1 g. of benzophenone, and no N-benzohydryliminobenzophenone. Considerable mercury formed indicating extensive oxidation of the amine.

It was found also that N-benzohydryliminobenzophenone was not appreciably oxidized by mercuric oxide, or a mixture of mercuric oxide and mercuric chloride at 190° during heating for ten to fifteen minutes. N-Benzohydryliminobenzophenone, m. p. 151°, is obtained readily by condensation of benzohydrylamine and benzophenoneimine (calcd. for $C_{26}H_{21}N$: N, 4.0. Found: N, 3.8).

Summary

1. There are discussed briefly certain aspects concerning the mechanism of controlled oxidation of primary amines and aminoacids. In the case of the amines, particularly, there are available few data regarding oxidations permitting persistence of the carbon skeletons of the parent compounds.

2. β,β,β-Triphenylethylamine, while not rapidly oxidized under certain conditions, is converted to triphenylcarbinol by the action of chromic acid and to N-triphenylethyltriphenylacetaldimine when the hydrochloride is heated with dry mercuric oxide. From N-chlorotriphenylethylamine upon thermal decomposition there is obtained a little of the aldimine derivative; and by the action of hot ethanolic alkali, triphenylmethane.

3. The following new compounds are described: N - monochloro - β,β,β - triphenylethylamine, N-monochloro-γ,γ,γ-triphenylpropylamine and N-(β,β,β-triphenylethyl)-triphenylacetaldimine.

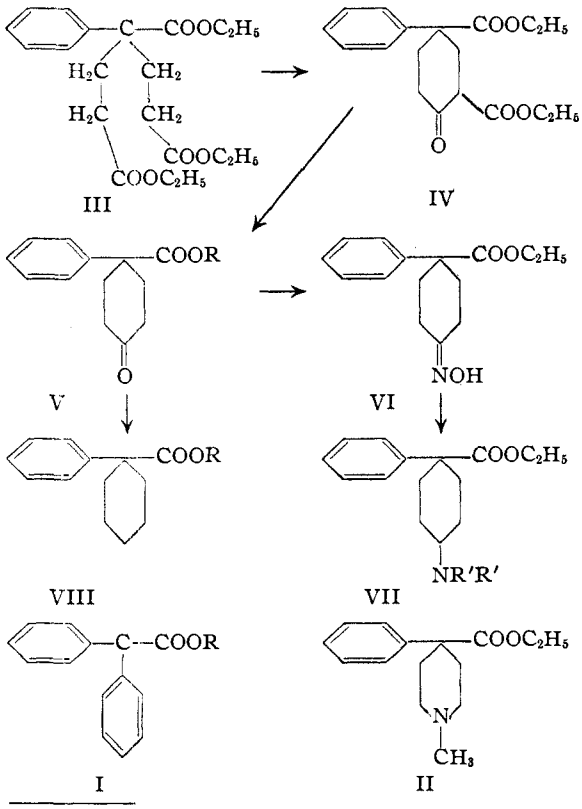
BALTIMORE, MD. RECEIVED DECEMBER 31, 1945

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WALLACE AND TIERNAN PRODUCTS, INC.]

1-Arylcyclohexanecarboxylic Acids*

BY MARTIN RUBIN AND HENRY WISHINSKY

The structural similarity of the antispasmodics derived from diphenylacetic acid,[1] I, and the antispasmodic, analgesic compound 4-phenyl-4-carbethoxy-N-methylpiperidine,[2,3] II, suggested to us that it would be of interest to investigate compounds of an intermediate type such as those related to the 1-arylcyclohexanecarboxylic acids, VIII.



1-Phenylcyclohexanecarboxylic acid has been previously prepared in poor yield by the condensation of 1,5-dibromopentane and benzyl cyanide with two equivalents of sodium amide, followed by hydrolysis of the nitrile to the acid.[4] A synthesis of greater versatility was achieved by utilization of the elegant procedure of Bruson and coworkers[5] for the preparation of γ-substituted pimelic acids by the cyanoethylation of active methylene groups. Dieckman cyclization of the triester of γ-phenyl-γ-carboxypimelic acid, III, prepared by this method yielded ethyl 1-phenyl-3-carbethoxy-4-ketocyclohexanecarboxylate, IV, which was hydrolyzed and decarboxylated to V, (R = H). Clemmensen reduction of V in 50% ethanol resulted in the formation of the ethyl ester of VIII (R = C_2H_5) as well as a small quantity of the free acid.[6] The alkylaminoalkanol esters of this acid exhibited a high degree

* Presented before a session of the Division of Medicinal Chemistry, 109th Meeting of the American Chemical Society, Atlantic City, New Jersey, April 11, 1946.

(1) Miescher and Hoffman, *Helv. Chim. Acta*, **24**, 458 (1941).

(2) Trade name "Demerol."

(3) Eisleb, *Ber.*, **74**, 1433 (1941).

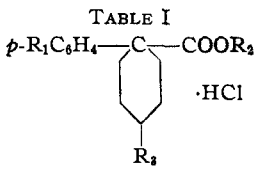
(4) Case, THIS JOURNAL, **56**, 715 (1934).

(5) Bruson and Riener, *ibid.*, **65**, 23 (1943).

(6) The unexpected esterification of the highly hindered carboxyl group was in such marked contrast to our experiences with similarly constituted compounds that a further study of these substances has been undertaken. This study, which we hope to report in a future publication, points to the facile intramolecular interaction of the carbonyl and carboxyl groups, possibly in the form of a ketolactol tautomerism. Appreciable esterification of 1-phenyl-4-ketocyclohexanecarboxylic acid occurs even in dilute alcoholic solution in the presence of mineral acid. From the method of their preparation it is possible [*cf.* Neuman and McCleary, THIS JOURNAL, **68**, 1537 (1941)] that the alkanolamine esters of 1-aryl-4-ketocyclohexanecarboxylic acids represent pseudo rather than normal esters.

of spasmolytic activity when tested in the usual manner on isolated intestinal segments of mice, Table I.

TABLE I



R_1	R_2	R_3	Acetyl choline[a]	Barium chloride[b]
	Atropine		10	..
	Trasentin[c]		0.67	0.2
NO_2	Diethylaminoethyl	H	.2	.2
NH_2	Ethyl	H	...	.1
Isopropyl	Diethylaminoethyl	H	.5	.25
Isopropyl	Piperidinoethyl	H	.05	.05
H	Ethyl	NOH	.05	.1
H	Ethyl	NH_2	.05	.1
H	Morphilinoethyl	H	.1	.1
Cl	Diethylaminoethyl	O	.05	.1
Cl	Diethylaminoethyl	H	.67	.25
Cl	Piperidinoethyl	H	.4	.2
H	Piperidinoethyl	H	.5	.25
H	Diethylaminoethyl	H	.67	.25
H	γ-Diethylaminopropyl	H	.5	.2
H	Diethylaminoethyl	O	...	.05
H	γ-Diethylaminopropyl[d]	O	...	..

[a] Dilutions × 10^{-6} which gave complete relief of spasm induced by acetyl choline. [b] Dilutions × 10^{-6} which gave complete relief of spasm induced by barium chloride. [c] We wish to thank Dr. C. R. Scholz of Ciba, Inc., for a supply of this material. [d] Methobromide.

Oximation of V, (R = C_2H_5) followed by catalytic reduction of the hydrochloride of the oxime of VI in glacial acetic acid resulted in the formation of two, presumably *cis trans* isomeric aminoesters, VII (R′ = H). Methylation of the higher melting isomer by formaldehyde-formic acid yielded ethyl 1-phenyl-4-dimethylaminocyclohexanecarboxylate, VII (R′ = CH_3). This may be considered as an exocyclic nitrogen analog of II. The analgesic activity of VII (R′ = CH_3) was less than that of II. The primary amine, VII (R′ = H), was devoid of any analgesic action.

We wish to thank Dr. O. Wyss for the pharmacological evaluations described above.

Experimental

γ-Phenyl-γ-carboxypimelic Acid.—A mixture of 500 g. of γ-phenyl-γ-cyanopimelonitrile, 500 cc. of glacial acetic acid, 500 cc. of concentrated sulfuric acid and 500 cc. of water was refluxed for twenty hours. The mixture was then concentrated *in vacuo* and the residual oil taken up in nitromethane. The γ-phenyl-γ-carboxypimelic acid which crystallized after several days could be further purified by recrystallization from the same solvent. The product, 224 g. (80%), melted at 153–154° and was identical with the material prepared through cyanoethylation of phenylacetone.[7]

(7) Bruson and Riener, THIS JOURNAL, **64**, 2850 (1942).

Anal. Calcd. for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75; neut. equiv., 93. Found: C, 60.00; H, 5.78; neut. equiv., 93.

Saponification with alkali or acid hydrolysis for a shorter period resulted in the formation of γ-phenyl-γ-carbamylpimelic acid, m. p. 182–183°, on recrystallization from water.

Anal. Calcd. for $C_{14}H_{17}O_5N$: C, 60.20; H, 6.14. Found: C, 60.25; H, 6.10.

Ethyl γ-Phenyl-γ-carbethoxypimelate, III.—The complete esterification of the acid could best be effected by the sulfuric acid-ethanol procedure described by Eisleb.[3] To a mixture of 560 g. of γ-phenyl-γ-carboxypimelic acid, 200 cc. of water, and 400 cc. of concentrated sulfuric acid was added, dropwise, a total of six liters of 95% ethanol. When worked up in the manner described, 550 g. (75%), of neutral ester, m. p. 33–34°, b. p. 165–175° at 0.2 mm., was obtained.

Anal. Calcd. for $C_{20}H_{28}O_6$: C, 65.90; H, 7.74. Found: C, 66.10; H, 7.72.

Ethyl 1-Phenyl-3-carbethoxy-4-ketocyclohexanecarboxylate, IV.—To 28 g. of sodium sand in 800 cc. of dry toluene was added 364 g. of III. The mixture was stirred and refluxed until all the sodium had reacted. The solution was then poured onto ice and acetic acid solution, the toluene layer separated, and the aqueous portion extracted with ether. The combined extracts were washed with water and concentrated *in vacuo*. Distillation of the residue gave 207 g. (65%) of product, b. p. 165–175° at 0.5 mm.

Anal. Calcd. for $C_{18}H_{22}O_5$: C, 67.90; H, 6.97. Found: C, 67.91; H, 7.18.

1-Phenyl-4-ketocyclohexanecarboxylic Acid A, from IV.—A mixture of 318 g. of IV, 1 liter of glacial acetic acid, 200 cc. of concentrated hydrochloric acid and 80 cc. of water was refluxed for twelve hours. The solution was then concentrated *in vacuo* and the residual oil treated with sodium carbonate solution. The neutral material was extracted with ether, the extracts washed with water and concentrated. Distillation of the residue gave 40 g. (16%), of ethyl 1-phenyl-4-ketocyclohexanecarboxylate, b. p. 144–146° at 0.5 mm.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.83; H, 7.78.

The oxime hydrochloride, prepared by the addition of dry hydrogen chloride to dry ethereal solution of the oxime, prepared in the usual way, melted at 152–154°.

Anal. Calcd. for $C_{15}H_{20}O_3NCl$: N, 4.70. Found: N, 4.75.

The sodium carbonate solution was acidified with acetic acid and treated with a solution of 100 g. of semicarbazide hydrochloride and 90 g. of sodium acetate. The semicarbazone, which precipitated rapidly, was filtered and washed with ethanol. It melted at 239–240° and was insoluble in most solvents. Calcd. for $C_{14}H_{17}O_3N_3$: neut. equiv. 275; found: neut. equiv. 272. The semicarbazone, (138 g.), was hydrolyzed by refluxing (with stirring), with 1 liter of 5% hydrochloric acid and 1.5 liters of benzene. When the solid had gone into solution (four hours), the benzene layer was separated, concentrated and the residue recrystallized from a mixture of 70–90° petroleum ether (70%) and ethyl acetate (30%). The product, 65.5 g. (30%), melted at 118.5–119.5°.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47; neut. equiv., 218. Found: C, 71.54; H, 6.48; neut. equiv., 217.

On recrystallization from water the material forms a hydrate, m. p. 94–95°. Calcd.: neut. equiv., 236. Found: neut. equiv., 236.

B. From γ-Phenyl-γ-carboxypimelic Acid.—A mixture of 16 g. of γ-phenyl-γ-carboxypimelic acid and 60 cc. of acetic anhydride was refluxed for four hours. After concentration *in vacuo* the residue was heated at a bath temperature of 220–240° *in vacuo* until decarboxylation was complete. The product was then refluxed with 8 g. of semicarbazide hydrochloride and 8 g. of sodium acetate in 50 cc. of 50% ethanol for one hour. After cooling, the

crystalline semicarbazone, 4 g., m. p. 235–240°, was removed by filtration. Hydrolysis to the acid was carried out as described above. *The oxime*, prepared in the usual way, melted at 155.5–156.5° after recrystallization from dilute ethanol.

Anal. Calcd. for $C_{13}H_{15}O_3N$: N, 6.01. Found: N, 5.54.

Methyl 1-Phenyl-4-ketocyclohexanecarboxylate.—To 2.23 g. of sodium dissolved in 50 cc. of methanol was added 21.8 g. of 1-phenyl-4-ketocyclohexanecarboxylic acid. Following the addition of 20 g. of methyl iodide the mixture was refluxed to neutrality. The methanol was removed by distillation, the residue treated with water, extracted with ether and the ethereal extract washed with sodium hydroxide solution and water. The ethereal extract was concentrated and the residue distilled. The ester, a clear colorless oil, b. p. 139–141° at 0.2 mm., 18.5 g. (80%), crystallized in the receiver. It melted at 76–77° after recrystallization from petroleum ether.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.40; H, 6.94; sapn. no., 232. Found: C, 72.43; H, 6.72; sapn. no., 232.

The semicarbazone melted at 188.5–189° after recrystallization from dilute ethanol. *Anal.* Calcd. for $C_{15}H_{19}O_3N_3$: C, 62.26; H, 6.62. Found: C, 62.03; H, 6.45.

Alkanolamine esters of 1-phenyl-4-ketocyclohexanecarboxylic acid and related acids described below, were prepared by reaction of the acid chloride with the appropriate aminoalcohol in an inert solvent. In those cases in which the crystalline hydrochloride of the ester did not separate out of the reaction mixture directly, the mixture was worked up by extraction with water, liberation of the base from aqueous solution by neutralization with alkali, extraction with ether and precipitation from the dried ethereal solution by addition of a suitable anhydrous acid or alkyl halide.

The acid chlorides were prepared by the addition of excess thionyl chloride to a dry benzene solution of the acid. After four hours at room temperature the solution was refluxed for one hour, the excess thionyl chloride and benzene removed by distillation *in vacuo* and the residue taken up in fresh solvent. Aliquots of this solution were used for the preparation of the esters.

Diethylaminoethyl 1-phenyl-4-ketocyclohexanecarboxylate hydrochloride melted at 208–210°. *Anal.* Calcd. for $C_{19}H_{26}O_3NCl$: C, 64.48; H, 7.98. Found: C, 64.42; H, 7.90.

γ-Diethylaminopropyl 1-phenyl-4-ketocyclohexanecarboxylate methobromide melted at 129–130°. *Anal.* Calcd for $C_{21}H_{32}O_3NBr$: N, 3.29. Found: N, 3.37.

Ethyl 1-Phenylcyclohexanecarboxylate.—The Clemmensen reduction of 20 g. of ethyl 1-phenyl-4-ketocyclohexanecarboxylate carried out in the usual manner in a mixture of 50% concentrated hydrochloric acid and 50% ethanol for twelve hours gave 15 g. (79%) of product, b. p. 105–110° at 0.1 mm.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.50; H, 8.68. Found: C, 77.50; H, 8.71.

The Clemmensen reduction of 1-phenyl-4-ketocyclohexanecarboxylic acid carried out in a mixture of equal volumes of ethanol and concentrated hydrochloric acid in the manner described above gave the same ester (60%) as well as some (20%) of 1-phenylcyclohexanecarboxylic acid, m. p. 123–124°, described below. Substitution of methanol for ethanol gave methyl 1-phenylcyclohexanecarboxylate and the acid.

1-Phenylcyclohexanecarboxylic Acid.—The ester was saponified by refluxing for forty-eight hours in alcoholic sodium hydroxide. After removal of the alcohol by distillation the alkaline solution was cooled and acidified with hydrochloric acid. The product was filtered and recrystallized from a minimum of 60–90° petroleum ether. A quantitative yield of acid, m. p. 123–124°, was obtained.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.51; H, 7.76.

Diethylaminoethyl 1-phenylcyclohexanecarboxylate hydrochloride melted at 159–160° on recrystallization from benzene.

Anal. Calcd. for $C_{19}H_{30}O_2NCl$: C, 67.10; H, 8.90. Found: C, 67.18; H, 8.82.

γ-Diethylaminopropyl 1-phenylcyclohexanecarboxylate hydrochloride melted at 139–140°.

Anal. Calcd. for $C_{20}H_{32}O_2NCl$: C, 67.87; H, 9.12. Found: C, 67.52; H, 8.97.

β-Piperidinoethyl 1-phenylcyclohexanecarboxylate hydrochloride melted at 196–197°.

Anal. Calcd. for $C_{20}H_{30}O_2NCl$: N, 3.98. Found: N, 4.28.

β-Morpholinoethyl 1-phenylcyclohexanecarboxylate hydrochloride melted at 184.5–186°.

Anal. Calcd. for $C_{19}H_{28}O_3NCl$: N, 3.92. Found: N, 3.62.

***p*-Nitrophenylcyclohexanecarboxylic Acid.**—To 75 cc. of rapidly stirred fuming nitric acid at −5 to 0° was added 5 g. of 1-phenylcyclohexanecarboxylic acid in the course of one hour. Stirring was continued for another hour while the mixture was allowed to warm to room temperature. The crystalline product which separated when the mixture was poured onto ice was filtered and recrystallized eight times from dilute ethanol. It then melted at 176–177°. The yield of pure product was 2 g. (33%).

Anal. Calcd. for $C_{13}H_{15}O_4N$: C, 62.64; H, 6.07. Found: C, 62.47; H, 5.94.

Diethylaminoethyl *p*-nitrophenylcyclohexanecarboxylate hydrochloride melted at 145–146° when recrystallized from a mixture of dioxane and petroleum ether.

Anal. Calcd. for $C_{19}H_{29}O_4N_2Cl$: N, 7.28. Found: N, 6.93.

Ethyl *p*-nitrophenylcyclohexanecarboxylate was prepared by nitration of ethyl 1-phenylcyclohexanecarboxylate as described above. It was obtained as a pale yellow oil, b. p. 158–160° at 0.2 mm. (80%).

Anal. Calcd. for $C_{15}H_{19}O_4N$: N, 5.05. Found: N, 5.22.

Ethyl *p*-Aminophenylcyclohexanecarboxylate Hydrochloride.—The catalytic reduction of 3 g. of ethyl *p*-nitrophenylcyclohexanecarboxylate in 50 cc. of ethanol using platinum oxide at room temperature and two atmospheres proceeded rapidly. When the theoretical quantity of hydrogen had been absorbed, the catalyst was removed by filtration and the solution concentrated *in vacuo*. The residue was taken up in ether, dried over anhydrous potassium carbonate and filtered. After the introduction of hydrogen chloride the ether solution was concentrated and the residue recrystallized from benzene–petroleum ether. The product, 2 g. (65%), melted at 150–150.5°.

Anal. Calcd. for $C_{15}H_{22}O_2NCl$: N, 4.94. Found: N, 5.30.

α- and β-Ethyl 1-Phenyl-4-aminocyclohexanecarboxylate Hydrochloride.—The catalytic reduction of 1.3 g. of VI with 0.5 g. of platinum oxide in 135 cc. of glacial acetic acid was complete in two hours at room temperature and two atmospheres pressure. The catalyst was removed by filtration and the solution concentrated *in vacuo*. The residue was converted to the free base with dilute alkali, extracted with ether, the extract dried over anhydrous potassium carbonate and filtered. The addition of hydrogen chloride precipitated a mixture of α- and β-isomers, melting at 223–227°. Recrystallization from dry dioxane resulted in the separation of the less soluble α form melting at 252–253°.

Anal. Calcd. for $C_{15}H_{22}O_2NCl$: N, 4.94. Found: N, 5.23.

The addition of three volumes of dry ether to the dioxane filtrate resulted in the separation of the β-isomer melting at 201–203°.

Anal. Calcd. for $C_{15}H_{22}O_2NCl$: N, 4.94. Found: N, 4.79, 4.89.

Ethyl 1-Phenyl-4-dimethylaminocyclohexanecarboxylate Hydrochloride.—A mixture of 2 g. of α-ethyl 1-phenyl-4-aminocyclohexanecarboxylate, 2 g. of formic acid and 4 cc. of aqueous 35% formaldehyde was refluxed for one hour. The solution was then made alkaline with aqueous potassium hydroxide, extracted with ether, the ethereal extracts dried over anhydrous potassium carbonate, filtered and the product precipitated by the addition of hydrogen chloride. After recrystallization from ethylene dichloride–petroleum ether it melted at 174–175°.

Anal. Calcd. for $C_{17}H_{26}O_2NCl$: N, 4.49. Found: N, 4.80.

1-Cyclohexylcyclohexanecarboxylic Acid.—A solution of 1 g. of 1-phenylcyclohexanecarboxylic acid in 135 cc. of acetic acid and 1 g. of platinum oxide was shaken for ten days at room temperature and two atmospheres of hydrogen. The catalyst was removed by filtration, the solvent distilled *in vacuo* and the residue dissolved in dilute alkali. The alkaline solution was extracted with ether to remove some neutral material and then acidified in the cold with hydrochloric acid. The crystalline product was filtered and after three recrystallizations from dilute ethanol melted at 122–123°. The mixed melting point with the starting acid was 85–90°.

Anal. Calcd. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.55. Found: C, 74.20; H, 10.68.

1-Phenyl-4-hydroxy-4-phenylcyclohexanecarboxylic Acid.—To the Grignard reagent from 47.1 g. (0.3 mole) of bromobenzene and 7.3 g. of magnesium in ether was added an ethereal solution of 33 g. (0.15 mole) of 1-phenyl-4-ketocyclohexanecarboxylic acid. The reaction mixture was refluxed for one hour, allowed to stand at room temperature for forty-eight hours and then decomposed with dilute sulfuric acid. The ethereal layer was extracted with dilute alkali and the alkaline extracts acidified with hydrochloric acid. The gummy acid which separated was extracted with ether, the extracts concentrated and the residue crystallized by the addition of a small amount of methanol. The product, 6 g. after recrystallization from dilute methanol, melted at 234–235°.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.63; H, 6.93.

γ-*p*-Nitrophenyl-γ-carboxypimelic Acid.—Hydrolysis of the trinitrile[6] gave 87% of product melting at 190–191° after recrystallization from nitromethane.

Anal. Calcd. for $C_{14}H_{15}O_8N$: C, 51.69; H, 4.65; neut. equiv., 107. Found: C, 51.38; H, 5.04; neut. equiv., 108.

γ-*p*-Aminophenyl-γ-carboxypimelic Acid.—A mixture of 16.3 g. of γ-*p*-nitrophenyl-γ-carboxypimelic acid, 135 cc. of glacial acetic acid and 0.5 g. of platinum oxide at room temperature and two atmospheres rapidly absorbed the theoretical quantity of hydrogen. The catalyst was removed by filtration and the solvent distilled *in vacuo*. The residue after recrystallization from water which contained a small amount of sodium bisulfite melted at 213–214°. The yield was quantitative.

Anal. Calcd. for $C_{14}H_{17}O_6N$: N, 4.74. Found: N, 5.17.

γ-*p*-Chlorophenyl-γ-cyanopimelonitrile.—The cyanoethylation in the usual way[5] of *p*-chlorobenzyl cyanide gave 80% of product melting at 124–125° after recrystallization from ethanol.

Anal. Calcd. for $C_{14}H_{12}N_2Cl$: C, 65.24; H, 4.69. Found: C, 65.45; H, 4.64.

γ-*p*-Chlorophenyl-γ-carboxypimelic Acid.—The acid hydrolysis of the trinitrile gave 70% of product m. p. 114–115° after several recrystallizations from nitromethane. Titration and analysis for carbon and hydrogen gave consistently low results. Further purification by recrystallization from a mixture of dioxane–ethylene dichloride raised the melting point to 153–154°.

Anal. Calcd. for $C_{14}H_{15}O_6Cl$: C, 53.43; H, 4.80. Found: C, 53.24; H, 4.85.

1-*p*-Chlorophenyl-4-ketocyclohexanecarboxylic Acid.—Cyclization of the triacid by the acetic anhydride procedure gave 30% of crude product, b. p. 270–295° at 0.1 mm. This material was converted to the semicarbazone melting at 239–240° which on hydrolysis afforded the pure material melting at 78–79° after recrystallization from dilute methanol.

Anal. Calcd. for $C_{13}H_{13}O_3Cl$: C, 61.35; H, 5.19. Found: C, 61.79; H, 5.19.

The oxime melted at 182.5–183° after recrystallization from dilute methanol.

Anal. Calcd. for $C_{13}H_{14}O_3NCl$: C, 58.69; H, 5.27. Found: C, 58.50; H, 5.55.

Diethylaminoethyl 1-*p*-chlorophenylcyclohexanecarboxylate hydrochloride melted at 190–191°.

Anal. Calcd. for $C_{19}H_{27}O_3NCl_2$: N, 3.61. Found: N, 3.95.

1-*p*-Chlorophenylcyclohexanecarboxylic acid, obtained from the alkali soluble fraction of the Clemmensen reduction product of 1-*p*-chlorophenyl-4-ketocyclohexanecarboxylic acid melted at 153–154° on recrystallization from dilute ethanol.

Anal. Calcd. for $C_{13}H_{15}O_2Cl$: C, 65.41; H, 6.33. Found: C, 65.15; H, 6.39.

Diethylaminoethyl 1-*p*-chlorophenylcyclohexanecarboxylate hydrochloride melted at 170–172°.

Anal. Calcd. for $C_{19}H_{29}O_2NCl_2$: N, 3.74. Found: N, 3.60.

β-Piperidinoethyl 1-*p*-chlorophenylcyclohexanecarboxylate hydrochloride melted at 162–164°.

Anal. Calcd. for $C_{20}H_{29}O_2NCl_2$: N, 3.62. Found: N, 3.67.

γ-*p*-Isopropylphenyl-γ-cyanopimelonitrile, prepared by the cyanoethylation of *p*-isopropylbenzyl cyanide, melted at 58–59° on recrystallization from methanol.

Anal. Calcd. for $C_{17}H_{19}N_3$: N, 15.83. Found: N, 16.08.

Ethyl γ-*p*-isopropylphenyl-γ-carboxypimelate was obtained by the hydrolysis of the trinitrile followed by esterification of the acidic material, as a clear colorless oil, b. p. 250–255° at 0.2 mm., m. p. 32.5–34°.

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 68.15; H, 8.23.

γ-*p*-Isopropylphenyl-γ-carboxypimelic acid was obtained in quantitative yield by overnight saponification of the ester in alcoholic sodium hydroxide solution, distillation of the alcohol and acidification as a crystalline product melting at 195–196° after recrystallization from nitromethane.

Anal. Calcd. for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.00; H, 7.05.

1-*p*-Isopropylphenylcyclohexanecarboxylic Acid.—The product of the sodium cyclization of ethyl γ-*p*-isopropylphenyl-γ-carbethoxypimelate could not be purified by distillation without considerable decomposition. It was accordingly hydrolyzed directly to 1-*p*-isopropyl-4-ketocyclohexanecarboxylic acid which was obtained as a noncrystalline gum. Clemmensen reduction of the gummy acid yielded, as the alkali soluble fraction, the crystalline acid which melted at 113–114° after recrystallization from dilute ethanol.

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.36; H, 9.09.

1-*p*-Isopropylphenylcyclohexanecarboxamide was prepared by reaction of the acyl chloride with aqueous ammonia. On recrystallization from petroleum ether it melted at 114–115°.

Anal. Calcd. for $C_{16}H_{23}ON$: N, 5.71. Found: N, 5.45.

Diethylaminoethyl 1-*p*-isopropylphenylcyclohexanecarboxylate hydrochloride melted at 155–156°.

Anal. Calcd. for $C_{22}H_{36}O_2NCl$: N, 4.00. Found: N, 3.75.

β-Piperidinoethyl 1-*p*-isopropylphenylcyclohexanecarboxylate hydrochloride melted at 194–195° after recrystallization from water.

Anal. Calcd. for $C_{23}H_{36}O_2NCl$: N, 3.56. Found: N, 3.45.

γ-α-Naphthyl-γ-cyanopimelonitrile was obtained in 55% yield by the cyanoethylation of α-naphthylacetonitrile. It melted at 103–104.5° on recrystallization from methanol.

Anal. Calcd. for $C_{18}H_{15}N_3$: C, 79.09; H, 5.53. Found: C, 79.65; H, 5.53.

γ-α-Naphthyl-γ-carbamylpimelic Acid.—Saponification of the trinitrile in alcoholic alkali resulted in the formation of the diacid amide which melted at 214–215° on recrystallization from water. All attempts at further hydrolysis or saponification were unavailing.

Anal. Calcd. for $C_{18}H_{19}O_5N$: C, 65.64; H, 5.81; N, 4.25; neut. equiv., 164.7. Found: C, 65.33; H, 6.24; N, 4.17; neut. equiv., 162.0.

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Summary

1. A general synthesis of 1-arylcyclohexanecarboxylic acids has been described.

2. Certain esters of this general type show pronounced antispasmodic and some analgesic activity.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, CORNELL UNIVERSITY MEDICAL COLLEGE]

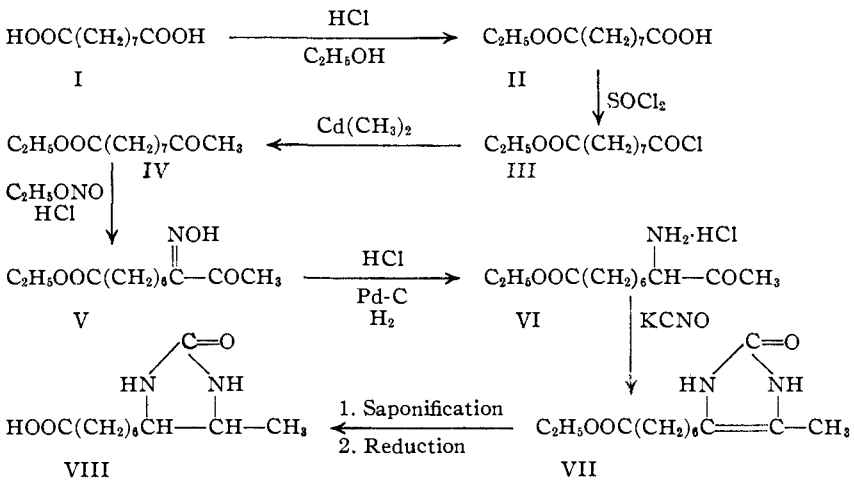
The Synthesis of Homodesthiobiotin and Related Compounds

BY HERBERT MCKENNIS, JR.,[1] AND VINCENT DU VIGNEAUD[2,3]

Previous communications[4,5] have described the preparation of desthiobiotin, 5-methyl-2-oxo-4-imidazolidinecaproic acid, and its methyl ester by hydrogenolysis of natural biotin in the presence of Raney nickel catalyst. In addition, the total synthesis of desthiobiotin from α-aminosuberic acid[6] as well as the resynthesis of desthiobiotin from ζ,η-diaminopelargonic acid[7] have been described.

In a continuation of the studies on the relation of the structure of biotin and desthiobiotin to biological activity, a number of related compounds including 5-methyl-2-oxo-4-imidazolidineheptanoic acid, *homodesthiobiotin*, were desired.

Although it appeared probable that the methods of synthesis which had been employed in this Laboratory for the synthesis of desthiobiotin[6,7] and related compounds[8] could be adapted to the synthesis of homodesthiobiotin, a consideration of the availability of starting materials and the labor involved in the preparation of intermediates has led us to the selection of a previously unexplored route.



Gilman and Nelson[9] have developed the reaction of dialkyl cadmium compounds with acid chlorides as a method for the preparation of ketones. This reaction has been applied to the preparation of ethyl 6-oxoheptanoate from δ-carbethoxyvaleryl chloride.[10] In view of the convenience of this method and the current availability of azelaic acid, a synthetic route to homodesthiobiotin with azelaic acid as the starting material was chosen. The steps in the synthesis are shown in the accompanying reactions.

Ethyl 9-oxodecanoate (IV) was prepared from η-carbethoxycapryiyl chloride (III) and dimethylcadmium. The keto ester was then treated with

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