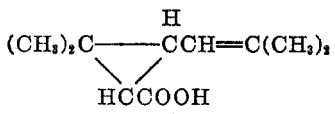
[CONTRIBUTION FROM THE UNITED STATES DEPARTMENT OF AGRICULTURE, BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, AGRICULTURAL RESEARCH ADMINISTRATION]

CONSTITUENTS OF PYRETHRUM FLOWERS. XXV. THE SYNTHESIS OF *d*-CINEROLONE, CINERIN I, AND ITS OPTICAL ISOMERS

F. B. LAFORGE AND NATHAN GREEN

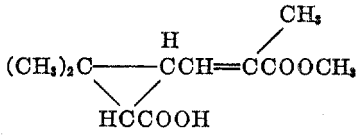
Received June 16, 1952

In 1924 Staudinger and Ruzicka (1) described the partial synthesis of the pyrethrins by esterification of the acid components with the natural keto alcohol "pyrethrolone." The structures of these acids had been established by them as I and II and the synthesis of *dl*-I had been realized.



Chrysanthemic acid

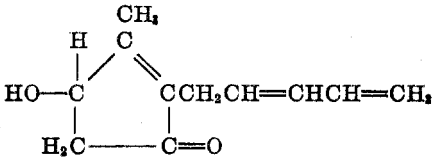
I



Chrysanthemum dicarboxylic acid monomethyl ester

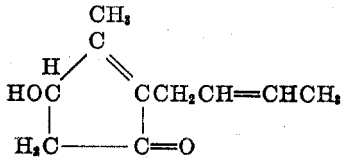
II

Their "pyrethrolone" has since been shown to be a mixture of two methylcyclopentenolones. The original name has been retained for the predominant one, and the minor constituent has been named "cinerolone" (2). Their revised structures are represented by III and IV.



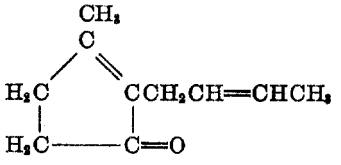
Pyrethrolone

III



Cinerolone

IV



Cinerone

V

Both compounds are optically active and dextrorotatory, and both contain unsaturated side chains which allow two geometrical isomeric forms. After the two-dimensional structures of pyrethrolone and cinerolone had been established, it was natural to attempt their synthesis. Cinerolone, having the less complicated structure, was given first consideration.

The general synthesis of 2,3-disubstituted cyclopentenolones (3) permitted the ready preparation of a number of compounds of this type, including one of structure IV. However, a comparison of several of its derivatives with those of *dl*-cinerolone from natural sources demonstrated their non-identity.

The same lack of agreement had been observed between corresponding derivatives of cinerone (desoxycinerolone) (V) and synthetic 2-(2-butenyl)-3-methyl-2-cyclopenten-1-one prepared with *trans*-crotyl chloride (4, 5), and Harper (4) had expressed the view that the discrepancy was due to *trans-cis* isomerism in the side chain and that the natural cinerolone had the *cis* configuration. The lack of identity between synthetic 4-hydroxy-2-(2-butenyl)-3-methyl cyclopentenone and *dl*-cinerolone was attributed to the same cause (3).

Crombie and Harper were the first to synthesize *dl-cis*-cinerolone, employing the general method referred to above (3) in the last steps. They (6, 7) employed two series of reactions in the preparation of the intermediates, and in this laboratory (8) still another order of reactions has been employed to the same end. The final product in each case has been found to be identical with *dl*-cinerolone from natural sources, and hence the *cis* configuration in the 2- (2- butenyl) side chain has been established.

It has been generally accepted that the *dl*-cinerolone obtained from pyrethrum flowers has resulted from partial racemization of the natural *d* compound (9) in the process of isolation. Therefore, to accomplish a total synthesis of cinerin I, it remained to effect the optical resolution of synthetic *dl*-cinerolone.

This article describes this accomplishment.

dl-Cinerolone prepared according to one of these methods (7 or 8) was acylated with *d-trans*-chrysanthemic acid chloride from the natural acid. From the mixture of *d*- and *l*-cinerolone *d-trans*-chrysanthemates, the semicarbazones were prepared in pyridine-ethanol in the usual manner (10). The semicarbazone of *d*-cinerolone *d-trans*-chrysanthemate alone crystallized from an ether-petroleum ether mixture, and from it *d*-cinerolone semicarbazone was obtained by ester exchange in methanol (11). By the same process the non-crystalline residue of cinerolone chrysanthemate semicarbazones, in which the semicarbazone of *l*-cinerolone *d-trans*-chrysanthemate strongly predominated, yielded by ester exchange optically impure *l*-cinerolone semicarbazone. The free keto alcohol obtained by acid hydrolysis, when esterified with *l-trans*-chrysanthemic acid, yielded *l*-cinerolone *l-trans*-chrysanthemate, which, although not optically pure, furnished the pure semicarbazone, identical, except for the opposite sign of its rotation, with the semicarbazone of the *d*-cinerolone *d-trans*-chrysanthemate. By ester exchange it yielded the semicarbazone of *l*-cinerolone, also identical, but for its opposite rotation, with the *d*-cinerolone semicarbazone.

Both semicarbazones were hydrolyzed to the respective optically active free *d*- and *l*-cinerolones.

By the synthesis of *d*-cinerolone the gap in the total synthesis of cinerin I is closed.

These two optical isomers have each been acylated with both the natural *d-trans*-chrysanthemic acid and its *l-trans* isomer, and thus all four possible

optical isomers of cinerin I have been made available for insecticidal comparison. The results of the biological tests will be published elsewhere; however, a brief table of the relative toxicities of these compounds to houseflies is given here.

It is interesting to note that the cinerolones and their semicarbazones rotate light in opposite directions. The cinerins rotate in the direction opposite to that of the cinerolone component or, in the case of the semicarbazones, in the direction of the cinerolone semicarbazone component, regardless of the sign of the acid component. Only those cinerins where both components have the same sign of rotation form crystalline semicarbazones.

TABLE I

TOXICITIES OF CINERINS TO HOUSEFLIES

ESTER		RELATIVE TOXICITY[a]
cis-cinerolone	*trans*-chrysanthemic acid	
d	*d*	0.67
l	*d*	1.2
d	*l*	.17
l	*l*	.12
Pyrethrin standards		1.0

[a] Campbell Turntable Method.

EXPERIMENTAL

dl-Cinerolone d-trans-chrysanthemate. Synthetic *dl*-cinerolone (7, 8), n_D^{25} 1.5155, (29.6 g., 0.178 mole), was esterified with 36.0 g. (0.192 mole) of *d-trans*-chrysanthemic acid chloride from the natural acid, in 200 ml. of benzene in the presence of 20 ml. (0.25 mole) of pyridine (10). The solvents were removed at 0.2 mm. Yield (undistilled) 59.4 g., n_D^{25} 1.5060.

Semicarbazone of d-cinerolone d-trans-chrysanthemate. From the 59.4 g. (0.19 mole) of the *dl*-cinerolone *d-trans*-chrysanthemate, the semicarbazone was prepared with 26 g. (0.23 mole) of semicarbazide hydrochloride in 30 ml. of water and 18 g. (0.23 mole) of pyridine in 100 ml. of ethanol. After 18 to 20 hours' standing, most of the solvent was removed in a vacuum and water was added, causing the separation of the semicarbazone, which was extracted with ether. After the excess of reagents had been removed by washing with water, dilute acid, and salt solution, the ether solution was dried and concentrated to about 150 ml. About two volumes of low-boiling petroleum ether was slowly added, with stirring, as crystallization of the semicarbazone of *d*-cinerolone *d-trans*-chrysanthemate proceeded. After standing a while in the refrigerator, the product was filtered off and washed with a 1:3 ether-petroleum ether mixture until free of the non-crystalline semicarbazone of *l*-cinerolone *d-trans*-chrysanthemate, which was obtained on evaporation of the solvents from the filtrate and washings as a resinous mass.

The yield of the crystalline product was 22.4 g. It has no sharp melting point, but softens to a glassy mass at about 75–80°. It may be recrystallized from methanol, but without much altering its melting point. $[\alpha]_D^{25}$ −143° (in methanol, *c*, 4.4).

Anal. Calc'd for $C_{21}H_{31}N_3O_3$: C, 67.53; H, 8.37.

Found: C, 67.41; H, 8.85.

The resinous impure semicarbazone of *l*-cinerolone *d-trans*-chrysanthemate, 46 g., was the source of the semicarbazone of *l*-cinerolone.

Semicarbazone of d-cinerolone. The semicarbazone of *d*-cinerolone *d-trans*-chrysanthem-

ate (12 g., 0.032 mole), was dissolved in 200 ml. of anhydrous methanol and cooled to about 0°, whereupon most of the material separated. Sodium (0.7 g., 0.03 mole), in a small quantity of methanol containing 0.5 ml. of water was cooled and added to the suspension of semicarbazone. After four days in the cold with frequent shaking, the separated material was filtered off and washed with methanol. The filtrate, on concentration and addition of water, yielded a further small quantity of crystalline material. The total quantity was recrystallized by dissolving in a boiling mixture of methanol and ethyl acetate, filtering from a small insoluble residue, m.p. 225°[1] (dimer semicarbazone) (12), and concentrating the solution. The yield of pure compound was 4.7 g., m.p. 208–210°, $[\alpha]_D^{25}$ −152° (in glacial acetic acid, *c*, 1.4).[2]

Anal. Calc'd for $C_{11}H_{17}N_3O_2$: C, 59.17; H, 7.68.
Found: C, 58.85; H, 7.82.

Anal. Calc'd for $C_{22}H_{30}N_6O_2$ (dimer semicarbazone): C, 64.36; H, 7.37.
Found: C, 64.44; H, 7.82.

Semicarbazone of l-(+dl)cinerolone. The 46 g. of resinous *l*-cinerolone *d-trans*-chrysanthemate from the first resolution was dissolved in 200 ml. of methanol in the cold, and to this was added a solution of 2.7 g. of sodium in a small quantity of the same solvent containing 1.7 ml. of water. The solution was allowed to stand at about 5° for four days, after which the separated optically impure semicarbazone was recrystallized as described for the preparation of *d*-cinerolone semicarbazone. The yield was 25.5 g.

l-(+dl)Cinerolone. The 25.5 g. of this semicarbazone was shaken with 140 g. of potassium hydrogen sulfate in 200 ml. of water and 200 ml. of ether for 60 hours, after which the free keto-alcohol was isolated and distilled. The yield was 13.2 g., b.p. 125°/0.2 mm., n_D^{25} 1.5136, $[\alpha]_D^{25}$ −4.1°.

Semicarbazone of l-cinerolone l-trans-chrysanthemate. The *l*-(+*dl*-)cinerolone (13. g., 0.08 mole), was esterified with 15.7 g. of *l-trans*-chrysanthemic acid chloride (0.085 mole) in 100 ml. of benzene and 7 ml. of pyridine. The yield of ester isolated in the usual manner and completely freed of solvent at 0.2 mm. was 24.6 g. (97%). It was converted to the semicarbazones as described above for the *d*-cinerolone *d-trans*-chrysanthemate derivative, the proportions being semicarbazide hydrochloride 12 g., pyridine 9.0 ml., and ethanol 180 ml. The semicarbazone of the *l*-cinerolone *l-trans*-chrysanthemate crystallized from the dried, concentrated ether solution on addition of petroleum ether. The yield was about 14.0 g., m.p. about 75° (but melt did not clear until about 100°), $[\alpha]_D^{25}$ +142° (in methanol, *c*, 1.67).

Anal. Calc'd for $C_{21}H_{31}N_3O_3$: C, 67.53; H, 8.37; N, 11.26.
Found: C, 67.88; H, 8.22; N, 11.72.

Semicarbazone of l-cinerolone. *l*-Cinerolone *l-trans*-chrysanthemate semicarbazone (14 g., 0.038 mole), in 200 ml. of anhydrous methanol was cooled and, after addition of a methanol solution of 0.8 g. of sodium and 0.5 ml. of water, was allowed to stand for five days at about 5° with occasional shaking. The semicarbazone of *l*-cinerolone was then isolated as described for the *d* isomer. The yield of recrystallized product was 5.5 g., m.p. 209–211°, $[\alpha]_D^{25}$ +143° (in glacial acetic acid, *c*, 1.46).

Anal. Calc'd for $C_{11}H_{17}N_3O_2$: N, 18.82. Found: N, 18.99.

d-Cinerolone. The semicarbazone, 4.7 g., was shaken for about 36 hours with 25 g. of potassium hydrogen sulfate in 50 ml. of water and 50 ml. of ether. The free keto-alcohol obtained on evaporation of the washed ether solution was distilled, b.p. 120°/ 0.35 mm., n_D^{25} 1.5161; $[\alpha]_D^{25}$ +10.5° (in ethanol[3], *c*, 11.7).

---

[1] All melting points are corrected.

[2] For *d*-cinerolone semicarbazone from a natural source, $[\alpha]_D^{25}$ −144° (in glacial acetic acid, *c*, 1.29).

[3] Reported for natural *d*-cinerolone, $[\alpha]_D^{25}$ +9.9° (in ethanol); *J. Org. Chem.*, **10**, 144 (1945).

Anal. Calc'd. for $C_{10}H_{14}O_2$: C, 72.24; H, 8.49.
Found: C, 71.84; H, 8.71.

l-Cinerolone. The semicarbazone, 5.5 g., was shaken with aqueous potassium hydrogen sulfate and ether for 40 hours and the keto-alcohol isolated as described for the *d*-isomer. B.p. about 119°/0.3 mm.; n_D^{25} 1.5157; $[\alpha]_D^{25}$ −10.7° (in ethanol, *c*, 8.9).

d-Cinerolone d-trans-chrysanthemate (identical with natural cinerin I). *d-trans*-Chrysanthemum acid chloride (3.55 g., 0.02 mole), in benzene solution was added to a benzene solution of 3.15 g. (0.019 mole) of *d*-cinerolone containing 2 ml. (0.025 mole) of pyridine. Total solvent about 60 ml. After about 18 hours the reaction product was isolated as described above for the *dl* compound. The yield of product freed of solvent at 0.2 mm. was 5.75 g. (96%), n_D^{25} 1.5052, $[\alpha]_D^{25}$ −15.5° (in kerosene, *c*, 16).[4]

Anal. Calc'd for $C_{20}H_{28}O_3$: C, 75.94; H, 8.91.
Found: C, 75.75; H, 9.05.

l-Cinerolone d-trans-chrysanthemate. This ester was prepared in the same manner. The proportions employed were *l*-cinerolone 2.55 g. (0.0154 mole), *d*-chrysanthemic acid chloride (3.0 g., 0.016 mole), and 1.2 ml. of pyridine (0.02 mole). The yield was 4.8 g., n_D^{25} 1.5047, $[\alpha]_D^{25}$ +16.4° (in kerosene, *c* 16).

Anal. Found: C, 75.09; H, 9.02.

d-Cinerolone l-trans-chrysanthemate. The proportions employed were *d*-cinerolone 1.5 g., *l-trans*-acid chloride 1.77 g., and pyridine 0.8 ml. The yield was 2.75 g., n_D^{25} 1.5048, $[\alpha]_D^{25}$ −16.3° (in kerosene, *c* 16).

Anal. Found: C, 75.31; H, 8.91.

l-Cinerolone l-trans-chrysanthemate. The same proportions of the reactants as above were employed in the preparation of this isomer $[\alpha]_D^{25}$ +12.2°.[5]

Anal. Found: C, 76.05; H, 8.99.

Resolution of dl-trans-chrysanthemic acid. The method employed to obtain the *l*-isomer follows closely the one described by Campbell and Harper (13). A solution of 65 g. of quinine in 90 ml. of 95% ethanol was mixed with 30 g. of *dl-trans*-chrysanthemic acid in 75 ml. of the same solvent. The next day the separated quinine salt was filtered off and washed with 75% ethanol. A dried sample melted at 157–160°. The product was recrystallized from 75% ethanol and when washed and dried melted at 162.5–163°. The yield was 25 g., $[\alpha]_D^{25}$ −122.5° (in ethanol, *c* 0.86). Only a few grams, which melted a few degrees lower, could be obtained from the mother liquor and washings. The acid liberated from the quinine salt with hydrochloric acid showed the following constants: b.p. 102–104°/0.5 mm., n_D^{25} 1.4760, $[\alpha]_D^{25}$ −19.9° (without solvent), −14.7° (in ethanol, *c* 4.1).

d-trans-Chrysanthemic acid (13) was obtained from natural pyrethrum.[6] It showed the following constants: b.p. 105°/0.5 mm., n_D^{25} 1.4762, $[\alpha]_D^{28}$ +19.1° (without solvent), +13.9° (in ethanol, *c* 3.15), +14.5° (in ethanol *c* 12.3).

The optically active chrysanthemic acids were recovered from the ester exchange operations as their methyl ester and the acids were used in subsequent acylations. No racemization was observed, $[\alpha]_D^{25}$ +19.5° (undiluted).

SUMMARY

The synthesis of cinerin I is completed by the resolution of synthetic 2-(*cis*-2-butenyl)-4-hydroxy-3-methylcyclopenten-1-one into its *d* and *l* isomeric forms,

[4] The rotations of the cinerin isomers were measured in purified kerosene in order to conserve material for biological tests made in the solvent.

[5] Possibly the *l*-cinerolone employed was not optically pure; $[\alpha]_D^{25}$ should be about +15°.

[6] We express our appreciation to Dr. Adolf Zimmerli, of Benzol Products Company, for the donation of *dl-trans*-chrysanthemic acid, and to Dr. H. Greenberg, of U. S. Industrial Chemicals Company, for *d-trans*-chrysanthemic acid.

the previous steps having already been accomplished. All four optical isomers of cinerin I have been synthesized by acylation of *d*- and *l*-cinerolone with the *d* and *l* isomeric forms of *trans*-chrysanthemic acid.

BELTSVILLE, MD.

REFERENCES

(1) STAUDINGER AND RUZICKA, *Helv. Chim. Acta*, **7**, 448 (1924).
(2) LAFORGE AND BARTHEL, *J. Org. Chem.*, **10**, 114 (1945); **12**, 199 (1947).
(3) SCHECHTER, GREEN, AND LAFORGE, *J. Am. Chem. Soc.*, **71**, 3165 (1949).
(4) HARPER, *J. Chem. Soc.*, 892 (1946).
(5) LAFORGE, GREEN, AND GERSDORFF, *J. Am. Chem. Soc.*, **70**, 3707 (1948).
(6) CROMBIE AND HARPER, *J. Chem. Soc.*, 1152 (1950).
(7) CROMBIE, EDGAR, HARPER, LOWE, AND THOMPSON, *J. Chem. Soc.*, 3552 (1950).
(8) SCHECHTER, GREEN, AND LAFORGE, *J. Am. Chem. Soc.*, **74**, 4902 (1952).
(9) HARPER, *Ann. Repts. on Progress Chem. (Chem. Soc. London)*, **45**, 162 (1948).
(10) HALLER AND LAFORGE, *J. Org. Chem.*, **1**, 38 (1936).
(11) STAUDINGER AND RUZICKA, *Helv. Chim. Acta*, **7**, 212 (1924).
(12) LAFORGE, GREEN, AND SCHECHTER, *J. Am. Chem. Soc.*, **74**, 5392 (1952).
(13) CAMPBELL AND HARPER, *J. Chem. Soc.*, 283 (1945).