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

The Synthesis of Substituted Penicillins and Simpler Structural Analogs. VI. The Synthesis of a 6-Phenylacetylamino-β-lactam-thiazolidine

BY JOHN C. SHEEHAN AND ELIAS J. COREY[1]

The synthesis of a fused 6-phenylacetylamino-β-lactam-thiazolidine has been carried out by a new, indirect method. The reaction of 2-benzylidene-4,5-diketo-3-oxazolidineacetyl chloride (I) with 2-phenyl-2-thiazoline led to a fused β-lactam-thiazolidine bearing a 6-(2-benzylidene-4,5-diketo-3-oxazolidyl) substituent (II). Subsequent aminolytic cleavage of the oxazolidine-4,5-dione nucleus in II resulted in formation of the desired phenylacetamido-β-lactam (III). Oxidation of III produced the corresponding sulfone which is identical with a compound obtained previously by an independent route. A monocyclic β-lactam has also been prepared using I and has been related stereochemically to monocyclic β-lactams prepared earlier.

In the preceding article[2] of this series there was described the application of 5-phenyloxazolidine-2,4-diones in the indirect formation of a fused β-lactam-thiazolidine substituted by a phenylacetylamino grouping. The general requirements were also discussed for the constitution of the acid chloride component in the synthesis of benzylpenicillin-like structures by the acid chloride–thiazoline reaction.[3] In this communication there is reported a second general method for the indirect introduction of the phenylacetylamino grouping on a β-lactam-thiazolidine nucleus.

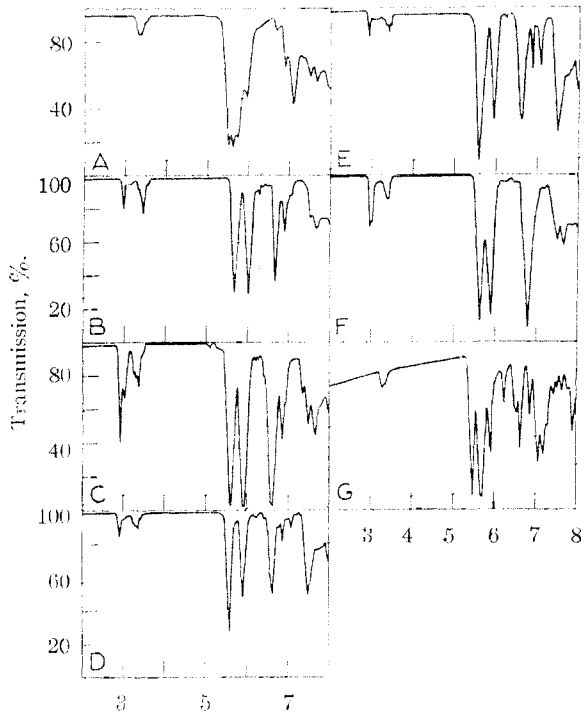


Fig. 1.—Infrared spectra: curve A, 2-phenyl-α-(2-benzylidene-4,5-diketo-3-oxazolidyl)-2-thiazolidineacetic acid β-lactam (II), 5% in $Cl_2CHCHCl_2$; B, 2-phenyl-α-(phenylacetylamino)-2-thiazolidineacetic acid β-lactam (III), 5% in $Cl_2CHCHCl_2$; C, 2-phenyl-α-(N-benzyloxalamylamino)-2-thiazolidineacetic acid β-lactam (IV), 10% in $Cl_2CHCHCl_2$; D, sulfone of III, prepared from II, 5% in $Cl_2CHCHCl_2$; E, sulfone of III, prepared from VIII, 6% in $Cl_2CHCHCl_2$; F, X, 5% in $Cl_2CHCHCl_2$; G, 1,4-diphenyl-3-(2-benzylidene-4,5-diketo-3-oxazolidyl)-2-azetidinone (XI), 5% in $Cl_2CHCHCl_2$.

The use of 2-benzylidene-4,5-diketo-3-oxazolidineacetyl chloride (I)[4] in the synthesis of fused β-lactam-thiazolidines possessing a phenylacetylamino substituent seemed feasible, because I appeared to fulfill to a large extent the stringent requirements outlined previously.[2] The acid chloride is a readily accessible, stable compound and its derivatives can be converted to phenylacetamides under relatively mild conditions.

The reaction of the acid chloride I with 2-phenyl-2-thiazoline and triethylamine was first studied. The transformations to be described are outlined in the accompanying equations. Addition of triethylamine under high-dilution conditions to a solution of I and the thiazoline in methylene chloride resulted in a 45% yield of the β-lactam II. The infrared spectrum of II is in complete accord with the β-lactam formulation. In addition to bands at 5.50, 5.73 and 5.95 μ characteristic of the oxazolidinedione nucleus there appears a strong band at 5.62 μ which is assignable to the β-lactam carbonyl. Treatment of the β-lactam II with two equivalents of benzylamine produced the desired phenylacetylaminolactam III in 32% yield and the β-lactam derived from the alternative cleavage (IV) in 21% yield.[5] The infrared spectra of both III and IV exhibit bands near 5.6 μ indicating that the β-lactam ring has not been ruptured. The lactam III is the first synthetic β-lactam-thiazolidine which possesses a 6-phenylacetylamino substituent.

Oxidation of III under carefully controlled conditions led to the sulfone VII in 32% yield. The sulfone VII is identical with the compound prepared by Sheehan and Laubach[2] by hydrogenolysis of the heterocyclic lactam VIII. Samples prepared by the two routes had the same decomposition point, and they possessed essentially identical infrared spectra and X-ray powder diffraction patterns.

(1) Bristol Laboratories Fellow, 1948–1950. Department of Chemistry, University of Illinois.

(2) J. C. Sheehan and G. D. Laubach, THIS JOURNAL, **73**, 4752 (1951).

(3) J. C. Sheehan, E. L. Buhle, E. J. Corey, G. D. Laubach and J. J. Ryan, *ibid.*, **72**, 3828 (1950).

(4) This acid chloride can be prepared in high yield by interaction of phenaceturic acid (phenylacetylglycine) and oxalyl chloride, followed by treatment with phosphorus pentachloride: G. B. Brown, *Arch. Biochem.*, **24**, 429 (1949); J. C. Sheehan and E. J. Corey, THIS JOURNAL, in press.

(5) The benzylamine cleavage of the lactam II occurred much less rapidly than the corresponding reaction with either the anilide (V) or the benzyl ester (VI) of 2-benzylidene-4,5-diketo-3-oxazolidineacetic acid.[4] This fact together with the formation of both of the possible cleavage products from II, indicates that the substituent attached to the nitrogen atom in oxazolidine-4,5-diones exerts a significant effect upon the ease and nature of ring cleavage. The same effect appears to be operative in the basic hydrolyses of V and VI which were described previously.[4]

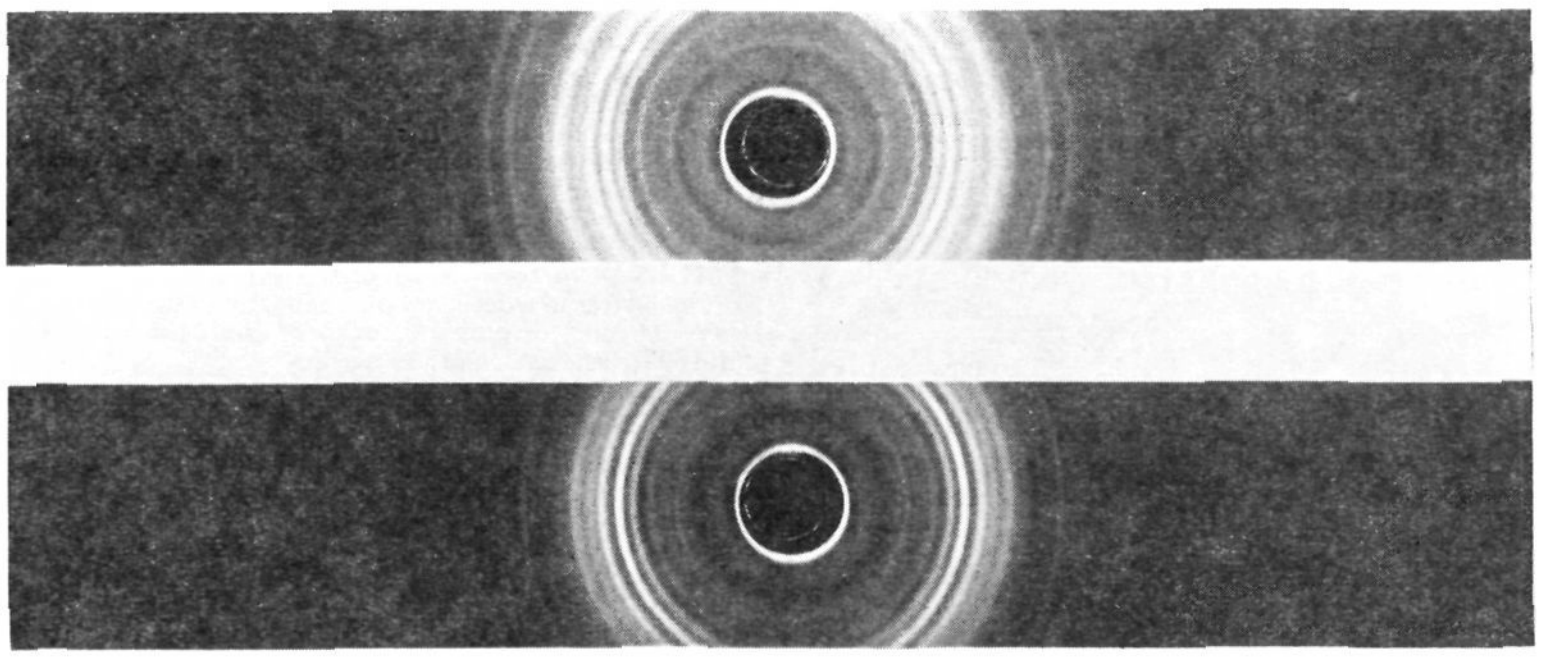
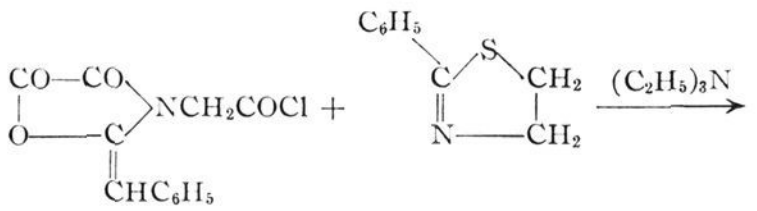
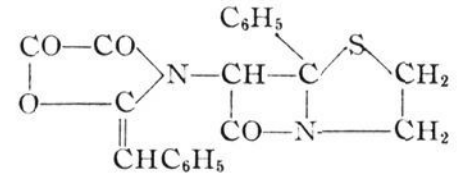


Plate I.—X-Ray powder diffraction patterns [radius 114.6 mm., λ = 1542 Å. (Cu K α)]: upper pattern, VII from III; lower pattern, VII (slight impurity of VIII) from VIII.

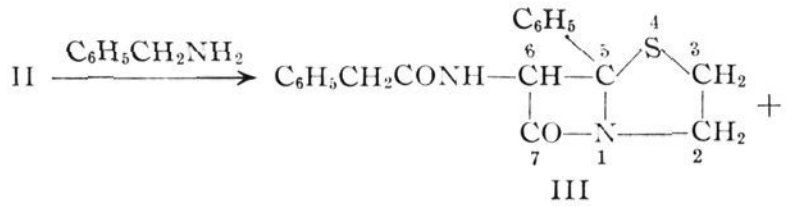
The infrared spectrum of VII shows a band due to the β-lactam carbonyl at 5.56 μ, whereas the unoxidized lactam exhibits a band at 5.67 μ. A similar shift occurs in going from penicillin methyl ester to the corresponding sulfone.[6] Since samples prepared by two routes are identical, the reaction of 2-phenyl-2-thiazoline with the acid chloride I follows the same stereochemical course as the reaction with the acid chloride (IX) used by Sheehan and Laubach.



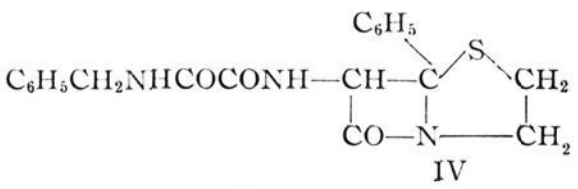
I



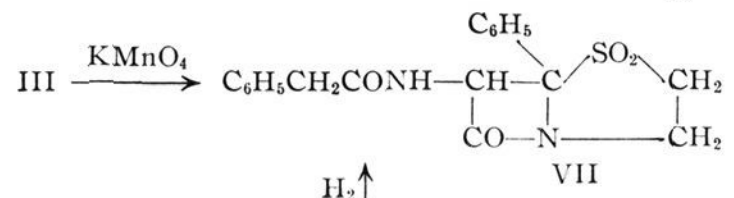
II



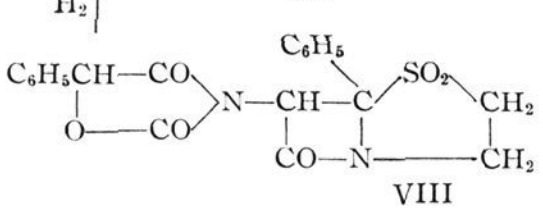
III



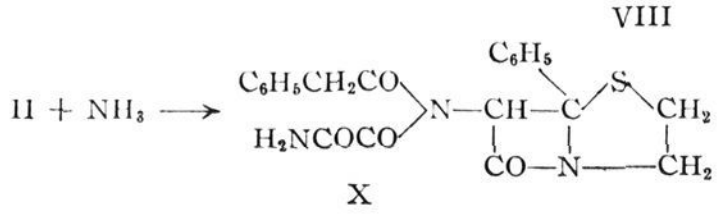
IV



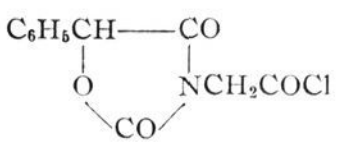
VII



VIII



X



IX

Treatment of II with excess ammonia under anhydrous conditions resulted in a 44% yield of X. The infrared spectrum of the ammonolysis product has a band at 5.63 μ, indicating the presence of the β-lactam ring.

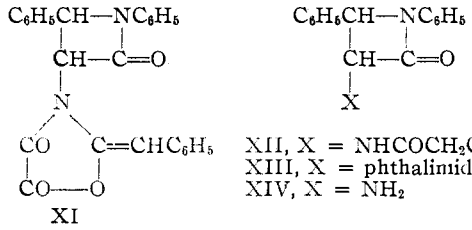
Reaction of the acid chloride I with benzalaniline and triethylamine yielded the β-lactam XI in 16% yield. The infrared spectrum of XI possesses sharp bands at 5.50 and 5.90 μ characteristic of the oxazolidine-4,5-dione nucleus[4] and a broad band with a center at 5.7 μ, which probably arises from both the β-lactam carbonyl and the oxazolidine-dione nucleus. Although there is a possibility of forming two pairs of stereoisomeric lactams, only one could be isolated. The lactam XI reacts slowly and incompletely with two equivalents of benzylamine to yield only 15% of the theoretical N,N′-dibenzyloxamide along with a complex mixture of other products. This appears to be another example of the significant effect of the nitrogen substituent on the cleavage of oxazolidine-4,5-diones.

The same β-lactam (XI) can be prepared in low yield (17%) by the action of oxalyl chloride on 1,4-diphenyl-3-phenylacetylamino-2-azetidinone (XII), which was first synthesized by Sheehan and Ryan.[7] In their synthesis, the phthalimido-lactam XIII, which was prepared from phthaloylglycyl chloride and benzalaniline, was converted by hydrazinolysis

(6) H. T. Clarke, J. R. Johnson and R. Robinson, editors, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, Chapter XIII, p. 409.

(7) J. C. Sheehan and J. J. Ryan, THIS JOURNAL, **73**, 1204 (1951).

to the free amino lactam XIV, which in turn was phenylacetylated to give the desired product, XII.



The racemic β-lactams, XI, XII and XIII are thus interrelated as members of the same stereochemical series, the reaction of benzalaniline proceeding stereochemically in the same direction with the acid chloride I as with phthaloylglycyl chloride. This evidence, together with that presented earlier, seems to indicate that the stereochemical course of the acid chloride–imine or –thiazoline reaction is not highly dependent upon the nature of the acid chloride.

Experimental[8]

2-Phenyl-α-(2-benzylidene-4,5-diketo-3-oxazolidyl)-2-thiazolidineacetic Acid β-Lactam (II).—To 3.00 g. (0.01134 mole) of the acid chloride I dissolved in 20 ml. of dry dioxane in a 200-ml., three-necked flask was added 1.85 g. (0.01140 mole) of 2-phenyl-2-thiazoline[9] in 20 ml. of methylene chloride (dried over Drierite). The solution was stirred and heated to rapid reflux in an atmosphere of nitrogen, while a solution of 1.15 g. (1.6 ml., 0.0114 mole) of triethylamine in 45 ml. of methylene chloride was added dropwise through a high-dilution cycle. The time required for the addition was 6.5 hours. The resulting dark solution was concentrated under reduced pressure to a volume of 10 ml., treated with 40 ml. of benzene and the mixture was filtered to remove the insoluble triethylammonium chloride, 1.425 g. (91%). Evaporation of the filtrate under reduced pressure yielded a sirup from which a crystalline solid soon separated. Trituration of the magma with a mixture of 20 ml. of methylene chloride and 5 ml. of benzene provided, after filtration and washing with two 5-ml. portions of methylene chloride–benzene (4:1), 1.55 g. of a bright yellow solid, m.p. 186–187° (dec., in bath at 180°). After concentration of the filtrate to a volume of 5 ml., the oily residue was seeded with lactam and allowed to stand overnight. The resulting mixture was triturated with 100 ml. of acetone–water (65:35) and filtered. Further trituration of the insoluble solid with six 10-ml. portions of acetone–water (7:3) furnished an additional 0.425 g. of light yellow solid, m.p. 187–187.5° (dec., in bath at 184°). The total yield of II was 2.02 g. (44.5%). Recrystallization from methylene chloride–methylcyclohexane yielded the pure lactam, m.p. 189.2–190.4° (dec., in bath at 184°), as bright, yellow prisms.

Anal. Calcd. for $C_{21}H_{16}N_2O_4S$: C, 64.27; H, 4.11; N, 7.14. Found: C, 64.32; H, 4.18; N, 7.31.

Attempted oxidation of II to a sulfone using potassium permanganate in a buffered water–dioxane solution (*p*H 6.7) did not lead to any crystalline product. A qualitative test on II for sulfur was positive.

Reaction of II with Benzylamine.—To 0.150 g. (0.382 millimole) of pure II dissolved in 5 ml. of dry dioxane was added 0.90 ml. (0.863 millimole) of a solution of 1 ml. of benzylamine in 9 ml. of dioxane. The solution was allowed to stand for 17 hours at room temperature and then for two hours at 65°. Removal of the solvent under reduced pressure and trituration of the residue with petroleum ether afforded 0.215 g. of a light yellow powder. The crude mixture upon trituration with 6 ml. of acetone–benzene solution (5:1) and filtration furnished 0.051 g. (49.5%) of N,N′-dibenzyloxamide, m.p. 221–223°. To the filtrate was added 5 ml. of benzene and the resulting solution was concentrated to a volume of 6 ml. and cooled to 10°. The insoluble solid, m.p. 185–200° (dec.) (0.009 g.) was discarded and the solution was evaporated to dryness under reduced pressure. The residue was treated with 7 ml. of hot ethanol (95%) and the solution was filtered while hot. Upon cooling, 0.031 g. (21%) of a colorless solid, m.p. 173–174° (dec., in bath at 167°) separated. Recrystallization of this material from 7 ml. of ethanol and four drops of water gave 0.021 g. of pure IV, m.p. 173.6–174.0 (dec., in bath at 169°), as fine, colorless needles.

Anal. Calcd. for $C_{20}H_{19}N_3O_3S$: C, 62.97; H, 5.02; N, 11.02. Found: C, 62.96; H, 5.23; N, 11.00.

The ethanol filtrate was evaporated to a volume of 2 ml. and treated slowly with 5 ml. of hot water. Upon cooling, a faintly yellow, oily solid was deposited which amounted to 0.081 g. Trituration of the solid with two 4-ml. portions of ether–petroleum ether (1:1) yielded 0.060 g. of a colorless powder, which was further purified by boiling with 7 ml. of carbon tetrachloride and removing the insoluble material, 0.0074 g., m.p. 160–170° (dec.), by filtration. The soluble material was recovered by evaporation of the filtrate to 1.5 ml. and addition of 4 ml. of hot ligroin. The resulting solid was recrystallized from 4 ml. of hot ethanol and 1 ml. of water to yield 0.041 g. (31.7%) of III, m.p. 124.8–126.5°. Recrystallization from ethyl acetate–methylcyclohexane (Norit) led to 0.030 g. of pure lactam as fine needles, m.p. 126.0–126.5°.

Anal. Calcd. for $C_{19}H_{18}N_2O_2S$: C, 67.40; H, 5.36; N, 8.28. Found: C, 67.66; H, 5.49; N, 8.57.

Sulfone of 2-Phenyl-α-(phenylacetylamino)-2-thiazolidineacetic Acid β-Lactam (VII).—To 0.0340 g. (0.100 millimole) of III in 3 ml. of acetone was added 2 ml. of a solution made up from 0.8 g. of glacial acetic acid, 3.0 g. of sodium acetate trihydrate and 9 ml. of water. The resulting solution was cooled to 0° and 0.030 g. (0.195 millimole) of potassium permanganate dissolved in 4 ml. of acetone–water (1:1) was added dropwise over a period of five minutes. The reaction mixture was allowed to stand at 0° for 3.5 hours and at the end of this period was treated dropwise with 3% hydrogen peroxide until a clear, colorless solution resulted. After diluting the solution with 2 ml. of water, the colorless, insoluble solid was collected by filtration. It amounted to 0.0050 g., m.p. 194.0–194.5° (dec., in bath at 187°).

The filtrate was treated with 5 ml. of water and concentrated in a stream of air until most of the acetone had been removed. The insoluble solid was collected by filtration, 0.0120 g. (32.4%), m.p. 140.0–140.5° (dec.) (reported 140.5°, dec.).[2] A mixture of this product and a sample prepared by Sheehan and Laubach[2] had a m.p. of 140.0–140.5° (dec.). Recrystallization from chloroform–carbon tetrachloride furnished 0.010 g. of VII as fine needles, m.p. 144.5–145° (dec.).

Ammonolysis of II.—To a cold (0°) solution of 0.150 g. (0.382 millimole) of the lactam II in 5 ml. of dry dioxane and 5 ml. of ether was added 9.45 ml. of a 0.121 *N* solution of anhydrous ammonia in dioxane. The flask was tightly stoppered, and the reactants were allowed to stand at 0° for two hours and at room temperature for six days. The resulting pale yellow solution was evaporated under reduced pressure to an oil which, when triturated with 10 ml. of ether, afforded 0.101 g. of a light tan powder. Recrystallization of the crude material from 5 ml. of ethanol (Norit) yielded 0.050 g. of colorless needles, m.p. 138.5–139.0° (dec.). An additional 0.018 g. of X was obtained from the mother liquors, m.p. 138.5–139.0° (dec.). An analytical sample which was prepared by recrystallization from ethanol–water had the same m.p.

Anal. Calcd. for $C_{21}H_{19}N_3O_4S$: C, 61.60; H, 4.68; N, 10.26; S, 7.83. Found: C, 61.69; H, 4.89; N, 10.39; S, 7.75.

1,4-Diphenyl-3-(2-benzylidene-4,5-diketo-3-oxazolidyl)-2-azetidinone (XI). A.—To a well-stirred solution of 3.62 g. (0.020 mole) of benzalaniline and 1.01 g. (1.39 ml., 0.010 mole) of triethylamine in 50 ml. of dry methylene chloride was added dropwise a solution of 2.65 g. (0.010 mole) of the acid chloride I in 20 ml. of dioxane and 50 ml. of methylene chloride. The time required for the addition was one-half

(8) All melting points are corrected. Infrared spectra were measured with a Baird Infrared Recording Spectrophotometer, Model B (cell thickness 0.10 mm.). We are indebted to Mr. S. M. Nagy and associates for the microanalyses and infrared determinations. The X-ray diffraction apparatus was made available by Prof. A. R. von Hippel of the M.I.T. Insulation Laboratory.

(9) J. C. Sheehan and J. J. Ryan, THIS JOURNAL, **73**, 4370 (1951).

hour. The dark solution was concentrated to a volume of 30 ml. after addition of 40 ml. of dioxane and the insoluble triethylammonium chloride (1.14 g., 83%) was separated by filtration. The filtrate was evaporated under reduced pressure to a dark brown oil which was triturated with 100 ml. of anhydrous ether and dissolved in 15 ml. of chloroform. The chloroform solution was treated with 15 ml. of carbon tetrachloride and allowed to stand. After two hours there was obtained from the ether and chloroform–carbon tetrachloride solutions 1.12 g. and 0.150 g., respectively, of impure product. Recrystallization of the combined, crude fractions from chloroform–carbon tetrachloride yielded 0.650 g. (15.85%) of the lactam XI as fine, yellow needles, m.p. 247–248°. A second recrystallization from the same solvent furnished analytically pure material, m.p. 248.0–249.3°.

Anal. Calcd. for $C_{25}H_{18}N_2O_4$: C, 73.16; H, 4.42; N, 6.83. Found: C, 73.27; H, 4.57; N, 6.80.

When treated with two equivalents of benzylamine the lactam XI reacted sluggishly, yielding a mixture from which only 15% of the theoretical amount of N,N′-dibenzyloxamide was isolated.

B.—To a solution of 0.150 g. (0.423 millimole) of 1,4-diphenyl-3-phenylacetylamino-2-azetidinone[7] in 10 ml. of dry dioxane was added 2 ml. of oxalyl chloride. After standing at room temperature for four hours, the solution was concentrated to an orange oil which was taken up in 25 ml. of methylene chloride and washed with 20 ml. of 5% sodium bicarbonate solution. The clear, yellow solution was dried by filtration, evaporated to a volume of 5 ml., treated with 10 ml. of carbon tetrachloride and allowed to stand in a loosely stoppered flask for two days. The yellow precipitate (0.040 g.) which had appeared was collected by filtration and was recrystallized from methylene chloride–carbon tetrachloride. The yield of XI as fine, yellow needles was 0.030 g. (17.4%), m.p. 246–247°, undepressed upon admixture with a sample prepared by method A.

CAMBRIDGE 39, MASSACHUSETTS RECEIVED MAY 10, 1951

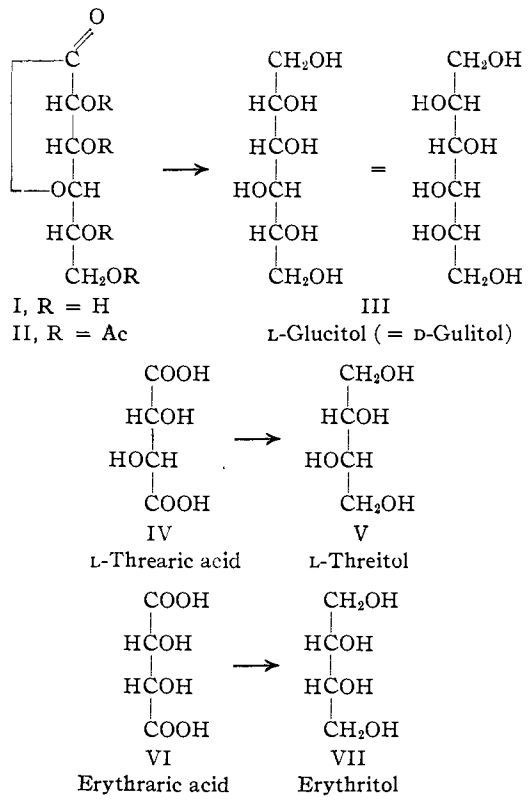
[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, FEDERAL SECURITY AGENCY]

The Reduction of Various Sugar Acids to Glycitols with Lithium Aluminum Hydride

BY ROBERT K. NESS,[1] HEWITT G. FLETCHER, JR., AND C. S. HUDSON

Reduction of tetraacetyl-D-gulono-γ-lactone with an excess of lithium aluminum hydride has given L-glucitol (= D-gulitol) in 47% yield. In a similar fashion diacetyl-L-threaric anhydride has been reduced to L-threitol in 18% yield, dibenzoylerythraric acid to erythritol in 27% yield and erytharic acid to erythritol in 18% yield. The compound recorded in the literature as dibenzoylerythraric anhydride has been shown to be dibenzoylerythraric acid; authentic dibenzoylerythraric anhydride has been prepared and characterized.

In the course of recent investigations in this Laboratory need arose for a small quantity of L-glucitol (III). The logical starting point in the synthesis of this hexitol is D-gulono-γ-lactone (I) which may readily be prepared through the application of the Kiliani synthesis to D-xylose.[2] While the reduction of D-gulono-γ-lactone (I) to D-gulose has been extensively studied[3,4,5] and sirupy D-gulose reduced both with sodium amalgam[3,6] and through the use of hydrogen in the presence of a nickel catalyst,[7] previous work in this Laboratory on the reduction of sugar derivatives with lithium aluminum hydride[8] influenced us to investigate the application of this reducing agent in the direct reduction of D-gulono-γ-lactone (I) to L-glucitol (III) (= D-gulitol).[9,9a]



The very low solubility of D-gulono-γ-lactone in ether and in tetrahydrofuran necessitated conversion of the substance to a more soluble derivative, its readily crystallizable tetraacetate (II).[10] Treatment of tetraacetyl-D-gulono-γ-lactone (II),

(1) Senior Research Fellow, National Institutes of Health, 1948–1950.

(2) C. S. Hudson, O. Hartley and C. B. Purves, THIS JOURNAL, **56**, 1248 (1934).

(3) E. Fischer and R. Stahel, *Ber.*, **24**, 528 (1891).

(4) H. S. Isbell, *Bur. Standards J. Research*, **5**, 741 (1930).

(5) F. J. Bates and Associates, "Polarimetry, Saccharimetry and the Sugars," U. S. Govt. Printing Office, Washington, 1941, p. 465.

(6) E. Fischer and R. Stahel, *Ber.*, **24**, 2144 (1891).

(7) M. L. Wolfrom, B. W. Lew, R. A. Hales and R. M. Goepp, Jr., THIS JOURNAL, **68**, 2342 (1946).

(8) (a) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, THIS JOURNAL, **72**, 4547 (1950); (b) **73**, 3742 (1951).

(9) Catalytic hydrogenation affords an equally attractive approach to this reaction since E. Baer and H. O. L. Fischer [*ibid.*, **61**, 761 (1939)] found that L-mannonic acid was converted to L-mannitol in 65% yield when its aqueous solution, containing a platinum oxide–iron oxide catalyst, was held for several days under 80 atmospheres of hydrogen.

(9a) NOTE ADDED SEPTEMBER 13, 1951.—In a paper which appeared while the present one was in press, M. L. Wolfrom and H. B. Wood [THIS JOURNAL, **73**, 2933 (1951)] have shown that D-gluco-D-*gulo*-heptonic γ-lactone may be reduced to either the corresponding aldose or glycitol in *ca.* 65% yields through the action of sodium borohydride. Since this reducing agent may be used in aqueous solution it is expected that it will prove superior to lithium aluminum hydride for reductions of the type described here.

(10) F. W. Upson, J. M. Brackenbury and C. Linn, *ibid.*, **58**, 2549 (1936).