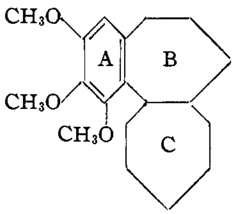
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF CALIFORNIA]

The Synthesis of 2,3,4-Trimethoxybenzcyclohepten-6-one[1]

BY HENRY RAPOPORT AND JOHN E. CAMPION

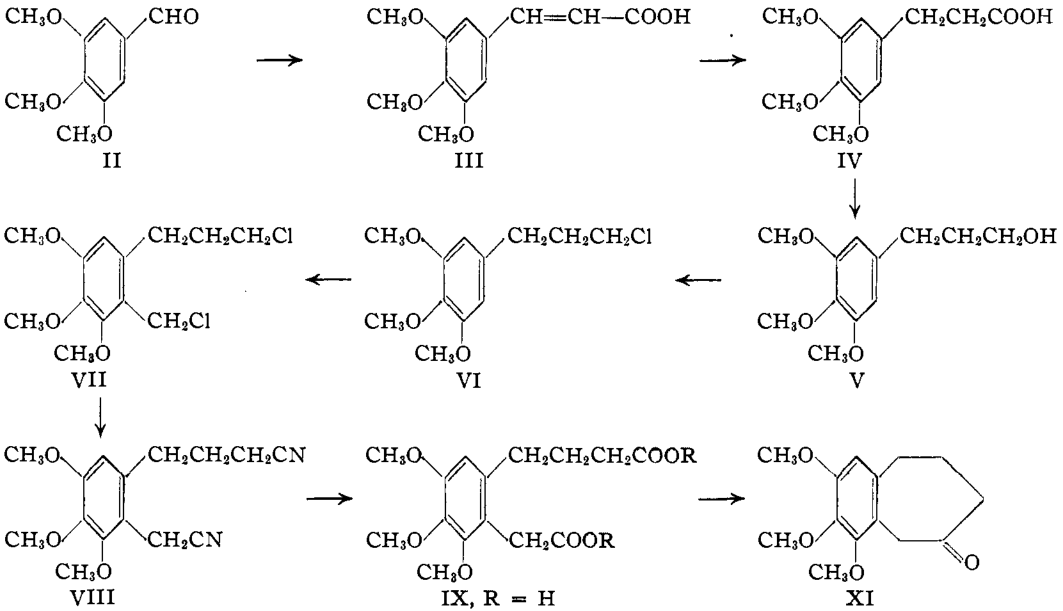
The preparation of 2,3,4-trimethoxybenzcyclohepten-6-one, a compound of possible importance for the synthesis of colchicine degradation products and related compounds, is described.

The synthesis of colchinol methyl ether[2] has left the seven-membered nature of ring C and the positions of the oxygen functions in this ring as the two remaining features in the proposed structure for colchicine for which definitive confirmation would be desirable. Conceivably, colchicine might be degraded to a compound of structure I by a series of reactions involving no rearrangements, and the synthesis of this compound would then supply the desired evidence for the size of ring C.



I

A synthetic plan with this as its objective has been recently proposed by Gutsche,[3] involving the preparation of the appropriately substituted phenylcycloheptane followed by cyclization to form ring B. We are proceeding by a different route; namely, the synthesis of a compound containing the fused A/B ring system on which ring C may then be built up. The subject of this report is the synthesis of 2,3,4-trimethoxybenzcyclohepten-6-one (XI), a compound containing the necessary fused A/B ring system which should prove applicable for the preparation of I as well as for other compounds related to colchicine.



Fused, cyclic ketones similar to XI, containing the β-carbonyl group, are relatively uncommon except for the β-tetralones. These, however, are prepared by reduction of the corresponding β-naphthols, a method unadaptable to the synthesis of XI. The analogous compound with an α-carbonyl group has been prepared[4] recently, but we sought to obtain the increased activity of both the α-methylene group and the carbonyl group that results when the latter is β to the aromatic nucleus. The path used for the synthesis of IX is outlined in the formula diagram and appears to be fairly general.

Condensation of 3,4,5-trimethoxybenzaldehyde (II) with malonic acid and hydrogenation of the resulting cinnamic acid (III) gave a 95% over-all yield of β-(3,4,5-trimethoxyphenyl)-propionic acid (IV). Reduction with lithium aluminum hydride then produced the γ-phenylpropanol (V) which was readily and in good yield converted to the chloride (VI) using thionyl chloride in dimethylaniline.[5]

The chloromethylation was carried out in the manner described for mono-chloromethylating veratrole,[6] and the course of the reaction was followed

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[1] This work was supported in part by a grant from the A. L. Hobson Memorial Donation, Cancer Research Institute, University of California Medical School, San Francisco.

[2] H. Rapoport, A. R. Williams and M. E. Cisney, THIS JOURNAL, **73**, 1414 (1951).

[3] C. D. Gutsche, *ibid.*, **73**, 786 (1951).

[4] D. Caunt, W. D. Crow, R. D. Haworth and C. A. Vodoz, *J. Chem. Soc.*, 1631 (1950).

[5] A. Cohen, *ibid.*, 429 (1935).

[6] O. Gawron, THIS JOURNAL, **71**, 744 (1949).

by titrating the unreacted chloromethyl ether.[7] After about six hours and the consumption of 100 mole % of chloromethyl ether the rate of chloromethylation decreased markedly and the reaction was stopped. A 62% yield of the chloromethyl derivative (VII) was isolated by distillation.

To obtain the desired dinitrile (VIII), a two-step cyanation process was employed. The first step consisted of treating a benzene solution of the chloromethyl derivative with aqueous potassium cyanide. The crude product from this reaction was then heated with ethanolic potassium cyanide and 2 mole % of potassium iodide to give the dinitrile. When an attempt was made to effect the cyanation in one step using an aqueous ethanolic solution of potassium cyanide, appreciable replacement of the chloride of the chloromethyl group by ethoxyl occurred.[8]

In order to gain further purification, the dinitrile (VIII) was hydrolyzed to the readily crystalline dibasic acid (IX). The latter, as dimethyl ester (X), was cyclized using sodium in boiling toluene, and the intermediate β-keto ester(s) was saponified and decarboxylated. Crystalline 2,3,4-trimethoxybenzcyclohepten-6-one (XI) resulted. It forms a water soluble sodium bisulfite addition product and with alcoholic potassium hydroxide, open to the air, gives a green[9] solution which becomes orange on acidification.

Experimental[10]

3,4,5-Trimethoxybenzaldehyde (II).—Trimethoxybenzoic acid was converted to acid chloride and thence to aldehyde *via* the Rosenmund reduction in an over-all 75% yield.[2]

3,4,5-Trimethoxycinnamic Acid (III).—Condensation of 3,4,5-trimethoxybenzaldehyde with malonic acid following the general directions of Livshits and co-workers[11] improved the yield of 3,4,5-trimethoxycinnamic acid from the previously reported 80[12] to 98% of material melting at 126–127°.

β-(3,4,5-Trimethoxyphenyl)-propionic Acid (IV).—Hydrogenation of the cinnamic acid in 10% excess of 2 *N* potassium carbonate using 10% of a 5% palladium-on-charcoal catalyst proceeded readily at room temperature and 30 p.s.i. pressure and ceased after two hours with the absorption of 1.03 moles of hydrogen. After filtering, the filtrate was acidified, and the precipitate was recrystallized from water to give a 97% yield of the propionic acid, m.p. 103–104° (reported[13] m.p. 104°).

γ-(3,4,5-Trimethoxyphenyl)-propanol (V).—In a flask equipped with a Soxhlet extractor was placed 70 ml. of 1.90 *M* ethereal lithium aluminum hydride solution and 400 ml. of absolute ether, and 20.0 g. (0.083 mole) of the propionic acid was placed in the extraction thimble. After heating under reflux for 4 hours, the reaction mixture in the flask was decomposed by the cautious addition of cold water followed by sufficient 4 *N* sulfuric acid to dissolve all the precipitate. The aqueous phase was washed with chloroform and the combined organic phase was washed with 2 *N* potassium carbonate and water. Distillation of the residue after drying and evaporating the ether and chloroform afforded 16.6 g., 88% yield, of γ-(3,4,5-trimethoxyphenyl)-propanol, b.p. 136–139° (0.3 mm.) $n^{25}\text{D}$ 1.5299.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.7; H, 8.0. Found: C, 63.4; H, 8.3.

The 3,5-dinitrobenzoate was prepared in the usual manner and crystallized from absolute ethanol, m.p. 93.5–94°.

Anal. Calcd. for $C_{19}H_{20}N_2O_9$: C, 54.3; H, 4.8; N, 6.7. Found: C, 54.0; H, 4.7; N, 7.0.

γ-(3,4,5-Trimethoxyphenyl)-propyl Chloride (VI).—Over a period of 30 minutes a solution of 45 g. (0.38 mole) of thionyl chloride in 55 ml. of chloroform was added dropwise and with vigorous stirring to a solution of 56 g. (0.25 mole) of the propanol and 45 g. (0.37 mole) of dimethylaniline in 55 ml. of chloroform, cooled in an ice-bath. The solution was stirred in the ice-bath for an additional ten minutes and then was heated on the steam-bath until hydrogen chloride evolution ceased (about 45 minutes). After cooling, the deep red solution was poured into 560 ml. of cold 1 *N* hydrochloric acid and the aqueous phase was extracted thoroughly with chloroform. The combined chloroform extracts were washed with 1 *N* hydrochloric acid, water, 2 *N* sodium bicarbonate, and water before drying and distilling. A yield of 56 g., 92%, of γ-(3,4,5-trimethoxyphenyl)-propyl chloride boiling at 139° (0.6 mm.) was obtained; $n^{25}\text{D}$ 1.5315.

Anal. Calcd. for $C_{12}H_{17}ClO_3$: Cl, 14.5. Found: Cl, 14.4.

γ-(2-Chloromethyl-3,4,5-trimethoxyphenyl)-propyl Chloride (VII).—To a solution of 43.4 g. (0.177 mole) of the propyl chloride in 92 ml. of glacial acetic acid, cooled to 20°, was added 29.3 ml. (0.354 mole) of chloromethyl ether (distilled and analyzed[7] immediately before use). The reaction mixture was stirred vigorously at 20° for 6.25 hours after which it was poured into 150 g. of ice and 75 ml. of chloroform. When the ice had melted, the aqueous phase was extracted thoroughly with chloroform and the combined chloroform extracts were washed with water, sodium bicarbonate solution, and again with water. Evaporation of the chloroform and distillation of the residue gave 32.3 g., 62% yield, of the chloromethyl compound, b.p. 156–158° (0.4 mm.), $n^{25}\text{D}$ 1.5422.

Anal. Calcd. for $C_{13}H_{18}Cl_2O_3$: Cl, 24.2. Found: Cl, 24.6.

γ-(2-Cyanomethyl-3,4,5-trimethoxyphenyl)-butyronitrile (VIII).—A solution of 14.6 g. (0.05 mole) of the chloromethyl propyl chloride in 20 ml. of benzene and a solution of 16.6 g. (0.26 mole) of potassium cyanide in 60 ml. of water was heated under reflux for three hours with stirring. The organic phase was separated, washed thoroughly with water, dried, and evaporated to leave 13.7 g. of crude residue which was dissolved in 100 ml. of 95% ethanol. A solution of 7.6 g. (0.11 mole) of potassium cyanide and 0.41 g. (0.002 mole) of potassium iodide in 35 ml. of water was added and the mixture was heated under reflux for ten hours. After distilling 90 ml. of ethanol, 80 ml. of water was added and the solution was acidified and extracted with benzene. Evaporation of the benzene after washing with carbonate and drying left 11.8 g., 86%, of the crude dinitrile which was used for hydrolysis without further purification.

γ-(2-Carboxymethyl-3,4,5-trimethoxyphenyl)-butyric Acid (IX).—A solution of 11.8 g. (0.043 mole) of the crude dinitrile in 215 ml. of 2 *N* ethanolic potassium hydroxide was heated under reflux until ammonia evolution ceased (about 40 hours). Most of the ethanol was removed by distillation, 175 ml. of water was added, and the mixture was washed with ether. The aqueous phase was then acidified, extracted thoroughly with ether and the ether evaporated after washing with water and drying. The residue consisted of 10.7 g., 80% yield, of the crystalline dibasic acid, m.p. 116–117° after several recrystallizations from benzene–hexane.

Anal. Calcd. for $C_{15}H_{20}O_7$: C, 57.7; H, 6.5; OCH_3, 29.8; equiv. wt., 156. Found: C, 57.9; H, 6.5; OCH_3, 29.3; equiv. wt., 157.

Methyl γ-[2-(Carbomethoxy)-methyl-3,4,5-trimethoxyphenyl]-butyrate (X).—The dibasic acid was esterified by heating under reflux for 24 hours a solution of 17.7 g. (0.057 mole) in 175 ml. of methanol containing 7.5 ml. of concentrated sulfuric acid. After neutralizing the solution with saturated aqueous sodium carbonate, the methanol was removed under reduced pressure and 200 ml. of water was added. The mixture was acidified, extracted thoroughly with chloroform, and the chloroform extracts were washed with water, carbonate solution, and again with water. Distillation of the chloroform solution gave 17.6 g., 91% yield,

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[7] G. Vavon, J. Bolle and J. Calin, *Bull. soc. chim. France*, **6**, 1025 (1939).

[8] A. E. Bide and P. A. Wilkinson, *J. Soc. Chem. Ind.*, **64**, 84 (1945).

[9] β-Tetralone gives a blue color in this test; J. W. Cornforth, R. H. Cornforth and R. Robinson, *J. Chem. Soc.*, 689 (1942).

[10] All melting points are corrected; microanalyses were performed by the Microchemical Laboratory, University of California.

[11] R. S. Livshits and co-workers, *J. Gen. Chem.* (*U. S. S. R.*), **17**, 1671 (1947).

[12] K. H. Slotta and H. Heller, *Ber.*, **63**, 3029 (1930).

[13] H. R. Frank, P. E. Fanta and D. S. Tarbell, THIS JOURNAL, **70**, 2314 (1948).

of the dimethyl ester, b.p. 174–177° (0.3–0.4 mm.), $n^{25}\text{D}$ 1.5089.

Anal. Calcd. for $C_{17}H_{24}O_7$: C, 60.0; H, 7.1; OCH_3, 45.6; sapn. equiv., 170. Found: C, 59.8; H, 7.2; OCH_3, 45.3; sapn. equiv., 173.

2,3,4-Trimethoxybenzcyclohepten-6-one (XI).—Over a period of four hours in a nitrogen atmosphere a solution of 5.25 g. (0.0154 mole) of the dimethyl ester in 15 ml. of toluene was added to a stirred, refluxing mixture of 1.35 g. (0.059 mole) of sodium and 30 ml. of toluene to which a few drops of methanol had been added. Stirring and reflux were continued overnight, the excess sodium was decomposed by dropwise addition of methanol, and the solution was acidified in the cold with 50 ml. of 2 *N* hydrochloric acid. The aqueous phase was extracted with benzene and the combined benzene–toluene extracts were washed with water and sodium bicarbonate solution and evaporated. The residue, dissolved in 100 ml. of 0.5 *N* ethanolic potassium hydroxide, was allowed to stand at room temperature overnight after which 20 ml. of 3 *N* hydrochloric acid was added and the solution heated under reflux until carbon dioxide evolution ceased. This solution was then concentrated under reduced pressure to remove the alcohol and the residue was extracted with benzene. After washing with carbonate solution, the benzene solution was distilled to give 2.41 g., 64% yield, of the ketone as a solid distillate, b.p. 144° (0.4 mm.). After crystallization from ethanol–water, it melted at 46–46.5°.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.2; H, 7.3; OCH_3, 37.2. Found: C, 67.1; H, 7.3; OCH_3, 37.2.

The ketone forms a soluble bisulfite addition product and when dissolved in alcoholic potassium hydroxide in the presence of air forms a green solution which changes to orange on acidification.

The **semicarbazone** was prepared in the usual manner and was crystallized from methanol–water, m.p. 184–185°.

Anal. Calcd. for $C_{15}H_{24}N_3O_4$: C, 58.6; H, 6.9; N, 13.7; OCH_3, 30.3. Found: C, 58.7; H, 7.1; N, 13.6; OCH_3, 30.3.

The **oxime**, prepared as usual, melted at 130.5–131° after crystallization from methanol–water.

Anal. Calcd. for $C_{14}H_{19}NO_4$: C, 63.4; H, 7.2; N, 5.3. Found: C, 63.4; H, 7.5; N, 5.1.

The **2,4-dinitrophenylhydrazone** was crystallized from methanol, m.p. 177–178°.

Anal. Calcd. for $C_{20}H_{22}N_4O_7$: C, 55.8; H, 5.2; N, 13.0. Found: C, 56.0; H, 5.4; N, 12.9.

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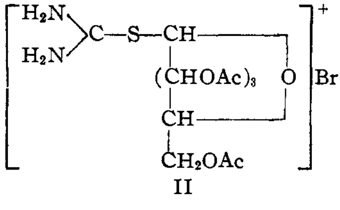
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

A Study of Some S-(Polyacetyl-β-D-glycopyranosyl)-thiuronium Halides

BY WILLIAM A. BONNER AND JAMES E. KAHN

Several new S-(polyacetyl-β-D-glycosyl)-thiuronium halides have been prepared by the interaction of thiourea with the corresponding polyacetyl-α-D-glycosyl halide in 2-propanol. The structure of S-(tetraacetyl-β-D-glucosyl)-thiuronium bromide has been substantiated by reductive desulfurization. With bromine in acetic acid this salt reverts to α-D-glucose pentaacetate. The specific rotation of these salts is strongly dependent on the solvent. Their molecular rotation is partially determined by their anionic component. The kinetics of formation of these salts have been found second order, and a mechanism proposed in agreement with this fact. The salts are polarographically reducible in phosphate buffer of *p*H 6. The half-wave potentials lie in the neighborhood of −1.2 volts, and are rather independent of the structure of the cation. The infrared spectra of six of these salts have been measured and found dependent on both the anion and the carbohydrate cation. The ultraviolet spectra of these salts appear independent of the structure of the carbohydrate cation. The rotatory dispersion of four of these salts obeyed a simple Drude equation. In two cases, the position of an "active" absorption band predicted on the basis of dispersion measurements corresponded to the position of a band suggested by spectrophotometric measurement.

The reaction of alkyl halides with thiourea to form S-alkylthiuronium halides is well known. Only once, however, has this reaction been extended to the carbohydrate series. In 1928 Schneider and Eisfeld[1] obtained a 37% yield of a solid, m.p. 192°, $[\alpha]^{20}\text{D}$ −8.72° (water) on refluxing tetraacetyl-α-D-glucosyl bromide (I) in dry toluene with thiourea. By analysis, analogy and the formation of the silver salt of 1-thio-D-glucose on its treatment with ammoniacal silver nitrate, this substance was designated as S-(tetraacetyl-β-D-glucopyranosyl)-thiuronium bromide (II). Similar results were obtained with phenylthiourea. Since wider data on this class of compounds are lacking, we have been interested in extending the earlier study, especially along the lines of physico-chemical information.



II

When I and thiourea in 2-propanol solution were either heated briefly or allowed to stand for longer periods at room temperature, II, m.p. 205°, $[\alpha]^{25}\text{D}$ −7.6° (water) resulted in 64% yield. Similar results were obtained with the acetylated halides of xylose, galactose and cellobiose. The resulting salts were readily soluble in water, sparingly so in alcohol and insoluble in non-polar media. II was non-reducing, giving a brownish-green solution on prolonged heating with Fehling solution. The structure of II, as suggested by Schneider and Eisfeld, has been confirmed by reductive desulfurization, where tetraacetyl-1,5-anhydro-D-glucitol results. In common with thioglycosides[2] and selenoglycosides,[3] II reverts to α-D-glucose pentaacetate on treatment with bromine in acetic acid, presumably through an identical mechanism.

Since S-alkylthiuronium salts are useful in characterizing organic acids,[4–8] we have attempted to use II in this capacity. Such derivatives looked

(1) W. Schneider and K. Eisfeld, *Ber.*, **61**, 1260 (1928).

(2) W. A. Bonner, THIS JOURNAL, **70**, 3491 (1948).

(3) W. A. Bonner and A. Robinson, *ibid.*, **72**, 356 (1950).

(4) J. J. Donleavy, *ibid.*, **58**, 1004 (1936).

(5) R. J. Anderson, *J. Biol. Chem.*, **74**, 548 (1927).

(6) S. Veibel, *et al.*, *Bull. soc. chim.*, [5] **5**, 1153 (1938); **6**, 1434 (1939).

(7) B. T. Dewey, *et al.*, THIS JOURNAL, **61**, 3251 (1939); **63**, 3526 (1941).

(8) W. A. Bonner, *ibid.*, **70**, 3508 (1948).