NOTES

The Preparation of *t*-Butylmalonic Acid from Neopentyl Chloride

BY MILTON T. BUSH

The preparation of *t*-butylmalonic acid from *t*-butylacetic acid has been reported recently.[1] Previously an unsuccessful effort had been made to obtain this substance from neopentyl chloride by application of the method of Ivanov and Spassov,[2] who reported a 60% yield of phenylmalonic acid from benzylmagnesium chloride by carbonating this substance in the usual manner, treating the complex with ethylmagnesium bromide, and carbonating again. Familiarity with the properties of *t*-butylmalonic acid suggested certain modifications in the isolation procedure, and a second attempt to prepare the substance from neopentyl chloride was successful. Although the yield was only 5%, the method may be of sufficient interest to warrant description.

Experimental

The Grignard reagent from 8.88 g. of neopentyl chloride[3] was obtained in 120 ml. of ether under nitrogen, and treated with carbon dioxide below −5°, in the usual manner. Part of the ether (60 ml.) was distilled off in a stream of nitrogen. The reaction mixture was treated with 75 ml. of ethylmagnesium bromide in ether (1.64 molar), stirred and refluxed for half an hour, and allowed to stand at 20–25° for twenty-two hours. The solution was diluted with 40 ml. of ether, refluxed again for one and one-fifth hours, and finally carbonated at −10 to +4° during seven-tenths of an hour. The reaction mixture (a thick suspension of granular solid) was decomposed by the addition of 180 ml. of cold 3 molar sulfuric acid. The aqueous layer was extracted three times with 50-ml. portions of pure ether, and the ether solutions were combined and evaporated. The residual liquid (17 g.) dissolved almost completely in 100 ml. of petroleum ether. This solution was extracted with 20-ml. portions of water, each of which was extracted in turn with two equal volumes of ether. Evaporation of the combined ether extracts to dryness left white crystals of impure *t*-butylmalonic acid. In each case the evaporation (at 60°) of the last ml. of liquid appeared to involve removal of *n*-propionic acid. Four extractions of the petroleum ether solution gave, respectively, 700, 200, 60, and 17 mg. of the crude product. One recrystallization from ether–petroleum ether left 760 mg. (5.7% yield) of material having m. p. 153–156°. The malonic acid

was identified by converting it to *t*-butylmalon-N,N'-diethylamide, m. p. 151–152°. A mixed melting point with the specimen previously described[1] was the same.

By distillation of the petroleum ether solution remaining from the extractions there was obtained 3 g. (22% yield) of *t*-butylacetic acid. This was identified by conversion to the amide, m. p. 131–132°. A mixed melting point with an authentic specimen was the same.

DEPARTMENT OF PHARMACOLOGY
VANDERBILT UNIVERSITY SCHOOL OF MEDICINE
NASHVILLE, TENNESSEE   RECEIVED FEBRUARY 14, 1939

Composition of a Hydrated Double Salt of Nickel and Potassium Oxalates

BY STUART R. BRINKLEY, JR.

In a recent study of the system nickel oxalate, potassium oxalate and water at 30°, Vosburgh, Israel and Birch[1] demonstrated the formation of a double salt $K_2Ni(C_2O_4)_2 \cdot xH_2O$, but were unable to assign a definite value to the hydration number x. During the course of a similar study, the author prepared a sample of the double salt of sufficient purity to permit an exact determination of the number of molecules of water of crystallization. The preparation of the salt and its analysis were carried out as follows.

A large volume of solution was prepared with the composition 12.44% $K_2C_2O_4$ and 3.53% NiC_2O_4. Water was removed by placing the solution in a desiccator over calcium chloride. The temperature was maintained carefully at 30°. Crystals of the double salt were deposited slowly until the solution had the composition 23.1% $K_2C_2O_4$ and 3.1% NiC_2O_4. The crystals were then removed from the solution and quickly pressed between thick layers of filter paper. Three samples were immediately delivered into tared glass-stoppered bottles and weighed. The crystal size (*ca.* 1 mm.) allowed such efficient removal of the mother liquor that the samples lost only 0.3% of moisture upon being air-dried at room temperature. The solid resulting from the evaporation of this small amount of water was assumed to be double salt. The samples were then heated to constant weight at 120°, losing 18.6, 18.7 and 18.9% of water, respectively. The formula $K_2Ni(C_2O_4)_2 \cdot 4H_2O$ corresponds to

(1) Bush, THIS JOURNAL, **61**, 637 (1939). This malonic acid was first isolated by Buck and Hjort, *ibid.*, **59**, 2568 (1937).
(2) Ivanov and Spassov, *Bull. soc. chim.*, [4] **49**, 19–23 (1931).
(3) Supplied by the Mallinckrodt Chemical Works.

(1) Vosburgh, Israel and Birch. THIS JOURNAL, **58**, 2282 (1936).

18.7%, and this is submitted as the composition of the double salt.

STERLING CHEMISTRY LABORATORY
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NEW HAVEN, CONN.   RECEIVED FEBRUARY 27, 1939

Isolation of the Active Principle in Claviceps Paspali—A Progress Report[1]

BY MARVIN GIEGER AND B. F. BARRENTINE

Review of Literature.—According to Brown and Ranck,[2] *Paspalum dilatum* Poir, commonly known as Paspalum, or Large Water Grass, was found to contain a fungus poisonous to livestock. These workers found the fungus to be *Claviceps paspali* (Stevens and Hall). The fungus attacks the pistils and grows as a parasite until it occupies the space between the glumes of the spikelet. Thus, the disease grows where the seed are normally produced. This was proved by feeding the sclerotia, picked from infected paspalum heads, to guinea pigs, resulting in trembling and in some cases death to the guinea pig.

Work by Dr. W. F. Hand[3] corroborates the conclusions of Brown and Ranck that the poison comes from the *Claviceps* sclerotia. Dr. Hand's ether extract of the sclerotia gave an oily residue of which 5 to 10 ml. would kill a guinea pig when given by mouth. Upon discontinuation of the isolation of the poison by Dr. Hand, the work was later taken up by this department.

Experimental

Six hundred pounds (272 kg.) of scalpings or whole paspalum seed spikes infected with the Claviceps paspali was passed through a small slow speed hammer mill containing $^5/_{16}$-inch (8-mm.) holes in the sieve. The slow speed of the mill combined with the large holes in the screen enabled the seed to be broken apart from the fungus without pulverizing either. The seed and fungus mixture was then passed over a screen containing slits just large enough to allow the paspalum seed to pass through, as they are flat, but small enough to retain the round sclerotial. The mixture retained on the screen was about 90% sclerotia.

The sclerotia were then ground and extracted with petroleum naphtha (Skelly-solve F −95°) to remove most of the oil. After most of the oil was removed and the naphtha allowed to evaporate, the oil-free sclerotia were again extracted with one of several solvents to remove the

(1) Contribution from the Department of Chemistry, Mississippi Agricultural Experiment Station, State College, Mississippi. Published with the approval of the Acting Director, Mississippi Agricultural Experiment Station. Paper No. 9, New Series, December 29, 1938.

(2) H. B. Brown and E. M. Ranck, "Forage Poisoning Due to Claviceps on Paspalum," Tech. Bull. No. 6. Miss. Expt. Sta., 1915.

(3) W. F. Hand (unpublished notes).

poison: namely, ethyl ether, benzene, ethyl acetate. chloroform, ethyl alcohol, or methyl alcohol. The solvent was evaporated in vacuum leaving a sticky, tarry residue. This was further purified by taking up the residue with petroleum naphtha, which dissolved some of the impurities while at the same time precipitating a cream-colored amorphous precipitate containing the active principle. The precipitate was filtered, washed three or four times with petroleum naphtha, and on standing soon dried.

One gram of this amorphous compound was dissolved in 25 ml. of ethyl ether, the solution placed in an Erlenmeyer flask with 25 ml. of a 0.5% solution of tartaric acid, and agitated by an end-over-end motion in a shaking machine for one hour. These solutions were poured into a separatory funnel and after standing long enough to separate the aqueous tartaric acid solution was drawn off, rendered just alkaline to litmus with sodium bicarbonate and extracted with ether. The ether extract was evaporated to dryness in vacuum. The very small residue obtained gave a negative test for ergot alkaloids with Smith's[4] reagent.

The foregoing procedure was repeated, using ethyl acetate, benzene and chloroform as solvents for the amorphous compound and extracting separate solutions in each case with 0.5% aqueous solutions of tartaric, malic, citric, hydrochloric, nitric, and sulfuric acids. These acid extracts were rendered just alkaline with sodium bicarbonate and extracted with ether, the ether extract evaporated in vacuum and the residue tested with Smith's reagent for ergot alkaloids, all giving negative results.

The ether, chloroform, benzene, and ethyl acetate solutions above, after having been extracted with different weak acids, were washed with water to remove any acid and evaporated to dryness in vacuum. Thirty milligrams of each residue was given to guinea pigs. Each guinea pig was badly affected in about three hours' time with intense trembling, body drawn up in knot, and the pupil of the eye presenting a glossy appearance.

Numerous and varied attempts to purify the amorphous compounds further by crystallization have been without success and, due to this fact, attempts to determine any constants other than a melting point have been postponed. The melting point was approximately 130°. The compound is not soluble in water, but is very soluble in all other organic solvents, such as ether, chloroform, acetone, benzene, ethyl acetate, and ethyl and methyl alcohols. It is not soluble in weak acids, but slowly soluble in weak alkalies. It is very easily extracted from the fungus with liquid ammonia.[5] Qualitative tests show it to contain only carbon, hydrogen, oxygen, and nitrogen. Due to not being able to purify the amorphous compound, a quantitative determination of nitrogen only was made. The nitrogen was 2.5%. A water suspension of the amorphous powder containing a solution of a mixture of emulsion and maltase for hydrolyzing agents was allowed to incubate at 37° for fifteen hours. This was then tested for hydrocyanic acid and glucose, but none was found.

A study of the therapeutic value shows that a 1 to 1000 solution of the amorphous compound administered to the

(4) M. I. Smith, *Pub. Health Repts.*, **45**, 1466–1481 (1930).

(5) E. H. Stuart, U. S. Patent 2,067,866, 1937, to Eli Lilly & Co.,

isolated uterus of a rabbit and also a guinea pig failed to give a single contraction. Fifty milligrams was dissolved in Wesson oil and fed to a pregnant guinea pig. After a few hours the pig developed the characteristic tremble. The following day she was much worse and died the following night, but without aborting the foetus.

A post mortem showed the lungs filled with blood, congested. The heart was flabby or soft and blood coagulated. The kidneys were congested and filled with coagulated blood. The large intestine and stomach were filled with gas; the liver was soft, brownish in color and very tender. The adrenal was enlarged and the outside walls of the uterus were very congested and inflamed. Five embryos measured approximately 3 inches (7 cm.) in length from crown to rump. The union between placenta discs was lost and embryos fell out as soon as the uterus was opened. If administered to anesthetized cats, this amorphous compound caused a fall in blood pressure. It was estimated that one milligram of this material has a depressor action equivalent to 0.002 mg. of histamine hydrochloride. By intravenous injection in mice, the lethal dose of the amorphous compound was found to be 22.5 mg. per kg.

Discussion

It may be definitely concluded that the active constituent in this compound is not an ergot alkaloid, as the experimental data show the base could not be combined with a weak acid, nor did it respond to the alkaloidal test characteristic of the ergot alkaloids. Methods for the isolation of alkaloids of ergot of rye by Thompson,[6] Stuart,[5] Arthur Stoll and Ernst Burckhardt,[7] Smith, Sidney and Timmis,[8] Tswett perfected by Kuhn, Winterstein, and Karrer,[9] have been used in this work, but all were of no value thus far.

Hydrolysis with enzymes leads one to believe it is not a glucoside.

It was thought at one time the fungus contained the same alkaloids as ergot of wheat or rye, but the pharmacological data prove this to be an erroneous idea.

Acknowledgments.—The authors wish to acknowledge the helpful suggestions from Dr. W. F. Hand, State Chemist, and also the use of his unpublished notes on some preliminary work which he has done on the problem; the valuable assistance of M. J. Thomas, former associate in the Chemistry Department, in the laboratory work; the splendid coöperation of R. E. Lambert & Sons, Darlington, Alabama, in supplying us with paspalum scalpings from which we obtained the

(6) Marvin R. Thompson, *J. Am. Pharm. Assoc.*, **24**, Nos. 1–3 (1935).

(7) Arthur Stoll and Ernst Burckhardt. U. S. Patent 2,080,954.

(8) Sidney, Smith and G. M. Timmis, English Patent 460,387.

(9) M. Tswett perfected by R. Kuhn, A. Winterstein and P. Karrer, French patent, démandé le 9 janvier 1935, à 16h 25m. à Paris.

fungus; the Pharmacological tests made in the Lilly Research Laboratory under the direction of H. W. Rhodehamel; the post mortem of test animals by Dr. V. R. Berliner, Associate in Animal Husbandry, State College, Mississippi.

CHEMISTRY DEPARTMENT
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On the Hydration of Dihydropimaric Acid

BY TORSTEN HASSELSTROM AND BURT L. HAMPTON

In recent communications we described the formation of a lactone on hydration of dihydroabietic acid present in heat-treated rosin [Hasselstrom, U. S. Patents 2,121,032, 2,121,033 (1938); Hasselstrom, Brennan and McPherson. THIS JOURNAL, **60**, 1267 (1938); Hasselstrom and McPherson, *ibid.*, **60**, 2340 (1938)].

We have now been able to prepare a similar lactone by hydration of dihydropimaric acid, m. p. 241–243° (corr.), (α)D +19.2°, obtained on recrystallization of hydrogenated rosin (Staybellite A-2, by courtesy of the Hercules Powder Company) with methanol according to the procedure described in a previous paper [Hasselstrom and Bogert, THIS JOURNAL, **57**, 2118 (1935)]. The methyl ester of dihydropimaric acid was obtained by means of diazomethane, m. p. 78.5–79.5 (corr.). *Anal.* Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 78.8; H, 10.8. Ruzicka and Frank (*Helv. Chim. Acta*, **15**, 1297 (1932)] have recorded the melting point 79–80° for the methyl ester of the dihydropimaric acid.

A mixture of 3.5 g. of dihydropimaric acid and 40 cc. of sulfuric acid, sp. gr. 1.84, was stirred intermittently for about twenty minutes at 5°, then poured onto cracked ice. The mixture was extracted with ether, the ether solution washed with water, with dilute potassium hydroxide solution and with water. After drying with anhydrous sodium sulfate, the ether was evaporated and the residue, a yellow oil, was dissolved in hexane. On standing, 1.6 g. of white crystals separated which, after recrystallization from acetone, melted constantly at 143–144° (corr.). *Anal.* Calcd. for $C_{20}H_{32}O_2$: C, 78.9; H, 10.5. Found: C, 78.9; H, 10.6; (α)D −40° (in ethanol). In a mixed melting point test with an authentic sample of the lactone of hydroxytetrahydroabietic acid a depression was observed, the melting point of the mixture being 102–112° (corr.).

The lactone of the hydroxytetrahydropimaric acid was then saponified with a 10% solution of butyl alcoholic potassium hydroxide. After removal of the alcohol by steam distillation, the potassium salt of the hydroxy acid was dissolved in water and some unsaponified lactone removed by filtration. The alkali solution was made acid with dilute acetic acid and the product recrystallized from acetone, m. p. 143–144° (corr.). This product was insoluble in alkali and did not lower the melting point in the mixed melting point test with the original lactone, showing that the intermediately formed hydroxytetrahydropimaric acid had been transformed into the original lactone.

This investigation is being continued.

G. & A. Laboratories, Inc.
Savannah, Georgia   Received March 10, 1939

A Modification of Bettendorff's Arsenic Test. II. Catalyzed by Mercury[1]

By W. Bernard King and F. E. Brown

In a previous paper[2] the authors reported that traces of mercuric chloride hastened markedly the reduction of arsenic compounds with stannous chloride. They also found that the time required for the appearance and development of the arsenic suspension was a function of the concentration of mercuric chloride in the solution. This behavior was utilized to determine the concentration of mercuric chloride in concentrations as low as 2×10^{-8} molar mercuric chloride. The authors, following the example of other investigators, used the terms "inductor" and "its inductive effect" without questioning the correctness of these terms. In the following report, data are presented which show that the modified Bettendorff test is catalytic and not induced.

Reagents and Procedure

The Preparation of Mercurous and Mercuric Chloride Solutions of Identical Concentrations.—By means of a microbalance a few milligrams of mercurous chloride was weighed out, dissolved in concentrated hydrochloric acid and diluted with the same solvent until the solution was 9×10^{-7} molar. One hundred cubic centimeters of this solution was thoroughly saturated with chlorine gas which was passed through some of the same solvent before going into the sample. The chlorine was allowed to stand overnight in contact with the mercurous chloride solution, after which the excess was swept out completely by a cur-

(1) Original manuscript received May 9, 1938.
(2) King and Brown, *Ind. Eng. Chem., Anal. Ed.*, **5**, 168 (1933).

rent of hydrogen chloride gas. It required about two hours for the greenish yellow color of the chlorine to disappear. Another sample of this 9×10^{-7} molar mercurous chloride solution was then saturated with hydrogen chloride gas in order to have both the oxidized and nonoxidized portions at the same concentration of hydrogen chloride. The mercuric chloride solution, i. e., the oxidized portion, and the mercurous chloride solution, the non-oxidized portion, were then compared with regard to their catalytic effects.

The data reported were secured by the use of 50-cc. Nessler tubes. Two comparison tubes A and B were employed. The time at which a changing suspension becomes darker than an unchanging standard is more easily determined than the time at which reduction is complete. This required of course that the unchanging standard be less dense than the completely reduced experimental sample. The values obtained are shown in Table I. The times required to match the colors or densities of reference solutions A and B are expressed in minutes and seconds.

Table I

A Comparison between the Catalytic Effects of Mercurous and Mercuric Chloride Solutions of Identical Concentration

Tube	Cc. HgCl	Cc. HgCl₂	Cc. HCl	Cc. SnCl₂	Cc. As₂O₃	Time for reduction A	B
1	10	0	35.5	2.5	2	3:40	6:55
2	0	10	35.5	2.5	2	3:45	7:00
3	10	0	35.5	2.5	2	3:36	6:58
4	0	10	35.5	2.5	2	3:37	7:00
5	10	0	35.5	2.5	2	3:30	6:56
6	0	10	35.5	2.5	2	3:36	6:30
7	0	0	45.5	2.5	2	11:00	19:40

The concentration of the arsenious oxide solution was 0.001 M, of the stannous chloride approximately 8.0 M. Standard A consisted of completely reduced arsenious oxide in which the final concentration after dilution was 0.00001 M. Standard B had a final concentration which was double that of A.

The results show quite conclusively that mercuric and mercurous chloride solutions have equal catalytic power in the reduction of arsenic compounds with stannous chloride. They also suggest that the actual catalyst is the mercury atom formed by the reduction of the mercury salt.

Confirmation of the probability that free mercury was the catalytic agent, and not the mercury ions or its salts was established by a simple experiment. All that needed to be changed in the previous experiments was the order of adding the reagents. Instead of adding stannous chloride last, as had been the practice, it was added just after putting in the mercury salts, causing them to be reduced to free mercury. The arsenious oxide solution was added last. A glance at the values as shown in Table II shows that com-

pletely reduced mercury is just as effective as the salt itself.

TABLE II

A COMPARISON BETWEEN THE CATALYTIC EFFECTS OF MERCURIC CHLORIDE AND FREE MERCURY SOLUTIONS OF IDENTICAL CONCENTRATIONS

Tube	Cc. HgCl₂	Cc. HgCl₂ re- duced	Cc. As₂O₃	Cc. SnCl₂	Cc. HCl	Time for reduction A	B
1	15	0	2	2	31	4:30	8:55
2	0	15	2	2	31	4:14	8:50
3	10	0	2	2	36	5:34	10:22
4	0	10	2	2	36	5:12	10:28
5	5	0	2	2	41	6:58	12:55
6	0	5	2	2	41	6:44	12:30
7	1	0	2	2	45	10:10	18:30
8	0	1	2	2	45	10:08	18:40
0	0	0	2	2	46	12:20	19:40

Preliminary investigation of some other reactions which have been called induced reactions show that they are catalytic just as the modified Bettendorff test is catalytic. The investigation of these reactions will be continued.

CHEMICAL LABORATORY
IOWA STATE COLLEGE
AMES, IOWA　　　　　RECEIVED FEBRUARY 6, 1939

The Preparation of *m*-Bromophenol

BY C. FREDERICK KOELSCH

The usual procedure involved in the replacement of an aromatic amino group by an hydroxyl group consists in warming an aqueous solution of the corresponding diazonium salt. This procedure, however, when applied to the preparation of *m*-bromophenol is quite unsatisfactory,[1] and the suggestion recently has been made[2] that this phenol is best obtained from *m*-bromoaniline through *m*-bromobenzenediazonium borofluoride and *m*-bromophenylacetate, the over-all yield in this series of three reactions being approximately 37.5%.

In the patent literature[3] it has been reported that *m*-bromophenol and the other *m*-halogenophenols can be prepared "in nearly quantitative yields" from *m*-halogenoanilines by the choice of the proper conditions for the hydrolysis of the corresponding diazonium sulfates. It has been found in this Laboratory that this patent claim is substantially true; by following the procedure described below one can obtain good yields (75–80%) of *m*-bromophenol rapidly and with a minimum expenditure of labor.

(1) Diels and Bunzl, *Ber.*, **38**, 1486 (1905).
(2) Smith and Haller, THIS JOURNAL, **61**, 143 (1939).
(3) English Patent 200,714 (1922); *Chem. Zentr.*, **96**, II, 2297 (1925).

Experimental

m-Bromoaniline (50 g.) is dissolved by boiling in a mixture of water (400 ml.) and sulfuric acid (50 ml.). The solution is then cooled to 10° and diazotized by the addition of sodium nitrite (21 g.) dissolved in a small amount of water. The resulting diazonium salt solution is run in a thin stream during fifteen to thirty minutes into a boiling mixture of water (300 ml.) and sulfuric acid (100 ml.) contained in a flask fitted with a dropping funnel, a steam inlet tube reaching to the bottom of the flask, and an efficient condenser set for downward distillation. During the addition of the diazonium salt solution the acid solution is heated so that its volume remains constant, and steam is passed in at such a rate that at the end of the addition approximately 1 liter of distillate has been collected. Steam distillation is then continued until 2-liters of distillate has been collected. To this is added sodium chloride (150 g.), and the phenol is extracted with ether, using portions of 200, 100, and 100 ml. The ether is removed from the combined extracts and the product is distilled under reduced pressure.

Eight runs[4] of 50 g. each of *m*-bromoaniline gave 330 g. of crude *m*-bromophenol boiling at 100–140° (20–30 mm.). Redistillation gave 313 g. (77.8%) of *m*-bromophenol which boiled at 125–130° at 25 mm.

Treatment of this 313 g. of product with sodium hydroxide and methyl sulfate gave 285 g. of *m*-bromoanisole, b. p. 100° at 20 mm.

(4) The last five of the eight batches were steam distilled from the accumulating sulfuric acid and sodium sulfate solution whose volume was allowed to increase somewhat during the successive runs. No drop in yield resulted from this procedure.

SCHOOL OF CHEMISTRY
UNIVERSITY OF MINNESOTA
MINNEAPOLIS, MINNESOTA
　　　　　RECEIVED NOVEMBER 25, 1938

The Melting Point of Barium Molybdate

BY H. A. LIEBHAFSKY, E. G. ROCHOW AND A. F. WINSLOW

Barium molybdate, precipitated from an ammoniacal ammonium molybdate solution by adding aqueous barium chloride, washed until only a trace of chloride remained, charged into a platinum crucible that was placed in an electric furnace, then melted and cooled (7° per minute) in air, gave a cooling curve with a sharp break at 1480 ± 5° (platinum to platinum–10% rhodium thermocouple). This result confirms an earlier, less accurate, melting point determination, also made in air, in which an induction oil and an optical pyrometer were used. Attack of the platinum was absent or negligible, and there was no indication that the molybdate had been decomposed.

When melted in vacuum, the surface of the molybdate darkened, indicating partial decomposition, and some evaporation occurred; rough

observations show that its melting point in vacuum does not differ greatly from that in air.

RESEARCH LABORATORY
GENERAL ELECTRIC COMPANY
SCHENECTADY, NEW YORK   RECEIVED FEBRUARY 23, 1939

Study of the Reformatsky Reaction; Efficient Procedure for the Preparation of Bromoacetic Ester in Large Quantities

BY SAMUEL NATELSON AND SIDNEY P. GOTTFRIED

In the preparation of intermediates in certain synthetic studies, it was found necessary to prepare large quantities of the esters of dihydro- and tetrahydrophenylacetic acid. It was decided to proceed by means of the Reformatsky reaction.[1]

The procedures reported in the literature were repeated carefully. However, the yields were found to be poor and not suitable for the preparation of large quantities. A systematic study of the individual factors influencing the reaction was, therefore, initiated. Temperature, solvents, form of zinc or magnesium and methods of dehydration of the condensation product were studied. A procedure was developed wherein the reaction proceeds smoothly and gives good yields by controlling a few simple conditions.

The optimum temperature of the reaction mixture was found to be between 90–105°. At this temperature the reaction proceeds at a rapid rate, but not so rapidly as to become uncontrollable. The use of benzene alone as a solvent is not advisable except when the concentration of reactants is such as to raise the boiling point of the mixture to the required temperature. Numerous authors have employed conditions where a low boiling solvent or no solvent at all was used, but on checking their conditions we found that in the cases where the best yields were obtained the concentration of reactants was such as to give a temperature within the desirable range. A simple way of achieving and maintaining the desired temperature is to use as solvent, approximately a 1:1 mixture of benzene and toluene.

For best yield, smoothness of reaction, rapidity and convenience zinc is preferable to magnesium. The zinc used in the reaction should be in the form of zinc foil. This must be carefully scraped with sandpaper to cut through any impurities which may cover it. Cleaning the zinc by means of alkali is not recommended. The use of mossy zinc was found to be unsatisfactory, for it is not of

uniform thickness, difficult to clean and consequently uncertain in its reaction. Powdered zinc is not recommended for it is difficult to clean and hence occasionally the reaction is slow in starting. Once the reaction is started, it often becomes quite violent and is difficult to control. Copper–zinc couples have practically no advantage over zinc foil in our experience.

After the condensation product has been formed, and the zinc salt is hydrolyzed, it is sometimes a problem to dehydrate the resulting product. After trying numerous reagents such as potassium bisulfate, phosphorus pentoxide in various solvents, zinc chloride and sulfuric acid,[2] it was observed that the best method for obtaining good yields without decomposition is by the use of dry hydrogen chloride, hot or cold. The dehydration is usually quantitative. Numerous β-hydroxy esters can be dehydrated in this manner. Typical examples are the compounds obtained from the action of bromoacetic esters on cyclohexanones, the 1, 2 and 3-methylcyclohexanones, ethyl methyl ketone, methyl butyl ketone and 3,7-dimethyloctanal-1. In the terpene series a few cases were encountered where the dry hydrogen chloride polymerized the resultant product and was therefore of no use. In some cases, of course, it is not necessary to dehydrate the product formed, splitting out of water being spontaneous. An example of this type was encountered with the condensation of bromoacetic ester with methylcyclohexenone to form dihydroethylphenylacetate.[3]

An example of the recommended procedure is given below. These conditions have been applied by the authors and co-workers with consistent results to numerous aldehydes and ketones of various types. The yields rarely fall below 60% and are usually about 70%.

During these studies the authors had occasion to use large amounts of bromoacetic ester. A rapid and economical laboratory method for producing this compound in good yields was devised and is described herein. Acetic anhydride with pyridine makes an efficient catalyst for smooth bromination.
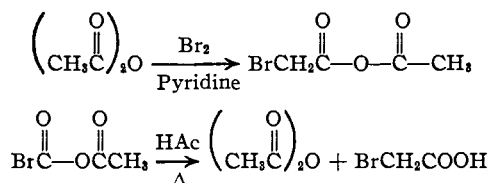
If the halogen carrier, pyridine, is omitted the bromination will take place, but the reaction here is from two to three times as long. Acetic an-

(1) Wallach, *Ann.*, **343**, 287 (1905); **365**, 261 (1909).

(2) Wallach and Salkind, *Ann.*, **314**, 153 (1901); Tetry, *Bull. soc. chim.*, [3], **27**, 600 (1902); DeFazi, *Gazz. chim. ital.*, [1], **45**, 555 (1915).

(3) Wallach, *Ann.*, **323**, 138 (1902).

hydride itself is readily brominated in the presence of pyridine. If glacial acetic acid is added subsequently and the reaction mixture is boiled, acetic anhydride is regenerated, liberating bromoacetic acid. The two products can then be separated by distillation. These observations would indicate that the reaction probably proceeds as follows:

$$\left(\underset{\substack{\|\\O}}{CH_3C}\right)_2 O \xrightarrow[\text{Pyridine}]{Br_2} \underset{\substack{\|\\O}}{BrCH_2C}-O-\underset{\substack{\|\\O}}{C}-CH_3$$

$$\underset{\substack{\|\\O}}{BrC}-\underset{\substack{\|\\O}}{OCCH_3} \xrightarrow[\Delta]{HAc} \left(\underset{\substack{\|\\O}}{CH_3C}\right)_2 O + BrCH_2COOH$$

Experimental

Bromoacetic Acid Ester.—The reaction is carried out in a hood. An all-glass outfit is advisable. If not available, one-hole asbestos stoppers may be made by soaking strips of asbestos in water, wrapping them around pieces of glass tubing of slightly less than the desired diameter, to the desired outer diameter, and allowing them to dry at 110°. A mixture of 1000 cc. of glacial acetic acid, 200 cc. of acetic anhydride and 1 cc. of pyridine is added to a 5-liter three-necked flask fitted with reflux condenser, drying tube and dropping funnel. The mixture is heated to boiling, the flame is removed and 1100 g. of bromine is dropped in at a rate designed to keep the mixture just refluxing. At the beginning there is a lag (ten minutes) before the reaction starts. The mixture clears up and decolorizes the bromine as rapidly as it is added. Toward the end the reaction slows up and the solution remains colored. Heat is then applied and the reaction mixture is refluxed until decolorized (one hour). The excess acetic anhydride and glacial acetic acid are now removed under slight vacuum (about 300 cc. recovered), 2 liters of 95% ethyl alcohol and 200 cc. of concentrated sulfuric acid (less may be used if absolute alcohol is used) is added to the residue. The mixture is refluxed for two hours and then poured into four liters of water. The bromoacetic ester is separated, dried over sodium sulfate and distilled: b. p. 159°; yield 785 g. of product boiling within 0.5°.

Reformatsky Reaction.—A mixture of 800 cc. of benzene and 700 cc. of toluene is made with 334 g. (2 moles) of bromoacetic ester and (2 moles) of the required ketone. Three hundred cc. of this mixture is added to a five-liter three-necked flask fitted with mechanical stirrer, condenser with drying tube and dropping funnel; 130 g. (2 moles) of zinc foil which has been scraped with sandpaper is cut up in strips and added to the flask. A few crystals of iodine are added and the stirrer is started. The mixture is heated by means of a boiling water-bath. A vigorous reaction sets in. The remainder of the reaction mixture is now added through the dropping funnel at a rate designed to keep the mixture refluxing but not too vigorously. After the addition is complete, stirring is continued for two hours more. Practically all the zinc dissolves. The mixture is cooled. The condensation product is decomposed with dilute sulfuric acid (sufficient to dissolve

all the zinc hydroxide). The benzene–toluene layer is separated, dried over sodium sulfate and vacuum distilled on a water-bath to remove the benzene and toluene. Through the residue heated on a boiling water-bath is passed dry hydrogen chloride for two hours. The material is vacuum distilled. The water which has split out comes over first and then the unsaturated ester; yield 60–70%. For tetrahydrophenylethyl acetate the yield is 238 g. (about 71%).

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BROOKLYN, NEW YORK   RECEIVED JANUARY 21, 1939

## Dehydration of Hydroxy Compounds by Pyrolysis of their Potassium Sulfate Esters; Cholesterilene and Camphene

BY SAMUEL NATELSON AND SIDNEY P. GOTTFRIED

While carrying out investigations on methods for the isolation of sterols from natural occurring sources,[1] it was observed that if anhydrous potassium cholesteryl sulfate is heated at 100° for an hour in a sealed tube or autoclave, complete decomposition takes place with the separation of a colorless oil which crystallizes on cooling. The crystals were readily identified as cholesterilene (3,5-cholestadiene), the yield being excellent. Potassium acid sulfate was split out yielding the unsaturated compound.

$$\underset{\substack{|\\|}}{-C}-\underset{\substack{|\\|}}{COSO_3K} \xrightarrow{\Delta} \; >C=C< \; + \; KHSO_4$$
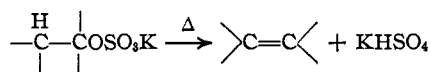
Since a method for preparing potassium cholesteryl sulfate in quantitative yields is described herein, this is by far the best method for preparing large amounts of cholesterilene.[2]

If water is present, the reaction takes another route, cholesterol being regenerated. This hydrolysis is catalyzed by small amounts of hydrogen ion.

$$ROSO_3K \xrightarrow[\text{HOH}]{\Delta} ROH + KHSO_4$$
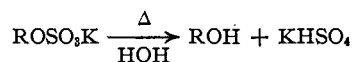
The ease with which the unsaturated compound is formed, encouraged us in the hope that this method might be applied as a general method for the dehydration of compounds where there existed danger of rearrangement. Potassium bornyl sulfate was therefore chosen as a test compound. It is well known that dehydration of borneol yields a variety of dehydration products and

(1) Natelson and Sobel, *J. Biol. Chem.*, **109**, 687 (1935); Natelson, Sobel and Kramer, *ibid.*, **105**, 763 (1934).
(2) Haltori, THIS JOURNAL, **60**, 3082 (1938); Bergmann, *J. Org. Chem.*, **1**, 567 (1937).

only the method of Tchugaev will give fair yields of bornylene.[3]

Anhydrous potassium bornyl sulfate is much more stable than potassium cholesteryl sulfate and only after heating to relatively high temperatures (200°) can decomposition be induced. Rearrangement does occur and the main product of the reaction is camphene in about 60% yield. If water is present borneol is regenerated readily before decomposition can set in.

Experimental

Potassium Cholesteryl Sulfate.—The procedure described herein is adapted from a method previously reported[4] for estimating small amounts of cholesterol as pyridine cholesteryl sulfate.

Pyridine sulfur trioxide is prepared by adding 100 g. (1 mole) of sulfur trioxide to 200 g. (excess) of pyridine dissolved in 300 cc. of chloroform, in an ice-bath. The almost quantitative yield of pyridine sulfur trioxide is filtered off under anhydrous conditions, washed with chloroform and dried in a sulfuric acid desiccator.

Twenty-five grams of cholesterol is added to 100 cc. of anhydrous benzene with mechanical stirring and cooling using an ice-bath. A mixture of 25 cc. of acetic anhydride and 25 cc. of pyridine is added, followed by 25 g. of pyridine sulfur trioxide (excess), with vigorous stirring. The pyridine cholesteryl sulfate separates almost immediately. The reaction mixture is heated to 50° for thirty minutes with continual stirring. The mixture is cooled, an equal volume of petroleum ether is added and the mixture filtered. The residue which consists of pyridine cholesteryl sulfate mixed with some excess pyridine sulfur trioxide is transferred to an Erlenmeyer flask and treated with 8 g. of potassium hydroxide in 80 cc. of water, shaking vigorously for about fifteen minutes. The insoluble potassium cholesteryl sulfate separates at the top and is filtered off, washed with water and then with several portions of boiling anhydrous methyl alcohol. The residue is now transferred to a vacuum desiccator where the last traces of solvent are removed: yield 30 g.; m. p. 212° (dec.). A small portion was crystallized from 70% methyl alcohol. Anal. Calcd. for $C_{27}H_{45}OSO_3K$: K, 7.74; S, 6.35. Found: K, 7.88; S, 6.56.

Potassium Bornyl Sulfate.—Prepared as for potassium cholesteryl sulfate. Potassium bornyl sulfate should be precipitated in and washed with a limited volume of water for it is very water soluble; m. p. 220° (dec.). Anal. Calcd. for $C_{10}H_{17}OSO_3K$: K, 14.34; S, 11.76. Found: K, 14.31; S, 11.80.

Cholesterilene.—Twenty-five grams of anhydrous potassium cholesteryl sulfate is placed in a sealed tube from which the air has been evacuated. The tube is placed in an oven at 100° for one hour. A colorless liquid separates from the potassium acid sulfate. The tube is allowed to cool and the crystallized cholesterylene is recrystallized

from alcohol: yield 14 g.; m. p. 79°. Anal. Calcd. for $C_{27}H_{44}$: C, 88.04; H, 11.96. Found: C, 87.74; H, 12.20.

Camphene.—Anhydrous potassium bornyl sulfate (100 g.) is placed in a distilling flask heated by means of an oil-bath. The temperature is raised to 200°. The salt decomposes and material begins to distill over. When no more distillate is obtained the distillate is fractionated. The main fraction distills from 158–162°, and crystallizes on cooling, m. p. 50°. Anal. Calcd. for $C_{10}H_{16}$: C, 88.23; H, 11.76. Found: C, 87.99; H, 11.90.

Cholesterol from Potassium Cholesteryl Sulfate.—Twenty-five grams of potassium cholesteryl sulfate is suspended in 100 cc. of water to which 1 drop of concd. sulfuric acid is added. The mixture is heated at 100° in a sealed tube or autoclave for one hour. The mixture is cooled, filtered and the residue is recrystallized from alcohol: yield 15 g.; m. p. 145°.

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The Preparation of Lead Tetraacetate

BY RALPH E. OESPER AND CLARA L. DEASY

Lead tetraacetate is usually prepared by warming red lead with acetic acid containing acetic anhydride sufficient to combine with the water formed[1]

$$Pb_3O_4 + 8HOAc \longrightarrow Pb(OAc)_4 + 2Pb(OAc)_2 + 4H_2O$$

Colson[1] (p. 891) found that a precipitate containing some tetraacetate is formed when chlorine is passed into a cold glacial acetic acid solution of lead diacetate

$$2Pb(OAc)_2 + Cl_2 \longrightarrow Pb(OAc)_4 + PbCl_2$$
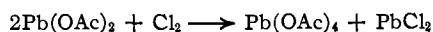
We have made a systematic study of these procedures, varying the temperature, time of reaction and proportions of the reactants, and have found that improved yields result when these procedures are combined. Purification of the acetic acid by distillation over permanganate and then over phosphorus pentoxide raises the yield, but not enough to make this extra precaution profitable. The acetic anhydride content must not be unduly increased, nor may the total volume of the acetic acid–anhydride mixture be too drastically diminished.

Procedure.—The reaction is best carried out in a three-necked flask fitted with a gas-inlet tube, a thermometer and a mechanically driven stirrer (seal unnecessary). A mixture of 600 ml. of glacial acetic acid and 150 ml. of acetic anhydride is heated to 65°, the stirrer is started and a not

(3) Tchugaev, J. Russ. Phys.-Chem. Soc., **36**, 1039; Chem. Centr., **76**, I, 94 (1905).

(4) Sobel, Drekter and Natelson, J. Biol. Chem., **115**, 381 (1936); Drekter, Sobel and Natelson, ibid., **115**, 391 (1936).

(1) Hutchinson and Pollard, J. Chem. Soc., **63**, 1136 (1893); **69**, 212 (1896); Dimroth, Friedemann and Kämmerer, Ber., **53**, 481 (1920); Dimroth and Schweizer, Ber., **56**, 1375 (1923); Ruff, "Die Chemie des Fluors," Verlag von Julius Springer, Berlin, 1920, p. 41; Colson, Compt. rend., **136**, 675 (1903); Hellmuth, Dissertation, Würzburg, 1930.

too rapid stream of dry chlorine led in. The red lead, 120 g. (dried at 150° for one to two hours) is introduced in five approximately equal portions, each addition being delayed until the color due to the previous portion has faded. The temperature is held at 65–80° throughout the reaction; higher temperatures decrease the yield. The reaction is complete in sixty to ninety minutes. The hot decolorized suspension is decanted promptly through a preheated filter. This filtrate, on cooling, will deposit about 65 g. of a material containing more than 90% tetraacetate.[2] The residual solid is returned from the filter to the reaction flask, and mechanically stirred for ten to fifteen minutes at 70–80° with 100 ml. of glacial acetic acid, or with a like volume of the cooled filtrate from a previous extraction. The hot suspension is decanted through a preheated filter, and the residue again extracted. About 33 g. of 90–95% tetraacetate is thus recovered, in addition to the original deposit, making a total yield of approximately 100 g. of high-grade tetraacetate. The contaminants (lead diacetate, lead chloride, acetic acid) ordinarily will not interfere in the use of the product. If pure tetraacetate is demanded, recrystallization from glacial acetic acid will serve, but the loss is considerable.

Dimroth and Schweizer reported a yield of 300–350 g. of crude tetraacetate from 600–650 g. of Pb_3O_4; Hellmuth claims 350 g. of purified product from this weight of red lead.[3] On a comparative basis our procedure yields a product containing approximately 500 g. of tetraacetate.

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(2) A typical sample contained 92.9% tetraacetate, 2.2% diacetate, 3.5% lead chloride, 1.4% acetic acid (by difference).

(3) Hellmuth's crude product contains 30–50% lead tetraacetate.

DEPARTMENT OF CHEMISTRY
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The Entropy of Ionization in Solutions of Low Dielectric Constant

BY ELIJAH SWIFT, JR.

In a recent publication,[1] Bent and Keevil have reported figures derived from the conductances of some organic compounds in ether which indicate that the entropy of ionization at the temperature under consideration may have the same value for a number of compounds. Unfortunately, as they pointed out, the data were too few to warrant any definite statement to that effect.

There have been reported recently[2] some measurements in the same solvent of the conductance of sodium triphenylmethyl, a compound of somewhat smaller molecular diameter than those used by Bent and Keevil. In this case, the temperature coefficient of the equivalent conductance was zero between 0 and 25° within experimental error. Calculating ΔH in the same manner as was done by Bent and Keevil, it is found to be equal

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(1) H. E. Bent and N. B. Keevil, THIS JOURNAL, **60**, 193 (1938).

(2) E. Swift, Jr., ibid., **60**, 1403 (1938).

to −3.1 kcal., while ΔF = −15.1 kcal. The resulting value of ΔS is −65.6 E. U., considerably higher than the values reported by Bent and Keevil for the compounds they studied (ΔS = −81, −83 E. U.), but in fair agreement with the value calculated for sodium triphenylboron by Bent and Coolidge,[3] i. e., −60 E. U. This indicates that a generalization about the constancy of ΔS in this solvent cannot be made, except perhaps in the case where the ions being compared are of about the same diameter.

(3) H. E. Bent and A. S. Coolidge, ibid., **58**, 505 (1936).

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Polymers of Propylene from Isopropyl Alcohol and Boron Trifluoride

BY FRANK C. WHITMORE AND J. F. LAUCIUS

Although the action of boron trifluoride as a polymerizing agent was first observed in 1873[1] more than five decades elapsed before its use was exploited to any extent. Otto[2] reported the polymerization of ethylene and propylene with boron trifluoride and since then more than a score
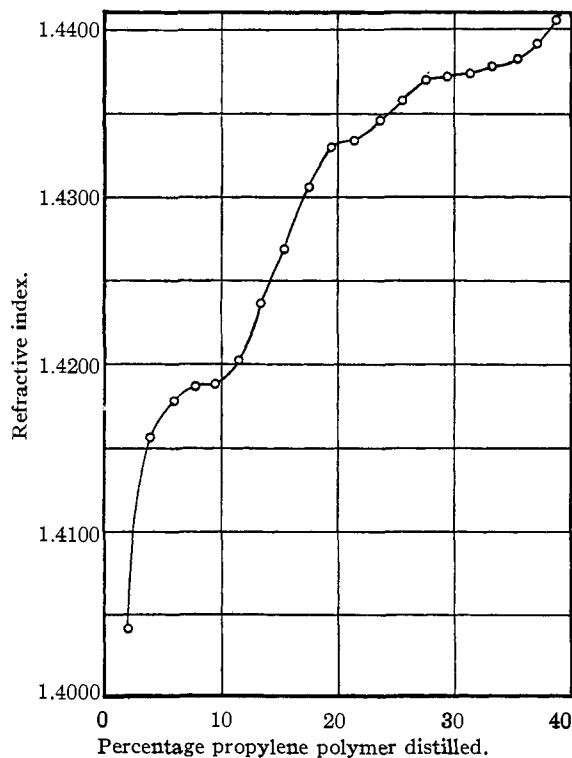

Fig. 1.

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(1) Butlerow and Gorianow, Ann., **169**, 147 (1873).

(2) Otto, Brennstoff-Chem., **8**, 321 (1927).

of patents on such polymerization of olefinic compounds have appeared. In continuing the theoretical studies[3] of olefin polymerization in this Laboratory, we have been led to investigate the action of boron trifluoride on alcohols, a type of reaction which has not been reported previously. This is of particular interest since this halide is believed to yield true polymerization products by its action on isobutylene at low temperatures.[4]

We have found that the action of boron trifluoride on isopropyl alcohol proceeds with the formation of polymerized products and from the reaction mixture we have isolated substantial yields of tetrapropylene.

Boron trifluoride (1400 g.) was dissolved in 2 kg. of isopropyl alcohol with external cooling and the resulting solution was heated in a loosely-

capped bomb at 100°. The reaction proceeded spontaneously with liberation of much boron trifluoride and other gases (propylene, the dimer, etc.). The contents of the bomb consisted of an upper layer of colorless polymer and a lower aqueous layer. The former was removed, washed free of acid, dried over anhydrous potassium carbonate and fractionated through a 12-plate distilling column of the type used in this Laboratory.[5] Figure 1 shows the course of the distillation. The tetrapropylene, b. p. 94–105° at 30 mm., $n^{20}D$ 1.4358–1.4406, is about 20% of the 1200 g. of polymer formed from two kilograms of isopropyl alcohol. Investigation of the products is in progress.

(3) Whitmore, *Ind. Eng. Chem.*, **26**, 94 (1934).
(4) I. G. Farbenindustrie, British Patent 401,297.
(5) Whitmore and Lux, THIS JOURNAL, **54**, 3448 (1932).

SCHOOL OF CHEMISTRY AND PHYSICS
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COMMUNICATIONS TO THE EDITOR

THE TOTAL SYNTHESIS OF THE SEX HORMONE EQUILENIN

Sir:

Although certain sex hormones such as estrone have been prepared from other naturally occurring compounds possessing similarities in structure, the total synthesis of none of them has yet been reported. We have now succeeded in accomplishing the total synthesis of the sex hormone equilenin, and in view of Marker's conversion of equilenin to estrone by reduction [THIS JOURNAL, **60**, 1897 (1938)] it follows that the total synthesis of both equilenin and estrone has been accomplished.

The reactions which were used are fairly obvious ones and the successful preparation of the hormone depended principally on developing the proper conditions for making the reactions proceed. As a matter of fact, some features of the method had been explored by other investigators without success. The starting point was the known 7-methoxy-1-keto-1,2,3,4-tetrahydrophenanthrene, prepared from 1-naphthylamine-6-sulfonic acid (Cleve's acid).

An eleven-step synthesis converted this compound to equilenin. First of all this ketone was

condensed with methyl oxalate to give a 1-keto-2-glyoxalate derivative which by elimination of carbon monoxide yielded 7-methoxy-1-keto-2-carbomethoxytetrahydrophenanthrene. As early as 1932 Haworth [*J. Chem. Soc.*, 1125 (1932)] prepared the corresponding ethyl glyoxalate from 1-keto-tetrahydrophenanthrene but was unable to eliminate carbon monoxide without decomposing the compound. Under the proper conditions we were able to obtain the 2-carbomethoxy ketone in 89–91% yields. This compound readily was converted to the important intermediate, 7-methoxy - 1 - keto - 2 - methyl - 2 - carbomethoxytetrahydrophenanthrene (m. p. 84.5–86°) in excellent yield. From this point more or less standard procedures were employed to build up the five-membered ring. The Reformatsky reaction followed by dehydration and reduction of the unsaturated acid served to introduce an acetic acid group in the 1-position. As was expected, the product consisted of two racemic mixtures. These readily were separated into the cis (m. p. 228–230°) and the trans (m. p. 208–210°) 7-methoxy - 1 - acetic acid - 2 - methyl - 2 - carboxytetrahydrophenanthrene. Each of the acids was car-