [i] Prepared by saponification of VIIa with barium hydroxide; purified by crystallization from aqueous methanol; m. p. 177–179° (dec.); see ref. 5. [j] Prepared by cyclization of X with hydrogen fluoride (ref. 5); purified by crystallization from ether–petroleum ether (b. p. 40–60°); m. p. 65–67°. [k] Prepared as described in ref. 5; purified by recrystallization from methanol; m. p. 105–107°. [l] Recrystallized from methanol; m. p. 147–149° (see ref. 6). [m] After recrystallization from benzene. [n] **3,4-Dihydro-1-phenanthrylsuccinic acid** prepared by saponification (two hours) of 6.4 g. of XIa with 12.8 g. of barium hydroxide octahydrate in 100 cc. of 50% alcohol; yield 5.6 g.; m. p. 203–205° (dec.). For decarboxylation experiment this was recrystallized once from dilute methanol; m. p. 207–208° (dec.). Repeated recrystallization gave colorless needles, m. p. 208–209° (dec.). *Anal.* Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.53; H, 5.22. [o] Crude half-ester, m. p. 142–148°. [p] Recrystallized from methanol; m. p. 125–126° (see ref. 6). [q] Recrystallized from benzene; m. p. 179–180° (see ref. 6).

pure over the purified half-ester. Results with impure samples, moreover, were not reproducible.[24]

(24) The procedure which was given for the preparation of XIV in ref. 6 is of this type. It now appears that in some instances this procedure may give significant amounts of the lactone XIII, which of course can be isomerized readily to XIV by methods given in the present paper.

Summary

The potassium *t*-butoxide-catalyzed Stobbe condensation of succinic ester has been studied with benzophenone, acetophenone and propiophenone. The acid-catalyzed decarbethoxylation of the resulting products, as well as those from the

Stobbe condensation with tetralone-1 and 1-keto-1,2,3,4-tetrahydrophenanthrene, has also been investigated. The γ-lactones and unsaturated acids thus produced were shown in three instances to be interconvertible in a true acid-catalyzed lacto-enoic tautomerism. In the polycyclic series the decarboxylation step proved to be faster than the tautomerism, making it possible to interrupt the process before equilibrium was reached, whereupon the lactone was always found in higher proportion than at equilibrium, suggesting that the lactone is the precursor of the unsaturated acid. This conclusion affords evidence in support of a hypothesis that paraconic acids are intermediates in the decarboxylation reaction.

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[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH, DIVISION OF ORGANIC CHEMISTRY]

Streptomycin. II.[1] Reduction and Oxidation Products of Streptomycin and of Streptobiosamine[2]

BY J. FRIED AND O. WINTERSTEINER

Recent investigations on the structure of streptomycin have shown that it is composed of a base, streptidine, $C_8H_{18}O_4N_6$ (I),[1,3,4,5] linked glycosidically to streptobiosamine, a nitrogen-containing bisaccharide of the formula $C_{13}H_{21-23}O_9N$ (II).[3] The glycosidic linkage between these two moieties is easily cleaved by hydrogen chloride in methanol with the formation of streptidine hydrochloride and methyl streptobiosaminide dimethyl acetal.[3] The characterization and degradation of streptidine has been carried out independently in several laboratories[1,3,5,6] and has led to its formulation as one of the eight possible *meso*-forms of 1,3-diguanido-2,4,5,6-tetrahydroxycyclohexane.[5,6]

One of the outstanding characteristics of streptomycin is its reactivity toward carbonyl reagents. The isolation of an amorphous oxime of streptomycin[3] and the ultraviolet absorption characteristics of streptomycin thiosemicarbazone and phenylhydrazone[7] leave little doubt that a free carbonyl group must be present in the streptobiosamine portion of the molecule. It is evidently this group which accounts for two of the three methoxyl groups in methyl streptobiosaminide dimethyl acetal, while the third methoxyl is introduced by methanolysis of the glycosidic linkage to streptidine. Methyl streptobiosaminide dimethyl acetal forms a crystalline tetraacetate, in which three of the acetyl groups are attached to oxygen and the fourth to nitrogen.[3]

On hydrolysis with strong mineral acid methyl streptobiosaminide dimethyl acetal is cleaved into its components, one of which was identified as N-methyl-L-glucosamine (III).[8] For the other, as yet unidentified, component of streptobiosamine, which must have the composition $C_6H_{8-10}O_5$(IV), we propose the term streptonose.[9] Direct evidence for the presence of a six-carbon moiety in streptomycin other than N-methyl-L-glucosamine and streptidine has been adduced by Schenck and Spielman,[10] who showed that exposure of streptomycin to the action of dilute cold alkali results in the formation of the γ-pyrone maltol (V). The striking ease with which this reaction proceeds is not without analogy in sugar chemistry. Thus, tetraacetyl glucosone hydrate (VI), as well as the corresponding galactose derivative are transformed into diacetylkojic acid (VII) by pyridine and acetic anhydride at 0°.[11] While there is little doubt that maltol arises from the streptonose moiety, no conclusions as to the structure of this sugar can be drawn from this observation, in view of the known tendency of some dicarbonyl sugars to undergo rearrangement in alkaline media.[12] Thus the positions of the carbonyl groups, the points of attachment of streptidine and N-methyl-L-glucosamine, and the functions of the remaining oxygen atoms are still unknown.

It was felt that some information regarding the structure of streptonose could be gained by ascertaining the nature of the free carbonyl group in streptomycin. The present paper deals with derivatives of streptomycin and streptobiosa-

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(2) Most of the material in this paper was presented before the Division of Biological Chemistry of the American Chemical Society at the Chicago meeting in September, 1946.

(3) N. G. Brink, F. A. Kuehl, Jr., and K. Folkers, *Science*, **102**, 506 (1945).

(4) H. E. Carter, R. K. Clark, Jr., S. R. Dickman, Y. H. Loo, J. S. Meek, P. S. Skell, W. A. Strong, J. T. Alberi, Q. R. Bartz, S. B. Binkley, H. M. Crooks, Jr., I. R. Hooper and M. C. Rebstock, *Science*, **103**, 53 (1946).

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(6) H. E. Carter, R. K. Clark, Jr., S. R. Dickman, Y. H. Loo, P. S. Skell and W. A. Strong, *Science*, **103**, 540 (1946).

(7) R. Donovick, G. Rake and J. Fried, *J. Biol. Chem.*, **164**, 173 (1946).

(8) F. A. Kuehl, Jr., E. H. Flynn, F. W. Holly, R. Mozingo and K. Folkers, THIS JOURNAL, **68**, 536 (1946).

(9) It will be clear from the following that streptonose contains an aldehyde group and at least one additional carbonyl group. This terminology is therefore in line with the customary designation of dicarbonyl sugars as onoses.

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(12) B. Helferich and N. M. Bigelow, *Z. physiol. Chem.*, **200**, 263 (1931).