[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Formation of Five- and Six-membered Rings by the Acyloin Condensation. III. Cyclization of Diethyl 2-Carboxy-2-methylcyclohexane-1-acetate

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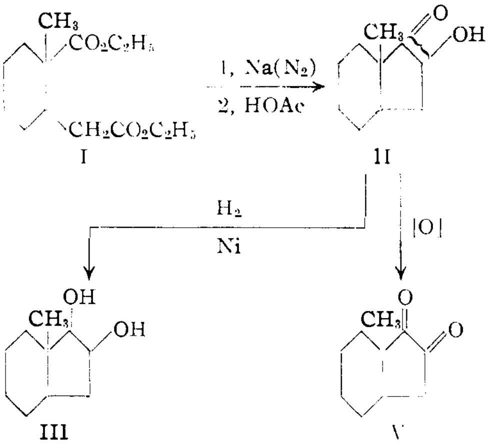
A *cis–trans* mixture of diethyl 2-carboxy-2-methylcyclohexane-1-acetate (I) has been cyclized to an acyloin mixture II under various conditions, most effectively by the use of sodium in liquid ammonia. Hydrogenation of the acyloins II gave 6-methylbicyclo[4.3.0]nonane-7,8-diol (III), a compound possessing structural features characteristic of estriol (a fused cyclopentanediol with an angular methyl group). The acyloin product II was reduced to a mixture of *cis*- and *trans*-6-methylbicyclo[4.3.0]nonan-7-one, which were individually identified.

This communication describes an application of the acyloin condensation to the preparation of a model bicyclic compound containing the fused cyclopentanediol structure with an angular methyl group characteristic of estriol. Cyclization of the diethyl ester of 2-carboxy-2-methyl-cyclohexane-acetic acid (I) with sodium in boiling toluene or with sodium in liquid ammonia solution yielded an intermediate acyloin II, which was hydrogenated to give 6-methylbicyclo[4.3.0]nonane-7,8-diol (III). Recently Sheehan and O'Neill[1] prepared a bicyclic hydroxyindanone identical in structure to II except for the absence of the angular methyl group.



Cyclization was effected on a *cis–trans* mixture of diethyl 2-carboxy-2-methylcyclohexane-1-acetate (I).[2] Condensation with sodium in boiling toluene under high dilution conditions yielded 42% of viscous, colorless liquid acyloin II, which turned yellow rapidly in air. Without use of high dilution addition of the diester, the yield was reduced to 30%.

When the acyloin condensation of I was carried out with sodium in liquid ammonia solution, 50% of II was obtained. Of the three procedures, the liquid ammonia reaction is the most convenient in the laboratory and produced the smallest quantity of by-products. It is desirable to remove completely the ammonia before acidification of the acyloin sodium salt. Acyloins react rapidly with ammonia to form complex, non-distillable, nitrogenous condensation products. This secondary reaction may account for the markedly lower yields of acyloins obtained previously from the interaction of esters and sodium in liquid ammonia as compared with the heterogeneous reaction.[3]

A determination of the infrared spectra of freshly distilled II showed all the characteristics of a highly enolic acyloin. There is a strong OH band at 2.88 μ, an intense C=O band at 5.73 μ, and a band of medium intensity at 6.17 μ which corresponds to -C=C- in a five-membered ring. The compound gives an intense color with ferric chloride solution.

Distillation of the reaction residues remaining after preliminary distillation of the acyloin led to the isolation of 12–20% of a yellow compound, m.p. 20–25°, the analysis of which corresponds to the α-diketone, 6-methylbicyclo[4.3.0]nonan-7,8-dione (V).

Catalytic reduction of the acyloin II with Raney nickel (W-4) gave a non-crystalline mixture of isomeric α-glycols (III) from which was obtained a crystalline acetonide, 6-methylbicyclo[4.3.0]nonane-7,8-diol-acetonide (IV).

By treatment of the liquid mixture of isomers II with zinc, acetic acid and concentrated hydrochloric acid,[4] the hydroxyl group of the acyloin was removed in 83% yield. The resulting ketone was isolated as the semicarbazone and was regenerated as a viscous, colorless oil which did not react with semicarbazide hydrochloride and sodium acetate at room temperature, but gave the semicarbazone readily after a one-hour reflux period in ethanolic solution. This behavior would indicate that the ketone group remaining from the original acyloin was adjacent to the angular methyl group, as in VI, for the semicarbazone of 6-methylbicyclo-[4.3.0]nonan-8-one forms instantly in the cold, while those of *cis*- and *trans*-6-methylbicyclo-[4.3.0]nonan-7-one, VI do not form without heating.[5]

Convincing evidence for structures of the product obtained from the acyloin was afforded by conversion to the 2,4-dinitrophenylhydrazones. Chromatography over alumina of the yellow material obtained, m.p. 112–126° after recrystallization from ethanol, gave two compounds, m.p. 140–141° and 152.5–153.5°, which were shown to be the 2,4-dinitrophenylhydrazones of *cis*- and *trans*-6-methyl-

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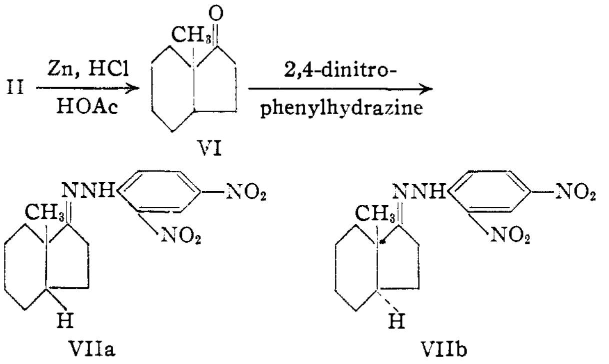
[1] J. C. Sheehan and R. C. O'Neill, THIS JOURNAL, **72**, 4614 (1950).

[2] Prepared from ethyl 2-carbethoxy-1-hydroxy-2-methylcyclohexane-1-acetate (W. E. Bachmann and S. Kushner, *ibid.*, **65**, 1963 (1943)) by dehydration with thionyl chloride and pyridine followed by hydrogenation over palladium after pretreatment with Raney Nickel (95% over-all yield, b.p. 141–145° at 7 mm.; n^{25}_{D} progressed from 1.4587 to 1.4619 during distillation).

[3] M. S. Kharasch, E. Sternfield and F. R. Mayo, *J. Org. Chem.*, **5**, 362 (1940).

[4] V. Prelog, L. Frenkiel, M. Kobelt and P. Barman, *Helv. Chim. Acta*, **30**, 1741 (1947).

[5] W. S. Johnson, THIS JOURNAL, **66**, 215 (1944).



VI

VIIa VIIb

bicyclo[4.3.0]nonan-7-one, VIIa and VIIb, respectively, by analysis and comparison with authentic samples.[6] It is evident that both *cis*- and *trans*-fused rings were formed in the acyloin cyclization, presumably from the corresponding forms of I.

We wish to express our appreciation to the U. S. Public Health Service for the support of a fellowship for R.C.C.

Experimental[7]

Acyloin Condensation of Diethyl 2-Carboxy-2-methylcyclohexane-1-acetate (I) **with Sodium in Boiling Toluene.**—To a 1-l. creased flask fitted with a high-speed stirrer, dropping funnel, high-dilution reflux cycle and nitrogen system were added 2.84 g. (0.124 mole) of sodium and 400 ml. of dry, sulfur-free toluene. After the entire system had been thoroughly swept free of air with "prepurified" nitrogen (less than 0.001% oxygen), the toluene was heated to vigorous reflux. The molten sodium was then dispersed to a fine powder by stirring at high speed (*ca.* 10,000 r.p.m.) for one minute.

Addition of the diester I[2] (7.9 g., 0.308 mole) in 200 ml. of dry, sulfur-free toluene was started immediately through the high dilution reflux cycle. The toluene was stirred at reflux temperature at about 5,000 r.p.m. throughout the 4-hour and 20-minute addition and for an additional 90 minutes.

The solution was cooled to 0° and 7.4 g. (0.124 mole) of glacial acetic acid in 60 ml. of dry toluene was added over a 10-minute period with stirring. All traces of air were carefully excluded from the apparatus during the acidification step. The precipitated sodium acetate was removed by filtration with the aid of Filter-Cel, the cake washed well with dry toluene and the combined filtrates concentrated under reduced nitrogen pressure. There remained 5.8 g. of a yellow-brown viscous oil which still retained some toluene. An aliquot of this oil, oxidized by a gravimetric Fehling determination,[8] indicated a total acyloin yield of 62%.

The oil was subjected to a rapid, short-path vacuum distillation without fractionation. The distillate consisted of a yellow-orange viscous oil (*ca.* 4 g.), and a dark tar remained in the flask. The distillate was fractionated under reduced pressure in a small column,[9] to give a colorless, viscous oil, b.p. 71° at 1.5 mm., which rapidly became yellow upon contact with air, yield 2.18 g. (42%), $n^{25}\text{D}$ 1.4940. This liquid mixture of isomeric methyl hydroxyindanones (II) reduced Fehling and Tollens reagents immediately at room temperature, and gave an intense color with ferric chloride solution. Carbon-hydrogen and infrared spectral analyses were completed within 40 minutes after distillation of the pure product.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.58. Found: C, 71.25; H, 9.61.

Upon treatment with excess 2,4-dinitrophenylhydrazine sulfate in ethanol, the acyloin gave a 2,4-dinitrophenylosazone; m.p. 293–294°, after three recrystallizations from ethyl acetate.

Anal. Calcd. for $C_{22}H_{22}O_8N_8$: C, 50.19; H, 4.21. Found: C, 50.50; H, 4.51.

Treatment of the α-ketol mixture II with semicarbazide hydrochloride, phenyl isocyanate and 3,5-dinitrobenzoyl chloride did not yield crystalline derivatives.

6-Methylbicyclo[4.3.0]nonan-7,8-dione (V).—The dark residues (2.0 g.) from the distillation of the liquid acyloin II were combined and subjected to short-path distillation without ebullition at 120° (heating block temperature) and 0.07 mm. About 1.4 g. of yellow, viscous liquid was obtained, which solidified partially on storage at room temperature. This product gave negative Fehling tests even upon heating. Analysis of the yellow semisolid, m.p. 20–25°, obtained after three similar distillations gave values corresponding to the oxidation product of the acyloin, 6-methylbicyclo[4.3.0]nonan-7,8-dione (V).

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 73.94; H, 8.69. Found: C, 74.18; H, 8.90.

The yield of V based on the diester used in the acyloin condensation, was 20%. This α-diketone was converted to the bis-2,4-dinitrophenylhydrazone which, after three recrystallizations from ethyl acetate, melted at 293–294°. The melting point of a mixture with the 2,4-dinitrophenylosazone obtained directly from the acyloin showed no depression.

Acyloin Condensation of I without High Dilution Addition.—The acyloin condensation of the diester I in boiling toluene was repeated under conditions similar to those described but without addition of the diester through the high dilution cycle. Nine grams (0.0352 mole) of the diester in 250 ml. of dry, sulfur-free toluene was added to 3.24 g. (0.1408 mole) of finely dispersed sodium in 400 ml. of dry, sulfur-free toluene through a dropping funnel during 7 hours. After 80 minutes of additional refluxing the reaction mixture was worked up as before. A gravimetric Fehling determination on the crude product prior to distillation showed the yield of total acyloin to be 46%. The yield of purified liquid acyloin II was 1.8 g. (30%) and, in addition, 0.70 g. (12%) of the diketone V was obtained.

The Acyloin Condensation of I with Sodium in Liquid Ammonia.—To a 500-ml., 3-necked flask equipped with stirrer, Dry-Ice condenser, dropping funnels and nitrogen system was introduced 250 ml. of anhydrous liquid ammonia. One and eight-tenths grams (0.0781 mole) of sodium cut in thin strips was added in 5 minutes. The system was swept thoroughly with a vigorous stream of prepurified nitrogen for 20 minutes. The diester I (5.0 g., 0.0195 mole), dissolved in 60 ml. of anhydrous ether, was then added over a period of 100 minutes with stirring. After stirring for an additional 30 minutes, the solution changed color suddenly from blue-black to light yellow, indicating complete reaction of the dissolved sodium.

The bulk of the liquid ammonia was evaporated within 80 minutes. Two hundred ml. of dry ether was added and the removal of ammonia from the stirred solution was facilitated by the passage of a current of nitrogen through the system. After another addition of ether and 12 hours sweeping with nitrogen the exit gases showed only traces of ammonia to be present. The colorless sodio-enolate of the acyloin was then acidified by the addition of 150 ml. of 3 *N* hydrochloric acid over a period of 10 minutes. Until this acidification was completed all traces of oxygen were carefully excluded from the system.

The ether and acid layers were separated and the water layer saturated with ammonium chloride and extracted with two 50-ml. portions of ether. After drying over sodium sulfate, the ether extracts were concentrated at room temperature under a reduced pressure in a nitrogen atmosphere. There remained 3.37 g. of viscous, yellow liquid which was subjected to short-path distillation without ebullition at 0.2 mm. and 75° (heating block temperature) to give 1.62 g. (50%) of slightly yellow acyloin, $n^{25}\text{D}$ 1.5060. Similar distillation of the residue at 0.08 mm. and 120° gave 0.45 g. (14%) of the yellow diketone V.

6-Methylbicyclo[4.3.0]nonan-7,8-diol (III).—To a solution of 0.465 g. (0.00277 mole) of liquid acyloin II and 25 ml. of ethyl acetate in a semimicro hydrogenator was added two-thirds of a teaspoonful of Raney nickel catalyst (W-4). After 22 hours, 98% of the theoretical volume of hydrogen

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[6] Kindly supplied by Dr. W. S. Johnson.

[7] All melting points are corrected. We are indebted to Dr. S. M. Nagy and his associates for the microanalyses.

[8] C. A. Browne and F. W. Zerban, "Physical and Chemical Methods of Sugar Analysis," John Wiley and Sons, New York, N. Y., 1941, pp. 765–772.

[9] C. W. Gould, G. Holtzmann and C. Niemann, *Ind. Eng. Chem., Anal. Ed.*, **20**, 361 (1948).

had been absorbed. After removal of the catalyst and concentration of the filtrate, there was obtained a colorless liquid mixture of α-glycols.

A portion of this liquid mixture of isomeric 6-methylbicyclo[4.3.0]nonan-7,8-diols, 142 mg., was dissolved in 11.7 g. of pure acetone containing 0.8 g. of freshly fused zinc chloride and the mixture was stored for 4 days at room temperature. A solution of 0.55 g. of potassium carbonate in 2.3 ml. of water was added with shaking, the precipitated basic zinc carbonate was removed by filtration, and the dried acetone solution was concentrated to about 5 ml. Fluffy, colorless crystals (0.025 g.) of the acetonide derived from one of the *cis*-glycols separated. After two recrystallizations from ethanol, an analytical sample of IV melted at 68–69°.

Anal. Calcd. for $C_{13}H_{22}O_2$: C, 74.25; H, 10.54. Found: C, 74.41; H, 10.40.

Oxidation of Liquid Acyloin (II) with Copper Acetate.—Liquid acyloin II (0.170 g.) was dissolved in 30 ml. of methanol, 2.0 g. of crystalline cupric acetate was added and the solution heated under reflux for one hour with occasional shaking. Red cuprous oxide precipitated almost immediately. After storage overnight, 300 ml. of ether was added and the ether solution washed successively with 0.5 *N* hydrochloric acid, 5% sodium bicarbonate and water, and then dried over sodium sulfate. The ether was evaporated, leaving 0.150 g. of a heavy yellow oil V which gave no reaction with Fehling solution, even when heated. After two recrystallizations from ethyl acetate, the 2,4-dinitrophenylosazone melted at 293–294°, and gave no depression of melting point when mixed with a sample of the 2,4-dinitrophenylosazone obtained directly from the acyloin II.

6-Methylbicyclo[4.3.0]nonan-7-one, *cis*- and *trans*-.—A mixture of 1.148 g. (0.0068 mole) of liquid acyloin II, 2.86 g. (0.044 mole) of zinc (20 mesh) in 2.5 g. of glacial acetic acid and 2.4 ml. of concentrated hydrochloric acid was heated for 160 minutes at 100°. Three additional 2.5-ml. portions of concentrated hydrochloric acid were added at 30-minute intervals. The red solution was poured into ice-water, extracted with ether, and the combined ether extracts washed with dilute sodium carbonate solution and water, dried over anhydrous sodium sulfate and the solvent evaporated. The ether extracts did not reduce Fehling solution upon heating. The colorless liquid ketone (1.05 g., 83%) which had an odor reminiscent of camphor, was converted directly to the semicarbazone by treatment with 1.06 g. of semicarbazide hydrochloride and 1.55 g. of sodium acetate in 10 ml. of 95% ethanol and 8 ml. of water. No reaction was evident after 24 hours at room temperature and 18 hours at 0°. The contents of the flask were then heated on a steam-bath for one hour. After storage at 0°, 1.3 g. of colorless crystals deposited. The melting point was 201.6–206° after repeated crystallization from methanol–water.

Anal. Calcd. for $C_{11}H_{19}ON_3$: C, 63.12; H, 9.15; N, 20.08. Found: C, 63.01; H, 9.33; N, 20.01.

One gram of the semicarbazone obtained from the mixed methyl hydrindanones, m.p. 201.6–206°, was suspended in 250 ml. of water, 10.0 g. of oxalic acid dihydrate added, and the mixture distilled. The distillate was extracted with ether and the combined extracts dried and concentrated. The product was not obtained crystalline, but was converted to the 2,4-dinitrophenylhydrazones. The yellow needles, m.p. 112–126°, after two crystallizations from methanol, were dissolved in petroleum ether and the solution chromatographed over a 70 × 3 cm. column of alumina. By washing with petroleum ether a complete separation of two compounds was achieved. After elution with methanol the lower band yielded 150 mg. of short, yellow needles, m.p. 152.5–153.5°, of *trans*-6-methylbicyclo[4.3.0]nonan-7-one 2,4-dinitrophenylhydrazone, VIIb, which showed no depression of melting point when mixed with an authentic specimen,[6] m.p. 152.5–153.5°.

Anal. Calcd. for $C_{16}H_{20}N_4O_4$: C, 57.81; H, 6.07. Found: C, 57.86; H, 6.08.

From the upper band there was obtained 350 mg. of *cis*-6-methylbicyclo[4.3.0]nonan-7-one 2,4-dinitrophenylhydrazone VIIa, m.p. 140–141°, which gave no depression of melting point upon mixture with an authentic sample,[6] m.p. 140–141°.

Anal. Calcd. for $C_{16}H_{20}N_4O_4$: C, 57.81; H, 6.07. Found: C, 57.96; H, 6.04.

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[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

The Synthesis of Two Seven-membered Ring Homologs of Demerol[1]

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When the product obtained by condensation of phenyl-α-(β-dimethylaminoethyl)-acetonitrile, trimethylene chlorobromide and sodamide was heated, 1-methyl-4-phenyl-4-cyanohexamethylenimine was obtained. Phenyl-α-(β-diethylaminoethyl)-acetonitrile, trimethylene chlorobromide and sodamide yielded 1-ethyl-4-phenyl-4-cyanohexamethylenimine. The two nitriles were hydrolyzed to the corresponding acids, and the latter were esterified to produce the ethyl esters.

This paper deals with the synthesis of two seven-membered ring homologs V and XV of the analgesic Demerol.

Phenyl-α-(β-dimethylaminoethyl)-acetonitrile (I) was converted, with the aid of sodamide and trimethylene chlorobromide,[4] into phenyl-α-(β-dimethylaminoethyl)-α-(γ-chloropropyl)-acetonitrile (II). The latter compound was not isolated but was converted, by heat, into 1-methyl-4-phenyl-4-cyanohexamethylenimine methochloride (III). This product, when heated, lost methyl chloride with the formation of 1-methyl-4-phenyl-4-cyanohexamethylenimine (IV). Hydrolysis and esterification of IV yielded 1-methyl-4-phenyl-4-carbethoxyhexamethylenimine (V) which was converted by lithium aluminum hydride into 1-methyl-4-phenyl-4-(hydroxymethyl)-hexamethylenimine (VI). The alcohol VI was characterized by the preparation of the acetate and the benzoate.

The structure of VI was confirmed by its synthesis from 4-phenyl-4-carbethoxycyclohexanone (VII). The latter compound was converted by sodium azide and hydrochloric acid into δ-phenyl-δ-carbethoxy-ε-caprolactam (VIII) which was reduced by lithium aluminum hydride to 4-phenyl-4-(hydroxymethyl)-hexamethylenimine. After formylation oft he latter compound with chloral[5] and reduction of the formyl derivative with lithium

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(1) Abstract of Papers, 123rd Meeting of the American Chemical Society, Los Angeles, Calif., March 15–19, 1953, p. 14L.

(2) This paper represents part of a dissertation submitted by Eu-Phang Tsao in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1952.

(3) Parke, Davis and Company Fellow.

(4) Ethylene chlorobromide was used by H. Kägi and K. Miescher (*Helv. Chim. Acta*, **32**, 2489 (1949)) for the preparation of Demerol and a number of its homologs.

(5) F. F. Blicke and Chi-Jung Lu, THIS JOURNAL, **74**, 3933 (1952).