[CONTRIBUTION FROM THE INSTITUTE OF POLYMER RESEARCH, POLYTECHNIC INSTITUTE OF BROOKLYN]

Cyclic Sulfones. III.[1,2] Methylation of 2,5-Diphenyl-3,4-dihydroxythiophene-1-dioxide with Methyl Sulfate and Diazomethane

BY C. G. OVERBERGER AND JOHN M. HOYT

Methylation of the sodium salt of 2,5-diphenyl-3,4-dihydroxythiophene-1-dioxide with methyl sulfate has yielded 2,5-diphenyl-3-keto-4-methoxy-2-methylthiophene-1-dioxide (carbon and oxygen alkylation). On the other hand, methylation of the 2,5-diphenyl-3,4-dihydroxy-1-dioxide itself with diazomethane has largely given the expected dimethoxy compound (oxygen alkylation) and a small amount of the mixed carbon–oxygen alkylated product. The structures on all compounds have been well established by independent methods. The methylation of the sodium salt followed by hydrolysis has provided a new method for the methylation of arylmethyl sulfones, a reaction which cannot be achieved directly. The alkylation of 2,5-di-*p*-chlorophenyl-3,4-dihydroxythiophene-1-dioxide has given products analogous to those from the phenyl compounds.

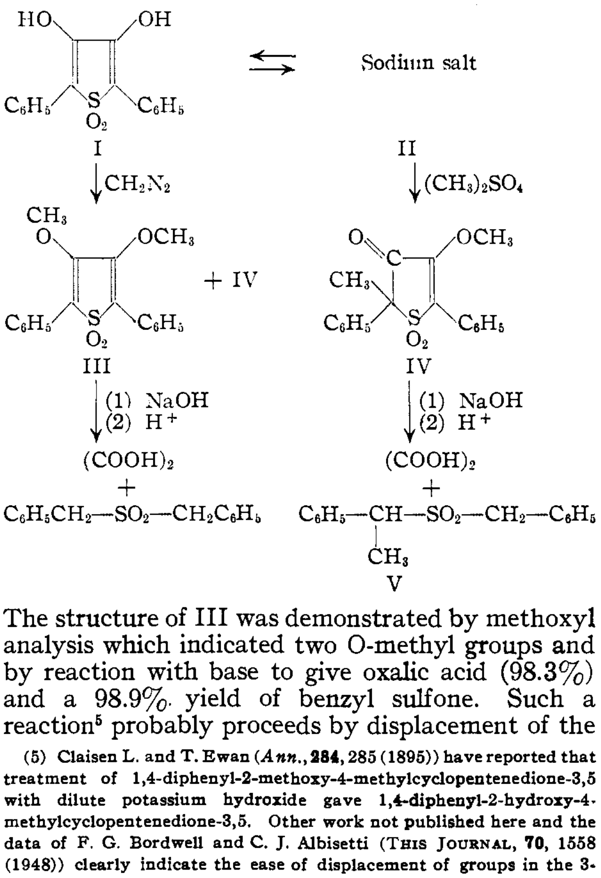
A previous paper[3a] reported the preparation of 2,5-diaryl-3,4-dihydroxythiophene-1-dioxides. Initially, we were interested in preparing the O,O-dimethyl derivative in order to study certain displacement reactions in the 3-position of the thiophene dioxide ring as well as reactions of this diene in the Diels–Alder reaction. When the sodium salt obtained from the condensation of ethyl oxalate and benzyl sulfone was treated with methyl sulfate, a product was isolated, the analysis of which corresponded to a dimethylated derivative but which on analysis contained only one O-methyl group. These facts necessitated a study of the structure of this and related methyl derivatives.

This paper will describe the preparation and proof of structure[4] of the methyl derivatives obtained from reaction of the sodium salt (II) previously referred to, with methyl sulfate and from reaction of the dihydroxy compound (I) with diazomethane.

The proof of structure of the C-methyl-O-methyl product (IV) (reaction with base) is a new procedure for the preparation of diaryl-α-methyl sulfones.

Discussion

2,5 - Diphenyl - 3,4 - dihydroxythiophene - 1-dioxide (I) when allowed to react with diazomethane gave 2,5-diphenyl-3,4-dimethoxythiophene-1-dioxide (III) in 76% yield. A small amount (1.8%) of IV (see below) was also isolated. The reactions are indicated schematically



The structure of III was demonstrated by methoxyl analysis which indicated two O-methyl groups and by reaction with base to give oxalic acid (98.3%) and a 98.9% yield of benzyl sulfone. Such a reaction[5] probably proceeds by displacement of the

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[1] This is the third in a series of papers describing the chemistry of substituted thiophene dioxides. For the second paper in this series, see C. G. Overberger, H. J. Mallon and R. Fine, THIS JOURNAL, **72**, 4958 (1950).

[2] A portion of this work was supported by a contract from the Office of Naval Research.

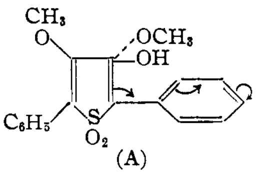
[3] (a) C. G. Overberger, S. P. Ligthelm and E. A. Swire, THIS JOURNAL **72**, 2856 (1950); (b) see also R. H. Eastman and R. M. Wagner, *ibid.*, **71**, 4089 (1949).

[4] It should be emphasized that no structure can be assumed for products prepared by displacement reactions of the type described here based on reasoning by analogy of the usual course of a specific reagent in other systems. It is fairly obvious that the electron distribution in the anion of the sodium salt of I can give rise to different methylated products even though C-alkylation is generally favored in many similar reactions. Since the mechanism of the reaction of diazomethane with acidic compounds may be

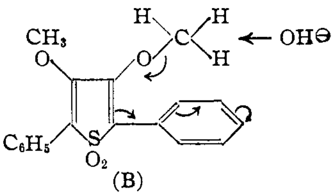
$$RH + \overset{\ominus}{C}H_2-\overset{\oplus}{N}_2 \longrightarrow \overset{\ominus}{R}: \longrightarrow CH_3-\overset{\oplus}{N}_2 \longrightarrow R-CH_3 + N_2$$

it cannot be assumed that all diazomethane alkylations in such enolic systems result in O-methylation although this is usually the case. Thus, proton transfer could result in a displacement reaction as indicated giving C-methyl products. In fact, we have succeeded in isolating a small amount of IV from the reaction of I with diazomethane. For other examples of carbon alkylation with diazomethane, see F. Arndt and C. Martius, *Ann.*, **499**, 228 (1933).

[5] Claisen L. and T. Ewan (*Ann.*, **284**, 285 (1895)) have reported that treatment of 1,4-diphenyl-2-methoxy-4-methylcyclopentenedione-3,5 with dilute potassium hydroxide gave 1,4-diphenyl-2-hydroxy-4-methylcyclopentenedione-3,5. Other work not published here and the data of F. G. Bordwell and C. J. Albisetti (THIS JOURNAL, **70**, 1558 (1948)) clearly indicate the ease of displacement of groups in the 3-position in a substituted thiophene dioxide or benzthiophene dioxide. In this case, the transition state might be represented as in (A), the phenyl group contributing to the resonance of the transition state. A less likely but alternate mechanism is indicated by (B), displacement on the carbon of the methoxyl group. Experiments are now under way to elucidate these possibilities. Such a displacement would give rise to the dihydroxy compound which would then give benzyl sulfone and oxalic acid by normal reversal of the Claisen condensation. A similar reaction has been reported by Arndt and Martius (see footnote 4) who treated 3-methoxybenzthiophene-1-dioxide with 2 *N* sodium hydroxide to obtain *o*-carboxyphenylmethylsulfone. Reaction of the methoxy dioxide with sodium methoxide in anhydrous methanol gave 3,3-dimethoxy-2,3-dihydrobenzthiophene-1-dioxide. This is an indication that mechanism A may be operative.



(A)



(B)

methoxyl group in the 3 and 4 positions of the thiophene-1-dioxide by hydroxide ion followed by the reversal of the Claisen condensation used to prepare I.

When the sodium salt (II) was treated with one equivalent of purified methyl sulfate, the only product isolated was IV in 39% yield. The structure of IV was demonstrated by methoxyl analysis, the infrared spectrum which indicated the presence of carbonyl frequencies, and reaction with dilute alcoholic base to give oxalic acid (96.7%) and benzyl-α-phenethyl sulfone (V) (96.5%). V was synthesized as shown below; a mixed melting point with the sulfone obtained on hydrolysis was not depressed.

$$C_6H_5\text{—}CH(Br)CH_3 + C_6H_5CH_2SH \xrightarrow{NaOC_2H_5}$$

$$C_6H_5\text{—}CH(CH_3)S\text{—}CH_2\text{—}C_6H_5 \longrightarrow \text{sulfone} \quad (V)$$

The keto group is very inert and attempts to prepare ketone derivatives were unsuccessful. Fisher–Hirschfelder models indicate considerable steric hindrance would be expected toward any carbonyl addition reaction. The mechanism of the reaction with base probably proceeds by displacement of the methoxyl group followed by cleavage as previously indicated.

It should be noted that this procedure, methylation of the sodium salt (II) followed by hydrolysis, represents a new procedure for methylating arylmethyl sulfones. It is recalled that the direct methylation of benzyl sulfone[6] is not feasible.

2,5 - Di - (*p* - chlorophenyl) - 3,4 - dimethoxythiophene-1-dioxide was likewise prepared from the corresponding hydroxy compound in 79% yield with diazomethane. The corresponding dimethylated analog of IV by the reaction of the sodium salt of 2,5-di-(*p*-chlorophenyl)-3,4-dihydroxythiophene-1-dioxide with methyl sulfate is also described (86%). Although hydrolysis experiments were not carried out to confirm rigorously the structure of these products, it is inferred by analogy that they are similar to the phenyl analogs. A methoxyl analysis of the chloro analog of IV indicated one methoxyl group.

Two new derivatives of I, a monoxime and a monoanil are described in the experimental section.

Experimental[7]

2,5-Diphenyl-3,4-dihydroxythiophene-1-dioxide.—This compound was prepared by the method of Overberger, Lighthelm and Swire.[3a]

Derivatives of 2,5-Diphenyl-3,4-dihydroxythiophene-1-dioxide. (A) Monoxime.—The monoxime was prepared according to the method of Shriner and Fuson.[8] From 1.0 g. (0.0033 mole) of 2,5-diphenyl-3,4-dihydroxythiophene-1-dioxide and 2.0 g. of hydroxylamine hydrochloride in 10 ml. of absolute ethanol and 10 ml. of anhydrous pyridine, there was obtained, after removal of the solvents at reduced pressure, a yellow-green solid. The crude product was washed with 2% hydrochloric acid solution to remove pyridine, then with water, and dried over phosphorus pentoxide. This treatment afforded 0.96 g. (92%) of a white powder which decomposed at 237.5° (uncor.). Recrystallization with charcoal from ethanol–water gave an analytical sample which decomposed[9] at 239° (uncor.).

Anal.[10] Calcd. for $C_{16}H_{13}NSO_4$: C, 60.94; H, 4.15. Found: C, 61.14; H, 4.29.

(B) **Monoanil.**—To a boiling solution of 1.0 g. (0.0033 mole) of 2,5-diphenyl-3,4-dihydroxythiophene-1-dioxide in 10 ml. of absolute ethanol was added 1.5 ml. of aniline. The solution was refluxed for 5 minutes, and finally allowed to cool. After several hours, a brilliant orange powder crystallized, 1.06 g. (85%), m.p. 224–226° (uncor.). This product was repeatedly recrystallized for analysis from acetone, m.p. 228–229° (uncor.).

Anal. Calcd. for $C_{22}H_{17}NSO_3$: C, 70.38; H, 4.56. Found: C, 70.21; H, 4.69.

Dimethylation of the Sodium Salt of 2,5-Diphenyl-3,4-dihydroxythiophene-1-dioxide with Methyl Sulfate. 4-Methoxy-3-keto-2,5-diphenyl-2-methyl-2,3-dihydrothiophene-1-dioxide.—The sodium salt was prepared by a procedure previously described.[3a] From the reaction of 24.6 g. (0.1 mole) of benzyl sulfone and 100 ml. of ethyl oxalate in the presence of sodium ethoxide from 5.0 g. (0.217 gram-atom) of freshly cut sodium and 65 ml. of anhydrous ethanol, there was obtained, after standing overnight, an orange solid. A volume of liquid equal to that of the ethanol used was removed by distillation, and the solid was washed by decantation three times with 50-ml. portions of toluene, each portion being heated briefly with the salt before decanting.

To the solid, moist with toluene, was added 26.6 g. (0.211 mole) of freshly distilled methyl sulfate and the resulting paste was heated with stirring in an oil-bath at 110–120° for one-half hour. During this period 4.1 g. of anhydrous sodium carbonate was gradually added. When the mixture had cooled to room temperature, it was stirred 1.75 hours with 11.0 g. of sodium hydroxide dissolved in 375 ml. of water. The slurry obtained was transferred to a two-liter separatory funnel with 200 ml. of benzene and about 1 liter of water, and the mixture shaken thoroughly until the layers separated. Some additional water was found to facilitate this process. The benzene layer was separated, washed with 5% sodium hydroxide solution until the wash-layer no longer showed the characteristic orange color of the sodium salt, and then washed with water until the water layer no longer gave a basic color with litmus. After drying over anhydrous magnesium sulfate, the benzene layer was evaporated on a water-bath and the residue crystallized by the addition of petroleum ether (60–68°). The pale yellow crystals were collected, washed twice with ether, and dried. The product weighed 12.8 g. (39%), m.p. 93–95.5°. Recrystallization several times from absolute ethanol gave an analytical sample, m.p. 96.5–98.7°.

Anal. Calcd. for $C_{18}H_{16}SO_4$: C, 65.84; H, 4.91; $-OCH_3$, 9.45. Found: C, 66.00; H, 4.63; $-OCH_3$, 9.41.

This compound is readily soluble in benzene in the cold, moderately soluble in cold ethanol and methanol, and slightly soluble in ether and petroleum ether in the cold. On standing, the compound slowly acquired a yellow-orange color at the exposed surface.

A number of attempts to form a carbonyl derivative ended in failure. Infrared analysis,[11] however, confirmed the presence of the carbonyl group.

Preparation of 2,5-Diphenyl-3,4-dimethoxythiophene-1-dioxide.—A solution of 6.36 g. (0.0212 mole) of 2,5-diphenyl-3,4-dihydroxythiophene-1-dioxide in 10 ml. of methanol and 40 ml. of pure dioxane [an ether–benzene mixture may be used] was prepared. After cooling the solution in an ice-bath, an ether solution of diazomethane[12] prepared from 9.0 g. of nitrosomethylurea, was added slowly. The temperature of the reaction was held at 5–12°. Toward the end of the addition a solid appeared. After allowing the reaction mixture to stand for one day [acetic acid may be added to destroy excess diazomethane] the solvents were

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[6] R. L. Shriner, H. C. Struck and J. W. Jorison, *ibid.*, **52**, 2060 (1930).

[7] All melting points are corrected unless otherwise noted.

[8] R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd edition, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 202.

[9] The decomposition point is the temperature at which a sample in a capillary tube, when inserted into a metal block heated at the rate of 2° per minute, completely decomposes in 30 seconds.

[10] Analyses by Mr. H. S. Clark, Urbana, Illinois; Dr. K. Ritter, Basel, Switzerland; Dr. F. Schwarzkopf, New York, N. Y.; Drs. Weiler and Strauss, Oxford, England.

[11] We are indebted to Professor R. C. Lord of the Massachusetts Institute of Technology for the infrared spectrum and its interpretation.

[12] F. Arndt, "Organic Syntheses," Coll. Vol. II, 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

removed at reduced pressure and the residue was dissolved in methylene chloride. The methylene chloride solution was washed with 5% sodium hydroxide solution until the washings were no longer colored yellow by unreacted material, and then with water until the wash-layer no longer turned red litmus blue. The solvent layer was dried over anhydrous magnesium sulfate and evaporated. The residue was dissolved in excess absolute ethanol, decolorized with charcoal, and concentrated just short of crystallization. On cooling, there was obtained 5.27 g. (76%) of white rods, m.p. 146–148.5°. A number of recrystallizations from absolute ethanol gave an analytical sample, m.p. 148.3–149.3°.

Anal. Calcd. for $C_{18}H_{16}O_4S$: C, 65.84; H, 4.91; $-OCH_3$, 18.9. Found: C, 66.06; H, 4.74; $-OCH_3$, 19.2.

The filtrate from an experiment in which an ether-benzene solution was used, was concentrated and a yellow solid separated, m.p. 78–98°. Recrystallization from methanol with Norite gave a small amount of white crystals, m.p. 143–147°. From the filtrate there was obtained crude material melting at 94–96°; successive recrystallization from ethanol gave a m.p. 97–98°, mixed m.p. 97–98.2°. From 3 g. (0.01 mole) of 2,5-diphenyl-3,4-dihydroxythiophene-1-dioxide, there was obtained 0.06 g. (1.8%) of IV.

When the methanol–dioxane mixture was used it was not possible to obtain IV in a pure state.

2,5-Di-(*p*-chlorophenyl)-3,4-dimethoxythiophene-1-dioxide.—A solution of 2.5 g. (0.0068 mole) of 2,5-di-(*p*-chlorophenyl)-3,4-dihydroxythiophene-1-dioxide[3a] in acetone was prepared, cooled to 0–5° on an ice-bath, and treated with an ether solution of diazomethane from 5 g. of nitrosomethylurea.[12] After several hours the solvent was removed and the residue was recrystallized from a mixture of absolute ethanol and acetone. There was obtained 1.38 g. of yellow columns, m.p. 207–209° (uncor.), and on concentration of the mother liquor, 0.75 g. of additional product, m.p. 204–207.5° (uncor.) (79%, total yield). Two recrystallizations from an absolute ethanol–acetone mixture gave an analytical sample, m.p. 207.5–208.5° (uncor.).

Anal. Calcd for $C_{18}H_{14}O_4SCl_2$: C, 54.42; H, 3.55. Found: C, 54.31; H, 3.81.

4-Methoxy-3-keto-2,5-di-(*p*-chlorophenyl)-2-methyl-3,3-dihydrothiophene-1-dioxide.[13a]—The procedure was adapted from that of Fager.[13b] When the solid sodium salt prepared from the condensation of 63 g. (0.2 mole) of sulfone reacted with 150 g. (1.2 moles) of methyl sulfate under nitrogen at 110–120° for two hours, and the product stirred with cooling in 300 ml. of 6% sodium hydroxide solution for one hour, a crude product was obtained weighing 89.8 g., m.p. 121–135°. This crude product was dissolved in a minimum of acetone and recrystallized at −50°. Subsequent recrystallization from absolute ethanol gave 68.3 g. (86%), m.p. 154.7–155.2°.

Anal. Calcd. for $C_{18}H_{14}Cl_2O_4S$: C, 54.42; H, 3.55; $-OCH_3$, 7.81. Found: C, 54.28; H, 3.81; $-OCH_3$, 8.18.

Decomposition of 4-Methoxy-3-keto-2,5-diphenyl-2-methyl-2,3-dihydrothiophene-1-dioxide with Alcoholic Sodium Hydroxide Solution. Isolation and Identification of Benzyl-α-phenethyl Sulfone.—A 1 *m* solution of sodium hydroxide in 95% ethanol was prepared by heating 4.13 g. (0.01 mole) of 97% assay sodium hydroxide in 100 ml. of 95% ethanol until solution was complete. To the hot solution was added 3.28 g. (0.01 mole) of 4-methoxy-3-keto-2,5-diphenyl-2-methyl-2,3-dihydrothiophene-1-dioxide. The slurry turned orange instantly, and, before the compound all dissolved, a second solid was observed. The slurry was refluxed gently on the water-bath until its color, which slowly faded from orange to yellow, was completely discharged (1.75 hours). The colorless slurry was then refluxed an additional one-half hour.

After standing overnight, the slurry was concentrated by removal of 78 ml. of solvent. The residue was treated with about 400 ml. of water, allowed to stand, and the white solid which remained was collected. The solid was washed well with water, the washings added to the filtrate, and the solid was dried, 2.51 g. (96.5%), m.p. 91–93.6°. Two recrystallizations from ethanol-water with decolorization yielded 1.97 g. of white needles which melted at 100–101.3°. A mixed melting point determination with an authentic sample of benzyl-α-phenethyl sulfone, m.p. 100.1–101.4°, was not depressed, m.p. 100.1–101.4°.

The Identification and Estimation of Oxalic Acid.—The combined filtrate and washings were diluted to 500 ml. in a volumetric flask. A volume of 300 ml. of the stock solution was evaporated on a water-bath to 50–75 ml. and transferred to a continuous liquid–liquid extractor. The solution was acidified with 7 ml. of concentrated hydrochloric acid solution, and extracted continuously for three days with ether. The ether was removed, and the solid residue was used to prepare the di-*p*-toluidide of oxalic acid according to the directions of Huntress and Mulliken.[14] The product obtained melted at 266–267.5° (uncor.). A mixed melting point determination with a known sample of the di-*p*-toluidide of oxalic acid, m.p. 267–268.5° (uncor.) (268°),[14] showed no depression, m.p. 266.5–268° (uncor.).

The amount of oxalic acid formed in the decomposition was estimated by precipitation of calcium oxalate from 150 ml. of the stock solution and titration with standard potassium permanganate solution according to a standard method.[15] The titration indicated that 0.87 g. (96.7%) of oxalic acid was formed.

Decomposition of 2,5-Diphenyl-3,4-dimethoxythiophene-1-dioxide with Alcoholic Sodium Hydroxide Solution.—The decomposition was carried out in a manner similar to that described above, with the exception that 2.32 g. (0.00707 mole) of 2,5-diphenyl-3,4-dimethoxythiophene-1-dioxide was decomposed in 70 ml. of 1 molar alcoholic sodium hydroxide solution for a period of 3.5 to four hours before the color had completely disappeared, and than an additional reflux period of 2.5 hours was employed. A total of 60 ml. of solvent was removed by distillation before water was added to precipitate the sulfone. The weight of dibenzyl sulfone isolated was 1.72 g. (98.9%), m.p. 150.6–151.6°. A mixed melting point with an authentic sample of benzyl sulfone, m.p. 150.7–152.1° was not depressed, m.p. 150.8–152.1°. Continuous extraction of a 300-ml. aliquot of the filtrate and washings for three days with ether yielded a solid which gave a di-*p*-toluidide, m.p. 266–267.5°, mixed m.p. 266.5–268°. A permanganate titration indicated that a total of 0.625 g. (98.3%) of oxalic acid had been formed in the decomposition.

Preparation of Benzyl-α-phenethyl Sulfide.—In a 200-ml. three-necked flask equipped with a stirrer, reflux condenser, and dropping funnel, a sodium ethoxide solution was prepared from 40 ml. of absolute ethanol and 2.3 g. (0.1 gram-atom) of freshly cut sodium. To this cooled solution was added 12.4 g. (0.1 mole) of redistilled benzyl mercaptan (Eastman Kodak Co., b.p. 95–98° (32–33 mm.)). A solution of 18.5 g. (0.1 mole) of α-phenethyl bromide (The Matheson Co., redistilled, b.p. 83–84 at 9.5–10 mm.) in 20 ml. of absolute ethanol was added over a period of 23 minutes with stirring. A white solid appeared at once, and the mixture became warm. After standing for three hours, the mixture was refluxed for one hour with stirring, allowed to stand overnight, and then refluxed for an additional three hours with stirring. When the contents of the flask had cooled, the suspended solid was collected and washed three times with 20- to 30-ml. portions of absolute ethanol. The filtrate was concentrated at reduced pressure until most of the solvent was removed, and the residue transferred to a separatory funnel with 200 ml. of water and sufficient ether to dissolve the oily product. After washing the ether solution with water, drying over anhydrous magnesium sulfate, and removal of the solvent, the product was submitted to vacuum distillation. A colorless, viscous liquid was obtained, 14.6 g. (63%), b.p. 133–135° (1–1.5 mm.). Redistillation for analysis yielded a sample which boiled at 134–135° at 1.5 mm., $n^{25}\text{D}$ 1.5898, $d^{25}{}_4$ 1.0571.

Anal. Calcd. for $C_{15}H_{16}S$: C, 78.89; H, 7.06. Found: C, 79.19; H, 7.43.

Preparation of Benzyl-α-phenethyl Sulfone.—A solution of 1.02 g. (0.0045 mole) of benzyl-α-phenethyl sulfide in a mixture of 5 ml. of glacial acetic acid and 1.5 g. of a 30% solution of hydrogen peroxide was heated in a water-bath for one and one-third hours at 100°. Following this treatment, 1.5 g. of 30% hydrogen peroxide was washed into the

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(13) (a) This compound was prepared by Mr. Edwin A. Swire; (b) E. W. Fager, THIS JOURNAL, 67, 2217 (1945).

(14) E. H. Huntress and S. P. Mulliken, "The Identification of Pure Organic Compounds," Order I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 99.

(15) I. M. Kolthoff and E. B. Sandell, "Textbook of Quantitative Inorganic Analysis," The Macmillan Co., New York, N. Y., revised edition, 1947, p. 606.

reaction with 1 ml. of glacial acetic acid, and the process was repeated at one-hour intervals an additional two times. The heating was continued for a total of six hours. On cooling, 0.64 g. of white needles were collected, m.p. 99.5–100.5°. Addition of water to the filtrate yielded 0.39 g. of white powder, m.p. 98.5–100.5°, total yield 88%. Two recrystallizations from ethanol gave an analytical sample, m.p. 100.1–101.4°.

Anal. Calcd. for $C_{15}H_{16}O_2S$: C, 69.20; H, 6.20. Found: C, 69.33; H, 6.14.

BROOKLYN, N. Y. RECEIVED JANUARY 17, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

A Convenient Synthesis of the Monoalkylpyridines; a New Prototropic Reaction of 3-Picoline[1,2]

BY HERBERT C. BROWN AND WILBUR A. MURPHEY[3]

The monoalkylpyridines, 2-, 3- and 4- ethyl-, isopropyl and *t*-butylpyridines, have been synthesized and isolated in a state of high purity, as established by freezing point determinations. The reaction of methyl chloride with 2-, 3- and 4-picoline in the presence of sodium amide has been developed into a convenient synthesis for these monoalkylpyridines. The reaction presumably involves a prototropic reaction of the picoline, followed by an attack of the carbanion on the alkyl halide. Contrary to published reports, methyl chloride, methyl iodide and ethyl bromide can all be used successfully to alkylate 2-picoline, although it had been previously considered that only the higher alkyl chlorides were satisfactory. Quite surprisingly, 3-picoline reacts smoothly, although prototropic reactions of this isomer have not been previously reported.

Introduction

In order to estimate quantitatively the effect of steric strain on displacement reactions of monoalkylpyridines,[4] we required 2-, 3- and 4-methyl-, ethyl-, isopropyl- and *t*-butylpyridines. The picolines are commercially available. Unfortunately, the remaining nine compounds are not available and a search of the literature revealed that two (2- and 3-*t*-butylpyridine) had not been previously prepared, while several others had been obtained only by relatively unsatisfactory procedures and had been poorly characterized. It was therefore considered essential to undertake the development of convenient procedures for the synthesis of these compounds to permit their ready preparation in quantity, their rigorous purification, and careful characterization.

It appeared that the alkylation of 2- and 4-picoline by methyl halides in the presence of sodium amide might be developed into a satisfactory procedure. Unfortunately, published information on the applicability of this reaction did not appear promising for the synthesis of all the derivatives needed in our studies.

In 1914 Chichibabin and Seide[5] reported that their attempts to alkylate 2-picoline by treating it with sodium amide and methyl iodide were unsuccessful. In 1931 Bergstrom[6] attempted to prepare homologs of pyridine derivatives (2-methyl-, 2,6-dimethyl- and 2,4,6-trimethylpyridine) by the action of ethyl bromide and potassium amide on the bases, but failed. However, he was successful in alkylating 2- and 4-methylquinoline in this way. Later Chichibabin[7] was successful in alkylating 2- and 4-picoline, utilizing predominantly the higher primary alkyl chlorides. Either one or two groups, such as *n*-butyl, could be introduced. Recently, Bergstrom, Norton and Seibert[8] reported the arylalkylation of 2- and 4-picoline with potassium amide in liquid ammonia.

2- and 4-picoline have also been condensed with esters,[9,10] aldehydes[9] and α,β-unsaturated ketones or esters.[11]

Fortunately, a detailed study of the alkylation of 2- and 4 picoline with methyl chloride and sodium amide led to the discovery of conditions suitable for the introduction of one, two or three methyl groups into the side-chain. In this way 2- and 4- ethyl-, isopropyl- and *t*-butylpyridines were prepared, purified, and characterized.

The synthesis of the 3-alkylpyridines at first offered greater difficulties. Both 3-ethylpyridine[12,13,14] and 3-isopropylpyridine[15,16] were synthesized in several steps from nicotinic acid. (Conditions were established for the successful hydrogenation of 3-isopropenyl- to 3-isopropylpyridine.) However, a number of attempts to prepare 3-*t*-butylpyridine by similar common reactions failed.

There seemed little reason to doubt that 3-picoline would be inert to methyl chloride and sodium amide. The literature abounds with evidence that 2- and 4-picoline undergo prototropic reactions with ease,[10,11] but no prototropic reactions of the 3-isomer could be located. However, an experiment confirming this conclusion appeared desirable. Accordingly, 3-picoline in liquid ammonia was treated with sodium amide and methyl chloride in the usual manner. Surprisingly, the reaction proceeded smoothly to form 3-ethylpyridine. 3-Isopropyl- and 3-*t*-butylpyridine could be prepared by the same reaction (the latter in relatively low conversion).

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(1) Steric Effects in Displacement Reactions. I.

(2) This paper is taken from a thesis submitted by Wilbur A. Murphey in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) E. I. du Pont de Nemours and Company Fellow, 1948–1949.

(4) H. C. Brown and G. K. Barbaras, THIS JOURNAL, **69**, 1137 (1947); H. C. Brown and N. R. Eldred, *ibid.*, **71**, 445 (1949).

(5) A. E. Chichibabin and D. A. Seide, *J. Russ. Phys.-Chem. Soc.*, **46**, 1216 (1914); *C. A.*, **9**, 1901 (1915); *Chem. Zentr.*, **86**, I, 1064 (1915).

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