distilled to yield 0.32 g. (30%) of a viscous, colorless liquid: b.p. 75–85° (heating block, 0.025 mm.); λ_{max}^{neat} (μ) 5.72 (carbonate) and 5.90 (urethan); $[\alpha]^{25}D$ +74° (*c* 1.00, chloroform).

Anal. Calcd. for $C_{15}H_{27}NO_7$: C, 54.04; H, 8.16; N, 4.20. Found: C, 54.09; H, 8.03; N, 4.27.

Ethyl Des-N-methyldesosaminide (VII).—To a solution of 1.3 g. (0.004 mole) of ethyl O,N-dicarbethoxydes-N-methyldesosaminide in 5 ml. of ethanol was added 6 ml. of 20% aqueous sodium hydroxide. The resulting two-phase system was heated under reflux for 5 hr., cooled, and poured into methylene chloride. More water was added and the aqueous phase thoroughly extracted with methylene chloride. The methylene chloride extracts were dried and evaporated yielding 0.6 g. (80%) of a colorless solid, m.p. 100–112°. The analytical sample was obtained by recrystallization from acetone: m.p. 119–120.5°; $[\alpha]^{25}D$ +191° (*c* 0.99, chloroform).

Anal. Calcd. for $C_9H_{19}NO_3$: C, 57.11; H, 10.12; N, 7.40. Found: C, 57.02; H, 10.63; N, 7.22.

Ethyl O,N-Ditrifluoroacetyldes-N-methyldesosaminide (VIII).—To a partial solution of 1 g. (0.005 mole) of ethyl des-N-methyldesosaminide in 15 ml. of anhydrous ether was added 6 g. (0.07 mole) of sodium carbonate. The mixture was cooled and vigorously stirred, and 8 ml. (0.057 mole) of trifluoroacetic anhydride was added at as rapid a rate as possible without the reaction getting out of control (*ca.* 5 min.). The cooling bath was removed and the vigorous stirring continued for 20 min. The reaction mixture was poured into chloroform, the excess anhydride was destroyed with ice, and the chloroform solution was washed with water, dried, and evaporated. The yellow liquid residue was distilled *in vacuo* to yield 1.5 g. (75%) of VIII as a colorless, fairly viscous liquid: b.p. 83–85° (0.15–0.2 mm.); $[\alpha]^{25}D$ +49.5° (*c* 1.00, chloroform); λ_{max}^{neat} (μ) 5.60 (ester) and 5.90 (amide).

Anal. Calcd. for $C_{13}H_{17}NO_5F_6$: F, 29.90; N, 3.67. Found: F, 29.61; N, 3.86.

2-O-Trifluoroacetyl-3-N-methyltrifluoroacetamido-3,4,6-trideoxyglucosyl Bromide (I).—A solution of 0.7 g. (0.0018 mole) of VIII in 2 ml. of 32% hydrogen bromide in acetic acid (Eastman) containing 0.25 cc. of acetic anhydride was kept at room temperature for 2 hr., then evaporated to dryness *in vacuo* at 25–40° (oil pump). The pasty solid residue was crystallized from boiling petroleum ether (b.p. 30–60°) and the hygroscopic white crystalline solid obtained was subjected to high vacuum pumping at room temperature over potassium hydroxide overnight: yield, 0.45 g. (59%); m.p. 73–77°; λ_{max}^{neat} (μ) 5.59 (ester) and 5.90 (amide). Because of its hygroscopic nature, the compound was not analyzed.

Cholesteryl Des-N-methyldesosaminide *via* the Ditrifluoroacetyl Derivative II.—To a solution of 1.9 g. (0.005 mole) of cholesterol (recrystallized from ethanol and dried at 100° *in vacuo* over P_2O_5 for 24 hr.) in 60 cc. of anhydrous 1,2-dichloroethane was added 1.3 g. of dried (P_2O_5, 56°, overnight *in vacuo*) mercuric cyanide and 2 g. of Drierite (the commercially available 8 mesh material was pulverized and dried *in vacuo* at 150° for 24 hr.). The suspension was stirred at room temperature for 1 hr., 2.1 g. (0.005 mole) of the bromo sugar I was added, and the mixture was stirred at room temperature for 23 hr. The insoluble salts were separated by filtration and the organic solution was washed with water, dried, and evaporated. The residue was twice taken up in petroleum ether and evaporated to yield 3.6 g. of an off-white solid, m.p. 147–152°, λ_{max}^{Nujol} (μ) 5.57 and 5.90, which was hydrolyzed directly by heating a suspension of the material in a mixture of 50 ml. of methanol and 50 ml. of 10% sodium hydroxide at reflux for 0.75 hr. The methanol was removed *in vacuo*, water was added, and the organic product was extracted with ether. The ether extracts were washed, dried, and evaporated, and the residue was washed with petroleum ether (b.p. 30–60°) (to remove unreacted cholesterol) to give 1.2 g. of a colorless solid, m.p. 146–152°. A suspension of this material in methanol was heated to boiling, cooled, and collected. Cholesteryl des-N-methyldesosaminide was thus obtained in 42% yield (1.1 g.) from the bromo sugar I: m.p. 151–156° (the cloudy melt cleared at 165°); $[\alpha]^{26}D$ +29° (*c* 1.01, chloroform).

Anal. Calcd. for $C_{34}H_{59}NO_3$: C, 77.07; H, 11.22; N, 2.64. Found: C, 77.09; H, 11.14; N, 2.66.

Cyclododecyl Des-N-methyldesosaminide *via* Its Ditrifluoroacetyl Derivative III.—To a solution of 0.184 g. (0.001 mole) of cyclododecanol in 50 ml. of anhydrous 1,2-dichloroethane was added 0.3 g. (0.0012 mole) of dried mercuric cyanide and 1 g. of pulverized predried Drierite. The suspension was stirred at room temperature for 1 hr., 0.42 g. (0.001 mole) of I was added, and the mixture was stirred at room temperature for 26 hr. The insoluble salts were removed by filtration, chloroform was added to the filtrate, and the organic solution was washed with water, dried, and evaporated to yield 0.55 g. of a green-yellow sirup, λ_{max}^{neat} (μ) 5.59 and 5.90, which was hydrolyzed directly by stirring in 14 ml. of a 7% solution of potassium carbonate in aqueous methanol (2:5, v./v.) at room temperature for 4.5 hr. The reaction mixture was poured into water and the organic product extracted with ether. The 0.3 g. of viscous yellow sirup obtained by drying and evaporating the ether absorbed in the 3-μ region in the infrared and showed no bands in the 5.5–6.0-μ region. Evaporative distillation of the crude product at *ca.* 110° (0.005 mm.) yielded 0.15 g. (46%) of a very viscous sirup (practically a glass), $[\alpha]^{25}D$ +76.5° (*c* 1.09, chloroform).

Anal. Calcd. for $C_{19}H_{37}NO_3$: C, 69.68; H, 11.39; N, 4.28. Found: C, 69.81; H, 11.27; N, 4.35.

Acknowledgment.—We thank Dr. G. Berkelhammer for his continued interest and Mr. William Fulmor and staff for the optical rotation data.

New Synthesis of L-Xylose-5-*t*

SUSANNE VON SCHUCHING AND GLENN H. FRYE

Radioisotope Service, Veterans Administration Center, Martinsburg, West Virginia

Received November 19, 1964

L-Xylose labeled with high specific activity of tritium at the C-5 position was needed as an intermediate in the synthesis of L-ascorbic-6-*t* acid for use in biologic studies.

A survey of the literature showed that L-xylose has been obtained from D-glucose requiring four steps.[1,2] It is possible to introduce tritium at the first step if the sodium borohydride reduction of D-glucose to D-glucitol[3] is carried out with tritiated sodium borohydride. Since prolonged handling of radioisotopes is a distinct disadvantage, a different sequence of reactions was sought.

Following the general outline given by Heyns,[4] 1,2:3,5-di-O-cyclohexylidene-L-xylofuranose (I) was preferentially hydrolyzed to 1,2-mono-O-xylofuranose (II). Catalytic oxidation of II gave 1,2-mono-O-cyclohexylidene-L-xyluronic acid (III).

Several improvements were made in the preparation of III: (1) partial hydrolysis of 1,2:3,4-di-O-cyclohexylidene-L-xylofuranose (I) to the monocyclo compound II with 60% acetic acid, (2) construction of an efficient apparatus for catalytic oxidation, and (3) hydrolysis of the calcium salt of III to the acid. The methyl ester of 1,2-mono-O-cyclohexylidene-L-xyluronic acid (IV), not previously recorded in the literature, was prepared and the ester group was reduced with tritiated sodium borohydride. The purification of 1,2-mono-O-cyclohexylidene-L-xylofuranose-5-*t* after reduction was aided

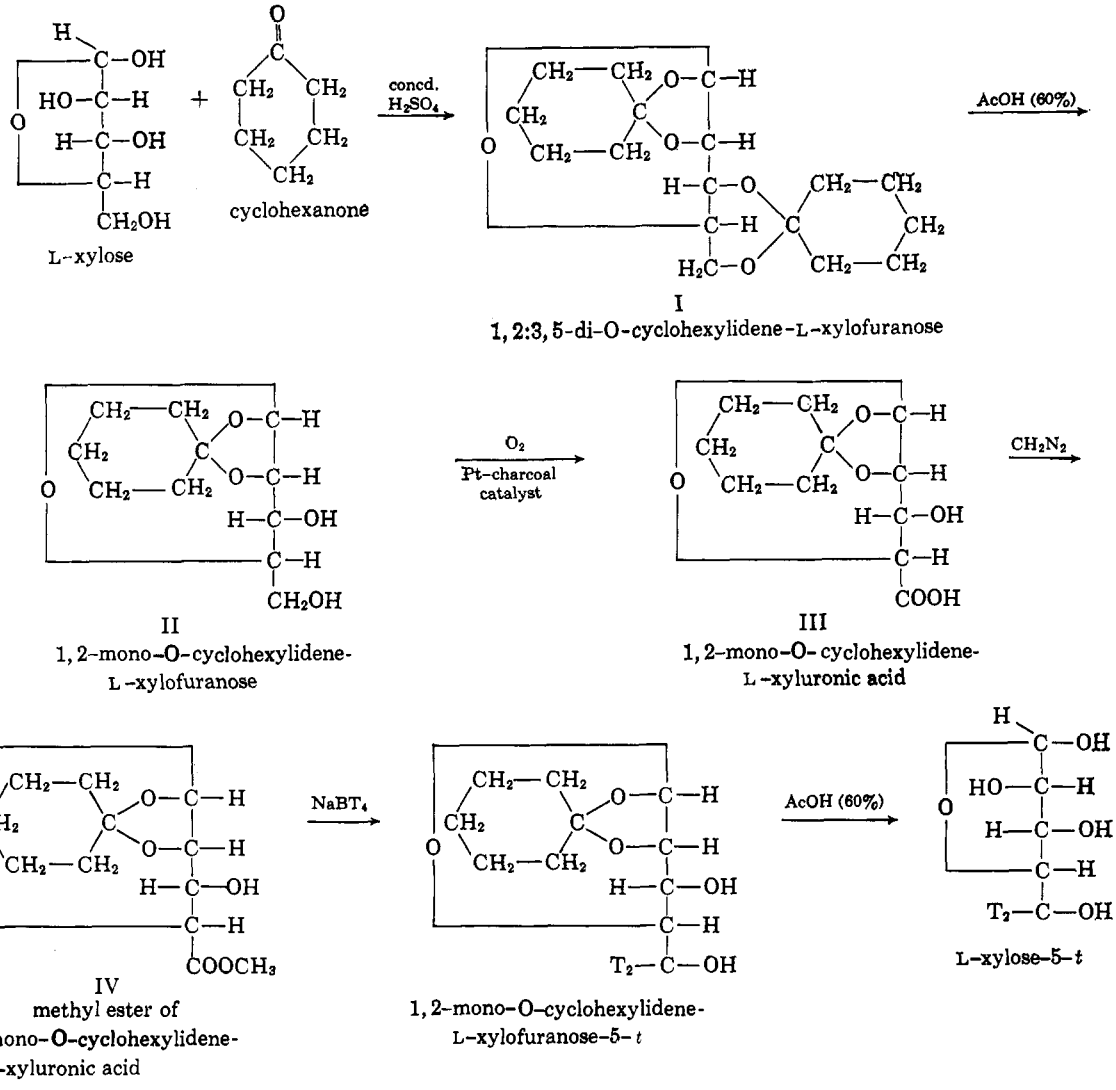
(1) R. K. Ness, "Methods in Carbohydrate Chemistry," Vol. 1, R. L. Whistler and M. L. Wolfrom, Ed., Academic Press Inc., New York, N. Y., 1962, p. 90.

(2) H. L. Frush, H. S. Isbell, and A. J. Fatiadi, *J. Res. Natl. Bur. Std.*, **64A**, 433 (1960).

(3) M. Abdel-Akher, J. K. Hamilton, and F. Smith, *J. Am. Chem. Soc.*, **73**, 4691 (1951).

(4) K. Heyns and J. Lenz, *Chem. Ber.*, **94**, 348 (1961).

SCHEME I



by the use of a cation-exchange resin in the hydrogen form.[5]

L-Xylose-5-*t* obtained from hydrolysis was isolated with carrier L-xylose in a 52% radiochemical yield. In an inactive run L-xylose was isolated in 32% yield by crystallization from alcohol (see Scheme I).

Experimental[6]

Preparation of Catalyst.—To a solution of 1 g. (0.017 mole) of chloroplatinic acid $Cl(H_2PtCl_6 \cdot 6H_2O)$ (400 mg. of Pt) in 60 ml. of water in a beaker was added 9 g. of activated charcoal.[7] The mixture was stirred mechanically and neutralized by the addition of sodium bicarbonate. It was then heated to 80° in a wax bath and 5.5 ml. of formaldehyde was added dropwise. Sodium hydrogen carbonate was added in portions to neutralize the formic acid formed. Care was taken to maintain the mixture slightly alkaline. Heating and stirring were continued for another 2 hr.; during this time the level of the liquid was held constant by adding water periodically. After 2 hr. the mixture was cooled and filtered; the catalyst was washed well with water. It was next dried in air or under vacuum. The dried catalyst contained 4.5% platinum by weight.

Apparatus for Catalytic Oxidation.—A standard chromatographic column, 45 × 600 mm.,[8] containing a fused coarse sinter at its lower end above the constriction was cut off 240 mm. above the disk. The top of the tube was left open and a brushless mechanical stirrer, maximum speed 1400 r.p.m.,[9] was centered above it. The stirring rod (7-mm. diameter), whose end was drawn into a butterfly shape only slightly shorter than the diameter of the column, extended to a few millimeters above the disk. In order to keep the rod steady at this high speed the rod was enclosed by an outer glass tube of 13-mm. o.d. Two soft bushings were cut from a piece of Teflon tubing and placed around the rod inside this guard tube.

Heating was effected by wrapping an electric heating tape regulated by a rheostat around the lower part of the tube to the height of the liquid.

Assay of Radioactivity.—Radioactivity was determined in a Packard Tri-Carb liquid scintillation spectrometer. The material to be analyzed was dissolved in the ethyl alcohol and 0.1 ml. was added to 15 ml. of liquid scintillation fluid, containing 4 g. of 2,5-diphenyloxazole (PPO)[10] and 0.5 g. of 2,2′-*p*-phenylenebis(5-phenyloxazole) (POPOP)[10]/l. of toluene. A high voltage setting of 5–300 v. was used. The efficiency for tritium counting under these conditions was 22%, determined with an internal standard.

(5) Since unreacted tritium is liberated at this point, special precautions have to be taken during the addition of the resin for personnel protection.

(6) Paper chromatography was carried out using the ascending technique (Whatman 3MM filter paper) with 4:1:5 butanol–acetic acid–water system according to R. J. Block, E. L. Dunn, and G. Zweig ("A Manual of Paper Chromatography and Paper Electrophoresis," Academic Press Inc., New York, N. Y., 1955, p. 131) for a period of 18 hr. The xylose spot was located with 3% *p*-anisidine–hydrochloric acid solution and the strip was scanned for the location of radioactivity with a windowless chromatogram scanner. Melting points are uncorrected; they were taken on a Fisher-Jones melting point apparatus.

(7) Activated charcoal, Merck.

(8) Arthur H. Thomas Co., Catalog No. 3076-C05.

(9) Welch motor stirrer, Catalog No. 5230.

(10) Obtained from Packard Instrument Co.

1,2:3,5-Di-O-cyclohexylidene-L-xylofuranose (I).—L-Xylose[1] (25 g., 0.167 mole) was suspended in cyclohexanone (264 ml., 2.5 mole) in a 1-l. long-neck flask and concentrated sulfuric acid (3.61 ml., sp. gr. 1.84) was added dropwise. After the addition of sulfuric acid the reaction mixture was shaken at room temperature for 24 hr.

The sulfuric acid was neutralized by addition of sodium bicarbonate (11.1 g.) with cooling; the sodium sulfate which was formed was filtered off. The solution was concentrated *in vacuo* at 65° to a thick sirup. The sirup was diluted with methanol and cooled at −20°. Crystallization began after a few minutes and 47 g. (95% of theory) of crude I was recovered after 3 days at −20°. The material was recrystallized from alcohol, m.p. 103–104°, yield 41 g. (79% of theory).

The compound was soluble in methanol, ethanol, ether, petroleum ether (b.p. 60–110°), dioxane, ethyl acetate, and acetone, but it was insoluble in water. It did not reduce hot Fehling's solution: $[\alpha]^{20}D$ −2.88° (*c* 9.1, acetone).

1,2-Mono-O-cyclohexylidene-L-xylofuranose (II).—A suspension of 1,2:3,5-di-O-cyclohexylidene-L-xylofuranose (I, 5 g., 0.016 mole) in 150 ml. of 60% acetic acid (v./v.) was vigorously shaken in a 300-ml. Kjeldahl flask for 24 hr. at room temperature.

The resulting clear solution was concentrated *in vacuo* at 50° to a sirup. Water (100 ml.) was added and removed *in vacuo*. The sirup was thoroughly dried on a high vacuum pump. It was then dissolved in 10 ml. of acetone. The acetone solution was added dropwise to 700 ml. of rapidly stirred petroleum ether. This effects the separation of any unreacted dicyclo compound, since the dicyclo compound I is soluble in petroleum ether and the monocyclo compound II is insoluble in this solvent. After 24 hr. at 4°, white crystals of II (4.3 g., 85% of theory) were obtained. This product melted at 83–84°. It was soluble in water, methanol, ethanol, ether, dioxane, ethylacetate, and acetone. It is insoluble in petroleum ether and did not reduce hot Fehling's solution: $[\alpha]^{20}D$ +0.41° (*c* 9.1, acetone).

1,2-Mono-O-cyclohexylidene-L-xyluronic Acid (III).—To 2.3 g. (0.01 mole) of 1,2-mono-O-cyclohexylidene-L-xylofuranose (II), 300 mg. of sodium bicarbonate, and 1.7 g. of 4.5% platinum–charcoal catalyst (680 mg. of Pt) was added 100 ml. of water in the oxidation apparatus described above. The stirrer was started at maximum speed and oxygen was blown in the suspension at 50 ml./min. The reaction mixture was maintained at 50°. After 30 min. of reaction time another 1.7 g. of the catalyst together with 300 mg. of sodium bicarbonate were added. The total reaction time was 2 hr. A few minutes after the start of the reaction the solution began to foam considerably.

The oxidation was stopped after 2 hr. The catalyst was removed by suction filtration and washed well with water. The filtrate was concentrated *in vacuo* at 50° to about 50 ml. and adjusted to pH 2 with dilute hydrochloric acid to destroy any excess bicarbonate. The solution was then brought to pH 5 with the addition of dilute ammonium hydroxide. Ten milliliters of 10% calcium chloride was added and the precipitation of the calcium salt of III began after 30 sec. The mixture was allowed to stand overnight. The precipitate was filtered and washed with water and acetone, yielding 1.73 g. (70% of theory).

The calcium salt of III (1 g.) was dissolved in 50 ml. of 1 *N* hydrochloric acid and 1,2-mono-O-cyclohexylidene-L-xyluronic acid (III) was extracted with three 50-ml. portions of ethyl acetate. The extract was concentrated *in vacuo* at 50° to dryness and dissolved in 5 ml. of acetone, and the solution was then added dropwise to 800 ml. of rapidly stirred petroleum ether. A quantitative yield of III was obtained, m.p. 159–161°. The compound is soluble in water and acetone, but insoluble in ether and petroleum ether: $[\alpha]^{20}D$ +3.67° (*c* 9.1, acetone).

Methyl Ester of 1,2-Mono-O-cyclohexylidene-L-xyluronic Acid (IV).—1,2-Mono-O-cyclohexylidene-L-xyluronic acid (1 g.) was thoroughly dried and an excess of ethereal solution of diazomethane was poured over it.[11] Vigorous evolution of nitrogen occurred and the compound dissolved immediately. The solution was allowed to decolorize and after spontaneous evaporation of the ether the ester crystallized. The crude crystals were dissolved in 10 ml. of acetone and dropped slowly in 500 ml. of petroleum ether. The solution became cloudy and after 3 days at −20° white fluffy crystals of IV were obtained weighing 0.93 g. (88% of theory): m.p. 93–95°, $[\alpha]^{25}D$ +1.5° (*c* 9.1, acetone).

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.08; H, 7.0. Found: C, 54.82; H, 7.05.

L-Xylose by Reduction of Methyl 1,2-Mono-O-cyclohexylidene-L-xyluronate (IV) with Inactive $NaBH_4$.—To a solution of 1 g. (0.0039 mole) of methyl 1,2-mono-O-cyclohexylidene-L-xyluronate (IV) in 50 ml. of water was added at once 148 mg. (0.0039 mole) of $NaBH_4$ and the solution was stirred magnetically for 30 min. at room temperature. Two more portions of $NaBH_4$, 148 mg. each, were added at 15-min. intervals. Total time of reaction was 1 hr. Next, enough water was added to bring the reaction mixture to 100 ml., and 8 g. of cation-exchange resin[12] in the hydrogen form was slowly added. The acidified solution was stirred for 30 min. after the evolution of hydrogen stopped. After filtration the solution was evaporated at 50° under reduced pressure to a sirup. The sirup was repeatedly dissolved in methanol, and the solution was evaporated under reduced pressure in order to remove the boric acid as volatile methyl borate. The resulting sirup was dissolved in 150 ml. of 25% acetic acid and hydrolyzed on a steam bath for 1 hr. Next acetic acid was thoroughly removed by repeated evaporation of the solution *in vacuo* at 50°. The solution was then taken up in 50 ml. of water and cyclohexanone was removed by shaking it with three 50-ml. portions of ether. The solution was then concentrated to a sirup and L-xylose was crystallized by dissolving the sirup in absolute alcohol and adding ether to the solution to the point of incipient turbidity. After 3 days at 4°, 186 mg. (32% of theory) of L-xylose was recovered, m.p. 143°. A paper chromatogram prepared from 0.5 mg. of the material showed a spot at a location identical with that of an authentic sample of L-xylose.

1,2-Mono-O-cyclohexylidene-L-xylofuranose 5-*p*-Toluenesulfonate.—One gram of IV was reduced with sodium borohydride and the solution was concentrated to a sirup and thoroughly dried. The residue was taken up in 20 ml. of dry pyridine and 0.76 g. (0.04 mole) of *p*-toluenesulfonyl chloride in 20 ml. of pyridine was added at 0°. The mixture was stirred for 1 hr. and then poured over cracked ice. The resulting crystals of 5-(*p*-tolylsulfonyl)-1,2-mono-O-L-xylofuranose were recrystallized from ether–petroleum ether. The melting point was 124° uncor. The tosyl derivative of II was prepared in an identical manner, m.p. 124°. A mixture melting point showed no depression.

L-Xylose-5-*t* by Reduction of Methyl 1,2-Mono-O-cyclohexylidene-L-xyluronate (IV) with $NaBT_4$.—The run with tritiated sodium borohydride was carried out under a well-ventilated hood. A solution of 516 mg. (0.002 mole) of the ester IV in 40 ml. of water was prepared in a 25-ml., two-neck, round-bottom flask under the hood. The outlet of one opening of the flask was connected through a piece of rubber tubing to the back of the hood. To the magnetically stirred solution at room temperature was added 34 mg. of $NaBT_4$[13] in two portions (0.001 mole) containing 90 mc. of tritium. After 30 min., 38 mg. of inactive $NaBH_4$ was added twice in 15-min. intervals. After 1 hr. the volume was brought to 100 ml. with water and 8 g. of cation-exchange resin[12] was slowly added from an erlenmeyer flask which was connected by a piece of soft rubber tubing directly to the second outlet of the reaction flask. The erlenmeyer flask was operated remotely by lifting it with a pair of long-handled tongs (50 cm.) in order to avoid any breathing of the unreacted tritium. Stirring was continued for 1 hr. after the evolution of gas stopped. The solution was then filtered and boron was removed as methyl borate as described above. Removal of the cyclohexanone group was carried out by hydrolysis of the residue with 150 ml. of 25% acetic acid on the steam bath. The solution was concentrated and the residue was dissolved in 50 ml. of water. Cyclohexanone was removed by extraction with etner. The solution was then alternately concentrated at 50° and reconstituted with distilled water to remove all labile tritium, which required five cycles. The residue was taken up in 10 ml. of water and 1 g. of inactive L-xylose was added as a carrier. The solution was again brought to dryness taken up in alcohol and ether was added to beginning turbidity. After 3 days at 4°, 670 mg. of crystallized L-xylose-5-*t* were obtained, m.p. 143°. A paper chromatogram prepared from 0.5 mg. of the material showed the location to be identical with an authentic sample of L-xylose, and the radioscan with a windowless chromatogram scanner showed the location of radioactivity in the same position. Assay of

(11) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., 1955, p. 312.

(12) Dowex 50, obtained from Dowex Co.

(13) Obtained from New England Nuclear Corp.

radioactivity showed 47.2 mc. (51.5%) total radioactivity in 670 mg. of L-xylose-5-*t*. The supernatant contained an additional 28.2% of radioactivity.

Acknowledgment.—The authors wish to express their appreciation to Dr. A. F. Abt for his encouragement during this work.

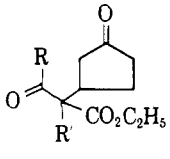
Steroidal Hormone Relatives. IX. Derivatives of Cyclopentanone[1]

J. H. BURCKHALTER AND BRUCE A. BROWN

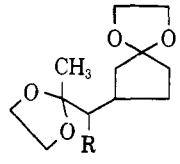
Laboratories of Pharmaceutical Chemistry, The University of Michigan College of Pharmacy, Ann Arbor, Michigan, and University of Rhode Island College of Pharmacy, Kingston, Rhode Island

Received August 1, 1963
Revised January 5, 1965

Ethyl α-(3-oxocyclopentyl)acetoacetate (I) has been made and used in a synthetic approach to steroids.[2] The related ethyl 3-oxocyclopentylmalonate (III) has been made for another purpose.[3] Preparative studies involving several compounds based upon I and III and designed as steroid intermediates constitute the subject matter of the present report.



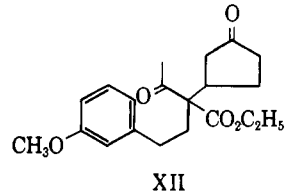
I, R = CH_3; R′ = H
II, R = C_6H_5; R′ = H
III, R = OC_2H_5; R′ = H
IV, R = OC_2H_5; R′ = C_2H_5
V, R = OC_2H_5; R′ = C_4H_9
VI, R = OC_2H_5; R′ = $C_6H_5CH_2$



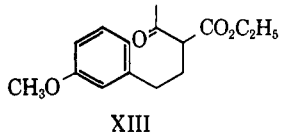
VII, R = $CO_2C_2H_5$
VIII, R = CH_2OH
IX, R = $CONHC_6H_5$

In seeking avenues to 6-aza steroids, the anilide IX was prepared by a Bodroux-type reaction but the yield was too small to encourage further synthesis. In model experiments, the ethylene ketal X of ethyl acetoacetanilide was prepared (see Experimental part), and the ketal of benzyl acetoacetate was converted to acetoacetanilide (XI). However, these procedures failed when applied to the synthesis of anilide IX from intermediates such as VII.

In an attempt to obtain XII as a possible estrone precursor, I was treated with potassium *t*-butoxide and *m*-methoxyphenethyl bromide.[4] However, isolation from the reaction mixture of starting bromide, ethyl acetoacetate, and ethyl 4-(*m*-methoxyphenyl)-2-acetobutyrate (XIII) indicated that a Michael retrogression[5] had occurred and that the anion of ethyl acetoacetate formed in the retrogression was alkylated by the *m*-methoxyphenylethyl bromide present to give XIII. XIII and its semicarbazone proved to be identical with the previously described compounds.[6]



XII



XIII

Experimental

General Procedure for the Michael Addition of Esters and 2-Cyclopentenone.—A pea of sodium was allowed to dissolve in 5 ml. of ethanol. To the solution was added 0.2 mole of the ester. The solution was stirred occasionally for 30 min. and then 0.1 mole of 2-cyclopentenone[7] was added. It was necessary to cool the reaction flask in cold water for 15 min. After 12 hr. the reaction mixture was dissolved in ether and extracted with 10 ml. of 10% acetic acid. The ethereal layer was distilled. When ethyl butylmalonate was employed, it was necessary to eliminate ethanol from the reaction and to replace the sodium with sodamide to accomplish the addition.

Ethyl α-(3-oxocyclopentyl)benzoylacetate (II) had b.p. 179–182° (0.3 mm.), $n^{23}D$ 1.5306, yield 61%.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.62; H, 6.55.

Ethyl α-ethyl-α-(3-oxocyclopentyl)malonate (IV) had b.p. 120–123° (0.15 mm.), $n^{23}D$ 1.4607, yield 74%.

Anal. Calcd. for $C_{14}H_{22}O_5$: C, 62.22; H, 8.14. Found: C, 62.08; H, 8.08.

Ethyl α-butyl-α-(3-oxocyclopentyl)malonate (V) had b.p. 138–140° (0.2 mm.), $n^{23}D$ 1.4630, yield 67%.

Anal. Calcd. for $C_{16}H_{26}O_5$: C, 64.40; H, 8.78. Found: C, 64.24; H, 8.75.

Ethyl α-benzyl-α-(3-oxocyclopentyl)malonate (VI) had b.p. 180–182° (0.25 mm.), $n^{23}D$ 1.5106, yield 67%.

Anal. Calcd. for $C_{19}H_{24}O_5$: C, 68.67; H, 7.23. Found: C, 68.46; H, 7.12.

Benzyl α-(3-oxocyclopentyl)acetoacetate[8] had b.p. 170–172° (0.2 mm.); $n^{27}D$ 1.5204; yield 56%; ν_{max} 1625, 1360, 1150 cm.$^{-1}$ (liquid film).

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.68; H, 6.57.

General Procedure for the Formation of Ethylene Ketals from the Corresponding Ketones.—In a 200-ml. flask, equipped with a dropping funnel, a Dean–Stark trap which contained magnesium sulfate, and a reflux condenser with a calcium chloride tube attached were placed 0.25 g. of *p*-toluenesulfonic acid monohydrate, 100 ml. of benzene, and 12.1 g. (0.05 mole) of ethyl α-(3-oxocyclopentyl)acetoacetate (I).[2] This solution was brought to reflux and 11.2 g. (0.18 mole) of ethylene glycol was added dropwise. The mixture was refluxed for 48 hr., cooled, extracted with a 10% solution of sodium hydroxide, and then extracted with water. After the solvent was removed from the organic layer, the residue was distilled.

Ethyl α-(3-oxocyclopentyl)acetoacetate bisethylene ketal (VII) had b.p. 133–134° (0.2 mm.); $n^{24}D$ 1.4733; yield 56%; $\nu_{max}^{CHCl_3}$ 3000, 1725, 1210, 1120, 1040 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 59.87; H, 8.12.

Ethyl α-(3-oxocyclopentyl)acetoacetate monoethylene ketal was prepared from equimolar quantities of ester I[2] and ethylene glycol in 70% yield: b.p. 118–120° (0.14 mm.); $n^{22}D$ 1.4702; ν_{max} 2950, 1725, 1120, 1030 cm.$^{-1}$ (liquid film). Ultraviolet spectrum of the product in dioxane and 0.1 *N* sodium hydroxide showed a peak at 272 mμ (ε 7320) with shoulders at 267 (7060) and 259.3 (3810). The peak is absent in the absence of base. Ethyl acetoacetate in base showed 272.5 mμ (ε 21,900).[9] Evidence suggests the ketal formed at the cyclic ketone.

Anal. Calcd. for $C_{13}H_{20}O_5$: C, 60.94; H, 7.81. Found: C, 60.70; H, 7.94.

Ethyl 3-oxocyclopentylmalonate ethylene ketal was prepared from ethylene glycol and ethyl 3-oxocyclopentylmalonate (III)[3]

(1) This investigation was supported by Research Grant HE-05915 from the National Heart Institute, U. S. Public Health Service.
(2) J. H. Burckhalter and J. A. Durden, *J. Org. Chem.*, **25**, 298 (1960).
(3) J. Meinwald and E. Frauenglass, *J. Am. Chem. Soc.*, **82**, 5235 (1960).
(4) W. E. Bachmann and D. G. Thomas, *ibid.*, **64**, 94 (1942).
(5) E. D. Bergmann, D. Ginsburg, and R. Rappo, *Org. Reactions*, **10**, 187 (1959).
(6) W. S. Rapson and R. Robinson, *J. Chem. Soc.*, 1533 (1935).
(7) The Aldrich Chemical Co., Inc., Milwaukee 10, Wis.
(8) Intermediate benzyl acetoacetate prepared by B. R. Baker, R. E. Schaub, M. V. Querry, and J. H. Williams, *J. Org. Chem.*, **17**, 77 (1952).
(9) F. N. McMillan, *Anal. Chem.*, **28**, 1532 (1956).