quantities of key cofactors present in the preparations. It appears unlikely that soluble extracts are less dependent upon cofactor generating systems than the more intact preparations.

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DEPARTMENT OF PHYSIOLOGY
SCHOOL OF MEDICINE
WESTERN RESERVE UNIVERSITY
CLEVELAND, OHIO

2-Pyrones. XVI. Benzylidene and Arylhydrazone Derivatives of Glutaconic Anhydride

BY RICHARD H. WILEY AND HENRY G. ELLERT

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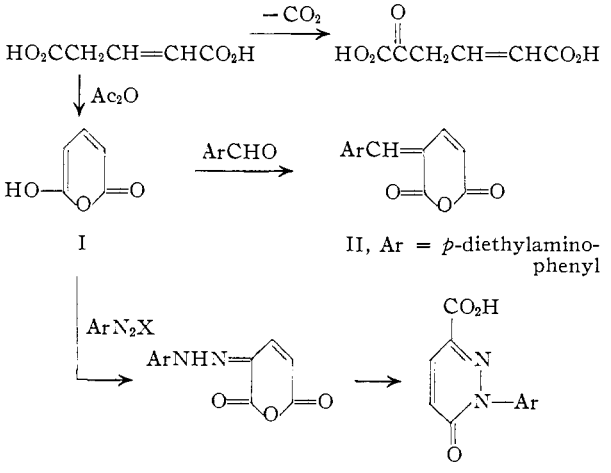
The procedures used previously[1,2] for the conversion of β-methylglutaconic anhydride to substituted benzylidene derivatives by condensation with aryl aldehydes and to arylhydrazone derivatives by coupling with aryl diazonium salts have been extended to glutaconic anhydride I. The preparation and characterization of the products obtained in these reactions and in the rearrangement of the arylhydrazones III to pyridazonecarboxylic acids IV are described in this report. The glutaconic anhydride used in these studies was prepared from glutaconic acid by anhydride interchange with acetic anhydride. The acid, which is available *via* several routes,[3] was prepared by hydrolysis and decarboxylation of diethyl oxalocrotonate[4] prepared in turn from ethyl oxalate and ethyl crotonate.[5]



(1) R. H. Wiley, E. L. DeYoung and N. R. Smith, THIS JOURNAL, **76**, 6175 (1954).

(2) R. H. Wiley and C. H. Jarboe, *ibid.*, **77**, 403 (1955).

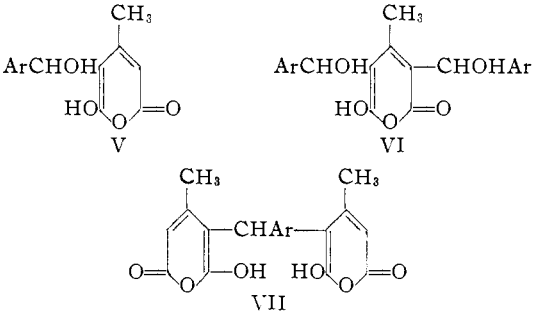
(3) P. E. Verkade, *Rec. trav. chim.*, **41**, 208 (1922).

(4) A. B. Boese, Jr., and R. T. Major, THIS JOURNAL, **56**, 949 (1934).

(5) R. H. Wiley and A. J. Hart, *ibid.*, **76**, 1942 (1954).

The reaction between glutaconic anhydride and *p*-diethylaminobenzaldehyde gave a purple product II, m.p. 219°, recrystallizable from toluene–petroleum ether. Although crystalline products were obtained from 3,4-dimethoxy- and *p*-dimethylaminobenzaldehydes, neither of these analyzed in acceptable agreement with the arylidene structure II. Apparently these products are too unstable to permit separation of analytically pure individual compounds from the mixtures formed by any techniques we have been able to devise to date. Varying analytical data were obtained on products obtained by altering minor details of the preparation.

In these reactions with aromatic aldehydes, the presence of the β-methyl group in the glutaconic anhydride clearly contributes to the ease with which characterizable arylidene derivatives are formed. This is probably partly a simple steric effect in which the β-methyl group shields the α-position from a continuing reaction. If, however, the products consist of mixtures of mono- and disubstituted products of the types V, VI and VII, a likely possibility corresponding to condensation of



aldehydes with *o*- and *p*-positions of phenols, then the β-methyl group, by virtue of its electron-releasing characteristics, may facilitate dehydration of V thus inhibiting formation of products such as VI, or dehydrated forms thereof, and VII. It is unlikely that any reaction with the aldehyde can occur in the free β-position.

By way of contrast the condensations of glutaconic anhydride with diazonium salts to give γ-phenylhydrazono structures III proceeds as does the reaction with β-methylglutaconic anhydride. Using similar procedures, yields of 57.3 to 87% were obtained. The products are formulated as phenylhydrazones on the basis of observations noted with the β-methyl types. Rearrangement of these products to the corresponding 1-aryl-2-pyridazone-5-carboxylic acids (IV) takes place in 28 to 74% yields.

Experimental[6]

γ-(4′-Diethylaminobenzylidene)-glutaconic Anhydride (II, Ar = *p*-Diethylaminophenyl).—A solution of 0.5 g. (0.00415 mole) of glutaconic anhydride and 0.73 g. (0.00415 mole) of *p*-diethylaminobenzaldehyde in 10 ml. of 95% ethanol immediately deposited a deep red precipitate. This precipitate was collected and recrystallized from toluene–petroleum ether to give 0.80 g., 66%, of γ-(4′-diethylaminobenzylidene)-glutaconic anhydride, m.p. 219°.

Anal. Calcd. for $C_{16}H_{17}O_3N$: C, 70.83; H, 6.32. Found: C, 70.57; H, 6.58.

γ-Ketoglutaconic Anhydride Phenylhydrazone (III, Ar = Phenyl).—A solution of 0.47 g. (0.005 mole) of aniline in 25

(6) Analyses by Micro Tech Laboratories, Skokie, Ill.

ml. of water containing 8 ml. of 12 *N* hydrochloric acid was cooled to 0°. A 10% aqueous solution of sodium nitrite was added until a starch–iodine test indicated an excess of nitrous acid. A solution of 0.56 g. (0.005 mole) of glutaconic anhydride in 25 ml. of water containing 0.2 g. of sodium carbonate was cooled to 0° and added to the diazotized amine to precipitate the crude product. Recrystallization from ethyl acetate gave 0.89 g., 87% of the theoretical amount, of γ-ketoglutaconic anhydride phenylhydrazone as orange plates, m.p. 165°.

Anal. Calcd. for $C_{11}H_8O_3N_2$: C, 61.11; H, 3.73. Found: C, 61.15; H, 3.75.

γ-Ketoglutaconic Anhydride *o*-Tolylphenylhydrazone (III, Ar = *o*-Tolyl).—This compound was prepared by the procedure given for the phenyl analog using diazotized *o*-toluidine. Recrystallization from ethyl acetate gave 0.66 g., 57.3%, of γ-ketoglutaconic anhydride *o*-tolylphenylhydrazone as orange crystals, m.p. 174–175°.

Anal. Calcd. for $C_{12}H_{10}O_3N_2$: N, 12.17. Found: N, 12.43.

γ-Ketoglutaconic Anhydride *p*-Tolylphenylhydrazone (III, Ar = *p*-Tolyl).—This compound was prepared by the procedure given for the phenyl analog using diazotized *p*-toluidine. Recrystallization from ethyl acetate gave 0.91 g., 79.3%, of γ-ketoglutaconic anhydride *p*-tolylhydrazone, yellow crystals, m.p. 201°.

Anal. Calcd. for $C_{12}H_{10}O_3N_2$: N, 12.17. Found: N, 12.14.

γ-Ketoglutaconic Anhydride *o*-Methoxyphenylhydrazone (III, Ar = *o*-Methoxyphenyl).—This compound was prepared by the procedure given for the phenyl analog using diazotized *o*-anisidine. Recrystallization from ethyl acetate gave 0.69 g., 56%, of γ-ketoglutaconic anhydride *o*-methoxyphenylhydrazone, red crystals, m.p. 169°.

Anal. Calcd. for $C_{12}H_{10}O_4N_2$: C, 58.53; H, 4.09. Found: C, 58.51; H, 4.21.

γ-Ketoglutaconic Anhydride β-Naphthylhydrazone (III, Ar = β-Naphthyl).—This compound was prepared by the procedure given for the phenyl analog using diazotized β-naphthylamine. Recrystallization from ethyl acetate gave 1.15 g., 86.5%, of γ-ketoglutaconic anhydride β-naphthylhydrazone as orange crystals, m.p. 252–253°.

Anal. Calcd. for $C_{15}H_{10}N_2O_3$: C, 67.66; H, 3.79. Found: C, 67.66; H, 3.96.

γ-Ketoglutaconic Anhydride α-Naphthylhydrazone (III, Ar = α-Naphthyl).—This compound was prepared by the procedure given above for the phenyl analog using diazotized α-naphthylamine. Recrystallization from ethyl acetate gave 1.13 g., 85.5%, of γ-ketoglutaconic anhydride α-naphthylhydrazone as orange crystals, m.p. 163–165°.

Anal. Calcd. for $C_{15}H_{10}N_2O_3$: C, 67.66; H, 3.79. Found: C, 68.06; H, 3.83.

γ-Ketoglutaconic Anhydride *o*-Carboxyphenylhydrazone (III, Ar = *o*-Carboxyphenyl).—This compound was prepared by the procedure given above for the phenyl analog using diazotized 2-anthranilic acid. Recrystallization from acetic acid gave 1.06 g., 80%, of γ-ketoglutaconic anhydride *o*-carboxyphenylhydrazone as yellow crystals, m.p. 268–270°.

Anal. Calcd. for $C_{12}H_8N_2O_5$: C, 55.39; H, 3.10. Found: C, 55.48; H, 3.22.

γ-Ketoglutaconic Anhydride *p*-Dimethylaminophenylhydrazone (III, Ar = *p*-Dimethylaminophenyl).—This compound was prepared by the procedure given above for the phenyl analog using diazotized N,N-dimethylphenylenediamine. Recrystallization from ethyl acetate gave 0.81 g., 64%, of γ-ketoglutaconic anhydride *p*-dimethylaminophenylhydrazone, deep blue needles, m.p. 200–201°.

Anal. Calcd. for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05. Found: C, 60.33; H, 4.83.

1-Phenyl-3-carboxy-6-pyridazone (IV, Ar = Phenyl).—A mixture of 0.5 g. (0.0024 mole) of γ-ketoglutaconic anhydride phenylhydrazone and 25 ml. of 10% aqueous potassium hydroxide was refluxed for two hours. During this time the anhydride dissolved and the color was discharged. The cooled reaction mixture was extracted with ether to remove unreacted starting materials and acidified. The acid solution was then extracted with several 25-ml. portions of ether which were dried over anhydrous potassium sulfate and evaporated to dryness to yield the crude product. Recrystallization from ethyl acetate gave 0.14 g., 28% of the theoretical amount, of 1-phenyl-3-carboxy-6-pyridazone, m.p. 210–212°.

Anal. Calcd. for $C_{11}H_8O_3N_2$: N, 12.96. Found: N, 12.74.

1-(*o*-Tolyl)-3-carboxy-6-pyridazone (IV, Ar = *o*-Tolyl).—This compound was prepared by the procedure given for the β-naphthyl analog from 0.5 g. of the *o*-tolylhydrazone. The crude product precipitated on acidification. There was obtained 0.21 g., 42%, of 1-(*o*-tolyl)-3-carboxy-6-pyridazone, m.p. 236°, recrystallized from ethyl acetate.

Anal. Calcd. for $C_{12}H_{10}O_3N_2$: N, 12.17. Found: N, 12.09.

1-(*p*-Tolyl)-3-carboxy-6-pyridazone (IV, Ar = *p*-Tolyl).—This compound was prepared by the procedure given for the *o*-tolyl analog from 0.5 g. of the *p*-tolylhydrazone. There was obtained 0.37 g., 74%, of 1-(*p*-tolyl)-3-carboxy-6-pyridazone, m.p. 229–230°, recrystallized from ethyl acetate.

Anal. Calcd. for $C_{12}H_{10}O_3N_2$: N, 12.17. Found: N, 12.19.

1-(*o*-Methoxyphenyl)-3-carboxy-6-pyridazone (IV, Ar = *o*-Methoxyphenyl).—This compound was prepared by the procedure given for the *o*-tolyl analog from 0.7 g. of the *o*-methoxyphenylhydrazone. There was obtained 0.49 g., 70%, of 1-(*o*-methoxyphenyl)-3-carboxy-6-pyridazone, m.p. 212–213°, recrystallized from ethyl acetate.

Anal. Calcd. for $C_{12}H_{10}O_4N_2$: C, 58.53; H, 4.07; neut. equiv., 244. Found: C, 58.69; H, 4.37; neut. equiv., 244.

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DEPARTMENT OF CHEMISTRY
UNIVERSITY OF LOUISVILLE
LOUISVILLE, KENTUCKY

1,3-*O*-Benzylidene-2,5-di-*O*-*p*-tolylsulfonyl-DL-arabitol

BY EMMANUEL ZISSIS AND NELSON K. RICHTMYER

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In a preceding communication[1] we described the tosylation of 1,3-*O*-benzylidene-D-arabitol. Under forcing conditions (25 molecular equivalents of *p*-toluenesulfonyl chloride in excess pyridine for 5 days at room temperature) the expected tri-*O*-tosyl derivative was obtained, but under milder conditions (6 molecular equivalents of reagent for 3 days at room temperature) the principal product was a di-*O*-tosyl derivative that we presumed, from general rules of substitution, to be 1,3-*O*-benzylidene-4,5-di-*O*-*p*-tolylsulfonyl-D-arabitol. Grewe and Pachaly,[2] in a paper that we had overlooked earlier, effected the unimolecular tosylation of 1,3-*O*-benzylidene-L-arabitol; in addition to a 50% yield of the desired 5-*O*-tosyl derivative, they isolated 12% of a di-*O*-tosyl derivative that melted at 136.5° and showed $[\alpha]^{19}D$ +11.3° in pyridine (*c* 1.1). Our di-*O*-tosyl compound melted at 135–136° and showed $[\alpha]^{20}D$ −18.1° in chloroform and, we now find, −10.3° in pyridine (*c* 1.1). Thus, Grewe and Pachaly's compound and our compound appeared to be enantiomorphs. Professor Grewe kindly sent us some of his product and we have verified the antipodal nature of the two substances by direct comparison of their infrared spectra and X-ray powder diffraction patterns, and finally through the preparation of a racemic compound whose melting point of 152–154° is nearly 20°

(1) E. Zissis and N. K. Richtmyer, THIS JOURNAL, **76**, 5515 (1954).
(2) R. Grewe and H. Pachaly, *Chem. Ber.*, **87**, 46 (1954).