methyl - 3,5,3′ - tricarbethoxy - 5′ - carboxyldipyrrylmethane (X) was suspended in 20 cc. of anhydrous glycerol containing ten drops of quinoline. The mixture was heated rapidly to 200° and held at this temperature for three minutes. Heating was discontinued and 30 cc. of alcohol added in a thin stream from a wash bottle. The solution was then set on ice and the product separated as an oil which crystallized slowly. It was filtered off and recrystallized from acetone; yield, 8.7 g. or 89.5%; m. p. 127–129°.

The product may be recrystallized from either acetone or methanol. From ethanol it came out as an oil which solidified slowly. A sample was recrystallized three times from methanol for analysis.

Anal. Calcd. for $C_{22}H_{33}N_2O_6$: C, 63.14; H, 7.23. Found: C, 63.36; H, 7.20.

Preparation of Tetrapyrrane XV.—Two grams of 1,4,1′,4′-tetramethyl-3,5,3′-tricarbethoxy-dipyrrylmethane (XII), 0.1 g. of paraformaldehyde, 10 drops of glacial acetic acid and 10 cc. of anhydrous butanol were refluxed together for one hour and the solution then placed in the ice box overnight. The entire mixture solidified. The snow-white product was filtered off and washed with ethanol; yield, 1.8 g. or 89%; m. p. 147–149°.

The product may be recrystallized from ethanol, methanol or dioxane. The latter is preferable and the analytical sample was prepared by recrystallizing three times from this solvent.

Anal. Calcd. for $C_{45}H_{60}N_4O_{12}$: C, 63.66; H, 7.12. Found: C, 63.77; H, 7.05.

Saponification of 1,4,1′,4′-Tetramethyl-3,5,3′-tricarbethoxy-dipyrrylmethane (XII).—Four and one hundredth grams (0.0096 mole) of dipyrrylmethane XII was dissolved in 200 cc. of 80% ethanol and 0.011 mole of sodium hydroxide added. The solution was refluxed overnight and evaporated to dryness. The residue was taken up in 100 cc. of hot water and filtered to remove a small amount of water-insoluble product. On cooling the filtrate, 3.24 g. of a soapy sodium salt was precipitated. This was dissolved in hot ethanol, acidified with hydrochloric acid to the congo red end-point and hot water added to incipient turbidity. On cooling, 2.85 g. of crystalline acid was deposited. An additional 0.80 g., somewhat less pure, was obtained on acidification of the aqueous mother liquor; total yield, 3.55 g. or 98%.

Re-esterification.—A 100-mg. sample of the acid was re-esterified with diazo-ethane by the process described above. The product melted at 126–129°; mixed m. p. with pure dipyrrylmethane XII, 127–129°.

Decarboxylation.—A 100-mg. sample of the acid was decarboxylated in glycerol and quinoline, yielding a product melting at 163–164° after two recrystallizations from acetone; mixed m. p. with 1,4,1′,4′-tetramethyl-3,3′-dicarbethoxy-dipyrrylmethane (described below), 164–165°.

1,4,1′,4′-Tetramethyl-3,3′-dicarbethoxy-dipyrrylmethane (XIII).—Two and eight-tenths grams of 1,4,1′,4′-tetramethyl - 3,3′ - dicarbethoxy - 5,5′ - dicarboxyldipyrrylmethane (XI) was suspended in 5 cc. of dry glycerol and two drops of quinoline in a Pyrex test-tube. The temperature was brought rapidly to 220° and maintained for three minutes. Cold alcohol was added cautiously in a thin stream from a wash bottle. The product started to crystallize immediately. After standing on ice for several hours, the product was filtered off and recrystallized from acetone. It deposited as beautiful, large, clear crystals; yield, 2.10 g. or 94%; m. p., 164–165°.

Anal. Calcd. for $C_{19}H_{26}N_2O_4$: C, 65.87; H, 7.57. Found: C, 65.67, 65.65; H, 7.57, 7.60.

Summary

1. An attempt to achieve a stepwise condensation of pyrrole derivatives to give linear tetrapyrryl compounds capable of producing porphyrins is described.

2. The proposed porphyrin synthesis is shown to be blocked by condensation of β-carbethoxy groups with imino nitrogens under the influence of alkali to give dipyrrolopyridones.

3. Minimum conditions under which such a synthesis could be achieved are stated as a result of these observations.

4. Conditions have been found for the selective saponification of a single carbethoxy group on two tetracarbethoxy dipyrrylmethanes.

5. A method for the identification of pyrrole and dipyrrylmethane carboxylic acids by re-esterification with diazo-ethane is reported.

6. A group of di-N-methyl dipyrrylmethane derivatives has been prepared.

7. Two new tetrapyrrane derivatives have been synthesized.

BALTIMORE, MD. RECEIVED MARCH 2, 1944

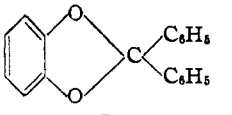
[CONTRIBUTION FROM THE DERMATOSES SECTION OF THE INDUSTRIAL HYGIENE DIVISION, BUREAU OF STATE SERVICES U. S. PUBLIC HEALTH SERVICE]

The Toxic Principles of Poison Ivy. II. Preparation and Properties of the Diphenylmethylene Ethers of Catechols[1]

BY HOWARD S. MASON

The difficulty with which 2-alkoxy derivatives of 3-alkyl-catechols are hydrolyzed[2] and the sensitivity of alkenyl-catechols to heat[3] and mineral acid have been serious hurdles to the synthesis of the toxic principles of poison ivy, 3-*n*-pentadecenyl catechols.[4] Accordingly, a derivative of catechols suitable for purposes of synthesis but cleavable under mild conditions has been sought in this investigation.

The diphenylmethylene ethers of catechol (I),



I

3-*n*-propylcatechol, and 4-*t*-butylcatechol have now been investigated from this point of view. These compounds, which may be regarded as

(1) For the first article in this series, see Mason and Schwartz, THIS JOURNAL, **64**, 3058 (1942).

(2) Majima and Takayama, *Ber.*, **53**, 1097 (1920).

(3) Majima, *ibid.*, **42**, 1418 (1909).

(4) Hill, Mattacotti and Graham, THIS JOURNAL, **56**, 2736 (1934).

cyclic ketals of benzophenone, are split rapidly and completely by dilute alcoholic hydrochloric acid to benzophenone and the catechol. In common with benzyl and cyclic benzal ethers they undergo hydrogenolysis in the presence of palladium catalyst.[5,6] It is therefore clear that the influence which hinders the splitting of the 2-alkoxy-3-alkyl-catechols has been overcome in this derivative. On the other hand, these ethers are stable to prolonged heating with 25% alcoholic potassium hydroxide and to continued refluxing with the Grignard reagent (*n*-butylmagnesium bromide).

Catechol diphenylmethylene ether has been prepared by mixing catechol and diphenyldichloromethane in the absence of solvent[7]; in our experience this method of preparation leads to the formation of considerable amounts of highly colored by-product.[8] The condensation may be carried out with more facility in benzene, or, following the observation of Aschan[9] that pinene has a remarkable avidity for hydrogen chloride, in pinene, with almost quantitative yield. The latter procedure should be of particular use whenever the hydrogen chloride produced in this condensation can attack other parts of more complex catechols, for when the reaction was carried out in the common basic solvents the yields were low.

The suggestions of Dr. Jonathan L. Hartwell and the technical assistance of Mary G. Geissler are gratefully acknowledged.

Experimental

All melting and boiling points are corrected values.

Catechol, m. p. 103–104°, was obtained from the Eastman Kodak Company.

4-*t*-Butylcatechol was kindly supplied by the Dow Chemical Company. This practical grade was recrystallized from peroxide-free petroleum ether as silky needles melting at 57–58°.

3-*n*-Propylcatechol was prepared through the reduction of 3-allylcatechol, obtained in turn by means of the Claisen rearrangement of monoallyl catechol ether. One hundred g. (0.91 mole) of catechol, 72.5 g. (0.55 mole) of allyl bromide, 83 g. (0.60 mole) of anhydrous potassium carbonate powder, and 150 cc. of reagent grade acetone were mixed and allowed to stand with occasional shaking for ten hours. The mixture was then heated under a reflux condenser for eight hours, the acetone was removed by distillation, and the oil which separated after the addition of water was dried and distilled, b. p. 94–98° (0.35 mm.). The product was dissolved in ether and extracted with 100 cc. of 5 *N* sodium hydroxide containing 0.5 g. of sodium hydrosulfite. The ether layer, after being dried and evaporated, yielded 5.5 g. of diallyl catechol ether. The alkaline solution was immediately acidified and extracted with ether; after drying with anhydrous sodium sulfate the solution was distilled, yielding a fraction of 43 g. (52% based on the allyl bromide used), b. p. 87–89° (0.3 mm.), of monoallyl catechol ether.

Forty-two grams of mono-allylcatechol ether (0.28 mole) was warmed in a Wood's metal-bath to 190°. At this point the internal temperature rose rapidly to 255–260°; the liquid was then distilled, yielding a fraction of 23 g. (55%) of 3-allylcatechol, b. p. 142–150° (13 mm.). Kawai[10] has reported this boiling point to be 141–146° (16 mm.). This compound was hydrogenated quantitatively with Adams catalyst at atmospheric pressure to 3-*n*-propylcatechol, m. p. after vacuum sublimation, 73–74°. Kurosawa[11] reports a value of 70–72° for this compound.

Diphenyldichloromethane was obtained in 93% yield from benzophenone and phosphorus pentachloride, following the method of Gattermann and Schulze.[12]

Pinene was distilled from a technical product (Eastman Kodak Company); the fraction boiling at 156–158° was employed in our experiments.

Catechol Diphenylmethylene Ether.—A. Preparation in the absence of solvent: 0.01 mole of catechol and of diphenyldichloromethane were mixed in a small flask and gently warmed. Hydrogen chloride was vigorously evolved; when the evolution ceased, the residue was taken up in dry ether and passed through a 50 × 50 mm. column of activated alumina. The red by-product remained on the column. The eluate was evaporated, taken up in alcohol and cooled. White needles formed rapidly; after sublimation they melted at 94–94.6°. The yield was 69.5%. When the reaction was carried out in anhydrous benzene the yield was 73%; the formation of by-product was somewhat abated.

Anal.[13] Calcd. for $C_{19}H_{14}O_2$: C, 83.25; H, 5.10. Found: C, 83.41; H, 5.20.

B. Preparation in Pinene.—To 23.7 g. (0.1 mole) of diphenyldichloromethane dissolved in 60 g. (0.44 mole) of freshly distilled pinene was added gradually and with stirring 11.0 g. (0.1 mole) of catechol, and the mixture, protected from moisture, was heated on a steam-bath for ten hours. There were no overt signs of reaction; the mixture was then distilled, all unreacted components and by-products being removed below 191° at 8 mm., the boiling point of the ether. The crude product solidified in the distillation apparatus; it weighed 26.9 g. (98%) and melted at 85–93°. Recrystallized from absolute alcohol and sublimed in vacuum, this material yielded 22.0 g. (80%) of white needles, m. p. 94–94.6°.

The same techniques produced corresponding yields of 70–80% with the other catechols, but in the case of 3-*n*-propylcatechol the reaction took three times as long as in the other cases to go to completion.

3-*n*-Propylcatechol Diphenylmethylene Ether.—This compound crystallized very slowly from absolute alcohol in triangular plates, m. p. 41.5–42°.

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.6; H, 6.33. Found: C, 83.5; H, 6.28.

4-*t*-Butylcatechol Diphenylmethylene Ether.—This compound crystallized readily from absolute alcohol in plates, m. p. 138–139°.

Anal. Calcd. for $C_{23}H_{22}O_2$: C, 83.7; H, 6.67. Found, C, 83.87; H, 6.72.

Acid Hydrolysis of the Ethers.—One gram of the ether was suspended in 15 cc. of 66% alcohol and 1 cc. of 12 *N* hydrochloric acid was added. The mixture was then refluxed for one hour after the cyclic ether had gone into solution; after distilling the alcohol the residue was taken up in 100 cc. of ether and extracted with four 25-cc. portions of 5 *N* sodium hydroxide containing 0.5% sodium hydrosulfite. The alkaline extract was quickly acidified and extracted continuously with ether for several hours; after drying with sodium sulfate and evaporation an almost quantitative yield of the catechol remained. Vacuum sublimation of the crude material produced the pure substance in 85–90% yields.

(5) See, for leading references, Richtmyer, THIS JOURNAL, **56**, 1633 (1934), and ref. 6.

(6) Baltzly and Buck, *ibid.*, **65**, 1984 (1943).

(7) Sachs and Thonet, *Ber.*, **37**, 3328 (1904).

(8) *Cf.* Fieser and Hartwell, THIS JOURNAL, **57**, 1484 (1935).

(9) Aschan, *Översikt Finska Vetenskaps-Soc. Förh.*, 58 (1916).

(10) Kawai, *Sci. Papers Inst. Phys. Chem. Research* (Tokyo), **3**, 263 (1925).

(11) Kurosawa, *Ber.*, **48**, 1603 (1915).

(12) Gattermann and Schulze, *ibid.*, **29**, 2944 (1896).

(13) We are indebted to Dr. Arthur T. Ness for the microchemicol analyses.

In one instance the alkali-insoluble fraction was isolated by drying and evaporating the ether solution. From the residue was obtained a 2,4-dinitrophenylhydrazone melting at 238–239°. Its equal mixture with authentic benzophenone 2,4-dinitrophenylhydrazone (m. p. 238–239°) melted at 238–239°.

Hydrogenolysis of Catechol Diphenylmethylene Ethers.—Palladium oxide was prepared according to the directions of Starr and Hixon.[14] Ten mg. of this catalyst took up 2.5 cc. of hydrogen. The activity of the catalyst with respect to the splitting of benzyl ethers was established by the hydrogenolysis of benzyl tetra-acetyl-β-glucoside ($[\alpha]_D$ −52.3°) kindly furnished for the purpose by Dr. N. K. Richtmyer. This compound was cleaved quantitatively under the conditions already described by Dr. Richtmyer and in duplication of his results.[5]

To 1.0 g. of the catechol diphenylmethylene ether in 100 cc. of absolute alcohol was added 0.5 g. of palladium oxide. This mixture took up the theoretical quantity of hydrogen in ten to twelve hours. After completion of the reduction the alcohol was evaporated; the residue was dissolved in ether and extracted as described above. The sublimed products possessed the melting points of the pure catechols and these were not depressed by mixture with the corresponding authentic catechol. The yields were 80–85% of the theoretical. The alkali-insoluble fraction in the ether solution was a low melting solid, presumably diphenylmethane, which was not further investigated.

(14) Starr and Hixon, "Organic Syntheses," A. H. Blatt, Editor, John Wiley and Sons, New York, N. Y., 1943, Coll. Vol. II, p. 566.

Action of Alkali on Catechol Diphenylmethylene Ethers.—One gram of the cyclic ether was added to 25 cc. of a 25% solution of potassium hydroxide in methanol and the mixture, protected from atmospheric carbon dioxide, was refluxed for seventy-two hours. It was then cooled at 0° for forty-eight hours; the crystals which formed were filtered off and washed with ice-cold methanol. The product was identical with the starting material and was recovered in 90–95% yields.

Action of the Grignard Reagent on Catechol Diphenylmethylene Ethers.—The Grignard reagent was formed from 1 g. of 1-bromobutane, b. p. 100–101°, and 0.2 g. of magnesium turnings in 50 cc. of dry ether. To this reagent, protected by dry nitrogen, was added 1 g. of the catechol diphenylmethylene ether; the mixture was refluxed for forty-eight hours. At the end of this period, the solution was thrown on ice and exactly neutralized with 1 *N* hydrochloric acid. The ether layer was dried and evaporated and the residue was recrystallized from absolute alcohol. The original cyclic ether was recovered in 90–95% yield.

Summary

The preparation and properties of the diphenylmethylene ethers of catechol, 3-*n*-propylcatechol, and 4-*t*-butylcatechol, have been studied. Although these ethers are resistant to alkali and to the Grignard reagent, they are cleaved by dilute mineral acid and by catalytic hydrogenation.

BETHESDA, MARYLAND RECEIVED APRIL 17, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

A Comparative Study of the Kinetics and Mechanisms of Formation of the Phenylhydrazone, Semicarbazone and Oxime of *d*-Carvone[1,2]

BY G. H. STEMPEL, JR., AND GERSON S. SCHAFFEL

The assumption that the reactions of a ketone with the carbonyl reagents, such as phenylhydrazine, semicarbazide and hydroxylamine, proceed by identical mechanisms has heretofore been generally accepted without direct experimental evidence.[3,4] The object of this investigation was to determine the correctness of this assumption by means of a comparative study of the kinetics of these reactions, as well as to obtain data which could lead to a better picture of such a common mechanism.

The kinetics of these reactions were followed by observing the change of rotation during the reactions of the carbonyl reagents with the optically active ketone, *d*-carvone. One of the more important considerations which led to the choice of *d*-carvone is that the optically active center of the molecule is not alpha to the carbonyl group, and consequently enolization of the ketone does not bring about racemization[5] as it does in the case of *l*-menthone.

In order to compare these reactions, the following four characteristics were studied: (1) effect of added neutral salts upon the velocity constants; (2) dependence of their rates upon the carvone concentration; (3) dependence of their rates upon carbonyl reagent concentration; and (4) determination of whether the reactions are general or specific acid catalyzed.

Experimental

Reagents.—The *d*-carvone used in these experiments was an Eastman Kodak Co. product which was further purified by the method of Wallach[6] through the formation of a "hydrosulfide" with hydrogen sulfide which was recrystallized several times from alcohol and then reconverted to *d*-carvone by refluxing with aqueous alkali. The regenerated *d*-carvone was carefully distilled, after which it exhibited the following properties: b. p. 230°, corrected to 760 mm. pressure; $[\alpha]^{30}_{5461}$ 73.33°; $n^{20}D$ 1.5005 ± 0.0003. In 83% aqueous alcohol, a solvent in which many of the rate experiments were performed, a 0.4000-g. sample dissolved in sufficient 83% alcohol to make 100 ml. of solution gave $[\alpha]^{30}_{5461}$ 68.53°.

The semicarbazide, phenylhydrazine and hydroxylamine hydrochlorides employed were Eastman Kodak Co. products which were recrystallized several times from

(1) Presented before the Division of Organic Chemistry of the American Chemical Society at Detroit in April, 1943.

(2) Abstracted from the thesis submitted by Gerson S. Schaffel to the Committee on Graduate Instruction at Carnegie Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Science.

(3) Conant and Bartlett, THIS JOURNAL, 54, 2881 (1932).

(4) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 333–334.

(5) Bartlett and Vincent, THIS JOURNAL, 55, 4992 (1933).

(6) Wallach, *Ann.*, 305, 224 (1899).