[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE CREIGHTON UNIVERSITY]

Synthesis of 1-(3'-Methoxy-4'-acetoxyphenyl)-2,6-dicarbethoxycyclohexanedione-3,5 I. Related Oximes and *p*,*p*'-Disazo-diphenyl Derivatives

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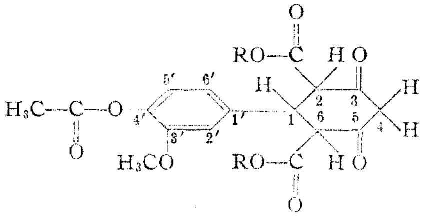
The present report is an extension of previous work published by Papadakis[1] and deals with the preparation of 1-(3'-methoxy-4'-acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5 (I) and derivatives. The sequence of the syntheses involved is given: vanillin → ethyl 3-methoxy-4-hydroxybenzalmalonate → ethyl 3-methoxy-4-acetoxybenzalmalonate → 1-(3'-methoxy-4'-acetoxyphenyl)-2,6-dicarbethoxycyclohexanedione-3,5 (I)

→ Oxime derivatives

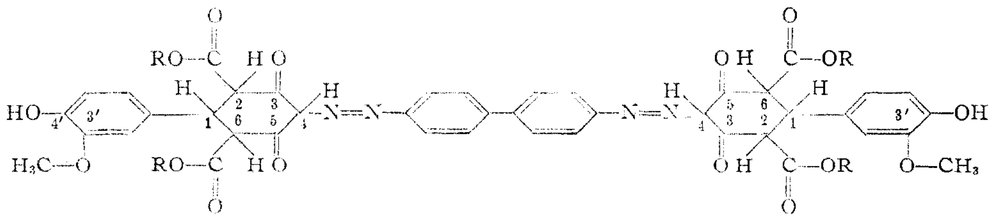
→ N,N'-Bis-}-4-[1-(3'-methoxy-4'-hydroxyphenyl)-2,6-dicarbethoxycyclohexanedione-3,5]}-*p*,*p*'-disazodiphenyl (II)

The purpose of this investigation is to prepare intermediates which may be used either for the further synthesis of compounds having structural relation to substances of the steroid group or of other derivatives of physiological importance. Compound (I) has structural advantages for such synthetic work. Derivatives of (I) made in this laboratory are studied and compared with analogous compounds of the 1,3-dicarbonyl type of derivatives found in the literature.



I

In the present work, the *p*,*p*'-tetrazonium derivative of benzidine was coupled with compound (I) to form compound (II). Various azo dyes of the type (bis-R)-4,4'-disazodiphenyl have been reported,[2,3,4,5,6] some of which are of physiological or industrial importance.



II

In the course of the preparation of acyl derivatives of compound (I) according to the general equation (I) + acid halide + NaOR $\xrightarrow{\Delta\ \text{ether}}$ acyl derivative + NaI, it was found that when the equivalent amount of NaOR was used, the acylation did not take place, because the NaOR was consumed in removing the acetyl part of the *p*-acetoxy group. This becomes convenient if one wishes to convert the resulting phenolic compound to a glycoside. Further work in connection with this point is in progress.

The preparation of oximes of structure (I) is described in the experimental part of this paper.

Experimental

Ethyl 3-Methoxy-4-hydroxybenzalmalonate.—The method of synthesis described by Knoevenagel and Albert[7] was used for the preparation of this substance, and the product, recrystallized from alcohol, melted at 110°.

Ethyl 3-Methoxy-4-acetoxybenzalmalonate.—A mixture of 148.5 g. of ethyl 3-methoxy-4-hydroxybenzalmalonate and 102 ml. of acetic anhydride was refluxed for five hours (oil-bath, temperature 170°). Upon cooling, 3-methoxy-4-acetoxy-benzalmalonate crystallized. After recrystallization from alcohol, it melted at 67.5–68°, yield 80%.

Anal. Calcd. for $C_{17}H_{20}O_7$: C, 60.70; H, 5.99. Found: C, 60.69; H, 5.82.

1-(3'-Methoxy-4'-acetoxyphenyl)-2,6-dicarbethoxycyclohexanedione-3,5 (I).—Twenty grams of sodium ethoxide and 39 ml. of ethyl acetoacetate were mixed with dry ether in a three-neck round-bottom flask provided with two condensers. To this mixture 100 g. of ethyl 3-methoxy-4-acetoxy-benzalmalonate in dry ether was added. The mixture was refluxed for five hours, the ether distilled and the residue heated (oil-bath 130°) under vacuum until dry. After cooling, cold distilled water was added and the mixture was allowed to stand in the refrigerator. After two hours, it was filtered and the filtrate was acidified with cold 3 *N* hydrochloric acid. The crystals formed were filtered off; yield of crude product, 95%. After several recrystallizations from hot water, the product melted at 157°.

Anal. Calcd. for $C_{21}H_{24}O_9$: C, 59.99; H, 5.75. Found: C, 60.32; H, 5.73.

1-(3'-Methoxy-4'-hydroxyphenyl)-2,6-dicarbethoxycyclohexanedione-3,5.—Three grams of substance (I) and 0.51 g. of sodium ethoxide in absolute alcohol were refluxed for two hours, and the alcohol distilled in vacuum.

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(1) Papadakis, THIS JOURNAL, **67**, 1799 (1945).

(2) Beilstein, 16 (343).

(3) Addinall, *Chem. Eng. News*, **22**, 1375 (1944).

(4) Ehrlich and Shiga, *Berl. Klin. Wochenschrift*, **41**, 330 (1904).

(5) Kraus, THIS JOURNAL, **36**, 962 (1914).

(6) Balkrishna and Iyer, *J. Ind. Inst. Sc.*, **21A**, Pt6, 65–75 (1938).

(7) Knoevenagel and Albert, *Ber.*, **37**, 4481 (1904).

To the dry residue distilled water was added. The water-insoluble material was filtered off and recrystallized three times from absolute alcohol; m. p. 187.5–188°.

Anal. Calcd. for $C_{19}H_{22}O_8$: C, 60.31; H, 5.86. Found: C, 59.84; H, 5.79.

1-(3′-Methoxy-4′-acetoxyphenyl)-4-isonitroso-2,6-dicarbethoxycyclohexanedione-3,5.—To a solution of 3 g. of 1-(3′-methoxy-4′-acetoxyphenyl)-2,6-dicarbethoxycyclohexanedione-3,5 in absolute alcohol, 0.492 g. of sodium nitrite and 0.5 ml. of glacial acetic acid were added. The reaction mixture was kept in a refrigerator for five days. The straw-colored precipitate which formed was filtered, washed with distilled water and then dried in a desiccator, m. p. 198°, yield 85%. The yellow salt of the monoxime was dissolved in cold water and filtered. To the cold filtrate 0.1 *N* cold hydrochloric acid was added dropwise until the solution was slightly acidic to litmus. (Excess acid converts the oxime to the original compound.) A white precipitate formed and was filtered and recrystallized from absolute methanol, m. p. 184°, yield 80%.

Anal. Calcd. for $C_{21}H_{23}O_{10}N$: C, 56.12; H, 5.16. Found: C, 55.93; H, 5.23.

1-(3′-Methoxy-4′-hydroxyphenyl)-4-isonitroso-2,6-dicarbethoxycyclohexanedione-3,5.—The procedure for this preparation is similar to that above. The starting material was 1-(3-methoxy-4-hydroxyphenyl)-2,6-dicarbethoxycyclohexanedione-3,5 instead of 1-(3-methoxy-4-acetoxyphenyl-2,6-, etc. This monoxime melts at 203°.

Anal. Calcd. for $C_{19}H_{21}O_9N$: C, 56.02; H, 5.19. Found: C, 56.38; H, 5.25.

1-(3′-Methoxy-4′-acetoxyphenyl)-4,5-dioxime-2,6-dicarbethoxycyclohexanetrione-3,4,5.—To 0.210 g. of hydroxylamine hydrochloride dissolved in a minimum amount of water, a solution of 0.070 g. of sodium in absolute alcohol was added. To the mixture, 1.5 g. of the sodium monoxime salt of 1-(3′-methoxy-4′-acetoxyphenyl)-4-oxime-2,6-dicarbethoxycyclohexanedione-3,4,5 was added and the solution allowed to stand for several days at room temperature. An intensely yellow precipitate was formed; m. p. 205–216°; yield 75%. The precipitate was dissolved in hot distilled water. The solution was cooled and treated with cold 0.1 *N* hydrochloric acid dropwise until it became faintly acid to litmus. The yellowish-white precipitate formed was filtered and recrystallized from absolute methanol; m. p. 194°; yield 80%.

Anal. Calcd. for $C_{21}H_{24}O_{10}N_2$: C, 54.31; H, 5.29. Found: C, 54.68; H, 5.25.

The use of this dioxime of structure (I) in the determination of nickel, cobalt and other metallic ions is under investigation.

N-N′-Bis{-4-[1-(3′-Methoxy-4′-hydroxyphenyl)-2,6-dicarbethoxycyclohexanedione-3,5]}-*p,p′*-disazo-diphenyl (II).—Benzidine tetrazonium dichloride, prepared by diazotizing 2.571 g. of benzidine dihydrochloride at 0°, was added to an alkaline cold water solution containing 8.40 g. of 1-(3-methoxy-4-acetoxyphenyl)-2,6-dicarbethoxycyclohexanedione-3,5 (I). The product of the coupling was soluble in the alkaline solution. The mixture was kept at 0°. After an hour, the solution was acidified with dilute hydrochloric acid and reddish-brown crystals were formed. The crystals were filtered, redissolved in alkali, reprecipitated by acid, washed with cold distilled water and dried in a vacuum desiccator. The melting point was too high to be determined by ordinary means.

Anal. Calcd. for $C_{50}H_{50}O_{16}N_4$: C, 62.36; H, 5.23. Found: C, 62.47; H, 5.11.

Acknowledgment.—The authors appreciate the interest which Dr. Christopher L. Kenny has shown in this research.

Summary

The syntheses of the following compounds are described:

1. 1-(3′-Methoxy-4′-acetoxyphenyl)-2,6-dicarbethoxycyclohexanedione-3,5 (I) and its deacetylated product.
2. 1-(3′-Methoxy-4′-hydroxyphenyl)-4-oxime-2,6-dicarbethoxycyclohexanedione-3,5.
3. 1-(3′-Methoxy-4′-hydroxy)-4,5-dioxime-2,6-dicarbethoxycyclohexanetrione-3,4,5.
4. N,N′-Bis-{4-[1-(3′-methoxy-4′-hydroxy)-phenyl-2,6-dicarbethoxycyclohexanedione-3,5]}-*p,p′*-disazodiphenyl (II).

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE STANDARD OIL CO. (INDIANA)]

Rearrangement of 4-Methylcyclohexene during Sulfuric Acid-catalyzed Reaction with Benzene

BY JACK LINSK

Under suitable conditions a carbonium ion can remove a hydride ion from another hydrocarbon.[1] This intermolecular transfer of hydrogen takes place readily between tertiary carbonium ions and tertiary hydrocarbons, and occurs frequently under the acid conditions of the olefin–isoparaffin alkylation reaction.[2,3,4] It was recently reported[5] that 4-methylcyclohexene in the presence of *p*-cymene and sulfuric acid is readily reduced to methylcyclohexane, but neither cyclohexene nor octene-1 is reduced to saturated hydrocarbons. This suggested that 4-methylcyclohexene must have rearranged prior to hydrogen transfer. The rearrangement probably yields the same tertiary carbonium ion intermediate as that obtained directly from 1-methylcyclohexene in the presence of the acid catalyst. Reaction by intermolecular transfer of a hydride ion from *p*-cymene or another suitable donor then gives methylcyclohexane.

The present work confirmed the ready rearrangement of methylcyclohexenes through a study of the sulfuric acid-catalyzed reaction of benzene with various methylcyclohexenes. The same

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[1] Whitmore, THIS JOURNAL **54**, 3274 (1932); *Chem. Eng. News*, **26**, 668 (1948).

[2] Bartlett, Condon and Schneider, THIS JOURNAL, **66**, 1531 (1944).

[3] Schmerling, *ibid.*, **67**, 1778 (1945).

[4] Pines and Ipatieff, *ibid.*, **67**, 1631 (1945).

[5] Ipatieff, Pines and Olberg, *ibid.*, **70**, 2123 (1948).