D-Ribose Hydrazone

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For comparison of its properties with those of D-ribosylamine,[2] the title compound was synthesized by condensation of D-ribose with hydrazine. Although innumerable *substituted* hydrazones of sugars (and of reducing, substituted sugars) have been described in the literature, this appears to be the first *unsubstituted* hydrazone of a sugar that has been prepared.

In order to minimize possible formation of 1,2-di-D-ribosylhydrazine or of the azine, the following conditions were used: A ten-fold excess of hydrazine was employed, the reaction solution was quite concentrated, and the condensation was conducted at room temperature.

Experimental

D-Ribose Hydrazone.—Anhydrous hydrazine (16 g.) was weighed into a 50-ml. Erlenmeyer flask and 16 ml. of absolute methanol was added; heat was evolved, and so the solution was cooled in ice–salt. Dry, finely powered D-ribose (7.5 g.) was now added and the flask was quickly stoppered. On swirling, part of the D-ribose dissolved and a new kind of colorless crystals rapidly formed. After the mixture had stood at room temperature for 24 hr., with occasional swirling, all of the crystals had dissolved to a clear, colorless solution. This was transferred to an evaporating dish and evaporated in a vacuum desiccator, over phosphorus pentoxide and soda lime, to a thick, viscous, colorless sirup which was dried at 0.1 mm. (Desiguard). The sirup was redissolved by stirring it with 10 ml. of absolute methanol; addition of 10 ml. of absolute ethanol now gave a white, gummy precipitate. The solution was decanted, and the precipitate was stirred with 20 ml. of absolute methanol, affording a suspension of colorless crystals which was filtered with suction (rubber dam); the crystals were washed with 10 ml. of absolute methanol and dried at 0.1 mm.; wt., 5.4 g.; m.p. 127–129°. The infrared absorption spectrum was recorded; it showed a band at 1613 cm.$^{-1}$, possibly indicative of C=N absorption. (The combined mother liquors were evaporated to dryness and the resulting crystalline mass, on stirring with 10 ml. of absolute methanol, gave a crop (1.9 g.) of less pure crystals, m.p. 115–117°.)

Anal. Calcd. for $C_5H_{12}N_2O_4$: C, 36.58; H, 7.37; N, 17.07. Found: C, 36.63; H, 7.64; N, 16.89.

The compound is practically insoluble in all organic solvents tested, except boiling acetic acid. It is sparingly soluble in water (<1 g. per 100 ml.); the saturated, aqueous solution had $\alpha^{25}\text{D}$ −0.13° (l = 2 dm.), and its ultraviolet absorption spectrum was recorded. A band at *ca.* 280 mμ suggested the presence of the open-chain, *aldehydo* form, rather than of a cyclic D-ribosylhydrazine.

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[2] R. S. Tipson, *J. Org. Chem.*, **26**, 2462 (1961).

The Synthesis of *trans*-3-Oxa-4-oxo- and *trans*-4-Oxa-3-oxobicyclo[5.4.0]undecanes

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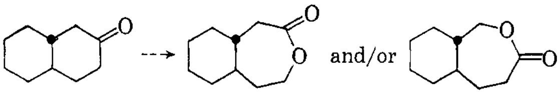
Notable by its absence in the work performed to date on the Baeyer–Villiger reaction[2] is a study of the more subtle differences prevailing in positions other than those alpha to the carbonyl function. In an attempt to study the requirements of the migrating group and yet avoid primary steric effects,[3] we were prompted to consider the Baeyer-Villiger oxidation of *trans*-β-decalone (I). The molecule could further serve as a model for rearrangements in steroids possessing an A/B *trans*-ring fusion.



I II III

Of the various approaches to the problem available to us, we chose first to prepare and characterize authentic samples of the lactones II and III. A knowledge of the physical properties of these substances might subsequently allow a method of composition analysis to be applied directly to the *trans*-β-decalone oxidation mixtures. The purpose of this paper is to report the unequivocal synthesis of *trans*-4-oxa-3-oxobicyclo[5.4.0]undecane (II) and *trans*-3-oxa-4-oxobicyclo[5.4.0]undecane (III).

Reaction of *trans*-β-(2-carboxycyclohexane) propionic acid (IV)[4,5] with diazomethane gave methyl *trans*-β-(2-carbomethoxycyclohexane)propionate (Va) which was selectively saponified with one equivalent of sodium hydroxide in refluxing aqueous methanol to produce *trans*-β-(2-carbomethoxycyclohexane)propionic acid (Vb). Near theoretical quantities of VI were obtained by reduction of Vb with sodium–ethanol–liquid ammonia.[6] Distillation of this hydroxy acid readily furnished *trans*-3-oxa-4-oxobicyclo[5.4.0]undecane (III).

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[2] For a recent review of this reaction see C. H. Hassall, *Org. Reactions*, IX, 73 (1957).

[3] The present status of knowledge on primary steric effects is discussed in R. R. Sauers and J. P. Ahearn, *J. Am. Chem. Soc.*, **83**, 2759 (1961) and references cited therein.

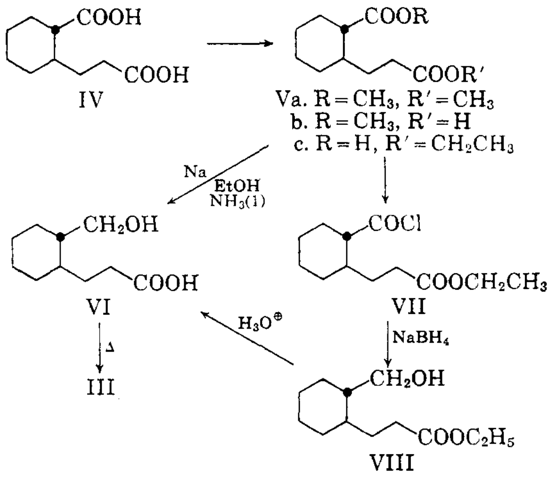
[4] G. A. Page and D. S. Tarbell, *Org. Synthesis*, **34**, 8 (1954).

[5] C. D. Gutsche and H. H. Peter, *J. Am. Chem. Soc.*, **77**, 5971 (1955).

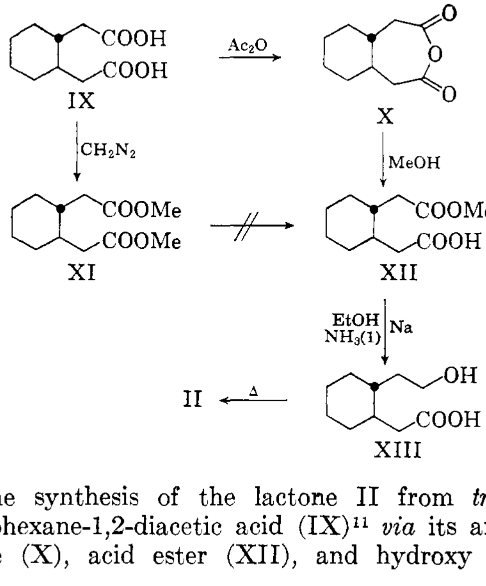
[6] The new selective reduction method described herein is far superior to the Bouveault-Blanc procedure[7,8] presumably because the temperature of the reaction, when performed in this medium, is sufficiently low to allow the reduction to proceed rapidly without the problem of concomitant ester hydrolysis.

[7] P. Chuit and J. Hausser, *Helv. Chim. Acta*, **12**, 463 (1929).

[8] D. C. Sayles and E. F. Degering, *J. Am. Chem. Soc.*, **71**, 3161 (1949).



To establish that no rearrangement had occurred during the sodium–ethanol–liquid ammonia reduction, an alternative approach to the synthesis of III was undertaken. Fisher esterification of IV in ethanol gave the primary monoester Vc which, on treatment with thionyl chloride followed by direct reduction of the acid chloride[9] with sodium borohydride, was transformed to ethyl *trans*-β-(2-hydroxymethylcyclohexane)propionate (VIII).[10] The conversion of VIII to the lactone III was effected by saponification and subsequent distillation of the resulting hydroxy acid.



The synthesis of the lactone II from *trans*-cyclohexane-1,2-diacetic acid (IX)[11] *via* its anhydride (X), acid ester (XII), and hydroxy acid (XIII) was performed in a similar fashion. It is noteworthy that the diester XI could not be selectively hydrolyzed with one equivalent of base to XII, the product being a mixture of diester, acid-ester, and diacid.

Very preliminary attempts to separate artificially compounded mixtures of II and III by vapor phase chromatography have proven disappointing. However, quantitative infrared spectroscopy should be possible as a means of analyzing the composition of β-tetralone oxidation products, because I, II, and III do possess characteristic absorption bands in their respective spectra (*cf.*, Experimental). Because of a change in laboratories[1] no further work on this problem is anticipated.

Experimental[12]

Methyl *trans*-β-(2-Carbomethoxycyclohexane)propionate (Va).—To 20.0 g. (0.10 mole) of *trans*-β-(2-carboxycyclohexane)propionic acid was added an etheral solution of excess diazomethane. The unchanged diazomethane was decomposed with dilute hydrochloric acid solution. The layers were separated and the ethereal layer was washed successively with 5% sodium bicarbonate solution, distilled water, and saturated salt solution. The ether extract was dried, filtered, and concentrated to give a residue which was distilled *in vacuo* to yield 22.7 g. (99.7%) of a colorless liquid, b.p. 105° (0.80 mm.), n^{28}D 1.4555. Redistillation of a small sample gave pure diester, b.p. 98° (0.55 mm.), n^{28}D 1.4558. $\tilde{\nu}_{\max}^{\mathrm{CCl_4}}$ 1740 cm.$^{-1}$ (s, ester carbonyl).

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.26; H, 8.83.

***trans*-β-(2-Carbomethoxycyclohexane)propionic Acid (Vb).**—In a 100-ml. flask fitted with a condenser was placed 4.56 g. (0.02 mole) of the diester Va, 40 ml. of anhydrous methanol, and 395 ml. of 0.506 *N* sodium hydroxide solution (0.02 mole). The mixture was heated under reflux for 4 hr. The solvent mixture was removed under reduced pressure, water was added, and the solution was extracted with ether. The aqueous layer was acidified with concd. hydrochloric acid and extracted with three 150-ml. portions of ether. The ether extract was dried, filtered, and concentrated to give a residue which was distilled *in vacuo* to yield a colorless liquid, 3.09 g. (72.3%), b.p. 135–138° (0.45 mm.), n^{26}D 1.4690. Redistillation of a small sample gave pure acid ester, b.p. 134° (0.40 mm.), n^{25}D 1.4694. $\tilde{\nu}_{\max}^{\mathrm{CCl_4}}$ 1700–1740 cm.$^{-1}$ (s, carboxyl and ester carbonyls).

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.50; H, 8.27.

Ethyl *trans*-β-(2-Carboxycyclohexane)propionate (Vc).—In a dry 500-ml. flask was placed 20.0 g. (0.10 mole) of the *trans*-diacid IV, 0.2 g. of *p*-toluenesulfonic acid, 100 ml. of absolute ethanol, and 75 ml. of dry benzene. The solution was refluxed on the steam bath with concurrent slow distillation of the solvent. This process required 17 hr., and the residual solvent was removed under reduced pressure. The remaining material was filtered to remove the *p*-toluenesulfonic acid, which was rinsed with ether. The oil was distilled *in vacuo* to give 19.5 g. (85.5%) of colorless liquid, b.p. 134–138° (0.135 mm.), n^{25}D 1.4636. Redistillation of a small sample gave pure acid ester, b.p. 134° (0.125 mm.), n^{27}D 1.4670. $\tilde{\nu}_{\max}^{\mathrm{CCl_4}}$ 1710 (s, carboxyl carbonyl) and 1740 cm.$^{-1}$ (s, ester carbonyl).

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(9) Although the tautomerism of acid halides of half-esters is observed when the ring is five- and six-membered [*cf.*, B. H. Chase and D. H. Hey, *J. Chem. Soc.*, 554 (1952); J. C. Bardham *ibid.* 2604 (1928); D. L. Turner *et al.*, *J. Am. Chem. Soc.*, **72**, 5654 (1950); S. Stallberger-Stenhagen *ibid.*, **69**, 2568 (1947); J. Cason, *J. Org. Chem.*, **13**, 227 (1948)], this type of isomerization appears unimportant when a seven-membered ring intermediate is required.

(10) Subsequent to the work reported herein, H. C. Brown and W. Korytnyk [*J. Am. Chem. Soc.*, **82**, 3866 (1960)] reported that carboxylic acids are reduced with marked ease by diborane while esters react sluggishly with this reagent. Presumably therefore, the acid ester Vc could also be converted to VIII with diborane. In addition the transformation XII → XIII should also be permissible by this procedure.

(11) R. J. Tudor and A. I. Vogel, *J. Chem. Soc.*, 1250 (1934).

(12) Melting points and boiling points are uncorrected. The infrared spectra were determined with a Baird (Model B) spectrophotometer fitted with a sodium chloride prism. The microanalyses were performed by Dr. S. M. Nagy and his associates. Magnesium sulfate was employed as the drying agent.

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.26; H, 8.93.

Ethyl *trans*-β-(2-Hydroxymethylcyclohexane)propionate (VIII).—A mixture of 4.56 g. (0.02 mole) of the acid ester Vc and 4.72 g. (0.04 mole) of redistilled thionyl chloride was refluxed for 2 hr. At the end of this time, the solution was cooled and the thionyl chloride was removed overnight *in vacuo* at room temperature. The resulting crude brown oil was dissolved in 30 ml. of pure, dry dioxane and was added dropwise to a slurry of 1.13 g. of sodium borohydride in 15 ml. of pure, dry dioxane. After refluxing for 2.5 hr., the mixture was cooled in ice and 50 ml. of water was slowly added. The resulting solution was acidified to Congo Red with hydrochloric acid and extracted with three 100-ml. portions of ether. After washing the combined ether layers with water, the organic layer was dried, filtered, and evaporated to yield a residual oil which was distilled *in vacuo* to give 1.80 g. (42.1% over-all) of a colorless oil, b.p. 100–110° (0.7 mm.). Two additional distillations of this material gave pure hydroxy ester, b.p. 86° (0.07 mm.). $\tilde{\nu}_{\max}^{CCl_4}$ 3525 (m, hydroxyl stretching) and 1740 cm.$^{-1}$ (ester carbonyl).

Anal. Calcd. for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.53; H, 10.24.

***trans*-3-Oxa-4-oxobicyclo[5.4.0]undecane (III). A. From VIII.**—A mixture of 0.95 g. (4.44 mmoles) of VIII and 15 ml. of 10% sodium hydroxide solution was refluxed for 4 hr. The reaction mixture was cooled and extracted with ether; the resulting aqueous solution was acidified and re-extracted with ether. The combined ether layers from the latter extraction were washed with water to neutrality, dried, filtered, and evaporated to give an oil which upon distillation *in vacuo* gave 330 mg. (44.3%) of crude lactone as a crystalline distillate. Three recrystallizations of the white solid from benzene–petroleum ether gave pure lactone as white needles, m.p. 77.5–78.0°. $\tilde{\nu}_{\max}^{CCl_4}$ 1740 cm.$^{-1}$ (lactone carbonyl); analytical bands at 1335, 1125, and 900 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.14; H, 9.58.

B. From Vb.—Into a dry 200-ml. flask was placed 4.28 g. (0.02 mole) of Vb, 10 ml. of absolute ethanol, and 100 ml. of liquid ammonia. To the rapidly stirred solution was added 4.6 g. (0.20 g.-atom) of sodium metal in small portions. Upon completion of the addition, a small amount of absolute ethanol was added to neutralize the remaining sodium. The solution was stirred until most of the ammonia had evaporated, water was added, and the solution was acidified with hydrochloric acid. The acid solution was extracted with ether, and the combined ether layers were washed with water. After the ether extract was dried, filtered, and concentrated, there remained 3.72 g. of a brownish oil which was distilled *in vacuo* to give 2.41 g. (71.7%) of a crystalline distillate, m.p. 65–72°. Recrystallization of this material from benzene–petroleum ether gave white, fluffy needles, m.p. 77–78°. A mixed melting point of this sample with a sample of the material prepared in section A gave no depression.

Dimethyl *trans*-Cyclohexane-1,2-diacetate (XI).—The diacid IX (4.00 g.) was treated with excess ethereal diazomethane as described for the preparation of Va. The residual oil was distilled *in vacuo* to yield 4.18 g. (91.8%) of a colorless liquid, b.p. 95° (0.40 mm.), n^{26}D 1.4600. Redistillation of a small sample of this material gave pure diester, b.p. 94° (0.40 mm.), n^{25}D 1.4600.[13]

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.29; H, 8.71.

Methyl Hydrogen *trans*-Cyclohexane-1,2-diacetate (XII). A mixture of 6.0 g. (0.03 mole) of IX, 9.4 ml. (10.2 g., 0.10 mole) of acetic anhydride, and 4 drops of acetyl chloride was heated on the steam bath for 3 hr. At the end of this time, the solution was cooled and 50 ml. of anhydrous methanol was added and the solution heated at reflux for 0.5 hr. After removal of the solvent mixture under reduced pressure, the residue was distilled *in vacuo* to give 4.7 g. (72.8% for the two steps) of colorless liquid, b.p. 135–139° (0.275–0.35 mm.). A small sample was redistilled to give pure acid ester, b.p. 137° (0.14 mm.), n^{26}D 1.4730. $\tilde{\nu}_{\max}^{CCl_4}$ 1700 (s, carboxyl carbonyl) and 1740 cm.$^{-1}$ (s, ester carbonyl).

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.81; H, 8.44.

***trans*-4-Oxa-3-oxobicyclo[5.4.0]undecane (II). A. By the Sodium in Liquid Ammonia Procedure.**—A 3.50-g. (0.0163 mole) sample of XII was treated with 4.6 g. (0.20 g.-atom) of sodium, 10 ml. of absolute ethanol, and 100 ml. of liquid ammonia as described for the preparation of III. There was obtained 3.04 g. of a brownish oil which was distilled *in vacuo* to give 1.76 g. (64.2%) of colorless oil, b.p 108–113° (0.2 mm.). Redistillation of a small sample gave pure lactone, b.p. 113° (0.2 mm.), m.p. 31–32°, n^{26}D 1.4892 (super-cooled), $\tilde{\nu}_{\max}^{CCl_4}$ 1740 cm.$^{-1}$ (s, lactone carbonyl); analytical bands at 1430, 1300, 1240, and 1015 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.20; H, 9.65.

B. By the Bouveault-Blanc Procedure.—To a solution of 4.0 g. (0.0187 mole) of XII in 250 ml. of refluxing absolute ethanol was slowly added 9.2 g. (0.40 g.-atom) of sodium metal in small portions with rapid stirring. When all the sodium had dissolved, the alcohol was removed under reduced pressure. To the solid residue was added 250 ml. of water. With ice-cooling, the solution was acidified slowly with hydrochloric acid and extracted with three 150-ml. portions of ether. The ether extract was dried, filtered, and evaporated to give 1.5 g. of crude cyclohexane-1,2-diacetic acid, m.p. 158–162°. The remaining aqueous solution was re-extracted with two 150-ml. portions of chloroform. The combined chloroform layers were dried, filtered, and evaporated to give a yellow brown oil. Vacuum distillation of this material gave 0.63 g. (20%) of colorless oil, b.p. 108–110° (0.4 mm.), n^{26}D 1.4850 (super-cooled). A comparison of the infrared spectra of this material with that of the lactone prepared in section A indicated by the virtual superimposability of bands that they were identical in structure.

Synthesis of Ring C^{14}-Labeled Anthranilic and 3-Hydroxyanthranilic Acid

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The stimulus for the syntheses reported in this note arose from the desire to study the metabolism of anthranilic and 3-hydroxyanthranilic acid, the latter an important intermediate in tryptophan metabolism and a known precursor of nicotinic acid.[1]

Starting materials used in the preparation of nuclear (1,2)-C^{14}-labeled anthranilic acid (III) were butadiene and maleic anhydride (I, C^{14}-labeled at the ethylenic carbons) which, in benzene underwent Diels-Alder condensation to yield 90% of 1,2,3,6-tetrahydro-*cis*-phthalic anhydride (II).[2]

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(13) *After completion of this work, this diester was synthesized via an alternate route by M. E. Ali and L. N. Owen, J. Chem. Soc.,* 2111 (1958); *they report for this substance b.p.* 115° (0.7 mm.), n^{19}D 1.4625, *in excellent agreement with the above work.*

(1) H. K. Mitchell and J. F. Nyc, *Proc. Soc. Acad. Sc.*, **34**, 1 (1948).

(2) E. F. Jenkins and E. J. Costello. *J. Am. Chem. Soc.*, **68**, 2733 (1946).