Synthesis of the Acetylamino Compounds

6,7,7a,8,9,10,11,11a-Octahydro-7-carbomethoxy-5H-dibenzo[a,c]cycloheptatriene (α_1-XI).—Following the directions of Rosenmund and Karg,[23] a solution of 0.86 g. of α_1-VII in 40 ml. of glacial acetic acid was hydrogenated for 30 minutes in the presence of 0.3 g. of 10% palladium-on-charcoal catalyst and 0.6 ml. of perchloric acid. Removal of the catalyst and concentration of the filtrate yielded the desoxy compound in quantitative amount, and three recrystallizations from aqueous ethanol produced glistening, colorless needles, m.p. 82–82.5°; $\lambda_{\max}^{\text{EtOH}}$ (ϵ) 257 mμ (257), 263 (310), 271 (256).

Anal. Calcd. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.82; H, 8.39.

6,7,7a,8,9,10,11,11a-Octahydro-7-carboxy-5H-dibenzo[a,c]cycloheptatriene (α_1-XII).—A 1.34-g. sample of the keto acid[6] α_1-VIII was hydrogenated as described above for the keto ester to give 1.1 g. (88%) of a solid, m.p. 199–200°, which after four recrystallizations from aqueous ethanol existed as fine, glistening needles, m.p. 201–202°.

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.36; H, 8.20.

The *p*-bromophenacyl derivative of α_1-XII was obtained as very fine, colorless needles after several recrystallizations from aqueous ethanol, m.p. 163.5–164.5°.

Anal. Calcd. for $C_{24}H_{25}BrO_3$: C, 65.31; H, 5.71. Found: C, 65.02; H, 5.75.

6,7,7a,8,9,10,11,11a-Octahydro-7-N-acetylamino-5H-dibenzo[a,c]cycloheptatriene (XIII).—The acid chloride prepared from 0.50 g. of the desoxy acid (XII) by the oxalyl chloride method was converted to the azide by the "wet procedure" described by Smith.[24] The oily azide, obtained by ether extraction of the reaction mixture, was heated at 80–90° in 20 ml. of xylene until nitrogen evolution ceased (30 minutes). The xylene was removed, the residue was heated with 25 ml. of concd. hydrochloric acid (carbon dioxide evolution), and the reaction mixture was then worked up in the usual fashion to yield 0.1 g. of oily, neutral material and an acid-soluble amine fraction which, without purification, was acetylated with acetic anhydride. The 0.3 g. (57% over-all) of solid so obtained was recrystallized four times from ethanol containing a small amount of water to give clusters of opaque needles, m.p. 175–176°.

Anal. Calcd. for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.18; H, 8.97; N, 5.54.

ST. LOUIS, MISSOURI

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[23] K. W. Rosenmund and E. Karg, *Ber.*, **75**, 1850 (1942).

[24] P. A. S. Smith, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 387.

[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, AGRICULTURAL RESEARCH ADMINISTRATION U. S. DEPARTMENT OF AGRICULTURE]

Pellitorine Isomers. II. The Synthesis of N-Isobutyl-*trans*-2,*trans*-4-decadienamide[1,2,3]

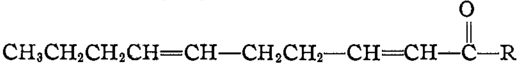
BY MARTIN JACOBSON

RECEIVED OCTOBER 2, 1952

The synthesis of N-isobutyl-2,4-decadienamide, isomeric with the natural insecticides pellitorine and spilanthol, is described. According to the method of synthesis used, it possesses the *trans* configuration about both double bonds. The compound is both physiologically and insecticidally active. Proof of structure is shown by hydrogenation to N-isobutylcapramide and by oxidation to cleave the double bonds, yielding *n*-caproic, oxalic and N-isobutyloxamic acids.

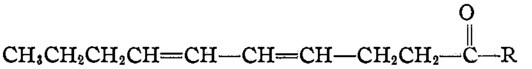
Since the advancement of structure I for pellitorine,[4] a pungent, insecticidal amide present in pellitory root,[5] the *cis–cis*,[6] *trans–cis*,[7] and *trans–trans*[2] isomers of this structure have been synthesized.[8] Each of these isomers proved to be insecticidally inert, although the *trans–cis* isomer was physiologically active, causing profuse salivation and partial insensitivity of the tongue as shown by natural pellitorine.[4]

Spilanthol (II) is an isomer of pellitorine, being the N-isobutylamide of 4,6-decadienoic acid (configuration about the double bonds unknown). This natural compound also has been reported to be both physiologically and insecticidally active.[9] It was therefore decided to synthesize N-isobutyl-2,4-decadienamide (III), to determine whether it too had these properties.[10]



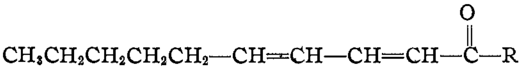
$$\mathrm{CH_3CH_2CH_2CH{=}CH{-}CH_2CH_2{-}CH{=}CH{-}\overset{O}{\overset{\|}{C}}{-}R}$$

(I)



$$\mathrm{CH_3CH_2CH_2CH{=}CH{-}CH{=}CH{-}CH_2CH_2{-}\overset{O}{\overset{\|}{C}}{-}R}$$

(II)



$$\mathrm{CH_3CH_2CH_2CH_2CH_2{-}CH{=}CH{-}CH{=}CH{-}\overset{O}{\overset{\|}{C}}{-}R}$$

(III)

$\mathrm{R = NH{-}CH_2{-}CH(CH_3)_2}$

The steps employed in this synthesis are shown in the accompanying chart.

n-Caproaldehyde was condensed with malonic acid in the presence of pyridine to give *trans*-2-octenoic acid[11] in 68% yield. This acid has been previously reported by several investigators.[12]

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[1] Report of a study made under the Research and Marketing Act of 1946. Article not copyrighted.

[2] This paper was presented before the Division of Organic Chemistry, at the Atlantic City meeting of the American Chemical Society, September 18, 1952 [see *Chem. Eng. News*, **30**, 4131 (1952)].

[3] The first paper in this series is THIS JOURNAL, **72**, 1489 (1950).

[4] M. Jacobson, *ibid.*, **71**, 366 (1949).

[5] J. M. Gulland and G. U. Hopton, *J. Chem. Soc.*, 6 (1930).

[6] R. A. Raphael and F. Sondheimer, *Nature*, **164**, 707 (1949); *J. Chem. Soc.*, 120 (1950).

[7] L. Crombie and S. H. Harper, *Nature*, **164**, 1053 (1949).

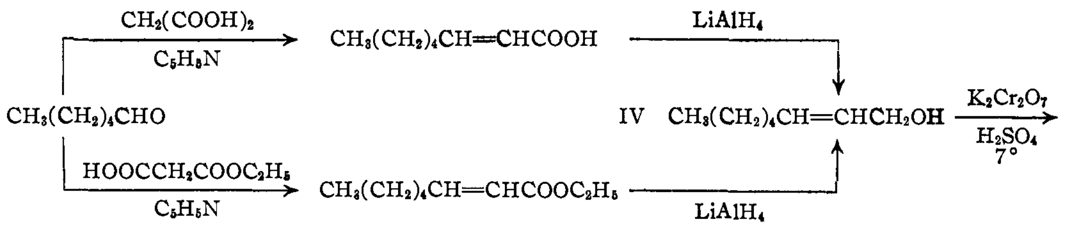
[8] After this paper was submitted for publication, Crombie [*Chemistry and Industry*, 1034 (1952)] reported the synthesis of the fourth (*cis–trans*) isomer, which was not identical with natural pellitorine. He considers the latter to be either impure N-isobutyl-*trans*-2,*trans*-4-decadienamide or a stereoisomer thereof.

[9] G. S. Pendse, *et al.*, *Current Sci.* (*India*), **14**, 37 (1945); *J. Univ. Bombay*, **15A**, [3] 26 (1946).

[10] After this paper was submitted for publication, Crombie, ref. 7, reported his independent synthesis of this compound (*trans–trans* isomer) and of several of the intermediates reported in the present paper.

[11] The condensation of an aldehyde with malonic acid in the presence of pyridine has been shown to yield the *trans* unsaturated acid. See E. Knoevenagel, *Ber.*, **31**, 2602 (1898); O. Doebner, *ibid.*, **34**, 53 (1901); R. Stoermer and P. Heymann, *ibid.*, **45**, 3099 (1912); K. von Auwers and H. Wissebach, *ibid.*, **56**, 715 (1923); R. A. Letch and R. P. Linstead, *J. Chem. Soc.*, 455 (1932); L. Crombie and S. H. Harper, ref. 7.

[12] M. Bourguel, *Compt. rend.*, **188**, 1494 (1929); G. Bachmann, THIS JOURNAL, **55**, 4279 (1933); A. Seldner, *Am. Perfumer*, **54**, 295 (1949).



$$\underset{\text{V}}{CH_3(CH_2)_4CH{=}CHCHO} \xrightarrow[C_5H_5N]{CH_2(COOH)_2} \underset{\text{VI}}{CH_3(CH_2)_4CH{=}CHCH{=}CHCOOH} \xrightarrow{SOCl_2}$$

$$\underset{\text{VII}}{CH_3(CH_2)_4CH{=}CHCH{=}CHCOCl} \xrightarrow[\text{amine}]{\text{iosbutyl-}} \text{III}(\textit{trans–trans})$$

Reduction of the acid with lithium aluminum hydride gave *trans*-2-octen-1-ol[13] (IV) in 59% yield. IV was also prepared, in 31% over-all yield, by condensing *n*-caproaldehyde with ethyl hydrogen malonate to give the ethyl ester of *trans*-2-octenoic acid, which was then reduced with lithium aluminum hydride to IV. Dichromate oxidation of the unsaturated alcohol IV by the low-temperature method of Delaby and Guillot-Allégre[14] resulted in a 42% yield of *trans*-2-octen-1-al (V). A previous attempt to prepare this aldehyde directly by condensing *n*-caproaldehyde with acetaldehyde had been unsuccessful, yielding mainly cyclic products and polymers.

Treatment of V with malonic acid in pyridine gave *trans*-2-,*trans*-4-decadienoic acid (VI)[11] in 41% yield. Hilditch[15] has reported the isolation of a 2,4-decadienoic acid from stillingia oil obtained from the seeds of *Sapium sebiferum* Roxb. He considers the natural acid to have the *cis–cis* configuration.[16] Hilditch reports an ultraviolet absorption peak in "alcohol" at 260 mμ for the acid and at 264 mμ for its methyl ester. We have found a well-defined peak at 257 mμ for the *trans–trans* acid and at 262 mμ for its methyl ester, using 95% ethanol as the solvent. When these determinations were repeated in absolute ethyl alcohol, however, the *trans–trans* acid and methyl ester exhibited their peaks at 250 and 260 mμ, respectively.

The acid chloride VII was prepared in 73% yield by the use of thionyl chloride in low-boiling petroleum ether, and addition of VII to isobutylamine in anhydrous ether solution yielded 66% of N-isobutyl-*trans*-2,*trans*-4-decadienamide (III). This compound is a colorless, crystalline solid melting at 88° and boiling at 144–145° at 0.3 mm. It exhibits a single broad absorption band in the ultraviolet spectrum with a well-defined peak at 259 mμ, both in 95% ethanol and in absolute ethanol, and is soluble in all the usual organic solvents, including petroleum ether.

Compound III proved to be both physiologically and insecticidally active. One crystal placed on the tongue caused increased salivation and a marked burning sensation on the tongue and on the mucous membranes of the mouth. In tests conducted with houseflies (*Musca domestica* L.),[17] a Deobase (refined kerosene) solution of III, used as a spray, showed paralyzing action equal to and mortality about one-half that of pyrethrins tested at the same concentration. It is rather unstable in the presence of air and light, showing signs of discoloration after several weeks at room temperature. However, it is much more stable when kept in a nitrogen atmosphere, and may be kept unchanged for months under nitrogen at 5°.

The structure of compound III was confirmed by hydrogenation with platinum oxide to N-isobutylcapramide, and by oxidation to yield *n*-caproic, oxalic and N-isobutyloxamic acids.

The synthesis of the remaining three geometrical isomers of compound III is being investigated.

Experimental[18,19]

trans-**2-Octen-1-ol (IV). Method 1.**—Two hundred and seventy grams (2.69 moles) of *n*-caproaldehyde, b.p. 128–130°, n^{25}D 1.4030, was added, with stirring, to a solution of 270 g. (2.60 moles) of malonic acid in 434 g. of dry pyridine, while cooling with ice-water. When about half of the aldehyde had been added, the mixture turned semi-solid, but stirring was still effectively performed. After addition was complete, the mixture was allowed to stand at room temperature for 65 hours, and the clear solution was then heated on the steam-bath for 8 hours. The solution was poured into 850 ml. of water, and the upper oily layer was stirred with 815 ml. of 25% hydrochloric acid and taken up in ethyl ether. After being washed with water, the ether solution was dried over sodium sulfate and then freed of solvent. Distillation of the residue gave 260.5 g. (68%) of *trans*-**2-octenoic acid** as a colorless, viscous liquid, b.p. 95–100° (0.4 mm.), n^{25}D 1.4560 (Bachmann[12] reports b.p. 154° at 22 mm., n^{25}D 1.4587).

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92; neut. equiv., 142.2. Found: C, 67.49; H, 10.03; neut. equiv., 140.9.

To a solution of 30.0 g. (0.79 mole, 14% excess) of lithium aluminum hydride in 1500 ml. of anhydrous ether was added, with stirring, 130.0 g. (0.91 mole) of 2-octenoic acid. The addition was carried out at such a rate that steady refluxing of the ether took place and no cooling was necessary. When addition was complete (3.5 hours), the mixture was cooled in an ice-bath and water was carefully added, followed by the addition of 950 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, after a very small forerun, 68.7 g. (59%) of colorless, mobile liquid with a pleasant odor, b.p. 91° (11 mm.), n^{25}D 1.4400 (lit.[13] b.p. 98° at 21 mm., n^{21}D 1.4437).

Anal. Calcd. for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 75.12; H, 12.49.

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[13] B. Gredy, *Bull. soc. chim.*, [5] **3**, 1093 (1936).

[14] R. Delaby and S. Guillot-Allégre, *ibid.*, [4] **53**, 301 (1933).

[15] T. P. Hilditch, *J. Oil Colour Chem. Assoc.*, **32**, 5 (1949); A. Crossley and T. P. Hilditch, *J. Chem. Soc.*, 3353 (1949).

[16] T. P. Hilditch, private communication.

[17] These tests were made by W. A. Gersdorff and N. Mitlin of this Bureau.

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

[19] All microanalyses except neutralization equivalents and chlorine determinations were made by Oakwold Laboratories, Alexandria, Virginia, and by Clark Microanalytical Laboratory, Urbana, Illinois.

A fairly large residue due to partial polymerization of the alcohol remained in the distillation flask.

The phenylurethan crystallized from petroleum ether (b.p. 30–40°) at −10° as clusters of needles, m.p. 45°.

Method 2.—A mixture of 80.1 g. (0.80 mole) of *n*-caproaldehyde, 211.0 g. (1.6 moles) of ethyl hydrogen malonate,[20] 387 ml. (4.8 moles) of dry pyridine, and 1.2 ml. of piperidine was heated on the steam-bath for 6 hours, during which time carbon dioxide was vigorously evolved. The pyridine and piperidine were then removed under reduced pressure (bath at 40–45°), and distillation of the residue gave 117.5 g. (86%) of **ethyl *trans*-2-octenoate** as a colorless mobile liquid, b.p. 70–72° (1.5 mm.), n^{25}D 1.4385.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.65. Found: C, 70.49; H, 10.53.

Lithium aluminum hydride reduction of the ester by the procedure given above for the acid gave a 41% yield of the *trans* alcohol IV.

***trans*-2-Octen-1-al (V).**—To a stirred solution of 210 g. of potassium dichromate and 210 g. of concentrated sulfuric acid in 1400 ml. of water, cooled to 7° in an ice-bath, there was added, all at once, 67 g. of 2-octen-1-ol emulsified with 75 ml. of water. The solution became dark brown, and the temperature rose to 20° in three minutes. At the end of four minutes the mixture was extracted with four 200-ml. portions of ether, and the combined ethereal solution was washed with a saturated solution of sodium bicarbonate and then with water and dried over sodium sulfate. Removal of the solvent and distillation of the residue gave 27.9 g. (42%) of pale yellow, mobile liquid, b.p. 75–78° (13 mm.), n^{25}D 1.4445.[21]

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.01; H, 11.35.

***trans*-2,*trans*-4-Decadienoic Acid (VI).**—Fifty-three grams (0.42 mole) of 2-octen-1-al was added, with ice-cooling and shaking, to a solution of 53 g. (0.51 mole) of malonic acid in 87 g. of dry pyridine. No solid formation was noted. The mixture was allowed to stand at room temperature for 66 hours, and was then heated on the steam-bath for 8 hours. The solution was poured into 170 ml. of water, and the separated oily layer was shaken with 165 ml. of 25% hydrochloric acid and taken up in ether. The ethereal solution was washed with water and then extracted with 10% sodium carbonate solution. This alkaline solution was extracted with a small portion of ether and then made acid to congo red with cold 25% hydrochloric acid. The acid solution was extracted with ether, and the extract was then dried over sodium sulfate. Evaporation of the solvent and distillation of the residue gave, after a small forerun (b.p. 70–90° at 0.3 mm.), 29.0 g. (41%) of colorless, viscous liquid, b.p. 114° (0.3 mm.), that crystallized in the receiver. Two recrystallizations from petroleum ether (b.p. 30–40°) at −10° gave colorless, glistening plates, m.p. 49° (λ_{max} 257 mμ in 95% ethanol, 250 mμ in absolute ethanol).

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.95; neut. equiv., 168.2. Found: C, 71.25; H, 9.50; neut. equiv., 168.0.

The methyl ester, prepared from the acid chloride described below, was a colorless liquid, b.p. 70° (0.2 mm.), n^{25}D 1.4805 (λ_{max} 262 mμ in 95% ethanol, 260 mμ in absolute ethanol.)[22]

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.40; H, 10.12.

***trans*-2, *trans*-4-Decadienoyl Chloride (VII).**—To a solution of 15.0 g. (0.09 mole) of the acid VI in 70 ml. of dry petroleum ether (b.p. 30–40°) was added 16.6 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 12.3 g. (73%) of pale yellow, mobile liquid, b.p. 136° (14 mm.), n^{25}D 1.5260.

Anal. Calcd. for $C_{10}H_{15}ClO$: Cl, 19.00. Found: Cl, 19.12.

N-Isobutyl-*trans*-2,*trans*-4-decadienamide (III).—To an ice-cold solution of 9.7 g. (100% excess) of isobutylamine in 75 ml. of anhydrous ether was added slowly, with stirring, an anhydrous ether solution of 6.1 g. (0.03 mole) of the acid chloride prepared above. 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, then dried and evaporated. Distillation of the residue in an atmosphere of nitrogen yielded 4.4 g. (66%) of pale yellow, viscous oil, b.p. 144–145° (0.3 mm.), which rapidly solidified to a mass of feathery needles. Two recrystallizations from petroleum ether (b.p. 30–40°) at −10° gave colorless, glistening needles, m.p. 88° (λ_{max} 259 mμ in 95% or absolute ethanol).

Anal. Calcd. for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27. Found: C, 75.21; H, 11.30; N, 6.25.

The substance was soluble in all organic solvents, and insoluble in water, acid and alkali. It was very pungent and toxic to adult houseflies.

Hydrogenation of III.—An ethereal solution of 0.2074 g. of compound III was hydrogenated with 50 mg. of reduced platinum oxide catalyst. In seven minutes 39.0 ml. (cor.) of hydrogen was taken up, and the reaction abruptly ceased. (The theoretical requirement for 2 moles of hydrogen for this weight of a substance of molecular weight 223 is 39.9 ml.) The reaction mixture was separated from the catalyst, and the solvent was removed at reduced pressure, leaving 200 mg. of a colorless oil which crystallized in rosettes of needles, m.p. 37.5–38.0°.

The product was identical with N-isobutylcapramide, m.p. 38–38.5°; mixed m.p. with an authentic sample, 37.5–38.0°.

Oxidation of III.—To a stirred suspension of 1 g. of compound III in 100 ml. of water, maintained at 75°, 3.8 g. of finely powdered potassium permanganate was added in small portions. When the reaction mixture had become colorless, the manganese dioxide was filtered and washed thoroughly with warm water. The combined aqueous filtrates were concentrated down to 20 ml. and made acid to congo red with sulfuric acid (a small quantity of yellow oil was seen floating on top of the water). The entire solution (plus oil) was steam distilled to remove the volatile acids and then extracted with ether in a continuous extractor. The ether solution was freed of solvent and extracted with two small portions of boiling petroleum ether (b.p. 60–80°). Cooling of the hydrocarbon solution caused the separation of 477 mg. (72%) of colorless, feathery needles, m.p. 106°.

Anal. Calcd. for $C_6H_{11}NO_3$: neut. equiv., 145. Found: neut. equiv., 143.

The mixed melting point with an authentic sample of N-isobutyloxamic acid was 106°.

The insoluble residue from the hydrocarbon extraction above was subjected to sublimation in a micro sublimator. Two hundred and forty-two milligrams of colorless solid was obtained, which sublimed at 100–105° (15 mm.) and melted at 185–186° (dec.). It rapidly reduced an aqueous solution of potassium permanganate.

Anal. Calcd. for $C_2H_2O_4$: neut. equiv., 45. Found: neut. equiv., 45.

The mixed m.p. with an authentic specimen of anhydrous oxalic acid was 186–187° (dec.). The yield of oxalic acid was 60%.

The solution of steam-volatile acids was neutralized with sodium hydroxide solution and concentrated to 10 ml., then acidified to congo red and extracted with ether in a continuous extractor. The ether solution was dried over sodium sulfate, freed of solvent, and distilled, giving 468 mg. (90%) of a colorless oily liquid, b.p. 204°.

Anal. Calcd. for $C_6H_{12}O_2$: neut. equiv., 116. Found: neut. equiv., 115.

It was identified as *n*-caproic acid by preparation of the *p*-phenylphenacyl ester, m.p. and mixed m.p. with authentic *p*-phenylphenacyl caproate, 68–69°.

BELTSVILLE, MARYLAND

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(20) D. S. Breslow, *et al.*, THIS JOURNAL, **66**, 1286 (1944).

(21) P. Van Romburgh, *Rec. trav. chim.*, **57**, 494 (1938), reported the isolation, from the essential oil of *Achasma walang* Val., of 2-octen-1-al boiling at 83° at 14 mm. (configuration about the double bond unknown).

(22) T. P. Hilditch, ref. 15, reports λ_{max} 260 mμ for the naturally occurring acid and λ_{max} 264 mμ for its methyl ester, b.p. 86° (0.2 mm.), using "alcohol" as solvent.