from methylene chloride-petroleum ether (b.p. 32–36°) to give the products listed in Table I.

Reaction of I and 1,2-epoxides without pyridine present. These reactions were carried out exactly as described, above, but no pyridine was added. After standing at least 12 hours, at room temperature, cyclohexene (1.0 ml.) was added and the mixture was allowed to stand for several hours. Chromatographing, as above, gave the known adduct of I and cyclohexene, m.p. 117–118°, in the yields shown in Table I.

Reaction of I and chlorohydrins in the presence of pyridine. These reactions were carried out in exactly the same way as were the epoxide reactions. The yields, melting points, and analytical figures are reported in Table I.

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5-(1′,2′,3′-Trimethoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3

PHILIPPOS E. PAPADAKIS AND ROBERT MATHIESEN

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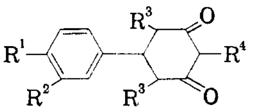
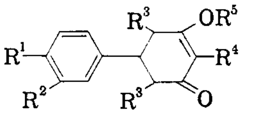
Compounds of the types (I) and (II) below with different substituents for R^1, R^2, R^3, R^4 and R^5 have been synthesized in the Department of Therapeutics of New York University and in this laboratory by Papadakis and co-workers. Some of these derivatives have been reported previously.[1–5]

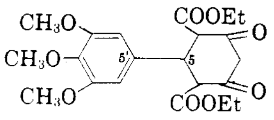


I



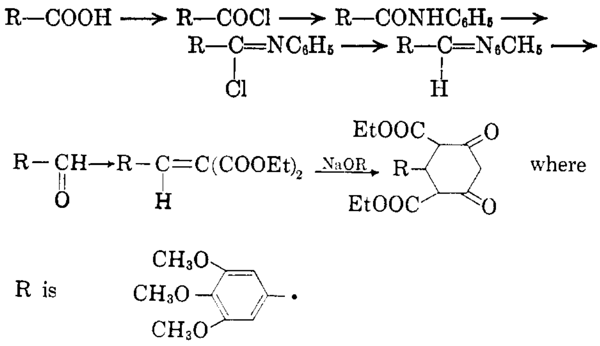
II

The present report is an extension of previous work and deals with the preparation of 5-(1′,2′,3′-trimethoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3 (III). The purpose of this investigation is the preparation of III as an intermediate for the synthesis of compounds having structural relation to known anticancer agents or to other substances of physiological importance.



III

The sequence of synthesis is as follows:



EXPERIMENTAL

The preparation of *trimethoxybenzaldehyde* from trimethoxybenzoyl chloride is described by A. Sonn and E. Muller[6] and by J. W. Cook and co-workers.[7] The trimethoxybenzaldehyde was distilled at 163–166° and 10 mm. pressure. The distillate crystallized and gave a melting point of 75–76°. (Melting points are uncorrected.) The over-all yield from trimethoxybenzoylanilide to trimethoxybenzaldehyde was 59%.

Ethyl trimethoxybenzylidenemalonate. A mixture of 6.2 g. of 3,4,5-trimethoxybenzaldehyde, 5.1 g. of diethyl malonate, and 0.3 ml. of piperidine was refluxed for five hours at 150°. The product was dissolved in a small amount of alcohol and was reprecipitated with distilled water, m.p. 71–71.5°. The mixture m.p. of the product with trimethoxybenzaldehyde was 58–60°. The yield of pure product was 5.6 g.

Anal. Calc'd for $C_{17}H_{22}O_7$: C, 60.34; H, 6.55. Found: C, 60.08; H, 6.45.

5-(1′,2′,3′-Trimethoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3. To a solution of 0.4 g. of sodium in absolute ethanol 2.2 g. of ethyl acetoacetate was added and the mixture was refluxed for an hour. To this, 5.6 g. of ethyl-3,4,5-trimethoxybenzylidenemalonate was added and the mixture was further refluxed for five hours at 110–115°. After cooling to 0°, cold dilute acetic acid was added. The yellowish crystals which formed were recrystallized from ethyl alcohol and were washed with dioxane; yield 3.6 g. of white needles, m.p. 191–192°.

Anal. Calc'd for $C_{21}H_{26}O_9 \cdot {}^1/_2\ H_2O$: C, 58.45; H, 6.07. Found: C, 58.31; H, 6.04. *Anal.* Dried at 100° in a vacuum, Calc'd for $C_{21}H_{26}O_9$: C, 59.71; H, 6.16. Found: C, 59.60; H, 5.84. *Anal.* Calc'd for 3($—OCH_3$) and 2($—OC_2H_5$): % alkoxy, 43.36. Found: 43.35, 43.10.

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(1) Papadakis, *J. Am. Chem. Soc.*, **67**, 1799 (1945).

(2) Papadakis, Scigliano, Chin, and Adrian, *J. Am. Chem. Soc.*, **72**, 4256 (1950).

(3) Papadakis, Scigliano, and Pirruccello, *J. Am. Chem. Soc.*, **75**, 5436 (1953).

(4) Papadakis and Scigliano, *J. Am. Chem. Soc.*, **75**, 5437 (1953).

(5) Papadakis, *J. Org. Chem.*, **19**, 51 (1954).

(6) Sonn and Muller, *Ber.*, **52**, 1934 (1919).

(7) Cook, Graham, Cohen, Lapsley, and Laurence, *J. Chem. Soc.*, 322 (1944).

Meta Amination as a 1,3-Addition Process

AVERY A. MORTON

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The "benzyne" intermediate[1,2] for *meta* amination is a product of a theory that many reactions be-

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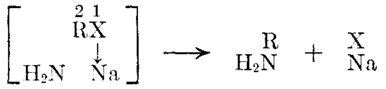
(1) Roberts, Simmons, Carlsmith, and Vaughan, *J. Am. Chem. Soc.*, **75**, 3290 (1953).

(2) Roberts, Semenow, Simmons, and Carlsmith, *J. Am. Chem. Soc.*, **78**, 601 (1956).

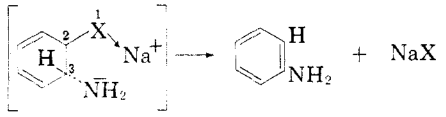
tween alkali metal salts and halogen compounds begin with proton removal and follow with halogen ejection. Essentially the intermediate is a stripped-down molecule, an acetylenic system in a 6-membered ring. Lately the idea has been adopted for a Wurtz-Fittig reaction.[3] It is interesting to apply the ion-pair concept to this amination. Here the intermediate would be essentially an additive product, a built-up molecule approaching the type of dihydrobenzene. In succeeding paragraphs, this idea will be developed. The ordinary reaction, usually called displacement, will be pictured as 1,2-addition, halogen being numbered 1. *Meta* amination would begin as 1,3-addition followed by common steps that permit accounting for all of the effects so far observed.

For all cases the carbon-halogen bond is presumed to have a degree of unsaturation. The polar end of the carbo-halyl system has unshared electrons and at the instant of reaction is adjacent to the positively charged cation. This contact is denoted in (a) with an arrow, probably as a coordination. As sodium halide emerges from the complex the amino group adds to carbon. The over-all process is 1,2-addition as unsaturation develops at the carbon end

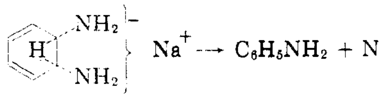


$$\left[\begin{matrix} \overset{2\ 1}{RX} \\ \downarrow \\ H_2N \quad Na \end{matrix}\right] \longrightarrow \overset{R}{H_2N} + \overset{X}{Na} \qquad (a)$$

A 1,3-addition is shown in (b). The amino group might add (dotted line) at the 3-position as sodium halide emerges and hydrogen shifts. A random mixture of 1,2- and 1,3-additions might occur. However the halogen has become very labile and of the type of an activated aliphatic halogen atom. Its displacement by an amide ion would give the complex in (c) from which a loss of sodamide in one of two equivalent ways would give aniline. All facts connected with C^{14} halobenzenes would thereby be accounted for and with an intermediate far less strained than a "benzyne" structure.

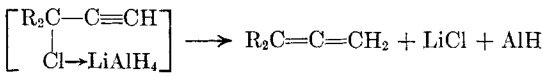


(b)



(c)

This general picture for halogen removal is made more complete by an example of 1,4-addition. The novel formation of allenes[4,5] from some chloromethylacetylenes and lithium hydride (from lithium aluminum hydride) fits nicely into this category. As lithium chloride emerges from the complex illustrated in (c), addition occurs at the 4-position. Accompanying shifts produce a double bond between the 2- and 3-positions, just as in many other 1,4-processes.



$$\left[\begin{matrix} R_2C{-}C{\equiv}CH \\ | \\ Cl{\rightarrow}LiAlH_4 \end{matrix}\right] \longrightarrow R_2C{=}C{=}CH_2 + LiCl + AlH_3 \qquad (d)$$

These additions involve both ions of the reagent. Electrons and charges move into appointed places, but such features and numerous details are avoided as far as possible in order to keep in focus the main issue of an intermediate that is achieved by stripping off atoms to give an acetylenic type structure *versus* one which is reached by adding atoms or ions to give a complex in which an unstrained dihydroaromatic system is approached. This discussion is not to be construed as a statement that the "benzyne" intermediate is wrong, but all facts so far presented[2] in its behalf can be interpreted equally well by some variant of the ion-pair concept.

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A New Technique for the Chromatographic Separation of Organic Compounds

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Ion-exchange resins have been used as the stationary phase in chromatographic separations of the following types: (1) separation of two or more ions by elution with a solution of an electrolyte, (2) separation of an electrolyte from a nonelectrolyte by elution with water (ion exclusion),[1,2,3] and (3) separation of two or more nonelectrolytes by elution with water.[2] The purpose of this communication is to report that the separation of nonelectrolytes is greatly improved simply by using a salt solution instead of water as the eluant.

For example, the elution with water of a mixture of diethylene glycol and dipropylene glycol on a 70-cm. column of Dowex 1X8, sulfate form, 200–300 mesh, yields no separation, whereas elution on a 10-cm. column with 3.0 *M* ammonium sulfate yields a quantitative separation, diethylene glycol emerging from the column first. As illustrated in Fig. 1, the separation of methanol, ethanol, and propanol-1 is much better with 3.0 *M* ammonium sulfate as

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[3] Jenny and Roberts, *Helv. Chim. Acta*. **38**, 1248 (1955).

[4] Wotiz, *J. Am. Chem. Soc.*, **73**, 693 (1951).

[5] Bailey and Pfeifer, *J. Org. Chem.*, **20**, 95 (1955).

[1] Wheaton and Bauman, *Ind. Eng. Chem.*, **45**, 228 (1953).

[2] Simpson and Wheaton, *Chem. Eng. Progr.*, **50**, 45 (1954).

[3] Simpson and Bauman, *Ind. Eng. Chem.*, **46**, 1958 (1954).