

Experimental

Preparation of Amines: N,N-Dimethylfurfurylamine and N,N-Diethylfurfurylamine.—One mole of the desired dialkyl amine (dimethylamine and diethylamine), liberated from the corresponding hydrochloride, was bubbled slowly with stirring into one mole of formic acid (87%, sp. gr. 1.20) in the cold. The mixture was then distilled up to a temperature of 135°, the residues being for the most part crude N,N-dimethylformamide and N,N-diethylformamide. The residue in each case was placed in a one-liter round-bottom flask. One-fifth of a mole of furfural was added slowly over a period of thirty minutes. The mixture was heated under reflux on an oil-bath at a temperature of 150–170° for three to four hours, at which time the reaction had subsided. The mixture was cooled and diluted with 200 ml. of water, made strongly alkaline with sodium hydroxide and distilled until all volatile substances were carried over by the steam. The residue was then steam distilled, the volatile dimethylfurfurylamine in the one case and diethylfurfurylamine in the other distilling over. The distillate was then treated with strong alkali and extracted with ether. The ether-base mixture was dried over solid sodium hydroxide. The ether was removed by distillation. The resulting di-alkylfurfurylamine was purified by distillation. For dimethylfurfurylamine: b. p. 142–145°; yield 20.5 g. (85%). For diethylfurfurylamine: b. p. 169–172°; yield 20 g. (68%). The corresponding picrates of the above amines were pre-

pared as suitable derivatives. Dimethylfurfurylamine picrate, m. p. 102–103°. *Anal.* Calcd. for $C_{13}H_{14}N_4O_8$: N, 15.82. Found: N, 15.71. Diethylfurfurylamine picrate, m. p. 84–85°. *Anal.* Calcd. for $C_{15}H_{18}N_4O_8$: N, 14.66. Found: N, 14.55.

Preparation of Trialkylfurfurylammonium Iodides.—Dimethylalkylfurfurylammonium iodides and diethylalkylfurfurylammonium iodides were prepared by the following general method. The alkyl group varied from methyl to stearyl inclusive. To 0.02 mole of the dialkylfurfurylamine, in a 25-ml. round-bottom flask equipped with condenser, was added 0.02 mole of the appropriate alkyl iodide. The mixture was heated at 40–100° for one to twenty-four hours, depending on the volatility and reactivity of the alkyl iodide in question. The tri-alkylfurfurylammonium iodides obtained in good yields (av. 95%) were recrystallized from absolute alcohol-ethyl acetate or absolute alcohol-petroleum ether (see table).

Summary

1. Dimethylfurfurylamine and diethylfurfurylamine were prepared. The corresponding picrates were prepared as suitable derivatives of these amines.

2. A series of dimethylalkylfurfurylammonium iodides and of diethylalkylfurfurylammonium iodides were prepared.

ST. LOUIS, MISSOURI

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(7) All temperatures listed are corrected.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF MISSOURI]

The Synthesis of Acetylenic Ketones from Acid Anhydrides and Sodium Phenylacetylene

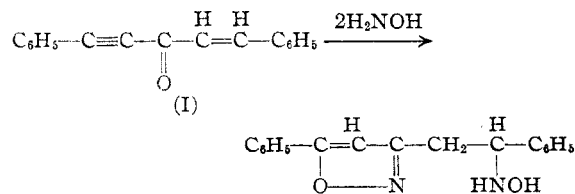
BY DOROTHY NIGHTINGALE AND FRANCIS WADSWORTH^{1,2}

This investigation was undertaken preliminary to a problem requiring acetylenic ketones in large amounts. The reaction of sodium phenylacetylene with low molecular weight acid chlorides³ is troublesome and yields are variable. Ethyl phenylpropiolate for use with a Grignard reagent as described by Hurd and Cohen⁴ is not readily available. Kroeger and Nieuwland⁵ reported a 40–45% yield of phenylethynyl methyl ketone from phenylethynylmagnesium chloride and acetic anhydride, but all attempts in this Laboratory to prepare the ketone by this method, either by adding the anhydride to the Grignard reagent or *vice versa*, have resulted only in bis-phenylethynylmethylcarbinol.

Sodium phenylacetylene reacts smoothly with acid anhydrides and gives consistently better yields of ketone than do the corresponding acid chlorides. Neff³ reports a satisfactory yield of ketone from acetic anhydride but apparently the

use of anhydrides in this reaction has not been extended.

The product (I) of the reaction of sodium phenylacetylene with cinnamic anhydride differs markedly in its properties from the cinnamoylphenylacetylene reported by Worrall.⁶ (I) has the composition required for cinnamoylphenylacetylene and reacts with hydroxylamine hydrochloride presumably as follows



(I) gives a dark red color with cold concentrated sulfuric acid rather than the purple color produced with Worrall's compound, and the sulfuric acid solution has only a slight fluorescence. Our ketone (I) does not give a color with Folin's reagent whereas Worrall's compound gives a positive test at once. The properties listed by Worrall for his compound, notably its behavior with the Grignard reagent and the fact that it does not react with hydroxylamine hydrochloride, are

(6) Worrall, *ibid.*, 60, 1266 (1938).

(1) Present address: Pan American Oil Company, Texas City, Texas.

(2) (a) Presented at the 105th meeting of the American Chemical Society, Detroit, Michigan, April, 1943. (b) Abstract of a portion of the dissertation to be submitted by Francis Wadsworth in partial fulfillment of the requirement for the degree of Doctor of Philosophy at the University of Missouri.

(3) Neff, *Ann.*, 308, 275 (1903).

(4) Hurd and Cohen, *This Journal*, 53, 1068 (1931).

(5) Kroeger and Nieuwland, *ibid.*, 58, 1861 (1936).

quite unusual for a ketone of the structure of cinnamoylphenylacetylene. It is possible that his compound is an isomer of cinnamoylphenylacetylene. Further work will be required to establish the relationship of the two compounds.

Crotonic anhydride reacts vigorously with sodium phenylacetylene to form crotonylphenylacetylene. Worrall was unable to obtain this ketone from ethyl crotonate and sodium phenylacetylene.

Ketones,⁷ ketoacids⁸ and ketoesters⁹ have been prepared in good yields from cadmium alkyls or aryls and acid chlorides, acid anhydrides and acid chlorides of half esters. It seemed reasonable that *bis*-phenylethynylcadmium could be prepared from phenylethynylmagnesium bromide and that it would react with acid chlorides or acid anhydrides to yield acetylenic ketones. The only product identified from the reaction of *bis*-phenylethynylcadmium and either acetyl chloride or acetic anhydride was *bis*-phenylethynylmethylcarbinol in 13% yield. The test of Gilman and Schulze¹⁰ was positive and indicated that the conversion of phenylethynylmagnesium bromide to *bis*-phenylethynylcadmium was incomplete.

For comparison, several cadmium alkyls were added to cinnamoyl chloride and crotonyl chloride, but none of the unsaturated ketones could be isolated from the viscous oils which were formed. Diethylcadmium and diphenylcadmium were added to phenylpropionyl chloride with similar results, but diphenylcadmium and cinnamoyl chloride yielded benzalacetophenone.

Acetylphenylacetylene apparently reacted with one mole of butadiene. The adduct reacted with semicarbazide hydrochloride but analyses of both products indicated that they contained impurities. No pure product could be obtained from *n*-butylphenylacetylene or benzoylphenylacetylene and dienes.

Work on this problem will be continued at a later date.

Acknowledgment.—The special chemicals for this problem were purchased from a grant by the University Research Council.

Experimental¹¹

The liquid acid anhydrides were carefully fractionated just before use to remove free acid. Dry ether was used in all reactions.

Acetylphenylacetylene.—Phenylacetylene (76 g., 0.75 mole) in 50 cc. of ether was converted to sodium phenylacetylene¹² by reaction with 16.8 g. of sodium in 100 cc. of ether. After the addition of 100 cc. of ether, the suspension of sodium phenylacetylene was siphoned slowly with stirring into acetic anhydride (76 g., 0.75 mole) in 200 cc. of ether in a one liter three-necked flask fitted with a condenser and stirrer and immersed in an ice-bath. The mixture was stirred for several hours. Cold dilute hydro-

chloric acid was added to the reaction product and the mixture allowed to stand until the anhydride was hydrolyzed. The ether layer was washed thoroughly with sodium carbonate solution, dried over magnesium sulfate and vacuum distilled; yield, 58 g. (55%), b. p. 120–125° (14 mm.).

When acetyl chloride was used in place of acetic anhydride in the above procedure, the yield of ketone was 25%. If the acid chloride was added to the sodium phenylacetylene, the product distilled over a wide range and a large amount of resin remained in the distilling flask.

The yields of ketones from propionic anhydride and *n*-butyric anhydride were 53%. The ketones were identified by conversion to isoxazoles or pyrazoles.¹³

Benzoylphenylacetylene.—The ketone was prepared from benzoic anhydride; yield, 60%, b. p. 175° (7 mm.).

Benzoylphenylacetylene was also prepared as follows: Benzoic anhydride (82 g.) and sodium (8.4 g.) were suspended in 300 cc. of ether. To this was slowly added 37 g. of phenylacetylene in 50 cc. of ether. Stirring was continued until there was no further evidence of reaction; yield, 25.5 g. (34%).

***n*-Caproylphenylacetylene.**—This ketone was prepared from *n*-caproic anhydride; yield, 24%; b. p. 135° (19 mm.).

Anal. Calcd. for C₁₄H₁₈O: C, 84.00; H, 8.00. Found: C, 84.00; H, 8.23.

3-Amyl-5-phenylpyrazole.—M. p. 75–76° (alcohol).

Anal. Calcd. for C₁₄H₁₈N₂: C, 78.51; H, 8.41. Found: C, 78.58; H, 8.52.

Cinnamoylphenylacetylene (I).—The ketone was prepared from cinnamic anhydride (0.18 mole). The crude ketone was recrystallized from petroleum ether; yield 14 g. of pure ketone. The pale yellow needles melted at 69–70° as compared with 140–141° for Worrall's compound. A mixture of the two compounds melted at 61–110°.

Anal. Calcd. for C₁₇H₁₂O: C, 87.93; H, 5.17. Found: C, 87.57; H, 5.56.

The ketone (1 g.), 0.5 g. of hydroxylamine hydrochloride and 0.75 g. of sodium acetate were dissolved in 8.5 cc. of alcohol and refluxed for ten hours. After removal of the sodium chloride, 0.25 g. of solid separated from the filtrate. It crystallized from benzene in white needles, m. p. 172–173.5°.

Anal. Calcd. for C₁₇H₁₆N₂O₂: C, 72.85; H, 5.71. Found: C, 72.90; H, 6.01.

Crotonylphenylacetylene.—Sodium phenylacetylene from 37 g. (0.36 mole) of hydrocarbon in 100 cc. of ether was added to 56.2 g. (0.36 mole) of crotonic anhydride in 100 cc. of ether at 0°. The solution was stirred for fifteen hours at room temperature; yield, 30.8 g. (49%); b. p. 140° (6 mm.).

Anal. Calcd. for C₁₂H₁₀O: C, 84.70; H, 5.88. Found: C, 84.30; H, 6.00.

The ketone soon changed to a dark viscous oil on standing. No pure product could be isolated from the reaction with hydroxylamine hydrochloride or hydrazine sulfate. It is an intense lachrymator and skin irritant.

Sodium Phenylacetylene and Succinic Anhydride.—Sodium phenylacetylene from 28 g. (0.27 mole) of hydrocarbon in 80 cc. of ether was added slowly to 30 g. (0.3 mole) of succinic anhydride suspended in 300 cc. of ether. The reaction mixture was stirred twelve hours. The product was decomposed in the usual manner and the ether layer extracted with sodium carbonate. The viscous oily layer which separated when the aqueous layer was acidified was crystallized from a benzene-petroleum ether (80–100°) mixture. The nearly colorless needles melted at 80°; yield, 14 g. (21%).

Anal. Calcd. for C₁₂H₁₀O₂: C, 71.30; H, 4.95; n. e., 202. Found: C, 71.13; H, 4.62; n. e., 203.

(13) Moureu and Brachin, *Bull. soc. chim.*, [3] 31, 170 (1904).

(7) Gilman and Nelson, *Rec. trav. chim.*, 518 (1936).

(8) deBenneville, *J. Org. Chem.*, 6, 462 (1941).

(9) (a) Cason, *THIS JOURNAL*, 64, 1106 (1942); (b) Cason and Prout, *ibid.*, 66, 46 (1944).

(10) Gilman and Schulze, *ibid.*, 47, 2002 (1925).

(11) Semimicroanalyses by D. R. Smith and E. Milberger.

(12) Gilman and Young, *J. Org. Chem.*, 1, 315 (1936).

β -3-(5-Phenylisoxazolyl)-propionic Acid.—A solution of 2 g. of the above 6-phenyl-4-oxo-5-hexynoic acid, 1 g. of hydroxylamine hydrochloride and 1.5 g. of sodium acetate in 15 cc. of alcohol was refluxed for eight hours and allowed to stand overnight. The white solid was crystallized from benzene, m. p. 163–163.5°.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.36; H, 5.07. Found: C, 66.20; H, 5.19.

Phthalic anhydride and sodium phenylacetylene yielded a small amount of a solid soluble in carbonate but of indefinite composition. Most of the phenylacetylene was recovered.

Ethyl phenylpropionate did not react appreciably with sodium phenylacetylene by Worrall's procedure for ethyl cinnamate. Only a small amount of resin was formed and most of the phenylacetylene was recovered.

Acetylphenylacetylene and Butadiene.—The ketone (21 g.) and butadiene (16 g.) were sealed in a Carius tube and heated at 170° for six hours. The reaction product was distilled at 4 mm. The fraction (8.7 g.) which distilled at 140° (4 mm.) was the only one for which analytical data approximated the theoretical.

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.84; H, 7.07. Found: C, 85.68, 85.80; H, 7.04, 7.08.

This fraction reacted with semicarbazide hydrochloride in pyridine solution to form a solid which melted at 187°.

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 70.60; H, 6.6. Found: C, 71.55; H, 6.55.

These data correspond approximately to an adduct with one mole of butadiene and one mole of acetylphenylacetylene. The condensation was repeated under a variety of conditions but only in this one case was a constant boiling fraction obtained. Cyclopentadiene and 2,3-dimethylbutadiene gave no better results. The products boiled over a wide range and none of the fractions would form a semicarbazone.

Preparation of Benzalacetophenone from Cinnamoyl Chloride and Diphenyl Cadmium.—Cadmium chloride (30 g., 0.16 mole) was added to 0.16 mole of phenylmagnesium bromide in 160 cc. of ether. The solution was stirred for

three hours. Cinnamoyl chloride (27.7 g., 0.16 mole) in 100 cc. of ether was added slowly to the stirred suspension of diphenyl cadmium. After the vigorous reaction was over, the mixture was refluxed for one hour and decomposed with cold dilute sulfuric acid. The product was worked up in the usual manner. The benzalacetophenone melted at 50° and did not depress the melting point of an authentic sample; yield, 15.6 g. (44%).

Reaction of Bis-phenylethynylcadmium with Acetic Anhydride and Acetyl Chloride.—Phenylethynylmagnesium bromide was prepared from 0.16 mole of ethylmagnesium bromide in 100 cc. of ether and 0.18 mole of phenylacetylene in 50 cc. of ether. The solution was refluxed for two hours. Cadmium chloride (0.08 mole) was added to the Grignard solution and the mixture stirred for one hour. The acetic anhydride (15.8 g., 0.15 mole) in 15 cc. of ether was added slowly to the cadmium compound.

The product was decomposed with cold dilute acid, the ether layer separated, washed and dried. The dark oil which remained after the removal of the ether crystallized on standing. Extraction with hot alcohol and repeated crystallization from alcohol yielded nearly colorless needles, m. p. 110–111°; yield, 4.5 g. (13.8%). The recorded melting point of *bis*-phenylethynylmethylcarbinol is 111.5–112°. The same compound resulted when acetyl chloride was substituted for acetic anhydride, whether the acid chloride was added to the cadmium compound or *vice versa*. The viscous oils could not be distilled even at 1 mm. without extensive decomposition.

Summary

Sodium phenylacetylene reacts smoothly with various types of acid anhydrides to form acetylenic ketones.

Viscous oils or resins were the principal products from the reaction of cadmium alkyls and unsaturated acid chlorides.

COLUMBIA, MISSOURI

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The Toxic Principles of Poison Ivy. III. The Structure of Bhilawanol¹

BY HOWARD S. MASON

This investigation was undertaken to test degradative methods upon an accessible substance closely related to the toxic principles of poison ivy^{2,3,4,5} preliminary to application of the methods to the poison ivy problem itself.

Bhilawanol is the allergenic oil which has been isolated from the shell of the Indian marking nut tree; it has been shown that hydrobhilawanol

is identical with 3-*n*-pentadecylcatechol, and, by means of bromine titration, that there are two aliphatic double bonds in the parent compound.³ In this study the latter was isolated by a method essentially the same as that previously used³; its physical properties were found to be similar to those already reported and its reactions with qualitative reagents for phenols and catechols were identical. The substance was readily reduced by hydrogen in the presence of Adams catalyst, and 3-*n*-pentadecylcatechol was isolated from the product in 70% yield. However, only 59% of the hydrogen required to saturate two double bonds was absorbed. This is equivalent to 118% of that required for one double bond. In the light of the rapidity with which phenols react with bromine, it seems reasonable to conclude that the degree of unsaturation observed by Pillay and Siddiqui may be explained in part by ring substitution. It was found in fact that 3-*n*-

(1) For the second article in this series, see Mason, *THIS JOURNAL*, **66**, 1156 (1944).

(2) Among the numerous species of the family *Anacardiaceae* is a large group of plants, including poison ivy, which elaborate oils of a powerful allergenic nature. This has been reviewed by Wasserman and Dawson, *J. Chem. Ed.*, **20**, 448 (1943). It must be noted, however, that these authors imply bhilawanol to be a homogeneous substance containing "one double bond in the side chain," and refer to the paper of Pillay and Siddiqui for evidence. Pillay and Siddiqui (see ref. 3), on the other hand, indicated that bhilawanol was doubly unsaturated. Data are presented in this investigation which make it likely that bhilawanol is a mixture.

(3) Pillay and Siddiqui, *J. Indian Chem. Soc.*, **8**, 517 (1931).

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

(5) Goldsmith, *J. Am. Med. Assoc.*, **123**, 27 (1943).