82. *Studies on Chrysanthemic Acid. IV. Synthesis of Chrysanthemumdicarboxylic Acid from Chrysanthemic Acid*

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Chrysanthemumdicarboxylic acid (I) is an acidic component of pyrethrins II and cinerin II which are two constituents of natural pyrethrins occurring in pyrethrum flowers, *Chrysanthemum cinerariae-folium*. Natural chrysanthemumdicarboxylic acid is the d-trans isomer of the structure (I). Racemic trans-chrysanthemumdicarboxylic acid was synthesized recently by Harper and Sleep,1' and by Inouye, Takeshita, and Ohno2' by the method which is shown here:

\[
\begin{align*}
\text{CH}_3\text{CHBrCOOC}_2\text{H}_5 & \xrightarrow{\text{Zn}} \text{CH}_3\text{C} = \text{CH} - \text{CH} = \text{C} \text{CH}_3 \\
\text{CH}_3\text{C} = \text{CHCHO} & \xrightarrow{\text{N}_2\text{CHCOOC}_2\text{H}_5} \text{CH}_3\text{C} = \text{CH} - \text{CH} = \text{C} \text{CH}_3 \\
\text{CH}_3\text{C} = \text{CHCOOC}_2\text{H}_5 & \xrightarrow{\text{Ag}_2\text{O}} \text{CH}_3\text{C} = \text{CHCOOR} \\
\text{CH}_3\text{C} = \text{CHCOOR} & \xrightarrow{\text{NaOH}} \text{CH}_3\text{C} = \text{CHCOOH}
\end{align*}
\]

The d-trans-chrysanthemumdicarboxylic acid was obtained by Inouye et al.3' by resolving dl-trans-acid with (−)-α-phenylethylamine, but the details have not been published.

The present authors have synthesized dl-cis-, dl-trans-, and d-trans-chrysanthemumdicarboxylic acids via a different route. Our method is as follows:

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\begin{align*}
\text{CH}_3\text{C} = \text{CHCH} = \text{C} \text{CH}_3 & \xrightarrow{\text{SeO}_2} \text{CH}_3\text{C} = \text{CHCH} = \text{C} \text{CHO} \\
\text{CH}_3\text{C} = \text{CHCOOR} & \xrightarrow{\text{Ag}_2\text{O}} \text{CH}_3\text{C} = \text{CHCOOR} \\
\text{CH}_3\text{C} = \text{CHCOOR} & \xrightarrow{\text{NaOH}} \text{CH}_3\text{C} = \text{CHCOOH}
\end{align*}
\]


Experimental*)

1) dl-cis-Chrysanthemumdicarboxylic acid

Methyl cis-chrysanthemate1' (10 g) in 50 ml of dioxane was refluxed for one hour with 9 g of selenium dioxide. Separation of solution from precipitated selenium and distillation and redistillation

*) All melting points are uncorrected.
afforded 6 g of the desired aldehydic ester (III, R = CH₃) boiling at 140-145°C/17 mm nD 1.4994, which is thought to be a mixture of two stereoisomers. Analysis: C, 66.8; H, 8.4%; Calculated for C₇H₁₆O₂: C, 67.3; H, 8.1%. 2,4-Dinitrophenylhydrazone was prepared and recrystallized from ethyl alcohol, forming scarlet crystals, of m.p. 192°. Analysis: C, 54.0; H, 5.5; N, 15.0%; Calculated for C₁₇H₂₅O₆N₄: C, 54.2; H, 5.3; N, 14.9%.

The aldehydic ester (5 g) was stirred for 30 min at 70° in 140 ml of 5% sodium hydroxide solution with silver oxide which was freshly prepared from 7 g of silver nitrate and sodium hydroxide solution. The solution was separated from silver, acidified with 40 g of 25% sulfuric acid and left standing in a refrigerator. dl-cis-Chrysanthemum-dicarboxylic acid which precipitated was collected and washed with water. Recrystallization from aqueous ethyl alcohol using a small amount of active carbon, afforded 3.5 g of colorless dl-cis-chrysanthemum dicarboxylic acid melting at 204°. Analysis: C, 60.9; H, 7.2%; Calculated for C₁₀H₁₄O₄: C, 60.6; H, 7.1%. By ozonolysis dl-cis-caronic acid, m.p. 175°, was obtained. Additional dl-cis-chrysanthemum-dicarboxylic acid, less pure in quality, was obtained by condensation of mother liquors.

2) dl-trans-Chrysanthemum-dicarboxylic acid

Methyl trans-chrysanthemate (10 g)⁴⁵ in 50 ml of dioxane was refluxed for 1 hour with 7.3 g of selenium dioxide. Separation of the solution from precipitated selenium, distillation, and redistillation afforded the desired aldehydic ester (III, R = CH₃) (6.5 g) boiling at 135-145°C/11 mm, nD 1.4956 the middle distillate of which is analysed as C, 67.1; H, 8.1%; Calculated for C₇H₁₆O₂: C, 67.3; H, 8.1%. 2,4-Dinitrophenylhydrazone, recrystallized from alcohol, formed scarlet needles, m.p. 157°. Analysis: C, 54.1; H, 5.5; N, 15.1%; Calculated for C₁₇H₂₅O₆N₄: C, 54.2; H, 5.3; N, 14.9%.

The aldehydic ester (6 g) was stirred for 30 min at 70° in 150 ml of 4% aqueous sodium hydroxide solution with silver oxide which had been freshly prepared from 8 g of silver nitrate and sodium hydroxide solution. Separation from silver and acidification with sulfuric acid afforded dl-trans-chrysanthemum dicarboxylic acid which precipitated in the aqueous solution. Pure dl-trans-chrysanthemum dicarboxylic acid (3.5 g), melting at 200°, was obtained by recrystallization from aqueous ethyl alcohol using active carbon. Analysis: C, 60.8; H, 6.9%; Calculated for C₁₀H₁₄O₄: C, 60.6; H, 7.1%. By ozonolysis, dl-trans-caronic acid, m.p. 212°, was obtained. Some less pure dl-trans-chrysanthemum dicarboxylic acid (0.9 g) was obtained from the mother liquors by ether extraction.
3) \textit{d-trans-Chrysanthemum dicarboxylic acid (natural pyrethric acid)}

Methyl \textit{d-trans-chrysanthemate} (17 g), which was obtained from free acid\textsuperscript{6} and diazomethane, was refluxed for 1 hour in 50 ml of dioxane with 10 g of selenium dioxide. The subsequent procedures, which were identical with those described above, afforded 3.5 g of recovered starting ester boiling at 85-130°/10 mm and 10 g of aldehydic ester (III, R=CH\textsubscript{3}), \textit{n\textsubscript{D}}\textsuperscript{20} 1.4970 which is thought to be a mixture of two stereoisomers. Analysis: C, 67.1; H, 7.6\%; Calculated for C\textsubscript{11}H\textsubscript{16}O\textsubscript{3}: C, 67.3; H, 8.1\%. 2,4-Dinitrophenylhydrazone was produced as scarlet needles, and melted at 116° after recrystallization from alcohol. Analysis: C, 54.0; H, 5.6; N, 14.9\%; Calculated for C\textsubscript{17}H\textsubscript{20}O\textsubscript{6}N\textsubscript{4}: C, 54.2; H, 5.3; N, 14.9\%. The aldehydic ester (3 g) was oxidized in 100 ml of 6\% aqueous sodium hydroxide solution with silver oxide which was freshly prepared from 6 g of silver nitrate under the same conditions as described for the preparation of \textit{dl-trans-chrysanthemum dicarboxylic acid}. The pure \textit{d-trans-chrysanthemum dicarboxylic acid} was obtained as colorless needles (1.2 g) after recrystallization from water, m.p. 163-164°, \([\alpha]_{D}^{20}+72.0\), (c, 1.987 in methyl alcohol); It was found to be identical with the natural acid by mixed melting point determination.

Using free \textit{dl-trans-chrysanthemic acid}, selenium dioxide oxidation followed by silver oxide oxidation, was performed by the procedure already described, but the result was not so satisfactory. The yield of \textit{dl-trans-chrysanthemum dicarboxylic acid} was small (2 g of chrysanthemum dicarboxylic acid from 30 g of chrysanthemic acid).

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\textbf{References}