[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, UNION CARBIDE CHEMICALS CO.]

A New Synthesis of Phenylglyoxal Acetals

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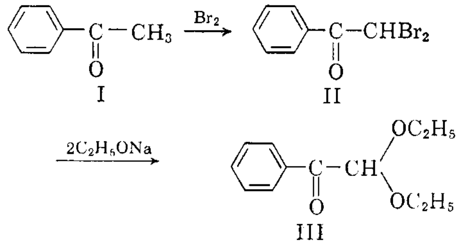
The reaction of nitrosyl chloride with acetophenone in ethanol solution at approximately 25–60° produces phenylglyoxal diethyl acetal in yields as high as 53%. By-product esters, formed in smaller yields, are readily removed by treatment of the reaction mixture with hot aqueous sodium hydroxide enabling recovery of the acetal in pure form. DL-Mandelic acid is recoverable in 24.0% yield from the aqueous basic hydrolysate and probably results from the action of base upon free phenylglyoxal, which has not been converted to the acetal. By replacing the ethanol medium with other alcohols, this reaction serves as a general preparative method for phenylglyoxal acetals. Thus the reaction of nitrosyl chloride with acetophenone in methanol and in propylene glycol solution produces phenylglyoxal dimethyl acetal in 35% yield and 2-(4-methyl-1,3-dioxolan-2-yl)-2-phenyl-4-methyl-1,3-dioxolane in 36% yield, respectively.

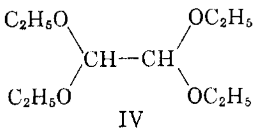
A recent study[1] of the complex reactions occurring upon treatment of acetophenone (I) with nitrosyl chloride in an ethanolic medium containing pyridine revealed the major reaction products to be ethyl phenylglyoxylate and phenylglyoxal diethyl acetal (III), obtained in yields of 18% and 12% respectively. In addition, somewhat smaller yields of phenylglyoxal aldoxime, benzoic acid, ethyl benzoate, and ethyl phenylacetate were also observed. Despite the fact that phenylglyoxal diethyl acetal was readily recoverable from the high-boiling fractions following saponification of the ester by-products, this method is of limited value as a synthetic route to the acetal because of the low yield obtained. The synthesis of phenylglyoxal diethyl acetal has previously been reported by Evans and Parkinson[2] who employed the following two-step approach. A similar sequence was employed by Madelung and Oberwegner[3] in preparing the corresponding dimethyl acetal. Phenylglyoxal diethyl acetal may also be prepared by prolonged treatment of phenylglyoxal with ethanol in the presence of sulfuric acid.[1]



It has now been found that when the reaction of nitrosyl chloride with acetophenone in ethanol solution is performed in the absence of pyridine, the yield of phenylglyoxal diethyl acetal is increased to as high as 53%, while the yields of the lower boiling esters were decreased. Under these conditions ethyl phenylglyoxylate was not observed in the high-boiling fraction. In recovering phenylglyoxal diethyl acetal it is not necessary to subject the reaction residue to fractional distillation prior to hydrolysis of by-product esters. A more convenient procedure is collective saponification of the esters, either immediately following the reaction and prior to removal of ethanol or by contacting the ethanol-free residue with hot aqueous sodium hydroxide. Following either procedure, the acetal is readily recoverable by simple vacuum distillation, no laborious fractionation procedures being necessary.

In addition to the compounds previously mentioned, other by-products have been identified in the phenylglyoxal diethyl acetal synthesis. Acidification of the basic aqueous layer following the saponification treatment afforded, in addition to benzoic acid (17% yield), a 24% yield of DL-mandelic acid. Since the latter probably arises from free phenylglyoxal, which would undergo the Cannizzaro reaction during the basic hydrolytic treatment, it appears that the potential yield of phenylglyoxal in the reaction is higher than that realized as the diethyl acetal. Moreover, this observation is in agreement with the previous interpretation[1] that phenylglyoxal, itself, is first formed and is subsequently converted to the acetal by reaction with ethanol.

Another by-product observed is 1,1,2,2-tetraethoxyethane (IV) which survives the basic hydrolysis and is obtained, in low yield, as the forerun during the distillation of phenylglyoxal diethyl acetal. 1,1,2,2-Tetraethoxyethane arises from interaction of nitrosyl chloride and ethanol in a competing process currently under study.


IV

That the reaction of nitrosyl chloride with acetophenone in solutions of various alcohols may offer a general preparative method for phenylglyoxal acetals is suggested by the successful extension of

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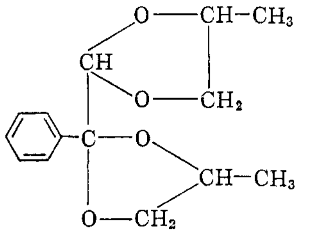
[1] D. T. Manning and H. A. Stansbury, Jr., *J. Am. Chem. Soc.*, **81**, 4885 (1959).

[2] W. L. Evans and C. R. Parkinson, *J. Am. Chem. Soc.*, **35**, 1770 (1913).

[3] W. Madelung and M. E. Oberwegner, *Ber.* **65**, 931 (1932).

this method to include the preparation of phenylglyoxal dimethyl acetal (35% yield) and 2-(4-methyl-1,3-dioxolan-2-yl)-2-phenyl-4-methyl-1,3-dioxolane (V) in 36% yield by replacing the ethanolic medium by methanol and 1,2-propanediol, respectively. In the latter case, the somewhat unexpected reaction of the keto group with the diol may be rationalized by consideration of the driving force attending the formation of a five-membered ring.[4]



V

EXPERIMENTAL

Phenylglyoxal diethyl acetal (III). (a). To a stirred solution of 120 g. (1.0 mole) of acetophenone in 1500 ml. of ethanol was added 1.6 moles (75 ml. at −30°) of nitrosyl chloride (purchased from the Matheson Co.) over a 51-min. period with cooling to maintain a temperature of 23–30°. Upon completing the feed, the reaction mixture was heated to 60° over a period of 1.37 hr. and held at this temperature for an additional 1.8-hr. interval. Ethanol was then removed from the reaction mixture by flash distilling under reduced pressure to a final internal temperature of 60° at 20 mm., leaving 185 g. of a liquid residue. Hydroxylamine titration[1] of the distilled material showed 19.5 g. of unchanged acetophenone to be present.

The high-boiling residue was diluted with ether and acidic materials (including residual hydrogen chloride, small amounts of benzoic acid and phenylglyoxal aldoxime) were then removed by successive extractions with aqueous sodium bicarbonate and sodium carbonate. The organic phase was dried, freed of ether by evaporation and subjected to fractional distillation which yielded a series of cuts, b.p. 82–134°/10 mm. The lower boiling cuts (82–129°/10 mm.) were found by infrared and mass spectrometric analysis[1] to consist of acetophenone, ethyl benzoate, benzoyl cyanide, and ethyl phenylacetate and constituted 21.6% by weight of the total volatile material. The remainder of the material distilled at 129–134°/10 mm. and was phenylglyoxal diethyl acetal containing esters as impurities.

Phenylglyoxal diethyl acetal was recovered in pure form from a portion (60 g.) of the high boiling material by hydrolysis of the contaminant esters with 2*N* sodium hydroxide according to the method of Baer and Kates.[5] Distillation of the unsaponified organic layer gave 52.9 g. (41.9% yield) of the acetal as a colorless liquid, b.p. 129–133.5°/10 mm., n_D^{20} 1.4998, d_{20}^{20} 1.044.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.19; H, 7.63.

(b) To a stirred solution of 120 g. (1.0 mole) of acetophenone in 1500 ml. of ethanol was added 2.61 moles (120 ml. at −30°) of nitrosyl chloride over a 53-min. period with cooling to maintain a temperature of 24–30°. Upon completion of the feed, the reaction mixture was warmed to 63° over a 53-min. interval and held at this temperature, with stirring, for a period of 2.5 hr. Volatile materials were then removed by evaporation *in vacuo* to a final temperature of 60° at 20 mm.

The stripped residue was added in one portion to 2000 ml. of aqueous 2*N* sodium hydroxide and the mixture heated under reflux, with vigorous stirring, for 1.5 hr. Upon cooling, the oily organic layer was separated by extracting with ethyl ether, dried, and distilled at reduced pressure. After removing 11 g. of low-boiling materials, 102 g. (48.5% yield) of phenylglyoxal diethyl acetal was obtained as a colorless oil, b.p. approximately 128°/10 mm., n_D^{20} 1.4986, further identified by comparison of the infrared spectrum with that of an authentic specimen.[1]

Infrared analysis of the low-boiling material (b.p. 72.5–128°/10 mm.) showed a mixture of by-products including one having a band in the triple-bond region (4.71–4.73 μ). Vapor-phase chromatography of the low-boiling material coupled with mass spectrometric and infrared analyses of the fractions indicated the presence of several compounds (including 5–10% of recovered acetophenone), the main constituent of which appeared to be 1,1,2,2-tetraethoxyethane.

The aqueous basic hydrolysate was acidified to *p*H 3 and extracted with ethyl ether to give, after evaporation, 18.6 g. of an acid mixture, m.p. 80–90°, neutralization equivalent 144.7. The *p*H of the aqueous solution was then reduced to 0.5 and extracted to give 45.1 g. of a substance, m.p. 97–102°, neutralization equivalent 149.2. The two acid fractions were combined, dissolved in 250 ml. of aqueous 2*N* sodium hydroxide, and, after washing with ethyl ether and treating with Norite, acidified to *p*H 2–3, causing 21.2 g. (17.4% yield) of benzoic acid, m.p. 119–120°, to precipitate. The filtrate was then extracted with ethyl ether to give, upon evaporation, 36.5 g. (24.0% yield) of crude DL-mandelic acid, m.p. 88–103°.

Anal. Calcd. for $C_8H_8O_3$: Neut. equiv., 154.2. Found: Neut. equiv., 156.8.

The crude product was washed with hot carbon tetrachloride and finally recrystallized from benzene-ethanol to obtain the pure acid, m.p. 117–118° (reported[6] m.p. 118–119°), undepressed by admixture with an authentic sample. The infrared scan was superposable with that of a known specimen of DL-mandelic acid.

When the reaction was repeated under essentially the above conditions, but adding the sodium hydroxide solution prior to evaporative removal of ethanol, phenylglyoxal diethyl acetal, b.p. 129.5–135°/10 mm., was obtained in 52.7% yield accompanied by a low yield of 1,1,2,2-tetraethoxyethane, b.p. 80–84°/10 mm., identified by comparison of its infrared spectrum with that of an authentic sample. That the 1,1,2,2-tetraethoxyethane results from the action of nitrosyl chloride upon ethanol was subsequently demonstrated by a repetition of the reaction in the absence of acetophenone.

Phenylglyoxal dimethyl acetal (IV). Nitrosyl chloride (4.35 moles) was treated with 240 g. (2.0 moles) of acetophenone in 3000 ml. of methanol under conditions similar to those described above. Following the reaction, the mixture was freed of methanol and the stripped residue treated in the usual manner with aqueous sodium hydroxide. The product, recovered by ether-extraction, was vacuum distilled to give three main fractions. Phenylglyoxal dimethyl acetal (124.8 g. 34.6% yield) occurred as a mid-

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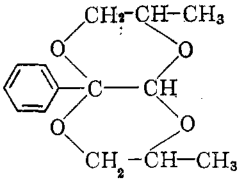
(4) Although structure V is proposed, we have no evidence excluding structures such as



(5) E. Baer and M. Kates, *J. Am. Chem. Soc.*, 67, 1482 (1945).

(6) Heilbron, *Dictionary of Organic Compounds*, Vol. III, Oxford University Press, New York, N. Y., 1953.

fraction, b.p. 133°/16 mm. (reported[3] b.p. 133–134°/16 mm.), 123°/10 mm., 109°/5 mm., n_D^{20} 1.5157.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.73; H, 6.76.

The low-boiling fraction (10 g., b.p. 97–121°/10 mm.) consisted of a mixture of unknown by-products. Infrared analysis indicated the presence of alcoholic (2.9 μ) and acetal functions (8.9 and 9.4 μ) as well as a compound absorbing at 4.73 μ. Upon redistillation of this material, a sirupy residue was obtained which showed a band in the infrared at 5.77 μ and appeared to be a nonaromatic ester with an acetal. A very similar material was obtained as a high-boiling (150–211°/2–3 mm.) fraction, 23.9 g., following the dimethyl acetal cut. It consisted of a viscous orange sirup with infrared characteristics similar to those of the residue described above, including carbonyl absorption at 5.77 μ. Most of this substance boiled at 175–185°/2 mm. The following analyses were obtained for this unknown.

Anal. Calcd. for $C_{18}H_{21}O_4$: C, 71.50; H, 7.33; mol. wt., 302.4. Found: C, 70.84; H, 7.10; mol. wt., 319.

The aqueous hydrolysate following the sodium hydroxide treatment was acidified and worked up in the manner previously described, yielding 38.4 g. (12.7% yield) of crude DL-mandelic acid and 52.2 g. (21.4% yield) of benzoic acid.

2-(4-Methyl-1,3-dioxolan-2-yl)-2-phenyl-4-methyl-1,3-dioxolane (V).[4] Acetophenone (120 g., 1.0 mole) was partially dissolved in a mixture of 1,2-propanediol (456 g., 8.1 moles) and 1000 ml. of benzene. The resulting mixture was stirred vigorously and 2.39 moles of nitrosyl chloride (110 ml. at −30°) was added dropwise at 20–30° over a period of 2.25 hr. During the addition, an exothermic reaction occurred, and cooling was required to keep the temperature below 30°. At the end of the feed period, stirring was continued for 1 hr. at 25–35° and then for 1.5–2 hr. at 60°. During the reaction, approximately 1 mole of gas was liberated and found to consist entirely of nitrous oxide, nitric oxide, and nitrogen.

The cool reaction mixture consisted of two liquid layers. The upper layer was extracted five times with 500-ml. portions of water and freed of benzene on the steam bath, leaving 200 ml. of an oil. The lower layer was diluted with 1000 ml. of water and extracted with six 500-ml. portions of ether. These extracts were combined, dried (sodium sulfate), and evaporated free of ether to give approximately 60 ml. of yellow oil.

The organic oils from the two layers were combined and heated under reflux with 2000 ml. of 2*N* sodium hydroxide for a 1.5-hr. period. The mixture was then cooled and extracted with ether to obtain (after evaporation of ether) 113 g. of an oil. Fractional distillation of the oil at reduced pressure gave 90.4 g. of 2-(4-methyl-1,3-dioxolan-2-yl)-2-phenyl-4-methyl-1,3-dioxolane (36% yield) as a heavy colorless sirup. The main fraction boiled at 147–152°/3 mm., n_D^{20} 1.5169.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.24, mol. wt. 250.3. Found: C, 66.37; H, 7.15, mol. wt. 250.

Infrared analysis revealed no bands in the carbonyl region and showed numerous bands in the 8–10 μ region in accord with the ketal-acetal structure. Surprisingly, no aromatic absorption occurred in the 6.2–6.35 μ region. The presence of a benzene ring was, however, confirmed by dichromate oxidation to benzoic acid. The material proved surprisingly inert toward permanganate oxidation.

The aqueous layer from the sodium hydroxide reaction was acidified to *p*H 1 to precipitate 58.6 g. of a gummy white solid having a neutralization equivalent of 205. The material was recrystallized from water to give 22.7 g. of benzoic acid, m.p. 121–122°. The balance of the material was not identified.

Following precipitation of the solid, the aqueous layer was extracted with ethyl ether to recover 35.3 g. of a viscous orange oil (neutralization equivalent 222). This material was distilled at reduced pressure to give 21.5 g. of oil, b.p. 110°–160°/3.5 mm. and a dark residue. The oil contained a small amount (1–3 g.) of benzoic acid and unknown, nonacidic, carbonyl compounds.

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Some Esters of 1,2,4-Butanetricarboxylic Acid

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The preparation of several saturated, unsaturated and epoxyalkyl esters of 1,2,4-butanetricarboxylic acid is described.

Higher trialkyl esters of 1,2,4-butanetricarboxylic acid are known to be effective plasticizers for poly(vinyl chloride) resins.[1] A variety of such materials were prepared (Table I), most of which are new compounds, for evaluation in this application. In general, these plasticizers exhibit excellent low-temperature properties and low volatility.

A series of unsaturated esters of 1,2,4-butanetricarboxylic acid was prepared by esterification with unsaturated alcohols or by vinylation with acetylene (Table II). The allyl and vinyl esters were evaluated as polymerizable plasticizers and found to be effective. The higher unsaturated esters in general proved to be effective plasticizers, but their major utility was as intermediates in the preparation of a new class of epoxides.

A wide variety of epoxyalkyl esters of 1,2,4-butanetricarboxylic acid was prepared by the epoxidation of the respective unsaturated esters by peracetic acid in ethyl acetate[2] (Table III). In general, high yields of materials with high oxirane content were obtained. The epoxyalkyl esters proved to be excellent plasticizer-stabilizers for poly(vinyl chloride) resins and could be poly-

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[1] British Patent 688,344 (1953), N. V. De Bataafsche Petroleum Maatschappij (The Netherlands).

[2] F. C. Frostick, B. Phillips, and P. S. Starcher, *J. Am. Chem. Soc.*, 81, 3350 (1959).