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Constituents of *Heliopsis* Species. IV. The Total Synthesis of *trans*-Affinin

BY MARTIN JACOBSON

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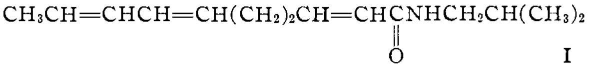
The all-*trans* isomer of affinin, the insecticidal amide isolated from the roots of *Heliopsis longipes*, has been synthesized and found to be identical with the compound previously obtained by ultraviolet or selenium isomerization of the natural isomer. N-Isobutyl-*trans*-4-*trans*-6-octadienamide, related to the natural insecticide spilanthol has also been prepared and found to be physiologically and insecticidally inactive.

In Part III of this series[1] the isomerization of natural affinin, the insecticidal amide from the roots of *Heliopsis longipes*,[2] to all-*trans*-affinin was reported. Acree, *et al.*,[3] had previously determined that natural affinin is N-isobutyl-2,6,8-decatrienamide (I), and chemical and spectral data[1]



$$CH_3CH{=}CHCH{=}CH(CH_2)_2CH{=}CH\underset{\underset{O}{\|}}{C}NHCH_2CH(CH_3)_2 \qquad I$$

showed that the all-*trans* isomer possesses the same over-all structure. Since a total synthesis of *trans*-affinin would also serve to establish unequivocally the structure (exclusive of geometrical configuration) of the natural insecticidal isomer, such a project was undertaken. The steps employed in this synthesis are shown below.

Sorbyl alcohol (II) was prepared in 90% yield by the lithium aluminum hydride reduction of sorbic acid,[4] according to the procedure of Nystrom and Brown.[5] Treatment of the alcohol with phosphorus tribromide gave a 79% yield of sorbyl bromide (III), which was condensed with sodiomalonic ester to give diethyl sorbylmalonate (IV) in 60% yield. Saponification of IV with aqueous potassium hydroxide, followed by acidification, resulted in a 56% yield of sorbylmalonic acid (V) which, when heated at 140–150°, was readily decarboxylated to *trans*-4-*trans*-6-octadienoic acid (VI) in 43% yield.

Spilanthol,[6] the pungent isobutylamide of 4,6-decadienoic acid, has been reported[6c,7] to be an effective mosquito larvicide. The isobutylamide of the closely related acid VI was therefore prepared for insecticidal evaluation. It proved to be non-pungent and almost devoid of activity against adult house flies.[8]

Reduction of VI with lithium aluminum hydride gave a 96% yield of *trans*-4-*trans*-6-octadien-1-ol (VII), which was oxidized with chromium trioxide and sulfuric acid to the corresponding unsaturated aldehyde (VIII) in 31% yield. Treatment of VIII with malonic acid in pyridine gave *trans*-2-*trans*-6-*trans*-8-decatrienoic acid (IX) in 19% yield.

The isobutylamide of IX, prepared *via* the unisolated acid chloride, proved to be a white solid that crystallized from petroleum ether as long, colorless needles showing a peak in the ultraviolet at 228.5 mμ (ε 37,150). Its melting point (91.5–92.5°) and that of its maleic anhydride adduct (175°), mixed melting point determinations, and ultraviolet and infrared spectra[9] showed it to be identical with all-*trans*-affinin.[1]

The synthesis of other isomers of affinin is being investigated.

$$CH_3CH{=}CHCH{=}CHCOOH \xrightarrow{LiAlH_4}$$

$$\underset{II}{CH_3CH{=}CHCH{=}CHCH_2OH} \xrightarrow{PBr_3}$$

$$\underset{III}{CH_3CH{=}CHCH{=}CHCH_2Br} \xrightarrow{CHNa(COOC_2H_5)_2}$$

$$\underset{IV}{CH_3CH{=}CHCH{=}CHCH_2CH(COOC_2H_5)_2} \xrightarrow[2,\ HCl]{1,\ KOH}$$

$$\underset{V}{CH_3CH{=}CHCH{=}CHCH_2CH(COOH)_2} \xrightarrow[140\text{–}150°]{}$$

$$\underset{VI}{CH_3CH{=}CHCH{=}CH(CH_2)_2COOH} \xrightarrow{LiAlH_4}$$

$$\underset{VII}{CH_3CH{=}CHCH{=}CH(CH_2)_2CH_2OH} \xrightarrow[H_2SO_4]{CrO_3}$$

$$\underset{VIII}{CH_3CH{=}CHCH{=}CH(CH_2)_2CHO} \xrightarrow[C_5H_5N]{CH_2(COOH)_2}$$

$$\underset{IX}{CH_3CH{=}CHCH{=}CH(CH_2)_2CH{=}CHCOOH}$$

$$\xrightarrow[2,\ \text{isobutylamine}]{1,\ SOCl_2} \text{all-}trans\text{-affinin}$$

Experimental[10]

Sorbyl Alcohol (II).—The lithium aluminum hydride reduction of sorbic acid by the procedure of Nystrom and Brown[5] gave the corresponding alcohol, b.p. 78–79° (16 mm.), m.p. 31, n^{25}_D 1.4970 (lit.[11] b.p. 77–78° at 14 mm., n^{23}_D 1.4971), in 90% yield.

The 3,5-dinitrobenzoate crystallized from ethanol in colorless needles, m.p. 86.5–87.5° (lit.[12] m.p. 85°).

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[1] M. Jacobson, THIS JOURNAL, **76**, 4606 (1954).

[2] M. Jacobson, F. Acree, Jr., and H. L. Haller, *J. Org. chem.*, **12**, 731 (1947).

[3] F. Acree, Jr., M. Jacobson and H. L. Haller, *ibid.*, **10**, 236 (1945); **10**, 449 (1945).

[4] The long-known form of sorbic acid melting at 134° has been shown beyond a doubt to possess the *trans,trans* configuration. See U. Eisner, J. A. Elvidge and R. P. Linstead, *J. Chem. Soc.*, 1372 (1953) and references cited therein.

[5] R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 2548 (1947).

[6] (a) E. Gerber, *Arch. Pharm.*, **241**, 270 (1903); (b) M. Asano and T. Kanematsu, *Ber.*, **65B**, 1602 (1932); (c) G. S. Pendse, *et al.*, *Current Sci.* (*India*), **14**, 37 (1945); (d) V. G. Gokhale and B. V. Bhide, *J. Indian Chem. Soc.*, **22**, 250 (1945).

[7] G. S. Pendse, *et al.*, *J. Univ. Bombay*, **15A**, N. S., Pt. 3, No. 20, 26 (1946).

[8] The tests against house flies were made by W. A. Gersdorff and N. Mitlin.

[9] The infrared spectrum was determined by Jonas Carol of the U. S. Food and Drug Administration.

[10] All melting points are corrected; boiling points are uncorrected.

[11] O. Kiun-Houo, *Ann. chim.*, [2] **13**, 226 (1940).

[12] T. Reichstein, C. Amman and G. Trivelli, *Helv. Chim. Acta*, **15**, 261 (1932).

Sorbyl Bromide (III).—To 176.0 g. (25% excess) of phosphorus tribromide, cooled in an ice–salt-bath, was added slowly, with stirring, 152.0 g. (1.55 moles) of sorbyl alcohol. After addition was complete (1 hour), the mixture was stirred at room temperature for 3 hours; the liquid was then decanted off, and the semi-solid layer was washed by decantation with two small portions of ether, which was added to the liquid layer. The solution was freed of solvent under reduced pressure, and the residue was distilled, giving, after a small forerun (b.p. 32–56° at 15 mm.), 195.0 g. (78%) of yellow liquid, b.p. 59–62° (14 mm.), n^{25}D 1.5356, possessing a sharp odor (lit.[11] b.p. 60–62° at 14 mm., n^{21}D 1.5381).

Anal. Calcd. for C_6H_9Br: C, 44.74; H, 5.63; Br, 49.62. Found: C, 44.68; H, 5.71; Br, 49.75.

Diethyl Sorbylmalonate (IV).—To 630 ml. of absolute ethanol, contained in a two-liter three-necked flask equipped with a reflux condenser and calcium chloride drying tube, a mercury-sealed stirrer, and a thermometer, was added, with stirring, 30.0 g. (1.3 atoms) of sodium in small portions. The solution of sodium ethylate was cooled to 50°, and 214.0 g. (1.34 moles) of diethyl malonate was added in a steady stream from a dropping funnel, followed by 194.0 g. (1.20 moles) of sorbyl bromide added slowly. The solution turned cloudy, a white solid separated, and the temperature of the mixture rose gradually to 76°. After addition was complete (0.5 hour), the mixture was refluxed for 2.5 hours, freed of most of the alcohol by distillation, and stirred with 420 ml. of water. After separation of the layers, the aqueous layer was washed with several small portions of ether, and the combined ether solutions were washed with water, 5% sodium bicarbonate solution and water, and dried over anhydrous sodium sulfate. Removal of solvent and distillation of the residue gave the desired product (171.1 g., 60%) as a colorless liquid, b.p. 150–153° (15 mm.), n^{25}D 1.4643.

Anal. Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.89; H, 8.32.

Sorbylmalonic Acid (V).—Diethyl sorbylmalonate (171.0 g., 0.71 mole) was added in a slow stream, with stirring, to a solution of 280.0 g. (75% excess) of potassium hydroxide in 355 ml. of water. After addition was complete (0.5 hour), the clear orange solution was stirred at room temperature for 23 hours, extracted once with ether to remove neutral materials, and made acid to congo red with ice-cold 20% hydrochloric acid. The acid solution was extracted with three 300-ml. portions of ether, and the combined ether solution was washed with water and dried over sodium sulfate. Removal of the solvent left a white crystalline cake, which was recrystallized from benzene–petroleum ether (b.p. 60–70°), giving 73.9 g. (56%) of colorless needles, m.p. 110–111° dec.

Anal. Calcd. for $C_9H_{12}O_4$: C, 59.23; H, 6.57; neut. equiv., 92.1. Found: C, 59.18; H, 6.50; neut. equiv., 92.7.

***trans*-4-*trans*-6-Octadienoic Acid (VI).**—Sorbylmalonic acid (146 g.) was heated in an oil-bath at 140–150° for 5 hours; after cooling sodium bicarbonate solution was cautiously added till the solution was basic to litmus. The solution was extracted once with ether to remove neutral materials, then acidified to congo red with 20% hydrochloric acid solution and extracted with three 200-ml. portions of ether. The combined ether solution was washed with water, dried over sodium sulfate, and freed of solvent. Distillation of the residue gave 48.0 g. (43%) of colorless, viscous liquid, b.p. 140–141° (16 mm.), which rapidly solidified to a mass of needles, m.p. 40°.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63; neut. equiv., 140.2. Found: C, 68.65; H, 8.57; neut. equiv., 139.4.

The acid was very thermostable, no decomposition occurring even on heating to 220°.

***trans*-4-*trans*-6-Octadienoyl Chloride.**—To a solution of 5.0 g. (0.035 mole) of the acid VI in 20 ml. of dry petroleum ether (b.p. 30–40°) was added 6.4 g. (50% excess) of thionyl chloride (purified by distillation over quinoline and boiled linseed oil). The solution was allowed to stand overnight at room temperature, and was then refluxed on the steam-bath for one hour. After removal of the solvent and excess thionyl chloride under reduced pressure, the residue was distilled to give 5.0 g. (89%) of colorless, mobile liquid, b.p. 90° (14 mm.), n^{25}D 1.4946.

Anal. Calcd. for $C_8H_{11}ClO$: Cl, 22.36. Found: Cl, 22.51.

N-Isobutyl-*trans*-4-*trans*-6-octadienamide.—To an ice-cold solution of 9.2 g. (100% excess) of isobutylamine in 100 ml. of anhydrous ether was added slowly, with stirring, an anhydrous ether solution of 4.9 g. (0.031 mole) of the acid chloride prepared above. After the mixture had stood at room temperature for two hours, the precipitated amine hydrochloride was dissolved by the addition of cold dilute hydrochloric acid, the ether layer was washed with water, 5% potassium hydroxide solution, and water, and then dried and evaporated. Distillation of the residue yielded 5.3 g. (86%) of colorless liquid, b.p. 118–119° (0.1 mm.), which rapidly solidified to a mass of needles, m.p. 59–60°.

Anal. Calcd. for $C_{12}H_{21}NO$: C, 73.79; H, 10.84; N, 7.17. Found: C, 73.69; H, 10.85; N, 7.06.

The substance was neither pungent nor toxic to adult house flies.

***trans*-4-*trans*-6-Octadien-1-ol (VII).**—To a solution of 17.5 g. (0.46 mole, 15% excess) of lithium aluminum hydride in 700 ml. of anhydrous ether was added, with stirring, a solution of 48.0 g. (0.34 mole) of 4,6-octadienoic acid VI in 400 ml. of anhydrous ether. When addition was complete (2 hours), the mixture was cooled in an ice-bath and water was carefully added, followed by 550 ml. of 10% sulfuric acid. The separated ether layer was washed with water and dried over sodium sulfate. Removal of the solvent and distillation of the residue gave 41.4 g. (96%) of colorless liquid with a pleasant, fruity odor, b.p. 101–102° (15 mm.), n^{25}D 1.4914.

Anal. Calcd. for $C_8H_{14}O$: C, 76.12; H, 11.19. Found: C, 76.00; H, 11.21.

The 3,5-dinitrobenzoate crystallized from ethanol as cream-colored needles, m.p. 67–68°.

On reduction with platinum oxide catalyst, VII rapidly absorbed 2.07 moles of hydrogen, giving a quantitative yield of colorless liquid, b.p. 195° (763 mm.), n^{25}D 1.4290; phenylurethan, m.p. 73°. A pure sample of 1-octanol showed b.p. 196° (763 mm.), n^{25}D 1.4275; phenylurethan, m.p. 74° (no depression on admixture with the phenylurethan of hydrogenated VII).

***trans*-4-*trans*-6-Octadien-1-al (VIII).**—To a stirred solution of 18.8 g. of chromium trioxide and 28 g. of concentrated sulfuric acid in 800 ml. of water there was added all at once 40.0 g. (0.31 mole) of 4,6-octadien-1-ol. The solution became brown; the temperature was kept at 30–40°. In 12 minutes the mixture had turned green and it was extracted with three 100-ml. portions of ether. The combined ethereal solution was washed with 10% sodium carbonate solution and then with water and dried over sodium sulfate. Removal of the solvent and distillation of the residue gave 12.3 g. (31%) of pale, yellow liquid, b.p. 106–110° (19 mm.), n^{25}D 1.4957.

Anal. Calcd. for $C_8H_{12}O$: C, 77.36; H, 9.74. Found: C, 77.22; H, 9.69.

All-*trans*-2,6,8-decatrienoic Acid (IX).—Twelve grams (0.09 mole) of 4,6-octadien-1-al was added, with ice cooling and shaking, to a solution of 12 g. (0.11 mole) of malonic acid in 20 g. of dry pyridine. No solid formation was noted. The mixture was allowed to stand at room temperature for 72 hours, and then heated on the steam-bath for 8 hours. The solution was poured into 150 ml. of water, and the separated oily layer was shaken with 60 ml. of 20% hydrochloric acid and taken up in ether. The ethereal solution was washed with water and then extracted with 10% potassium hydroxide solution. This alkaline solution was extracted with a small portion of ether and then made acid to congo red with cold 20% hydrochloric acid. The acid solution was extracted with ether, and the extract was then dried over sodium sulfate. Evaporation of the solvent left an oily solid, which was recrystallized from petroleum ether (b.p. 30–40°) to give 3.0 g. (19%) of colorless, stout rods pointed at one end, m.p. 105–107°.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.25; H, 8.50; neut. equiv., 166.2. Found: C, 72.19; H, 8.43; neut. equiv., 165.6.

All-*trans*-affinin.—To a suspension of 1.5 g. (0.009 mole) of the acid IX in 15 ml. of dry petroleum ether (b.p. 30–40°) was added 2.0 g. (50% excess) of purified thionyl chloride. The solid quickly went into solution, which was allowed to stand overnight at room temperature and was then refluxed on the steam-bath for one hour. After removal of the solvent and excess thionyl chloride under reduced pressure, the residual yellow, mobile oil was dissolved in 10 ml. of anhydrous ether and added slowly, with shaking, to an ice-cold solution of 2.4 g. (100% excess) of isobutylamine in 40 ml. of anhydrous ether. After the mixture had stood at room temperature for one hour, the precipitated amine hydrochloride was dissolved by the addition of cold dilute hydrochloric acid, and the ether layer was washed with water, 10% potassium hydroxide solution, and water, then dried and evaporated to dryness. The white solid remaining was recrystallized twice from petroleum ether (b.p. 60–70°) to give 1.0 g. (50%) of colorless needles, m.p. 91.5–92.5°, λ_{max} 228.5 mμ in 95% ethanol (ϵ 37,150).

Anal. Calcd. for $C_{14}H_{23}NO$: C, 76.08; H, 10.49; N, 6.32. Found: C, 76.20; H, 10.41; N, 6.25.

The mixed melting point with a sample of all-*trans*-affinin prepared by elaidinization of natural affinin[1] was 91.5–92.0°.

The maleic anhydride adduct crystallized from benzene as colorless needles, m.p. and mixed m.p. with the previously reported adduct[1] 175°.

BELTSVILLE, MARYLAND

[CONTRIBUTION FROM THE AMERICAN CYANAMID COMPANY]

The Alkaline Oxidation of 2-Naphthol

BY GOSTA BRUNNSTROM

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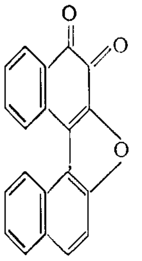
In studies of the action of air on 2-naphthol in the presence of sodium hydroxide, a new compound was isolated and identified as dinaphtho[2,1,1',2']furan-5,6-dione. Other products identified were 1,1'-bi-2-naphthol, 4-(2-carboxyphenyl)-5,6-benzocoumarin and dinaphtho[2,1,2',3']furan-8,13-dione.

The oxidation of 2-naphthol has been the subject of a number of investigations. Generally, mild oxidizing agents lead to the formation of such compounds as binaphthols and binaphthylene oxides, etc.[1–3] Stronger oxidizing agents usually disrupt the naphthalene ring, with the formation of acids, such as carboxyphenylglycolic acid, phthalonic acid, carboxycinnamic acid, etc.[4–8] Recently, Raacke-Fels, *et al.*,[8] using hydrogen peroxide and a small amount of ammonium molybdate under acid conditions, obtained from 2-naphthol a red substance, which was later identified by Bader[9] as 4-(2-hydroxy-1-naphthyl)-1,2-naphthoquinone. This seems to be the only case of the actual isolation of a quinone from the oxidation of 2-naphthol, although unidentifiable materials sometimes have been obtained.

This investigation was undertaken to study the oxidation of 2-naphthol in the presence of sodium hydroxide. On exposure to air, solutions of 2-naphthol in aqueous sodium hydroxide darken on standing. Also, small amounts of sodium hydroxide will cause 2-naphthol to turn almost black in air, particularly at elevated temperatures. To obtain relatively large amounts of the substances causing the discoloration, more extreme conditions were used. Mixtures of powdered 2-naphthol and powdered sodium hydroxide were heated at about 70° for about a week. Under these conditions, 40–60% of the 2-naphthol was converted into various reaction products. The presence of quinones was indicated by color test when the reaction product of 2-naphthol, sodium hydroxide and air was extracted with benzene. The yellow color of the extract changed to violet-red upon the addition of more 2-naphthol and shaking with ammonium hydroxide. Under similar conditions, 1,4-naphthoquinone gives a yellow color and 1,2-naphthoquinone gives a reddish color. The compound responsible for the violet color was isolated and purified.

Physical and chemical properties and the empirical formula $C_{20}H_{10}O_3$ indicated the compound to have structure I, dinaphtho[2,1,1',2']furan-5,6-dione.

Evidence for I being a 1,1'-binaphthyl derivative was obtained by: (a) zinc dust distillation to naphthalene and dinaphtho-[2,1,1',2']-furan, (b) oxidation to *o,o'*-oxalyldibenzoic acid (II) and (c) potassium hydroxide fusion to 2-naphthol, phthalic acid, oxalic acid and an acid III identified as α-[2-hydroxy-1-naphthyl]-*o*-toluic acid.[10] Compound III, obtained by degradation, as well as a sample prepared by the procedure of Fieser,[10] both had a melting point and a mixed melting point of 175°. Fieser reports 187°. The infrared spectrum, degradative oxidation product and ring closure to 1-hydroxy-7-pleiadone (IV), left little doubt as to its structure.



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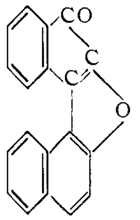

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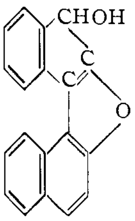

VI

The presence of a 1,2-quinoid group was indicated when a quantitative yield of the corresponding azine was obtained on reaction of I with *o*-phenylenediamine. No methylation resulted on treatment with dimethyl sulfate. The absence of hydroxyl groups was also confirmed by examination of the infrared absorption spectrum of I. Reduc-

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(4) E. Ehrlich and R. Benedikt, *Monatsh.*, **9**, 927 (1888).

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(9) A. Bader, THIS JOURNAL, **73**, 3731 (1951).

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