SYNERGISTS OF INSECTICIDES.

III. SYNTHESIS OF THE ETHYL ESTER OF CIS-(3,4)METHYLENEDIOXY)CINNAMIC ACID*

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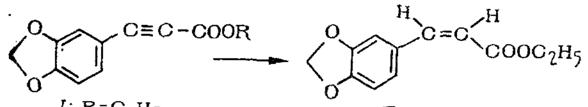
In a systematic study of the synergists of the naturally occurring pyrethrins we found that in many of the derivatives of methylenedioxybenzene the ethyl ester of trans-(3,4-methylenedioxy).cinnamic acid (IV) had a considerable synergistic effect [2]. To find how the biological properties of compounds of this group were related to their stereochemical structure, we synthesized the ethyl ester of cis-(3,4-methylenedioxy)-cinnamic acid (III).

In the method we chose, the key intermediate substance was ethyl 3,4-methylenedioxyphenylpropionate (I), whose hydration over Lindlar's catalyst should produce the required cis-ester (III).



I: $R=C_2H_5$
II: $R=H$

III

We investigated three ways of obtaining the acetyl ester I. In each case the starting point was piperonal (IX), the most readily available naturally occurring compound containing the 3,4-methylenedioxyphenyl group.

To perform the first step by Debner's reaction between IX and malonic acid we obtained tris-(3,4-methylenedioxy)cinnamic acid (V), which was esterified to produce the corresponding ethyl ester (IV), brominated as far as the dibromide (ΔI). Attempts to split off two molecules of hydrogen bromide by vigrous treatment with excess alkali failed to give the required acetylated acid, therefore compound VI was brominated in stages. In the first stage, by using an alcoholic solution of potassium hydroxide at room temperature we obtained the α-bromoacid (VIII). In the second stage this acid was boiled with potassium hydroxide in aqueous alcohol to convert it into the acid II, which was then esterified in boiling alcohol in the presence of sulfuric acid to produce the ethyl ester I, obtained in a yield of 13.8% (calculated as IX).

In the second method, by acting on IX with methyl magnesium iodide we obtained the secondary alcohol which by distillation was dehydrated to styrene. We also attempted to obtain this substance by decarboxylating the acid V; however, the yields obtained by this reaction were low. The styrene X was brominated at a low temperature to the dibromide XI which was then dehydrobrominated by boiling in alcoholic alkali to form the acetylene derivative XIII. Empirical analysis and IR spectra revealed that the com-

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*For previous papers I and II see [1, 2].

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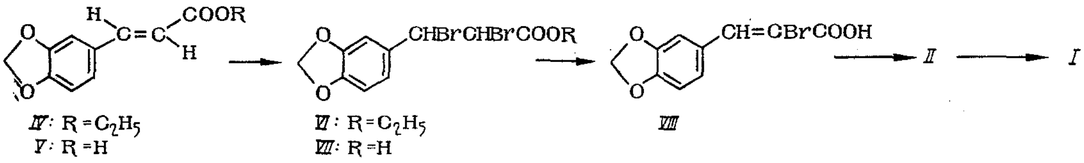
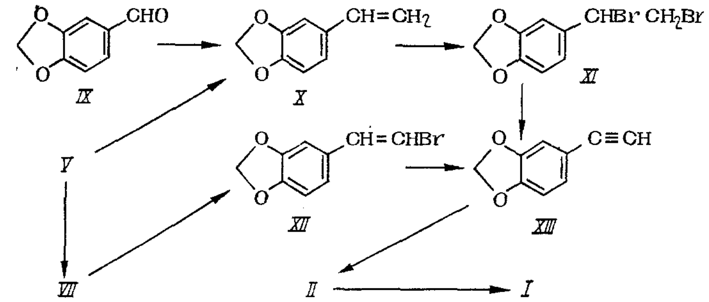
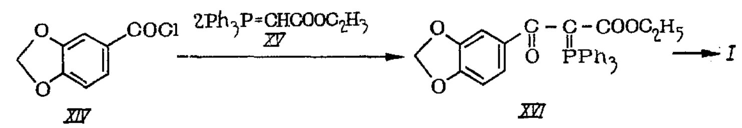


pound produced by this method contained impurities which were not eliminated by fractionation. Best results were obtained by brominating acid V to the corresponding dibromacid VII and then dehydrobrominating and decarboxylating, and splitting off the hydrogen bromide from the bromstyrole formed (XII). UV and IR spectra and empirical analysis established that XIII was a true compound. By treating XIII with ethyl magnesium bromide we produced Iotsich's reagent, which by treatment with solid carbon dioxide was transformed into the acid II, giving a yield of 1.95% (calculated as IX).



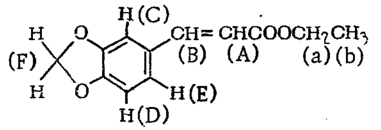
As far as preparation of the compounds is concerned, the most convenient method was the third. By the reaction of piperonylic acid chloranhydride (XIV) with triphenylphosphinecarbethoxymethylene (XV) we obtained the acid phosphoran (XVI). Pyrolysis of this substance at 280° (0.5 mm) led to the formation of the ester I in a yield of 64.5% (calculated as IX).



Thus the third way is the shortest, and gives the greatest yield of I.

The acetylene ester I was hydrolyzed over Lindlar's catalyst to form the cis-ester III. The paramagnetic resonance spectrum and gas—liquid chromatography both indicated that not less than 97% of the substance itself was present. In gas chromatography the retention time of III in final conditions differed greatly from the corresponding time for the trans-isomer IV and of the original reagent I.

The structural formula of III was confirmed by comparing its paramagnetic resonance spectrum with that of the trans-isomer of IV (see Table 1).

TABLE 1. 

Parameters of the Paramagnetic Resonance Spectra of Compounds III and IV in Carbon Tetrachloride

Compound	Chemical shifts, σ (ppm)								Constants of spin—spin interaction of I (Hz)			
	A	B	C	D	E	F	a	b	A,B	D,E	C,E	a,b
III	5,69	6,66	7,54	6,68	7,02	5,93	4,17	1,30	12,7	8,1	1,6	7,2
IV	6,13	7,45	6,95	6,71	6,93	5,93	4,16	1,28	15,9	8,1	1,6	7,2

In the paramagnetic resonance spectrum of the cis-isomer of III, as would be expected [3], the value of the vicinal constant of the spin–spin interaction between protons A and B is considerably less than in the trans-isomer of IV. Furthermore, the spectrum of the trans-isomer differs from that of the cis-isomer in that the signal of proton B is markedly displaced in a weak field ($\Delta\delta$ 0.79 ppm). This circumstance is evidently related to the unscreening influence of the carbonyl group, which lies closer to proton B in the trans- than in the cis-isomer.

A comparison of the IR-spectra of III and IV showed a considerable difference in the position of the strong bands due to valency oscillations of the C=C linkage. In the cis-isomer this band was at 1622 cm^{-1}, and in the trans-isomer at 1640 cm^{-1}.

In the UV spectra the intensity of absorption of III at 324 nm was much less than that of IV at 327 nm, a result in agreement with the relationship of the UV spectra of cis- and trans-cinnamic acids [4].

In a comparative study of the synergistic action of III and IV mixed with pyrethrins (25% extraction) when tested on the house fly *Musca domestica* it was found that the trans-isomer IV was more effective then the cis-isomer of III (synergistic coefficients were 2.8 and 1.56, respectively).

EXPERIMENTAL METHOD*

UV spectra were measured on a EPS-3T Hitachi spectrophotometer in alcohol; IR spectra were measured on an IR Spekord, a UR-10, and a Hitachi 215 instrument; paramagnetic resonance spectra were measured on a R20A Hitachi instrument (60 MHz) in carbon tetrachloride; for gas–liquid chromatography we used a Tsvet-6A instrument; thin-layer chromatography was carried out on silufol.

Ethyl β-(3,4-Methylenedioxyphenyl)-α,β-dibromopropionate (VI). To a suspension of 10 g of IV in 80 ml of methylene chloride we added 2.55 ml of bromine in 30 ml carbon tetrachloride over a period of 20 min; the mixture was then stirred for 1 h, left for 24 h at room temperature, washed with sodium thiosulfate solution, and dried with magnesium sulfate. After evaporation of the solvent the residue was washed with petroleum ether (bp 40-70°). We obtained 15.2 g (88%) VI, mp 81.5-83°; ν_{max} (in potassium bromide) 1740 cm^{-1} (C=O), 1618 cm^{-1} (aryl), 1045 cm^{-1} (O-CH_2O). Composition, found, %: C 38.01; H 3.09; Br 41.17. $C_{12}H_{12}Br_2O_4$. Composition, calculated, %: C 38.00; H 3.16; Br 42.10.

β-(3,4-Methylenedioxyphenyl)-α-bromoacrylic Acid (VIII). To a solution of 14 g of potassium hydroxide in 120 ml alcohol we added 33.1 g VI; the mixture was then stirred at room temperature for 6 h, and left to stand overnight. The precipitate which settled out was filtered, washed in alcohol, and dissolved in 2 liters of water; ice was added, and the solution acidified with sulfuric acid. The solid substance which separated out was filtered off, washed in water, and dried. The product consisted of 18.4 g (71%) VIII, mp 193-194.5; λ_{max} (in alcohol) 326 nm (ε 17,400), 292 nm (ε 11,900), 255 nm (ε 9200), 233 nm (ε 10,900); γ_{max} (in vaseline) 1680 cm^{-1} (C=O), 1622 cm^{-1} (C=C), 1590 and 1500 cm^{-1} (aryl), 10.4- and 9.35 cm^{-1} (O-CH_2-O). Percentage composition found: C 44.23; H 2.58. Formula $C_{10}H_7BrO_4$. Percentages calculated: C 44.31; H 2.60.

3,4-Methylenedioxyphenylpropionic Acid (II). A. To a solution of 20 g potassium hydroxide in alcohol (3 ml water and 100 ml alcohol) we added 18 g VIII, boiled for 10 h, and evaporated to dryness. The residue was taken up in water, ice was added, and the solution was acidified with hydrochloric acid. The precipitate was filtered off and dissolved in ether. The ethereal solution was dried with magnesium sulfate, and the solvent evaporated off. Yield was 7.8 g (61.8%) II, mp 166-168°, R_f 0.45 (n-dibutyl ether–methanol–acetic acid, 97:2:1); λ_{max} 310 nm (ε 14,100), 282 nm (ε 10,400), 231 nm

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(ε 10,010). Percentage composition, found: C 63.22; H 3.27. Formula $C_{10}H_6O_4$. Percentage calculated: C 63.18; H 3.12. B. To a solution of ethyl magnesiumbromide prepared from 0.36 g magnesium filings, 1.1 ml ethyl bromide, and 6 ml dry ether we added a solution of 1.46 g XIII (synthesis described below) in 25 ml of dry ether, and maintained the temperature of the mixture $\leq 10°$. When the addition was complete, the mixture was boiled for 40 min, cooled, and treated with solid acetic acid in ether. The ethereal solution was washed with water, acid was removed by alkali solution, and the aqueous alkaline solution was acidified with hydrochloric acid. The precipitate was filtered off, taken up in ether, and the ethereal solution was dried with sodium sulfate, and the ether evaporated off. Yield 0.33 g (17.5%) compound II, mp 165-169°.

1-Vinyl-3,4-methylenedioxybenzene (X). A. To methyl magnesium iodide cooled to 0° and prepared from 7.29 g magnesium filings, 19 ml of methyl iodide, and 150 ml of dry ether we gradually added a solution of 30 g IX in 200 ml dry ether while maintaining the mixture at 5-8°. After the addition the mixture was boiled for 30 min and left overnight at 20°. Next, 150 ml of 10% hydrochloric acid at 10° or below was added, the ethereal layer was separated, and washed successively with water and 5% aqueous sodium carbonate; it was then dried with magnesium sulfate, and evaporated to dryness. The residue was vacuum distilled in an atmosphere of helium. Yield 23.8 g (80.4%) compound X, bp 122-124° at 25 mm pressure; n_D^{20}=1.5810; R_f=0.82 (ethylacetate—hexane, 2:3); λ_{max} 226 nm (ε 7900), 265 nm (ε 10,500), 306 nm (ε 6700); ν_{max} (in film) 1615 cm^{-1} (C=C), 1602 cm^{-1} (aryl), 993 and 1021 cm^{-1} ($O-CH_2-O$). Percentage composition found: C 72.78; H 5.52. Formula $C_9H_8O_2$. Percentage calculated: C 72.96; H 5.44. B. A mixture of 3.84 g of V, 2 g of powdered copper, a small amount of hydroquinone and 15 ml of freshly prepared quinoline was heated for 5 h (time for elimination of carbon dioxide) at 215° (on bath); the mixture was then cooled and poured into 10 ml concentrated hydrochloric acid with 30 g ice. It was then steam distilled, and 600 ml of distillate collected. This distillate was extracted with chloroform; the organic solution was dried with magnesium sulfate, and evaporated to dryness. The residue was distilled under reduced pressure. Yield: 0.41 g (13.9%) of X; bp 124-126° at 25 mm pressure; n_D^{20}=1.5777.

1-(α,β-Dibromethyl)-3,4-methylenedioxybenzene (XI). To a solution of 7.45 g X in 60 ml chloroform at -10 to -15° we added 2.6 ml bromine while stirring, and allowing the mixture to reach room temperature; it was stirrrd for 20 min at 30°; the solvent was removed by evaporation and a crystalline residue remained. Yield 15.3 g (approximately 100%) XI. This product was used without further purification in the following reaction.

α, β-Dibrom-β-(3,4-methylenedioxyphenyl)propionic Acid (VII). To a suspension of 19.2 g V in 200 ml chloroform at 6-8°, over a period of 1 h we added a solution of 5.1 ml bromine in chloroform; the mixture was left for two days in a refrigerator. The precipitate was filtered off, and washed in chloroform and hexane. Yield 27.3 g (78%) VII, mp 144-145° (decomposing); the analytically pure substance was obtained by crystallization from chloroform, mp 143-144° (decomposing). Percentage composition, found: C 34.18; H 2.30; Br 45.50. $C_{10}H_8Br_2O_4$. Percentage composition, calculated: C 34.12; H 2.24; Br 45.46.

3,4-Methylenedioxybromstyrene (XII). A mixture of 16.8 g VII and 40 ml of 25% sodium carbonate solution was boiled for 1 h and then extracted with ether. The extract was washed in water, dried with sodium sulfate, and the ether evaporated off. The residue was crystallized from aqueous methanol (3:7). Yield 8.5 g (79%) XII, mp 59°. λ_{max} 244 nm (ε 7350), 275 nm (ε 1200), 307 nm (ε 7350). Percentage composition, found: C 47.64; H 3.07; Br 36.10. Formula $C_9H_7BrO_2$. Percentage composition, calculated: H 3.08; Br 35.24.

1-Ethynyl-3,4-methylenedioxybenzene (XIII). A. A mixture of 16.7 g XII, 12.5 g potassium hydroxide and 24 ml of absolute alcohol was boiled for 4 h (bath temperature 160°); the mixture was then cooled, treated with water, and extracted with ether; the extract was washed with water until neutral, dried with magnesium sulfate, and evaporated to dryness. Hydroquinone was added to the residue, and the mixture distilled in argon under reduced pressure. Yield 3.1 g (28.8%) XIII, bp 65° at 1 mm pressure; λ_{max}

259 nm (ε 22,900), 300 nm (ε 9500), 306 nm (ε 8950); γ (in film) 1045 cm^{-1} ($O-CH_2-O$), 1611 cm^{-1} (aryl), 3290 cm^{-1} (CH in acetylene residue). Percentage composition, found: C 73.57; H 4.31. Formula $C_9H_6O_2$. Percentage composition, calculated: C 73.98; H 4.14. To a boiling solution of 11.2 g potassium hydroxide in 15 ml methanol while stirring for 40 min we added 15.3 g XI; the mixture was boiled for 30 min, cooled, treated with 25 ml water, and extracted with ether. The extract was washed with water, dried with sodium sulfate, and evaporated to dryness. The residue was distilled under reduced pressure. Yield 5.5 g (75.5%) XIII, bp 128-130° at 15 mm pressure; n_D^{20}=1.5974. Empirical analysis and the IR spectrum revealed the presence of impurities.

Triphenylphosphine-α-carbethoxy-α-piperonylmethylene (XVI). To a solution of 20.88 g XV in 100 ml pure benzene at 20° we gradually added a solution of 5 g XIV in pure benzene, and stirred for 4 h. The precipitate which settled out was filtered off, washed in benzene, and recrystallized from a mixture of ethyl acetate and petroleum ether (2:3). Yield 10.3 g (70%) XVI, mp 176-178°; ν_{max} (in potassium bromide) 1662 cm^{-1} (complex carbonyl ester), 1638 cm^{-1} (acyl carbonyl), 1608 cm^{-1} (C=C), 1580 cm^{-1} (aryl), 998 and 1036 cm^{-1} ($O-CH_2-O$). Percentage composition, found: C 72.45; H 5.08. Formula $C_{30}H_{25}O_5P$. Percentage composition, calculated: C 72.50; H 5.08.

Ethyl 3,4-Methylenedioxyphenylpropionate (I). A. A flask containing 6 g XVI and fitted with a Claisen attachment with thermometer and receiver was heated on a bath filled with Bud's alloy; pressure was 0.5 mm. Heating continued until a temperature of 250-260° was reached, when decomposition of XVI started, and compound I distilled off (temperature of vapor 160-180°). Chromatograms of the product which crystallized out were run on columns of aluminum oxide; the washing substance was a mixture of ethyl acetate and heptane (1:1). After recrystallization from aqueous alcohol (1:9) the yield of I was 2.22 g (85%), mp 73-74°; λ_{max} 312 nm (ε 14,800), 284 nm (ε 1220), 230 nm (ε 16800); ν_{max} (in potassium bromide) 2210 cm^{-1} (C≡C), 1712 cm^{-1} (C=C), 1609 cm^{-1} (aryl), 1023 and 1042 cm^{-1} ($O-CH_2-O$). Percentage composition, found: C 66.06; H 4.53. Formula $C_{12}H_{10}O_4$. Percentage composition, calculated: C 66.05; H 4.64. B. A mixture of 5.7 g II, 5 ml of sulfuric acid, and 75 ml absolute alcohol was boiled for 6 h, evaporated to dryness; the residue was recrystallized from hexane and aqueous alcohol (1:9). Yield: 4.59 g (70%) I, mp 72-73°.

Ethyl cis-(3,4-Methylenedioxy)cinnamic Acid (III). To a mixture of 10 mg of previously hydrogenated Lindlar's catalyst [5] and 3 ml of absolute methanol we added a solution of 100 mg I in 7 ml absolute methanol, and hydrogenated for 35 min in an atmosphere of hydrogen; 17 ml hydrogen was absorbed. At the end of the hydrogenation the mixture was centrifuged, the catalyst was washed with methanol, and the washings were added to the solution which was then evaporated to dryness. Yield 95 mg (96%) III. Retention time in gas—liquid chromatography was 5 min 55 sec (length of column 2 m, diameter 3 mm, 5% SE-30 on chromaton N=AW, flame-ionization detector gas carrier — nitrogen; temperature of evaporator 280°; programming of temperature: from 180 to 220°, rate of rise of temperature 5° (per min); λ_{max} 325 nm (ε 6060), 293 nm (ε 5400), 241 nm (ε 2620); ν_{max} (in film) 1700 cm^{-1} (C=O), 1622 cm^{-1} (C=C), 1600 and 1498 cm^{-1} (aryl), 938 and 1040 cm^{-1} ($O-CH_2-O$). Percentage composition, found: C 65.42; H 5.54. $C_{12}H_{12}O_4$. Percentage composition, calculated: C 65.44; H 5.49. Under conditions for chromatography described, the retention time for IV was 6 min 37 sec.

LITERATURE CITED

1. B. B. Lurik, N. A. Kamenkov, and Yu. P. Volkov, Khim.–Farmats. Zh., No. 8, 15 (1971).
2. B. I. Vashkov, Yu. P. Volkov, G. M. Zubova, et al., Probl. Dex. Ster., 22, 152 (1972).
3. S. Sternhell, Quart. Rev. Chem. Soc., 23, 236 (1969).
4. A. Gillam and E. S. Stern, Introduction to Electronic Adsorption (second edition), Arnold, St. Martins (1957).
5. H. Lindlar, Helv. Chim. Acta, 35, 446 (1962).