dium–charcoal was conducted for 24 hr. Dilution of the filtered solution gave a solid product that after one recrystallization from methanol melted at 137–139° and gave a positive test with tetranitromethane. A second recrystallization gave a small amount of material, m.p. 142–143°, that gave no depression in m.p. when mixed with a sample of methyl **3α-acetoxy-Δ⁸-cholenate** (VIII, paper I).

7,11-Diketo-Δ²²-ergostenyl Acetate (W.P.S.).—The starting material was prepared from ergosterol *via* **5-dihydroergosteryl acetate**,[12,13] m.p. 180–182°, λ 282 mμ (370), which on dehydrogenation with mercuric acetate[14] afforded in 49% yield **Δ⁷,⁹(¹¹),²²-ergostatrienyl acetate**, m.p. 174–175.5°, $\alpha^{23}D$ +28.7 ± 0.4° Di, λ^{EtOH} 236, 243, 251 mμ (15,900, 17,400, 11,500).

A solution of 500 mg. of this triene in 60 cc. of warm *t*-butanol was cooled and treated with 20 cc. of 0.05 *N* sulfuric acid, when a cloudy precipitate separated. The suspension was stirred in an ice-bath during addition over one-half hour of 500 mg. of N-bromosuccinimide; the precipitate dissolved after 420 mg. had been added. The pale yellow solution was stirred at 0° for 1 hr., 5% silver nitrate was added until precipitation of bromide was complete and 0.9 g. of chromic anhydride in a little water was added. After stirring for 4 hr. the mixture was processed as described in the bile acid series and the crude product, a yellow oil, was chromatographed on 18 g. of alumina. Petroleum ether–benzene eluted a small fraction showing red fluorescence on the column and then benzene eluted 170 mg. of yellow solid, m.p. 128–139°, λ^{EtOH} 270 mμ. Ether–benzene mixtures and ether eluted Beilstein-positive yellow glasses, λ^{EtOH} 245–255 mμ, and methanol–acetic acid eluted 140 mg. of brown oil.

The crude enedione fraction (170 mg.) was refluxed for 20 min. with 1 g. of zinc dust in 9 cc. of acetic acid and 1 cc. of water. Dilution of the filtered solution gave a gelatinous precipitate that when dried melted at 160–175°. Crystallization from methanol–acetone and finally from benzene–ligroin gave 75 mg. of the **Δ⁸,²²-7,11-diketone** as colorless needles, m.p. 197–199°, $\alpha^{24}D$ −29.5 ± 1° Chf, in agreement with the constants reported by the Merck group.[5]

Anal. Calcd. for $C_{30}H_{46}O_4$ (470.67): C, 76.55; H, 9.85. Found: C, 76.47; H, 9.77.

7,11-Diketocholestanyl Benzoate.[15]—Δ⁷,⁹(¹¹)-Cholestadienyl benzoate (2 g.) was oxidized with N-bromosuccinimide and processed further exactly as described in the preceding example. Chromatography of the enedione fraction afforded, in the 3:1 petroleum ether–benzene eluate, 275 mg. (13%) of Beilstein-positive material that appeared to be impure 7,11-diketo-Δ⁸-cholestene-3β-ol benzoate (paper II), m.p. 156–158°, αD +46 ± 2° Di, λ^{EtOH} 269 mμ (6,300). Reduction with zinc dust and acetic acid gave pure 7,11-diketocholestane-3β-ol benzoate (paper II) as colorless needles, m.p. 197–199° (no depression in mixed m.p.).

In a second experiment 400 mg. of Δ⁷-cholestenyl benzoate in 15 cc. of dioxane, 50 cc. of *t*-butanol and 15 cc. of 0.05 *N* sulfuric acid was treated at 0° with 750 mg. of N-bromosuccinimide. After further processing as before, chromatography gave 38 mg. of yellow needles, m.p. 136–140°. Zinc and acetic acid reduction gave 25 mg. of 7,11-diketocholestanyl benzoate, m.p. and mixed m.p. 199–201°.

Acknowledgments.—We are greatly indebted to the du Pont Company for supplies of 7-dehydrocholesterol and to Dr. Max Tishler of Merck and Co., Inc., for suggestions and cooperation.

(12) A. Windaus and J. Brunken, *Ann.*, **460**, 225 (1928).
(13) S. v. Reichel, *Z. physiol. Chem.*, **226**, 146 (1934).
(14) A. Windaus and E. Auhagen, *Ann.*, **472**, 185 (1929).
(15) Experiments by Josef E. Herz.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

Studies of Configuration. II. The Configurations of the 3-Methylcyclohexylamines

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One pure isomer of 3-methylcyclohexanecarboxylic acid has been converted by a series of reactions which retain configuration to *cis*-1,3-dimethylcyclohexane and to *cis*-3-methylcyclohexylamine. The amine thus obtained is that which has previously been assigned the *"trans"* configuration. Thus another example of the inversion of configuration in the case of 1,3-disubstituted cyclohexane derivatives is established.

In the first paper of this series[1] it has been shown that the previous assignments of configuration of 3-methylcyclohexanol are inverted and must therefore be revised. It seemed likely that a similar situation prevailed with respect to the isomeric 3-methylcyclohexylamines, and it is the purpose of the present report to present evidence bearing on this problem.

Wallach[2] first prepared 3-methylcyclohexylamine (optically active) both by the reaction of ammonium formate with pulegone and by the reduction of 3-methylcyclohexanone oxime with sodium and alcohol. Knoevenagel and Klages[3] prepared a *dl*-3-methylcyclohexylamine. However, the first serious consideration of the preparation and characterization of the *cis* and *trans* isomer was given by Skita[4] who studied reduction of the toluidines and acetotoluides under a variety of conditions. The isomer which he called *"cis,"* obtained by reduction in acid media, gave a benzamide, m.p. 95–96°, and that which he called *"trans,"* by reduction in neutral or alkaline media, gave a benzamide, m.p. 126–127°. Skita comments on the physical properties of the two isomers by saying that the isomeric 3-methylcyclohexylamines are not in agreement with von Auwers[5] rule of relative density and index of refraction. Von Auwers[6] also discusses the isomer problem here.

More recently Mousseron[7] has reported numerous derivatives for optically active *cis*- and *trans*-3-methylcyclohexylamines.

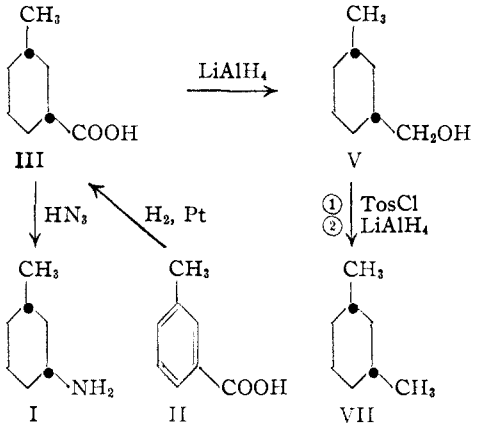
The correlation of the amines with other compounds of known stereochemistry has not been accomplished. However, the reaction of these amines with nitrous acid[4,8] is suggestive. In light of the recent revision of the configuration of

(1) D. S. Noyce and D. B. Denney, THIS JOURNAL, **74**, 5912 (1952).
(2) O. Wallach, *Ann.*, **272**, 123 (1893); **289**, 340 (1896).
(3) E. Knoevenagel and A. Klages, *ibid.*, **281**, 101 (1894).
(4) A. Skita, *Ber.*, **56**, 1014 (1923).
(5) K. von Auwers, *Ann.*, **420**, 91 (1919).
(6) K. von Auwers and A. Schmelzer, *Sitzb. Ges. Beförderung gesamten Naturwissenschaften Marburg*, **62**, 113 (1927); *C. A.*, **22**, 4486 (1928).
(7) M. Mousseron, *Compt. rend.*, **221**, 626 (1945).
(8) M. M. Claudon, *Bull. soc. chim. France*, **17**, 627 (1950).

the 3-methylcyclohexanols[1] and the recent demonstration that the nitrous acid deamination proceeds consistently with predominant retention of configuration in the decalol series,[9] the suggestion that the previous assignment of the configuration of these amines is reversed, would receive additional support.

To unequivocally establish this point, we have carried out a correlation of one of the isomeric amines with *cis*-1,3-dimethylcyclohexane. The sequence of reactions used is outlined in Chart I.

CHART I



3-Methylcyclohexanecarboxylic acid (III) was prepared by platinum and hydrogen reduction of *m*-toluic acid (II). Fractional crystallization of the amide afforded 50% of one pure isomer (IV), m.p. 158.0–158.8°. This amide has previously been prepared by Gutt,[10] who reports a melting point of 155–156°. By reaction with nitrous acid pure *cis*-III was regenerated. Reduction of *cis*-III with lithium aluminum hydride afforded *cis*-3-methylcyclohexanemethanol (V) in good yield. The physical properties are concordant with those reported by Mousseron[11] for an optically active sample of one of the isomers. Conversion of *cis*-V to the tosylate VI and reduction with lithium aluminum hydride afforded *cis*-1,3-dimethylcyclohexane (VII) which was characterized by its infrared spectrum, showing complete correspondence with that recorded for *cis*-1,3-dimethylcyclohexane in the API Tables No. 302.

There was no indication during the isolation of VII or in the infrared spectrum of the presence of the isomeric *trans*-1,3-dimethylcyclohexane. This thus establishes the configuration of III as *cis*-3-methylcyclohexanecarboxylic acid.

Treatment of *cis*-III with hydrazoic acid and sulfuric acid in the Schmidt reaction[12] afforded *cis*-3-methylcyclohexylamine (I), which was characterized by the preparation of the benzamide.

It is worthy of note that again the apparently more stable isomer is the *cis* rather than the *trans* compound in this case as well as in the case of the isomeric 3-methylcyclohexanols. Though there are no equilibration studies on the isomeric amines, one can suggest that the isomer predominating in the sodium and alcohol reduction of the oxime is the more stable.[13]

Experimental[14]

Hydrogenation of *m*-Toluic Acid (II).—A solution of 75 g. of *m*-toluic acid, m.p. 110.8–111.6° (prepared by carbonation of the Grignard reagent from *m*-bromotoluene), in 300 ml. of acetic acid was hydrogenated with hydrogen and platinum in a Parr low pressure apparatus. Hydrogen uptake was 90% complete in 30 hours. After filtering to remove the catalyst, the solution was distilled to afford 62.1 g. (84%) of 3-methylcyclohexanecarboxylic acid, b.p. 136–138° (17 mm.), $n^{21}D$ 1.4578, and a residue, 11.5 g., which consisted largely of recovered *m*-toluic acid.

***cis*-3-Methylcyclohexanecarboxamide (IV).**—To 58.5 g. of 3-methylcyclohexanecarboxylic acid in a 500-ml. flask protected with a calcium chloride tube was added 97 g. of thionyl chloride. After standing at room temperature for 24 hours, benzene (20 ml.) was added and the benzene and excess thionyl chloride were removed under reduced pressure, not allowing the temperature to rise above 40°. An additional 25 ml. of benzene was added and similarly removed. The crude acid chloride was added slowly with stirring to 175 ml. of cooled concentrated ammonium hydroxide. The precipitated amide was collected by filtration and dried, 55.5 g. (95%). Crystallization from ethanol–water afforded a first fraction, m.p. 156–157.5°, 37.6 g. (65%) and an additional 8 g. was recovered from the mother liquor. Systematic fractional crystallization (four steps) afforded 30 g. (52%) of pure *cis*-3-methylcyclohexylcarboxamide (IV), m.p. 158.0–158.8°. The recorded m.p. is 155–156°.[15]

Anal. Calcd. for $C_8H_{15}ON$: C, 68.05; H, 10.71; N, 9.92. Fonnd: C, 68.19; H, 10.59; N, 9.74.

***cis*-3-Methylcyclohexanecarboxylic Acid (III).**—A solution of 30 g. of *cis*-3-methylcyclohexanecarboxamide in 550 ml. of sulfuric acid was placed in a one-liter three-necked flask, equipped with a stirrer, condenser and dropping funnel. To this cooled solution was added over a period of two hours an ice-cooled solution of 40 g. of sodium nitrite in 160 ml. of water. The resulting mixture was warmed on the steam-bath for 15 minutes during which time nitrogen was evolved. After dilution with water the mixture was extracted with chloroform (300 ml.). Separation of unreacted amide and acid in the usual fashion and distillation of the acid afforded 24.2 g. (80%) of *cis*-3-methylcyclohexylcarboxylic acid, b.p. 133–134° (14.5 mm.), $n^{21}D$ 1.4571.

***cis*-3-Methylcyclohexylamine (I).**—To a mixture of 1.75 g. of *cis*-3-methylcyclohexanecarboxylic acid, chloroform (15 ml.) and sulfuric acid (30 ml.) was added 2.7 g. of sodium azide portionwise over a period of two hours, maintaining the temperature of the reaction mixture at 40–45°. After the addition was complete it was warmed to 50° for an additional one-half hour. The cooled mixture was diluted with water and the aqueous layer separated. The amine was not isolated; rather the aqueous layer was made basic, and treated directly with benzoyl chloride (5 g.) in the usual fashion. There was obtained after crystallization from aqueous ethanol 2.16 g. (63%) of N-(*cis*-3-methylcyclohexyl)-benzamide, m.p. 124.5–125.8°. Skita[4] reports 126–127°.

***cis*-3-Methylcyclohexanemethanol (V).**—To a stirred refluxing solution of 12 g. of lithium aluminum hydride in 250 ml. of anhydrous ether, 19.6 g. of *cis*-3-methylcyclohexanecarboxylic acid in 100 ml. of anhydrous ether was added over a period of one hour, and the mixture was allowed to reflux for an additional hour. Excess lithium aluminum hydride was decomposed by addition of ice-water, and the solution was acidified by the addition of dilute sulfuric acid. The ether layer was separated, and the aqueous layer was extracted twice with 50-ml. portions of ether. The combined ether extracts were washed with 50 ml. of 1 *N* sodium

(9) W. G. Dauben and E. Hoerger, THIS JOURNAL, **73**, 1504 (1951).

(10) J. Gutt, *Ber.*, **40**, 2063 (1907).

(11) M. Mousseron and R. Granger, *Compt. rend.*, **208**, 1500 (1939).

(12) The Schmidt reaction proceeds with retention of configuration; *cf.* A. Campbell and J. Kenyon, *J. Chem. Soc.*, 25 (1946).

(13) D. S. Noyce and F. W. Bachelor, THIS JOURNAL, **74**, 4577 (1952).

(14) Melting points and boiling points are corrected. Analyses are by the Microanalytical Laboratory of the University of California.

(15) N. Zelinsky, *Ber.*, **35**, 2689 (1902); W. Markownikoff and Hagemann, *J. prakt. Chem.*, [2] **49**, 71 (1894); see ref. 9.

carbonate, dried over magnesium sulfate and distilled to afford 15.5 g. (88%) of *cis*-3-methylcyclohexanemethanol (V), b.p. 90° (13.5 mm.), $n^{21}D$ 1.4588. Mousseron and Granger[10] report for an optically active sample of V, b.p. 95° (25 mm.), $n^{25}D$ 1.4557.

The α-naphthylurethan, prepared in the usual manner, crystallized from ligroin in fine needles, m.p. 80.5–81.7°.

Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.95; H, 7.89; N, 4.68.

The 3,5-dinitrobenzoate, prepared in the usual manner, crystallized from ethanol in large needles, m.p. 81.5–82.7°.

Anal. Calcd. for $C_{15}H_{13}N_2O_6$: C, 55.89; H, 5.63; N, 8.70. Found: C, 55.92; H, 5.80; N, 8.60.

Tosylate of *cis*-3-Methylcyclohexanemethanol (VI).—To an ice-cold solution of 13.7 g. of V in 50 ml. of pyridine was added 22.4 g. of *p*-toluenesulfonyl chloride dissolved in 22 ml. of pyridine. After the mildly exothermic reaction subsided, the mixture was warmed to 40° for one-half hour. The mixture was then poured into a mixture of 200 ml. of 6 *N* sulfuric acid and ice. The liberated oil was extracted with three 70-ml. portions of chloroform. The combined chloroform extracts were washed with dilute sulfuric acid and concentrated under reduced pressure to afford 30 g. (98%) of crude, clear oily tosylate. The tosylate was not purified further, but was reduced directly.

***cis*-1,3-Dimethylcyclohexane (VII).**—In a 500-ml. flask equipped with stirrer, reflux condenser and dropping funnel there were placed 275 ml. of anhydrous *n*-propyl ether and 11.75 g. of lithium aluminum hydride. After heating briefly to dissolve most of the lithium aluminum hydride, a solution of VI in 50 ml. of anhydrous *n*-propyl ether was added with stirring over a period of 40 minutes, maintaining the temperature at 70–75°. The mixture was stirred and heated at 70–75° for 24 hours. After cooling, excess lithium aluminum hydride was decomposed by the dropwise addition of water, followed by excess dilute sulfuric acid to dissolve the inorganic hydroxides. The *n*-propyl ether layer was separated, washed with 1 *N* sodium carbonate and dried over magnesium sulfate. Distillation through a 2-foot modified Podbielniak column afforded 3.79 g. (32% from V) of *cis*-1,3-dimethylcyclohexane, b.p. 119.8–120.3°, $n^{25}D$ 1.4206, d^{25}_4 0.7629. During the distillation there was no indication of a higher boiling fraction. The reported properties[16] for the *cis*-1,3-dimethylcyclohexane are b.p. 120.09°, $n^{25}D$ 1.42063, d^{25}_4 0.76196, whereas the following properties are reported for *trans*-1,3-dimethylcyclohexane; b.p. 124.45°, $n^{25}D$ 1.4284, d^{25}_4 0.7806.

(16) A. F. Forziati, A. R. Glasgow, C. B. Willingham and F. D. Rossini, *J. Research Natl. Bur. Standards*, **36**, 129 (1946).

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[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, FEDERAL SECURITY AGENCY]

1-Desoxy-D-xylitol and Some of Its Derivatives[1]

BY EMMANUEL ZISSIS AND NELSON K. RICHTMYER

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Sirupy 1-desoxy-D-xylitol, obtained by the reductive desulfurization of D-xylose diethyl mercaptal, has been characterized through its crystalline tetraacetyl, dibenzylidene and dimethylene derivatives. 1-Desoxy-2,4:3,5-dimethylene-D-xylitol is the enantiomorph of a compound prepared, in a different manner, by Ness, Hann and Hudson and reported in an accompanying paper. 1-Desoxy-2,4-methylene-D-xylitol, 1-desoxy-2,4-methylene-3,5-anhydro-D-xylitol, and other derivatives of 1-desoxy-D-xylitol have also been described.

In continuing our studies on the preparation and reactions of various ω-desoxy sugar alcohols,[1] we have desulfurized D-xylose diethyl mercaptal with Raney nickel and obtained 1-desoxy-D-xylitol (synonym, 5-desoxy-L-xylitol) as a thick, colorless sirup. The racemic form, 1-desoxy-D,L-xylitol, has been reported earlier from this Laboratory by Hann, Ness and Hudson,[2] and it also was a sirup; its synthesis from xylitol (a *meso* form) through 2,3,4,5-diisopropylidene-D,L-xylitol[3] could have produced only the racemic modification, whereas our reactions always involved optically active intermediates and produced the desired D-form. The new 1-desoxy-D-xylitol has been characterized through its crystalline tetraacetyl, dibenzylidene and dimethylene derivatives. Our 1-desoxy-2,3,-4,5-dibenzylidene-D-xylitol is recognized as one component of the racemic 1-desoxy-2,3,4,5-dibenzylidene-D,L-xylitol whose preparation from the long-known dibenzylidenexylitol is described in the accompanying paper from this Laboratory by Ness, Hann and Hudson.[4] Furthermore, our dimethylene derivative must be 1-desoxy-2,4:3,5-dimethylene-D-xylitol because it proved to be the enantiomorph of the 1-desoxy-2,4:3,5-dimethylene-L-xylitol described in the accompanying paper.[4] The location of the methylene groups in the latter compound follows from the earlier proof of structure of the 2,4:3,5-dimethylene-L-xylitol[5] from which it was derived. This pair of enantiomorphs composes the previously described racemic 1-desoxy-2,4:3,5-dimethylene-D,L-xylitol.[6] A comparison of melting points of these and other derivatives of 1-desoxy-D-xylitol and 1-desoxy-D,L-xylitol, together with their mixed melting points, is given in Table I.

Acetolysis of 1-desoxy-2,4:3,5-dimethylene-D-xylitol to 1-desoxy-2,4-methylene-3-acetoxymethyl-5-acetyl-D-xylitol[7] and subsequent saponification has furnished 1-desoxy-2,4-methylene-D-xylitol. The racemic 1-desoxy-2,4-methylene-D,L-xylitol was known from an earlier publication.[8] Tosylation of the new compound could be controlled to yield either the ditosyl or a monotosyl derivative. The ditosyl derivative appeared to be quite resistant to the exchange reaction with sodium iodide under the

(1) Presented in part before the Division of Sugar Chemistry at the Atlantic City Meeting of the American Chemical Society, September 15, 1952. For the preceding paper in this series, see E. Zissis and N. K. Richtmyer, THIS JOURNAL, **74**, 4373 (1952).

(2) R. M. Hann, A. T. Ness and C. S. Hudson, *ibid.*, **66**, 73 (1944).

(3) R. S. Tipson and L. H. Cretcher, *J. Org. Chem.*, **8**, 95 (1943).

(4) A. T. Ness, R. M. Hann and C. S. Hudson, THIS JOURNAL, **75**, 132 (1953).

(5) A. T. Ness, R. M. Hann and C. S. Hudson, *ibid.*, **66**, 665 (1944).

(6) R. M. Hann, A. T. Ness and C. S. Hudson, *ibid.*, **66**, 670 (1944).

(7) Allocation of the acetoxymethyl group to the secondary hydroxyl is based on the studies of the acetolysis of trimethylene-D-mannitol [A. T. Ness, R. M. Hann and C. S. Hudson, *ibid.*, **65**, 2215 (1943)] and dimethylene-L-xylitol (ref. 5).

(8) R. M. Hann, N. K. Richtmyer, H. W. Diehl and C. S. Hudson, *ibid.*, **72**, 561 (1950).