found to be oxidized by relatively large amounts of *Crotalus adamanteus* L-amino acid oxidase and the optical purity of the D-isomer could be readily determined by the procedure now routine in this Laboratory.[4,5] The D-α-aminoadipic acid was found to contain less than 1 part in 1,000 of the L-isomer. Furthermore, the L-isomer was quantitatively oxidized by the oxidase, thus excluding any appreciable contamination by piperidonecarboxylic acid. We have no explanation for the discrepancy between our rotation values and that of Borsook, *et al.*

Experimental Part

N-Chloroacetyl-DL-α-aminoadipic Acid.—One hundred and sixty-eight grams of aminoadipic acid[6] was treated with chloroacetyl chloride and chilled NaOH in the usual manner. The reaction mixture was acidified to a *p*H of about 0.5 with concd. HCl and extracted several times with ethyl acetate. The combined extracts were dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residual sirup was dissolved in dry ether from which crystals separated on chilling. The yield of N-chloroacetyl-DL-α-aminoadipic acid was 74 g., m.p. 127° (cor.). After recrystallization from ethyl acetate the m.p. was 129° (cor.). The yield was 31%, but from the aqueous layer 46 g. of unaltered DL-α-aminoadipic acid (N, calcd. 8.7, found 8.6) could be recovered.

Anal.[7] Calcd. for $C_8H_{12}O_5NCl$: N, 5.9; Cl, 14.9. Found: N, 5.8; Cl, 14.6.

Enzymatic Resolution of Chloroacetyl-DL-α-aminoadipic Acid.—Eighty-six and a half grams of chloroacetyl-DL-α-aminoadipic acid was suspended in 2 liters of water and brought into solution at *p*H 7.0 by addition of 2 *N* LiOH. Water was added to bring the final volume to 3,640 cc. (0.1 *M*) and 2.8 g. of acylase I powder was dissolved in the solution. The latter was brought back to *p*H 7.0 by addition of a few drops of LiOH, and placed in a water-bath at 38°.[8] After 10 hours of incubation, manometric ninhydrin analyses on an aliquot of the digest revealed 50% hydrolysis of the racemate. Further incubation of the digest up to 24 hours did not result in a change of this figure. Accordingly, acetic acid was added to *p*H 5, and the protein filtered off with the aid of Norit. The filtrate was evaporated to about 400 cc. *in vacuo*, and the small amount of protein which flocculated was again removed by filtration. The filtrate was treated dropwise with concd. HCl to *p*H 3.2. A copious crystallization of L-α-aminoadipic acid quickly ensued. Twice the volume of absolute ethanol was added, and the mixture chilled at 5° for several hours. The L-isomer was filtered and washed with ethanol, and the mother liquor and washings combined and set aside for the preparation of the D-isomer. The yield of L-α-aminoadipic acid was 27 g. or 93%; $[\alpha]^{25}D$ +24.6° (2% in 5 *N* HCl). It was recrystallized by adding sufficient boiling water to dissolve the solid, filtering rapidly through a heated filter, and chilling quickly in a −20° alcohol-water-bath to 5°. The final yield of pure L-α-aminoadipic acid was 22 g. or 76%; $[\alpha]^{25}D$ +25.0° (2% in 5 *N* HCl).

Anal. Calcd. for $C_6H_{11}NO_4$: C, 44.7; H, 6.9; N, 8.7. Found: C, 44.8; H, 6.9; N, 8.7.

The combined alcoholic mother liquor and washings contained chloroacetic acid, chloroacetyl-D-α-aminoadipic acid, and traces of unprecipitated L-α-aminoadipic acid. It was evaporated *in vacuo* nearly to dryness, concd. HCl was added with careful cooling to a *p*H of about 0.5, and the acid solution extracted several times with ethyl acetate. The combined extracts were dried over Na_2SO_4 and evaporated *in vacuo* to a residual oil. The oil was taken up in a liter of dry acetone, filtered, the acetone removed by a stream of air, and the residue dissolved in 500 cc. of 2 *N* HCl. The solution was refluxed for 2 hours, decolorized with a little Norit, and evaporated *in vacuo* to a thick sirup. The sirup was dissolved in 400 cc. of H_2O, and the solution treated dropwise with pyridine to *p*H 3.2. The D-α-aminoadipic acid which appeared was recrystallized from water as described for the L-isomer. Yield of pure product was 12 g. or 42%; $[\alpha]^{25}D$ was −25.0° for a 2% solution, and −24.9° for a 6% solution, in 6 *N* HCl.

Anal. Found: C, 44.5; H, 7.0; N, 8.7.

Optical Purity of D-α-Aminoadipic Acid.—One thousand micromoles of D-α-aminoadipic acid at *p*H 7.2, and in the presence of catalase, was practically inert to 30 mg. of *Crotalus adamanteus* venom. When, under the same conditions, 1 micromole of the L-isomer was mixed at the beginning of the run with the 1,000 micromoles of the D-isomer, there was an oxygen consumption equivalent to that of the 1 micromole of L-isomer added. The reaction reached completion in about 1 hour. There was evidently less than 1 part of the L-isomer present in 1,000 parts of the D. Ten micromoles of the L-isomer alone in the presence of large amounts of the venom and catalase, also consumed close to the theoretical amount of oxygen. The D-isomer itself was completely inert to hog kidney D-amino acid oxidase, and therefore the optical purity of the L-isomer could not be determined in this fashion.[4]

D-Piperidonecarboxylic Acid.—A solution of 2 g. of D-α-aminoadipic acid in 100 cc. of H_2O was refluxed, and aliquots removed at intervals for manometric ninhydrin analyses. After two hours an equilibrium value was established of 73% piperidonecarboxylic acid and 27% aminodicarboxylic acid. The *p*H of the solution was 3.2. On chilling, about half of the aminoadipic acid crystallized. It was filtered off, and the mother liquor evaporated to dryness. The residue was extracted several times with hot alcohol, the extracts were combined, filtered and evaporated to a low bulk from which the D-piperidonecarboxylic acid crystallized as large prisms. The yield was 80%; $[\alpha]^{25}D$ − 16.5° (2% in H_2O) and −41.5° (2% in 6 *N* HCl).

Anal. Calcd. for $C_6H_9O_3N$: C, 50.4; H, 6.3; N, 9.8. Found: C, 50.3; H, 6.3; N, 9.8.

No racemization of the piperidonecarboxylic acid occurred for when 250 mg. was refluxed for 2 hours with 25 cc. of 2 *N* HCl, and the resulting D-α-aminoadipic acid isolated by treatment with pyridine to *p*H 3.2 (yield 230 mg.), the latter possessed $[\alpha]^{25}D$ − 25.1° (2% in 6 *N* HCl).

Anal. Found: C, 44.5; H, 7.0; N, 8.7.

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(4) A. Meister, L. Levintow, R. B. Kingsley and J. P. Greenstein, *J. Biol. Chem.*, **192**, 535 (1952).

(5) S. M. Birnbaum and J. P. Greenstein, *Archiv. Biochem. Biophys.*, **39**, 108 (1952).

(6) Donated by Dr. Alton Meister.

(7) Analyses by R. J. Koegel and staff of this Laboratory.

(8) At *p*H 7.0 and 38°, the rate of hydrolysis of this substrate by crude hog kidney aqueous homogenate is 1.5 micromoles per hour per mg. *N*; with acylase I this rate is 45. Since the reaction is zero order, the amount of acylase added to the solution should be sufficient to hydrolyze the L-component of the racemate in about 8 hours.

C^{14} Tracer Studies in the Rearrangements of Unsymmetrical α-Diketones. III. *p*-Methoxybenzylideneacetophenone Oxide[1]

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Benzylideneacetophenone oxide, labeled with carbon-14 in the carbonyl group was found to rearrange in alkaline medium to 2-hydroxy-2,3-diphenylpropionic acid, labeled exclusively in the carbinol group.[3] These results if interpreted as due to a benzilic acid type of rearrangement of intermediate benzyl phenyl diketone suggest either a very

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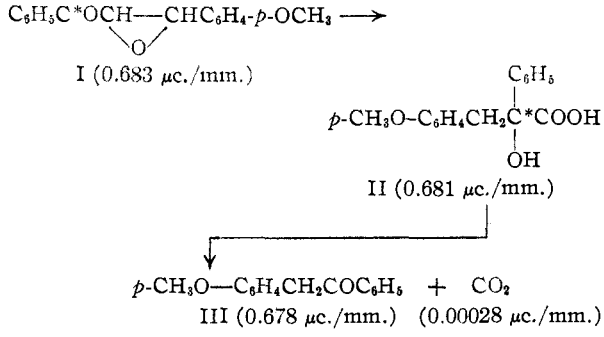
(3) C. J. Collins and O. K. Neville, THIS JOURNAL, **73**, 2471 (1951).

high migratory aptitude for the benzyl group in this rearrangement, or a great difference in the reactivities of the carbonyl groups.

When *p*-methoxybenzylidene-(aceto-1-C^{14})-phenone was prepared as an intermediate in another synthesis, it was of interest to determine its mode of reaction in the base-catalyzed rearrangement.

p-Methoxybenzylidene-(aceto-1-C^{14})-phenone oxide (I) was prepared by condensation of anisaldehyde with (aceto-1-C^{14})-phenone and treatment of the resulting *p*-methoxybenzylidene-(aceto-1-C^{14})-phenone with hydrogen peroxide. Rearrangement of the resulting oxide gave 2-hydroxy-2-phenyl-3-(*p*-methoxyphenyl)-propionic acid, labeled exclusively in the carbinol group, thus demonstrating no phenyl group migration. The radioactivities, reported as microcuries per millimole (μc./mm.) are shown in the reaction scheme below. Degradations and assays were carried out as described previously.[3] The reported radioactivities are subject to an error of ±1%.



Although the *p*-methoxyphenyl group has been shown to migrate less than phenyl in the benzilic acid rearrangement,[4] presumably because of their relative effects on the carbonyl group reactivities, the substitution of a *p*-methoxy group on the potential benzyl group ring of benzylideneacetophenone oxide does not promote phenyl group migration to a discernible level. Although the carbon dioxide obtained in the oxidation of the acid product in the present case contained slightly less radioactivity than did that previously reported, it seems unwise to attach significance to these small numbers.

Experimental

***p*-Methoxybenzylidene-(aceto-1-C^{14})-phenone.**—A 4.05-g. portion of (aceto-1-C^{14})-phenone was condensed with 5.11 g. of anisaldeyde in the presence of ethanolic alkali[3,5] to yield 7.00 g. (87%) of *p*-methoxybenzylidene-(aceto-1-C^{14})-phenone, m.p. 132–134°.

***p*-Methoxybenzylidene-(aceto-1-C^{14})-phenone Oxide (I).**—A 6.7-g. portion of *p*-methoxybenzylidene-(aceto-1-C^{14})-phenone was treated with alkaline hydrogen peroxide[3,6] to obtain 3.58 g. (50%) of I, m.p. 82–83°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.50; H, 5.55. Found: C, 75.37; H, 5.60.

Radioanal: 0.0276 microcurie C^{14} per 10.26-mg. sample.

2-Hydroxy-2-phenyl-3-(*p*-methoxyphenyl)-propionic Acid (II).—A 3.33-g. sample of I was rearranged by the previously described method to give 1.56 g. (44%) of II, m.p. 192.5–193.0°.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.52; H, 5.92. Found: C, 70.50; H, 5.98.

Radioanal: 0.0527 microcurie C^{14} per 21.37-mg. sample.

***p*-Methoxyphenyl(aceto-1-C^{14})-phenone (III).**—A 0.5-g. sample of II was oxidized as previously described[3] to give 0.358 g. (86%) of *p*-methoxyphenyl-(aceto-1-C^{14})-phenone (III), m.p. 96°, and 0.354 g. (96%) of barium carbonate.

Radioanal: II: 0.0430 microcurie C^{14} per 14.32-mg. sample. $BaCO_3$: 0.00098 microcurie C^{14} per 70-mg. sample.

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(4) J. D. Roberts, D. M. Smith and C. C. Lee, THIS JOURNAL, **73**, 618 (1951).

(5) E. P. Kohler and H. M. Chadwell, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, pp. 78–80.

(6) E. Weitz and A. Scheffer, *Ber.*, **54**, 2338 (1921).

Carveol and Carveol Acetate

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Two important constituents of spearmint oil, carveol and carveol acetate have been prepared by a convenient method. The reduction of carvone to carveol using aluminum isopropoxide has been reported several times.[1-3] It seemed of interest to investigate this reduction using lithium aluminum hydride as the reducing agent to compare yields and the nature of the isomers obtained.

The yield of crude carveol, $[\alpha]_D$ −36.2°, obtained was 92.8% of the theoretical amount. Reduction with aluminum isopropoxide has been reported to give carveol mixtures with rotations of 100.9–108.2°[2] and −109.0°[3] from *d*-carvone and *l*-carvone, respectively. This would indicate that nearly equal amounts of the *cis* and *trans* isomers formed since *d*-carvone leads to *d-cis*-carveol, $[\alpha]_D$ 23.9°, and *d-trans*-carveol, $[\alpha]_D$ 213.1°. Lithium aluminum hydride gives predominantly the *cis* configuration as can be seen from the rotation of the crude mixture which is $[\alpha]_D$ −36.2°. This would be the most favored configuration assuming that attack takes place at the less hindered side of the carbonyl group. The mixture was investigated by isolation of *l-cis*-carveol 3,5-dinitrobenzoate and by separation of the *p*-nitrobenzoate into the *cis* and *trans* isomers.

Experimental

Carvone was isolated from spearmint oil with sodium bisulfite and redistilled giving a product boiling 103–104.5° (11 mm.), α_D −59.55°. To 3.1 g. (0.33 equiv.) of lithium aluminum hydride in 75 ml. of anhydrous ether was added dropwise 45.0 g. (0.3 mole) of this carvone in 75 ml. of anhydrous ether. After all the carvone had been added, the mixture was boiled under reflux for an additional hour. About 15 ml. of water was added cautiously, followed by 200 ml. of 10% hydrochloric acid. The ether layer was separated and the aqueous extracts were dried over anhydrous sodium sulfate. Ether was evaporated leaving 43.9 g. (96%) oil, $[\alpha]_D$ −33.1°, $n^{24}D$ 1.4922. Distillation of the oil gave 92.9% of the theoretical amount of carveol, b.p. 109–111° (12 mm.), $[\alpha]_D$ −36.2°, $n^{20}D$ 1.4955, d^{25}_{25} 0.9527. This compares with *l-cis*-carveol, b.p. 101° (10 mm.), $[\alpha]_D$ 23.9°, $n^{25}D$ 1.4959, d^{25}_4 0.9521.[2]

To 1.0 g. of the product in 3 ml. of dry pyridine was added 1.7 g. of 3,5-dinitrobenzoyl chloride. The mixture was stirred thoroughly, allowed to cool to room temperature and poured into 1.5 ml. of water. The resulting oil was slurried with 10 ml. of 5% sodium carbonate giving a white solid which was washed with water and recrystallized from ethanol three times giving 0.68 g., m.p. 91–92.5°, $[\alpha]_D$ 45.0° ($CHCl_3$, *c* 3). This compares with the report[2] for

(1) W. Ponndorf, *Z. angew. Chem.*, **39**, 138 (1926).

(2) R. G. Johnson and J. Read, *J. Chem. Soc.*, 233 (1934).

(3) T. Nagasawa, *Repts. Osaka Imp. Ind. Research Inst.*, **19**, No. 4 (1938); *C. A.*, **34**, 2193 (1940).