was acidified with hydrochloric acid, and, after cooling, the precipitated pyridazone filtered. After washing with several liters of hot distilled water the 1-(*p*-nitrophenyl)-4-hydroxypyridazone-6 weighed 15 g. (76%) and melted with decomposition at 298–299°. Recrystallization from an alcohol–water mixture only raised the melting point of this product to 299–300°. Its neutral equivalent was 226 (calcd. 233).

Anal. Calcd. for $C_{10}H_7O_4N_3$: N, 18.0. Found: N, 17.9.

1 - (*p* - Aminophenyl) - 3 - carboxy - 4 - hydroxypyridazone-6 and 1-(*p*-aminophenyl)-4-hydroxypyridazone-6.—These amino compounds were prepared by shaking a solution (or suspension) of 0.03 mole of the sodium salt of the corresponding nitro compounds in 125 ml. of water with 1 g. of Raney nickel at 500 lb. pressure of hydrogen. The reductions proceeded rapidly at 50°. A 65% yield of 1-(*p*-aminophenyl)-3-carboxy-4-hydroxypyridazone-6, that melted at 297–299° with the evolution of carbon dioxide and had a neutral equivalent of 126 (calcd. 123.5), was obtained.

Anal. Calcd. for $C_{11}H_9O_4N_3$: N, 17.0. Found: N, 16.8.

The yield of 1-(*p*-aminophenyl)-4-hydroxypyridazone-6 was 60% of the theoretical. This compound melted at 250–251° and had a neutral equivalent of 203 (calcd. 202).

Anal. Calcd. for $C_{10}H_9O_2N_3$: N, 20.8. Found: N, 20.5.

Summary

The products of reaction of ketene diethylacetal with phenyl-, *p*-ethoxyphenyl-, *p*-nitrophenyl- and *p*-carbethoxyphenyldiazonium chloride are reported. Regardless of the nature of the substituent in the aryl nucleus of the diazonium salt, the main reaction product is a 1-aryl-4-ethoxypyridazone-6 (II) which was obtained in 25–35% yields. The formation of this product involves the addition of the diazonium salt across two molecules of the acetal.

With the substituted phenyldiazonium salts products that indicate the addition of the salt to a single molecule of the acetal are formed. The most important of these is ethyl *p*,*p*′-diethoxydiphenylformazyl formate (IV) which was obtained in 27% yields from the reaction of *p*-ethoxyphenyldiazonium chloride with ketene acetal.

MADISON, WISCONSIN RECEIVED AUGUST 5, 1943

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

Ketene Acetals. XIII. The Cyclic Trimerization of Ketene Diethylacetal by Hydrogen Fluoride: 1,1,3,3,5,5-Hexaethoxycyclohexane

BY S. M. MCELVAIN AND J. W. LANGSTON[1]

In the seventh paper[2] of this series the unusual behavior of ketene acetal with hydrogen fluoride was reported. This acid, instead of adding to one or two molecules of the acetal as did the other acids that were studied, caused a polymerization of the acetal. The nature of this polymeric product was not investigated but it appeared to consist of much more of the distillable liquid polymers of ketene acetal[3] than were obtained when cadmium chloride was used to bring about the polymerization. This latter catalyst converted the acetal mainly to a solid polymer composed of chains containing, on an average, 22–23 ketene acetal units.[4] However, it was possible to separate by distillation a small amount of liquid polymer from this solid polymer and then to separate further this liquid material into a dimer and a trimer fraction. Because of the fact that both γ-acetoacetoacetic ester and 1,3,5-triethoxybenzene (I) were isolated from the trimer fraction, it appeared that it contained both the open chain trimer and the cyclic trimer, 1,1,3,3,5,5-hexaethoxycyclohexane (II).

Since hydrogen fluoride converted ketene acetal mainly into liquid polymers, it seemed advisable to study further this polymerization in the hope that the yield of the trimer fraction might be materially increased and that the hexaethoxycyclohexane (II) could be isolated. The present paper is a report of the results of this investigation.

It is quite likely that one of the reasons that low molecular weight liquid polymers were obtained in the earlier work[2] with hydrogen fluoride was that the polymerization had occurred in an ethereal solution and that the separation of the monomer molecules by those of the solvent had favored the formation of these lower polymers. If this were true it appeared that the optimum yield of the trimer fraction would be dependent upon the nature of the reaction medium, the dilution and the ratio of the reactants. After a number of exploratory experiments it was found that diethyl ether was superior to such hydrocarbons as benzene and petroleum ether as a reaction medium and that about 5 mole per cent. of hydrogen fluoride gave the best yield of the distillable liquid polymers of ketene acetal. A 1% solution of the acetal in ether was found to be the concentration that gave the optimum yield of the trimer fraction; a 10% solution gave considerable of the solid polymer while with a 0.1% solution the amount of the trimer fraction was not substantially larger than that obtained with the 1% solution. From this latter dilution of ketene acetal in ether it was possible to obtain, with 5 mole per cent. of hydrogen fluoride, 12–14% of the weight of the acetal as a dimer fraction, which corresponded in properties to that previously reported,[4] and 40–45% of the weight of the acetal as a trimer fraction that boiled at 105–110° (0.5 mm.).

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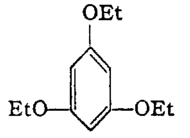
[1] Harshaw Chemical Company Fellow, 1942–1944.

[2] McElvain and Kundiger, THIS JOURNAL, **64**, 254 (1942).

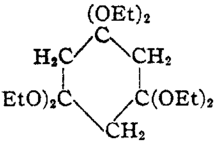
[3] D. G. Kundiger, Ph.D. Thesis, University of Wisconsin, 1942.

[4] Johnson, Barnes and McElvain, THIS JOURNAL, **62**, 964 (1940).

The trimer fraction on cooling partially solidified and yielded on filtration a white crystalline product which, after recrystallization from absolute alcohol, melted at 72–74°. This compound proved to be the cyclic trimer of ketene acetal, 1,1,3,3,5,5-hexaethoxycyclohexane (II), and in most of the runs it comprised about half the weight of the trimer fraction or about 22% of the ketene acetal that was used. The additional amount of this cyclic trimer that remained dissolved in the liquid portion of the trimer fraction was estimated by conversion to the ether (I). The quantity of this latter compound that may be obtained from the pyrolysis of the trimer fraction gives a fairly accurate measure of the amount of the cyclic trimer (II) that is present in this fraction.



I



II

The cyclic trimer II, as its ketal structure would indicate, is quite stable to alkali but very sensitive to acids. It may be heated in a refluxing aqueous solution of alkali without causing any change in melting point, but the slightest trace of acidity causes it to lose alcohol and pass, to varying extents, into enolic ethers of which I is the final product. As a matter of fact, it is necessary, if the yields of II that are mentioned above are to be obtained from the trimer fraction, that the interior of the apparatus in which this fraction is distilled be allowed to stand in contact with an aqueous solution of sodium hydroxide for twenty-four to forty-eight hours before rinsing, drying and carrying out the distillation. If this precaution is not taken, and particularly if the distillation of the trimer fraction is carried out in an apparatus that has been cleaned with an acidic cleaning solution, the distillate may not solidify and none of the product (II) may be obtained. It is advisable also to use alkali-washed beakers and flasks for the recrystallization of this product.

The cyclic trimer (II) may be converted in good (80–85%) yields into the phloroglucinol triethyl ether (I) by pyrolysis in the presence of a trace of acid. This ether boils at 97–98° (0.1 mm.) and melts at 42–43°. The trimer also may be hydrolyzed to phloroglucinol under weakly acid conditions. Carbonic acid was found to be most satisfactory for this purpose; stronger acids, both organic and inorganic, in dilute aqueous solutions convert the trimer into a dark red resin.

It is an interesting fact that methylketene acetal is not polymerized by either cadmium chloride or hydrogen fluoride.[5] In this behavior it resembles the halogenoketene acetals.[4] This homolog of ketene acetal reacts with hydrogen fluoride as it does with other acids to give ethyl propionate and ethyl fluoride, thus

$$CH_3CH{=}C(OEt)_2 + HF \longrightarrow CH_2CH_3COOEt + EtF$$

Experimental

Polymerization of Ketene Acetal with Hydrogen Fluoride: 1,1,3,3,5,5-Hexaethoxycyclohexane.—A solution of 25 g. of ketene acetal in 2.5 l. of absolute ether was placed in a 3-liter 3-necked flask that was fitted with an efficient mechanical stirrer, a drying tube and a small dropping funnel, the stem of which was of sufficient length to drop material directly onto the swirling liquid. Then a solution of 0.25 g. of anhydrous hydrogen fluoride in 17 ml. of absolute ether was dropped into the acetal solution over a period of five to ten minutes. The stirring was continued for a few minutes to ensure thorough mixing, and then the solution was allowed to stand tightly stoppered for seven to fourteen days. During this time a reddish color developed in the ether solution.

The ether then was distilled off until 150–200 ml. of solution remained. This residue was cooled and shaken with 10 ml. of 10% aqueous sodium hydroxide solution to remove any free acid and after washing twice with water, the ether layer was dried over potassium carbonate for several hours. After filtering off the potassium carbonate and distilling the ether, the remaining residue was fractionated under diminished pressure through a 10-cm. Widmer column. The following fractions were collected under 0.5 mm. of pressure: (a) 0.16 g., b. p. 51–60°; (b) 3.57 g., b. p. 60–71°; (c) 0.46 g., b. p. 71–105°; (d) 10.0 g., b. p. 107–120°; (e) 0.18 g., b. p. 120–125°; (f) 2.34 g. residue. In the cold trap of the distillation train 3.76 g. of material collected.

The properties of fraction (b) showed it to be the dimer.[4] Fraction (d) was the trimer. As it collected in the receiver it began to crystallize and after it was distilled the entire fraction appeared solid. It was kept overnight in an ice-bath and then filtered with suction. The crystals that were obtained weighed 5.0 g. and melted at 66–70° after pressing on a clay plate for a few minutes. The filtrate, which had become somewhat red in color, was kept in an ice-bath for two days during which time more crystals formed. After filtering and drying on a porous plate, these crystals weighed 0.6 g., bringing the total yield to 5.6 g. Recrystallization of this product from absolute ethyl alcohol gave 1,1,3,3,5,5-hexaethoxycyclohexane that melted at 72–74°.

Anal. Calcd. for $C_{18}H_{36}O_6$: C, 62.2; H, 10.4; C_2H_5O, 77.6. Found: C, 62.0; H, 9.8; C_2H_5O, 77.6.

The material in the cold trap when fractionated was found to consist of approximately one part of ethyl alcohol and two parts of ethyl orthoacetate.

Samples of the cyclic trimer on standing gradually lose alcohol and become liquid. This loss of alcohol, as seen in the following experiment, is catalyzed by acid. For this reason it is necessary that flasks, beakers, etc., in which the trimer is handled be allowed to stand for 24–48 hr. filled with a 20% solution of sodium hydroxide before use.

Pyrolysis of the Cyclic Trimer to Phloroglucinol Triethyl Ether.—One gram of the cyclic trimer was placed in a small distilling flask and melted. The surface of the liquid then was touched with the end of a glass rod moistened with concentrated sulfuric acid. A red color began to develop immediately. A boiling stick was added and the flask heated with a free flame to distil out the ethyl alcohol. Approximately 0.4 g. (100%) of alcohol was collected at 77–79°. The residue, which had darkened considerably, was washed out of the distillation flask with hot water into another flask for steam-distillation and the reaction product steam-distilled until no more oil came over. On cooling in an ice-bath the oily material in the distillate solidified. After filtering and drying on a clay plate, the solid phloroglucinol triethylether weighed 0.50 g. (83%) and melted at 40–43°. After recrystallization from dilute alcohol it melted at 42–43°.[4,6]

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[5] The experiments with methylketene acetal were carried out in this Laboratory by Mr. Carl M. Moser.

[6] Will and Albrecht, *Ber.*, **17**, 2107 (1884).

In some of the runs with ketene acetal and hydrogen fluoride the trimer fraction that was obtained failed to solidify. In such cases the above pyrolysis to the ether of phloroglucinol was used to estimate the amount of the cyclic trimer that was present in the trimer fraction. An 8.5 g. sample of this fraction was placed in a small distilling flask, a drop of concentrated sulfuric acid added, and the mixture heated (free flame) until no more ethyl alcohol distilled out. The residue then was transferred to a small 3-necked flask fitted with an efficient mechanical stirrer, treated with approximately 50 ml. of 20% sodium hydroxide solution and the mixture refluxed with stirring for two to three hours. The resulting mixture then was steam-distilled until no more oil came over. The oily distillate was taken up in ether, separated from the water layer, and dried. The phloroglucinol triethyl ether, after removal of the ether solvent, distilled at 98–106° (0.4 mm.), and weighed 2.12 g. On cooling in an ice-bath, it solidified to a product that melted at 41–43°. This weight of the ether corresponds to 3.68 g. of cyclic trimer. Assuming an 85% recovery of the triether (see above pyrolysis) this trimer fraction contained 4.34 g. of the cyclic trimer. This procedure also may be used to estimate the amount of cyclic trimer left in the filtrate after the initial crop of crystals of the solid trimer has been filtered off.

Hydrolysis of Cyclic Trimer to Phloroglucinol.—Two grams of the cyclic trimer was placed in a small flask with 10–15 cc. of water. Enough ethyl alcohol was added to give a clear solution when hot. Dry-ice (3–4 g.) was dropped into this solution over a period of fifteen to twenty minutes. During this time sufficient heat was applied to the flask to keep its contents just above room temperature. About one-third of the solvent was evaporated from the solution on a steam-bath and the remainder filtered into a small evaporating dish and the filtrate evaporated to complete dryness under a current of air. The remaining residue of phloroglucinol was dried in an oven at about 150° for an hour, after which it weighed 0.60 g. (83%) and melted at 195–205°. The product was recrystallized from water, after boiling with charcoal, filtering and adding a few drops of dilute hydrochloric acid just before cooling. The white crystals of phloroglucinol so obtained lost water of recrystallization without melting at 110–115° but did not melt until a temperature of 214–217° was reached.

Summary

Ketene acetal in dilute (1%) ethereal solution is converted by anhydrous hydrogen fluoride into the cyclic trimer, 1,1,3,3,5,5-hexaethoxycyclohexane, in approximately 22% yield.

This trimer is pyrolyzed in the presence of a trace of acid into phloroglucinol triethyl ether and hydrolyzed by aqueous carbonic acid into phloroglucinol. These products are obtained in 80–85% yields.

The homologous methylketene acetal is not polymerized by hydrogen fluoride or other catalysts such as cadmium chloride that are effective for the polymerization of ketene acetal. Hydrogen fluoride adds to methylketene acetal to form ethyl propionate and ethyl fluoride.

MADISON, WISCONSIN RECEIVED AUGUST 23, 1943

[CONTRIBUTION FROM THE SCHOOL OF CHEMICAL ENGINEERING OF PURDUE UNIVERSITY]

Studies in Azo Dyes. I. Preparation and Bacteriostatic Properties of Azo Derivatives of 2,6-Diaminopyridine[1]

BY R. NORRIS SHREVE, M. W. SWANEY[2a] AND E. H. RIECHERS[2b]

Many dyes exhibit the common characteristic of possessing a certain specificity in their properties. Some exert specific dyeing action on animal fibers, while others act specifically toward vegetable fibers or give characteristic precipitates with metals (analytical reagents). Likewise, a great many dyes have been observed to exhibit a similar specificity with respect to various organisms and have found widespread use in medicine. Typical of this class is 2,6-diamino-3-phenylazo-pyridine hydrochloride which, when ingested orally, goes via the blood stream to the kidneys whence it is eliminated by the urine to which it imparts a marked red color.

With a fundamental specificity existing in a dye, or in class of dyes, it then becomes of interest to consider the alteration of some portion of the molecule in order to modify its individual effect in medicine or in dyeing textiles. Thus, certain derivatives of diaminopyridine and hydroxyquinoline[3] have been prepared and their properties studied, with the object of ascertaining whether a wider field of application is possible for compounds of this type. This particular paper concerns itself with the synthesis and properties of azo dyes prepared by coupling various diazotized aromatic amines with 2,6-diaminopyridine, and naturally follows in line with the study carried on in these laboratories pertaining to the production of heterocyclic amines,[4] and the production of germicidal mercury compounds containing the pyridine nucleus.[5]

Chichibabin and Zeide[6] first published information concerning the first member of this series of dyes from diaminopyridine. This compound, 2,6-diamino-3-phenylazo-pyridine, possesses the formula

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(1) Abstracted from the Ph.D. theses of M. W. Swaney and E. H. Riechers. Details of the yields of each dye and of the color of the hydrochloride and of the base are given in a fuller tabulation deposited with the American Documentation Institute, 1719 N St., N.W., Washington, D. C.; order Document 1801, remitting 50¢ for microfilm or 50¢ for photocopies. Original manuscript received May 1, 1942.

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(2b) Present address, 6408 Van Buren St., Hammond, Indiana.

(3) R. Norris Shreve and R. B. Bennett, THIS JOURNAL, **65**, 2243 (1943).

(4) R. Norris Shreve, E. H. Riechers, H. Rubenkoenig and A Goodman, *Ind. Eng. Chem.*, **32**, 172 (1940).

(5) M. W. Swaney, M. J. Skeeters and R. Norris Shreve, *ibid.*, **32** 360 (1940).

(6) A. F. Chichibabin and O. A. Zeide, *J. Russ. Phys.-Chem. Soc.* **46**, 1216 (1914); *cf.* A. E. Chichibabin and E. O. Issitrowa, THIS JOURNAL, **56**, 1711 (1934).