Derivatives of Pyromellitic Acid. 1,2,4,5-Tetrasubstituted Cyclohexanes[1]

DANIEL T. LONGONE

Department of Chemistry, University of Michigan, Ann Arbor, Michigan

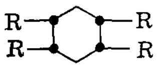
Received January 10, 1963

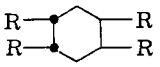
Catalytic hydrogenation of pyromellitic acid yields one of the five possible stereoisomeric 1,2,4,5-cyclohexanetetracarboxylic acids. The latter acid has been utilized as starting material for the preparation of a variety of tetrasubstituted cyclohexanes. 1,2,4,5-Tetrakis(iodomethyl)cyclohexane, precursor of 1,2,4,5-tetramethylenecyclohexane and its aromatized dimer tetramethyl[2.2]paracyclophane, has been derived from pyromellitic acid in an optimum over-all yield of 62%.

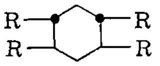
The commercial availability of pyromellitic acid (1,2,4,5-benzenetetracarboxylic acid, I) suggests the use of this compound for the preparation of tetrasubstituted cyclohexanes. We have utilized derivatives of pyromellitic acid as precursors of 1,2,4,5-tetramethylenecyclohexane[2] and its aromatized dimer tetramethyl[2.2]paracyclophane.[3] We wish to describe here the preparation of these precursors.

In an early attempt to reduce pyromellitic acid, Baeyer,[4] using sodium amalgam, obtained only a mixture of tetrahydro derivatives. We find that catalytic hydrogenation of this acid occurs with difficulty and that yields of completely reduced product are often erratic. However, in aqueous sodium carbonate solution utilizing W-2 Raney nickel catalyst and forcing conditions (3000 p.s.i. hydrogen at 150°), satisfactory yields (80–100%) of 1,2,4,5-cyclohexanetetracarboxylic acid (II) can be obtained. Less drastic conditions result in incomplete reduction or complete recovery of aromatic acid. Of the five possible stereoisomers of II (three *meso*, IIa, b, c; two *d,l*-pairs, IId, e) only one (m.p. 274–275° dec.) is formed under our hydrogenation conditions. Preliminary work[5] indicates that II is nonresolvable and is one of the three *meso* forms. There is no indication that II or its derivatives suffer isomerization when subjected to a variety of reaction media. While we suspect that II is the *trans–cis–trans*-tetraacid (IIc), a definitive assignment is not possible with the data presently available.[6]

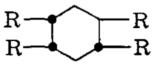
It is pertinent to indicate that four other syntheses of II have been reported in the literature. Gregory and Perkin[7] described the preparation of a stable cyclohexane-1,1,2,2,4,4,5,5-octacarboxylic acid by condensation of the disodium salt of tetraethyl propane-1,1,3,3-tetracarboxylate with the α,α′-dibromo derivative of the same compound, followed by acid hydrolysis. The octaacid decomposed above its melting point (218°) to yield a "*trans*" tetraacid (m.p. 175°) apparently assigned the *trans–trans–trans* structure IIe and a "*cis*" dianhydride whose hydrolysis product (m.p. 140°) was assigned the *cis–cis–cis* structure IIa.[8] Structural assignments were based on ease of formation of the "*cis*" dianhydride and the observation that the "*trans*" tetraacid gave only the "*cis*" dianhydride when treated with acetic anhydride.

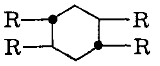

IIa


IIb


IIc

II. $R = CO_2H$


IId


IIe

Baker[9] reported the derivation of a 1,2,4,5-cyclohexanetetracarboxylic acid (m.p. 217° dec.) from a cyclohexanehexacarboxylic ester, the latter obtained by self-condensation of trimethyl 2-propene-1,1,2-tricarboxylate. The II thus obtained did not analyze well but was characterized by its tetramethyl ester (m.p. 88°) which did, and by subsequent dehydrogenation to pyromellitic acid.[10] Sieglitz and Horn hydrogenated pyromellitic acid (250° and 300 atmospheres) in aqueous sodium carbonate solution, utilizing an unspecified nickel catalyst.[11] Their reduced product II had m.p. 249–250° dec., after recrystallization from concentrated hydrochloric acid. Our crude II, formed under comparable hydrogenation conditions and precipitated from the aqueous medium by addition of concentrated hydrochloric acid, has m.p. 269–270° dec. On recrystallization from 50% ethanol we obtain analytically pure II with m.p. 274–275° dec.; however, if pure II is subsequently recrystallized from concentrated hydrochloric acid, the resulting sample has a decomposition range of *ca.* 250 to 270° and does not give a satisfactory analysis. That we obtain the same stereoisomeric tetraacid II as described by Sieglitz and Horn is further indicated by a comparison of the tetramethyl esters of II (III). The latter investigators obtain a III with m.p. 220°; our III, obtained from II in 70% yield by the method of Clinton and Laskowski,[12] has m.p. 223–225°.

Our interest in 1,2,4,5-tetramethylenecyclohexane[3] prompted the attempted conversion of the carboxylic acid groups in II to the dimethylaminomethyl groups in VI. Compound VI would serve as precursor of the tetramethylenecyclohexane *via* Hofmann degradation of the corresponding tetrakis-quaternary ammonium hydroxide. Previous work[13] has shown that the model exocyclic diene 1,2-dimethylenecyclohexane can be con-

---

[1] This work was supported in part by funds from the National Science Foundation (grant NSF-G-2626) and in part by the U. S. Army Research Office (Durham).

[2] D. T. Longone and F.-P. Boettcher, unpublished results.

[3] D. T. Longone and C. L. Warren, *J. Am. Chem. Soc.*, **84**, 1507 (1962).

[4] A. von Baeyer, *Ann., Suppl.*, **7**, 1 (1870); *Ann.*, **166**, 325 (1873).

[5] D. T. Longone and G. D. Mendenhall, unpublished results.

[6] We are investigating previously reported syntheses of II (*vide infra*) in order to verify somewhat tenuous structural assignments and to elucidate the stereochemistry of known 1,2,4,5-cyclohexanetetracarboxylic acids.

[7] T. W. D. Gregory and W. H. Perkin, Jr., *J. Chem. Soc.*, **83**, 780 (1903).

[8] In their structural assignments the investigators (ref. 7) considered the "*cis–trans*" isomer IId but made no mention of isomers IIb and IIc.

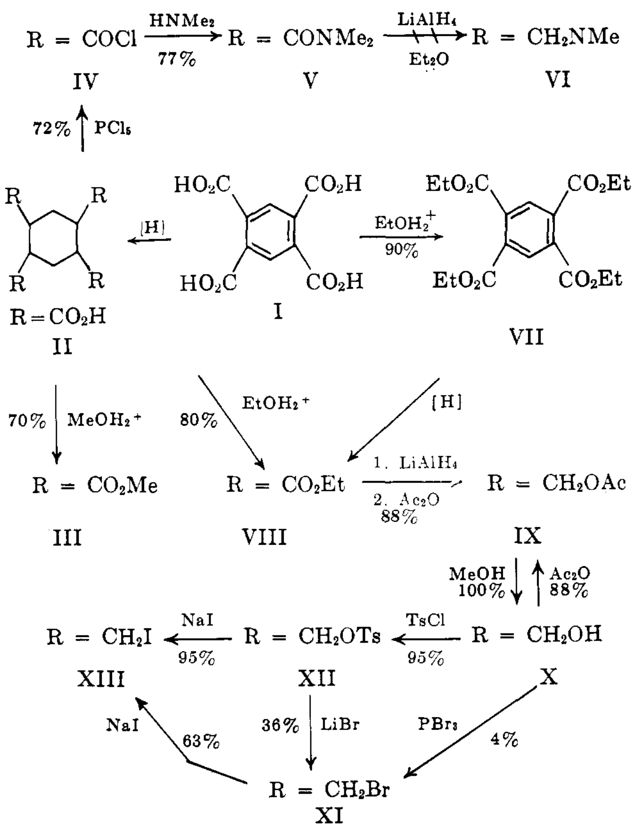
[9] J. W. Baker, *J. Chem. Soc.*, 188 (1935).

[10] Isolated as impure tetramethyl ester, "insufficient for further purification." Assignment of structure II to the aliphatic tetraacid has been questioned elsewhere (ref. 11).

[11] A. Sieglitz and O. Horn, *U. S. Dept. Comm., Office Tech. Serv., P. B. Rept.*, 777; German Patent 855,400 (1952); *Chem. Abstr.*, **47**, 4907 (1953).

[12] R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.*, **70**, 3135 (1948).

[13] A. T. Blomquist and D. T. Longone, *ibid.*, **79**, 3916 (1957).



veniently prepared by the Hofmann method. Reaction of acid II with phosphorus pentachloride in benzene gave the corresponding carbonyl chloride IV, m.p. 180–181°, in 72% yield. Aminolysis of IV in benzene solution with anhydrous dimethylamine produced the tetrakis-dimethylamide V, m.p. 296–298°, 77% yield. A single attempt to reduce V to VI with lithium aluminum hydride was unsuccessful. The infrared spectrum of the crude reaction mixture revealed the presence of large amounts of starting material and abnormal[14] reduction products. Strong absorption maxima occurred at 3400 (ROH), 1707 (RCHO), and 1633 cm.$^{-1}$ ($RCONMe_2$). If steric factors[14] determine the formation of abnormal products, they appear to be of the transannular type in this case. Both alicyclic *cis*- and *trans*-1,2-dimethylcarboxamides have given normal reduction products in relatively good yields.[15] Attempted reduction of V to VI was abandoned as it became apparent that the tetrakis-iodomethyl derivative XIII (*vide infra*) would serve as convenient progenitor of 1,2,4,5-tetramethylenecyclohexane.[3]

Azeotropic esterification of II affords tetraethyl 1,2,4,5-cyclohexanetetracarboxylate (VIII), m.p. 127–128° (80% yield). As a source of VIII we find catalytic hydrogenation of tetraethyl pyromellitate (VII) less satisfactory in that it yields a liquid mixture of stereoisomers.[16] Lithium aluminum hydride reduction of VIII, followed by acetylation with acetic anhydride,[18] gives the acetoxymethyl derivative IX, m.p. 102–103° (86% yield).[19] Methanolysis of IX affords, in quantitative yield, 1,2,4,5-tetrakis(hydroxymethyl)cyclohexane (X), m.p. 205–206°. Acetylation of X gives (88%) its precursor IX.

Reaction of tetraol X with phosphorus tribromide gave a poor yield (4%) of the bromomethyl compound XI. However, both XI and the corresponding iodomethyl derivative XIII can be derived from X *via* 1,2,4,5-tetrakis(tosyloxymethyl)cyclohexane (XII). Conversion of X to XII, m.p. 195–197° dec., was effected using *p*-toluenesulfonyl chloride (TsCl) in pyridine. Reaction of tetratosylate XII with sodium iodide in acetone gives 1,2,4,5-tetrakis(iodomethyl)cyclohexane (XIII), m.p. 245–246° (95% yield).[3] In like manner, XI, m.p. 207–208°, is obtained (36%) from XII using lithium bromide in acetone. Tetrabromide XI can be used to generate tetraiodide XIII (63% yield).

The over-all yield of tetraiodide XIII from tetraacid II (*via* XII) is 62%. The dehydroiodination of XIII to give 1,2,4,5-tetramethylenecyclohexane, tetramethyl-[2.2]paracyclophane,[3] and other products will be described in detail in a subsequent publication.

Experimental[20]

1,2,4,5-Cyclohexanetetracarboxylic Acid (II).—Neutral aqueous solutions (*ca.* 0.6 *M*) of tetrasodium pyromellitate were prepared from pyromellitic acid (or dianhydride) and the stoichiometric amount of sodium carbonate (or sodium hydroxide). As a representative hydrogenation, a volume of this solution containing 0.27 mole of acid salt and 6 g. W-2 Raney nickel was placed in a stainless steel hydrogenation bomb. The bomb, charged with hydrogen and heated to give 3000 p.s.i. at 150°, was kept at 150° for 3 days or until hydrogen consumption ceased. The resulting solution, filtered through Celite and a sintered glass filter to remove catalyst, exhibited no aromatic absorption in the ultraviolet. Addition of excess concentrated hydrochloric acid to a small portion of the solution gave a white precipitate which, after washing with cold water and drying *in vacuo*, had m.p. 269–270° dec. The remainder of the reaction solution was concentrated to incipient dryness (reduced pressure), 90 ml. of concentrated hydrochloric acid was added, and the resulting slurry (*ca.* pH 1.5) was filtered with suction. The filter cake was washed with cold water, broken up, and dried at 93° *in vacuo* to give a mixture of 69 g. (96%) II and 11 g. sodium chloride. Although the sodium chloride could be removed by careful recrystallization of the mixture from 50% ethanol, it was more convenient to remove it in a subsequent reaction (*e.g.*, esterification of II). Repetitive hydrogenations gave 81–99% yields of II.

Recrystallization of a portion of the acid–sodium chloride mixture from 50% ethanol gave analytically pure II, m.p. 274–275° dec.

Anal. Calcd. for $C_{10}H_{12}O_8$: C, 46.16; H, 4.65; N.E., 65.1. Found: C, 46.04; H, 4.72; N.E., 65.8, 65.9.

Tetramethyl 1,2,4,5-Cyclohexanetetracarboxylate (III).—Using the procedure of Clinton and Laskowski,[12] a mixture of 28.6 g. (0.110 mole) of II, 42.2 g. of methanol, 2 ml. of concentrated sulfuric acid, and 130 ml. of ethylene dichloride was refluxed for a total of 30 hr. During this time an aqueous layer developed and the suspended acid II was replaced by fine crystals of product ester. Water and chloroform were added to the mixture to dissolve all solids. The combined organic layer and chloroform extracts of the aqueous layer were washed successively with water, 5% sodium bicarbonate, and water. The resulting solution, after treatment with magnesium sulfate and

---

[14] N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, pp. 544–546.

[15] *Cf.* A. T. Blomquist and D. T. Longone, *J. Am. Chem. Soc.*, **81**, 2012 (1959); K. Alder, S. Hartung, and O. Netz, *Ber.*, **90**, 1 (1957.)

[16] Reported (ref. 17) b.p. 204° (2.5 mm.); H. I. X. Mager and W. Berends, *Rec. trav. chim.*, **76**, 28 (1957), obtained a single stereoisomer of III, m.p. 125°, on hydrogenation of tetramethyl pyromellitate.

[17] W. J. Bailey, E. J. Fetter, and J. Economy, *J. Org. Chem.*, **27**, 3479 (1962).

[18] W. J. Bailey and J. Economy, *J. Am. Chem. Soc.*, **77**, 1133 (1955).

[19] A liquid mixture of stereoisomers of IX has been used to generate 1,2,4,5-tetramethylenecyclohexane by the acetate pyrolysis method (ref. 17).

[20] Melting points are uncorrected.

Norit, was concentrated to give 17.3 g. of crystalline ester III, m.p. 223–225°. Two subsequent crops of crystals amounted to an additional 7.2 g. of product.

Anal. Calcd. for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 53.19; H, 6.41.

1,2,4,5-Cyclohexanetetracarbonyl Chloride (IV).—A mixture of 22.7 g. (0.0873 mole) acid II, 83.3 g. (0.400 mole) phosphorus pentachloride, and 200 ml. of dry benzene was refluxed, protected from atmospheric moisture, until evolution of hydrogen chloride ceased (2 days). The resulting hot solution was treated with Norit, filtered, and concentrated to give 14.7 g. of analytically pure IV, m.p. 180–181°. A second crop, 6.3 g. and m.p. 178–180°, gave a total yield of 72%.

Anal. Calcd. for $C_{10}H_8O_4Cl_4$: C, 35.96; H, 2.41. Found: C, 36.18; H, 2.51.

1,2,4,5-Tetrakis(dimethylcarboxamide)cyclohexane (V).—Gaseous dimethylamine was passed into a solution of 18.6 g. (0.0557 mole) of the acid chloride IV in 500 ml. of dry benzene with continuous stirring and intermittent cooling with tap water. Introduction of the dimethylamine was interrupted from time to time when the reaction mixture was cooled. Reaction was considered to be complete when heat no longer was evolved upon further introduction of the amine. The reaction mixture was filtered hot and the filter cake washed with hot solvent. The solid residue, obtained by evaporating to dryness (diminished pressure) the combined filtrate and washings, was dissolved in excess water. Concentration of the aqueous solution gave, in five crops, 14.2 g. of product with m.p. 290–292° dec. to 296–298° dec., after drying over phosphorus pentoxide at 100° and 0.2 mm. for 16 hr. An additional 1.6 g. of product, m.p. 295–298°, was obtained in a similar manner from the original reaction mixture filter cake. Total yield was 77%. An analytical sample, m.p. 296–298° dec., was prepared by recrystallization (water) of a portion of the product and drying as described above. Product V has amide carbonyl absorption (Nujol) at 1635 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{32}O_4N_4$: C, 58.67; H, 8.75. Found: C, 58.64, 58.87; H, 8.74, 8.71.

Tetraethyl 1,2,4,5-Cyclohexanetetracarboxylate (VIII). (A) From II.—An azeotropic esterification (6 days), essentially the procedure described elsewhere,[21] was carried out using 85.4 g. (0.328 mole) of tetraacid II, 245 ml. of absolute ethanol, 120 ml. of dry toluene, and 2 ml. of concentrated sulfuric acid. The reaction solution, on slow cooling, deposited colorless needles which, after drying *in vacuo* over phosphorus pentoxide at room temperature for 24 hr., amounted to 97.0 g. (80%) of analytically pure product VIII, m.p. 127–128°. Product VIII has strong ester-group absorptions (Nujol) at 1730 and 1190 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{28}O_8$: C, 58.05; H, 7.58. Found: C, 57.88; H, 7.48.

(B) From Tetraethyl Pyromellitate (VII).—Azeotropic esterification[21] (16 days) of 260 g. (1.192 moles) of pyromellitic dianhydride was carried out using 835 ml. of absolute ethanol, 1500 ml. of dry benzene, and 5 ml. of concentrated sulfuric acid. Ethanol and benzene were removed under diminished pressure and the residual liquid slowly solidified to massive crystals on standing at room temperature for several days. The crystalline solid was dissolved in ether and the etheral solution washed successively with water, 1% sodium hydroxide, and water. After treatment with magnesium sulfate and Norit, the etheral solution was concentrated and chilled to give 345 g. of crystalline tetraethyl pyromellitate, m.p. 55–56° (reported[22] m.p. 52°). A second crop, 37.4 g., m.p. 54–56°, and a third crop, 8.4 g., m.p. 53–54°, gave a total yield of 90%.

The ultraviolet spectrum of product VII has λ_{max} (absolute ethanol) 292 mμ, log ϵ 3.38.

Catalytic hydrogenation of 61.2 g. (0.167 mole) of VII in 600 ml. of absolute ethanol was carried out using 5 g. of W-2 Raney nickel and 3000-p.s.i. hydrogen at 175°. The reduction charge was treated with Norit, heated to reflux, and filtered with suction through Celite and a sintered glass filter. The resulting clear solution was concentrated and cooled to give 1.5 g. of crystalline solid, m.p. 127–128°. This material was identical (infrared spectrum and mixture melting point) to reduced ester VIII previously obtained by esterification of acid II. Complete removal of solvent (reduced pressure) from the residual filtrate gave an oil which did not solidify. The oil exhibited no aromatic absorption in the ultraviolet and did not decolorize bromine or permanganate solutions. This material, apparently a mixture of stereoisomers of VIII, was not investigated further.

(C) From Acid Chloride IV.—To 323 mg. (0.968 mmole) acid chloride IV was added 5 ml. of absolute ethanol. The mixture was heated over steam and the resulting solution concentrated to *ca.* 1 ml. The colorless crystals which quickly formed on cooling were separated by filtration, washed with 1 ml. of cold absolute ethanol, and dried over phosphorus pentoxide *in vacuo* at room temperature for 16 hr. The resulting ester, 309 mg. (86%), had m.p. 127–128° and was identical (infrared spectrum and mixture melting point) to ester VIII previously obtained by esterification of acid II.

1,2,4,5-Tetrakis(acetoxymethyl)cyclohexane (IX).—Into a 5-l., three-necked flask, equipped with a large Soxhlet extraction assembly and Hershberg stirrer, were placed 1920 ml. of dry ether and 42.5 g. (1.12 moles) of lithium aluminum hydride. The extractor thimble was charged with 70.4 g. (0.189 mole) of tetraethyl ester VIII and the solvent then heated to reflux. The solid ester was extracted from the thimble over a period of several hours and the entire reaction mixture refluxed for a total of 26 hr. At the end of this time the reaction flask was cooled in an ice bath and 190 ml. of acetic anhydride was added dropwise, followed by 360 ml. of glacial acetic acid, and finally, an additional 190 ml. of acetic anhydride. Ether then was distilled from the mixture until a vapor temperature of 47° was reached (arbitrary); after 19-hr. reflux at this temperature the remaining ether was removed (vapor temp. above 100°) and the mixture refluxed an additional hour. The resulting mixture was filtered under reduced pressure while still hot and the filter cake washed well with hot acetic anhydride. Acetic acid and anhydride were distilled (reduced pressure) from the combined filtrate and washings to leave a moist solid. This solid was cooled to room temperature and repeatedly triturated with hot ether. Combined ether extracts were washed successively with water, 10% sodium bicarbonate, and water, treated with magnesium sulfate and Norit, filtered, and concentrated. The concentrate soon deposited 40.3 g. of colorless crystals, m.p. 101–102°. A second crop, 20.2 g., m.p. 100–102°, gave a total yield of 86% of product IX. An analytical sample, recrystallized from ether, had m.p. 102–103°. Product IX has strong acetate–ester absorptions at 1730 and 1245 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{28}O_8$: C, 58.05; H, 7.58. Found: C, 58.20; H, 7.62.

An identical tetraacetate is obtained from acetylation of tetraol X (*vide infra*).

1,2,4,5-Tetrakis(hydroxymethyl)cyclohexane (X).—A solution of 15.1 g. (0.0406 mole) of IX and 0.3 g. of sodium methoxide in 55 ml. of absolute methanol was refluxed for 2 hr. During this time a white solid precipitated from solution. The mixture was then slowly distilled to remove methyl acetate as the methanol–methyl acetate azeotrope (b.p. 54°) and, subsequently, most of the remaining methanol. The resulting slurry was filtered with suction; the filter cake was washed with methanol and dried over phosphorus pentoxide at 0.2 mm. and room temperature for 24 hr. to give 8.4 g. (100%) of finely divided product X, m.p. 203–205°. The product is moderately soluble in cold water and quite soluble in hot water. An analytical sample was recrystallized from water and dried over phosphorus pentoxide at 100° and 0.2 mm. for 16 hr. to give m.p. 205–206°.

Anal. Calcd. for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.52; H, 9.84.

Acetylation of X on a 0.98-mmole scale using acetic anhydride in pyridine regenerates (88%) its precursor, tetraacetate IX.

1,2,4,5-Tetrakis(tosyloxymethyl)cyclohexane (XII).—A solution–suspension of 4.9 g. (0.024 mole) of tetraol X in 65 g. of reagent pyridine (dried over barium oxide) was immersed in an ice bath and 20.2 g. (0.106 mole) of *p*-toluenesulfonyl chloride was added in small portions, with stirring, over 20 min. The resulting mixture was stirred at 0° for 3 hr., by the end of which time a thick white slurry had formed. The slurry was allowed to warm to room temperature and then poured into 200 ml. of chilled 6 *M* hydrochloric acid. The mixture was filtered with suction and the filter cake washed with dilute hydrochloric acid and water, and subsequently dried *in vacuo* at room temperature over phosphorus pentoxide. The resulting product XII weighed 18.8 g. (95%) and had m.p. 195–197° dec. after recrystallization

---

(21) V. M. Micovic, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 264.

(22) J. v. Braun, W. Leistner, and W. Münch, *Ber.*, **59**, 1950 (1926).

from chloroform (or dioxane). Product XII exhibited characteristic tosylate-group absorptions at 1362 and 1178 cm.$^{-1}$.

Anal. Calcd. for $C_{38}H_{44}O_{12}S_4$: C, 55.59; H, 5.40. Found: C, 55.29; H, 5.33.

1,2,4,5-Tetrakis(bromomethyl)cyclohexane (XI). (A) From Tetratosylate XII.—A glass-lined stainless steel bomb charged with 15.0 g. (0.0183 mole) of tetratosylate XII, 8.6 g. of lithium bromide, and 150 ml. of reagent acetone was heated at 110° for 14.5 hr. The resulting mixture, consisting of a fairly homogeneous solid phase and a discolored acetone phase, was filtered with suction. The filter cake, a mixture of product XI and tosylate salt, was triturated with four 100-ml. portions of carbon tetrachloride. The combined extracts were concentrated to give, in two crops (m.p. 207–208° and 205–207°), 3.0 g. (36%) of tetrabromide XI. The acetone filtrate from the original reaction mixture afforded no additional product. An analytical sample of XI, recrystallized from carbon tetrachloride, had m.p. 207–208°.

Anal. Calcd. for $C_{10}H_{16}Br_4$: C, 26.35; H, 3.54; Br, 70.12. Found: C, 26.56; H, 3.71; Br, 70.38.

(B) From Tetraol X.—Attempted bromination of X using phosphorus tribromide in carbon tetrachloride and carried out in the usual manner gave only 4% of tetrabromide XI as the sole isolable solid. This product was identical to XI derived from XII as described previously.

1,2,4,5-Tetrakis(iodomethyl)cyclohexane (XIII). (A) From Tosylate XII.[23]—A solution of 12.2 g. (0.0149 mole) of tosylate XII and 18.0 g. of dry sodium iodide in 80 ml. of reagent acetone was refluxed for 4 hr. During this time a white solid separated. The reaction mixture was cooled and filtered with suction. The filter cake, a mixture of product and sodium tosylate, was washed first with acetone, then thoroughly with water, and subsequently dried to give 95% crude iodide XIII, m.p. 244° dec. Product XIII is somewhat soluble in hot chloroform and moderately soluble in hot tetrahydrofuran.

An analytical sample, recrystallized from chloroform, had m.p. 245–246°.

Anal. Calcd. for $C_{10}H_{16}I_4$: C, 18.65; H, 2.50; I, 78.84. Found: C, 18.88; H, 2.54; I, 78.58.

(B) From Tetrabromide XI.—To a solution of 0.67 g. of XI (1.47 mmoles) in 75 ml. of hot acetone there was added, with stirring, 2.64 g. (17.6 mmoles) of dry sodium iodide. The resulting hot solution, initially clear, quickly became turbid and soon deposited a white solid. The mixture, after refluxing for 90 hr. (arbitrary), was cooled and filtered. To the filtrate was added an equal volume of chloroform and the resulting precipitate of inorganic salts was removed by filtration. The acetone–chloroform solution, hot, was used to triturate the filter cake from the original reaction mixture. The extract was concentrated to give, in two crops, 0.60 g. (63%) of tetraiodide XIII, m.p. 245–246° dec.

Acknowledgment.—The author is indebted to Dr. C. S. Marvel (National Science Foundation grant NSF-G-2626) with whose encouragement this work was initiated.

---

(23) The author is indebted to Mrs. C. L. Warren for initially carrying out this reaction.

Glycolic Acids and Esters From Cortisone[1]

MARVIN L. LEWBART[2] AND VERNON R. MATTOX

Section of Biochemistry, Mayo Clinic and Mayo Foundation, Rochester, Minnesota

Received December 31, 1962

In methanolic cupric acetate the glyoxal from cortisone (20-keto-21-aldehyde) rearranges slowly to form the corresponding glycolic acids (20-hydroxy-21-acid) and methyl esters. Two 20-hydroxy acids (epimeric at C-20) and two epimeric 20-hydroxy esters are formed as main products. Reaction occurs slowly; 12% of starting material is present after two weeks. With alkali, rearrangement of the glyoxal to the same pair of epimeric 20-hydroxypregnenoic acids occurs rapidly. Acetylation of the epimeric acids under mild conditions gives the 17,20-diacetates whereas acetylation of the methyl esters under the same conditions gives the 20-monoacetates. Treatment of the methyl esters under vigorous acetylating conditions gives the 17,20-diacetates along with some of the corresponding C-3 enol acetates. The acetyl group is removed more readily from the 20α-acetate than from its 20β-epimer. The configurations at C-20 of the two series of epimers were determined.

In a previous paper it was shown that cupric acetate in methanol catalyzes the rearrangement of steroidal glyoxals to the methyl esters of steroidal glycolic acids.[3] From each glyoxal, two 20-epimeric 20-hydroxypregnan-21-oic esters were obtained. The rate of reaction of 17-hydroxy steroidal glyoxals was considerably less than that of the 17-deoxy analogs.

This paper describes the conversion of the glyoxal from cortisone into its 20-epimeric steroidal glycolates by catalysis with cupric acetate and with sodium hydroxide. Treatment of cortisone (I, Fig. 1) with methanolic cupric acetate for one hour[4] gave a good yield of glyoxal II. When this glyoxal was treated with methanolic cupric acetate at room temperature for two weeks, an 88% reduction in the Porter–Siber chromogenicity occurred. After the products of the reaction had been isolated, it was found that, in contrast to the analogous reaction with 3α-hydroxy-11,20-dioxo-5β-pregnan-21-al,[3] there was a significant acidic fraction (11%). This fraction was shown, by paper chromatography, to consist chiefly of the free glycolic acids (VIIIa[5] and VIIIb[5]) together with a small amount of the corresponding etienic acid (17-hydroxy-3,11-dioxoeti-4-enic acid).

The neutral fraction was acetylated and, after separation of a small amount of the 20α-acetoxy ester (IVa) by crystallization, the product was fractionated by column chromatography.[3] Small amounts of three compounds of unknown structure were obtained. The principal products were the 20α- and 20β-acetoxy esters (IVa and IVb) which were obtained in 27 and 22% yield, respectively.

Alkaline rearrangement of glyoxal II occurred much more rapidly and gave a higher yield of crystallizable product than did the cupric acetate-catalyzed rearrangement. Treatment of an aqueous suspension of glyoxal II at 0° under nitrogen with 1.25 equivalents of sodium hydroxide for thirty minutes resulted in almost complete disappearance of the glyoxal. Successive esterification and acetylation of the product, followed by

---

(1) Abridgment of thesis submitted by M. L. Lewbart to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Biochemistry.

(2) This investigation was carried out during the tenure of a Fellowship from the Division of General Medical Sciences, Public Health Service.

(3) M. L. Lewbart and V. R. Mattox, *J. Org. Chem.*, **28**, 1779 (1963).

(4) M. L. Lewbart and V. R. Mattox, *ibid.*, **28**, in press.

(5) "a" represents the 20 α-oxygen epimer; "b," the 20β-epimer.