

Anal. Calcd. for $C_{12}H_{18}N_4O_3S_2$: C, 44.43; H, 3.73; S, 19.77. Found: C, 44.36; H, 3.84; S, 19.87.

The presence of a free amino group was shown by diazotization and coupling with F-salt to form a deep red dye.

Condensation Product of Sodium Formaldehyde Sulfoxylate with 5-Sulfanilyl-2-furaldehyde Thiosemicarbazone (VII).—The condensation product was prepared in 93% yield, using the procedure of Raiziss.^{3b} Recrystallization of 21.5 g. of the product from 300 cc. of boiling water with the addition of 1 g. of sodium bicarbonate yielded 14.4 g. of colorless crystals. The solubility in water at 23° was about 0.4%.

Anal. Calcd. for $C_{12}H_{18}N_4NaO_3S_2 \cdot \frac{1}{2}H_2O$: C, 36.02; H, 3.26; N, 12.93; Na, 5.31; S, 22.19; H_2O , 2.08. Found: C, 35.97; H, 3.51; N, 13.10; Na, 4.96; S, 21.35; H_2O , 2.29.

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5-Methyl-2-cyclohexenone

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In connection with synthetic work now in progress, large quantities of 5-methyl-2-cyclohexenone (IV) were required. We have found that this compound can be conveniently synthesized from the readily available 5-methyl-1,3-cyclohexanedione¹ by a scheme which parallels that of Frank and Hall² for the preparation of 5-isopropyl-2-cyclohexenone.

Optically active IV^{3,4} as well as the inactive material^{5,6} have previously been reported by several workers. In cases where physical properties of IV are reported^{4,5} agreement among the earlier workers is satisfactory; however, considerable discrepancies in the melting points of the semicarbazone derivative have been observed.

Inasmuch as the product obtained in the present work has physical properties which differ considerably from the previously described material^{4,5} we have investigated the structure of our material. Analysis, ultraviolet absorption, reduction to 3-methylcyclohexanone and method of synthesis provided the necessary evidence for believing the structure to be 5-methyl-2-cyclohexenone.⁷ The ultraviolet spectrum was typical for singly substituted α,β -unsaturated ketones,⁸ showing a peak at 225.2 μ ($\log \epsilon$ 4.0).

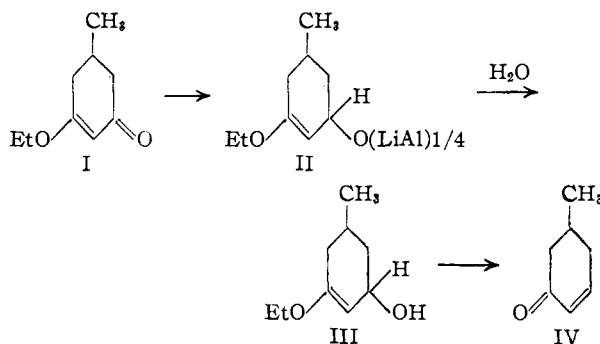
In order to clarify the discrepancies between 5-methyl-2-cyclohexenone obtained in our work and the material described in the literature^{4,5} we have repeated Godchot's synthesis and indeed obtained

- (1) A. W. Crossley and N. Renouf, *J. Chem. Soc.*, **107**, 602 (1915).
- (2) R. L. Frank and H. K. Hal, Jr., *THIS JOURNAL*, **73**, 1645 (1950).
- (3) A. Kotz and H. Steinhorst, *Ann.*, **379**, 1 (1911).
- (4) M. Mousseron, *et al.*, *Bull. soc. chim. France*, **11**, 610 (1946); M. Mousseron and F. Winternitz, *ibid.*, **12**, 67 (1945); M. Mousseron, F. Winternitz and R. Jacquier, *Compt. rend.*, **224**, 1062 (1947).
- (5) M. Godchot and P. Bedos, *Bull. soc. chim. France*, [4] **39**, 83 (1926).
- (6) A. J. Birch, *J. Chem. Soc.*, 1270 (1947).
- (7) Presumably this material contains the equilibrium amount of the β,γ -unsaturated isomer.
- (8) R. B. Woodward, *THIS JOURNAL*, **63**, 1123 (1941).

the material described by him. This material has not as yet been identified; however, comparison of physical properties and of derivatives clearly showed that the compound is not the alleged 5-methyl-2-cyclohexenone. The Birch synthesis⁶ was also investigated and found to give IV in low yield.

In the present synthesis 5-methyl-1,3-cyclohexanedione is converted to the enol ether I, which is subsequently reduced with lithium aluminum hydride to IV.

The conversion of an enol ether of a β -diketone to an α,β -unsaturated ketone by reduction with lithium aluminum hydride has previously been described²; however, this method involved an inverse addition and use of an excess of ketone. We have found that the inverse addition is not necessary and indeed gives a poorer conversion than does the general procedure of Nystrom and Brown⁹ for the reduction of ketones. The formation of a ketone, IV, from a reduction involving excess lithium aluminum hydride suggests the following reaction path in which the intermediate 1-ethoxy-3-hydroxy-5-methylcyclohexene (III) is converted to IV by hydrolysis to the β -hydroxy ketone followed by dehydration.



Basic¹⁰ as well as acid hydrolysis of the metal alcoholate (II) yields IV.

Experimental¹¹

5-Methyl-2-cyclohexenone (IV).—5-Methyl-1,3-cyclohexanedione, m.p. 128–129° (lit.^{4,12} 128° and 127°), was prepared in 55% yield from ethyl crotonate and ethyl acetoacetate by a modification of the procedure of Crossley and Renouf.¹ This modification consisted of removal of most of the ethanol by distillation under reduced pressure instead of by azeotropic distillation with water. The dioxime melted at 155.5–157.5° (lit.¹² 155–157°).

5-Methyl-1,3-cyclohexanedione was converted to 3-ethoxy-5-methyl-2-cyclohexenone (I), b.p. ca. 83° (0.1 mm.) in 93% yield by the method of Frank and Hall.² After crystallization from aqueous acetone it melted at 41–43° (reported for the monohydrate,¹² 42°). The enol ether was converted to IV by lithium aluminum hydride reduction. Best results were obtained by the general procedure of Nystrom and Brown⁹ for the reduction of aldehydes and ketones. In this way a 92% yield of IV was obtained, b.p. ca. 60° (8 mm.); n_D^{20} 1.4739; d_4^{20} 0.947; *MR* calcd. (no exaltation), 31.9; *MR* found, 32.7. Ultraviolet absorption showed a peak at 225.2 μ ($\log \epsilon$ 4.0, 0.006 g. per liter of 95% ethanol solution).

Anal. Calcd. for $C_7H_{10}O$: C, 76.32; H, 9.15. Found: C, 76.08; H, 8.99.

The inverse addition method of Frank and Hall² gave a

- (9) R. F. Nystrom and W. G. Brown, *ibid.*, **69**, 1197 (1947).
- (10) L. H. Amundsen and L. S. Nelson, *ibid.*, **73**, 242 (1951).
- (11) All melting points are corrected.
- (12) C. Gilling, *J. Chem. Soc.*, **103**, 2029 (1913).
- (13) D. Vorlander and F. Kalkow, *Ber.*, **30**, 1801 (1897).

69% yield and decomposition of the metal alcoholate by alkaline hydrolysis according to the procedure of Amundsen and Nelson¹⁰ gave a 49% yield. The 2,4-dinitrophenylhydrazone was obtained as red needles, m.p. 152–152.5°.

Anal. Calcd. for $C_{13}H_{14}O_7N_4$: C, 53.79; H, 4.86. Found: C, 53.89; H, 4.94.

The semicarbazone melted at 177.5–179° after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_8H_{13}ON_3$: C, 57.46; H, 7.83. Found: C, 57.29; H, 7.65.

A solution of 1.1 g. (0.01 mole) of IV in 15 ml. of absolute ethanol was hydrogenated at room temperature and atmospheric pressure with 0.2 g. of 30% palladium-on-charcoal. After the theoretical amount of hydrogen had been absorbed, the catalyst was removed by filtration and the alcoholic filtrate was used directly for the preparation of the 2,4-dinitrophenylhydrazone. This derivative melted at 161.5–163° after recrystallization from alcohol. The melting point was not depressed on admixture with an authentic sample of 3-methylcyclohexanone-2,4-dinitrophenylhydrazone (m.p. 161.5–163°).

5-Methyl-2-cyclohexenone was also obtained in low yield from 2,4-lutidine by the method of Birch⁶; n_D^{20} 1.4743. The 2,4-dinitrophenylhydrazone melted at 149.5–150.5°. The melting point was not depressed on admixture with an authentic sample of 5-methyl-2-cyclohexenone-2,4-dinitrophenylhydrazone.

The material reported by Godchot and Bedos⁵ was prepared according to their directions; n_D^{20} 1.4456 (reported⁵ n_D^{20} 1.44635). The semicarbazone melted at 178–179°. When mixed with an authentic sample of the semicarbazone of IV (m.p. 177.5–179°), the melting point was depressed considerably.

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Some Derivatives of 2,5-Dimethoxyacetophenone

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A number of compounds derived from 2,5-dimethoxyacetophenone have been prepared as intermediates in the synthesis of chloramphenicol analogs. 2,5-Dimethoxyacetophenone was brominated to give ω -bromo-3,5-dimethoxyacetophenone, which, on nitration, yielded a mixture of two mononitrated isomers. The lower melting isomer gave an indigo derivative when treated with ammonium sulfide,² hence is ω -bromo-3,6-dimethoxy-2-nitroacetophenone. The other isomer gave no indigo derivative, did not yield 2,5-dimethoxy-3-nitrobenzoic acid on oxidation with hypohalite, and hence is ω -bromo-2,5-dimethoxy-4-nitroacetophenone. ω -Bromo-3,6-dimethoxy-2-nitroacetophenone was converted by the method of Delepine to the ω -amino hydrochloride, which was then acetylated and reduced with aluminum isopropoxide to yield 1-(3,6-dimethoxy-2-nitrophenyl)-2-acetamidoethanol. This compound was hydrolyzed to the free amine, which on dichloroacetylation gave 1-(3,6-dimethoxy-2-nitrophenyl)-2-dichloroacetamidoethanol.

The procedures used in converting ω -bromo-3,6-dimethoxy-2-nitroacetophenone to 1-(3,6-dimethoxy-2-nitrophenyl)-2-dichloroacetamidoethanol were patterned after those of Long and co-workers in preparing various chloramphenicol derivatives.^{3,4}

* Deceased.

- (1) The Wm. S. Merrell Co. Fellow.
- (2) H. Gevekoht, *Ann.*, **221**, 330 (1883).
- (3) L. M. Long and H. D. Troutman, *THIS JOURNAL*, **71**, 2473 (1949).
- (4) L. L. Bambas, H. D. Troutman and L. M. Long, *ibid.*, **72**, 4445 (1950).

Experimental

ω -Bromo-2,5-dimethoxyacetophenone.—Forty-one ml. of bromine was added dropwise over 45 minutes to a stirred suspension of 2.5 g. of anhydrous aluminum chloride, 147 g. of 2,5-dimethoxyacetophenone⁵ and 200 ml. of anhydrous diethyl ether at 0°. The ether and hydrogen bromide were then removed at room temperature under reduced pressure. The crude product was shaken with a 1:1 water-petroleum ether mixture and recrystallized from 1.2 liters of absolute ethanol to give 143 g. (67%) of slightly yellowish needles, m.p. 84–85°. A second recrystallization from ethanol yielded long white needles, m.p. 86° (reported m.p. 91°).⁸

A small portion was converted with hypohalite to 2,5-dimethoxybenzoic acid, m.p. 76–77° (reported m.p. 76°),⁷ which, on treatment with thionyl chloride and then ammonium hydroxide, gave 2,5-dimethoxybenzamide, m.p. 138–139° (reported m.p. 140°).⁸

Anal. Calcd. for $C_9H_{11}O_3N$: N, 7.74. Found: N, 7.64.

Nitration of ω -Bromo-2,5-dimethoxyacetophenone.—To 135 ml. of stirred nitric acid (sp. gr. 1.42) at 0° was slowly added 25.9 g. of ω -bromo-2,5-dimethoxyacetophenone. After six hours of stirring at 0° the mixture was poured into 1.3 liters of ice-water and the crude product, which weighed 26.1 g., recovered by filtration. This was dissolved in 300 ml. of hot absolute ethanol and 2.7 liters of hot petroleum ether (b.p. 90–100°) was added. This solution on cooling yielded 19.2 g. (63%) of an ω -bromodimethoxynitroacetophenone as long yellow needles, m.p. 103–104°. Recrystallization from ethanol or ethanol-petroleum ether did not raise the melting point.

Anal. Calcd. for $C_{10}H_{10}O_5NBr$: C, 39.5; H, 3.32; N, 4.60; $-\text{OCH}_3$, 20.4. Found: C, 39.3; H, 3.52; N, 4.62; $-\text{OCH}_3$, 20.1.

The filtrate from the above was concentrated to one-half its volume and on cooling yielded 2.5 g. of ragged crystals, m.p. 107–111°. Recrystallization from absolute ethanol gave 2.0 g. (7%) of a second ω -bromodimethoxynitroacetophenone as fine yellow needles, m.p. 118.5–119.2° (mixed m.p. with the lower melting isomer, 85–90°). Recrystallization from ethanol did not raise the melting point.

Anal. Calcd. for $C_{10}H_{10}O_5NBr$: C, 39.5; H, 3.32; N, 4.60; $-\text{OCH}_3$, 20.4. Found: C, 39.8; H, 3.54; N, 4.58; $-\text{OCH}_3$, 20.3.

A solution of one gram of the lower melting isomer in 25 ml. of ethanol was refluxed for 30 minutes with 7 ml. of yellow ammonium sulfide solution.² The crude solid product was filtered, washed successively with hot ethanol and carbon disulfide, and sublimed *in vacuo*. The indigo-colored crystalline product thus obtained exhibited typical indigoid properties: color and solubility in aniline and nitrobenzene; reduction with sodium hydrosulfate to a colorless form, reoxidizable by air. It is undoubtedly 4,4',7,7'-tetramethoxyindigotin.

Anal. Calcd. for $C_{20}H_{18}O_6N_2$: N, 7.32. Found: N, 6.91.

Identical treatment of the higher melting isomer yielded no indigo-like product.

The lower melting isomer is hence ω -bromo-3,6-dimethoxy-2-nitroacetophenone. On treatment with hypohalite it gave 3,6-dimethoxy-2-nitrobenzoic acid, m.p. 192–193° (reported m.p., 192°).⁹

Anal. Calcd. for $C_9H_9O_6N$: N, 6.17. Found: N, 6.27.

The higher melting isomer on treatment with hypohalite yielded a dimethoxynitrobenzoic acid, m.p. 192–193.5° (mixed m.p. with 3,6-dimethoxy-2-nitrobenzoic acid, 163–173°).

Anal. Calcd. for $C_9H_9O_6N$: N, 6.17. Found: N, 6.28.

Since 2,5-dimethoxy-3-nitrobenzoic acid melts at 181–183°,^{9,10} this compound must be the hitherto unreported 2,5-dimethoxy-4-nitrobenzoic acid, and the higher melting isomer from which it is derived is hence ω -bromo-2,5-dimethoxy-4-nitroacetophenone.

(5) L. DeF. Abbott and J. D. Smith, *J. Biol. Chem.*, **179**, 365 (1949).

(6) J. Tambor, *Ber.*, **44**, 3215 (1911).

(7) F. Tiemann and W. H. M. Müller, *ibid.*, **14**, 1993 (1881).

(8) H. Kauffmann and A. Grombach, *Ann.*, **344**, 71 (1906).

(9) L. Rubenstein, *J. Chem. Soc.*, **127**, 1998 (1925).

(10) A. Klemenc, *Monatsh.*, **33**, 1254 (1912).