TABLE I

OXIDATION OF GLYOXAL, PIVALIC ALDEHYDE AND GLYCOLALDEHYDE BY HYDROGEN PEROXIDE

Part 1, Quantities of Reactants Used and Products Found

	Moles						
Compound	H_2O_2	H_2O_2 Unused	O_2 Found	H_2 Found	CO_2 Found	HCOOH Found	Other acids found, equiv.
Glyoxal 1	0.415	0.200	0.0580	0.0029	None	0.2084	0.0253	0.0499
Glyoxal 2	.800	.200	.0246	.0516	Trace	.3120	.0061	− .0308[a]
Glycolaldehyde	.0625	.125	None	.0008	0.0028	.0510	.0042	.0160
Pivalic aldehyde	.100	.370	None	.0052	.0192	.0414	.0042	.0386[b]

Part 2, Percentage of H_2O_2 Going to Reaction Products

	H_2O_2 Unused	$H_2O_2 \rightarrow O_2$	$H_2O_2 \rightarrow H_2$	$H_2O_2 \rightarrow$ HCOOH	$H_2O_2 \rightarrow CO_2$	$H_2O_2 \rightarrow$ Other acids	H_2O_2 total
Glyoxal 1	14.32	1.42	None	3.13	77.21	6.61	102.7
Glyoxal 2	30.74	12.89	None	0.38	58.51	−3.85[c]	98.7
Glycolaldehyde	None	1.10	2.24	−1.12[c]	82.40	12.80	97.4

[a] These values are negative because the reaction mixture titrated less than the original glyoxal, due to oxidation of the acetic acid present as an impurity. [b] 0.0150 mole of carbon monoxide and 0.0104 mole of isobutane were found also. [c] This value is negative because some of the formic acid produced by reactions b and c has been oxidized to CO_2 and hence appears also in column 5.

ceeded slowly, and ten hours were required for completion. Data on the average of the two runs are given in Table I.

From the table it will be noted that the reaction products are the same as found by Fry and Milstead[6] for glycolic acid. Probably the first step is the oxidation of glycolaldehyde to glycolic acid. The glycolic acid then suffers oxidation as found by Fry and Milstead. The data in Part 2 of the table are based upon the formaldehyde mechanism for the production of hydrogen. 97.4% of the total hydrogen peroxide is accounted for by this mechanism.

Summary

1. A quantitative study of the action of hydrogen peroxide upon glyoxal, benzaldehyde, pivalic aldehyde, and glycolaldehyde has been made.

2. Hydrogen is present in the oxidation products of pivalic aldehyde and glycolaldehyde, but not in the oxidation products of glyoxal and benzaldehyde.

3. A reaction mechanism is proposed which involves the intermediate production of formaldehyde in all compounds in which hydrogen is one of the products of oxidation by hydrogen peroxide.

HONOLULU, HAWAII RECEIVED JULY 12, 1940

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Structure of Monocrotaline. V. Retronecine, a Derivative of 1-Methylpyrrolizidine[1]

BY ROGER ADAMS AND E. F. ROGERS

Monocrotaline ($C_{16}H_{23}O_6N$), the alkaloid from the seed of *Crotalaria spectabilis*, upon saponification has been shown to yield monocrotic acid ($C_7H_{12}O_3$), carbon dioxide and retronecine ($C_8H_{13}O_2N$) and upon hydrogenation, to yield monocrotalic acid ($C_8H_{12}O_5$) and retronecanol ($C_8H_{15}ON$). Retronecine contains two hydroxyls and one double bond; retronecanol is saturated and contains merely one hydroxyl group. These two bases were shown to be identical with those obtained by Manske and Barger[2] by similar treatment of the alkaloid, retrorsine, and consequently were given the names assigned by them. The bases are isomeric and probably stereoisomeric with the analogous basic substances from the alkaloid heliotrine described by Menshikov.[3] Many other alkaloids from several genera of plants[1a] fall into the same family in that hydrolysis and hydro-

(1) For previous papers see (a) Adams and Rogers, THIS JOURNAL, 61, 2815 (1939); (b) Adams, Rogers and Sprules, *ibid.*, 61, 2819 (1939); (c) Adams, Rogers and Long, *ibid.*, 61, 2822 (1939); (d) Adams and Long, *ibid.*, 62, 2289 (1940).

(2) Manske, *Can. J. Research*, 5, 651 (1930); Barger, Seshadri, Watt and Yabuta, *J. Chem. Soc.*, 11 (1935).

(3) Menshikov and co-workers, (a) *Ber.*, 65, 974 (1932); (b) 66, 875 (1933); (c) 68, 1051; (d) 1555 (1935); (e) 69, 1110; (f) 1799; (g) 1802 (1936); (h) *Bull. Acad. Sci. U. R. S. S.*, 4, 969 (1936); (i) *J. Gen. Chem.* (U. S. S. R.), 7, 1632 (1937); (j) *Bull. Acad. Sci. U. R. S. S.*, 1035 (1937).

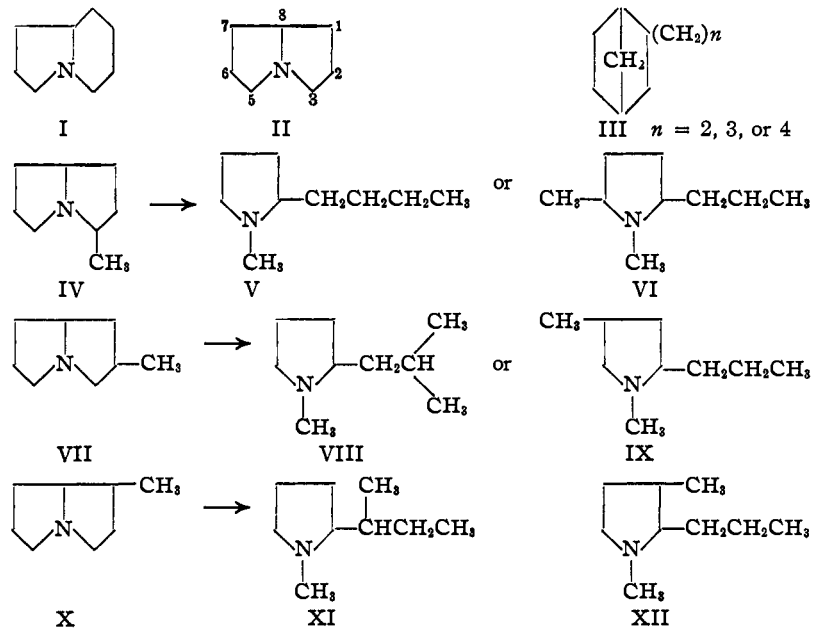
genolysis give bases identical with those resulting from retrorsine or heliotrine. A knowledge of the exact structure of these bases is, therefore, of major importance in the determination of the constitution of all these alkaloids.

Menshikov dehydrated oxyheliotridane, the isomer or analog of retronecanol, to an unsaturated base, heliotridene ($C_8H_{13}N$). This gave on hydrogenation the parent base, heliotridane ($C_8H_{15}N$).[3c] An apparently identical product, although of lower rotation, was obtained by treating heliotridine (analogous to retronecine) with thionyl chloride and reducing the resulting dichloride first with sodium and ethanol, then by catalytic hydrogenation.[3b] Konovalova and Orekhov[4] degraded retronecanol to heliotridene in a similar manner thus proving the parent nucleus of retronecanol or retronecine and oxyheliotridane to be identical.

After an extensive study, Menshikov proposed 1-methylpyrrolizidine (X) as the structure of heliotridane. A careful analysis of the experimental facts offered by him, from which he deduced the above-mentioned structure, leaves a little doubt concerning the justification of some of his conclusions. Confirmation or disproof of the structure of heliotridane, therefore, is desirable before an attempt is made to establish the position of the hydroxyls and double bond in retronecine and the hydroxyl in retronecanol. A brief résumé of Menshikov's experiments and a few comments on his deductions will be given before describing the results of the present investigation.

Menshikov[3a] showed that heliotridane was a tertiary base containing no N-alkyl group and, therefore, must be a bicyclic molecule with the nitrogen atom common to both rings. Exhaustive methylation[3d] of heliotridane, followed by reduction, gave a substance he called *l*-dihydro-des-N-methylheliotridane. This product was demonstrated to be a pyrrolidine by its smooth dehydrogenation to a pyrrole. Subsequent reduction[3i] of the pyrrole regenerated the pyrrolidine in optically inactive form and thus provided an advantageous substance for comparison with synthetic products. Excluding three- and four-membered rings on stereochemical grounds, five kinds of ring structures (formulas I, II and III) are possible for heliotridane on the basis of the experimental facts just described. Menshikov did not consider ring systems of the last three types (III, n = 2, 3 or 4).

The structure of the pyrrolidine, *dl*-dihydro-des-N-methylheliotridane, was deduced by him after comparison of several synthetic pyrrolidines with those possible from compound I and from the various monomethyl derivatives of compound II. Thus octahydropyrrocoline (I), on exhaustive methylation and subsequent reduction, could yield only one pyrrolidine, 1-methyl-2-*n*-butylpyrrolidine (V). There are four monomethyl pyrrolizidines, 1, 2, 3 and 8; of these a methyl group in the 8-position can be eliminated since the des- base could not dehydrogenate to a pyrrole without loss of carbon. 3-Methylpyrrolizidine (IV) would yield by this degradation procedure the pyrrolidine, 1-methyl-2-*n*-butylpyrrolidine (V)



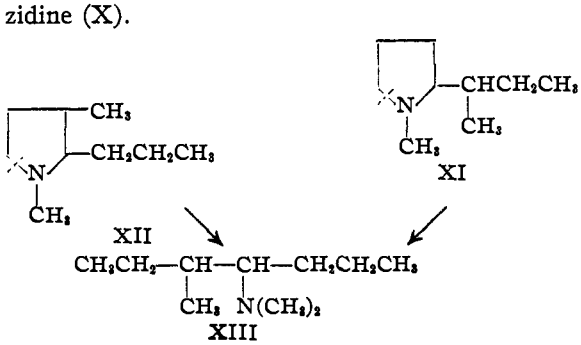
or 1,5-dimethyl-2-*n*-propylpyrrolidine (VI); 2-methylpyrrolizidine (VII) would yield 1-methyl-2-isobutylpyrrolidine (VIII) or 1,4-dimethyl-2-*n*-propylpyrrolidine (IX); 1-methylpyrrolizidine (X) would yield 1-methyl-2-*s*-butylpyrrolidine (XI) or 1,3-dimethyl-2-*n*-propylpyrrolidine (XII).

Menshikov synthesized the pyrrolidines with

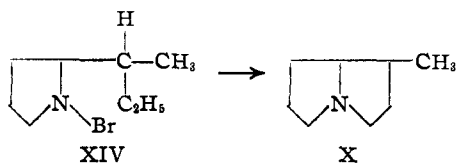
(4) Konovalova and Orekhov, *Bull. soc. chim.*, [5] 4, 1285 (1937).

structures V, VI, VIII, IX and XI. Since they were all liquids which boiled close together, the picrates of each were made and compared in melting point with the picrate of the optically inactive dihydro-des-N-methylheliotridane obtained from heliotridane as previously described. He stated that 1-methyl-2-*n*-butylpyrrolidine (V) was different from *dl*-dihydro-des-N-methylheliotridane but did not make clear on what grounds, since the picrates of each melted at the same point. Consequently in this investigation, 1-methyl-2-*n*-butylpyrrolidine was again synthesized; its picrate showed a sharp depression in melting point when mixed with *dl*-dihydro-des-N-methylheliotridane picrate. This experiment excludes the possibility of heliotridane being octahydropyrrocoline (I). Since the picrates of the synthetic compounds VI, VIII, IX, and XI were also not identical with the picrate of the product from heliotridane, Menshikov concluded that *dl*-dihydro-des-N-methylheliotridane must be 1,3-dimethyl-2-*n*-propylpyrrolidine (XII).

Menshikov did not synthesize the pyrrolidine (XII) but to confirm his postulated structure, he degraded further by exhaustive methylation and reduction *dl*-dihydro-des-N-methylheliotridane; the resulting compound he called tetrahydro-des-N-dimethylheliotridane and proposed for it structure XIII. The same substance (XIII) as shown by identity of the picrates, was prepared by similar treatment of 1-methyl-2-*s*-butylpyrrolidine (XI). An identical base by these two degradations establishes the structure of the product as 3-methyl-4-dimethylaminoheptane. Since the pyrrolidine (XI) had been shown previously to give a picrate not the same as that from *dl*-dihydro-des-N-methylheliotridane, Menshikov, in a second indirect way, thus demonstrated that *dl*-dihydro-des-N-methylheliotridane is 1,3-dimethyl-2-*n*-propylpyrrolidine (XII). Hence he concluded that heliotridane must be 1-methylpyrrolizidine (X).



Finally Menshikov synthesized *dl*-1-methylpyrrolizidine by the action of sulfuric acid on the bromo amine (XIV) derived from 2-*s*-butylpyrrolidine and sodium hypobromite. This last synthesis was accomplished with difficulty and only sufficient product was obtained for formation of a picrate which had a melting point identical with that of optically active heliotridane picrate and which gave no melting point depression when mixed with it.



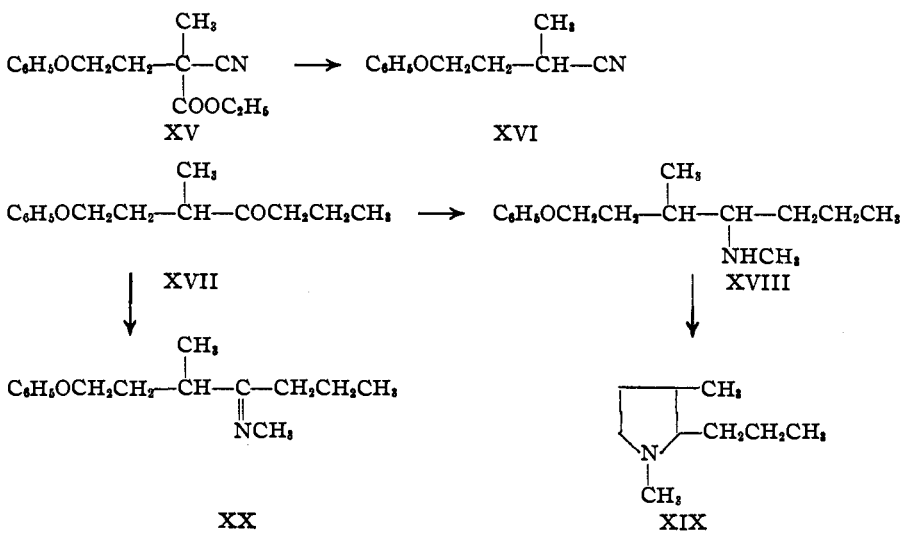
In reviewing these results, it should be pointed out that the formation of 3-methyl-4-dimethylaminoheptane (XIII) as described above definitely excludes the pyrrolidines (V, VI, VIII and IX) from consideration as the structure for *dl*-dihydro-des-N-methylheliotridane. Menshikov's deduction that formula XI also is excluded because of the non-identity of its picrate with that of *dl*-dihydro-des-N-methylheliotridane is not justified. He failed to take into account that two diastereoisomers of XI are possible and that the synthetic 1-methyl-2-*s*-butylpyrrolidine (XI) may have been a diastereoisomer of *dl*-dihydro-des-N-methylheliotridane. If this latter were the case, the picrates of the two probably would not melt at the same point. Thus, formula XI for *dl*-dihydro-des-N-methylheliotridane cannot be excluded, though his conclusion that 1-methylpyrrolizidine probably is the structure of heliotridane is not invalidated since both pyrrolidines XI and XII can be obtained only from the 1-methylpyrrolizidine.

The same melting points and no depression in the mixed melting point of Menshikov's synthetic *dl*-1-methylpyrrolizidine picrate and *l*-heliotridane picrate are not convincing evidence for structural identity of the two. Since in most cases the active forms of a substance melt at a different point from the racemic and since mixed melting points of closely related but non-identical salts often show no depression in mixed melting point determinations, this synthesis of *dl*-1-methylpyrrolizidine cannot be accepted as conclusive.

Menshikov's results and deductions could be clarified completely by the synthesis of 1,3-dimethyl-2-*n*-propylpyrrolidine (XII) and the proof

of its identity with *dl*-dihydro-des-N-methylheliotridane. This would confirm the structure of heliotridane as 1-methylpyrrolizidine (X). This synthesis has been undertaken and successfully concluded.

Ethyl β-phenoxyethylmethylcyanoacetate (XV) was prepared by condensation of phenoxyethyl bromide with ethyl methyl cyanoacetate. This product was saponified to the corresponding cyano acid which was then decarboxylated to α-methyl-γ-phenoxybutyronitrile (XVI). Treatment of XVI with *n*-propylmagnesium bromide gave 1-phenoxy-3-methyl-4-heptanone (XVII).



The ketone, on reduction with hydrogen in the presence of platinum-oxide catalyst at 70° in a methanol solution of methylamine, was smoothly converted to the corresponding methylamino derivative (XVIII). On cleavage of the phenoxy group with hydrobromic acid and treatment of the product with alkali, 1,3-dimethyl-2-*n*-propylpyrrolidine (picrate, m. p. 116°) was obtained. This picrate has the same melting point as *dl*-dihydro-des-N-methylheliotridane picrate and a mixed melting point showed no depression. The picrolonates and methiodides of the synthetic and natural bases had identical melting points and showed no depression in mixed melting point determinations. Thus it may be deduced that 1-methylpyrrolizidine is the proper structure for heliotridane and therefore represents the nucleus common to the bases of the various alkaloids under investigation.

As the character of the hydroxyl group in retronecanol is not well understood, the possibility that rearrangement of the nucleus during dehydration to heliotridene, which rearrangement would persist in heliotridane, had to be considered. Such modification of the original nucleus was shown to be unlikely by preparing heliotridane by a method not involving the rather vigorous conditions necessary for forming heliotridene from retronecanol. Retronecanol was converted to chlororetronecane by treatment with thionyl chloride. The chlorine was replaced smoothly by hydrogen, using Raney nickel and hydrogen at room temperature. The product was heliotridane and agreed in boiling point, rotation and melting point of the picrate when heliotridane prepared by dehydration of retronecanol followed by hydrogenation of the heliotridene.

The reduction of the ketone (XVII) under various conditions led to interesting results. If Raney nickel as catalyst was used with methanolic methylamine at 140°, a low yield of the pyrrolidine (XIX) was obtained directly; in this reaction, cleavage of the phenoxy group and ring closure had taken place simultaneously with the reductive amination. When the ketone (XVII) was heated with dry methylamine at 140°, the imine (XX) resulted, which with Raney nickel and hydrogen in dioxane at 140° gave the phenoxyamine (XVIII). However, with copper chromite catalyst, dry methylamine and hydrogen at 140°, the ketone (XVII) yielded a phenoxyamine which gave a 1,3-dimethyl-2-*n*-propylpyrrolidine (picrate, m. p. 126°) diastereoisomeric with *dl*-dihydro-des-N-methylheliotridane. In one run with Raney nickel which had been kept under absolute ethanol, the same results were obtained but could not be duplicated.

Proof of the diastereoisomeric character of the two synthetic bases which gave picrates, m. p. 116° and 126°, was established by dehydrogenation of the synthetic base, whose picrate melts at 126°, to the corresponding pyrrole followed by reduction using copper chromite. The pyrrolidine thus resulting gave a picrate, m. p. 116°, and was

identical with the base previously formed (picrate, m. p. 116°) as described above and with the base from the dehydrogenation of *l*-dihydro-des-N-methylheliotridane followed by reduction with copper chromite catalyst. These results show that where diastereoisomers are possible in the pyrrolidine degradation products, more than one may be formed and each must be synthesized before structural deductions, by comparison of the melting points of the picrates, are justified.

It was first planned to synthesize 1,3-dimethyl-2-*n*-propylpyrrolidine by the reaction of *n*-propylmagnesium bromide with 1,3-dimethylpyrrolidone-2, then reduction of the pyrroline formed. Craig[5] has described the preparation of a number of 1,2-substituted pyrrolidines by this procedure and Menshikov[3h] used the method in making 1,2-dimethyl-5-*n*-propylpyrrolidine. However, 1,3-dimethylpyrrolidone-2 did not react readily and when the reaction was forced the only product obtained was 1,3-dimethyl-2,2-di-*n*-propylpyrrolidine, formed presumably by an intermediate ring opening. In the preparation of N-methyl-2-*n*-butylpyrrolidine by this method, N-methyl-2,2-di-*n*-butylpyrrolidine was formed in 20% yield. 1,3-Dimethylpyrrolidone-2 was prepared by the following series of reactions

$$ClCH_2CH_2Br + NaC(CH_3)(COOC_2H_5)_2 \longrightarrow$$
$$ClCH_2CH_2C(CH_3)(COOC_2H_5)_2 \longrightarrow$$
$$CH_2\text{—}CH_2\text{—}CH(CH_3)CO\text{—}O \longrightarrow$$
$$CH_2\text{—}CH_2\text{—}CH\text{—}(CH_3)\text{—}CO\text{—}NCH_3$$

Attempted synthesis of the ketone (XVII) through α-methyl-γ-phenoxybutyric acid was not successful. This acid was prepared by condensation of phenoxyethyl bromide with sodiomethylmalonic ester in toluene, followed by saponification and decarboxylation of the product formed. Reaction of α-methyl-γ-phenoxybutyramide with propylmagnesium bromide gave a very poor yield of ketone. Treatment of α-methyl-γ-phenoxybutyryl chloride with propylcadmium chloride did not give the expected ketone, but a product which analyzed approximately for $C_{11}H_{16}O_2$, which was not investigated further.

Experimental

Ethyl β-Phenoxyethyl Methylcyanoacetate.[6]—A mixture of 254 g. (2.0 moles) of ethyl methylcyanoacetate, 201 g. (1.0 mole) of β-phenoxyethyl bromide and 144 g. of finely powdered anhydrous potassium carbonate was heated under reflux at 145° and 100 mm. pressure for twenty-four hours. The mixture was then cooled, washed with water until neutral and distilled. Unreacted ethyl methylcyanoacetate (180 g.) and β-phenoxyethyl bromide (95 g.) were recovered. The condensation product boiled at 180–181° (2 mm.); $n^{24}D$ 1.4975; d^{26}_4 1.081; yield, 129 g. (90% on the basis of unrecovered ester).

Anal. Calcd. for $C_{14}H_{17}O_3N$: N, 5.66. Found: N, 5.56.

β-Phenoxyethyl Methylcyanoacetic Acid.—A solution of 123 g. of ethyl β-phenoxyethyl methylcyanoacetate in 300 cc. of ethanol was treated with one equivalent of 30% aqueous potassium hydroxide. After about a minute the reaction mixture reacted neutral. The ethanol was removed and the cyano acid ether extracted from the acidified solution. It was crystallized from ether–petroleum ether (b. p. 30–60°) or from boiling water; white prisms, m. p. 109–110° (cor.); yield, 99 g. (91%).

Anal. Calcd. for $C_{11}H_{14}O_3$: N, 6.39. Found: N, 6.43.

α-Methyl-γ-phenoxybutyronitrile.—After heating 195 g. of β-phenoxyethyl methylcyanoacetic acid at 185° until carbon dioxide evolution ceased (approximately one hour), the product was washed with aqueous sodium carbonate and dried. The α-methyl-γ-phenoxybutyronitrile boiled at 165–170° (19 mm.); $n^{24}D$ 1.5060; d^{26}_4 1.015; yield, 49 g. (64%).

Anal. Calcd. for $C_{11}H_{13}ON$: N, 8.00. Found: N, 7.98.

A neutral by-product remained in the flask after the first distillation of the reaction product described above. Crystallization from ethanol gave 12 g. of a compound, m. p. 91–92°, which analyzed best for $C_{18}H_{24}O_3N_2$ (calcd.: C, 68.36; H, 7.59; N, 8.86. Found: C, 68.13; H, 7.65; N, 8.90). It was not further investigated.

During the decarboxylation approximately a gram of liquid, identified as α-methylbutyrolactone, was also obtained.

1-Phenoxy-3-methylheptanone-4.—To an ether solution of Grignard reagent prepared from 123 g. of *n*-propyl bromide and 23.3 g. of magnesium was added 44 g. of α-methyl-γ-phenoxybutyronitrile and the mixture allowed to stand overnight. The reaction mixture was then decomposed with ice and concentrated hydrochloric acid. After separating the ether layer, the aqueous layer was heated for one hour on the steam-bath and reëxtracted with ether. The combined extracts were dried and distilled. The 1-phenoxy-3-methylheptanone-4 boiled at 168–170° (19 mm.); $n^{23}D$ 1.4974; d^{26}_4 0.985; yield, 49 g. (89%).

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.36; H, 9.09. Found: C, 76.21; H, 9.11.

2,4-Dinitrophenylhydrazone of 1-Phenoxy-3-methylheptanone-4.—The product was prepared in ethanol; orange needles from ethyl acetate–ethanol, m. p. 85–87° (cor.).

Anal. Calcd. for $C_{20}H_{24}O_5N_4$: N, 14.00. Found: N, 14.05.

1-Phenoxy-3-methyl-4-methylaminoheptane.—A solution of 10 g. of 1-phenoxy-3-methylheptanone-4 in 50 cc. of

(5) Craig, THIS JOURNAL, **55**, 295, 2543 (1933).

(6) Compare Robinson and Watt, *J. Chem. Soc.*, 1536 (1934); Robinson, *ibid.*, **125**, 226 (1924).

methanol containing 8 g. of methylamine was hydrogenated at 70° in the presence of 0.20 g. of platinum oxide for two hours. The basic fraction (6.5 g.) obtained by evaporation of the solvent and excess methylamine, extraction with ether followed by dilute hydrochloric acid and neutralization, distilled sharply at 175–176° (20 mm.), $n^{24}D$ 1.4989, d^{24}_4 0.941.

Anal. Calcd. for $C_{15}H_{25}ON$: N, 5.98. Found: N, 6.15.

Picrate.—Prepared in and recrystallized from ethanol, the picrate formed yellow prisms, m. p. 115–116° (cor.).

Anal. Calcd. for $C_{21}H_{28}O_8N_4$: N, 12.06. Found: N, 12.16.

1,3-Dimethyl-2-*n*-propylpyrrolidine (low-melting picrate form).—A mixture of 6 g. of 1-phenoxy-3-methyl-4-methylaminoheptane and 15 cc. of 48% hydrobromic acid was refluxed for six hours. Extraction of the diluted, alkalized solution gave 3.3 g. (89%) of 1,3-dimethyl-2-*n*-propylpyrrolidine, b. p. 163–165°, $n^{24}D$ 1.4411, d^{26}_4 0.813.

Anal. Calcd. for $C_9H_{19}N$: C, 76.59; H, 13.47; N, 9.93. Found: C, 76.40; H, 13.31; N, 10.00.

Picrate.—Prepared in and recrystallized from ethanol, the picrate formed yellow needles, m. p. 115–116° (cor.). A mixed m. p. with *dl*-dihydro-des-*n*-methylheliotridane picrate showed no depression.

Anal. Calcd. for $C_{15}H_{27}O_7N_4$: N, 15.13. Found: N, 15.39.

Picrolonate.—Prepared in and recrystallized from ethanol, the picrolonate formed brown prisms, m. p. 162–163° (cor.).

Anal. Calcd. for $C_{19}H_{27}O_5N_5$: N, 17.28. Found: N, 17.11.

Methiodide.—Prepared in and recrystallized from acetone, the methiodide formed colorless plates, m. p. 159–160° (cor.).

Anal. Calcd. for $C_{10}H_{22}NI$: I, 44.85. Found: I, 45.07.

Hydrogenation of 1-phenoxy-3-methylheptanone-4 in 50 cc. of 16% methanolic methylamine solution with 2 g. of Raney nickel at 140° for eight hours gave 2.1 g. of 1,3-dimethyl-2-propylpyrrolidine (low-melting form, picrate m. p. 115–116°) and 2.2 g. of 1-phenoxy-3-methyl-4-methyliminoheptane (see below).

1-Phenoxy-3-methyl-4-methyliminoheptane.—A mixture of 10 g. of 1-phenoxy-3-methylheptanone-4 and 15 g. of methylamine was heated at 140° for four hours. After removal of methylamine, the reaction product was taken up in ether, the basic portion extracted with 3 *N* hydrochloric acid, then recovered by making the aqueous solution alkaline and extracting with ether. The product (7.6 g.) had a b. p. of 173–175° (19 mm.), $n^{26}D$ 1.5023, d^{26}_4 0.953.

Anal. Calcd. for $C_{15}H_{23}ON$: C, 77.21; H, 9.93; N 6.00. Found: C, 77.36; H, 9.98; N, 5.81.

A solution of 7 g. of 1-phenoxy-3-methyl-4-methyliminoheptane in 20 cc. of dioxane was hydrogenated for two hours at 140° in the presence of 1 g. of Raney nickel. The yield of amine was only 2.6 g. even though hydrogen absorption was quantitative; b. p. 175–176° (20 mm.), $n^{26}D$ 1.4491.

Anal. Calcd. for $C_{15}H_{25}ON$: C, 76.54; H, 10.68; N, 5.95. Found: C, 76.60; H, 10.79; N, 5.90.

Treatment with hydrobromic acid as described above gave 1,3-dimethyl-2-*n*-propylpyrrolidine (low-melting form, picrate, m. p. 115–116°).

1,3-Dimethyl-2-*n*-propylpyrrolidine (high-melting picrate form).—A mixture of 10 g. of 1-phenoxy-3-methylheptanone-4 and 15 g. of dry methylamine was hydrogenated for eight hours at 140° in the presence of 1.5 g. of copper chromite. The basic products were 1,3-dimethyl-2-*n*-propylpyrrolidine (2.0 g.) and 1-phenoxy-3-methyl-4-methyliminoheptane (1.6 g.). The pure pyrrolidine boiled at 163–165°, $n^{24}D$ 1.4395, d^{26}_4 0.815.

Anal. Calcd. for $C_9H_{19}N$: C, 76.59; H, 13.47; N, 9.93. Found: C, 76.77; H, 13.47; N, 10.12.

Picrate.—Prepared in and recrystallized from ethanol, the picrate formed yellow needles, m. p. 125–126° (cor.).

Anal. Calcd. for $C_{15}H_{22}O_7N_4$: N, 15.13. Found: N, 15.09.

Picrolonate.—Prepared in and recrystallized from ethanol, the picrolonate formed brown prisms, m. p. 158–159° (cor.).

Anal. Calcd. for $C_{19}H_{27}O_5N_5$: N, 17.28. Found: N, 17.08.

Methiodide.—Recrystallized from acetone, plates, m. p. 154–155° (cor.).

Anal. Calcd. for $C_{10}H_{22}NI$: I, 44.85. Found: I, 44.89.

No change in properties of the above pyrrolidine was observed on preparation of a "purified" sample through decomposition of the recrystallized picrate.

When 50–50 mixtures of the lower and higher melting picrates of the 1,3-dimethyl-2-*n*-propylpyrrolidines were melted, the following values were observed: picrate, m. p. 115–116°; picrolonate, m. p. 158–160°; methiodide, m. p. 154–156°.

1,3-Dimethyl-2-*n*-propylpyrrolidine; Conversion of High-melting Picrate Form to the Low-melting Picrate Form.—Dehydrogenation of 6 g. of 1,3-dimethyl-2-propylpyrrolidine (picrate, m. p. 125–126°) at 280° over 40% palladium asbestos, according to the method of Zelinsky,[7] gave a product, after one passage over the catalyst, which was taken up in ether and the ether solution washed repeatedly with *N* hydrochloric acid. The ether layer was then dried and the ether removed. The crude pyrrole was hydrogenated over copper chromite (0.5 g.) at 220° for three hours. 1,3-Dimethyl-2-propylpyrrolidine was obtained, b. p. 163–165°, $n^{24}D$ 1.4406, d^{26}_4 0.812; yield 2.5 g. (41%).

Anal. Calcd. for $C_9H_{19}N$: C, 76.59; H, 13.47; N, 9.93. Found: C, 76.26; H, 13.04; N, 10.10.

Picrate.—Prepared in and recrystallized from ethanol, the picrate formed yellow needles, m. p. 115–116° (cor.).

Anal. Calcd. for $C_{15}H_{22}O_7N_4$: N, 15.13. Found: N, 15.05.

Picrolonate.—Prepared in and recrystallized from ethanol, the picrolonate formed brown prisms, m. p. 161–162° (cor.).

(7) Zelinsky and Borisoff, *Ber.*, **57**, 150 (1924).

Anal. Calcd. for $C_{19}H_{27}O_5N_5$: N, 17.28. Found: N, 16.92.

Methiodide.—Prepared in and recrystallized from acetone, the methiodide formed colorless plates, m. p. 178–179° (cor.).

Anal. Calcd. for $C_{10}H_{22}NI$: C, 42.40; H, 7.77; N, 4.94; I, 44.85. Found: C, 42.63; H, 7.86; N, 4.54; I, 44.90.

The melting point of this compound is as yet inexplicable and requires further investigation. The picrate and picrolonate of this same base have identical melting points with those of the 1,3-dimethyl-2-*n*-propylpyrrolidine made by direct synthesis and showed no depression in mixed melting points. Moreover, the melting points are identical with and show no depression when mixed with the picrate and picrolonate of *dl*-dihydro-des-*n*-methylheliotridane. In the initial experiments, in the preparation of *dl*-dihydro-des-*n*-methylheliotridane by dehydrogenation of the *l*-form followed by hydrogenation, the product gave a picrate and a picrolonate agreeing in properties with those of the appropriate synthetic pyrrolidine but gave a methiodide which melted differently. Subsequent experiments demonstrated that the final pyrrolidine was not absolutely pure. Apparently the impurity in the formation of the picrate or picrolonate was readily removed but in the preparation of the methiodide contaminated the product and could not be removed by crystallization. When greater care was taken to remove pyrrolidine after the dehydrogenation and pyrrole after the hydrogenation, the resulting base gave a methiodide of the anticipated melting point.

Heliotridene.—Heliotridene was prepared from retronecanol according to the procedure of Konovalova and Orekhov.[4] The product boiled at 165–167° (d^{34}_4 0.932) and gave a picrate, m. p. 224–225°, thus agreeing with the constants previously reported. However, the rotation differed markedly from that observed by Konovalova. It was *dextro*- and not *levo*-rotatory.

Rotation. Freshly prepared heliotridene ($n^{20}D$ 1.4807) gave as pure liquid, $\alpha^{34}D$ +72.50°; *l*, 2; $[\alpha]^{34}D$ +38.89°.

After standing for ten days, the heliotridene was redistilled and the rotation again observed.

Rotation. Ten-day old heliotridene ($n^{20}D$ 1.4802) gave as pure liquid, $\alpha^{34}D$ +57.50°; *l*, 2; $[\alpha]^{34}D$ +30.84°.

Freshly prepared heliotridene was refluxed with sodium ethylate (10 g. in 100 cc. of 4 *N* sodium ethylate) for thirty-two hours.

Rotation. Sodium-ethylate heliotridene ($n^{20}D$ 1.4800) gave as pure liquid $\alpha^{34}D$ +51.20°; *l*, 2; $[\alpha]^{34}D$ +27.46°.

It appears that heliotridene gradually changes, due, possibly, to shifting of the double bond.

Heliotridane.—All of the samples of heliotridene of various rotations gave, on catalytic hydrogenation, heliotridane, b. p. 165–166°, $n^{20}D$ 1.4648, d^{34}_4 0.911; picrate, m. p. 232° (cor.).

Rotation. Pure liquid gave $\alpha^{34}D$ −83.15°; *l*, 1; $[\alpha]^{34}D$ −91.27°.

Dihydro-des-N-methylheliotridane.—This base was prepared according to the procedure of Menshikov,[3d] b. p. 165–166°, $n^{24}D$ 1.4400, d^{34}_4 0.815.

Anal. Calcd. for $C_9H_{19}N$: N, 9.93. Found: N, 10.01.

Rotation. Pure liquid gave $\alpha^{34}D$ +11.29°; *l*, 2; $[\alpha]^{34}D$ +6.92°.

Picrate.—Prepared in and recrystallized from ethanol, the picrate formed yellow needles, m. p. 125–126° (cor.).

Anal. Calcd. for $C_{15}H_{22}O_7N_4$: N, 15.13. Found: N, 14.93.

Methiodide.—Prepared in and recrystallized from acetone, the methiodide formed white plates, m. p. 134–135° (cor.).

Anal. Calcd. for $C_{10}H_{22}NI$: N, 4.94. Found: N, 4.92.

***dl*-Dihydro-des-*n*-methylheliotridane.**—Dihydro-des-*n*-methylheliotridane was dehydrogenated and hydrogenated as described above for the higher-melting picrate form of 1,3-dimethyl-2-*n*-propylpyrrolidine. The racemic base boiled at 163–165°, $n^{24}D$ 1.4401, d^{26}_4 0.810; yield 46%. It was optically inactive.

Anal. Calcd. for $C_9H_{19}N$: N, 9.93. Found: N, 10.02.

Picrate.—Prepared in and recrystallized from ethanol, the picrate formed yellow needles, m. p. 115–116° (cor.). Menshikov reported m. p. 114°.

Anal. Calcd. for $C_{15}H_{22}O_7N_4$: C, 48.64; H, 13.47; N, 15.13. Found: C, 48.78; H, 5.88; N, 15.03.

Picrolonate.—Prepared in and recrystallized from ethanol, the picrolonate formed brown prisms, m. p. 159–160° (cor.).

Anal. Calcd. for $C_{19}H_{27}O_5N_5$: N, 17.28. Found: N, 17.05.

Methiodide.—Prepared in and recrystallized from acetone, the methiodide formed colorless plates, m. p. 159–160° (cor.).

Anal. Calcd. for $C_{10}H_{22}NI$: C, 42.40; H, 7.77; N, 4.94; I, 44.85. Found: C, 42.46; H, 7.83; N, 4.63; I, 44.79.

Diethyl β-Chloroethylmethylmalonate.—Diethyl sodiomethylmalonate was prepared by treatment of 23.0 g. of powdered sodium suspended in 1 liter of toluene with 174 g. of diethyl methylmalonate. Reaction was completed by warming on a steam-bath. Addition of 160 g. of ethylene chlorobromide to the hot solution over the course of a few minutes was then made. After four hours of continued heating on the steam-bath a neutral reaction resulted. The solution was cooled and washed, the toluene removed and the product distilled under reduced pressure. The fraction boiling at 135–150° (20 mm.) yielded, on redistillation, diethyl β-chloroethyl methylmalonate, b. p. 144–145° (20 mm.), $n^{24}D$ 1.4320, d^{26}_4 1.077; yield 165 g. (70%).

Anal. Calcd. for $C_{10}H_{17}O_4Cl$: C, 50.74; H, 7.24; Cl, 14.97. Found: C, 50.61; H, 7.32; Cl, 14.81.

α-Methylbutyrolactone.—The following procedure is based on a preparation of α-ethylbutyrolactone from diethyl β-hydroxyethyl methylmalonate described by McElvain.[5] To a boiling, well-stirred solution of 44.8 g. of sodium hydroxide in 56 cc. of water was added during one hour 66 g. of diethyl β-chloroethylmethylmalonate. Stirring and heating was continued for two hours after addition was complete. The reaction mixture was cooled in

(5) McElvain, THIS JOURNAL, 57, 1444 (1935).

ice, carefully treated with a mixture of 31 g. of concentrated sulfuric acid and 42 cc. of water and then refluxed for five hours. The layer of lactone was separated and the solution extracted with two 100-cc. portions of benzene. After drying the combined lactone and benzene solutions, the benzene was removed and the lactone distilled, b. p. 200–201° (745 mm.), $n^{24}D$ 1.4282, d^{26}_4 1.047; yield 25.5 g. (92%).

Anal. Calcd. for $C_5H_8O_2$: C, 60.0; H, 8.00. Found: C, 59.43; H, 8.23.

1,3-Dimethylpyrrolidone-2.[9]—A mixture of 20 g. of α-methylbutyrolactone and 30 g. of methylamine was heated at 280° for three hours. After removal of excess methylamine, the product boiled at 105–110° (30 mm.); $n^{24}D$ 1.4560, d^{26}_4 0.981; yield 21.5 g. (94%).

Anal. Calcd. for $C_6H_{11}ON$: N, 12.39. Found: N, 12.48.

1,3 - Dimethyl - 2,2 - di - *n* - propylpyrrolidine.—1,3-Dimethylpyrrolidone-2 did not react on standing for twelve hours in an ether solution of two moles of *n*-propylmagnesium bromide.[5] Addition of a solution of 5.65 g. of 1,3-dimethylpyrrolidone-2 in 50 cc. of benzene to an ethereal solution of the Grignard reagent prepared from 12.3 g. of *n*-propyl bromide and 2.43 g. of magnesium, removal of ether and overnight refluxing of the benzene solution gave 2.1 g. of 1,3-dimethyl-2,2-di-*n*-propylpyrrolidine, b. p. 112–113° (30 mm.), $n^{24}D$ 1.4586, d^{26}_4 0.854.

Anal. Calcd. for $C_{12}H_{25}N$: C, 78.69; H, 13.65; N, 7.65. Found: C, 78.40; H, 13.68; N, 7.83.

Diethyl β-Phenoxyethyl Methylmalonate.—To a 1-liter toluene solution of diethyl sodiomethyl malonate (23.0 g. of powdered sodium and 174 g. of diethyl methylmalonate) prepared as previously described was added 201 g. of β-phenoxyethyl bromide. After five hours of refluxing, the solution was cooled, neutralized with glacial acetic acid, then washed several times with water. After removal of toluene, the product was distilled. It boiled at 180–185° (2 mm.), $n^{24}D$ 1.4672, d^{26}_4 1.081; yield 190 g. (65%).

Anal. Calcd. for $C_{16}H_{22}O_5$: C, 65.30; H, 7.48. Found: C, 65.20; H, 7.40.

On saponification and decarboxylation of the malonic acid according to the procedure of Bentley, Haworth and Perkin[10] α-methyl-γ-phenoxybutyric acid, m. p. 80° (cor.) was obtained.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.04; H, 7.22. Found: C, 68.13; H, 7.27.

α-Methyl-γ-phenoxybutyramide.—α-Methyl-γ-phenoxybutyramide, prepared by the usual procedure from the ester and ethanolic ammonia formed from dilute ethanol white needles, m. p. 97–98° (cor.).

Anal. Calcd. for $C_{11}H_{15}O_2N$: N, 7.25. Found: N, 7.21.

1-Phenoxy-3-methylheptanone-4.—By refluxing for twelve hours 9.6 g. (0.05 mole) of α-methyl-γ-phenoxybutyramide in 100 cc. of benzene with the Grignard reagent prepared from 12.3 g. (0.1 mole) of *n*-propyl bromide and 2.43 g. (0.1 mole) of magnesium, the ketone was obtained, b. p. 166–168° (19 mm.), $n^{23}D$ 1.4979; yield, 15%.

The 2,4-dinitrophenylhydrazone formed red crystals, m. p. 85–87° (cor.), and showed no mixed melting point depression with the corresponding phenylhydrazone of 1-phenoxy-3-methylheptanone-4 made by a superior method described above.

Chlororetronecane.—To 40 g. of thionyl chloride, cooled in an ice-bath, 15 g. of retronecanol was added slowly. When addition was complete, the solution was allowed to stand at room temperature for one hour. It was then refluxed for an hour on a steam-bath and poured, when cool, into a large excess of ice water. After precipitated material was filtered off, the solution was made alkaline with aqueous ammonia and extracted with ether. After removal of the ether, the base was distilled, b. p. 112° (32 mm.), d^{30}_4 1.055; yield, 6.5 g. (38%).

Anal. Calcd. for $C_8H_{14}NCl$: N, 8.80. Found: N, 8.86. *Rotation.* Pure liquid gave $\alpha^{30}D$ +113.50°; *l*, 2; $[\alpha]^{30}D$ +53.79°.

Heliotridane by Reduction of Chlororetronecane.—A solution of 5 g. of chlororetronecane in 30 cc. of ethanol was hydrogenated at 2–3 atm. pressure in the presence of 2 g. of Raney nickel. After ten hours, when reduction appeared complete, the solution was filtered, made acid to congo red with dilute hydrochloric acid and evaporated almost to dryness on a steam-bath. The material was taken up in water, made alkaline with sodium hydroxide and ether extracted. After removal of ether, the product was distilled, b. p. 165–166°; $n^{20}D$ 1.4641; d^{25}_4 0.935; yield, 3.1 g.

Anal. Calcd. for $C_8H_{15}N$: N, 11.20. Found: N, 11.42.

Rotation. Pure liquid gave $\alpha^{25}D$ −86.08°; *l*, 1; $[\alpha]^{25}D$ −92.06°.

Picrate.—Prepared in and recrystallized from ethanol, the picrate formed yellow needles, m. p. 236° (cor.).

Anal. Calcd. for $C_8H_{15}N \cdot C_6H_3O_7N_3$: N, 15.82. Found: N, 15.96.

Summary

1. A critical discussion is given of the experiments of Menshikov from which he deduced that heliotridane was 1-methylpyrrolizidine.

2. The synthesis of 1,3-dimethyl-2-*n*-propylpyrrolidine was completed. This product was shown to be identical with *dl*-dihydro-des-N-methylheliotridane by comparison of the picrates, picrolonates and methiodides. The structure of heliotridane is thus definitely established as 1-methylpyrrolizidine.

3. Heliotridane was prepared by two methods, (1) that previously described by Menshikov and (2) conversion of retronecanol to chlororetronecane followed by catalytic reduction. The physical constants were identical by both methods indicating the unlikelihood of any rearrangement of the nucleus during formation by the rather vigorous treatment involved in Menshikov's method.

(9) Späth and Lintner, *Ber.*, **69**, 2727 (1936), prepared N-methylpyrrolidone-2 by same method.

(10) Bentley, Haworth and Perkin, *J. Chem. Soc.*, **69**, 172 (1896).

4. Stereoisomeric forms of 1,3-dimethyl-2-*n*-propylpyrrolidine were isolated depending on the method of preparation. The form giving the higher-melting picrate was converted to the other by dehydrogenation followed by hydrogenation.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BARNARD COLLEGE]

Addition Reactions of *alpha*-Ketonic Acids. VII

BY MARIE REIMER AND ANNE L. MORRISON

In former papers of this series[1] it has been shown that the reactions of the side-chain of benzalpyruvic acid are strongly influenced by the nature and position of groups substituted in the benzene ring. A conspicuous effect is that of the *p*-methoxyl group which inhibits the sunlight reactions characteristic of the unsubstituted acid and to a less extent of its ortho- and meta-methoxy substitution products. This fact gave rise to the question as to whether the blocking of the light reaction were due to para substitution, in general, or to the *p*-methoxyl group, as such. In an attempt to answer this question *p*-methyl[2] and *p*-bromo[1]-benzalpyruvic acid were studied. Of these compounds, the *p*-methyl substituted acid is slightly, the *p*-bromo acid very markedly, light sensitive: the *p*-methoxyl is then the only group so far encountered in this series to completely block the light reaction. That the inhibiting effect is that of a *p*-alkoxyl, and not of the *p*-methoxyl group, specifically, is shown in the present paper which deals with the behavior of the *p*-ethoxy compound.

p-Ethoxybenzalpyruvic acid and its esters are found to be entirely unaffected by light. In other respects, too, the influence of the *p*-ethoxyl parallels that of the *p*-methoxyl group. The *p*-ethoxy acid and its derivatives give brilliantly colored compounds when dissolved in concentrated sulfuric acid. The acid forms no hydrate. It combines with bromine to form an unstable dibromide.

With all the benzalpyruvic acid dibromides of this series, treatment with boiling water has eliminated one molecular proportion of hydrogen bromide to form a colorless bromo compound with properties not to be expected of an unsaturated α-ketonic acid, a fact emphasized in the preceding paper on *p*-bromobenzalpyruvic acid.[1] In that case it was found possible to prepare an isomeric unsaturated bromo acid of more usual properties and evidence was obtained to show that the marked differences in behavior of the isomers could be accounted for on the assumption that the colorless isomer was a chelated, the other, an open chain compound. In the present case also, isomeric unsaturated bromo acids have been obtained and the evidence again indicates a chelated structure for the colorless acid. This pure white bromo acid, obtained by boiling aqueous suspensions of *p*-ethoxybenzalpyruvic acid dibromide, forms colorless methyl and ethyl derivatives with diazomethane and diazoethane, respectively. It does not react in the cold with alcohol saturated with hydrogen chloride, as is the case with all other analogous colorless acids of the series. On long heating in methanol–hydrogen chloride mixture the solution gradually becomes yellow and, on cooling, deposits brilliantly yellow crystals of a methyl ester isomeric with the one prepared by the diazomethane reaction. A yellow ethyl ester can be prepared by a similar procedure. A yellow, isomeric acid, corresponding to these two yellow esters, can be obtained from the colorless acid by prolonged treatment with sodium carbonate solution.

This yellow acid has the properties to be expected of a β,γ-unsaturated α-ketonic acid: it is brilliantly colored; it is fairly soluble in water, less so in benzene; it is esterified rapidly in the cold by alcohol saturated with hydrogen chloride; it forms a stable yellow sodium salt, very slightly soluble in alcohols, very readily soluble in water, this aqueous solution being oxidized rapidly by hydrogen peroxide to the corresponding cinnamic acid. The isomeric bromo acid is white; it is very slightly soluble in water, readily soluble in benzene; it is not esterified by alcohols and hydrogen chloride, isomerization to the yellow acid preceding esterification; it forms a colorless sodium salt, readily soluble in alcohols, very slightly soluble in water, transformed, in alkaline solution, into the isomeric yellow salt. From aqueous

(1) No. VI, Reimer and Tobin, THIS JOURNAL, **62**, 2515 (1940).
(2) Reimer and Chase, *ibid.*, **60**, 2469 (1938).