# The Synthesis of Esters of Angelic Acid[1,2]

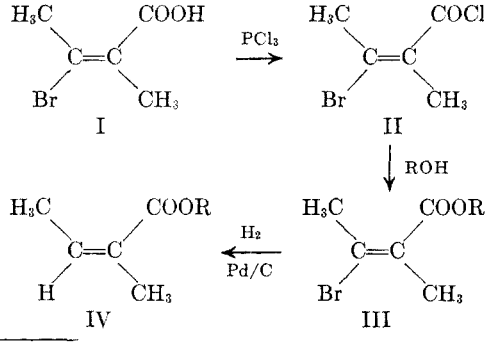
S. Morris Kupchan and Adriano Afonso

*Received April 6, 1960*

This report concerns the development of a general method for the synthesis of esters of angelic acid. The need for a widely applicable synthetic route arose during our studies of the structures of the naturally-occurring veratrum angelate esters germanitrine[3] and cevadine.[4] It was felt that ambiguity concerning the nature of the unsaturated acid residue present in each of these alkaloids could best be resolved by partial synthesis of authentic angelate esters for comparison with the natural materials.

Methyl angelate and ethyl angelate have been prepared by displacement reactions of the carboxylate ion with the appropriate alkyl halide.[5,6] *l*-Menthyl angelate was reportedly prepared by acylation of *l*-menthol with angeloyl chloride synthesized from sodium angelate and phosphorus oxychloride.[7] In our hands, repetition of Rupe's preparation yielded *l*-menthyl tiglate. Furthermore, the acid chloride prepared from sodium angelate and phosphorus oxychloride yielded tiglic acid upon hydrolysis. Subsequent attempts to prepare angeloyl chloride by other standard procedures invariably yielded tigloyl chloride. It became apparent that the well known[6] facile isomerization of angelic acid to tiglic acid precluded synthesis of angeloyl chloride by the standard procedures.

The method subsequently developed is shown in formulas I–IV. 3-Bromoangelic acid (I)[5] was converted to 3-bromoangeloyl chloride (II) by reaction with phosphorus trichloride. The absence of isomerization to the tigloyl isomer was demonstrated by subsequent conversion to the known methyl and ethyl esters of angelic acid. The relative stability of I toward isomerization is presumably attributable to the polar repulsion of the bromine atom and the carboxyl group and the consequent greater stability of the geometric isomer in which the bromine atom and carboxyl group are farthest from each other. The acid chloride (II) was allowed to react with various simple alcohols to yield the respective 3-bromoangelate esters (III). Catalytic hydrogenolysis of the latter compounds (III) yielded the desired angelate esters (IV). The hydrogenolyses were run under atmospheric pressure over potassium hydroxide–washed 10% palladium on charcoal in the presence of excess triethylamine. Triethylamine was found to be an efficient inhibitor which minimized the competing reduction of the double bond. In all cases, the hydrogenation was terminated after the uptake of one mole equivalent of hydrogen was complete. The yields and properties of the 3-bromoangelate and angelate esters of methyl, ethyl, and phenethyl alcohols and of *l*-menthol are summarized in Table I. The properties of *l*-menthyl tiglate are included for comparison purposes.




The same sequence of reactions was used to prepare the alkaloid angelate esters germanitrine,[3] cevadine,[4] and escholerine.[8] In the alkaloid series, sodium acetate was added to neutralize hydrogen bromide liberated in the hydrogenolysis step; in these cases, the alkaloid apparently served as the inhibitor. In each of the three cases, the synthetic ester was identical with the naturally-derived material, thereby confirming presence of the angelate residue in each ester alkaloid.

Certain spectral differences between the angelate and tiglate esters became apparent upon comparison of the two series. In the ultraviolet, the location of the absorption maximum (216 ± 1 mμ) was approximately the same for both series (see Table II). However, the extinction coefficients for the tiglate esters appeared to be consistently higher (*ca.* 11,000) than those of the angelate esters (*ca.* 9000). In the infrared, the tiglate esters in chloroform solution showed characteristic bands at 8.75 μ(s) and 15.30 μ(w) which were absent from the spectra of the angelate esters. On the other hand, the angelate esters in chloroform solution showed characteristic bands at 8.05–8.10 μ(s) and 11.80 μ(m) which did not appear in the spectra of the tiglate esters. These generalizations embraced the spectra of the alkaloidal esters as well. In the spectra of liquid films, the tiglate esters were characterized by a single band at 13.65 μ(s) and one at

(1) This is part XXXVI of a series entitled "Veratrum Alkaloids," Part XXXV, S. M. Kupchan and N. Gruenfeld, *J. Am. Pharm. Assoc.*, **48**, 727 (1959).

(2) This investigation was supported in part by a research grant from the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

(3) S. M. Kupchan and A. Afonso, *J. Am. Pharm. Assoc.*, **48**, 731 (1959).

(4) S. M. Kupchan and A. Afonso, *J. Am. Pharm. Assoc.*, **49**, 242 (1960).

(5) R. E. Buckles and G. V. Mock, *J. Org. Chem.*, **15**, 680 (1950).

(6) For an informative review of the chemistry of tiglic and angelic acids, see R. E. Buckles, G. V. Mock, and L. Locatell, Jr., *Chem. Revs.*, **55**, 659 (1955).

(7) H. Rupe, *Ann.*, **369**, 337 (1909).

(8) S. M. Kupchan and C. I. Ayres, *J. Am. Pharm. Assoc.*, **48**, 735 (1959).

TABLE I

PHYSICAL PROPERTIES OF SOME ANGELATE ESTERS

| Esters | B.P., mm. | Yield, % | $d_4^{22}$ | $n_D^{21}$ | Calcd. C, % | Calcd. H, % | Calcd. Br, % | Found C, % | Found H, % | Found Br, % |
|---|---|---|---|---|---|---|---|---|---|---|
| Methyl 3-bromoangelate | 96 (53) | 97.3 | 1.444 | 1.4890 | 37.33 | 4.70 | 41.41 | 37.25 | 4.97 | 40.90 |
| Ethyl 3-bromoangelate | 110 (51) | 88.5 | 1.342 | 1.4796 | 40.46 | 5.53 | 38.46 | 40.34 | 5.36 | 37.24 |
| *l*-Menthyl 3-bromoangelate | 112 (0.6) | 78.2 | 1.175 | 1.4906 | 56.76 | 7.94 | 25.19 | 56.53 | 7.99 | 24.99 |
| Phenethyl 3-bromoangelate | 144 (3) | 85.5 | 1.324 | 1.5418 | 55.12 | 5.34 | 28.23 | 55.13 | 5.13 | 27.75 |
| Methyl angelate | 128 (740) | 64.3 | 0.9202 | 1.4332 | 63.16 | 8.83 | — | 62.68 | 8.46 | — |
| Ethyl angelate | 142 (740) | 71.0 | 0.9272 | 1.4296 | 65.64 | 9.43 | — | 65.22 | 9.48 | — |
| *l*-Menthyl angelate[a] | 130 (5) | 89.0 | 0.9656 | 1.4651 | 75.57 | 10.99 | — | 75.42 | 10.96 | — |
| Phenethyl angelate | 109 (1.8) | 89.7 | 1.053 | 1.5101 | 76.47 | 7.90 | — | 76.40 | 7.97 | — |
| *l*-Menthyl tiglate[b] | 138 (9) | 91.7 | 0.9494 | 1.4668 | 75.57 | 10.99 | — | 75.77 | 11.08 | — |

[a] $[\alpha]_D^{25}$ −86° (*c*, 9.54, benzene. [b] $[\alpha]_D^{25}$ −87° (*c*, 9.54, benzene).

TABLE II

ULTRAVIOLET ABSORPTIONS

| Ester | $\lambda_{max}^{alc.}$, mμ | ε |
|---|---|---|
| Methyl tiglate | 215 | (11,300) |
| Ethyl tiglate | 215 | (11,100) |
| *l*-Menthyl tiglate | 216 | (11,200) |
| Phenethyl tiglate | [a] | |
| Methyl angelate | 217 | (9,100) |
| Ethyl angelate | 216 | (8,600) |
| *l*-Menthyl angelate | 217 | (8,800) |
| Phenethyl angelate | [a] | |

[a] Obscured by strong end absorption.

15.30 μ(w). The angelate esters showed a characteristic doublet at 13.20 (m) and 13.65 μ(m).

## EXPERIMENTAL[9]

*Attempted preparation of angeloyl chloride.* To sodium angelate (1.6 g.) was added slowly with stirring phosphorus oxychloride (1.6 ml.).[7] The suspension was allowed to stand at room temperature overnight and was then filtered. The inorganic residue was washed with benzene, and the filtrate and washings were combined and concentrated under reduced pressure at room temperature to a nonvolatile liquid acid chloride residue.

The crude acid chloride (0.1 ml.) was added to ice-water (5 ml.) and the mixture was shaken until separation of a solid appeared to be complete (*ca.* 5 min.). The solid was filtered, washed with water, and dried, whereby a material with m.p. 64° was obtained. The infrared spectrum of this material in chloroform was identical with that of tiglic acid in chloroform.

Treatment of the crude acid chloride (1.13 g.) with a solution of *l*-menthol (1.14 g.) in benzene (1.0 ml.) and pyridine (1.13 g.) according to the procedure of Rupe[7] yielded an ester (b.p. 120°/7–8 mm.) with infrared spectrum in chloroform identical with that of *l*-menthyl tiglate in chloroform.

In other experiments, angelic acid was treated with phosphorus trichloride or thionyl chloride, either at room temperature overnight or at 70° for 1 hr. Invariably, the crude acid chlorides yielded tiglic acid upon hydrolysis and *l*-menthyl tiglate upon reaction with *l*-menthol.

*3-Bromoangeloyl chloride.* 3-Bromoangelic acid[5] (4.7 g.) was added portionwise to phosphorus trichloride (2 ml.) at 40° and the mixture was heated at 60–65° for 2.5 hr. The supernatant liquid was decanted from the sirupy layer of phosphoric acid. Distillation of the decanted layer under reduced pressure yielded 3-bromoangeloyl chloride [4.6 g. (89%), b.p. 70°/30 mm., 84°/40 mm., $d_4^{21}$ 1.570].

*Anal.* Calcd. for $C_5H_6OBrCl$: C, 30.42; H, 3.03. Found: C, 30.96; H, 2.70.

*Esters of 3-bromoangelic acid and tiglic acid.* To 3-bromoangeloyl chloride or tigloyl chloride[10] (0.02 mole) heated on the steam bath was added slowly the appropriate alcohol (0.02 mole), and the reaction mixture was heated until evolution of hydrogen chloride fumes ceased (*ca.* 1 hr.). The reaction mixture was cooled, dissolved in ether, and washed with sodium carbonate solution (10%) and then water. The ether solution was dried over anhydrous sodium sulfate and concentrated through a 1.7 × 30 cm. column packed with glass helices (1/16 in. dia.). The concentrate was distilled under reduced pressure to yield the desired ester (Table I).

*Esters of Angelic Acid.* Palladium-on-charcoal (10%, Am. Plat. Works, Newark, N. J.) was suspended in about 10 parts by volume of 10% potassium hydroxide solution and the suspension was allowed to stand for 5 min. The catalyst was filtered, washed successively with ethanol, water, ethanol and finally ether, and dried under reduced pressure.

The appropriate 3-bromoangelate ester (0.02 mole) was added to a suspension of the potassium hydroxide–washed palladium-on-charcoal catalyst (1 part catalyst to 10 parts ester by weight) in ethanol (20 parts vol./wt. of ester) containing triethylamine (0.04 to 0.12 mole) which had been pre-saturated with hydrogen. The hydrogenolysis was allowed to proceed at room temperature under atmospheric conditions until the theoretical amount of hydrogen was consumed, and was then terminated. The average rate of consumption of hydrogen was 4 ml./min. The catalyst was removed by filtration and washed with ethanol. The combined filtrate was concentrated with a 1.7 × 30 cm. column packed with glass helices (1/16 in. dia.). The concentrate was treated with dilute hydrochloric acid and ether, and the ether layer was washed, dried over sodium sulfate, and concentrated as above. The concentrate was distilled under reduced pressure through a 1 × 14 cm. vacuum-jacketed Vigreux column to yield the desired ester of angelic acid (Table I).

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UNIVERSITY OF WISCONSIN
MADISON, WIS.

(9) Values of $[\alpha]_D$ have been approximated to the nearest degree. Ultraviolet absorption spectra were determined in 95% ethanol on a Cary recording spectrophotometer (Model 11 MS). Infrared spectra were determined on a Beckmann IR5 double-beam infrared recording spectrophotometer. Refractive indices were determined on a Zeiss Abbe refractometer. Microanalyses were carried out by Dr. S. M. Nagy and his associates at M. I. T.

(10) G. Barger, W. F. Martin, and W. Mitchell, *J. Chem. Soc.*, 1822 (1937).