the etching of the surface of the old autoclave and the consequent greater exposure of the active constituent of the stainless steel. This active constituent might well have been the nickel present in relatively large amounts therein.

The above experiments therefore demonstrate that in a high-temperature hydrogenation it is important to indicate the nature of the steel of which the bomb is made.

Acknowledgment.—The authors are indebted to Dr. M. J. Murray for the ultraviolet spectral analysis.

RESEARCH AND DEVELOPMENT LABORATORIES
UNIVERSAL OIL PRODUCTS COMPANY
RIVERSIDE, ILLINOIS RECEIVED DECEMBER 13, 1948

Resolution of *dl*-Methadone and *dl*-Isomethadone

BY E. E. HOWE AND MEYER SLETZINGER

Recently Larsen, *et al.*,[1] have reported practical methods for the resolution of *dl*-methadone, 6-methylamino-4,4-diphenylheptanone-3 and of *dl*-isomethadone, 6-dimethylamino-5-methyl-4,4-diphenylhepanone-3 with *d*-tartaric acid. We, too, have investigated this problem and inasmuch as our approach has differed in some respects from those of other workers we wish to report briefly on our observations.

d-Methadone forms an easily-purified, water-insoluble *d*-α-bromocamphor-π-sulfonate from which the pure *d*-isomer is readily prepared. l-Methadone *d*-tartrate may then be obtained from methadone residues derived from the mother liquors in a state of such high purity that no recrystallization is necessary. Should only the active *l*-form be desired the *d*-isomer may be conveniently removed from a butyl alcohol solution as the *p*-nitrobenzoyl-L-glutamate. The latter salt, however, does not readily lend itself to purification.

When a solution of *dl*-isomethadone in isopropyl alcohol is heated with *p*-nitrobenzoyl-L-glutamic acid the salt of the *d*-isomer separates and can be obtained in the pure state. The enantiomorph may be isolated from the mother liquors.

To our knowledge this is the first reported use of *p*-nitrobenzoyl-L-glutamic acid as a resolving agent.

Experimental

***d*-Methadone.**—Ten grams (0.029 mole) of *dl*-methadone hydrochloride and 5 g. (0.015 mole) of ammonium *d*-α-bromocamphor-π-sulfonate were dissolved in 25 cc. of hot 80% ethanol. The solution was cooled and the impure *d*-methadone salt was precipitated by the slow addition of 220 cc. of water. The mixture was chilled overnight and filtered. The collected salt was washed twice with ice-water and dried at 45°. It is important that the greater portion of the moisture be removed during the filtration step since the wet salt melts at 45°. The yield was 7.6 g. (85.0%), m. p. 125–127°.

The crude *d*-methadone bromocamphor sulfonate was dissolved in 10 cc. of ethanol and precipitated with 60 cc. of water. There was recovered 6.5 g. (85.5%) of product melting at 135–138°. This salt by conventional methods was converted in 95% yield to *d*-methadone hydrochloride; m. p. 243–244°; $[\alpha]^{23}D$ 1% in aqueous solution (+127.0°).

Anal. Calcd. for $C_{21}H_{28}ONCl$: C, 72.91; H, 8.16. Found: C, 72.90; H, 8.36.

***l*-Methadone.**—All mother liquors and washes from the preparation of *d*-methadone-*d*-α-bromocamphor-π-sulfonate were combined and treated with 5 cc. of 40% sodium hydroxide solution. The methadone precipitated immediately and after chilling overnight was collected, washed twice with water and dried. This product and 2.4 g. of *d*-tartaric acid were dissolved in 35 cc. of *n*-butanol by heating to boiling. The solution was cooled and seeded with *l*-methadone-*d*-tartrate whereupon crystallization occurred. After two hours at room temperature 35 cc. of petroleum ether was added. The mixture was refrigerated overnight, was filtered and the collected salt was washed first with 1:1 butanol–petroleum ether and then with petroleum ether. The yield was 5.9 g. of *l*-methadone-*d*-tartrate (86.5%) melting at 149–150°. By successive treatment with sodium hydroxide and hydrochloric acid this salt was converted in 92% yield to *l*-methadone hydrochloride, m. p. 237–239°; $[\alpha]^{23}D$ (1% in aqueous solution) −127.0°.

Anal. Calcd. for $C_{21}H_{28}ONCl$: C, 72.91; H, 8.16. Found: C, 72.95; H, 7.99.

***d*-Isomethadone *p*-Nitrobenzoyl-L-glutamate.**—A mixture of 105 g. (0.32 mole) of isomethadone base and 59.5 g. (0.18 mole) of *p*-nitrobenzoyl-L-glutamic acid in 595 cc. of isopropyl alcohol was boiled under reflux until solution was completed. The solution was allowed to cool to room temperature with stirring. The mixture was filtered and the crystalline product was washed with 20 cc. of cold isopropyl alcohol and then with ether. The yield was 73 g.; m. p. 168–171°. Recrystallization from isopropyl alcohol raised the melting point to 171–172°; $[\alpha]^{25}D$ (1% in methanol) +60°.

***d*-Isomethadone Hydrochloride Monohydrate.**—A mixture of 73 g. of *d*-isomethadone-*p*-nitrobenzoyl-L-glutamate dissolved in 74 cc. of water and 44 cc. of chloroform was made alkaline with 130 cc. of 30% sodium hydroxide. After vigorous agitation of the mixture, the lower chloroform layer was separated, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The oily residue was dissolved in 33 cc. of isopropyl alcohol and made acidic with 32.5 cc. of 4.9 *N* hydrochloric acid in isopropyl alcohol. Ethyl ether (256 cc.) was added and the white precipitate was filtered, washed with 50 cc. of isopropyl alcohol–ether solution (1:8) and dried at room temperature. The yield was 24 g. (38.9%), m. p. 173–174°; $[\alpha]^{25}D$ (1% in methanol) +90°. This substance analyzed correctly for a monohydrate.

Anal. Calcd. for $C_{21}H_{28}ONCl \cdot H_2O$: C, 69.28; H, 8.31; N, 3.84. Found: C, 69.55; H, 8.28; N, 4.03.

***l*-Isomethadone Hydrochloride Monohydrate.**—The isopropyl alcohol mother liquors from the preparation of *d*-isomethadone-*p*-nitrobenzoyl-L-glutamate were evaporated to dryness *in vacuo*. The residue was dissolved in 140 cc. of water, then 140 cc. of chloroform was added. The mixture was made basic with 140 cc. of 30% sodium hydroxide and the chloroform layer was separated, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The oily residue was dissolved in 70 cc. of isopropyl alcohol and treated with 70 cc. of 4.9 *N* hydrochloric acid in isopropyl alcohol. One liter of ether was added and the white precipitate was filtered, washed with 25 cc. of isopropyl alcohol–ether (1:8) and dried at room temperature. The yield was 31 g.; m. p. 170–172°.

Recrystallization by dissolving in 80 cc. of isopropyl alcohol and precipitating with 325 cc. of ether yielded 26.5 g.; m. p. 173–174°; $[\alpha]^{25}D$ (1% in methanol) −90°. This substance analyzed correctly for a monohydrate.

Anal. Calcd. for $C_{21}H_{28}ONCl \cdot H_2O$: C, 69.28; H, 8.31; N, 3.84. Found: C, 69.52; H, 8.08; N, 3.91.

(1) A. A. Larsen, B. F. Tullar, B. Elpern and J. S. Buck, THIS JOURNAL, **70**, 4194 (1948).

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

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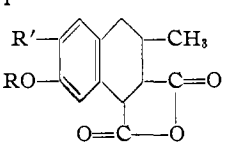
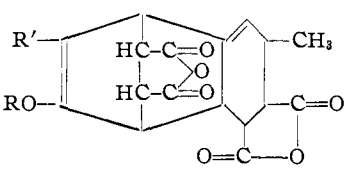
The Diels–Alder Reaction between Isosafrole and Cinnamic Acid Derivatives[1]

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]

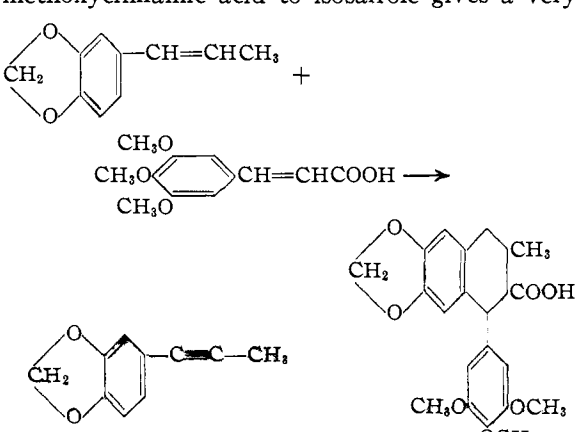


I



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.



IV III

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

(1) Aided by a grant from the National Institute of Healtb.

(2) Beaunit Mills Fellow, 1947–1948. Present address: Naugatuck Chemical Division of the United States Rubber Company, Naugatuck, Connecticut.

(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).