

combined extracts from the main zone were evaporated to dryness and the cryptoxanthin was crystallized from benzene + methanol; yield 426 mg. After three recrystallizations, 300 mg. of analytically pure crystals were obtained:  $E_{1\text{ cm.}}^{\text{mol.}} = 14.0 \times 10^4$  at 451  $m\mu$  (in hexane);  $E_{1\text{ cm.}}^{\text{mol.}} = 13.55 \times 10^4$  at 464  $m\mu$  (in benzene).

**Neocryptoxanthin U.**—Thirty-six portions, each of 6 mg. of cryptoxanthin in 30 ml. of petroleum ether, were illuminated (in 50-ml. volumetric flasks) in the presence of 0.1 mg. of iodine with two 3500° Mazda lamps (length of tube, 120 cm.; distance, 60 cm.) for forty-five minutes. The combined solution was developed on eighteen calcium hydroxide-celite columns (26 × 5.8 cm.) with petroleum ether-8% acetone, for three hours. The main section of each chromatogram was composed of an intensely orange all-*trans* zone, above which the dull brownish-orange neo-U zone was located, while under the all-*trans* zone several yellow zones appeared (the latter constituted the starting material for the isolation of neocryptoxanthin A). The eighteen combined neo-U zones were rechromatographed on thirty-six columns. Although only a 2-3 mm. colorless interzone appeared between neo-U and marked amounts of the all-*trans* form, a clean isolation of the former was possible when the column was cut. In order to increase yield, the iodine catalysis was repeated twice by using the combined zones of unchanged all-*trans*-cryptoxanthin; finally, all neo-U fractions were combined, eluted with methanol, transferred into petroleum ether, washed fourteen times with doubly distilled water (in order to eliminate ash), completely evaporated, dissolved in a minimum amount of benzene and crystallized in a centrifuge tube by cautious addition of methanol at room temperature. After standing overnight in the cold room, the crystals were collected by centrifugation and were washed repeatedly with ice-cold methanol, the yield was 20 mg. For analysis the sample was recrystallized and dried in high vacuum at 56°; m. p. 95-96° (cor., Berl block, sealed capillary tube).

*Anal.* Calcd. for  $C_{40}H_{56}O$ : C, 86.87; H, 10.22. Found (after correction for 0.5% ash): C, 86.56; H, 10.66.

Neocryptoxanthin U forms long needles or, when slowly crystallized, characteristic plates (Fig. 4). It is consider-

ably more soluble in benzene or methanol than its all-*trans* isomer.

**Neocryptoxanthin A.**—The yellow zones mentioned, located under the all-*trans* form, were rechromatographed on three calcium hydroxide columns (26 × 5.8 cm.) and developed with 6% acetone-ligroin. The combined main zones constituted the starting material for the isolation of neo-A and the minor zone immediately below them that for neo-B. The neo-A zones appeared, after rechromatography, to be homogeneous. They were eluted with methanol, transferred into petroleum ether, washed, dried and evaporated to dryness *in vacuo* without delay at 22-24°. The oily residue was taken up in two drops of benzene and crystallized in a small centrifuge tube by cautious addition of methanol with stirring at room temperature (Fig. 5); yield, after washing with ice-cold methanol and recrystallization; 5 mg., m. p. 75-76° (cor.),  $E_{1\text{ cm.}}^{\text{mol.}}$  at  $\lambda_{\text{max.}} = 10.4 \times 10^4$  (established by weighing) and  $10.8 \times 10^4$  (indirect determination based on iodine "equilibrium" data). For analysis the sample was dried in high vacuum at room temperature for three hours.

*Anal.* Calcd. for  $C_{40}H_{56}O$ : C, 86.87; H, 10.22. Found (after correction for 0.55% ash): C, 87.68; H, 10.62.

Neocryptoxanthin A is more soluble in benzene, petroleum ether or methanol than neo-U or the all-*trans* form.

**Neocryptoxanthin B.**—The total amount of this isomer (see above) was about 2 mg. This isomer is best chromatographed by using petroleum ether + 5% acetone on a calcium hydroxide-celite column. Although neo-B has not been crystallized, quantitative extinction curves are given in Fig. 3 on the basis of concentrations as established by iodine catalysis, as we believe with an accuracy of  $\approx 5\%$ .

## Summary

Three *cis-trans* isomers of cryptoxanthin  $C_{40}H_{56}OH$ , are described and their relative stabilities as well as spectral characteristics are discussed.

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## 2,5-Dimethylcyclopentanecarboxylic Acids

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The stereoisomeric 2,5-dimethylcyclopentanecarboxylic and 2,6-dimethylcyclohexanecarboxylic acids offer an opportunity for the study of steric influences on the relative reactivity of a series of closely related compounds. A comparison of the corresponding cyclopentane and cyclohexane stereoisomers is of special interest because differences should arise largely from the non-planar nature of the latter. This paper describes the synthesis of the cyclopentane compounds and qualitative experiments on their reactivity.

2,5-Dimethylcyclopentanecarboxylic acid exists in four stereoisomeric forms. Two of these, Ia and Ib, are enantiomers while II and III are meso

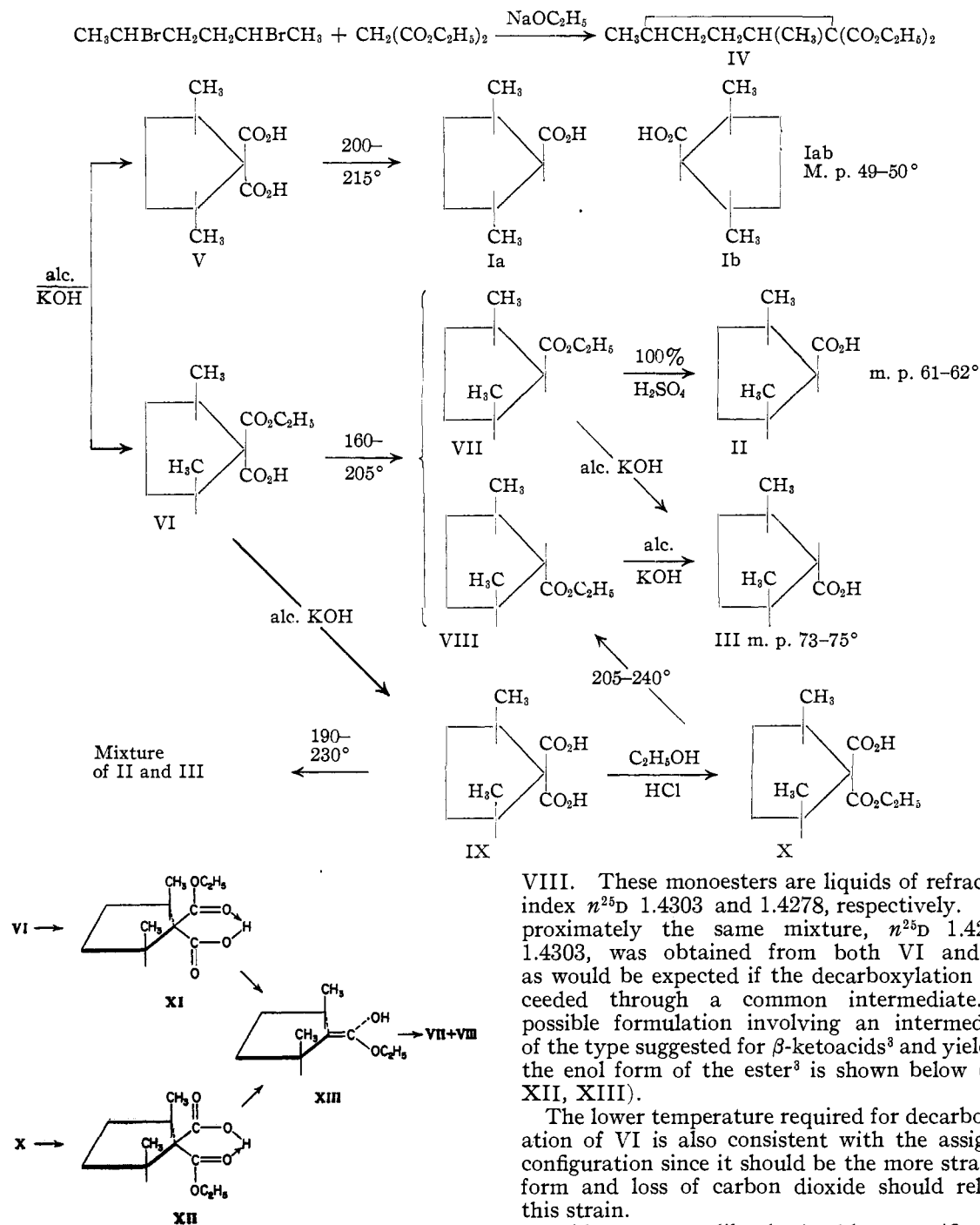
forms. The racemic modification and one pure meso form were prepared by Wislicenus and co-workers<sup>2</sup> who also isolated in very poor yield a low-melting acid which we have shown to be an eutectic mixture of the two meso forms. Their synthesis was used in the present work with modifications which permitted isolation of the second meso form. This synthesis is represented by the equations shown.

The diacid m. p. 201-202° (decarb.) was assigned configuration V by Wislicenus<sup>2</sup> because it gave a single monocarboxylic acid, Iab, m. p. 49-50° on heating, whereas IX, m. p. 190-194° (decarb.), gave a mixture of II and III. We have confirmed this configuration by partial resolution of Iab and by preparing from IX a second acid

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(1) An abstract of part of a thesis submitted by Warner H. Florsheim in partial fulfillment of the requirements for the Ph.D. degree in chemistry, May, 1948. A preliminary report of this work was presented before the Organic Division at the 112th meeting of the American Chemical Society, New York City, September, 1947.

(2) (a) Wislicenus, Peters, Schramm and Mohr, *Ber.*, **34**, 2565 (1901); (b) Peters, Inaugural Dissertation, Leipzig, 1892; (c) Schramm, Inaugural Dissertation, Leipzig, 1895; (d) Mohr, Inaugural Dissertation, Leipzig, 1901.



ester, X, m. p. 88.5–90°, different from the acid ester VI, m. p. 79.5–80.5°, which was a product of the partial saponification of the diester mixture IV. The assignment of configurations to VI and X was made on the hypothesis that the less hindered carboxyl group of IX would esterify first, and the corresponding carboxyl of the diester would hydrolyze first.

Both VI and X were decarboxylated by heat to a mixture of the two meso monoesters VII and

VIII. These monoesters are liquids of refractive index  $n_D^{25}$  1.4303 and 1.4278, respectively. Approximately the same mixture,  $n_D^{25}$  1.4297–1.4303, was obtained from both VI and X, as would be expected if the decarboxylation proceeded through a common intermediate. A possible formulation involving an intermediate of the type suggested for  $\beta$ -ketoacids<sup>3</sup> and yielding the enol form of the ester<sup>3</sup> is shown below (XI, XII, XIII).

The lower temperature required for decarboxylation of VI is also consistent with the assigned configuration since it should be the more strained form and loss of carbon dioxide should relieve this strain.

Acid III was readily obtained by saponification of VII, VIII or a mixture of these with alcoholic potassium hydroxide because an inversion of II or its ester to III occurred during the reaction. Its stereoisomer II was far more difficult to get. Wislicenus<sup>2</sup> isolated an impure acid m. p. 26–30°, in very low yield from the mixture of II and III produced by decarboxylation of the diacid IX.

(3) Westheimer and Jones, *THIS JOURNAL*, **63**, 3283 (1941); Pedersen, *J. Phys. Chem.*, **38**, 559 (1934); Schenkel and Schenkel-Rudin, *Helv. Chim. Acta*, **31**, 514 (1948).

We have shown that this impure acid was a mixture of II and III of approximately eutectic composition and have prepared a mixture of comparable melting point in excellent yield by dissolving the mixture of monoesters VII and VIII in cold, 100% sulfuric acid and pouring the mixture onto ice. The crude acids were separated from unchanged ester by distillation under reduced pressure; some inversion of II to III occurred unless a clean flask free from all traces of soap or detergent was used. It was very difficult to isolate pure II, m. p. 61–62°, from this mixture as is indicated in the experimental part, but this was accomplished through the benzylammonium salt.

The assignment of the *meso cis* configuration II to the acid of melting point 62–63° rests on the following evidence: (a) it esterifies much more slowly than III<sup>4</sup>; (b) it is the principal product of the catalytic hydrogenation of 2,5-dimethyl-1-cyclopentenecarboxylic acid with Adams catalyst in acid solution, which accords with predictions for this type of hydrogenation<sup>5</sup>; (c) it is isomerized to III in excellent yield by hydrochloric acid in acetic acid at 180°; *cis*-2,2,6-trimethylcyclohexanecarboxylic acid is isomerized similarly to the *trans* isomers.<sup>6</sup>

The pure ethyl esters VII and VIII were prepared from the acids by means of diazoethane. The more hindered compound, VII, was completely hydrolyzed in ten minutes at 25° by 100% sulfuric acid to II; the stereoisomer VIII was hydrolyzed in only poor yield under similar conditions to give III. The corresponding methyl esters were prepared similarly with diazomethane; they behaved in the same manner. The methyl ester of the racemate, Iab, was also prepared; it was hydrolyzed to an intermediate extent by the 100% sulfuric acid treatment. The mixture of VII and VIII obtained from VI was isomerized cleanly to VIII by refluxing with an alcoholic solution of sodium ethylate. The composition of the mixture was not known with accuracy because the spread in refractive indices was not great enough for analysis with any precision. Moreover, the ester mixture composition varied as indicated by the variable refractive index  $n_D^{25}$  1.4297–1.4300 and as would be expected from the case of conversion of VII to VIII. However, a rough calculation shows that VII constituted 75 to 85% of the mixture. This suggests that the proton adds preferentially to the less hindered side of XIII. Since the conditions of the decarboxylation were not such as to permit rearrangement of the *cis meso* ester VII to VIII, it is not surprising that this less stable isomer was obtained in greater amount.

The acid chloride of II was also very readily isomerized, since it gave the same amide as was

obtained from III even when the acid chloride was formed with thionyl chloride in cold pyridine. This amide was hydrolyzed by 100% phosphoric acid to III<sup>7</sup>; the new *cis* acid, II, was stable under these conditions. A second amide, presumably of *meso cis* configuration, was obtained in very low yields by carrying out the preparation of the acid chloride at even lower temperatures.

It was possible to interrelate the racemic and *meso* series by converting the racemic acid, Iab, through the  $\alpha$ -bromoacid to 2,5-dimethyl-1-cyclopentenecarboxylic acid. Hydrogenation of the latter gave a mixture of isomers from which II was isolated in the form of its benzylamine salt or its *p*-phenylphenacyl ester.

### Experimental

All melting points are corrected.

**2,5-Dibromohexane.**—Commercial acetylacetone was hydrogenated over copper chromite<sup>8</sup> to give 2,5-hexanediol, b. p. 133–135° (25 mm.) in 70–83% yield. The pure diol is extremely viscous even at elevated temperature, but the presence of a few per cent. of acetylacetone causes a marked decrease in viscosity. The diol was converted in 70% yield to 2,5-dibromohexane, b. p. 104–106° (25 mm.), with hydrobromic acid saturated with hydrogen bromide at –3°.<sup>9</sup> The separation of the dibromo compound into its stereoisomeric forms<sup>2a,d,10</sup> was not necessary in this work.

**2,5-Dimethyl-1,1-dicarbethoxycyclopentane.**—To a cooled solution of 107 g. (4.6 g. a.) of sodium in 2 l. of absolute alcohol was added 362 g. (2.3 m.) of diethyl malonate and, after the solution had cooled to 40°, 567 g. (2.3 m.) of 2,5-dibromohexane in one portion. The suspension was stirred without heating for sixteen hours and refluxed for two hours; one liter of alcohol was distilled off rapidly, one liter of water added, the pH adjusted to about 5 by adding concd. hydrochloric acid, and the residual alcohol removed. The residue was extracted twice with ether and the extracts dried, concentrated and distilled. A 300 ml. forerun was collected below 130° (35 mm.) and the product, 242 g., was collected at 130–138° (35 mm.). The forerun was stirred with 2 l. of 10% sodium hydroxide for two hours and extracted with ether; the extract was dried, concentrated and distilled to give an additional 68 g., b. p. 130–138° (35 mm.). The total yield was 55%. Redistillation gave a purer product but the losses involved more than offset the slightly increased yield in the next step. Attempts to improve the yield by adding the sodium ethylate in two portions were unsuccessful.

**Partial Hydrolysis of the Diester Mixture.**—This step in the synthesis gave somewhat erratic results. The procedure of Schramm<sup>2c</sup> was not available until this portion of the work was completed; the procedure which we adopted after many trials is nearly identical with his. To a solution of 55 g. of potassium hydroxide in 300 ml. of 95% alcohol was added 50 g. of the diester. The mixture was refluxed on a steam-bath for one hour and about 200 ml. of alcohol distilled off in forty minutes. The solution was diluted with 700 ml. of water and extracted once with chloroform. The aqueous phase was acidified and extracted with ether; the ether was removed from the extract and the oily residue triturated with petroleum ether (Skellysolve F, b. p. 30–60°) until crystallization was complete. The yield of crude, racemic, 2,5-dimethylcyclopentanedicarboxylic acid, V was 5–17.5 g. (13–46%). After two recrystallizations from water it melted at 201–

(4) Jacobs and Florsheim, *THIS JOURNAL*, **72**, 261 (1950).

(5) Linstead, Doering, Davis, Levine and Whetstone, *ibid.*, **64**, 1985 (1942).

(6) Shive, Horeczy, Wash and Lochte, *ibid.*, **64**, 385 (1942).

(7) Berger and Olivier, *Rec. trav. chim.*, **46**, 600 (1927).

(8) Adkins and Connor, *THIS JOURNAL*, **53**, 1091 (1931); Hill and Adkins, *ibid.*, **60**, 1033 (1938).

(9) Duden and Lemme, *Ber.*, **35**, 1335 (1902).

(10) Kornblum and Eicher, *THIS JOURNAL*, **71**, 2259 (1949).

202° with brisk decarboxylation. The m. p. is dependent on the rate of heating.

*Anal.* Calcd. for  $C_9H_{14}O_4$ : C, 58.05; H, 7.58. Found: C, 57.92; H, 7.64.

The petroleum ether was removed from the filtrates and the oily layer recrystallized from aqueous formic acid (about 80%) to give 10–34% yield of crystalline material melting about 75°. After several recrystallizations from aqueous formic acid, the meso acid ester VI was obtained as shiny platelets, m. p. 79–80.5°. It was also recrystallized from petroleum ether which gave large rectangular prisms of the same m. p.

*Anal.* Calcd. for  $C_{11}H_{18}O_4$ : C, 61.66; H, 8.47. Found: C, 61.33; H, 8.67.

**Meso Dicarboxylic Acid IX.**—Acid ester VI was refluxed for forty-eight hours with a 3-fold excess of saturated methanolic potassium hydroxide and the diacid IX isolated in 76% yield by the same procedure as was used for V. After recrystallization from water, stubby needles, m. p. 190–194° (decarb.), were obtained.

*Anal.* Calcd. for  $C_9H_{14}O_4$ : C, 58.05; H, 7.58. Found: C, 57.56; H, 7.51.

The petroleum ether filtrate yielded 21% of somewhat impure III.

Decarboxylation of IX at 190–230° gave a mixture of II and III in proportions depending upon the previous treatment of the reaction vessel. If this was washed with soap and rinsed with distilled water and acetone, the decarboxylation gave a crude product, m. p. 62–68° corresponding to 85% *trans meso* acid III. This with diazoethane gave an ethyl ester which was purified by fractionation at reduced pressure, b. p. 86° (35 mm.),  $n_D^{20}$  1.4281. If the decarboxylation tube was washed with hot sulfuric acid, and rinsed repeatedly with water and acetone, the product, m. p. 30–37°, was about 70% *cis meso* acid II.

**Racemic 2,5-Dimethylcyclopentanecarboxylic Acid, Iab, and Its Derivatives.**—Diacid V was maintained at 200–215° for one hour and the amber residue was recrystallized from 80% formic acid to give Iab, m. p. 47.5–49° in almost quantitative yield. Diazomethane was used to prepare the methyl ester, b. p. 63° (15 mm.),  $n_D^{20}$  1.4327, which had a strong camphor-like odor.

*Anal.* Calcd. for  $C_9H_{16}O_2$ : C, 69.19; H, 10.33. Found: C, 69.35; H, 10.53.

Hydrolysis of this ester with 100% sulfuric acid as described for the ester of II gave 20% of Iab, m. p. 43–47°; a fair recovery of starting ester could be effected.

The *p*-phenylphenacyl ester was prepared as usual,<sup>11</sup> m. p. 70–71.5° from alcohol.

*Anal.* Calcd. for  $C_{22}H_{24}O_3$ : C, 78.54; H, 7.19. Found: C, 78.48; H, 7.29.

The acid was refluxed for three hours with a large excess of pure thionyl chloride to give the acid chloride, b. p. 70° (15 mm.), which reacted slowly with water. No precipitate formed when the acid was added to concd. ammonium hydroxide, but the amide was isolated by chloroform extraction and obtained in fine needles, m. p. 172.5–174° after two recrystallizations from acetonitrile; it sublimed slowly at 100°.

*Anal.* Calcd. for  $C_8H_{15}NO$ : C, 68.04; H, 10.71. Found: C, 67.99; H, 10.61.

The benzylamine salt of the acid was prepared by adding a slight excess of benzylamine to a solution of the acid in petroleum ether (b. p. 30–60°). The precipitate was recrystallized from 85–100° ligroin, m. p. 102–104.5°, yield 95%.

*Anal.* Calcd. for  $C_{15}H_{23}O_2N$ : C, 72.25; H, 9.30. Found: C, 72.25; H, 9.25.

Resolution of Iab through the quinine or brucine salt failed because these salts crystallized poorly from non-aqueous solvents and were hydrolyzed by water. A partial resolution was accomplished through the cinchonine

metho salt<sup>12</sup> which was recrystallized from absolute alcohol and ether. The acid recovered from the least soluble portion had m. p. 46–59°;  $\alpha$   $-1.41^\circ$  (4 dm. tube);  $\epsilon$ , 3.9 g./100 ml. in acetone,  $\alpha_D^{20}$   $-9.0^\circ$ .

**Acid ester X** was obtained in 84% yield by passing dry hydrogen chloride for seven hours into a solution of 6.7 g. of IX in 125 ml. of absolute alcohol, refluxing the resultant clear solution overnight, and pouring the reaction mixture into water. The crude ester was recrystallized once from 80% formic acid in short, stubby needles, m. p. 88.5–90.0°, 85% recovery. This compound depressed the m. p. of VI.

*Anal.* Calcd. for  $C_{11}H_{18}O_4$ : C, 61.66; H, 8.47. Found: C, 61.13; H, 8.55.

**Decarboxylation of the Meso Acid Esters VI and X.**—VI, m. p. 78–80°, was heated in an acid-washed test-tube as described above and began to evolve carbon dioxide at 160°. The reaction was essentially complete at 205°. The monoester mixture, VII and VIII, was obtained in 90–97% yield, b. p. 87–88° (35 mm.), 70–71° (15 mm.), 185–186° (760 mm.),  $n_D^{20}$  1.4300  $\pm$  0.0003. X did not begin to lose carbon dioxide until the temperature reached 205°, and 230–240° was required for a convenient rate. The product was the same as from VI ( $n_D^{20}$  1.4298) and the yield was 86%.

**meso trans Acid III.**—The monoester mixture was refluxed with an excess of saturated methanolic potassium hydroxide for two hours, the methanol removed and the cooled residue acidified to give an almost quantitative yield of III, m. p. 69–73°. Crystallization from 80% formic acid gave shiny scales, m. p. 72.5–75.5°, with excellent recovery.

*Anal.* Calcd. for  $C_8H_{14}O_2$ : C, 67.57; H, 9.92. Found: C, 67.68; H, 9.99.

III and diazomethane gave the methyl ester, b. p. 62° (15 mm.),  $n_D^{20}$  1.4291, odor intermediate between camphor and cedar.

*Anal.* Calcd. for  $C_9H_{16}O_2$ : C, 69.19; H, 10.33. Found: C, 69.15; H, 10.53.

III and diazoethane gave the ethyl ester, b. p. 81.5–83° (26 mm.),  $n_D^{20}$  1.4278.

The *p*-phenylphenacyl ester was prepared as usual,<sup>11</sup> m. p. 71.4–71.6°.

*Anal.* Calcd. for  $C_{22}H_{24}O_3$ : C, 78.54; H, 7.19. Found: C, 78.60; H, 7.36.

The benzylamine salt crystallized from 85–100° ligroin in long, silky needles, m. p. 109–110.5°.

*Anal.* Calcd. for  $C_{15}H_{23}O_2N$ : C, 72.25; H, 9.30; N, 5.62. Found: C, 72.16; H, 9.31; N, 6.01 (Dumas).

The amide, prepared using thionyl chloride but without isolating the acid chloride, was only slightly soluble in cold concd. ammonium hydroxide. Crystallization from acetonitrile gave fine needles, m. p. 170–172°, which depressed the m. p. of the racemic amide of Iab.

*Anal.* Calcd. for  $C_8H_{15}ON$ : C, 68.04; H, 10.71. Found: C, 68.20; H, 10.97.

The amide could not be hydrolyzed with nitrous acid in concd. sulfuric acid but gave a low yield of III when heated in a sealed tube at 190–220° for one hour with 100% phosphoric acid.<sup>7</sup> The amide was recovered unchanged from 100% phosphoric acid at lower temperatures. The m. p. of III was unaffected and that of II only slightly lowered by similar treatment with this reagent.

**meso cis Acid II.**—A 14-g. sample of the monoester mixture,  $n_D^{20}$  1.4300, was dissolved in 100 ml. of sulfuric acid of m. p. 9° (99.7%  $H_2SO_4$  and 0.3%  $H_2O$ )<sup>13</sup> at an initial temperature of 30°. The solution warmed to 40° rapidly and after standing for five minutes it was poured onto ice. An oily solid which contained some unhydrolyzed ester separated. It was purified by extraction into sodium bicarbonate solution or by distillation, b. p. 115–116° (15 mm.), from a distilling apparatus that had been washed

(12) Major and Finkelstein, *ibid.*, **68**, 1368 (1941).

(13) Hammet and Deyrup, *ibid.*, **55**, 1900 (1933).

(11) Drake and Bronitsky, *This Journal*, **58**, 3715 (1930).

carefully with acid, water and acetone to retard isomerization. The product was a mixture of II and III of m. p. 25–30°, yield 70–80%.

The isolation of pure II from this mixture was tedious and difficult. A mixture of benzylamine salts, m. p. between 95° and 115°, usually with a range of about 5°, was prepared in almost quantitative yield as described under the racemic acid and fractionally crystallized from carbon tetrachloride until the m. p. was above 122°. A final recrystallization from 85–100° ligroin gave well-formed needles, m. p. 124–125°, which depressed the melting points of the isomeric salts.

*Anal.* Calcd. for  $C_{15}H_{23}O_2N$ : C, 72.25; H, 9.30. Found: C, 72.42; H, 9.34.

If the original m. p. of the mixture of salts was 105–115°, the yield of pure salt was about 20%; if lower, it was very difficult to isolate any of the pure salt.

The pure salt was decomposed by brief shaking with a two-fold excess of dilute sulfuric acid. The crude acid, m. p. 60.5–62°, was recrystallized from acetonitrile and water which gave poorly formed crystals, m. p. 61–61.5°.

*Anal.* Calcd. for  $C_8H_{14}O_2$ : C, 67.57; H, 9.92. Found: C, 67.57; H, 10.04.

A m. p.-composition diagram was prepared for mixtures of this acid with the *meso trans* isomer, III, from the following data which record the % of the *trans* isomer III and the upper limit of the melting range of the mixtures:

% of III	0	4.8	8.4	11.5	16.3	21.2
M. p., °C.	61.5	59.5	57.5	55.1	51.8	45.3
% of III	25.0	34.0	37.5	43.8	51.4	58.6
M. p., °C.	42.6	33.0	28.6	32.0	40.6	46.3
					75.5	

The  $\beta$ -phenylethylamine salts could be used instead of the benzylamine salts but offered no advantage.

A mixture of *p*-phenylphenacyl esters was prepared from the hydrolysis mixture of II and III by the usual procedure.<sup>11</sup> Fractional crystallization from alcohol gave the pure ester of II, m. p. 70–70.5°, in about 40% yield, but no procedure was found for hydrolyzing the ester to give pure II.

*Anal.* Calcd. for  $C_{22}H_{24}O_3$ : C, 78.54; H, 7.19. Found: C, 78.50; H, 7.32.

Mixtures of the *p*-phenylphenacyl esters of II and III showed m. p. lowering, with a eutectic at 33% of the *meso trans* isomer, m. p. 61–61.5°. These esters also depressed the m. p. of this derivative of the racemic acid, Iab.

Attempts to separate the mixture of II and III by chromatographic adsorption on acid washed alumina columns made fluorescent with zinc sulfide<sup>14</sup> or by partition chromatography<sup>15</sup> were unsuccessful.

**Isomerization of II to III.**<sup>6</sup>—Two grams of the eutectic mixture of II and III was heated with 5 ml. of glacial acetic acid and 1 ml. of concd. hydrochloric acid for twenty-six hours at 180° in a sealed tube. The product crystallized at once when the reaction mixture was poured on ice; one crystallization from 80% formic acid gave pure III, m. p. 72–74.5°. A sample of II heated with 90% formic acid at 100° for sixteen hours was unchanged.

**Inversion of the mixture of VII and VIII,**  $n_D^{25}$  1.4300, was realized by refluxing 10 g. of the mixture with 30 ml. of anhydrous ethanol containing 0.02 mole of sodium ethoxide for three hours. The product was thrown into water, taken up in ether, washed four times with saturated ammonium chloride solution and distilled, b. p. 81.5–83° (26 mm.),  $n_D^{25}$  1.4278, yield 75%. Its behavior toward 100% sulfuric acid or alcoholic potassium hydroxide was the same as pure VIII.

**Derivatives of II.**—The ethyl ester VII was prepared by allowing 2 g. of pure II to stand for one hour with the diazoethane prepared from 30 g. of *N*-nitrosoethylurea.<sup>16</sup>

The product was distilled through a short column which had been rinsed with nitric acid, water and acetone. The yield was 1 g., b. p. 87–89° (35 mm.),  $n_D^{25}$  1.4303. This ester was hydrolyzed for ten minutes with 10 ml. of 100% sulfuric acid at 25° and the reaction mixture poured onto ice. The acid was extracted with ether, washed with water and saturated ammonium chloride solution and concentrated in a stream of air. The acid was dried and had a m. p. of 57–61°.

The methyl ester was prepared with diazomethane. It was purified like the ethyl ester, b. p. 60–60.5° (11 mm.),  $n_D^{25}$  1.4321.

The *p*-phenylphenacyl ester was prepared as usual<sup>11</sup> from pure II; it melted at 70–70.5° and showed no m. p. depression with the product isolated from the eutectic mixture of II and III.

Attempts to prepare the amide of II by the method used for III gave only the amide of III, but a new amide presumably corresponding to II in configuration was obtained by dissolving 3 ml. of pure thionyl chloride in 12 ml. of dry pyridine at –60° and adding 0.55 g. of II in 3 ml. of pyridine at the same temperature. The solution gradually darkened on slowly warming to 5° and standing for two hours. The brown solution was added to 500 ml. of concd. ammonium hydroxide at –20°, allowed to warm to room temperature, extracted with chloroform and the latter washed with water. Evaporation of the chloroform at 15 mm. gave a dark oil which crystallized partially on standing. The solid was centrifuged out, crystallized from acetonitrile and water, and sublimed at 100° (5 mm.) as a white powder, m. p. 129–131°, that depressed the m. p. of III amide.

*Anal.* Calcd. for  $C_8H_{15}ON$ : C, 68.04; H, 10.71. Found: C, 68.08; H, 10.38.

The benzimidazole prepared from II by heating with *o*-phenylenediamine<sup>17</sup> gave the same m. p., 93–95°, as the benzimidazole from III and gave no m. p. depression with it.

*Anal.* Calcd. for  $C_{14}H_{19}N_2$ : C, 78.09; H, 8.89. Found: C, 78.50; H, 8.83.

**Interconversion of the *dl*- and *meso*-Acids.**<sup>18</sup>—To 27.5 g. of Iab was added 46 g. of phosphorus pentachloride with stirring. After the evolution of hydrogen chloride ceased, the liquid residue was heated at 100° with 9.1 g. of bromine for three hours in a sealed tube. The product was poured into water and washed by decantation with water and sodium bicarbonate solution. An amber oil remained which could not be distilled at 15 mm. without excessive decomposition. The same product resulted when 8.5 g. of pure *dl*-2,5-dimethylcyclopentanecarboxylic acid chloride, b. p. 70° (15 mm.), prepared by using thionyl chloride, was treated with 7.6 g. of bromine at 100° for forty minutes.

The crude product failed to react with aqueous potassium carbonate at 100° but reacted vigorously with methanolic potassium hydroxide to give an ester and an inorganic precipitate containing both bromide and chloride ions. The ester was hydrolyzed and dehydrohalogenated to 2,5-dimethyl-1-cyclopentanecarboxylic acid by long refluxing with saturated ethanolic potassium hydroxide. It was somewhat better to hydrolyze the acid halide by shaking it in dioxane solution with saturated aqueous potassium hydroxide for ten minutes or by refluxing it with 98% formic acid.<sup>18</sup> This gave a crude *a*-halo-acid, m. p. between 60° and 90° in 60 to 70% yield. The crude acid was refluxed for three hours with excess saturated ethanolic potassium hydroxide to give 2,5-dimethyl-1-cyclopentanecarboxylic acid in almost quantitative yield. The acid was recrystallized three times from petroleum ether, m. p. 82.5–83°.

*Anal.* Calcd. for  $C_8H_{12}O_2$ : C, 68.54; H, 8.63. Found: C, 68.88; H, 8.66.

(17) Brown and Campbell, *J. Chem. Soc.*, 1699 (1937).

(14) Sease, *THIS JOURNAL*, **69**, 2242 (1947).

(15) Martin and Syngé, *Biochem. J.*, **35**, 1358 (1941).

(16) From ethylamine hydrochloride and urea, "Org. Syntheses," Coll. Vol. II, 461 (1943); Arndt and Scholz, *Angew. Chem.*, **46**, 47 (1933).

(18) The procedure is similar to that used by Hufferd and Noyes, *THIS JOURNAL*, **43**, 925 (1921), for the preparation of 2,6-dimethyl-1-cyclohexanecarboxylic acid.

The unsaturated acid was hydrogenated with Adams catalyst in glacial acetic acid containing 1% of concd. hydrochloric acid. The theoretical volume of hydrogen was absorbed rapidly. Filtration and evaporation of the solvent at 30 mm. gave a liquid, m. p. 10°, which was converted to a mixture of benzylamine salts, m. p. 92–94°. Repeated fractional crystallization from ligroin (b. p. 85–100°) gave the pure benzylamine salt of the *cis meso* acid II in 15% yield. The *cis meso* acid was also isolated as the *p*-phenylphenacyl ester, but the yield was lower.

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### Summary

2,5-Dimethylcyclopentanecarboxylic acid exists as four stereoisomers: *cis meso*, *trans meso* and two optically active forms. All of these were obtained from the stereoisomeric 2,5-dimethylcyclopentane-1,1-dicarboxylic acids or esters

which were readily synthesized from malonic ester and 2,5-dibromohexane. The racemic form was identified by resolution. The *cis meso* configuration was assigned to that isomer which (a) esterified most slowly, (b) was obtained by hydrogenation over platinum in acid solution from 2,5-dimethyl-1-cyclopentencarboxylic acid, and (c) could be isomerized by acid to a more stable isomer (the *trans meso*). The ester of the *cis meso* acid was hydrolyzed without isomerization by 100% sulfuric acid, but was completely isomerized to *trans meso* ester by sodium ethylate; on hydrolysis with alcoholic potassium hydroxide it gave only *trans meso* acid. The *cis meso* acid chloride was also isomerized readily. The racemic isomer was converted through the  $\alpha$ -bromo acid to 2,5-dimethyl-1-cyclopentencarboxylic acid.

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## Hindrance in the Stereoisomeric 2,5-Dimethylcyclopentanecarboxylic Acids and their Esters

BY THOMAS L. JACOBS\* AND WARNER H. FLORSHEIM<sup>1</sup>

The stereoisomeric 2,5-dimethylcyclopentanecarboxylic acids offer an excellent opportunity for the study of steric hindrance because the polar influences of the substituents should be constant in reactions involving only the carboxyl group. Models show that the methyl groups interfere with the carboxyl group to different extents in the different isomers and indicate that the *cis meso* acid should be the most hindered. This also seems to be true when an attempt is made to approximate with models the transition states of the esterification and hydrolysis reactions in which hindrance would be expected.

The esterification reaction under the conditions of the Fischer-Speier method has been widely used for investigations of steric hindrance and appears to be especially suitable for the purpose.<sup>2</sup> Fewer studies of the reverse reaction, acid-catalyzed ester hydrolysis, have been made, but it is also useful. Kinetic studies were made of the stereoisomers in both of these reactions and as an example of a reaction in which hindrance would not be expected, the investigation was extended to the formation of phenacyl esters from phenacyl bromide and the sodium salts of the acids. The dissociation constants of the acids were also determined.

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(1) An abstract of part of a thesis submitted by Warner H. Florsheim in partial fulfillment of the requirements for the Ph.D. degree in chemistry, May, 1948. A preliminary report of this work was presented before the Organic Division at the 112th meeting of the American Chemical Society, New York City, September, 1947.

(2) The suitability of this reaction has been discussed by Hughes, *Quart. Rev.*, **2**, 107 (1948), who also gives many of the references to earlier work.

### Experimental

The preparation of the 2,5-dimethylcyclopentanecarboxylic acids and their methyl esters was described in the preceding article.<sup>3</sup> Trimethylacetic acid was prepared from *i*-butylmagnesium chloride and carbon dioxide.<sup>4</sup> It was carefully fractionated and the center cut, b. p. 162°, m. p. 34–35°, was used. Some of the pure acid was converted by using diazomethane into methyl trimethylacetate, b. p. 99.5–100°. Ethyl butyrate (Eastman Kodak Co. white label grade) was redistilled, b. p. 117–118°. Phenacyl bromide (Eastman white label grade) was recrystallized four times from ligroin, b. p. 85–100°; the m. p. of the sample used was 57–58°.

**Acid-Catalyzed Esterification.**—Anhydrous methanol<sup>5</sup> was fractionated carefully and made approximately 0.06 *N* in hydrogen chloride using the pure, dry gas.

The organic acids were weighed into 50-ml. volumetric flasks and placed in a thermostat which was maintained at 40.00 ± 0.01°. The methanol solution at the same temperature was then added and after thorough mixing the reaction was followed by titrating aliquots with standard sodium hydroxide using phenolphthalein as the indicator.

The reaction of methanol and hydrogen chloride, which decreases the catalyst concentration, was a significant factor only in the case of the *cis-meso*-2,5-dimethylcyclopentanecarboxylic acid. An approximate correction was made possible in this case by determining the hydrogen chloride concentrations at various times in a control solution containing no organic acid. These values are given in Table I.

**Acid-Catalyzed Ester Hydrolysis.**—The method chosen was that of Anantkrishnan and Krishnamurti.<sup>6</sup> The catalyst solution was prepared from 600 g. of pure dioxane<sup>7</sup> and 400 g. of 0.5 *N* hydrochloric acid; it was kept at 40.0°

(3) Jacobs and Florsheim, *THIS JOURNAL*, **72**, 256 (1949).

(4) "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, New York, N. Y., 1941, p. 524.

(5) Lund and Bjerrum, *Ber.*, **64**, 210 (1931).

(6) Anantkrishnan and Krishnamurti, *Proc. Indian Acad. Sci.*, **14A**, 270 (1941).

(7) Hess and Frahm, *Ber.*, **71**, 2627 (1938).