after purification by crystallization from alcohol, m. p. 117–117.5° (cor.).

Anal. Calcd. for $C_{22}H_{21}NO$: N, 4.1. Found: N (Dumas), 4.3.

α-Methyl-γ,γ,γ-triphenylpropylamine Hydrochloride, $(C_6H_5)_3CCH_2CH(CH_3)NH_3Cl$.—Methyl triphenylethyl ketoxime, 8.3 g., and 50 ml. of absolute ethanol were placed in a flask fitted with a reflux condenser protected from moisture, and clean sodium, 4.5 g., was added; the reduction was permitted to proceed briskly. The reaction was completed by heating; residual sodium was destroyed with ethanol, and the mixture was acidulated with hydrochloric acid. After ethanol was removed in a vacuum, there remained a white salt which was collected, washed with water and dried; yield 8.5 g. The product was extracted with boiling ether and recrystallized from hot ethanol and ether; dec. pt. 256° (in a bath preheated to 250°).

Anal. Calcd. for $C_{22}H_{24}NCl$: N, 4.15. Found: N (Dumas), 4.10.

Urethan Derivative, $(C_6H_5)_3CCH_2CH(CH_3)NHCOOC_2H_5$.—To a suspension of 8.4 g. of the above amine hydrochloride in 100 ml. of water was added 3.8 g. of ethyl chlorocarbonate and 3.2 g. of sodium hydroxide. The mixture was vigorously shaken for half an hour, crushed in a mortar, and triturated thoroughly during which additional portions of ethyl chlorocarbonate and potassium carbonate were added; it was treated with excess sodium carbonate, collected, washed with warm, dilute hydrochloric acid and with hot water. It was dried and recrystallized from ligroin; yield 7.7 g.; m. p. 84.5–86° (cor.).

Anal. Calcd. for $C_{25}H_{27}NO_2$: N, 3.7. Found: N (Dumas), 3.7.

Summary

1. Evidence regarding a rather remarkable degree of stability, or non-reactivity, in the grouping $(C_6H_5)_3C-\overset{H}{\underset{H}{C}}-$, is afforded by several avenues of approach, including especially investigation of the reactions of β,β,β-triphenylpropionitrile and organomagnesium halides, which have been found to lead to the formation of the corresponding ketimine salts.

2. There have been prepared and characterized the following compounds, hitherto undescribed: the hydrochlorides of phenyl, ethyl, and methyl β,β,β-triphenylethyl ketimines; phenyl β,β,β-triphenylethyl ketimine; triphenylmethylacetophenone, methyl β,β,β-triphenylethyl ketoxime, α-methyl-γ,γ,γ-triphenylpropylamine hydrochloride, and its urethan derivative.

BALTIMORE, MARYLAND RECEIVED DECEMBER 31, 1945

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, THE JOHNS HOPKINS UNIVERSITY]

The Oxidation of Compounds Possessing the Primary Amino Group. II. β,β,β-Triphenylethylamine[1]

BY LESLIE HELLERMAN

An important objective of these studies[2,3] has been to gain additional information concerning the mechanism or patterns of oxidation of certain primary amino compounds, as well as to try to discover some of the factors underlying apparent differences in behavior occasionally observed among this group in reactions involving oxidation. Despite careful studies in a number of laboratories there exists little clear-cut data on the controlled oxidation of the alkyl or aralkylamines, particularly when oxidizing reagents other than those of the peroxide type have been employed.[3]

In one segment of the field, of paramount importance especially to biochemistry, significant advances recently have been recorded. These concern the enzymatic oxidations of α-amino-acids of the *l*- and *d*-configuration,[4,5] yielding the corresponding ketoacids, most probably through hydrolysis of intermediate iminoketonic acids. The oxidizing substrate here is oxygen, and the catalysts, specific flavoenzymes; the partial reaction depicting oxidation of the aminoacid with preservation of its carbon skeleton[6] may be designated schematically

$$R-\overset{H}{\underset{NH_2}{C}}-COO^- \longrightarrow R-\overset{}{\underset{NH}{C}}-COO^- + 2H^+ + 2e \quad (1)$$

Thermodynamic reversibility has not been demonstrated, and no derivative of an imino intermediate, other than the ketoacid, has been isolated. No mention need be made here concerning many collateral studies, nor of other special processes, such as transamination. Studies in this laboratory concerning the enzymatic catalysis will be recorded elsewhere. Certain physiologically significant *amines*, *e. g.*, tyramine, are considered also to be oxidized to imino compounds in processes involving specific enzymes.[7]

In this paper are recorded observations concerning the oxidation of β,β,β-triphenylethylamine (I) the structural features of which suggested[2] its investigation. Collaterally, there are described certain transformations of N-chloro-β,β,β-tri-

(1) This investigation was completed some years ago. During initial experiments in the Department of Chemistry, The University of Chicago, the work gained much through the collaboration and interest of Dr. J. Elton Cole.

(2) Hellerman, THIS JOURNAL, **49**, 1735 (1927).

(3) Hellerman and Sanders, *ibid.*, **49**, 1742 (1927).

(4) Krebs, *Z. physiol. Chem.*, **217**, 191 (1933); **218**, 157 (1933).

(5) Warburg and Christian, *Biochem. Z.*, **298**, 150 (1938).

(6) In the course of non-enzymatic oxidations of the amino acids decarboxylation often is experienced; compare, for example, Langheld, *Ber.*, **42**, 392 (1909); Dakin, *J. Biol. Chem.*, **4**, 63 (1908); **5**, 405 (1909); *Biochem. J.*, **11**, 79 (1917); Herbst and Clarke, *J. Biol. Chem.*, **104**, 769 (1934); Van Slyke, Dillon, MacFayden and Hamilton, *J. Biol. Chem.*, **141**, 627 (1941).

(7) Compare Richter, *Biochem. J.*, **31**, 2022 (1937); Bernheim and Bernheim, *J. Biol. Chem.*, **123**, 317 (1938), and references therein.

phenylethylamine (II), which may bear upon the problem to the extent that oxidation–reductions of N-chloroamines, probably intramolecular at least in part, parallel under appropriate conditions[3] the action of halogens in non-aqueous media upon the parent amines. Some additional interest attaches to intramolecular changes, inasmuch as the enzymatic oxidations discussed above possibly may proceed virtually through intramolecular oxidation–reductions of catalyst–substrate addition compounds. It was shown previously that benzohydrylamine[3] is oxidized rapidly by bromine in an ethanolic solution containing sodium ethylate to a product (iminobenzophenone) hydrolyzable to benzophenone and ammonia; N-chlorobenzohydrylamine is readily transformed at room temperature to iminobenzophenone, a product obtainable also when the parent amine in acetone solution[8] is treated at 0° with permanganate. In contrast, it is demonstrated here that the amine (I) and also its N-chloro derivative (II) are unattacked under the conditions first named; at higher temperatures reaction is slow, and its course complex. N-Chloro-γ,γ,γ-triphenylpropylamine appears to react somewhat more rapidly.[9]

That triphenylethylamine is found to be oxidized to triphenylcarbinol[10] by hot chromic acid contributes little to the problem of mechanism, although results obtained from the thermal decomposition of compound (II) are of greater interest.[9] However, conditions have been found under which oxidation of I proceeds in a more orderly fashion; heating of the amine hydrochloride with mercuric oxide produces N-triphenylethyltriphenylacetaldimine (III). It is considered that the over-all course of this rather drastic oxidation may reasonably be represented as shown.

$$2(C_6H_5)_3CCH_2NH_3Cl + HgO \longrightarrow 2(C_6H_5)_3CCH_2NH_2 + (HgCl_2) + H_2O \quad (2)$$

$$\underset{(I)}{(C_6H_5)_3CCH_2NH_2} + (HgCl_2) + HgO \longrightarrow \underset{H}{(C_6H_5)_3CC{=}NH} + 2HgCl + H_2O \quad (3)$$

$$\underset{H}{(C_6H_5)_3CC{=}NH} + H_2N{-}CH_2C(C_6H_5)_3 \longrightarrow \underset{(III)}{(C_6H_5)_3CC(H){=}NCH_2C(C_6H_5)_3} + NH_3 \quad (4)$$

No amine remains unchanged, and other reaction products have not been investigated. Treatment of benzohydrylamine hydrochloride under similar conditions gives benzophenone.[9] A small quantity of III has been isolated also after thermal decomposition of Compound II.

An interesting transformation of Compound II is observed[9] upon treatment with hot ethanolic potassium hydroxide. The products are triphenylmethane obtained quantitatively, and potassium chloride, cyanide-ion and some ammonia. The following equations may depict the changes,[11] although there are other possibilities.

$$\underset{II}{\overset{H}{(C_6H_5)_3CCH_2NCl}} + KOH \longrightarrow \underset{H}{(C_6H_5)_3CC{=}NH} + KCl + H_2O \quad (5)$$

$$(C_6H_5)_3CCH(=NH) + OH^- \longrightarrow (C_6H_5)_3CH + HOH + CN^- \quad (6a)$$

$$(C_6H_5)_3CC(H){=}NH + H_2O \xrightarrow{(OH^-)} NH_3 + (C_6H_5)_3CCHO \left[\longrightarrow (C_6H_5)_3CH\right] \quad (6b)$$

In conclusion it may be pointed out that one factor underlying relative resistance to oxidation under specified mild conditions observed with Compound I may be related to a certain stability in the β,β,β-triphenylethyl grouping; the matter has been discussed in some detail in another place.[13]

Experimental Part

Triphenylcarbinol from β,β,β-Triphenylethylamine by Action of Chromic Anhydride.—To 100 ml. of glacial acetic acid were added 2.0 g. of β,β,β-triphenylethylamine and 2 g. of chromic anhydride (CrO_3); the mixture was heated at 100° under reflux for four and one-half hours. There was added 500 ml. of water; after violent agitation of the mixture it was possible to collect the precipitated product, which was washed with water and dried. The crude product was washed with cold ligroin and recrystallized from ligroin or acetic acid; m. p. 163°; melting point of a mixture with authentic triphenylcarbinol, 163°; yield of pure carbinol, 1.0 g.

At 50° the amine was found to be oxidized slowly when water was initially absent from the reaction mixture; at 18° the reaction was decidedly slow.

N-Monochloro-β,β,β-triphenylethylamine, $(C_6H_5)_3CCH_2NHCl$.—For the preparation of the monochloroamine, the hydrochloride of β,β,β-triphenylethylamine was treated with an exactly equivalent amount of potassium hypochlorite free of any excess alkali.[3] The hypochlorite was prepared in the usual manner by treatment of an excess of potassium hydroxide solution at 5° with chlorine gas and conveniently assayed for hypochlorite-ion and for excess alkalinity as follows: (1) of the alkaline hypochlorite solution, 1.00 ml. was added to 1 to 2 g. of iodate-free sodium iodide dissolved in 10 ml. of water, 10 ml. of 10% acetic acid was added, and the liberated iodine at once titrated with standard thiosulfate solution.

The titration was found to agree with the thiosulfate titration after acidification with standard hydrochloric acid in (2) below, indicating the absence of appreciable iodate.

(2) The above titration was repeated with the modification that acidification with excess acid was effected with a measured amount of 0.1 *N* hydrochloric acid instead of acetic acid. After the titration with thiosulfate, phenolphthalein indicator was added, and 0.1 *N* sodium hydroxide run in to the end-point.

(3) **Calculation.**—Let A = ml. of 0.1 *N* hydrochloric acid added; B = ml. of 0.1 *N* sodium thiosulfate required; C = ml. of 0.1 *N* sodium hydroxide finally required; then $A - C$ = ml. of 0.1 *N* hydrochloric acid used up initially, and $A - (B + C)$ = ml. of 0.1 *N* hydrochloric acid required to neutralize the excess alkali in 1 ml. of the potassium hypochlorite solution.

(8) Goldschmidt, *Ann.*, **437**, 197 (1926).

(9) See the Experimental Part.

(10) Concerning structural aspects, *cf.* Hellerman, Colin and Hoen, THIS JOURNAL, **50**, 1722 (1928); footnote 26 therein refers to certain results recorded in this paper.

(11) Note that triphenylacetaldehyde is cleaved in the presence of alkali, giving triphenylmethane and a formate (ref. 12).

(12) Daniloff and Danilova, *Ber.*, **59**, 387 (1926).

(13) (a) Hellerman and Garner, THIS JOURNAL, **68**, 819 (1946); (b) Garner and Hellerman, *ibid.*, **68**, 823 (1946).

$\frac{A - (B + C)}{10{,}000}$ = mole free sodium hydroxide in 1 ml.

$\frac{B}{20{,}000}$ = mole sodium hypochlorite in 1 ml.

For the preparation of the monochloroamine, there was used potassium hypochlorite found to be 2.082 *M* with respect to potassium hypochlorite and 0.07 *M* with respect to excess potassium hydroxide. To 1.55 ml. of this solution *at* 0° there was added 0.135 ml. of 0.8 *N* hydrochloric acid slowly and with careful mixing, so that no gaseous material was lost; the hypochlorite was poured into a vigorously shaken, rather dilute aqueous solution of 1 g. of β,β,β-triphenylethylamine hydrochloride, also at 0°. A flaky product formed at once. This was removed by rapid filtration, washed with iced water, and dried in a vacuum desiccator over phosphorus pentoxide; yield 0.99 g.; m. p. with decomposition, 118-119°.

Active ("positive") chlorine was determined by titration with thiosulfate of the iodine formed when freshly acidified sodium iodide was added to a sample of the monochloroamine freshly dissolved in ethanol.

Anal. Calcd. for $C_{20}H_{18}NCl$: Cl, 11.5. Found: active Cl, 11.4.

The preparation of N,N-dichloro-β,β,β-triphenylethylamine was attempted by treatment of 2.0 g. of the amine hydrochloride with 9.3 ml. (6 mole-equivalents) of "neutral" 2.082 *M* potassium hypochlorite (see above). There was obtained 2.0 g. of a product; dec. pt., 118-119°; mixed with monochloroamine, dec. pt., 118°; active chlorine content, found, 11.4% (calcd. for $C_{20}H_{18}NCl$: Cl, 11.5; for $C_{20}H_{17}NCl_2$, 20.7). Accordingly, the product in this instance also was the monochloroamine.

Thermal Decomposition of N-Monochloro-β,β,β-triphenylethylamine.—The monochloroamine, contained in a Pyrex ignition tube closed with a calcium chloride tube, was heated at its decomposition point (119°). The gaseous products were chlorine and hydrogen chloride. Treatment with ether of the cooled reaction mixtures from several runs gave, after addition of dry hydrogen chloride to the ether extracts, β,β,β-triphenylethylamine hydrochloride in 40% yield; and the gums recoverable by concentration of the ether filtrates, after being boiled with water (*i. e.*, subjected to hydrolysis) gave triphenylcarbinol which after crystallization from glacial acetic acid was obtained in pure form in 25% yield. From the filtrates there was obtained a colored oil (unidentified) and a small amount of a solid substance which was crystallizable from acetic acid, and found to melt at 170°. This was later found to be identical with N-(β,β,β-triphenylethyl)-triphenylacetaldimine, $(C_6H_5)_3CCH{=}NCH_2C(C_6H_5)_3$, described below.

Triphenylmethane from N-Chloro-β,β,β-triphenylethylamine by Action of Etnanolic Potassium Hydroxide.—The N-chloroamine, 0.5 g., was added to 10 ml. of a 20% solution of potassium hydroxide in ethanol, and the mixture permitted to boil under reflux for two hours. Ammonia was evolved, potassium chloride precipitated, and the reaction mixture was found by test to contain cyanide-ion. A precipitate was obtained when 100 ml. of water was added to the yellow reaction mixture. This was collected, washed well with water, and dried; m. p. 91-92°; m. p. of a mixture with authentic triphenylmethane, 92°; yield 0.44 g.

Action of N-Chloro-β,β,β-triphenylethylamine and Sodium Ethylate in Ethanol Solution.—To some of the monochloroamine, dissolved in absolute ethanol, were added two molecular equivalents of sodium ethylate. A precipitate of sodium chloride appeared only after the solution had been boiled for some time. After refluxing for several hours, moisture being excluded, the reaction mixture was found by test to have remained basic and to contain abundant active halogen.

N-Monochloro-γ,γ,γ-triphenylpropylamine, $(C_6H_5)_3CCH_2CH_2NHCl$.[13a]—γ,γ,γ-Triphenylpropylamine hydrochloride,[13a] 0.5 g., was dissolved in 60 ml. of boiling water, the solution cooled to 0°, and just enough ethanol added during good shaking to bring into solution at 0° the hydrochloride that had crystallized. Into the solution, shaken vigorously, there was poured 0.74 ml. of 2.082 *M* potassium hypochlorite (one mole-equivalent), which had been freed of excess alkalinity by the method described above. The monochloroamine, which precipitated at once, was collected, washed with iced water, and dried in a vacuum desiccator over phosphorus pentoxide; yield 0.48 g.; dec. pt., 95°.

Anal. Calcd. for $C_{21}H_{20}NCl$: Cl, 10.9. Found: active Cl, 10.6.

No change occurred when this monochloroamine in absolute ethanol solution was treated at room temperature with two mole-equivalents of sodium ethylate; however, in the boiled solution active halogen decreased more rapidly than was observed in similar tests with N-monochloro-β,β,β-triphenylethylamine already described.

β,β,β-Triphenylethylamine Hydrochloride with Dry Mercuric Oxide: N-(β,β,β-Triphenylethyl)-triphenylacetaldimine, $(C_6H_5)_3CC(H){=}NCH_2C(C_6H_5)_3$.—Finely powdered yellow mercuric oxide that had been freshly prepared and dried, 20 g., and β,β,β-triphenylethylamine hydrochloride, 2.26 g., were well mixed and placed in a Pyrex test-tube. The mixture was heated at 135 to 140° for half an hour after which it was cooled and extracted well with ether. The ether extract was washed with cold 5% hydrochloric acid, with water, and dried with sodium sulfate. After evaporation of the solvent, there remained 2 g. of a viscous product which was treated with a small amount of low-boiling petroleum ether; the residual solid was recrystallized twice from absolute ethanol; m. p. 168-169°; yield of the pure imine, 0.6 g. or more.

Hydrolysis.—Of the substance, 0.1 g. was dissolved in 30 ml. of moist ether, previously saturated with hydrogen chloride. After spontaneous evaporation of the ether, the residue was extracted with petroleum ether, b. p. 30-40°, and slow evaporation of this solvent left a crystalline residue, m. p. 103°, and not depressed by admixture with authentic triphenylacetaldehyde,[12] m. p. 105°. The ligroin-insoluble product was heated with dilute hydrochloric acid; from the solution by treatment with excess ammonia there was obtained 0.04 g. of a product, m. p. 132°; melting point of a mixture with authentic β,β,β-triphenylethylamine[2] 132°.

Proof of the identity of the substance was completed as follows: Triphenylacetaldehyde, 0.07 g., and β,β,β-triphenylethylamine, 0.08 g. were heated in a test-tube, immersed in a glycerol-bath, at 150° for forty minutes. The cooled product was treated with a little petroleum ether and the residual viscous gum dissolved in the minimum quantity of hot absolute ethanol; prismatic platelets crystallized; m. p. 170°; recrystallized from ethanol, m. p. 171°. The melting point of a mixture of this condensation product with the substance obtained above from the oxidation of β,β,β-triphenylethylamine was 169°.

Anal. Calcd. for $C_{40}H_{33}N$: C, 91.0; H, 6.3; N, 2.6. Found: C, 90.5; H, 6.6; N (Kjeldahl), 2.4.

Notes on Variations of Procedure.—An appreciable quantity of the imine was not obtained when triphenylethylamine, in place of its hydrochloride, was heated with dry mercuric oxide.

When the nitrite of triphenylethylamine was heated with dry mercuric oxide as directed by Hellerman, Cohn and Hoen,[10] with subsequent separation of unchanged amine from the ether extracts with cold dilute acid rather than by saturation with hydrogen chloride, there was obtained from the separated ether solution a small amount of triphenylacetaldehyde, as originally described by the authors, and not N-triphenylethyltriphenylacetaldimine which would have been secured unhydrolyzed, if present, under these conditions.

Benzohydrylamine Hydrochloride with Dry Mercuric Oxide.—A mixture of 2.2 g. of benzohydrylamine hydrochloride and 10 g. of dry mercuric oxide was heated at 135° for half an hour or at 190° for fifteen minutes. The cooled products then were extracted with ether, and the solvent evaporated. There was obtained approximately

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.

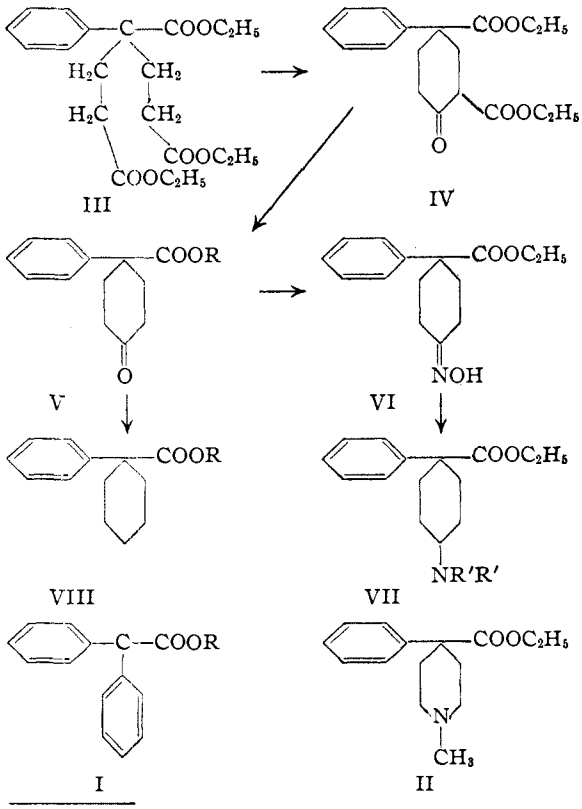
BALTIMORE, MD. RECEIVED DECEMBER 31, 1945

[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 keto-lactol 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.