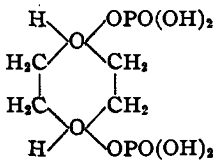
NOTES

Dioxane Diphosphate

By Erich Baer

Dioxane readily forms coördination compounds with several types of organic and inorganic substances. The oxonium salts of sulfuric acid[1] and perchloric acid[2] for example are well known. A phosphate, however, has not been described.[3] In the following the preparation and some of the properties of dioxane diphosphate[4] (I) are reported.


I

Experimental

The dioxane diphosphate (I) is easily obtained in good yields from an 88% aqueous solution of orthophosphoric acid by any one of the following three procedures. (a) Dioxane (one mole) and phosphoric acid (two moles) are mixed and crystallization is induced. The temperature of the mixture rises immediately to approximately 60°. To increase the yield of dioxane diphosphate the mixture is cooled. (b) Dioxane and phosphoric acid in separate containers are kept in a vessel under reduced pressure and at room temperature. The evaporating dioxane is absorbed by phosphoric acid and dioxane diphosphate precipitates. Any excess of absorbed dioxane, which decreases the yield of diphosphate,[5] can be readily removed *in vacuo*. (c) A dry current of air saturated with dioxane at 85° is bubbled through phosphoric acid kept at 100 to 120° until an excess of dioxane has passed into the reaction mixture. The product on cooling thickens to a crystalline sludge.

To isolate the very hygroscopic dioxane diphosphate from the crude reaction mixture obtained by any one of the above methods, the mother liquor is removed either by spreading the thick paste on porous clay plates in a desiccator or by filtering with suction using the rubber sheet technique.[6] The product is dried in a high vacuum over sodium hydroxide. The oxonium salt crystallizes in prisms and is obtained in yields as high as 84%; m. p. 83–87°[7] (sintering at 78°). A recrystallization from ether (10 g. of substance in 20 cc. of dry ether at −60°) does not change this melting point. The diphosphate is readily soluble at 25° in several solvents: water (giving a strongly acid solution), ethyl alcohol, *n*-butyl alcohol, cyclohexanol, benzyl alcohol, acetone, cyclohexanone, acetic acid, ether, dioxane, glycol dimethyl ether, ethyl acetate, trimethyl phosphate, and very slightly soluble or insoluble in benzene, cyclohexane, petrol ether, chloroform and bromoform. Dioxane diphosphate is unstable in water. Its aqueous solution gives all the usual reactions of phosphoric acid and loses dioxane on concentration. The dissociation of the molecular compound in organic solvents has not yet been investigated. *Anal.* Calcd. $C_4H_{14}O_{10}P_2$ (284): C, 16.9; H, 4.93; P, 21.82. Found: C, 16.9; H, 4.84; P, 21.80.

Dioxane diphosphate when kept dry is stable at room temperature. It remains apparently unchanged when heated for a short time in a glass vessel to 150°. Above 175° the substance rapidly turns dark brown and gives off fumes which when condensed form a colorless liquid. This distillate consisting mainly of dioxane [b. p. (756 mm.) 100°, n^{25}D 1.4190] also contains an appreciable amount of acetaldehyde[8] [2,4-dinitrophenylhydrazone m. p. 147°,[9] from chloroform]. If a dry mixture of one mole of dioxane diphosphate with either 2.2 moles of Na_2HPO_4[10] or 1.1 mole of K_3PO_4[10] or 1.1 mole of anhydrous Na_3PO_4[10] is heated in an oil-bath to approximately 120 to 130° dioxane distils over in almost the theoretical yield. After redistilling the dioxane over metallic sodium, its refractive index and boiling point are n^{26}D 1.4190, b. p. (751 mm.) 99.5–100.5°. The readily obtainable molecular compound should prove to be a valuable intermediate for the purification of dioxane.

Dioxane diphosphate, which is soluble in many organic liquids, may perhaps be used as a substitute for crystalline phosphoric acid, when a dry solution of phosphoric acid in an organic solvent is required.

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[1] A. Faworski, *J. Russ. Phys.-Chem. Soc.*, **38**, 741 (1906).

[2] C. Smeets, *Natuurw. Tijdschr.*, **19**, 12 (1937).

[3] In spite of an intensive search of the literature no record of the substance could be found. A coördination compound of dioxane with a substituted phosphoric acid, the dioxanate of dimeric glyceraldehyde-1-bromide-3-phosphate has been used successfully where other methods failed to obtain this phosphate in an analytically pure state (Baer and Fischer, *J. Biol. Chem.*, **150**, 226 (1943).

[4] Patent applied for.

[5] Dioxane diphosphate is readily soluble in dioxane.

[6] L. F. Fieser, "Experiments in Organic Chemistry," 2d. ed., 1941, p. 321.

[7] The melting point was taken in a sealed tube. According to Kelley and McCusker (This Journal, **65**, 1307 (1943)) an unsharp melting point seems to be normal for a molecular compound containing a volatile component.

[8] The distillation of dioxane with a small amount of sulfuric acid yields dioxane containing acetaldehyde (Faworski, *loc. cit.*).

[9] Purgotti, reports a m. p. of 147° for acetaldehyde 2,4-dinitrophenylhydrazone, *Gazz. chim. ital.*, **24**, I, 565 (1894).

[10] A slight excess over the amount which is needed to convert all phosphoric acid into NaH_2PO_4 or KH_2PO_4.

Banting Institute
Department of Chemistry
University of Toronto
Toronto, Canada

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The Preparation of Certain Phenolic Esters[1]

By Erwin Baumgarten, Howard G. Walker and Charles R. Hauser

Phenolic esters have been prepared from the sodium salt of the phenol in aqueous solution and the acid anhydride,[2] from the phenol and anhydride in the presence of the sodium salt of the acid from which the anhydride is derived,[3] and from the phenol and acid chloride in the presence of pyridine with[4] or without[5] an inert solvent. For the preparation of the rather large quantities of certain phenolic esters required in another investigation, the method involving the acylation of the phenol with the acid chloride in pyridine

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[1] This work was supported by a grant from the Duke University Research Council.

[2] Chattaway, *J. Chem. Soc.*, 2495 (1931); Abramovitch and Hauser, This Journal, **64**, 2271 (1942).

[3] Hazlet and Kornberg, *ibid.*, **61**, 3037 (1939).

[4] Hazlet, Hensley and Jass, *ibid.*, **64**, 2449 (1942).

[5] Einhorn and Hollandt, *Ann.*, **301**, 95 (1898); Reichstein, *Helv. chim. acta*, **9**, 800 (1926).

has been found very satisfactory. By this method three new phenolic esters have been prepared on a one to three mole scale.

Ethyl 4-Phenylphenyl Carbonate.—To a solution of 510 g. (3 moles) of 4-phenylphenol in 720 ml. of pyridine (dried over potassium hydroxide pellets) in a 2-liter reaction flask, carrying a reflux condenser, dropping funnel and mercury-sealed "Hershberg" stirrer, there was added, with stirring at 0°, over a period of 30 minutes, 365 g. (3.4 moles) of ethyl chlorocarbonate. A bulky precipitate formed. Stirring was continued for thirty minutes after addition was complete. The reaction mixture was stirred to a paste with 500 ml. of water and filtered under suction; the precipitate was washed with three 200-ml. portions of ice-water prior to fusion *in vacuo*. The fused material was recrystallized from 800 ml. of 95% ethanol. There was obtained 430 g. (60%) of ethyl 4-phenylphenyl carbonate, m. p. 73.2–74.3°. A sample, recrystallized repeatedly from methanol, melted at 73.9–75.0°.

Anal.[6] Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 73.90; H, 5.88.

4-Phenylphenyl Isobutyrate.—The acylation of 255 g. (1.5 moles) of 4-phenylphenol in 360 ml. of pyridine by means of 180 g. (1.7 moles) of isobutyryl chloride as described for ethyl 4-phenylphenyl carbonate gave 294 g. (82%) of 4-phenylphenyl isobutyrate, m. p. 73.2–74.8°. A sample, recrystallized repeatedly from methanol, melted at 74.2–74.8°.

Anal.[6] Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.53; H, 6.80.

Phenyl Isobutyrate.—A solution of 94 g. (1 mole) of phenol in 240 ml. of pyridine was acylated by means of 128 g. (1.2 moles) of isobutyryl chloride essentially as described above. After reaction was complete, the mixture was diluted with water and ether to produce two clear phases. The aqueous phase was extracted with ether and the combined ether phases were dried over anhydrous sodium sulfate followed by "Drierite." After removal of the solvent at atmospheric pressure, the residue was distilled through an eight-inch Vigreux column. Fractions boiling at 60–110° (55 g.) and 110–112° (131 g.) were obtained. The lower boiling fraction was distilled up to 105° at 25 mm. and the residue combined with the fraction boiling at 110–112°. Distillation of the mixture gave 4 g. of a fore-run, b. p. 105–111° at 25.5 mm., and 144 g. (87%) of phenyl isobutyrate, b. p. 111–112.2° at 25.5 mm. A mid-fraction (b. p. 112° at 25.5 mm., const.) was analyzed.

Anal.[6] Calcd. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 72.84; H, 7.32.

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[6] Analysis by T. S. Ma, University of Chicago, Chicago, Illinois.

DEPARTMENT OF CHEMISTRY
DUKE UNIVERSITY
DURHAM, NORTH CAROLINA

RECEIVED DECEMBER 6, 1943

The Preparation of 1- and 2-Phenylpyrrole

BY F. F. BLICKE AND J. L. POWERS

Recently we have been able to synthesize relatively large quantities of 1- and 2-phenylpyrrole by means of the procedures reported below.[1]

The apparatus used for the preparation of 1-phenylpyrrole consisted of two round, cast-iron shells with flanges which were clamped together by means of eight short bolts fitted with wing nuts (only two bolts are shown in the drawing); several "cranite" asbestos gaskets placed between the shells prevented leakage.[2] Each of the shells was sixteen inches in diameter and three inches high at the point at which the pipe was attached. Two iron pipes, one inch in diameter, were screwed into the shells as shown in the diagram. The upper, outlet pipe was attached by rubber tubing to a Pyrex glass tube (combustion type) about six feet long which served as a condenser. At the beginning of the process it was found necessary to cool the condenser with wet cloths, but during the end of the operation it was essential, in some instances, to warm the glass tube with a flame to prevent the condensed material from clogging the tube.

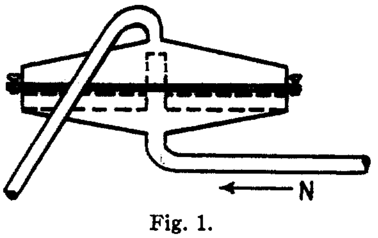

Fig. 1.

The mucic acid salt was placed in a shallow galvanized iron tray. A short, metal tube had been inserted through the center of the tray in order that a stream of nitrogen could be passed through the apparatus.

The apparatus was supported on a tripod, and heated from below with eight Meker burners. Since it was found that rubber tubing attached to the burners melted in a short time, due to the intense heat, it was necessary to unscrew the side arms from the burners and replace them with threaded iron pipes about eighteen inches long.

The upper shell of the apparatus was covered with several removable layers of heavy asbestos, and the whole apparatus was surrounded with a large sheet of the same material.

1-Phenylpyrrole.—In order to prepare the required aniline salt of mucic acid, an intimate mixture of 1116 g. of aniline and 1260 g. of mucic acid was placed in a large evaporating dish, 60 cc. of water added, and the mixture stirred and heated on a steam-bath until it became solid. The material was then pulverized and air-dried.

The salt (396 g.) was placed in the apparatus and the distillate was collected in a 2-liter, round-bottomed flask which contained 110 cc. of concd. hydrochloric acid and 400 cc. of water. The aniline dissolved and the insoluble pyrrole was obtained as a brown, crystalline material. After one-half hour the reaction was complete. The crude material was subjected to steam distillation. The phenylpyrrole separated in the distillate in the form of colorless crystals while a tarry residue remained in the distillation flask. The average yield was 60 g. (42%). The product melted at 58°,[3] and boiled at 230–234°.

2-Phenylpyrrole.—A five-foot length of Pyrex combustion tubing was bent, twenty inches from one end, at a 75° angle, and placed in a combustion furnace. To facilitate the flow of the product through the tube, one end of the furnace was raised about two inches above the level of the laboratory table. Fifty grams of 1-phenylpyrrole were put into a 125-cc. distillation flask in which the usual side arm had been replaced by another 10 cm. long and 9 mm. in thickness, sealed close to the bulb and fitted to the tube by a cork. The tube was heated to a dull red heat, and the pyrrole was distilled through the tube at such a rate that about thirty minutes were required to empty the distillation flask. Since the rearrangement was not complete, the product was distilled through the hot tube two more times.

The material was fractionated, and the recovered 1-phenylpyrrole was subjected to the rearrangement process. From 200 g. of 1-phenylpyrrole there was produced 127 g. (63%) of 2-phenylpyrrole; b. p. 272–278°.[4] A completely colorless product could be obtained only by distillation under reduced pressure; b. p. 151–154° (5 mm.).

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[1] Other methods described during the last few years are those of Allen, Gilbert and Young (*J. Org. Chem.*, **2**, 230 (1937)) and of Adkins and Coonradt (THIS JOURNAL, **63**, 1566 (1941)).

[2] When new gaskets are used, the bolts must be tightened again after the apparatus has become hot.

[3] Köttnitz (*J. prakt. Chem.*, [2] **6**, 148 (1873)) found 62°.

[4] Pictet and Crépieux (*Ber.*, **28**, 1905 (1895)) found 271–272°.

But even this material soon turned pink when exposed to air. However, after several recrystallizations of the vacuum-distilled product from 70% alcohol the pyrrole was obtained in a form which remained colorless; m. p. 128–129°.[5]

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(5) The melting point has been reported to be 129° (ref. 4).

College of Pharmacy
University of Michigan
Ann Arbor, Michigan
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Reactions of *t*-Butyl Cinnamate and *t*-Butyl Benzoate with Phenylmagnesium Bromide[1]

By Fred Frostick, Erwin Baumgarten and Charles R. Hauser

Kohler and Heritage[2] showed that methyl cinnamate undergoes both 1,2- and 1,4-addition with phenylmagnesium bromide yielding a mixture of products. We have found that *t*-butyl cinnamate (in which the carbonyl group is relatively hindered) undergoes apparently only 1,4-addition yielding *t*-butyl β,β-diphenylpropionate.

$$C_6H_5CH{=}CHCOOC(CH_3)_3 \xrightarrow{C_6H_5MgBr} (C_6H_5)_2CHCH_2COOC(CH_3)_3$$

To a stirred solution of phenylmagnesium bromide, prepared from 5.6 g. (0.23 mole) of magnesium and 46.1 g. (0.23 mole) of bromobenzene in 100 ml. of dry ether, was added during twenty minutes 23.5 g. (0.115 mole) of *t*-butyl cinnamate.[3] The reaction mixture refluxed gently and a precipitate formed. After refluxing for three hours, the mixture was poured into an ice-cold saturated ammonium chloride solution. The ether layer was shaken with cold 10% sulfuric acid, and then with cold 5% potassium hydroxide solution. After drying with anhydrous sodium sulfate followed by "Drierite," the solvent was distilled, finally using the water aspirator. The solid residue (29.5 g.) was recrystallized from petroleum ether (b. p. 30–60°), yielding 15 g. (44%) of essentially pure *t*-butyl β,β-diphenylpropionate. Four recrystallizations yielded a product melting at 55.5–55.6°.

Anal.[4] Calcd. for $C_{19}H_{22}O_2$: C, 80.85; H, 7.86. Found: C, 80.93; H, 7.60.

The product was further identified by hydrolysis in the presence of concentrated hydrochloric acid to β,β-diphenylpropionic acid, which, after recrystallization from acetone–water mixture, melted at 152–154° (reported, 155°).[5]

Analogous to methyl or ethyl benzoate, *t*-butyl benzoate has been found to undergo the "normal" carbonyl addition reaction with phenylmagnesium bromide, yielding triphenylcarbinol. Some benzoic acid (which might have resulted from hydrolysis of the ester) was also isolated. Neither isobutene nor *t*-butylbenzene was found; these products would have resulted had the elimination or substitution reaction occurred.

To a stirred solution of phenylmagnesium bromide (prepared from 0.5 mole each of magnesium and bromobenzene in 150 ml. of ether), contained in a reaction flask equipped with a U-tube immersed in a dry ice-bath, was added during one-half hour 0.3 mole of *t*-butyl benzoate[6] in 100 ml. of ether. After standing overnight the reaction mixture was refluxed for five hours. The liquid condensed in the U-tube did not absorb an appreciable amount of bromine in carbon tetrachloride solution, indicating that no significant amount of isobutene was formed. After decomposition of the reaction mixture with ammonium chloride, the ether solution was shaken with bicarbonate (from which was isolated a 10% yield of benzoic acid), dried and the solvent distilled. The residue was subjected to steam distillation until oily material (containing diphenyl but apparently no *t*-butylbenzene) ceased to pass over, and then recrystallized from alcohol, yielding triphenylcarbinol (41%), m. p. 159–162°.

In a similar experiment, carried out with *t*-butyl benzoate and methylmagnesium iodide, no isobutene appeared to be formed.

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(1) This work was supported by a grant from the Duke University Research Council.

(2) Kohler and Heritage, *Am. Chem. J.*, **33**, 21 (1905); see also Allen and Blatt in "Organic Chemistry," Gilman, Editor-in-Chief, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 681.

(3) Abramovitch, Shivers, Hudson and Hauser, This Journal, **65**, 986 (1943).

(4) Analysis by T. S. Ma, University of Chicago, Chicago, Illinois.

(5) Bacon, *Am. Chem. J.*, **33**, 84 (1905).

(6) Norris and Rigby, This Journal, **54**, 2097 (1932).

Department of Chemistry
Duke University
Durham, North Carolina
Received December 6, 1943

Nature of Carotenes in Alfalfa

By A. R. Kemmerer and G. S. Fraps

According to Beadle and Zscheile,[1] spinach and some other plants contain appreciable amounts of "neo-β-carotene," stereoisomer of β-carotene, which can be produced by heating β-carotene in petroleum ether. This pigment is the same as that termed pseudo-α-carotene by Gillam and El Ridi,[2] and neo-β-carotene B, by Polgár and Zechmeister.[3] Kemmerer and Fraps,[4] by chromatographic analysis with calcium hydroxide, found, besides β-carotene and this "neo-β-carotene" in plants, another pigment which they termed "carotenoid X." "Carotenoid X" did not possess vitamin A potency, while "neo-β-carotene" had one-half the potency of β-carotene. Polgár and Zechmeister,[4] by various treatments of β-carotene, secured about twelve neo-β-carotenes including neo-β-carotenes B and U. Since the identification of the carotenes in plants is of both practical and scientific importance, both the "neo-β-carotene" and "carotenoid X" in alfalfa were studied.

Neo-β-carotene B was prepared by refluxing a solution of 20 mg. of crystalline carotene in 100 ml. of hexane for one hour.[4] The solution was chromatographed on calcium hydroxide and the neo-β-carotene B was separated and extracted. Then it was purified by another chromatographic treatment. This pigment is just below the β-carotene band in the chromatogram. Neo-β-carotene U was prepared by dissolving about 10 mg. of crystalline carotene in petroleum naphtha (Skellysolve F), adding a small crystal of iodine, and allowing the solution to stand an hour.[4] The neo-β-carotene U was separated and purified by absorption on calcium hydroxide. The neo-β-carotene U is just above the β-carotene in the chromatogram.

"Carotenoid X" and "neo-β-carotene" were prepared from alfalfa leaf meal by extraction with alcholic potassium hydroxide and petroleum naphtha (Skellysolve F) and chromatographic separation on calcium hydroxide.[3]

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(1) B. W. Beadle and F. P. Zscheile, *J. Biol. Chem.*, **144**, 21 (1942).

(2) A. E. Gillam and M. S. El Ridi, *Biochem. J.*, **30**, 1735 (1936).

(3) A. Polgár and L. Zechmeister, This Journal, **64**, 1856 (1942).

(4) A. R. Kemmerer and G. S. Fraps, *Ind. Eng. Chem., Anal. Ed.*, **15**, 714 (1943).

Solutions of neo-β-carotene U and "carotenoid X" were mixed and subjected to chromatographic analysis on calcium hydroxide. There was no separation of bands, showing that the two pigments were identical. By a similar experiment neo-β-carotene B and "neo-β-carotene" from alfalfa were found to be identical.

Direct comparisons of the absorption of light by the preparations were made by means of a quartz spectrograph. In petroleum naphtha (Skellysolve F) solutions, photographed at different settings of the photometer, "carotenoid X" and neo-β-carotene U both had absorption maxima at 468 and 443 mμ; "neo-β-carotene" from alfalfa and neo-β-carotene B likewise had the same absorption curve with maxima at 473 and 446 mμ.

The pigments were also compared by dissolving approximately equal quantities in hexane, treating with iodine and analyzing the product by chromatographic separation on calcium hydroxide. The colorimetric ratio of the pigments formed from neo-β-carotene U was, unknown pigment: neo-β-carotene U: β-carotene: neo-β-carotene B: neo-β-carotene E = 2:22:42:29:5 and from "carotenoid X" of alfalfa = 3:23:46:24:4. For neo-β-carotene B the ratio was, 2:25:45:28:0 and for neo-β-carotene from alfalfa 1:22:43:34:0. The ratios of stereoisomers produced by this treatment were nearly the same in the two comparisons, another evidence of the identity of the carotenes compared from alfalfa. The same carotenes have been found in the chromatographic analysis of other plants (spinach, collards, grasses, etc.).

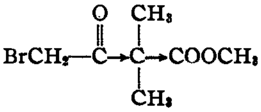
DIVISION OF CHEMISTRY
TEXAS AGRICULTURAL EXPERIMENT STATION
COLLEGE STATION, TEXAS
RECEIVED NOVEMBER 22, 1943

The Action of Sodium Cyanide on Methyl γ-Bromo-α,α-dimethylacetoacetate

BY C. F. KOELSCH

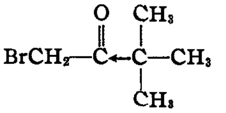
The reaction of sodium cyanide with an α-halogenated ketone usually leads to the formation of a β-ketonitrile; for example, bromopinacolone yields pivaloylacetonitrile.[1] A few α-haloketones, however, furnish α,β-oxidonitriles; for example, desyl chloride yields α,β-epoxy-α,β-diphenylpropionitrile.[2]

On the basis of the polarizations indicated in formulas I and II, it was anticipated that methyl γ-bromo-α,α-dimethylacetoacetate (I) might not parallel bromopinacolone (II) in its behavior toward sodium cyanide, but might suffer attack at its carbonyl group, leading to an oxide (IV).



$$\mathrm{BrCH_2{-}\overset{\overset{\displaystyle O}{\|}}{C}{\rightarrow}\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}{\rightarrow}COOCH_3}$$

I



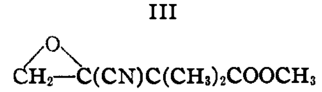
$$\mathrm{BrCH_2{-}\overset{\overset{\displaystyle O}{\|}}{C}{\leftarrow}\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}{-}CH_3}$$

II

The reaction had been studied long ago[3,4,5] and the product had been assigned structure III. But a survey of the old data indicated that the properties of the product were more in accord with structure IV.

$$\mathrm{CNCH_2COC(CH_3)_2COOCH_3}$$

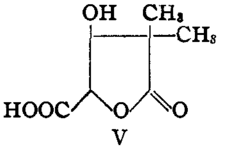
III



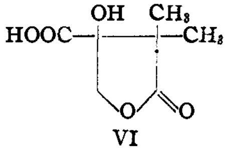
$$\mathrm{\overset{\;O\;}{\overbrace{CH_2{-}C}}(CN)C(CH_3)_2COOCH_3}$$

IV

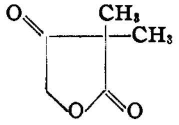
In the present work it was demonstrated that IV is correct. This was done by showing that the hydrolysis product of the nitrile, previously considered to be formed through hydration of the enol of III and formulated as V, actually is VI. The hydrolysis product was identical with the acid obtained by adding hydrogen cyanide to VII and hydrolyzing the resulting cyanohydrin, procedures which can lead only to VI.



V



VI



VII

2,4-Diketo-3,3-dimethyltetrahydrofuran[6] (VII), b. p. 200–210° (740 mm.) or 103–107° (16 mm.), was obtained in 86% yield when 25 g. of methyl γ-acetoxy-β-keto-α,α-dimethylbutyrate[7] was boiled for two hours with 5 g. of 10 molar alcoholic hydrogen chloride (contrary to the statement of Conrad and Gast,[6] the acetoxy ester was unchanged after it had been kept for three months; it also was unaffected when it was heated with potassium carbonate). When 1.3 g. of VII was shaken for fifteen minutes with a solution of 0.6 g. of sodium cyanide and 0.8 ml. of hydrochloric acid in 4 ml. of water, it furnished an oily cyanohydrin. This was removed with ether and boiled for one hour with 6 ml. of 20% hydrochloric acid; when the solution was cooled, it deposited 0.5 g. of VI, colorless prisms from water, m. p. 213–217° alone or mixed with the compound obtained from I by the procedure of Lawrence.[3] When it was boiled with methanol and sulfuric acid, VI gave a methyl ester that melted at 104–105° alone or mixed with Lawrence's ester.

Recognition of the correct structure (IV) for the nitrile previously considered to be III necessitates changes in the structures of substances derived from this compound. Simple esters, etc., need not be specifically mentioned here, but the following revisions must be pointed out. "3-Acetoxy-4,4-dimethyl-5-ketotetrahydro-furoic acid"[4] is actually 3-acetoxy-4,4-dimethyl-5-ketotetrahydrofuran-3-carboxylic acid; "4,4-dimethyl-5-ketotetrahydrofuroic acid"[4,5] is actually 4,4-dimethyl-5-ketotetrahydrofuran-3-carboxylic acid; "ethyl α′-chloro-β-hydroxy-α,α-dimethylglutarate"[3] is actually ethyl α-chloromethyl-α-hydroxy-β,β-dimethylsuccinate; "α,α-dimethyl glutaconic acid"[5] is actually[8] α,α-dimethylitaconic acid. Some doubt now attaches to the structures formerly assigned[3] to homologs of III and V, *viz.*, ethyl γ-cyano-β-keto-α-ethyl-α-

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[1] Widman and Wahlberg, *Ber.*, **44**, 2065 (1911).

[2] Kohler and Brown, THIS JOURNAL, **55**, 4299 (1933). Other examples may be found in the work of Justoni [*Gazz. chim. ital.*, **71**, 41 (1941), *Chem. Abs.*, **36**, 1016 (1942)] and of Delbaere [*Bull. soc. chim. Belg.*, **51**, 1 (1942), *Chem. Abs.*, **37**, 5018 (1943)].

[3] Lawrence, *J. Chem. Soc.*, **75**, 417 (1899).

[4] Conrad and Gast, *Ber.*, **32**, 137 (1899).

[5] Conrad, *ibid.*, **33**, 1920 (1900).

[6] Conrad and Gast, *ibid.*, **31**, 2728 (1898).

[7] Conrad and Kreichgauer, *ibid.*, **30**, 857 (1897).

[8] *Cf.* Perkin, *J. Chem. Soc.*, **81**, 249 (1902).

methyl-(and α,α-diethyl)-butyrate, and 3-hydroxy-4-ethyl-4-methyl- (and 4,4-diethyl)-5-ketotetrahydrofuroic acid, but circumstances will not permit a continuation of the present study to include these substances.

SCHOOL OF CHEMISTRY
UNIVERSITY OF MINNESOTA
MINNEAPOLIS, MINNESOTA RECEIVED NOVEMBER 5, 1943

Observations on the Rare Earths. L.[1] The Separation of Erbium from Yttrium by Fractional Precipitation of the Ferrocyanides[2]

BY THERALD MOELLER AND H. E. KREMERS

Yttrium and erbium oxide mixtures which accumulate during bromate fractionations of the yttrium earths are usually further separated by basicity methods, although the very favorable solubility difference between the ferrocyanides of these elements[3,4] renders ferrocyanide fractionation more rapid. In spite of the gelatinous nature of the precipitates, comparatively pure yttrium material has been prepared by this procedure,[5,6,7,8] and Prandtl,[9] using large quantities of nitric acid to promote crystallinity, has obtained erbium oxide of high purity. The lack of specificity in Prandtl's directions suggested a further study of the problem, and the resulting modified procedure gives consistently reproducible results, is rapid, and is free from undesirable oxidation of the ferrocyanide.

Experimental

Ferrocyanide Precipitation.—Erbium-yttrium chloride solutions were prepared in 3 *N* hydrochloric acid to contain 2% rare earth oxide and 10% ammonium chloride. To these solutions at room temperature, sufficient 20% potassium ferrocyanide solution (calculated as the trihydrate) to precipitate about one-half the rare earth material was added slowly with constant stirring. Experimentally, about 15 ml. precipitated the equivalent of 1 g. of rare earth oxide from material analyzing 85–100% Er_2O_3 and 20 ml. for lower erbium concentrations. Slow precipitation began only after complete addition of the ferrocyanide. After several hours, the precipitates were removed by suction filtration on qualitative paper.

Recovery of Rare Earth Materials.—Part of the iron was removed from the precipitates by boiling the solids with 50% sodium hydroxide, diluting, and filtering. After ignition of these hydroxides, the remainder of the iron was removed by oxalate precipitation of the rare earths from chloride solutions. The ferrocyanide mother liquors gave iron-free oxides after two precipitations with oxalic acid.

Fractionation of Erbium-Yttrium Mixtures.—Erbium-yttrium mixtures showing no absorption lines for holmium or thulium were fractionated by the above procedure. Each fractionation was followed by means of spectrophotometric analyses (based upon the 489 and 653 mμ erbium absorption bands)[10] of oxides recovered from both precipitates and mother liquors. Oxides of approximately the same composition were combined and refractionated.

The fractionation of 43 g. of a mixture (ER-18) containing 57% Er_2O_3 gave 4.8 g. of 89% Er_2O_3, 2.1 g. of 86% Er_2O_3, 5.9 g. of 80% Er_2O_3, 6.8 g. of 62% Er_2O_3, 6.7 g. of 38% Er_2O_3, and 15 g. of an oxide mixture low in erbium after twenty-eight fractional precipitations (five series with five or six fractions in each).

A series of fractions (ER-34) obtained from a urea separation[11] and a previous ferrocyanide fractionation and consisting of (1) 6.9 g. of 87% Er_2O_3, (2) 5.9 g. of 80% Er_2O_3, (3) 13.8 g. of 59% Er_2O_3, (4) 20.3 g. of 27% Er_2O_3, and (5) 45 g. of 17% Er_2O_3 yielded ultimately 3.14 g. of 98.5% Er_2O_3 (two precipitations of fraction (1)); 1.3 g. of 94% Er_2O_3, 2.35 g. of 93% Er_2O_3 and 2.8 g. of 80% Er_2O_3 (four precipitations of fractions (2), (3), and (4), respectively); and 5.6 g. of 48% Er_2O_3 (three precipitations of fraction (5)). In addition, 5.0 g. of 65% Er_2O_3, 17.6 g. of 44% Er_2O_3, and 9.5 g. of 27% Er_2O_3 were recovered from the final mother liquors.

Success of the ferrocyanide procedure is dependent upon the complete removal of iron, since even traces of iron yield gelatinous blue precipitates which nullify the effects of crystallinity in the rare earth ferrocyanides. Although some unavoidable loss is inherent in the oxalate precipitations, the speed and efficiency of the method recommend it.

Acknowledgment.—The authors wish to express their appreciation to Dr. C. J. Rodden of the National Bureau of Standards for the analysis of an erbium oxide sample used in the calibration of our spectrophotometer.

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(1) For the preceding communication in this series see Kleinberg, Taebel and Audrieth, *Ind. Eng. Chem., Anal. Ed.*, **11**, 368 (1939).

(2) Presented before the Division of Physical and Inorganic Chemistry at the 106th meeting of the American Chemical Society at Pittsburgh, Pa., September 6, 1943.

(3) Rowland, *Chem. News*, **70**, 68 (1894).

(4) Prandtl and Mohr, *Z. anorg. allgem. Chem.*, **236**, 243 (1938).

(5) Bettendorf, *Ann.*, **352**, 88 (1907).

(6) Meyer and Wuorinen, *Z. anorg. Chem.*, **80**, 7 (1913).

(7) Prandtl, *Z. anorg. allgem. Chem.*, **143**, 277 (1925).

(8) Canneri, *Atti accad. Lincei*, **8**, 164 (1928).

(9) Prandtl, *Z. anorg. allgem. Chem.*, **198**, 157 (1931).

(10) Rodden, *J. Research Natl. Bur. Standards*, **28**, 265 (1942).

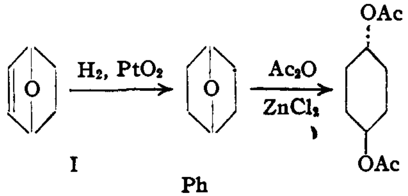
(11) Fogg and Hess, THIS JOURNAL, **58**, 1751 (1936).

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS RECEIVED SEPTEMBER 20, 1943

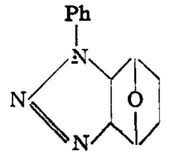
3,6-Epoxycyclohexene from Furan and Ethylene[1]

BY WALTER NUDENBERG AND LEWIS W. BUTZ

3,6-Epoxycyclohexene (I) has now been prepared by the procedure and with the apparatus previously employed in similar preparations.[2] It has been characterized as indicated below.



I



II

Into a mixture of 30–35 g. of furan and a few crystals of hydroquinone ethylene was introduced in two or three portions with intermittent shaking up to an initial pressure of 1100–1200 lb. per sq. in. at room temperature. The bomb was heated to 155° and kept at 150–155°, the pressure dropping and ultimately becoming constant after six-

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(1) Not subject to copyright. This work was supported by an allotment from the Special Research Fund (Bankhead-Jones Act of June 29, 1935).

(2) Joshel and Butz, THIS JOURNAL, **63**, 3350 (1941).

teen hours. After cooling the bomb, the gas was allowed to escape through a trap cooled by solid carbon dioxide, and the deposited furan was returned to the reaction mixture. The whole was distilled in three fractions: the first, of unreacted furan, 14–16 g.; the second, b. p. 40–118°, chiefly furan, 1.5 g., the third, a colorless liquid, b. p. 118–122°, 1.2–1.5 g. This last was 3,6-epoxycyclohexene, b. p. 118–119°, $n^{20}D$ 1.4629; yield, 5–8% on the furan consumed.

The triazoline derivative, formula II,[3] was prepared by mixing a few drops of phenyl azide with a similar quantity of epoxycyclohexene and allowing the resulting yellow solution to crystallize in the ice box overnight. Repeated crystallization from ethyl acetate gave fine white needles, m. p. 166–167° (cor.) (after drying over phosphorus pentoxide).

Anal.[4] Calcd. for $C_{12}H_{13}ON_3$: C, 67.0; H, 6.1; N, 19.5. Found: C, 67.1; H, 6.1; N, 19.5.

The epoxycyclohexene (4.5 g.) in 12 ml. of methanol was hydrogenated using 50 mg. of Adams catalyst. Distillation of the residue remaining after removal of the catalyst and methanol gave a fraction b. p. 110–120°. This material was refluxed, without further purification, with acetic anhydride and several crystals of zinc chloride for two hours. The excess acetic anhydride was distilled off and the remaining brown oil poured into hot water. Crystallization did not occur. The oil was extracted with ether, the solution dried and the ether evaporated. The residual oil on standing deposited crystals, m. p. 102–103.6°, from aqueous ethanol. A mixture with authentic ester,[5] m. p. 102–104°, also melted at 102–103.6°.

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[3] Alder and Stein, *Ann.*, **501**, 1 (1935).

[4] Analysis by Dr. T. S. Ma, University of Chicago.

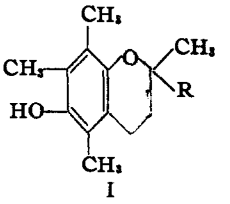
[5] Baeyer, *Ann.*, **278**, 93 (1894). The *trans*-quinitol diacetate was kindly furnished by Mr. A. M. Gaddis, who prepared it from hydroquinone.

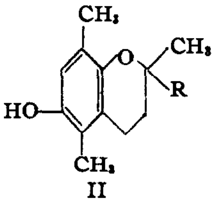
BUREAU OF ANIMAL INDUSTRY
AGRICULTURAL RESEARCH ADMINISTRATION
UNITED STATES DEPARTMENT OF AGRICULTURE
BELTSVILLE, MARYLAND
RECEIVED OCTOBER 2, 1943

Coupling of Gamma Tocopherol and Failure of β-Tocopherol to Couple with Diazonium Salts

BY MARY LOUISE QUAIFE

Inspection of the structural formulas of α-tocopherol (I), β-tocopherol (II), and γ-tocopherol (III) suggests that both II and III are capable of coupling with diazonium salts.[1] We have found that γ-tocopherol couples readily, but the beta isomer, surprisingly, does not. Consequently, III can be determined in the presence of I and II. This note describes the reaction upon which the procedure is based and also experiments showing the failure of β-tocopherol to couple.


I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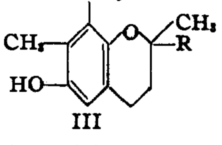
III

R = $C_{16}H_{33}$

γ-Tocopherol is determined by photometric estimation of the red dye produced by its reaction with diazotized *p*-nitroaniline in aqueous alcohol·solution at *p*H of about 6. The dye, extracted with Skellysolve H, gives a stable color with absorption maxima at 530 mμ and 380 mμ. Over the range of quantity of γ-tocopherol employed in the analysis (0.2 to 0.5 mg.) absorption at either wave length is proportional to concentration. It is measured at 520 mμ for convenience. The method has been applied to estimation of γ-tocopherol content of tocopherol concentrates with results as shown in Table I. Total tocopherols were determined by the method of Emmerie and Engel.[2]

TABLE I

γ-TOCOPHEROL CONTENT OF VEGOL (CONCENTRATE OF NATURAL MIXED TOCOPHEROLS) FRACTIONS (DUPLICATE ANALYSES)

Sample	γ-Tocopherol, %	% total tocopherols	Ratio of γ- to total tocopherol: % γ-
Vegol (C)	2.8	4.3	65
	3.1	4.5	69
Vegol (I)	16.3	26.3	62
	17.8	26.7	67
Vegol (II)	21.4	42.0	51
	19.7	42.3	47
Vegol (III)	9.0	40.2	22
	9.5	40.2	24

When the procedure was applied to natural β-tocopherol, it required 12 mg. to give absorption at 520 mμ, equivalent to that given by only 0.05 mg. of γ-tocopherol. Since in this case the *p*H was about 6, the ability of β-tocopherol to couple with benzenediazonium chloride was tested over a *p*H range of 4.5 to 11. The test procedure was similar to that used in the analytical method except for increased amounts of β-tocopherol. Control series were run using equal amounts of γ-tocopherol as well as aqueous alcohol blanks. The resultant Skellysolve extracts of the reaction mixtures of the tocopherols (0.4 mg./cc.) and of the blank had colors as shown in Table II.

TABLE II

COLORS OF COUPLING PRODUCTS OF TOCOPHEROLS AND BENZENEDIAZONIUM CHLORIDE

*p*H	Blank	β-Tocopherol	γ-Tocopherol
4.5	Colorless	Colorless	Colorless
9.0	Light yellow	Light yellow	Deep orange
11.0	Light yellow	Light yellow	Deep orange

Absorption spectra over the range of 310 to 620 mμ of the reaction products at *p*H 9 show no difference in absorption between the Skellysolve extracts of the β-tocopherol reaction mixture and the blank. The γ-tocopherol azo dye formed at *p*H 9 had a density of 1.7 at 475 mμ, the peak of absorption.

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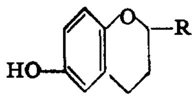
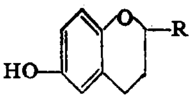
[1] Scudi and Buhs, *J. Biol. Chem.*, **146**, 6 (1942).

[2] Emmerie and Engel, *Rec. trav. chim.*, **57**, 1351 (1938).

This difference in coupling ability of γ- and β-tocopherols suggests possible fixation of the bond structure in the benzenoid nucleus of the tocopherols according to IV instead of V. The substituted tetralins, which have a ring system similar to that of the tocopherols, are considered to have a double bond between the rings. The observed difference in the tocopherol isomers may also be related to the Mills–Nixon effect.[3,4]



IV



V

The advice of Dr. C. F. H. Allen is gratefully acknowledged.

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[3] Mills and Nixon, *J. Chem. Soc.*, 2510 (1930).

[4] Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943. 2nd Ed., Vol. I, p. 136.

COMMUNICATION NO. 56
FROM THE LABORATORIES OF
DISTILLATION PRODUCTS, INC.
ROCHESTER, NEW YORK RECEIVED DECEMBER 7, 1943

The Alkylation of Isopropylmalonic Ester Using Sodium Triphenylmethide[1]

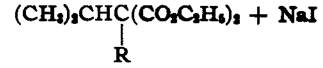
BY J. C. SHIVERS, B. E. HUDSON, JR., AND CHARLES R. HAUSER

The difficulty of alkylation of secondary alkyl malonic esters, for example, isopropylmalonic ester, by the ordinary procedure using sodium ethoxide[2] in alcoholic solution has been ascribed to the incomplete formation of the sodio derivative.[3]

$$\mathrm{RCH(CO_2C_2H_5)_2 + NaOC_2H_5 \rightleftarrows [RC(CO_2C_2H_5)_2]Na + C_2H_5OH}$$

Wallingford and co-workers[3b] found that, by substituting an alkyl carbonate for alcohol as a reaction medium and distilling all alcohol produced from the reaction with sodium ethoxide, certain secondary alkyl malonic esters could be alkylated. We have found that alkylation of isopropylmalonic ester may be achieved by using the stronger base, sodium triphenylmethide, in an inert solvent. The yields of alkylation product with ethyl iodide and isopropyl iodide were 73 and 23%, respectively.

$$\mathrm{(CH_3)_2CHCH(CO_2C_2H_5)_2 + NaC(C_6H_5)_3 \longrightarrow Na[(CH_3)_2CHC(CO_2C_2H_5)_2] + HC(C_6H_5)_3}$$



$$\mathrm{RI + Na[(CH_3)_2CHC(CO_2C_2H_5)_2] \longrightarrow (CH_3)_2CH\underset{\substack{|\\ R}}{C}(CO_2C_2H_5)_2 + NaI}$$

Crossley and Le Sueur[2b] found that ethylisopropylmalonic ester (R = ethyl, prepared by isopropylating ethylmalonic ester using sodium ethoxide) undergoes alkaline hydrolysis to form partly ethylisopropylmalonic acid and partly ethylisopropylmalonic acid ester, which on decarboxylation gives ethyl ethylisopropylacetate. We have found that di-isopropylmalonic ester (R = isopropyl) undergoes alkaline hydrolysis only with difficulty yielding di-isopropylmalonic acid ester, which undergoes decarboxylation with difficulty.

Experimental

Diethyl isopropylmalonate (b. p. 217–218°)[4] was prepared in 56% yield essentially according to the directions given in "Organic Syntheses"[5] for the preparation of diethyl *n*-butyl malonate.

Diethyl Ethylisopropylmalonate.—To sodio-isopropylmalonic ester, prepared from 42.0 g. (0.205 mole) of the ester and 0.205 mole of an ether solution of sodium triphenylmethide,[6] was added 32 g. (0.205 mole) of ethyl iodide. After standing for seven days, the ether solution (above the thin layer of sodium iodide crystals) was transferred by means of nitrogen pressure to a flask and the solvent distilled through a column up to 40°. More ethyl iodide (11.6 g.) in 100 cc. of dry benzene was added to the residue and the mixture was refluxed eighteen hours. On working up the mixture there was obtained 35 g. (73%) of diethyl ethylisopropylmalonate, b. p, 118–120° (15 mm.) (234–236° at atm. pres.).[2b]

Refluxing diethyl ethylisopropylmalonate ten hours with 95% alcoholic potassium hydroxide and decarboxylation of the resulting malonic acid gave a 48% yield of ethylisopropylacetic acid, b. p. 104–105° (15 mm.). Neutral equivalent, calculated for $C_7H_{14}O_2$: 130.18. Found: 131.28. With aniline the acid gave the anilide, melting at 118–119°. (*Anal.*[7] Calcd. for $C_{12}H_{17}ON$: N, 6.83. Found: N, 6.53). No attempt was made to isolate ethyl ethylisopropylacetate obtained by Crossley and Le Sueur.[2b]

Diethyl Di-isopropylmalonate.—Sodio-isopropylmalonic ester was prepared by the decolorization of 0.1 mole of sodium triphenylmethide solution with 20.2 g. (0.1 mole) of isopropyl malonic ester, and practically all of the ether was distilled from the mixture in an atmosphere of nitrogen. To the residue was added 10 cc. of dry benzene followed by 21.2 g. (0.125 mole) of isopropyl iodide in 40 cc. of benzene. After standing overnight, the mixture was refluxed twenty-four hours, additional (4.3 g.) isopropyl iodide was added, and the mixture refluxed for twenty-four hours longer. On working up the mixture there was obtained 5.6 g. (23%) of diethyl di-isopropylmalonate, b. p. 122–124° (15 mm.).

Anal.[7] Calcd. for $C_{13}H_{24}O_4$: C, 63.90; H, 9.90. Found: C, 63.52; H, 9.79.

Long refluxing (eighteen to twenty-four hours) of diethyl di-isopropylmalonate with alcoholic potassium hydroxide yielded unchanged ester and ethyl hydrogen di-isopropylmalonate, m. p. 71–72°. Neutral equivalent, calculated for $C_{11}H_{20}O_4$: 216.3. Found: 213.6. The mono acid-ester on heating slowly decarboxylated to form a neutral material, b. p. 71–72° (15 mm.), which was apparently ethyl di-isopropylacetate (*Anal.* Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 68.71; H, 11.31).[7]

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[1] Paper XXII on "Condensations."

[2] (a) Fischer and Dilthey, *Ann.*, **335**, 337 (1904); (b) Crossley and Le Sueur, *J. Chem. Soc.*, **77**, 83 (1900).

[3] (a) See Shonle, Kelch and Swanson, THIS JOURNAL, **52**, 2440 (1930); (b) Wallingford, Thorpe and Homeyer, *ibid.*, **64**, 580 (1942).

[4] Conrad and Bischoff, *Ann.*, **204**, 144 (1880), report a boiling point of 213–214°.

[5] Adams and Kamm, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 245.

[6] Renfrow and Hauser, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc', New York, N. Y., 1943, p. 607.

[7] Microanalyses by Dr. T. S. Ma, University of Chicago.

DEPARTMENT OF CHEMISTRY
DUKE UNIVERSITY
DURHAM, NORTH CAROLINA RECEIVED NOVEMBER 8, 1943

Color Reactions for Certain Amino Acids

BY HENRY TAUBER

We have observed that certain amino acids are converted to chromogens when heated. Alcoholic extracts containing these chromogens become more deeply colored when alkali is added, but on subsequent acidification become colorless or much lighter in color.

The procedure has been as follows. Ten mg. of the amino acid in a dry Pyrex test-tube is heated over a burner until the first color change occurs, which may be to yellow or brown depending on the amino acid. Overheating should be avoided since it destroys the chromogens. After cooling, 3 cc. of ethyl alcohol is added and the solution boiled for thirty seconds and the resulting solution divided equally among three small test-tubes. To the first is added 0.2 cc. of 0.1 *N* sodium hydroxide, to the second 0.2 cc. of 0.1 *N* sulfuric acid, and to the third 0.2 cc. of water.

Twenty-one biologically important amino acids have been found to behave as follows: three (*dl*-alanine, *dl*-valine and *dl*-iso-leucine) when heated sublime completely, leaving no pigment or residue. Twelve (*l*-cystine, *l*-cysteine, glycine, *l*-hydroxyproline, *dl*-methionine, glutamic acid, *dl*-aspartic acid, *dl*-serine, *l*-proline, *d*-arginine-monohydrochloride, *dl*-lysine, and *d*-lysine) change to yellow, brown or black decomposition products without chromogenic properties. Six (phenylalanine, *l*-tyrosine, *l*-leucine, *l*-histidine, *l*-tryptophan and *dl*-threonine) form chromogens which react as follows when subjected to the above tests: *l*-tyrosine, *l*-tryptophan and *dl*-threonine turn reddish brown on heating, exhibit a light brown or reddish color in alcoholic solution, become more deeply colored on the addition of alkali and turn a light brown or, in the case of *l*-tyrosine, a yellow color on acidification. *l*-Histidine-monohydrochloride becomes light brown on heating, light yellow in alcoholic solution, deep yellow on the addition of alkali and almost colorless on acidification. *dl*-β or *l*-β-phenylalanine and *l*-leucine on heating partially sublime, turn yellow and give a yellow or light yellow color in alcoholic solution. This color turns to a deep yellow on addition of alkali and becomes almost colorless on subsequent acidification. In the case of the β-phenylalanines the alkaline alcoholic solution exhibits a greenish-yellow fluorescence which is particulary strong in ultraviolet light, without the addition of alkali.

This fluorescent pigment from phenylalanine has been isolated in a more concentrated form as follows. One gram of phenylalanine is heated in a large Pyrex test-tube and stirred with a thermometer until the temperature of the material reaches 250°. After cooling, the crystalline reaction mixture is extracted four times with 15-cc. portions of acetone. The deep yellow, fluorescent solution is concentrated to 10 cc., filtered and evaporated to dryness in vacuum. Ninety-five mg. of reddish-brown hygroscopic material is obtained. Dilute alcoholic solutions of this pigment show intense fluorescence in ultraviolet light but not in daylight. On the addition of alkali, however, deep greenish-yellow fluorescence is shown in daylight. In acetone the fluorescence is much stronger than in alcoholic solution. The pigment gives a much more intense xanthoproteic reaction (deep orange-red) than phenylalanine. After acetone extraction of the pyrolyzed reaction mixture there is left 550 mg. of white material and some substance is lost owing to sublimation.

We are aware that these amino acids are not the only compounds that react in this manner. We believe, however, that these observations are interesting enough to warrant recording. Especially remarkable is the strongly fluorescent compound that forms on the pyrolysis of phenylalanine.

AGRICULTURAL RESEARCH ADMINISTRATION
U. S. DEPARTMENT OF AGRICULTURE
WASHINGTON, D. C.
RECEIVED SEPTEMBER 28, 1943

Substituted α-Amyl-cinnamylaldehydes

BY A. WEIZMANN

α-Amyl-cinnamylaldehyde is, because of its jasmin-like odor, manufactured industrially from heptanal and benzaldehyde.[1] It seemed possible that the same synthesis with substituted benzaldehydes, which by themselves exhibit pleasant odors, would give especially valuable products. This was, however, not the case. 4-Methoxy-, 3,4-methylene-dioxy- and 3,4-dimethoxy-α-amyl-cinnamylaldehydes have been synthesized and studied; the first of them has been described briefly before.[2] The substituted benzaldehydes proved less reactive than benzaldehyde itself in this condensation, as in other similar cases.[3] In all these experiments, a mixture of pyridine and piperidine proved a more convenient catalyst, than the commonly used potassium hydroxide. Vanillin did not react at all with oenanthal under these conditions.

Experimental

4-Methoxy-α-amyl-cinnamylaldehyde.—A mixture of heptanal (12 g.), anisaldehyde (14 g), pyridine (100 cc.) and piperidine (10 cc.) was heated on the water-bath for eight hours, poured out into ice-cold dilute sulfuric acid and extracted with ether. The product was twice distilled at 0.3 mm.; b. p. 145°; yield, 10 g.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.6; H, 8.6. Found: C, 77.6; H, 9.0.

The **semicarbazone** separated from a mixture of the aldehyde (1.5 g.), semicarbazide hydrochloride (0.75 g.) and potassium acetate (0.6 g.) in aqueous alcohol at room temperature. It formed needles, m. p. 143–145°, when crystallized from propyl alcohol. Calcd. for $O_{16}H_{23}O_2N_8$: N. 14.5. Found: N, 14.3.

3,4-Dimethoxy-α-amyl-cinnamylaldehyde.—Veratraldehyde (13 g.) and heptanal (9.5 g.) were condensed by heating for eight hours in presence of pyridine (50 cc.) and piperidine (5 cc.). The condensation product had b. p. 165° (0.6 mm.).

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.3; H, 8.4. Found: C, 73.4; H, 8.7.

The semicarbazone, prepared as above, was recrystallized from propyl alcohol and formed needles, m. p. 175°.

Anal. Calcd. for $C_{17}H_{25}O_3N_3$: C, 64.0; H. 7.8; N, 12.7. Found: C, 64.4; H, 8.4; N, 13.0.

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(1) Rutowski and Korolew. *J. prakt. Chem.*, [2] **119**, 272 (1928).

(2) I. G. Farbenindustrie A. G., French Patent 628.739 (1927).

(3) Molt, *Rec. trav. chim.*, **56**, 233 (1937).

3,4-Methylenedioxy-α-amyl-cinnamylaldehyde was prepared analogously from heptanal (11.4 g.) and piperonal (15 g.). The fraction 150-160° (0.8 mm.) of the condensation product was purified *via* the semicarbazone as above. From butyl alcohol long needles, m. p. 155°, were obtained.

Anal. Calcd. for $C_{16}H_{21}O_3N_3$: N, 13.9. Found: N, 14.0. The pure aldehyde had b. p. 158-159° (0.9 mm.).

THE DANIEL SIEFF RESEARCH INSTITUTE
REHOVOTH, PALESTINE
RECEIVED NOVEMBER 26, 1943

NEW COMPOUNDS

Some Aryl and Aralkyl Ureas

In connection with a study of the hypnotic properties of aryl ureas carried out by a pharmacological group in these Laboratories, a number of halogenated unsymmetrical aryl alkyl ureas have been prepared. Data on these and on some related unhalogenated ureas and symmetrically substituted ureas are presented in Table I.

TABLE I

SECONDARY ARYL AND ARALKYL UREAS $R_1R_2NCONH_2$

	R_1	R_2	M. p., °C.[a]	Appearance	Cryst. solvent[b]	Empirical formula	Analyses, % Calcd. C	H	Found C	H
I	C_6H_5	CH_2CH_2OH	110		Æ	$C_9H_{12}O_2N_2$	59.97	6.71	59.68	7.05
II[c]	2-Me-4-Cl-C_6H_3	C_2H_5	93	Stout prisms	Æ-H	$C_{10}H_{13}ON_2Cl$	56.46	6.16	56.59	6.19
III[d]	2-Me-4-Br-C_6H_3	C_2H_5	88.5-89	Rect. prisms	E-H	$C_{10}H_{13}ON_2Br$	46.70	5.10	47.00	5.35
IV	The same	*n*-C_3H_7	94.5-95.5	Prisms	H	$C_{11}H_{15}ON_2Br$	48.70	5.58	48.76	5.78
V[e]	2-Me-5-Cl-C_6H_3	C_2H_5	166-167	Felted needles	A-Aq	$C_{10}H_{13}ON_2Cl$	56.46	6.16	56.52	6.37
VI[f]	The same	*n*-C_4H_9	79.5-80	Prisms	H	$C_{12}H_{17}ON_2Cl$	59.86	7.12	59.84	7.44
VII[g]	4-Me-2-Br-C_6H_3	C_2H_5	116	Tiny prisms	E	$C_{10}H_{13}ON_2Br$	46.70	5.10	46.82	5.21
VIII[h]	2-Et-4-Br-C_6H_3	C_2H_5	95	Small stout prisms	E-H	$C_{11}H_{15}ON_2Br$	48.70	5.58	48.45	5.86
IX[i]	4-Et-C_6H_4	C_2H_5	122-124	Stout prisms	Æ-H	$C_{11}H_{16}ON_2$	68.70	8.39	68.99	8.62
X[j]	4-Et-2-Br-C_6H_3	C_2H_5	114	Stout prisms	E-H	$C_{11}H_{15}ON_2Br$	48.70	5.58	48.65	5.76
XI	2,4-$Me_2C_6H_3$	C_2H_5	73-74	Prisms	H	$C_{11}H_{16}ON_2$	68.70	8.39	68.75	8.50
XII	$C_6H_5CH_2$	CH_3	135	Needle prisms	Æ	$C_9H_{12}ON_2$	65.82	7.37	65.99	7.32
XIII	The same	*n*-C_4H_9	61-62	Needles	H	$C_{12}H_{18}ON_2$	69.84	8.80	69.80	8.72
XIV[k]	2-EtO-5-Br-C_6H_3	C_2H_5	124-124.5	Needles	Æ-H	$C_{11}H_{15}O_2N_2Br$	45.98	5.27	46.24	5.50
XV	4-MeO-C_6H_4-CH_2	CH_3	140-141	Flattened needles	A-Aq	$C_{10}H_{14}O_2N_2$	61.82	7.27	62.12	7.46
XVI	4-MeO-3-Cl-$C_6H_3CH_2$	CH_3	169-169.5	Leaflets	A	$C_{10}H_{13}O_2N_2Cl$	52.49	5.73	52.52	5.64
XVII	4-MeO-3-Br-$C_6H_3CH_2$	CH_3	178	Leaflets	A	$C_{10}H_{13}O_2N_2Br$	43.95	4.80	44.22	5.10
XVIII	4-MeO-3-Cl-$C_6H_3CH_2CH_2$	CH_3	117.5-118	Prisms	Æ	$C_{11}H_{15}O_2N_2Cl$	54.41	6.23	54.49	6.38
XIX	4-MeO-3-Br-$C_6H_3CH_2CH_2$	CH_3	116.5-117	Prisms	Æ-H	$C_{11}H_{15}O_2N_2Br$	45.97	5.27	46.03	5.30
	Symmetrically substituted ureas									
XX	2-Me-4-Br-C_6H_3NHCONHEt		230-232	Tiny felted needles	HAc	$C_{10}H_{13}ON_2Br$	46.70	5.10	47.00	5.45
XXI	2,4-Me_2-C_6H_3NEtCONHEt		76	Stout prisms	H	$C_{13}H_{20}ON_2$	70.86	9.16	70.62	9.19
XXII	2-Et-C_6H_4NEtCON(COC_6H_5)$_2$		128-129	Needles	B	$C_{25}H_{24}O_3N_2$	74.97	6.04	75.00	6.38
							(N = 7.00)		(N = 6.95)	
	Secondary Aralkylamine Hydrochlorides $R_1R_2NH\cdot HCl$									
XXIII	4-MeO-3-Cl-$C_6H_3CH_2$	CH_3	201-201.5	Needle prisms	A	$C_9H_{13}ONCl_2$	48.64	5.90	48.76	6.03
XXIV	4-MeO-3-Br-$C_6H_3CH_2$ (hydrobromide)	CH_3	202-203	Needles	A	$C_9H_{13}ONBr_2$	34.73	4.21	35.08	4.44
XXV	4-MeO-3-Cl-$C_6H_3CH_2CH_2$	CH_5	196	Felted needles	Æ	$C_{10}H_{15}ONCl_2$	50.84	6.41	51.00	6.50
XXVI	4-MeO-3-Br-$C_6H_3CH_2CH_2$	CH_3	215-216	Fine needle prisms	A	$C_{10}H_{15}ONClBr$	42.78	5.39	42.94	5.49

[a] All melting points corrected. [b] A = ethanol; Æ = ethyl acetate; E = ether; H = hexane; Aq = water; HAc = acetic acid; B = benzene. [c] B. p. (13 mm.) of secondary amine, 136°. [d] B. p. (0.25 mm.) of secondary amine, 96-99°. [e] B. p. (27 mm.) of secondary amine, 141°. [f] B. p. (1 mm.) of secondary amine, 125°. [g] B. p. (17 mm.) of secondary amine, 137°. [h] B. p. (3 mm.) of secondary amine, 135°. [i] B. p. (22 mm.) of secondary amine, 122-123°. [j] B. p. (3 mm.) of secondary amine, 107°. [k] B. p. (0.25 mm.) of secondary amine, 111°.

The secondary amines corresponding to the ureas I, XI-XIII and XV are known. The amines corresponding to ureas XVI-XIX were characterized as salts and data thereon are also included in Table I. For the other secondary bases boiling points are given. The derived ureas are themselves satisfactory as compounds of characterization.

Preparation of Secondary Amines.—The 3-chloro and bromo anisyl methyl and homo anisyl methyl amines (leading to ureas XVI-XIX) were prepared by halogenation of N-methyl anisyl and N-methyl homo anisyl amines in hydrochloric acid solution (XXIV in hydrobromic acid).

Whereas non-halogenated aromatic secondary amines are readily prepared by alkylation with alkyl halides, isolation of the secondary amine as the nitrosamine followed by reduction with stannous chloride, the alkyl bromides and iodides are unsuitable for reaction with halogenated aromatic amines,[1] the halogen being removed or displaced with resulting complications. By use of alkyl sulfates and alkyl toluene-sulfonates the desired alkyl groups can be introduced satisfactorily.

Ethylation was accomplished by stirring the primary amine with ethyl sulfate and water on the steam-bath until the layers had disappeared after which the conventional nitrosamine procedure was followed.

The secondary propyl and butyl amines corresponding to ureas IV and VI were obtained by warming 1 mol of alkyl toluene sulfonate with 2 mols of primary amine for three hours at 110-120°. The partially cooled melts were sludged with benzene and the bulk of the primary amines separated as salts of *p*-toluenesulfonic acid. Addition to the filtrate of alcoholic hydrogen chloride equivalent to about half of the remaining base precipitated virtually all of the remaining primary amines, after which the hydrochlorides of the secondary amines could be separated without trouble. In some runs sulfonamide formation was encountered.

Preparation of Ureas.—The symmetrically substituted ureas XX and XXI were prepared from ethyl isocyanate and the appropriate aromatic bases.

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[1] Baltzly and Buck, THIS JOURNAL, **63**, 1757 (1941).