**Acknowledgment.**—Thanks are due to Max Tishler for much helpful advice throughout the course of this investigation.

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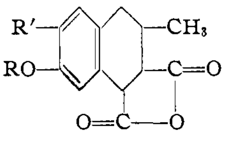
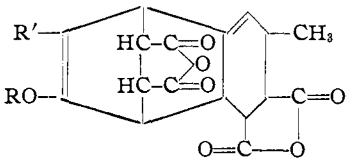
## The Diels-Alder Reaction between Isosafrole and Cinnamic Acid Derivatives[1]

BY ROBERT G. NELB[2] AND D. STANLEY TARBELL

In connection with synthetic studies directed toward the formation of podophyllotoxin analogs,[3] we have investigated the reaction between isosafrole and dienophiles of the cinnamic acid type. It is well known that maleic anhydride will add to certain alkoxylated propenylbenzenes, to give either tetrahydronaphthalene anhydrides (I) or bis-adducts (II) formed from two moles of maleic anhydride and one of the propenyl compound.[4] The addition of maleic anhydride to 1,1-diaryl-ethylenes goes similarly to form 1:2 adducts, which can be converted to the 1:1 products.[5]

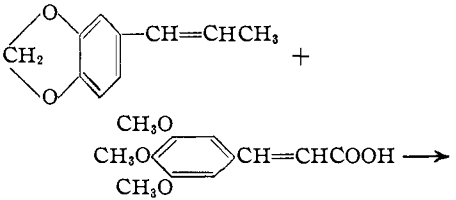


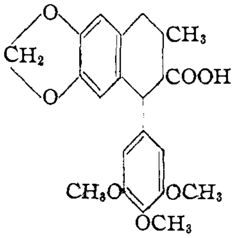
I



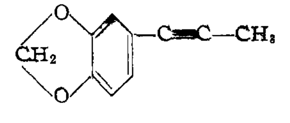
II

We have found that the addition of 3,4,5-trimethoxycinnamic acid to isosafrole gives a very small yield of adduct, which, from its analysis and neutral equivalent, appears to be III (or isomer) and not a 2:1 adduct corresponding to II. A large number of runs in which the time, temperature and solvent were varied, gave no useful amount of the adduct. Treatment of isosafrole with cinnamic acid, cinnamaldehyde or ethyl cinnamate under various conditions gave no simple adduct, although there was evidence of polymer formation in some cases. The reaction of cinnamic acid with 1-(3,4-methylenedioxyphenyl)-propyne ("Piperonylallylene," IV, for which an improved method of preparation is given), did not give the desired adduct.





III



IV

### Experimental[6]

**Adduct from 3,4,5-Trimethoxycinnamic Acid and Isosafrole (III).**—3,4,5-Trimethoxycinnamic acid[7] (5 g., 0.021 m.), isosafrole (40 g., 0.25 m.) and dry xylene (10 cc.) were heated in a sealed tube at 200° for eighty hours; the reaction mixture was washed out of the tube with chloroform and extracted three times with dilute alkali. Ether or benzene was less satisfactory as solvent at this point because it did not dissolve a dark red tar which was present. The alkaline extract was acidified with dilute hydrochloric acid, and the precipitate which formed crystallized after standing for a day. The dark brown product (2.5 g.) was collected, boiled with 200 cc. of water, and filtered hot; this procedure removed the unchanged starting acid. The dark brown water-insoluble residue (100 mg.) was recrystallized from methanol with Norite, yielding 80 mg. of white crystalline solid. Two more crystallizations from dilute acetic acid gave 20 mg. of material, m. p. 259–261°, which gave no phenolic tests.

*Anal.* Calcd. for $C_{22}H_{24}O_7$ (III): C, 65.99; H, 6.04; neut. equiv., 400. Calcd. for $C_{34}H_{38}O_{12}$ (2:1 adduct): C, 63.94; H, 6.00; neut. equiv., 319. Found: C, 64.87, 65.01; H, 5.87, 6.07; neut. equiv., 382.

The possibility that the acidic material is a dimer of trimethoxycinnamic acid is definitely ruled out by the analysis and the neutral equivalent. The *methyl ester* was prepared by allowing 27 mg. of the acid to stand with excess ethereal diazomethane for a day. The white crystalline product was recrystallized twice from methanol, and melted at 196–198° (cor.).

*Anal.* Calcd. for $C_{23}H_{26}O_7$ (methyl ester of III): C, 66.65; H, 6.32. Calcd. for $C_{36}H_{42}O_{12}$ (methyl ester of 2:1 adduct): C, 64.85; H, 6.35. Found: C, 67.00; H, 6.15.

In eleven runs using isosafrole and trimethoxycinnamic acid under varying conditions, no better result was obtained than in the above experiment; the use of dimethylaniline, found by Bruckner and Kovacs[4b] to favor the formation of the 1:1 adduct from maleic anhydride and anethole, was without effect. In the course of this work, it became desirable to know the rate of decarboxylation of trimethoxycinnamic acid, and it was found that 50% of the acid could be recovered unchanged after heating in xylene solution in a sealed tube at 205° for ninety-six hours.

**1-(3,4-Methylenedioxyphenyl)-propyne (IV).**—Isosafrole (30 g., 0.185 m.) was brominated according to Foulds and Robinson,[8] but their further procedure for obtaining the acetylenic compound IV was inconvenient. Because of the explosive decomposition encountered in the

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[3] For the structure of podophyllotoxin, see Haworth, Richardson and Sheldrick, *J. Chem. Soc.*, 1576 (1935).

[4] (a) Bruckner, *Ber.*, **75**, 2034 (1942); (b) Bruckner and Kovacs, *J. Org. Chem.*, **13**, 641 (1948); (c) Hudson and Robinson, *J. Chem. Soc.*, 715 (1941).

[5] Wagner-Jauregg, *Ber.*, **63**, 3213 (1930); *Ann.*, **491**, 1 (1931); F. Bergmann and co-workers, THIS JOURNAL, **70**, 2748 (1948), and earlier papers.

[6] Analyses by Mrs. G. Sauvage; melting points uncorrected unless indicated.

[7] Prepared from trimethoxybenzaldehyde (Huang, Tarbell and Arnstein, THIS JOURNAL, **70**, 4181 (1948)) and malonic acid following Slotta and Heller, *Ber.*, **63**, 3042 (1930).

[8] Foulds and Robinson, *J. Chem. Soc.*, **105**, 1971 (1914).

distillation of large quantities of isosafrole dibromide,[9] the crude dibromide was dissolved in 260 g. of dry diethylene glycol containing 44 g. of potassium hydroxide, and the mixture was heated with stirring at 130° for five hours. Potassium bromide precipitated during the heating. The reaction mixture was poured into twice its volume of water, extracted twice with ether, the ether extract dried over anhydrous potassium carbonate, and the ether removed. In addition to the desired propyne IV, the residue contained some 3,4-methylenedioxypropiophenone; the product was best purified by extracting the red oil three times with *n*-pentane, in which IV was very soluble and the ketone was only slightly soluble. The yellow *n*-pentane solution was dried over potassium carbonate, the solvent removed, and the residual oil distilled *in vacuo*. The propyne was obtained as a colorless oil (16 g., 54%) b. p. 136–138° (14 mm.); it solidified on cooling, m. p. 40.5–42° (reported,[8] 42–43°). There was much residue in the distilling flask.

Two other procedures for purification of the crude material were investigated. The dry pentane solution (see above) was chromatographed on alumina; the propyne IV was not adsorbed, and was thus separated from a ketonic fraction which was adsorbed and which gave a highly fluorescent band under ultraviolet light. This procedure was unsatisfactory for large quantities because of the amount of alumina required.

Steam distillation, applied to the residue from the ether extract above, gave at first quite pure propyne, and the ketone appeared in the distillate as the distillation proceeded. The ketone obtained as a by-product in this reaction was shown to be 3,4-methylenedioxypropiophenone by preparation of the oxime, m. p. 103.5–104.5°.[10] The 2,4-dinitrophenylhydrazone was also prepared; m. p. 256–257° (uncor.) with decomposition.

*Anal.* Calcd. for $C_{16}H_{14}N_4O_6$: C, 53.63; H, 3.94. Found: C, 53.77; H, 3.85.

This ketone was also prepared from the propyne IV by the method of Foulds and Robinson,[8] and was found by its derivatives to be identical with the ketone obtained above as a by-product from the action of alkali on isosafrole dibromide.

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[9] Waterman and Priester, *Rec. trav. chim.*, **48**, 941 (1929); their observations have been duplicated by us.

[10] This oxime is reported by Wallach and Pond, *Ber.*, **28**, 2719 (1895), to melt at 104°.

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## Solubility of Nitroaminoguanidine

BY WILLIAM MCBRIDE,[1] RONALD A. HENRY AND G. B. L. SMITH

The solubility of nitroaminoguanidine, $NH_2NHC(NH)NHNO_2$, in unbuffered aqueous solutions (*p*H 6.40 at 30°) has been determined in the temperature range 10 to 50° (Fig. 1) and can be expressed with an accuracy of two per cent. by the equation: log (solubility in g./100 g. of water) = $(-1916.7/T) + 5.9632$, calculated from the data by the method of least squares. In a 0.25 molal solution of sodium phosphate (*p*H 6.96 to 7.04 at 30°) the solubility is approximately six per cent. greater throughout the same range (Fig. 1) and can be expressed as: log (solubility in g./100 g. of water) = $(-1914.1/T) + 5.9801$.

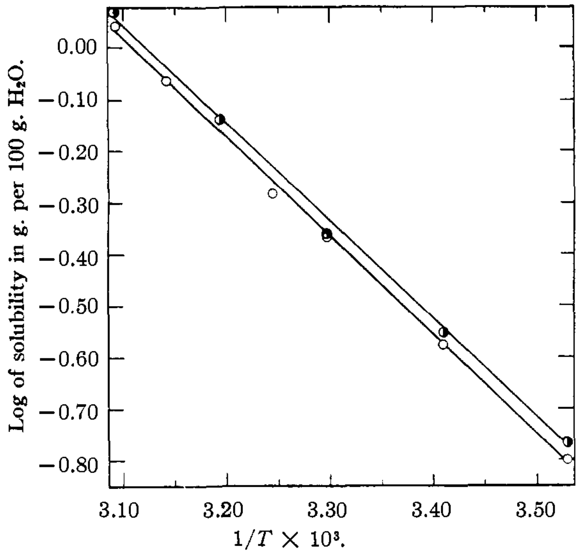

Fig. 1.—Solubility of nitroaminoguanidine in distilled water (○), and in a 0.25 molal solution of sodium phosphate (◑); *p*H 6.96–7.04 at 30°.

The effect of *p*H on the solubility of nitroaminoguanidine at 30° is shown in Fig. 2 and indicates the amphoteric nature of the compound; this is in agreement with the reported behavior of nitro-[2,3] and nitrosoguanidine.[3,4]

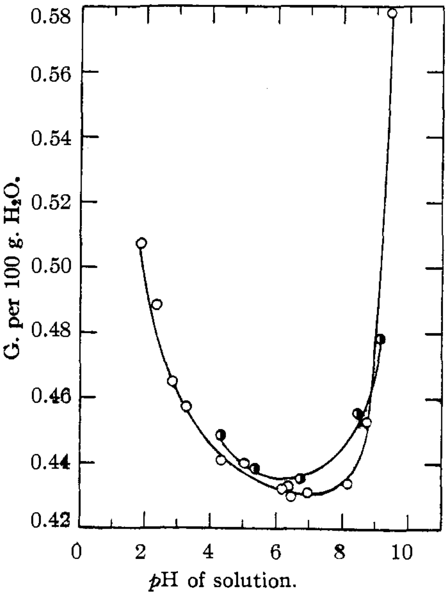

Fig. 2.—Solubility of nitroaminoguanidine at 30° as a function of *p*H: in water (○), and in 0.25 molal solution of sodium phosphate (◑).

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[2] Thiele, *Ann.*, **270**, 1 (1892).

[3] Hahn, Pribyl, Lieber, Caldwell and Smith, THIS JOURNAL, **66**, 1223 (1944).

[4] Thiele, *Ann.*, **273**, 133 (1893); Robertson, M.S. Thesis, Polytechnic Institute of Brooklyn, 1935; Sabetta, Himmelfarb and Smith, THIS JOURNAL, **57**, 2478 (1935).