rated taken up in ether. The ether solution was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* yielded 2.1 g. of crude oily acid $\lambda_{max.}^{C_2H_5OH}$ 3460 Å., $E_{1\,cm.}^{1\%}$ 882. On the basis of an $E_{1\,cm.}^{1\%}$ of 1510 for the pure acid (see below), this material was estimated to contain *ca.* 1.2 g. of pure vitamin A acid, representing an over-all conversion of *ca.* 25%, from *cis*-β-ionylideneacetaldehyde.[24] The crude oily acid crystallized on addition of ether. Recrystallization from ether afforded the acid as fine, yellow needles, m.p. 180.5–181.5°, $\lambda_{max.}^{C_2H_5OH}$ 3530 Å., $E_{1\,cm.}^{1\%}$ 1510 (Fig. 3).

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.96; H, 9.36. Found: C, 80.26; H, 9.55.

(B) In an identical manner crude vitamin A acid ethyl ester obtained from 4 g. of C_{20}-hydroxy ester in the *trans*-series was saponified to give *ca.* 1.1 g. of crude vitamin A acid as a yellow semi-sold $\lambda_{max.}^{C_2H_5OH}$ 3475–3500 A., $E_{1\,cm.}^{1\%}$ 905[24] (*ca.* 20% over-all from *trans*-β-ionylideneacetaldehyde). The latter was crystallized from ether affording the acid as yellow needles m.p. 179–180° $\lambda_{max.}^{C_2H_5OH}$ 3500 Å., $E_{1\,cm.}^{1\%}$ 1415.

Anal. Found: C, 80.39; H, 9.09.

A mixed melting point of this acid with the one obtained from the *cis*-series melted at 180–181°.

Vitamin A Acid from the C_{20}-Hydroxy Acid (VII).—A solution of 3 g. of C_{20}-hydroxy ester preparation from the *trans*-series was saponified as already described for vitamin A acid ester. There was obtained in this way crude C_{20}-hydroxy acid as an orange oil $\lambda_{max.}^{isooctane}$ 2920 Å., $E_{1\,cm.}^{1\%}$ 595. This oil was dehydrated by refluxing with 50 mg. of iodine in 50 cc. of petroleum ether (b.p. 95–110°) in the manner already described. The cooled reaction product was extracted with 5% aqueous sodium carbonate solution. The sodium carbonate extract was washed in turn with ether. Acidification of the aqueous layer precipitated an oil which was taken up in ether, washed with water and evaporated to a residue of 1.5 g. of crude vitamin A acid $\lambda_{max.}^{C_2H_5OH}$ 3470 Å., $E_{1\,cm.}^{1\%}$ 750. The crude acid crystallized on seeding and was recrystallized from ether m.p. 179–180°.

The neutral extracts from the iodine dehydration were combined and concentrated *in vacuo* to a dark brown oil (wt. 1 g.). This oil was chromatographed on 25 g. of acid-washed alumina. The eluate giving a purple color with antimony trichloride in chloroform was concentrated to an orange oil identified as desmethylaxerophthene (XI) by its absorption spectrum (Fig. 4); $\lambda_{max.}^{isooctane}$ 3310, 3460 and 3660 Å.

Vitamin A from Vitamin A Acid.—In a 100-cc. 3-necked flask, equipped with stirrer, reflux condenser, dropping funnel and nitrogen inlet was placed a solution of 300 mg. of lithium aluminum hydride in 50 cc. of anhydrous ether. The contents of the flask were cooled to 0°, stirred and maintained under a nitrogen atmosphere while a solution of 65 mg. of crystalline vitamin A acid in anhydrous ether was added dropwise over a period of 15 minutes. After addition was complete, the reaction mixture was stirred an additional 30 minutes. The reaction mixture was then decomposed by the cautious addition of 15 cc. of water. The ether layer was separated and 100 cc. of 5% aqueous potassium hydroxide was added to the aqueous layer and the latter extracted several times with small portions of ether. The combined ether extracts were washed with water until neutral to litmus and then dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* afforded 62 mg. of a pale yellow oil $\lambda_{max.}^{isooctane}$ 3260 Å., $E_{1\,cm.}^{1\%}$ 1340 (80%) (Fig. 3).

Acknowledgment.—The authors are indebted to Mr. R. N. Boos for the microanalyses reported in this paper.

Summary

1. The synthesis of β-ionylideneacetaldehyde and its resolution into two stereoisomeric forms is described.

2. The independent conversion of the two isomeric forms to the same vitamin A acid and thence to vitamin A has been effected.

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(24) Ahrens and van Dorp[18] reported for pure Vitamin A acid: m.p. 181.5°, $\lambda_{max.}^{C_2H_5OH}$ 3470 Å., log $E_{max.}$ 4.64. The position of maximum absorption observed by these authors for their pure acid approximates what we observed for our crude product. The absorption spectral curve reported by these authors, however, possessed a considerable band spread in the region of maximum absorption. In this connection, Schwartzkopf, *et al.*,[21] reported for the ethyl ester of vitamin A acid, $\lambda_{max.}^{hexane}$ 3470 Å., ε 44500; the methyl ester obtained from crystalline vitamin A acid with diazomethane, however, was reported to absorb at 3540–3550 Å., ε 43600. The exact significance of these discrepancies in the absorption spectra is not clear, but very probably are associated with stereomutations in solution about the center of α,β-unsaturation (see the discussion of this point with regard to vitamin A aldehyde by Wendler, Rosenblum and Tishler[15]).

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

The Synthesis of Octahydrocoumarins and their Reaction with Phosphorus Pentoxide

BY ROBERT L. FRANK AND RUTH C. PIERLE

The reaction of γ-lactones with phosphorus pentoxide[1,2,3] or similar reagents[4] has been shown to result in the formation of substituted cyclopentenones, a transformation analogous to the formation of cyclopentenones by ring closure of unsaturated acids.[4–8] In the present investigation the reaction has been extended to a group of δ-lactones, the four octahydrocoumarins XIV, XV, XVI and XVII.

Preparation of Octahydrocoumarins.—Direct hydrogenation of coumarins, if feasible, would yield a wide variety of octahydro derivatives, due to the many excellent methods for substituted coumarins.[9] de Benneville and Connor[10] have studied such hydrogenations and have found that, although octahydrocoumarin can be obtained in good yield from coumarin, the product is contaminated by dihydrocoumarin,[11] a by-product difficult to separate. Exhaustive hydrogenation to eliminate this impurity results in cleavage of the

(1) Frank, Arvan, Richter and Vanneman, THIS JOURNAL, **66**, 4 (1944).

(2) Frank, Armstrong, Kwiatek and Price, *ibid.*, **70**, 1379 (1948).

(3) LaForge and Barthel, *J. Org. Chem.*, **10**, 222 (1948).

(4) Johnson, Johnson and Petersen, THIS JOURNAL, **67**, 1366 (1945).

(5) Haberland and Heinrich, *Ber.*, **72B**, 1222 (1939); Chuang, Tien and Ma, *ibid.*, **69B**, 1494 (1936).

(6) Cook and Lawrence, *J. Chem. Soc.*, 1637 (1935).

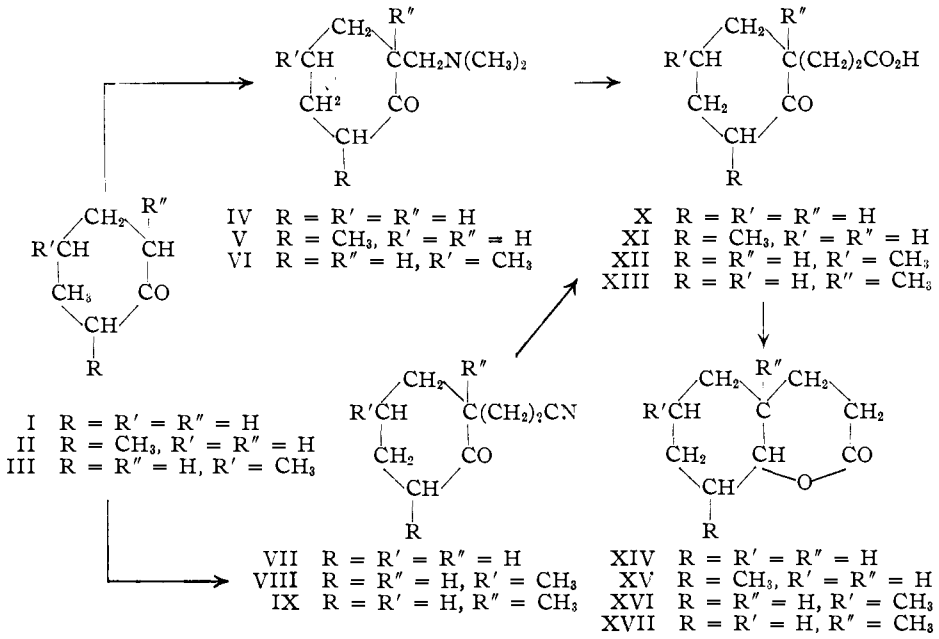
(7) Nenitzescu and Przemetzky, *Ber.*, **74B**, 676 (1941).

(8) Johnson, Davis, Hunt and Stork, THIS JOURNAL, **70**, 3021 (1948).

(9) Sethna and Shah, *Chem. Revs.*, **36**, 1 (1945).

(10) de Benneville and Connor, THIS JOURNAL, **62**, 283, 3067 (1940).

(11) Preparation of a completely pure sample of octahydrocoumarin by another method in this investigation and determination of its refractive index ($n^{20}D$ 1.4912) indicates that the purest octahydrocoumarin yet obtained by hydrogenation still contains 10–12% of the dihydro derivative.



desired product. Substituted coumarins give even less promise of hydrogenation to the octahydro derivatives.[10]

A more satisfactory approach is the reduction of the corresponding β-(2-oxocyclohexyl)-propionic acids (X–XIII). Cook and Lawrence[12] and Nenitzescu and Przemetzky[7] have prepared octahydrocoumarin itself by this means.

Two satisfactory methods are herein evaluated for the preparation of the keto acids X–XIII, one involving alkylation of ethyl malonate by means of the Mannich base of a substituted cyclohexanone, the other involving cyanoethylation of the cyclohexanone. The Mannich base alkylation is useful for Compounds X, XI and XII, but not XIII, and the cyanoethylation process for Compounds X, XII and XIII, but not XI.

The Mannich bases IV, V and VI were prepared in yields of 56–70%.[13] 2-(Dimethylaminomethyl)-6-methylcyclohexanone (V) has not previously been reported, but du Feu, McQuillin and Robinson[14] have prepared its diethyl analog and shown it to have the structure corresponding to V rather than to the other possible isomer, 2-(dimethylaminomethyl)-2-methylcyclohexanone.

The alkylation of ethyl malonate required shorter reaction times and gave higher yields (42–68%) with the use of the modification of Robinson and co-workers,[14] in which the methiodides of the Mannich bases are employed, than by means of the Mannich bases themselves. The free Mannich base V, for example, failed to react at all, while its methiodide alkylated ethyl malonate to the extent of 42%.

In none of the alkylations was the pure substituted ethyl malonate obtained as the product. Each reaction mixture yielded liquid products varying widely in b.p., refractive index, specific gravity and analysis. These data indicate that the products were chiefly mixtures of the substituted malonic esters (XVIII) and the corresponding acetic esters (XIX). The formation of monoesters is to be explained by the alcoholysis reaction described by Wallingford and co-workers,[15] since excess ethanol was used as the reaction medium.

$$\underset{\text{XVIII}}{RCH(CO_2C_2H_5)_2} + C_2H_5OH \underset{}{\overset{NaOC_2H_5}{\rightleftharpoons}} \underset{\text{XIX}}{RCH_2CO_2C_2H_5} + CO(OC_2H_5)_2$$

The mono- and diesters were difficult to separate and were therefore hydrolyzed for the most part as mixtures. The hydrolyses were best accomplished by refluxing the esters with concentrated hydrochloric acid to form the keto acids (X–XII) in yields up to 65%. Saponification with cold ethanolic sodium hydroxide[16] or hot aqueous sodium hydroxide was not satisfactory, the yield in either case being less than 30%.

Cyanoethylation offers a more direct and satisfactory method of preparing cyclohexanonepropionic acids. Bruson and Riener[17] have investigated the polycyanoethylation of cyclohexanone and the methylcyclohexanones, but less study has been directed toward the monocyanoethylation of these compounds. In this work it has been found that if acrylonitrile is added slowly to a large excess of cyclohexanone or 4-methylcyclohexanone, polycyanoethylation is largely eliminated, while monocyanoethylation is increased to provide yields of 21–28%. The excess ketone can be recovered, so the reaction is feasible as a preparative method.

One difficulty in the cyanoethylation process is the formation of 2-cyclohexylidenecyclohexanones under the influence of the basic catalyst. These

(12) Cook and Lawrence, *J. Chem. Soc.*, 817 (1937).

(13) Mannich and Braun, *Ber.*, **53**, 1874 (1920); Mannich and Honig, *Arch. Pharm.*, **265**, 598 (1927); Dimroth, Resin and Zetzch, *Ber.*, **73**, 1399 (1940).

(14) du Feu, McQuillin and Robinson, *J. Chem. Soc.*, 53 (1937).

(15) Wallingford, Homeyer and Jones, THIS JOURNAL, **63**, 2056 (1941); Wallingford, Thorpe and Homeyer, *ibid.*, **64**, 580 (1942).

(16) Mannich and Koch, *Ber.*, **75B**, 803 (1942).

(17) Bruson and Riener, THIS JOURNAL, **64**, 2850 (1942); Bruson, U. S. Patent 2,386,736, 2,386,737 (October 9, 1945) and 2,394,986 (February 12, 1946); *C. A.*, **39**, 2848, 7234, 7235 (1946).

boil in the same range and are difficult to separate from the monocyanoethylation products. In the present work this was no disadvantage as the mixtures were subjected to saponification and the cyclohexylidenecyclohexanones then readily separated from the saponification products.

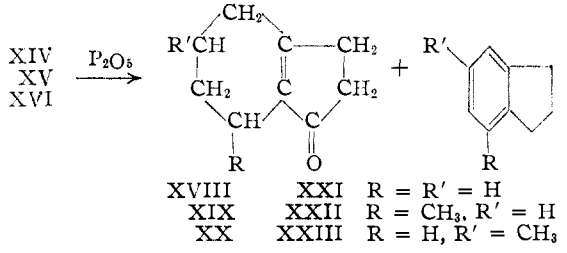
In the case of 2-methylcyclohexanone, monocyanoethylation occurs readily with the reactive tertiary hydrogen atom to form the nitrile IX in 80% yield, free from 2-(2-methylcyclohexylidene)-6-methylcyclohexanone.

The nitriles VII, VIII and IX were hydrolyzed to the keto acids X, XII and XIII in yields of 65–92% by refluxing with 10% aqueous alkali.[17]

Catalytic hydrogenation of the sodium salts of the cyclohexanonepropionic acids (X–XIII) over Raney nickel, followed by acidification, resulted in the formation of octahydrocoumarins (XIV–XVII) in yields of 73–83%. With all but one example the only products isolated after the acidification step were the desired lactones (XIV, XVI and XVII). In one case, the reduction of β-(3-methyl-2-oxocyclohexyl)-propionic acid (XI), acidification of the hydrogenated solution gave a mixture of liquid lactone (44%) and solid hydroxy acid, β-(2-hydroxy-3-methylcyclohexyl)-propionic acid (33%). This acid liquefied on standing in a desiccator over phosphorus pentoxide, and crystallized again on addition of water. It lactonized on distillation, presumably to the geometric isomer of the 8-methyloctahydrocoumarin obtained on acidification.

All the octahydrocoumarins (XIV–XVII), like some other lactones of comparable molecular weight,[18] have a distinct odor and flavor of coconut, especially when diluted.

Reaction of Octahydrocoumarins with Phosphorus Pentoxide.—The reaction of octahydrocoumarin (XIV) with phosphorus pentoxide



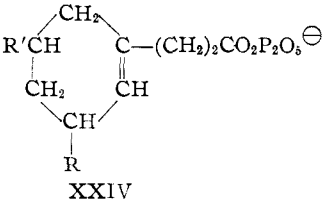
XIV, XV, XVI → P_2O_5 → XVIII, XIX, XX + XXI, XXII, XXIII

XXI R = R′ = H
XXII R = CH_3, R′ = H
XXIII R = H, R′ = CH_3

gave 4,5,6,7-tetrahydroindanone (XVIII) and indan (XXI) in yields of 13 and 17%, respectively. 4,5,6,7-Tetrahydroindanone has been prepared before,[7,8] and our product agreed in constants and m.ps. of derivatives with the reported descriptions. None of the previous preparations, however, gave any assurance that the double bond was actually in the 8,9-position (as in XVIII) rather than in the 7,8-position. Since we wished to use the compound as a reference structure for interpreting the ultraviolet absorption spectra of its substituted analogs, we have confirmed the 8,9-position of the double bond by ozonolysis, the products being γ-ketoazelaic acid, succinic acid and adipic acid. The ultraviolet spectrum of 4,5,6,7-tetrahydroindanone (XVIII) shows strong absorption at 236 mμ (log ε 4.09), further evidence for the 8,9-double bond.[19,20] The 7,8-unsaturated isomer would be expected to absorb at 245 ± 5 mμ, according to recent work by French and Wiley.[21]

Indan (XXI) was characterized by physical properties, formation of its tetrabromide, and by its ultraviolet absorption spectrum. The ultraviolet spectra of substituted indans are distinctive, as discussed in the Experimental Part.

The 6- and 8-methyl substituted octahydrocoumarins (XVI and XV) were chosen for study in order to gain information on the course of the reaction. It seems logical that the transformation of the lactone to the cyclopentenone proceeds through an open-chain intermediate[22] such as the corresponding unsaturated acid or an anion of Type XXIV, followed by acylation of the usual Friedel–Crafts type. In a strongly acidic medium



XXIV

the double bonds of such open-chain intermediates might readily migrate around the ring, with the result that ring closure could occur at either of two points, one adjacent to R (Structure XXIV), the other adjacent to R′. With the 6- and 8-methyloctahydrocoumarins (XVI and XV) such behavior would result in mixtures of the same two tetrahydroindanones (XX and XIX).

Experimentally it was found that each lactone gave rise to a single ketone (23–28%) and its corresponding methylindan (30–36%), ring closure occurring at the point of attachment of the original lactone oxygen. The structures of the products were deduced from the positive identification of the methylindans by oxidation to the corresponding tricarboxybenzenes and by interpretation of their ultraviolet absorption spectra. The ketones and indans from a given reaction were assumed to have the same carbon skeleton. Thus if an open-chain unsaturated intermediate exists, it must cyclize to the tetrahydroindanone without double bond migration.[23]

The occurrence of indans or substituted indans in all these reactions can be explained as arising from the tetrahydroindanones by enolization, dehydration and migration of double bonds under the influence of phosphoric acid.

10-Methyloctahydrocoumarin (XVII) gave only the hydrocarbon 4-methylindan (XXII) in 60% yield when heated with phosphorus pentoxide, a result indicative of a rearrangement of the carbon

(18) Wiggins and Overend, *Mfg. Chemist*, **19**, 369 (1948); *C. A.*, **43**, 784 (1949).

(19) Woodward, THIS JOURNAL, **63**, 1123 (1941); **64**, 76 (1942).

(20) Gillam and West, *J. Chem. Soc.*, 486 (1942).

(21) French and Wiley, THIS JOURNAL, **71**, 3702 (1949).

(22) Evidence that the unsaturated acids are intermediates is the finding of Johnson and co-workers (ref. 4) that the unsaturated acids give higher yields of cyclopentenones than do the lactones.

(23) One bit of evidence indicates a small amount of such rearrangement. The reaction of 8-methyloctahydrocoumarin (II) with phosphorus pentoxide yielded a sample of 4-methylindan (VIII) which possessed a weak absorption maximum at 279 mμ, characteristic of 5-methylindan (XXIII) (see Table I).

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF SUBSTITUTED INDANS

Indan	Source (lactone)	Concn. (g./liter 95% EtOH soln.)	λmax. (mμ)	ε	λmax. of corresponding methylbenzenes[a]
Indan (XXI)	XIV	0.0458	261	766	
			267	1098	264
			273	1192	271
4-Methylindan (XXII)	XVII	.0512	260	475	258
			265	634	262
					266
			272.5	647	270
4-Methylindan (XXII)	XV	.0418	261	541	258
			265.5	620	262
					266
			273.5	660	270
			279[b]	304	
5-Methylindan (XXIII)	XVI	.0782	261	634	
			266.5	858	263
			273	1029	268
			279	660	276

[a] See ref. 39. [b] This weak absorption band at 279 mμ indicates the presence of some 5-methylindan. See footnote 23.

skeleton. This can be explained by considering the close relationship of the lactone XVII to an ester of a neopentyl alcohol. A rearrangement of the type described by Whitmore,[24] followed by cyclization of the Friedel–Crafts type, would give the carbon skeleton of 4-methylindan.

Experimental

Hydrogenation of Coumarin.—In a series of hydrogenations similar to the experiments of de Benneville and Connor,[10] using methylcyclohexane as the solvent, a temperature of 200° and pressures of 100–150 atmospheres, followed by slow distillation through a four-foot Podbielniak-type column[25] having a solid core, there were obtained fractions in the boiling range 138–149° (16 mm.), the refractive indices (n^{20}D) of which (in a typical case) started at 1.5275 (dihydrocoumarin and hexahydrochroman), rose to a maximum of 1.5461 (nearly pure dihydrocoumarin; lit.,[10] n^{25}D 1.5541), and then decreased to a minimum of 1.5036 near the end of the distillation (88.5% octahydrocoumarin–11.5% dihydrocoumarin, assuming only these two components).

Mannich Bases of Cyclohexanones (IV–VI).—Dimethylamine hydrochloride (one equivalent) was prepared by evaporation under reduced pressure of a mixture of aqueous dimethylamine and excess concentrated hydrochloric acid. To the solid residue was added an aqueous solution of the cyclohexanone (two equivalents) and formaldehyde (one equivalent). The two-phase mixture was heated carefully (reaction is exothermic) to boiling under a long reflux condenser, boiled for about five minutes, then cooled to room temperature. Water (125–200 ml.) was added, the layers separated, the aqueous layer saturated with sodium chloride, washed with four 50-ml. portions of ether, and then made basic with 30% aqueous potassium hydroxide (1.3 equivalents). The Mannich base separated as a yellow upper layer with a strong amine odor. The layers were separated, the aqueous layer extracted with five 30- to 100-ml. portions of ether, and the combined organic layer and ether extracts dried over magnesium sulfate and distilled in a ten-inch helix-packed column.

2-(Dimethylaminomethyl)-cyclohexanone (IV).—From 45 g. (1.00 mole) of dimethylamine (as 25% aqueous solution), 196 g. (2.00 moles) of cyclohexanone and 30 g. (1.00 mole) of formaldehyde (as 40% aqueous solution) was obtained 87 g. (56%) of Mannich base, b.p. 60° (1 mm.) (lit.,[13] 93–94° (11.5 mm.)); n^{20}D 1.4670.

When the molar ratio of cyclohexanone to other reagents was five-to-one rather than two-to-one as above, the yield of Mannich base was somewhat lower (35–47%).

2-(Dimethylaminomethyl)-6-methylcyclohexanone (V) from the same quantities of dimethylamine and formaldehyde as in the reaction above and 218 g. (1.94 moles) of 2-methylcyclohexanone was obtained 118.4 g. (70%) of Mannich base, b.p. 71° (1.3 mm.); n^{20}D 1.4650; sp. gr.$^{20}_{20}$ 0.937; *MR* calcd., 50.31; *MR* found, 49.94.

Anal.[26] Calcd. for $C_{10}H_{19}ON$: N, 8.28. Found: N, 8.11.

2-(Dimethylaminomethyl)-4-methylcyclohexanone (VI).—From 22.5 g. (0.500 mole) of dimethylamine, 15 g. (0.50 mole) of formaldehyde and 112 g. (1.00 mole) of 4-methylcyclohexanone was obtained 51 g. (60%) of Mannich base, b.p. 70° (1 mm.) (lit.,[13] 123–125° (30 mm.)); n^{20}D 1.4625.

Mannich Base Methiodides.—A one-equivalent excess of methyl iodide in absolute ether was added dropwise with constant swirling over a one-hour period to an ice-cold ether solution of the Mannich base (0.386–0.665 mole). The white sludge which formed was allowed to warm gradually to room temperature, then collected and dried in a vacuum desiccator over calcium chloride.

The Mannich base IV gave 2-(dimethylaminomethyl)-cyclohexanone methiodide in a yield of 94%; the Mannich base VI formed its methiodide in a yield of 97%. Both were cream-colored powders which decomposed on heating.[13]

The Mannich base V was converted in 97.5% yield to 2-(dimethylaminomethyl)-6-methylcyclohexanone methiodide, m.p. 163–164° (with formation of a solid which decomposed at 195° with evolution of a gas).

Anal. Calcd. for $C_{11}H_{22}ONI$: C, 42.45; H, 7.13. Found: C, 42.67; H, 7.29.

Alkylations of Ethyl Malonate by Means of Mannich Bases and Their Methiodides.—One example is described in detail. Those which follow were carried out in similar fashion with the same ratios of solvents.

Ethyl (2-Oxocyclohexylmethyl)-malonate and Ethyl β-(2-Oxocyclohexyl)-propionate.—To a solution of sodium ethoxide prepared from 250 ml. of absolute ethanol and 13.0 g. (0.565 gram-atom) of sodium was added 90.5 g. (0.565 mole) of ethyl malonate, followed by a solution of 137 g. (0.461 mole) of the methiodide of the Mannich base IV in 500 ml. of hot absolute ethanol. The solution was refluxed for ten hours, and most of the ethanol then removed by distillation. The residue, about 200 ml., was cooled, forming a white precipitate, then diluted with 500 ml. of water and acidified at once with 10 ml. of concentrated hydrochloric acid. The yellow upper layer was separated, the lower aqueous layer saturated with sodium chloride and extracted with five 40-ml. portions of ether, and the ether extracts combined with the yellow oil. Fractional distillation in a ten-inch helix-packed column, after drying over magnesium sulfate, yielded 75.4 g. of colorless liquid, b.p. 135–195° (7 mm.); n^{20}D 1.4610. Judging from the analyses and molar refractivities of the fractions collected, the product was a mixture of the mono- and diesters (about 60%) and cyclohexylidenecyclohexanone. It was not further separated.

In an experiment using the free Mannich base IV a mixture of 20.0 g. (0.129 mole) of the Mannich base and 25.8 g. (0.161 mole) of ethyl malonate was allowed to stand at 25° for 24 hours, then acidified and worked up as above to yield 21.2 g. (61%) of ethyl (2-oxocyclohexylmethyl)-malonate, b.p. 155–157° (2 mm.); n^{20}D 1.4656.

Ethyl (3-Methyl-2-oxocyclohexylmethyl)-malonate and Ethyl β-(3-Methyl-2-oxocyclohexyl)-propionate.—From 17.2 g. (0.749 gram-atom) of sodium in ethanol, 120 g. (0.749 mole) of ethyl malonate and 180 g. (0.579 mole) of 2-(dimethylaminomethyl-6-methylcyclohexanone methiodide were obtained 25.9 g. of liquid, b.p. 124–127° (4 mm.), n^{20}D 1.4563; and 35.6 g., b.p. 156–160° (1 mm.), n^{20}D 1.4643, sp. gr.$^{20}_{20}$ 1.060 (total yield of mono- and diesters not greater than 42%). Redistillation of the first fraction gave pure monoester, b.p. 117° (2 mm.); n^{20}D 1.4611; sp. gr. $^{20}_{20}$ 1.022; *MR* calcd., 57.10; *MR* found, 57.01.

Anal. Calcd. for $C_{12}H_{20}O_5$: C, 67.89; H, 9.50. Found: C, 67.57; H, 9.49.

Redistillation of the latter fraction did not result in a pure sample of the diester.

(24) Whitmore, THIS JOURNAL, **54**, 3274 (1932).

(25) Podbielniak, *Ind. Eng. Chem., Anal. Ed.*, **3**, 177 (1931).

(26) Microanalyses were performed by Miss Emily Davis, Miss Rachel Kopel, Mrs. Jane Wood, Mr. Maurice Dare and the Clark Microanalytical Laboratory.

Ethyl (5-Methyl-2-oxocyclohexylmethyl)-malonate and Ethyl β-(5-Methyl-2-oxocyclohexyl)-propionate.—From 8.6 g. (0.37 gram-atom) of sodium in ethanol, 60 g. (0.37 mole) of ethyl malonate and 90 g. (0.29 mole) of 2-(dimethylaminomethyl)-4-methylcyclohexanone methiodide was obtained 17.3 g. (28%) of monoester, b.p. 123–125° (1 mm.), $n^{20}D$ 1.4590, sp. gr.$^{25}_{25}$ 1.025, *MR* calcd., 57.10; *MR* found, 56.62, and 32.7 g. (40%) of diester, b.p. 162° (2 mm.), $n^{20}D$ 1.4609, sp. gr.$^{25}_{25}$ 1.057, *MR* calcd., 72.61; *MR* found, 73.80.

Anal. (of monoester) Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.17; H, 9.37.

Anal. (of diester) Calcd. for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.72; H, 8.55.

Cyanoethylation Reactions.—These were carried out by placing the cyclohexanone (previously washed with dilute aqueous alkali and distilled) and Triton B[17] (*ca.* 1 g. for each 40 g. of cyclohexanone) in a three-necked round-bottomed flask equipped with a stirrer, reflux condenser, dropping funnel and thermometer. To this was added dropwise the freshly distilled acrylonitrile (0.25 mole per mole of cyclohexanone) over a period of 30 to 60 minutes. The mixture was cooled intermittently with an ice-bath to keep the temperature below 35°. Stirring was then continued for 5 to 16 hours, followed by acidification with dilute hydrochloric acid, washing with three portions (10 ml. for each 60 g. of cyclohexanone used) of saturated aqueous sodium chloride, drying over magnesium sulfate, and distillation in a ten-inch helix-packed column.

β-(2-Oxocyclohexyl)-propionitrile (VII).—From 1178 g. (12.00 moles) of cyclohexanone and 159 g. (3.00 moles) of acrylonitrile was obtained 88.2 g. (19.4%) of product, b.p. 138–142° (10 mm.); $n^{20}D$ 1.4755; along with 835 g. (8.50 moles) of recovered cyclohexanone and 77.6 g. of a mixture of the desired product and 2-cyclohexylidenecyclohexanone, b.p. 112–116° (1 mm.); $n^{20}D$ 1.4911 (total yield of nitrile 28%).

β-(5-Methyl-2-oxocyclohexyl)-propionitrile (VIII).—From 224 g. (2.00 moles) of 4-methylcyclohexanone and 26.5 g. (0.500 mole) of acrylonitrile were obtained 157 g. (1.40 moles) of unreacted 4-methylcyclohexanone and 22.4 g. of colorless liquid, b.p. 115–124° (1 mm.); $n^{20}D$ 1.4808–1.4707 (assuming this fraction to be a mixture of nitrile and 2-(4-methylcyclohexylidene)-4-methylcyclohexanone, $n^{20}D$ 1.4986, the yield of nitrile is 21%). An analytical sample was obtained by redistillation, b.p. 92° (0.5 mm.); $n^{20}D$ 1.4699; sp. gr.$^{20}_{20}$ 0.998; *MR* calcd., 45.96; *MR* found, 46.19.

Anal. Calcd. for $C_{10}H_{15}NO$: N, 8.48. Found: N, 8.63.

β-(1-Methyl-2-oxocyclohexyl)-propionitrile (IX).—From 224 g. (2.00 moles) of 2-methylcyclohexanone and 26.5 g. (0.500 mole) of acrylonitrile were obtained 156 g. (1.39 moles) of unreacted 2-methylcyclohexanone and 66.2 g. (80%) of the desired nitrile, b.p. 131° (1 mm.); $n^{20}D$ 1.4778; sp. gr.$^{20}_{20}$ 1.023; *MR* calcd., 45.96; *MR* found, 45.70.

Anal. Calcd. for $C_{10}H_{15}NO$: N, 8.48. Found: N, 8.72.

The Keto Acids X–XIII.—These were made by acid hydrolysis of the esters from the Mannich base alkylations or by alkaline hydrolysis of the cyanoethylation products. A typical example of each is described; descriptions of the other keto acids are confined to their yields and physical constants.

β-(2-Oxocyclohexyl)-propionic Acid (X) (from the Nitrile).—Eighty-five grams (0.56 mole) of the nitrile VII was refluxed with 300 ml. of 10% aqueous sodium hydroxide for 24 hours. The mixture was then saturated with sodium chloride, extracted with two 100-ml. portions of ether, filtered to remove silicates, then acidified with concentrated hydrochloric acid. An oily upper layer formed, which solidified on standing to yield 87 g. of crude product. One recrystallization from high-boiling petroleum ether gave 79.5 g. (83%) of tiny needles, m.p. 64° (lit.,[16] 65°).

In other runs the cyanoethylation product was hydrolyzed directly, without preliminary removal of the cyclohexylidenecyclohexanone. In these cases the keto acid did not crystallize from the reaction mixture, but was extracted with ether as an oil. Evaporation of the ether then yielded the crystalline acid.

β-(3-Methyl-2-oxocyclohexyl)-propionic Acid (XI) (from the Esters).—Twenty-eight grams (*ca.* 0.115 mole) of a mixture containing approximately equal weights of the mono- and diester obtained from the Mannich base V was refluxed for 6 hours with 168 ml. of concentrated hydrochloric acid. The two-phase mixture was then partially evaporated *in vacuo*, diluted with a solution of 70 g. of ammonium sulfate in 100 ml. of water, extracted with four 75-ml. portions of ether, and the ether extracts dried and evaporated to yield 20 g. of a brown oil which crystallized on standing. One recrystallization from high-boiling petroleum ether gave 13.8 g. (about 65% from the esters; 28.5% from the Mannich base V methiodide) of keto acid, m.p. 70° (lit.,[27] 71°).

β-(5-Methyl-2-oxocyclohexyl)-propionic Acid (XII).—From 4.1 g. (0.025 mole) of the nitrile VIII was obtained 3.0 g. (65%) of keto acid, m.p. 45–46°. An analytical sample, crystallized five times from high-boiling petroleum ether, formed microscopic mica-like plates, m.p. 53°.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 65.43; H, 8.97.

The same product was obtained in 12% yield by an alkaline hydrolysis of the ester mixture from the Mannich base VI.

β-(1-Methyl-2-oxocyclohexyl)-propionic Acid (XIII).—From 19.8 g. (0.120 mole) of the nitrile IX was obtained 20.2 g. (91.4%) of the keto acid, m.p. 45–48°. An analytical sample, microscopic plates after five recrystallizations from petroleum ether, melted at 48°.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 65.36; H, 8.86.

Octahydrocoumarins (XIV–XVII).—Catalytic hydrogenations were carried out as follows: the sodium salts of the acids were formed by dissolving the acids in 10% aqueous sodium hydroxide containing one equivalent of sodium hydroxide, so that the solutions were just basic to phenolphthalein. After a preliminary refluxing over Raney nickel, followed by filtration, the solutions were hydrogenated over 10 g. of Raney nickel at 85–90° and 125 atmospheres initial (25°) pressure. Acidification of the resulting solutions with four equivalents of concentrated sulfuric acid, saturation with sodium chloride, extraction with four 100-ml. portions of ether, drying over magnesium sulfate, and distillation in a ten-inch helix-packed column gave the pure octahydrocoumarins.

Octahydrocoumarin (XIV).—From 112 g. (0.658 mole) of β-(2-oxocyclohexyl)-propionic acid (X) was obtained 82.1 g. (81%) of octahydrocoumarin, b.p. 110° (1 mm.); $n^{20}D$ 1.4912; sp. gr.$^{20}_{20}$ 1.096; *MR* calcd., 41.03; *MR* found, 40.76.

A similar hydrogenation of the free keto acid (X) gave the lactone in 71.5% yield. An attempt to hydrogenate the mixture of esters from the Mannich base IV, followed by acid-catalyzed ester interchange to form the desired lactone, was not successful, apparently because of resistance of the esters to hydrogenation.

8-Methyloctahydrocoumarin (XV) and β-(2-Hydroxy-3-methylcyclohexyl)-propionic Acid.—From 15 g. (0.081 mole) of the keto acid XI was obtained a solution which on acidification with 11 ml. of concentrated sulfuric acid in 30 ml. of water gave a colorless oil and a crystalline solid. After removal of the solid, the oil was purified as above to yield 6.0 g. (44%) of 8-methyloctahydrocoumarin, b.p. 103–106° (1 mm.); $n^{20}D$ 1.4876; sp. gr. $^{20}_{20}$ 1.068; *MR* calcd., 45.65; *MR* found, 45.35. This lactone did not crystallize on standing in water.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.67; H, 9.79.

The solid hydroxy acid, 5.0 g. (33%), melted gradually at about 80° with evolution of a gas. It could be recrystallized from dilute sulfuric acid, but was converted on warming with organic solvents to an oil which did not resolidify on cooling. The solid was stable in air, but was converted to an oil when allowed to stand in a vacuum desiccator over phosphorus pentoxide. The oil crystallized on treatment with water. The solid was soluble in alkali, and infrared analysis[28] showed hydroxyl absorption at 3332 cm.$^{-1}$ and carbonyl absorption at 1685 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 63.90; H, 9.75.

(27) Chatterjee and Bose, *J. Ind. Chem. Soc.*, **18**, 196 (1941).

(28) The infrared spectrum was determined by Miss Elizabeth Petersen using a Perkin-Elmer Model 12B infrared spectrometer with rock salt optics.

The hydroxy acid was lactonized by vacuum distillation, b.p. 99–101° (1 mm.); $n^{20}D$ 1.4878.

6-Methyloctahydrocoumarin (XVI).—From 25.0 g. (0.136 mole) of the keto acid XII was obtained 16.6 g. (73%) of lactone, b.p. 94° (1 mm.); $n^{20}D$ 1.4841, sp. gr.$^{20}_{20}$ 1.06; *MR* calcd., 45.65; *MR* found, 45.41.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39, H, 9.59. Found: C, 71.36; H, 9.77.

10-Methyloctahydrocoumarin (XVII).—From 48.5 g. (0.263 mole) of the keto acid XIII was obtained 36.7 g. (83%) of lactone, b.p. 110° (1 mm.); $n^{20}D$ 1.4924; sp. gr.$^{20}_{20}$ 1.077; *MR* calcd., 45.65; *MR* found, 45.35.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.05; H, 9.74.

Reactions with Phosphorus Pentoxide.—The phosphorus pentoxide (1 mole per mole of lactone) was placed in a round-bottomed glass-jointed flask. The lactone was added and the flask immediately attached to a short helix-packed column. The system was evacuated to 15 mm., the reaction initiated by warming if necessary, and the product distilled. A free flame was used for the distillation after the initial exothermic reaction had subsided. The product was then redistilled.

Of Octahydrocoumarin (XIV).—From 30.8 g. (0.200 mole) of octahydrocoumarin was obtained 8.2 g. of liquid, refractionated to yield 3.5 g. (13%) of 4,5,6,7-tetrahydroindanone, b.p. 128–129° (18 mm.), $n^{20}D$ 1.5200, sp. gr.$^{20}_{20}$ 1.043, *MR* calcd., 38.92; *MR* found, 39.70; and 4.0 g. (17%) of indan, b.p. 70–71° (18 mm.), $n^{20}D$ 1.5367, sp. gr.$^{20}_{20}$ 0.963, *MR* calcd.,37.97; *MR* found, 38.34.[29]

4,5,6,7-Tetrahydroindanone had absorption maxima in the ultraviolet at 236 mμ (log ε 4.09) (3.8×10^{-3} g. per liter of 95% ethanol solution) and at 295 mμ (log ε 1.92).[30] Its semicarbazone melted at 240° (lit.,[7] 243°) and had maximum absorption at 265 mμ (log ε 4.32) (5.6×10^{-3} g. per liter of 95% ethanol solution). Its 2,4-dinitrophenylhydrazone, prepared according to the procedure of Johnson and co-workers,[8] fine red needles from ethyl acetate, melted at 228° (lit.,[8] 238.5–239.5°).

Treatment of 0.5 ml. of the indan with 2 ml. of bromine containing a crystal of iodine and cooled to 0° gave 4,5,6,7-tetrabromoindan, white needles after four crystallizations from absolute ethanol, m.p. 197° (lit.,[31] 200°).

Anal. Calcd. for $C_9H_6Br_4$: C, 24.92; H, 1.39. Found: C, 24.73; H, 1.70.

Oxidation of 0.5 ml. of the indan was carried out by refluxing with 2.0 g. of potassium permanganate and 40 ml. of 0.12% aqueous sodium hydroxide for 2 hours. After acidification with dilute sulfuric acid, addition of sodium bisulfite, filtration and evaporation, there was obtained a white solid, m.p. 208° (dec.). After heating to 220°, the product remelted at 131° (lit. for phthalic anhydride,[32] 131°).

Of 8-Methyloctahydrocoumarin (XV).—From 4.80 g. (0.0285 mole) of lactone was obtained 1.2 g. (28%) of 7-methyltetrahydroindanone, b.p. 92° (2 mm.); $n^{20}D$ 1.5180; sp. gr. $^{20}_{20}$ 1.019; *MR* calcd., 43.54; *MR* found, 44.67; and 1.15 g. (30.5%) of 4-methylindan, b.p. 84–85° (20 mm.); $n^{20}D$ 1.5323; sp. gr.$^{20}_{20}$ 0.956; *MR* calcd., 42.59; *MR* found, 42.87.

Anal. (for the ketone) Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.39; H, 10.02.

7-Methyl-4,5,6,7-tetrahydroindanone showed an absorption maximum at 237 mμ (log ε 3.93) (4.8×10^{-3} g. per liter of 95% ethanol solution). Its semicarbazone, shiny plates after three recrystallizations from absolute ethanol, melted at 219–220° and gave maximum absorption of ultraviolet light at 273–276 mμ (log ε 4.22) (1.7×10^{-3} g. per liter of 95% ethanol solution). A mixed m.p. with the semicarbazone obtained from 5-methyltetrahydroindanone, described below, was 209–210° (dec.).

Anal. Calcd. for $C_{11}H_{17}N_3O$: N, 20.27. Found: N, 20.12. Its 2,4-dinitrophenylhydrazone, short red needles from ethyl acetate, melted at 200°.

Anal. Calcd. for $C_{16}H_{18}N_4O_4$: N, 16.96. Found: N, 16.74.

A 0.5-g. sample of the 4-methylindan was oxidized with 4.5 g. of potassium permanganate in 90 ml. of water containing 2.5 ml. of 10% sodium hydroxide, according to the method of Schultze[33] for the oxidation of 1,2,4-trimethylbenzene. The crystalline product, colorless hemimellitic acid, after three recrystallizations from acetone–chloroform, melted at 194–197° (dec.) (lit.,[34] 197° (dec.) and[35] 188–190° (dec.)). When heated to 220°, cooled and remelted, the product melted at 187–193° (lit. for hemimellitic anhydride,[36] 196°). The acid did not depress the m.p. of the acid formed by oxidation of the hydrocarbon obtained from 10-methyloctahydrocoumarin (XVII), but did depress the m.p. of that obtained from the methylindan from 6-methyloctahydrocoumarin (XVI).

Of 6-Methyloctahydrocoumarin (XVI).—From 9.20 g. (0.0546 mole) of lactone was obtained 1.9 g. (23%) of 5-methyl-4,5,6,7-tetrahydroindanone, b.p. 120° (19 mm.), $n^{20}D$ 1.5160, sp. gr.$^{20}_{20}$ 1.020, *MR* calcd., 43.54; *MR* found, 44.48; and 2.6 g. (36%) of 5-methylindan, b.p. 82° (17 mm.), $n^{20}D$ 1.5316, sp. gr.$^{20}_{20}$ 0.951, *MR* calcd., 42.59; *MR* found, 43.17.

Anal. (for the ketone) Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.82; H, 9.32.

Anal. (for the indan) Calcd. for $C_{10}H_{12}$: C, 90.85; H, 9.15. Found: C, 90.85; H, 9.13.

5-Methyl-4,5,6,7-tetrahydroindanone showed ultraviolet absorption maxima at 237.5 mμ (log ε 4.05) (6.0×10^{-3} g. per liter of 95% ethanol solution) and at 293 mμ (log ε 1.83). Its semicarbazone melted at 235° (dec.) and showed maximum absorption at 261-262 mμ (log ε 4.31) (2.1×10^{-3} g. per liter of 95% ethanol solution).

Anal. Calcd. for $C_{11}H_{18}N_3O$: N, 20.27. Found: N, 20.40. Its 2,4-dinitrophenylhydrazone, fine dark red needles from ethyl acetate, melted at 225°.

Anal. Calcd. for $C_{16}H_{12}N_4O_4$: N, 16.96. Found: N, 16.88.

A 0.5-g. sample of the 5-methylindan was oxidized as described above[33] to yield a solid acid which melted after four crystallizations from acetone–chloroform at 200–204° (dec.). After heating to 220°, cooling and remelting, the sample melted at 161° (lit. for trimellitic anhydride,[33] 162.5–163°).

Of 10-Methyloctahydrocoumarin (XVII).—From 14.3 g. (0.085 mole) of lactone was obtained 6.7 g. (60%) of 4-methylindan, b.p. 59–60° (2 mm.); $n^{20}D$ 1.5309; sp. gr.$^{20}_{20}$ 0.951; *MR* calcd., 42.59; *MR* found, 43.00.

Anal. Calcd. for $C_{10}H_{12}$: C, 90.85; H, 9.15; C-methyl, 11.37. Found: C, 90.38; H, 9.48; C-methyl, 1.13. A C-methyl value of 10% of theoretical is characteristic of a methyl group attached to a benzene ring.[37]

Permanganate oxidation as described above gave hemimellitic acid, m.p. 190–191° (dec.) (lit.,[34,35] 197°, 188–190° (dec.)) after four crystallizations from acetone–chloroform. Its anhydride melted at 190° without decomposition.[36] A mixture with the trimellitic acid from the 5-methylindan from 6-methyloctahydrocoumarin melted at 185–195°.

Ozonolysis of 4,5,6,7-Tetrahydroindanone (XIV).—A stream of ozone and oxygen at a rate of 0.326 millimole of ozone per minute was passed through a solution of 1.01 g. (0.0074 mole) of tetrahydroindanone in 15 ml. of methylene chloride for 39 minutes. A solution of 4 ml. of 30% hydrogen peroxide, 0.2 ml. of concentrated sulfuric acid and 30 ml. of water was then added, the mixture refluxed for one hour, and the methylene chloride and about three-fourths of the water removed by distillation. The residue was further acidified with sulfuric acid, saturated with ammonium sulfate, and extracted with three 50-ml. portions of ether. Evaporation of the dried ether extracts yielded 0.9 g. of a yellow oil and a white solid. The white solid, after washing

(29) The ratio of tetrahydroindanone to indan varied considerably from one expt. to another. This may be connected with the amount of water absorbed by the phosphorus pentoxide, as we have observed that the proportion of hydrocarbon was usually higher when the reactions were performed in humid weather than in dry weather.

(30) Ultraviolet absorption spectra were obtained by Dr. and Mrs. J. C. Brantley and Mr. John Gardner using a Beckman model DU spectrophotometer.

(31) Meyer and Meyer, *Ber.*, **51**, 1571 (1918).

(32) van de Stadt, *Z. physik. Chem.*, **41**, 359 (1902).

(33) Schultze, *Ann.*, **359**, 129 (1908).

(34) Dziewoński, *Ber.*, **46**, 2156 (1913).

(35) Kruber, *ibid.*, **57**, 1010 (1924).

(36) Graebe and Bossel, *Ann.*, **290**, 206 (1896).

(37) Kuhn and L'Orsa, *Z. angew. Chem.*, **44**, 847 (1931).

with chloroform, melted at 174–175° (a later trial gave material of m.p. 178–179°) and had a neutral equivalent of 63 (calcd. for succinic acid, 59). A mixed m.p. with pure succinic acid, m.p. 188°, was 184–188°. Concentration of the yellow chloroform washings yielded a small amount of white solid, m.p. 148–152°; neutral equivalent 74 (calcd. for adipic acid, 73). A mixed m.p. with adipic acid, m.p. 152°, was 148–152°. Further evaporation gave a yellow solid slightly soluble in cold benzene, ether and chloroform, but readily soluble in water and hot organic solvents. Four crystallizations of this material from benzene and chloroform gave a small quantity of γ-ketoazelaic acid, m.p. 110–111° (lit.,[38] 108–109°); neutral equivalent 100 (calcd. for γ-ketoazelaic acid, 101). Its semicarbazone, microcrystals from water, melted at 197–198° (dec.) (lit.,[38] 197°). Mixed m.p.'s of the ketoazelaic acid and the semicarbazone with available authentic samples were 109.5–111° and 196.5–198°, respectively.

Ultraviolet Absorption Spectra of Indans.—Table I summarizes the ultraviolet data on the indans prepared in this work. The spectra vary sufficiently to make possible the differentiation of indans unsubstituted in the aromatic nucleus, 4-alkyl derivatives and 5-alkyl derivatives. Of interest is the comparison of these data with those of the corresponding methylbenzenes. The spectra are parallel, with the indans absorbing at wave lengths 2–5 mμ higher than the alkyl benzenes, as indicated by the last column of Table I taken from the work of Conrad-Billroth.[39]

(38) Brown and Farmer, *Biochem. J.*, **29**, 631 (1935).

Summary

Two synthetic routes to the substituted octahydrocoumarins have been investigated, one using the Mannich bases of cyclohexanones and the other involving the cyanoethylation of cyclohexanones. Octahydrocoumarin and the 6-, 8- and 10-methyloctahydrocoumarins have been prepared by these methods.

These four octahydrocoumarins have been treated with phosphorus pentoxide, the products characterized and the reactions discussed. Octahydrocoumarin is converted to 4,5,6,7-tetrahydroindanone and indan, 8-methyloctahydrocoumarin to 7-methyl-4,5,6,7-tetrahydroindanone and 4-methylindan, 6-methyloctahydrocoumarin to 5-methyl-4,5,6,7-tetrahydroindanone and 5-methylindan and 10-methyloctahydrocoumarin to 4-methylindan.

(39) Conrad-Billroth, *Z. physik. Chem.*, **B29**, 170 (1935).

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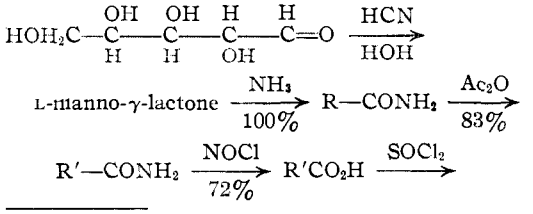
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

L-Mannoheptulose (L-Manno-L-*tagato*-heptose)[1]

BY M. L. WOLFROM AND HARRY B. WOOD

In extension of our previous work on ketose synthesis, we herein describe the synthesis of a new ketoheptose, L-mannoheptulose (L-manno-L-*tagato*-heptose). This is the enantiomorph of D-mannoheptulose, the naturally occurring ketoheptose isolated by LaForge[2] from the fruit of the avocado tree (*Persea gratissima* Gaert.). D-Mannoheptulose ("mannoketoheptose") has been synthesized: by Montgomery and Hudson[3] from D-manno-D-*gala*-heptose through alkaline rearrangement; by Sowden[4] from D-arabinose through condensation with the sodium salt of 2-nitroethanol and subsequent hydrolysis; and by Ettel and Liebster[5] from natural volemitol (D-manno-D-*talo*-hepitol) by oxidation with *Acetobacter suboxydans* (though not with *Acetobacter xylinum*[6]).

In this work, L-mannoheptulose has been synthesized from L-arabinose through the reactions



The procedure of Kiliani[7] was employed in converting natural L-arabinose to L-mannono-γ-lactone. In crystallizing this lactone from ethanol, a considerable quantity of ethyl L-mannonate was obtained in crystalline condition. It would thus appear that mannonic acid has some stability in its acyclic form, albeit the ester may be easily converted[8] to the lactone. The enantiomorph of this ester has been reported by Nef and Hedenburg[8] who encountered it in their classical studies on the γ and δ forms of D-mannonolactone.

L-Mannonamide was found by us to be surprisingly hydrolytically unstable (see Fig. 1). To our knowledge, this behavior has not been reported previously. The polarimetric data of Fig. 1 would indicate that the final product in solution is mainly the ammonium salt. Recently, Hockett and co-workers[9] recommended that aldonamides be recrystallized from methyl cellosolve (ethylene glycol monomethyl ether) to avoid hydrolysis.

(1) Paper No. 13 in the series entitled "The Action of Diazomethane upon Acyclic Sugar Derivatives"; previous communication, M. L. Wolfrom and P. W. Cooper, THIS JOURNAL, **72**, 1345 (1950).

(2) F. B. LaForge, *J. Biol. Chem.*, **28**, 511 (1917).

(3) Edna M. Montgomery and C. S. Hudson, THIS JOURNAL, **61**, 1654 (1939).

(4) J. C. Sowden, *ibid.*, **73**, 3325 (1950).

(5) V. Ettel and J. Liebster, *Collection Czechoslov. Chem. Communs.*, **14**, 80 (1949).

(6) Laura C. Stewart, N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **71**, 3532 (1949).

(7) (a) H. Kiliani, *Ber.*, **19**, 3033 (1886); (b) **55**, 100 (1922).

(8) J. U. Nef (and O. Hedenburg), *Ann.*, **403**, 316 (1914); O. F. Hedenburg (and J. U. Nef), THIS JOURNAL, **37**, 345 (1915).

(9) R. C. Hockett, J. B. Ames, H. A. Hill and A. Scattergood, *Abstracts Papers Am. Chem. Soc.*, **114**, 3Q (1948); R. C. Hockett, private communication.