[COMMUNICATION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

THE SYNTHESIS OF CERTAIN ACIDS DERIVED FROM CYCLOPENTANE

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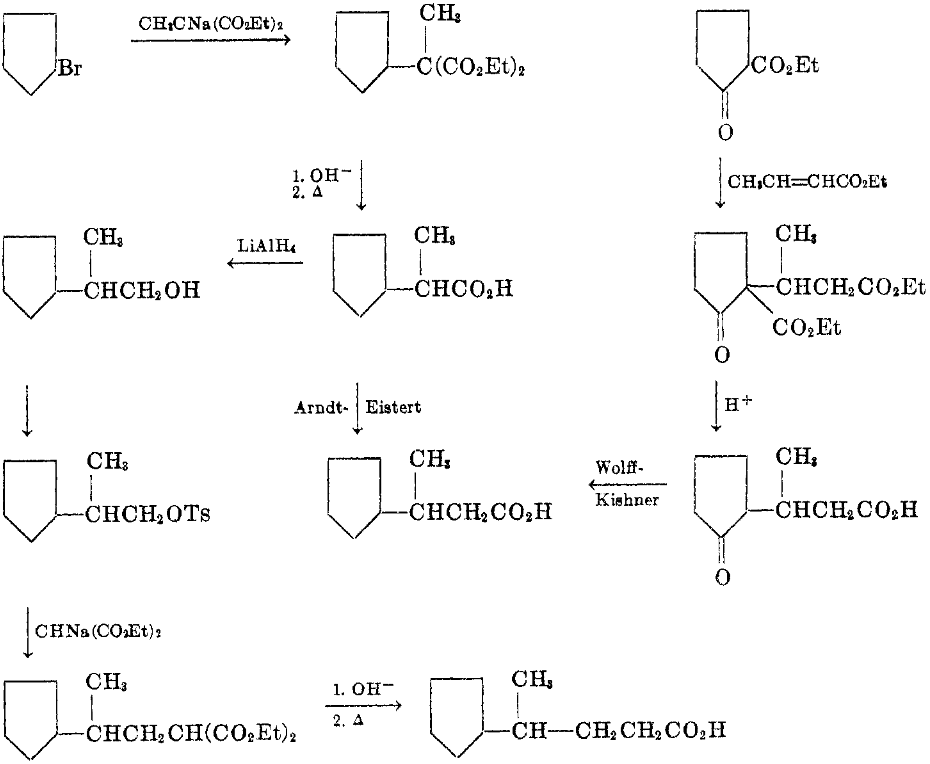
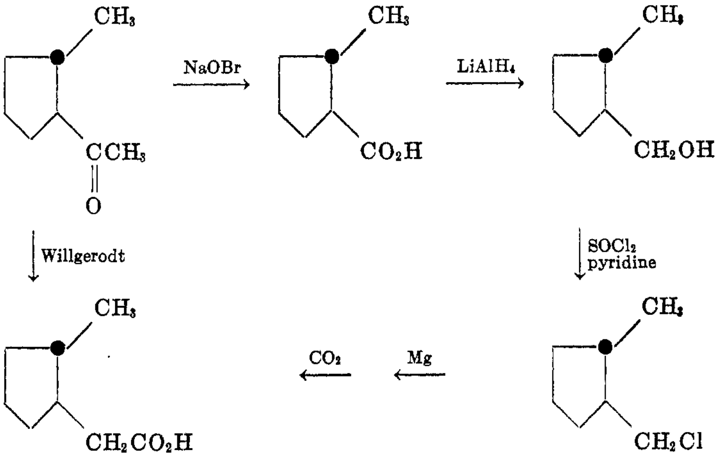
For comparison with compounds which were isolated as degradation products in the course of another problem (1), it was necessary to prepare several acids containing the cyclopentyl and the 2-methylcyclopentyl group. The following two series were needed: (a) 2-Cyclopentylpropionic, 3-cyclopentylbutyric and 4-cyclopentylvaleric acid and (b) (2-methylcyclopentyl) acetic, 2-(2-methylcyclopentyl) propionic, and 3-(2-methylcyclopentyl) butyric acid. Their synthesis is reported in this communication.

The methods used for the preparation of compounds of the first series are indicated below and need no further discussion.



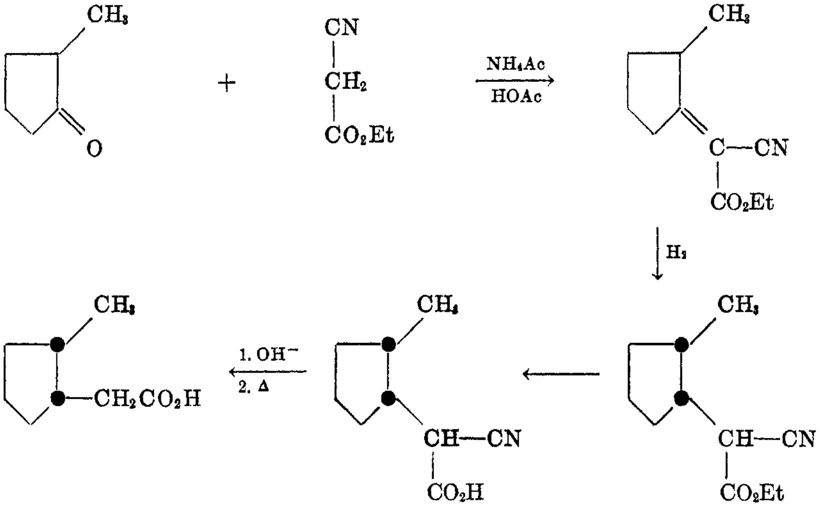
In the second series, the possibility of *cis-trans* isomerism seems to have been neglected by Nenitzescu, Isacescu, and Volrap (2) who claimed the synthesis of 2-methylcyclopentylacetic acid (m.p. of the amide given as 134°) from 2-methylcyclopentanol of unspecified configuration and purity by a series of reactions which undoubtedly would involve extensive configurational changes. We have been able to prepare two apparently isomeric 2-methylcyclopentylacetic acids by the following two sequences:

(A)



I

(B)



II III

Assignment of the *trans*-structure to the acid resulting from sequence A (m.p. of the amide 140.5–141°) was made possible by a report which appeared while this work was in progress. Pines and Hoffman (3) showed that the aluminum chloride-catalyzed reaction of cyclohexane with acetyl chloride (4) gives *trans*-1-acetyl-2-methylcyclopentane by converting the methyl ketone to *trans*-1-2-dimethylcyclopentane *via* *trans*-1-hydroxymethyl-2-methylcyclopentane. Our conversion of this alcohol to acid I by the route shown would not be expected to affect the configuration of a carbon atom of the cyclopentane ring (5, 6).

The acid resulting from sequence B, whose properties differed significantly from that of acid I (m.p. of the amide 149–149.5°) is therefore assigned the *cis* structure. This conclusion is also strongly favored by its mode of formation (hydrogenation of a 2-methylcyclopentylidene intermediate) (7). Further corroboration is found in the observation that the hydrogenation product was difficult to hydrolyze, presumably due to steric hindrance in a *cis* isomer, II being invariably accompanied by partially hydrolyzed III.

trans-1-Hydroxymethyl-2-methylcyclopentane was converted to *trans*-2-(2-methylcyclopentyl) propionic acid (IV) by the method of Nenitzescu and Vantu (8); the agreement in m.p. of the amide with the m.p. reported by the Rumanian workers indicates that they were also dealing with the *trans* isomer. *trans*-3-(2-Methylcyclopentyl) butyric acid was obtained from IV by reduction to the alcohol and carbonation of the Grignard reagent derived from the corresponding bromide.

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EXPERIMENTAL[1]

2-Cyclopentylpropionic acid. The amide of this acid, prepared according to the literature (9) melted at 140.5–141° instead of at 136.5–137° as reported.

3-Cyclopentylbutyric acid. Procedure A: A mixture of 9.5 g. of 3-(2-oxocyclopentane)-propionic acid (10), 45 ml. of triethylene glycol, 7 g. of potassium hydroxide, and 8 ml. of hydrazine hydrate was heated at 100° for one hour. The temperature then was raised to 200° and maintained at this level for two hours. The mixture was cooled, diluted with water, and extracted with ether. The product was collected at 100–103° (1.4 mm.), yield 5.6 g. (64%). The analytical sample boiled at 115–118° (3 mm.), n_D^{23} 1.4604.

Anal. Calc'd for $C_9H_{16}O_2$: C, 69.19; H, 10.32.

Found: C, 69.12; H, 10.24.

The *amide* was recrystallized from benzene-ligroin and melted at 120.5–121°.

Anal. Calc'd for $C_9H_{17}NO$: C, 69.63; H, 11.04.

Found: C, 69.80; H, 10.77.

The *p*-bromophenacyl ester was recrystallized from ethanol-water and melted at 77.5–78.5°.

Anal. Calc'd for $C_{17}H_{21}BrO_3$: C, 57.79: H, 5.99.

Found: C, 57.87: H, 5.88.

Procedure B: A solution of 10 g. of 2 cyclopentylpropionyl chloride, b.p. 74–78° (11 mm.), in anhydrous ether was added to a diazomethane solution prepared from 15 g. of nitrosomethylurea. The diazo ketone, obtained on removal of the solvent, did not crystallize. To a solution of 6 g. of the diazo ketone in 25 ml. of dioxane was added in portions a mixture of 35 ml. of ammonium hydroxide and 7 ml. of 10% silver nitrate solution with warming and stirring. Heating was continued for an additional hour. Cooling and dilution with water precipitated 4.1 g. of crude amide which was recrystallized several times from benzene-ligroin and did not depress the m.p. of the amide prepared by procedure *A*. Hydrolysis of the amide gave a 75% yield of the acid.

2-Cyclopentyl-1-propanol. Reduction of 68 g. of 2-cyclopentylpropionic acid with 23 g. of lithium aluminum hydride in anhydrous ether yielded 56 g. (91%) of alcohol, b.p. 65–67° (2.5 mm.), n_D^{24} 1.4607.

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[1] Melting points and boiling points are uncorrected. Analyses by Drs. Weiler and Strauss, Oxford.

Anal. Calc'd for $C_8H_{16}O$: C, 74.94; H, 12.58.
Found: C, 74.66; H, 12.42.

The *tosylate* was prepared by adding a solution of 54 g. of the alcohol in 54 g. of pyridine to a solution of 83 g. of *p*-toluenesulfonyl chloride in 150 ml. of benzene. The mixture was kept overnight in the icebox and several days at room temperature, filtered, and the precipitate was washed with benzene. The combined filtrate and washings were shaken with several portions of dilute acid and water. The dried benzene solution was concentrated *in vacuo* and yielded 94 g. (86%) of product which did not crystallize.

Ethyl 2-carbethoxy-4-cyclopentylvalerate. To a solution of 8.7 g. of sodium in 150 ml. of absolute ethanol was added 60 g. of malonic ester. After most of the ethanol had been removed by heating at reduced pressure, a solution of 94 g. of the tosylate in 150 ml. of dry benzene was added with heating and stirring. After 12 hours of stirring at reflux, the mixture was cooled and diluted with water. The organic layer was washed thoroughly, dried, and distilled. The main fraction boiled at 132–143° (2 mm.), wt. 54 g. (60%). A middle cut, b.p. 128–131° (1.8 mm.), n_D^{23} 1.4495, was used for analysis.

Anal. Calc'd for $C_{15}H_{26}O_4$: C, 67.13; H, 9.02.
Found: C, 67.00; H, 8.89.

4-Cyclopentylvaleric acid. A mixture of 54 g. of the preceding ester, 30 g. of potassium hydroxide, 30 g. of water, and 100 ml. of ethanol was refluxed for 22 hours. The alcohol was removed, and the residue was diluted with water, extracted with ether, acidified, and again extracted thoroughly with ether. The ether extracts containing the acid were dried and concentrated; the residue crystallized on standing. A small portion was recrystallized several times from a benzene-ligroin mixture. The analysis indicated that this material, which melted at 114–115°, was the malonic acid.

Anal. Calc'd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47.
Found: C, 61.52; H, 8.53.

The remainder of the crystalline material was decarboxylated by heating and distillation at reduced pressure, b.p. 145–150° (7 mm.), yield 16.5 g. The analytical sample boiled at 123–126° (2 mm.), n_D^{22} 1.4600.

Anal. Calc'd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66.
Found: C, 71.13; H, 10.73.

trans-1-Methyl-2-chloromethylcyclopentane. The yield of 1-methyl-2-acetylcyclopentane (4) was increased to 225 g. by very vigorous stirring for a 20-hr period. Hypobromite oxidation of the ketone gave a 66% yield of *trans*-2-methylcyclopentylcarboxylic acid (3, 4) whose reduction by means of lithium aluminum hydride furnished 90% of *trans*-1-methyl-2-hydroxymethylcyclopentane (4, 8). To a solution of 29 g. of this alcohol in 16 g. of pyridine cooled to −10° was added dropwise, with stirring, 35 g. of thionyl chloride at such a rate that the temperature did not exceed 0°. The resulting mixture was heated on the steam-bath for several hours, cooled, and diluted with water. Ether was added, and the ether layer was washed thoroughly with water, dilute base, and again with water and dried. Distillation furnished 17.5 g. (52%) of a product boiling at 70–72° (45 mm.) n_D^{22} 1.4530.

Anal. Calc'd for $C_7H_{13}Cl$: C, 63.40; H, 9.88.
Found: C, 63.43; H, 10.15.

trans-2-Methylcyclopentylacetic acid. The formation of the Grignard reagent from 16.5 g. of the preceding halide and 3.1 g. of magnesium was extremely sluggish. Stirring and refluxing were continued for 40 hours until all the magnesium had dissolved. The solution was poured over a Dry Ice-dry ether slurry and worked up in the usual way. The product distilled at 102–105° (3 mm.), yield 6.6 g. A middle cut, b.p. 98–100° (2 mm.) n_D^{22} 1.4502, was reserved for analysis.

Anal. Calc'd for $C_8H_{14}O_2$: C, 67.57; H, 9.93.
Found: C, 67.59; H, 10.12.

The *amide*, m.p. 140.5–141.5°, was recrystallized twice from benzene-ligroin (b.p. 60–110°).

Anal. Calc'd for $C_8H_{15}NO$: C, 68.04; H, 10.71.
Found: C, 67.79; H, 10.70.

The *p-bromophenacyl ester*, m.p. 65–66.5°, was recrystallized several times from ethanol-water.

Anal. Calc'd for $C_{16}H_{19}BrO_3$: C, 56.65; H, 5.65.

Found: 56.78; H, 5.74.

This acid was also prepared in poor yield by the Kindler modification of the Willgerodt reaction. A mixture of 25.2 g. of *trans*-1-methyl-2-acetylcyclopentane, 17 g. of morpholine, and 6.4 g. of sulfur was heated for six hours, cooled, and then refluxed with 100 ml. of 25% sodium hydroxide solution for another 15 hours. The mixture was extracted with ether, acidified, and again extracted thoroughly with ether. Distillation of the ether layer gave 1.5 g. of the acid, b.p. 105–108° (3.5 mm.), whose identity with the sample obtained as described above was established by infrared spectrum and m.p. of the amide.

Characteristic for acids of the *trans* series appears to be a sharp, well-developed band at 790 cm^{-1} which appears in the infrared spectra of *trans*-2-methylcyclopentylacetic acid and its homologs, but is absent from the spectrum of the *cis*-isomer.

trans-3-(2-Methylcyclopentyl)propionic acid. A solution of sodiomalonic ester, prepared from 103 g. of malonic ester and 14 g. of sodium, was alkylated by 152 g. of the tosylate of *trans*-1-methyl-2-hydroxymethylcyclopentane (3) in the manner described earlier. The yield of the substituted ester was only 51 g. (35%) due to extensive decomposition in the course of distillation. The analytical sample boiled at 118–123° (2 mm.), n_D^{23} 1.4441. This ester was prepared previously (8), but no analysis was given.

Anal. Calc'd for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44.

Found: C, 65.67; H, 9.43.

Hydrolysis of 46 g. of the above ester with 30 g. of potassium hydroxide, 30 ml. of water, and 100 ml. of ethanol yielded, on cautious acidification, extraction with ether, drying, and evaporation of solvent, an oil which crystallized on standing. Repeated recrystallization of a small sample from benzene-ligroin resulted in white needles of m.p. 100.5–101.5° (gas evolution).

Anal. Calc'd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05.

Found: C, 60.44; H, 8.00.

Decarboxylation of the remainder gave 21 g. of the desired acid, b.p. 111–114° (2.5 mm.), n_D^{24} 1.4540.

Anal. Calc'd for $C_9H_{16}O_2$: C, 69.19; H, 10.32.

Found: C, 69.83; H, 10.50.

The *amide* melted at 93–93.5°, in agreement with the literature value (8). The *p-bromophenacyl ester* was recrystallized several times from ethanol-water and melted at 68°.

Anal. Calc'd for $C_{17}H_{21}BrO_3$: C, 57.87; H, 5.88.

Found: C, 58.39; H, 5.52.

trans-3-(2-Methylcyclopentyl)-1-propanol. Lithium aluminum hydride reduction of 15 g. of the preceding acid gave 11 g. (80%) of the alcohol, b.p. 92–96° (7 mm.), n_D^{22} 1.4561.

Anal. Calc'd for $C_9H_{18}O$: C, 75.99; H, 12.76.

Found: C, 76.05; H, 13.15.

trans-3-(2-Methylcyclopentyl)-1-bromopropane. To 10.5 g. of the alcohol cooled to −10° was added dropwise with stirring 9 g. of phosphorus tribromide. After several hours at room temperature, the mixture was heated on the steam-bath, cooled, taken up in ether, washed thoroughly with water, and dried. Distillation furnished 12.5 g. (82%) of the bromide, b.p. 95–100° (14 mm.), n_D^{22} 1.4773.

Anal. Calc'd for $C_9H_{17}Br$: C, 52.68; H, 8.35.

Found: C, 52.58; H, 8.65.

trans-3-(2-Methylcyclopentyl)butyric acid. The Grignard reagent from 11.5 g. of the bromide and 1.4 g. of magnesium was carbonated in the usual way. The acid fraction boiled at 117–120° (1 mm.), n_D^{22} 1.4564, yield 6.9 g. (72%).

Anal. Calc'd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66.

Found: C, 70.89; H, 10.99.

The *amide*, m.p. 72.5–73°, was recrystallized several times from benzene-petroleum ether.

Anal. Calc'd for $C_{10}H_{19}NO$: C, 70.96; H, 11.32.
Found: C, 70.66; H, 11.41.

The *p-bromophenacyl ester* was recrystallized from ethanol and melted at 70–71°.

Anal. Calc'd for $C_{18}H_{23}BrO_3$: C, 58.86; H, 6.31.
Found: C, 59.22; H, 6.42.

Ethyl 2-methylcyclopentylidenecyanoacetate. A mixture of 63 g. of 2-methylcyclopentanone, 74 g. of ethyl cyanoacetate, 30 g. of acetic acid, 10 g. of ammonium acetate, and 500 ml. of benzene was refluxed in an apparatus fitted with a Dean-Stark trap until the evolution of water ceased. The solution was washed with water, dried, and distilled. The fraction boiling at 103–106° (1.6 mm.) n_D^4 1.4880, represented the product, yield 97.5 g. (79%). The isolation of this substance in poorer yield was reported earlier in an article whose abstract was published after the completion of this work (11).

Anal. Calc'd for $C_{11}H_{15}O_2$: C, 68.37; H, 7.82.
Found: C, 67.92; H, 7.82.

Ethyl 2-methylcyclopentanecyanoacetate. A solution of 67 g. of the unsaturated compound in 150 ml. of absolute ethanol was reduced catalytically (5% palladium plus charcoal) at 2–3 atmospheres until hydrogen uptake ceased. Two distillations furnished a product boiling at 96–98° (1.8 mm.), n_D^{23} 1.4520.

Anal. Calc'd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78.
Found: C, 67.41; H, 9.23.

cis-2-Methylcyclopentylacetic acid. A mixture of 66.5 g. of the cyanoacetic ester and 400 ml. of conc'd hydrochloric acid was refluxed for 16 hours. The acid fraction was taken up in ether and dried. Fractional distillation furnished two products, a low-boiling material of b.p. 91–98° (1.3 mm.), wt. 20 g. (41%) and higher-boiling material, b.p. 155–160° (3 mm.), wt. 7.2 g. (12%). The analytical sample of the first fraction had b.p. 95–97° (1.4 mm.), n_D^{22} 1.4560.

Anal. Calc'd for $C_8H_{14}O_2$: C, 67.57; H, 9.93.
Found: C, 67.49; H, 9.98.

The *amide* was recrystallized from benzene-ligroin and melted at 149–149.5°.

Anal. Calc'd. for $C_8H_{15}NO$: C, 68.04; H, 10.71.
Found: C, 67.79; H, 10.94.

The *methyl ester* boiled at 64–68° (2 mm.), n_D^{23} 1.4423.

Anal. Calc'd for $C_9H_{16}O_2$: C, 69.19; H, 10.32.
Found: C, 69.11; H, 10.20.

The *p-bromophenacyl ester*, m.p. 60.5–61.5°, was recrystallized from ethanol-water.

Anal. Calc'd for $C_{16}H_{19}BrO_3$: C, 56.65; H, 5.65.
Found: C, 56.86; H, 5.74.

cis-2-Methylcyclopentylcyanoacetic acid and 2-methylcyclopentylmalonic acid. Redistillation of the higher-boiling fraction of the previous preparation gave a sample of b.p. 146–148° (1.3 mm.), n_D^{22} 1.4702.

Anal. Calc'd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84.
Found: C, 64.39; H, 8.10.

The infrared spectrum indicated the presence of a $C\equiv N$ group.

Hydrolysis with alcoholic potassium hydroxide solution caused evolution of ammonia. After 12 hours at reflux the solution was acidified cautiously and estracted with ether. Removal of the ether yielded an oil which solidified on trituration with petroleum ether and chilling. The solid was recrystallized from ligroin (b.p. 65–100°) and melted at 85–86°.

Anal. Calc'd for $C_9H_{14}O_4$: C, 58.05; H, 7.58.
Found: C, 58.58; H, 7.85.

Decarboxylation of this material furnished *cis*-2-methylcyclopentylacetic acid.

SUMMARY

Synthesis and properties of 2-cyclopentylpropionic, 3-cyclopentylbutyric, 4-cyclopentylvaleric, *cis*- and *trans*-(2-methylcyclopentyl)acetic, *trans*-2-

(2-methylcyclopentyl)propionic, and *trans*-3-(2-methylcyclopentyl)butyric acid are described.

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NOTICE TO AUTHORS

On and after September 1, 1955, the Journal will accept *Notes*; the Journal will accept *Communications to the Editor* received on or after November 1, 1955 for publication in Volume 21. See revised Notice to Authors for details.

Effective with Volume 21, the Journal will use a double column format with a page size approximately 6½″ by 9″. Authors should consider this in connection with graph sizes, and table compositions.