[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

The Action of Nucleophilic Agents on 3α-Chlorotropane[1]

BY S. ARCHER, M. R. BELL, T. R. LEWIS, J. W. SCHULENBERG AND M. J. UNSER

RECEIVED APRIL 9, 1958

3α-Chlorotropane, prepared from pseudotropine and thionyl chloride, reacted with nucleophilic agents such as cyanide ion, azide ion or benzylamine to yield the corresponding 3α-substituted tropanes. Substitution proceeds with apparent retention of configuration. It is suggested that the ion XVII is an intermediate.

In a previous paper[2] we reported that pseudotropine toluenesulfonate (IV) and 3β-chlorotropane (III), which had been prepared from tropine (I) and thionyl chloride, reacted with potassium cyanide to give a mixture of 2-allyl-4-cyano-1-methylpyrrolidines (V). In view of this result we examined the reaction of cyanide ion with the epimeric chloride VI, obtained from pseudotropine (II) and thionyl chloride, and found that the major product was a crystalline 3-tropanylnitrile. When this nitrile was treated with phenylmagnesium bromide a benzoyl ketone was formed which, with phenyllithium, was converted to the corresponding diphenylcarbinol, a compound prepared by Zirkle in a different way.[3] Although this sequence did serve to show that the tropane ring was still intact, it did not permit assignment of configuration to the tropanylnitrile.

Accordingly, we studied the reactions of 3α-chlorotropane (VI) and tropine methanesulfonate (VII), which also has the α-configuration at C-3, with other nucleophilic agents. Benzylamine and azide ion were chosen because the expected reaction product could be related readily to either of the known 3-aminotropanes. The configurations of these epimers had been assigned on arguments based on analogy.[4] The enhanced importance of these compounds in connection with the present work made it desirable to obtain independent chemical evidence for the configurational assignments. Recently Zirkle[5] established the configuration of methyl tropane-3β-carboxylate. We treated this ester (XIV) with alcoholic ammonia and obtained the amide XV which was subjected to a Hofmann rearrangement, a reaction known to proceed with retention of configuration.[6] 3β-Aminotropane (XVI) was isolated as the phenylthioureide, a derivative which was identical in all respects with the compound obtained previously from tropinone oxime (XII) by sodium–alcohol reduction.[4] This result confirmed our previous structural assignment.

Earlier,[4] tropinone was reductively benzylaminated to 3α-benzylaminotropane (IX) which was catalytically debenzylated to 3α-aminotropane (XI). Both 3α-chlorotropane and tropine methanesulfonate (VII) were allowed to react with benzylamine to produce the same 3α-benzylaminotropane (IX). Direct comparison of the corresponding dihydrochlorides revealed that all were identical and finally, catalytic hydrogenolysis of the newly prepared sample furnished 3α-aminotropane (XI). These facts, coupled with our previous results with the epimeric chlorotropane (III) and the toluenesulfonate (IV)[2] show that the conversion of the alcohols I and II to the chlorides III and VI proceeds with inversion of configuration.

In a similar fashion sodium azide reacted with 3α-chlorotropane to give a liquid azide X. The very strong band at 4.77 μ in the infrared spectrum confirmed the presence of an azide function, while catalytic hydrogenation of X gave XI, thus proving that X was indeed a 3α-tropanyl compound.

Armed with the knowledge of the behavior of 3α-chlorotropane (VI) and tropine mesylate (VII) with other nucleophiles we resumed our study of their reaction with potassium cyanide. Both VI and VII yielded a crystalline nitrile VIII, m.p. 64–66°. An isomeric liquid nitrile XIII, m.p. 15–16°, was isolated as a by-product from the reaction of VI. Both the crystalline and liquid nitriles were methanolyzed to the same ester XIV. Zirkle[5] reported that both methyl 3α- and 3β-carboxylates hydrolyzed to tropane-3β-carboxylic acid.[7]

The stereochemical picture finally was clarified when it was found that treatment of the solid nitrile VIII with limited amounts of sodium methoxide in boiling ethanol or preferably with sodium amide in benzene under reflux caused virtually complete epimerization to occur. On the other hand, the liquid nitrile XIII was recovered unchanged when subjected to similar treatment. These results parallel those of Zirkle[5] who found that methyl tropane-3β-carboxylate was the thermodynamically more stable isomer. Therefore the liquid nitrile has the β-configuration as in XIII.

On conformational grounds it would be expected that XIII would be more stable than VIII. If the

---

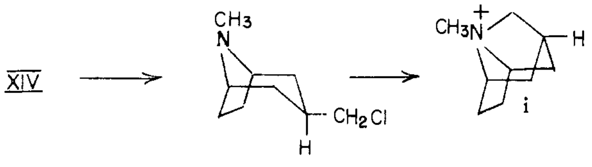
[1] A preliminary communication has been published; THIS JOURNAL, **79**, 6337 (1957).

[2] S. Archer, T. R. Lewis and B. Zenitz, *ibid.*, **80**, 958 (1958).

[3] C. Zirkle, U. S. Patent 2,800,480 (July 23, 1957).

[4] S. Archer, T. R. Lewis and M. J. Unser, THIS JOURNAL, **79**, 4194 (1957).

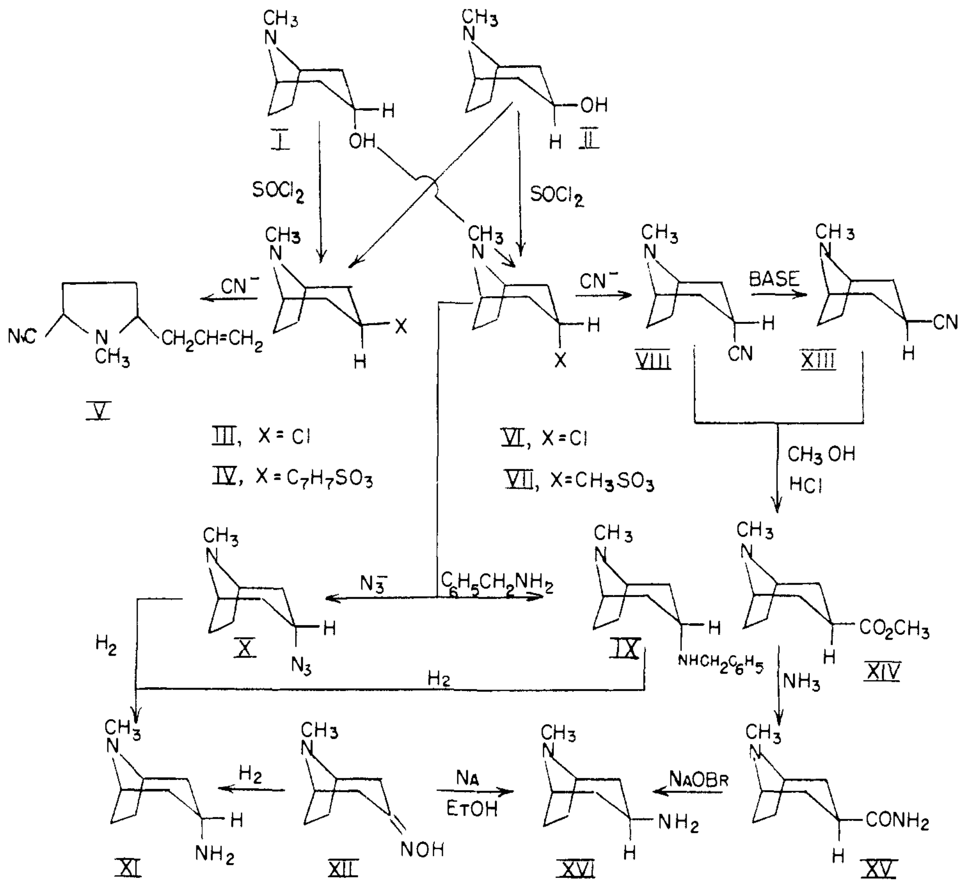
[5] C. Zirkle, *et al.*, "Abstracts XVI, International Congress for Pure and Applied Chemistry," Paris, July 1957, p. 153. The method he used is shown in the equations:



The epimeric 3α-ester did not give a cyclic ion corresponding to i. We are grateful to Dr. Zirkle for privately informing us of methods for preparing methyl tropane-3α- and 3β-carboxylates, of the procedure for epimerizing the 3α-ester and of the fact that both esters are hydrolyzed in either water or dilute acid to the same acid, tropane-3β-carboxylic acid. We wish also to take this opportunity to thank Dr. Zirkle for samples of derivatives of both esters.

[6] S. Archer, THIS JOURNAL, **62**, 1872 (1940).

[7] S. P. Findlay, *ibid.*, **76**, 2855 (1954), found that on treatment of ecgonine methyl ester with methyl iodide in methanol there was produced pseudoecgonine methyl ester methiodide and the hydriodide of ecgonine methyl ester. This is another case of easy acid-catalyzed epimerization in the tropine series at a carbon atom bearing a carbomethoxy group.

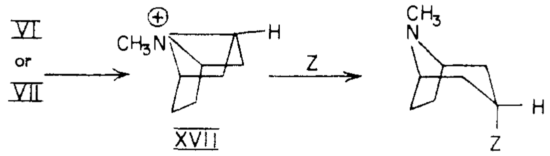


latter existed in the chair conformation then XIII would be more stable by virtue of its equatorial rather than axial nitrile group. If VIII were in the boat form then the nitrile group would be equatorial, too. Now, however, the greater stability of XIII would be due to its chair conformation.

It has now been established that the reaction of 3α-chlorotropane with nucleophilic agents occurs with retention of configuration. It is very probable that this retention is the result of two inversions, the first of which involves participation of the nitrogen with C-3 of the tropane ring to give the ion XVII. The stereochemical situation is favorable for such anchimeric assistance since the *anti* configuration of the chlorine atom permits rearward attack at C-3 by nitrogen. Subsequent attack with inversion at C-3 of XVII would give a 3α-substituted tropane.

In further support of this scheme we have the facts that (1) both tropine and pseudotropine react with thionyl chloride to give the corresponding chlorotropanes with inversion and not retention of configuration, and (2) the benzyl bromide quaternary salt of VI does not react in the same way with potassium cyanide under conditions sufficient to convert the base VI to the nitrile VIII. The only isolable product from this reaction was starting material. This sluggish behavior is reminiscent of cyclohexyl halides. In both of the above instances the nitrogen atom is positively charged, a circumstance which precludes participation with C-3 of the tropane nucleus.

The equatorial nitrile XIII which is formed in small amounts may be produced by either an SN2 type of reaction of cyanide ion with VI or by epimerization of VIII. If the latter alternative is true



then XIII is produced by a series of three inversions starting from VI. It is a bit ironic that neither 3α- nor 3β-chlorotropane reacts normally with cyanide ion, but as a result of the present investigation the original goal of obtaining both nitriles VIII and XIII has been achieved.

Experimental[8]

3α-Chlorotropane.—A solution of 97 g. of pseudotropine in 440 ml. of chloroform (analytical reagent) was cooled to 0°. Then 195 ml. of thionyl chloride was added dropwise with stirring while the internal temperature was kept below 20°. The dark solution was refluxed for three hours and then left overnight at room temperature.

The solvents were removed *in vacuo* and the residue was dissolved in a minimal amount of ice-water. The solution was neutralized with 35% sodium hydroxide, and then a large excess of solid potassium carbonate was added. The dark mixture was extracted with three 200-ml. portions of 1:1 methylene chloride–ether. The combined organic layers were dried over magnesium sulfate and then distilled.

---

[8] Analyses were carried out under the supervision of Mr. K. D. Fleischer. Infrared spectra were run under Dr. F. C. Nachod's supervision.

There was collected 50 g. (46%) of the desired product, b.p. 55–56° (0.01 mm.). The oil solidifies on cooling and then melts at 12–14°.

Anal. Calcd. for $C_8H_{14}ClN$: N, 8.77. Found: N, 8.66.

The picrate, prepared with alcoholic picric acid melted at 234–237°.

Anal. Calcd. for $C_{14}H_{17}ClN_4O_7$: neut. equiv.,[9] 389. Found: neut. equiv., 392.

The yield in the above procedure or some minor modifications thereof varied considerably from an occasional failure to 76% conversions. The cause of this inconsistency is not known as yet. A procedure which gives yields comparable to those obtained above is described.

Ten grams of pseudotropine was added to 125 ml. of thionyl chloride and stirred at 0°. The temperature rose to 25°. The mixture was stirred at room temperature for three hours and then refluxed for 19 hours. The material was worked up as in the previous experiment to give 4.8 g. (42%) of the chlorotropane, b.p. 80–82° (10 mm.).

Tropine Methanesulfonate Toluenesulfonic Acid Salt.—A solution of 70.5 g. of tropine in 125 ml. of dry, pure chloroform was kept at −10 to 3° as a solution of 49 ml. of methanesulfonyl chloride in 120 ml. of the same grade chloroform was added dropwise with stirring over a 2-hour period. The flask was stoppered and stored overnight at 5°. A crystalline solid had separated. The whole was stirred at 20° for 1.5 hours, cooled and treated with 100 ml. of water. Solid potassium carbonate was added until no more appeared to dissolve. The mixture was diluted with 50 ml. of water, filtered and the water layer was extracted thrice with chloroform. The combined oil layers were dried over sodium sulfate for two hours and then filtered. The chloroform solution was treated with a solution of 95 g. of toluenesulfonic acid monohydrate in 100 ml. of methanol. Dry ether was added to the warm solution until crystals appeared. After 3 hours cooling the solution was filtered. The white crystals were washed with 100 ml. of 1:1 ether–chloroform and then were slurried with 400 ml. of dry acetone. They were collected again and washed with 100 ml. of dry acetone. The desired ester salt melted at 160–162° and weighed 119.5 g. (64%) after drying overnight.

Anal. Calcd. for $C_{16}H_{25}NO_6S_2$: C, 49.08; H, 6.44; S, 16.38. Found: C, 49.11, 49.28; H, 6.92, 6.43; S, 16.27.

3α-Benzylaminotropane (A) from 3α-Chlorotropane.—A solution of 17.3 g. of 3α-chlorotropane and 14 g. of benzylamine in 50 ml. of ethanol was refluxed for 18 hours and then concentrated to dryness. Water and solid potassium carbonate were added. The oil layer was separated with the aid of ether. The organic phase was dried over potassium carbonate and distilled to give 14.2 g. of 3α-benzylaminotropane, b.p. 130–135° (0.3 mm.).

Anal. Calcd. for $C_{15}H_{22}N_2$: N, 12.16. Found: N, 12.06.

On redistillation the oil boiled at 134–137° (0.3 mm.), $n^{25}D$ 1.5456. The infrared spectrum was identical with that of the specimen previously prepared by reductive benzylamination of tropinone.

The oil furnished a **dihydrochloride**, m.p. 272° dec. after recrystallization from ethanol. It did not depress the melting point of the sample obtained from tropinone and benzylamine. The infrared spectra of the two salts were virtually superimposable.

Anal. Calcd. for $C_{18}H_{24}Cl_2N_2$: N, 9.24. Found: N, 9.16.

(B) **From Tropine Methanesulfonate.**—A solution of 39.1 g. (0.1 mole) of tropine methanesulfonate toluenesulfonic acid salt in 65 ml. of water was made alkaline with 25 g. of potassium carbonate and then extracted with methylene chloride. The organic solution was dried over sodium sulfate and then the solvent was evaporated *in vacuo* at a temperature below 40°. A crystalline solid remained. A small portion was ground under pentane, filtered and dried, m.p. 85–86.5°.

Anal. Calcd. for $C_9H_{17}NO_3S$: N, 6.39. Found: N, 6.17.

The solid was dissolved in 50 ml. of ethanol containing 11.8 g. of benzylamine and then was refluxed for 2 hours. The mixture was worked up as above to yield 7.5 g. (33%) of 3α-benzylaminotropane, b.p. 163–167° (2.5–3.0 mm.). The forerun, b.p. 50–75° (2.5–3.0 mm.), contained about 3.5 g. of benzylamine. The diamine furnished a dihydrochloride, m.p. 272–273° dec. after crystallization from alcohol, identical in melting point and infrared spectrum with the previous samples.

Hydrogenolysis of 3α-Benzylaminotropane.—A solution of 3.5 g. of 3α-benzylaminotropane, obtained from 3α-chlorotropane and benzylamine as described above, was dissolved in 150 ml. of absolute ethanol containing 2 ml. of saturated alcoholic hydrogen chloride and hydrogenated in the presence of 2.0 g. of 10% palladium-on-charcoal. After four hours, the mixture was filtered. The filtrate was concentrated to dryness, the residue was covered with ether and alcoholic hydrogen chloride was added to completely precipitate basic material. There was obtained 2.05 g. (64% of theoretical, calculated as the dihydrochloride) of a salt which was dissolved in water, and then treated with excess solid potassium carbonate. The aminotropane was removed with ether and dried over potassium carbonate. The solution was evaporated and the residue was dried azeotropically with benzene. The oil was dissolved in 10 ml. of ethyl acetate and to the solution excess phenyl isothiocyanate was added. After a few minutes the desired phenylthioureide was removed by filtration and recrystallized once from the same solvent to give the 3α-aminotropane phenylthioureide, m.p. 157–158°, undepressed by an authentic specimen.[4]

3α-Tropanyl Azide.—A solution of 3.9 g. of sodium azide in 10 ml. of water was mixed with a solution of 8.0 g. of 3α-chlorotropane in 50 ml. of ethanol and the whole was refluxed for 16 hours. The solvents were removed *in vacuo* on the steam-bath and the residue was dissolved in water, made very alkaline with excess potassium carbonate and then taken up in ether. The dried ethereal solution was distilled to give 5.8 g. (70%) of the required azide, b.p. 58–60° (0.2 mm.) (bath temp. 60–80°). The infrared spectrum has an exceedingly strong band at 4.77 μ.

Anal. Calcd. for $C_8H_{14}N_4$: N_{AP}, 8.43. Found: N_{AP}, 8.53.[10]

The hydrochloride was prepared in ether and recrystallized from acetone m.p. 167–169° dec.

Anal. Calcd. for $C_8H_{15}ClN_4$: C, 47.42; H, 7.46; N, 27.64; Cl, 17.49. Found: C, 46.55; H, 7.76; N, 27.54; Cl, 17.35.

Hydrogenation of the base (5.0 g.) was allowed to proceed in 100 ml. of ethanol in the presence of 1.0 g. of platinum oxide for 3 hours. The catalyst and solvent were removed to leave an oil which was dissolved in 10 ml. of ethyl acetate. Then 4.15 g. of phenyl isothiocyanate was added, whereupon the solution became hot. There deposited 5.42 g. (66%) of the thioureide, m.p. 147–153°, which after recrystallization from ethyl acetate melted at 156–158° and did not depress the melting point of the previous sample of the phenylthioureide of 3α-aminotropane.

3α- and 3β-Tropanylnitriles.—To a solution of 40 g. of potassium cyanide in 60 ml. of water there was added 93.4 g. of 3α-chlorotropane and 200 ml. of ethanol. The solution was refluxed for 18 hours and then concentrated to remove the alcohol. The residue was cooled, made strongly alkaline with excess potassium carbonate and extracted twice with ether. The dried ether solution was distilled. A forerun (6.1 g.), b.p. 55–88° (0.4 mm.), was obtained, followed by the main fraction (67.0 g.), b.p. 84–87° (0.25 mm.). The fractions solidified; total wt. 73.1 g. They were combined and recrystallized from pentane to give a crop, wt. 50 g., m.p. 61–62°. Our best material melted at 64–66°. This is 3α-tropanylnitrile (VIII).

Anal. Calcd. for $C_9H_{14}N_2$: N_{AP}, 9.33. Found: N_{AP}, 9.28.

The pentane filtrate was evaporated to leave an oil, wt. 19.0 g. This was distilled to give a fraction, b.p. 66–77° (0.05 mm.), which solidified. Trituration with pentane followed by cooling and filtration gave a less pure fraction of 3α-tropanylnitrile, m.p. 54–59°, wt. 3.4 g. The pentane filtrate was evaporated to leave an oil which was converted to the hydrochloride in ether. A gum separated, but when it was boiled with acetone it quickly crystallized. It was filtered and dried; wt. 8.5 g. After crystallization from a

---

(9) Neutral equivalents were determined by titration of the picric acid with sodium methoxide.

(10) N_{AP} refers to the acetic-perchloric acid titration for basic nitrogen.

mixture of methanol and isopropyl alcohol it melted at 303–306° dec. This is the hydrochloride of 3β-tropanylnitrile.

Anal. Calcd. for $C_9H_{15}ClN_2$: C, 57.90; H, 8.10; N, 15.00. Found: C, 58.26; H, 8.37; N, 14.60.

When 33 g. of tropine mesylate base was refluxed in a mixture of 65 ml. of ethanol, 11 g. of potassium cyanide and 15 ml. of water there was obtained 9.8 g. of a nitrile fraction, b.p. 64–77° (0.02 mm.), which was taken up in 30 ml. of pentane. Only 2.0 g. of the desired 3α-tropanylnitrile was obtained, although the filtrate yielded additional amounts of this nitrile as the hydrochloride.

The nitrile was converted to the hydrochloride, which after recrystallization from isopropyl alcohol–ether and then methanol–ether melted at 268–271° (darkened at about 250°). This is the hydrochloride of 3α-tropanylnitrile.

Anal. Calcd. for $C_9H_{15}ClN_2$: C, 57.90; H, 8.10; N, 15.00. Found: C, 57.74; H, 8.35; N, 14.65.

Epimerization of 3α-Tropanylnitrile.—Six grams (0.04 mole) of 3α-tropanylnitrile, 0.78 g. (0.02 mole) of sodium amide and 25.0 ml. of dry benzene were refluxed for 18 hours. All the sodium amide seemed to disappear and be replaced by a new solid. The mixture was cooled and then treated with a small amount of ethanol and water. The benzene solution was separated and concentrated to dryness. The residual oil was dissolved in ether and filtered. The filtrate was treated with excess absolute ethanolic hydrogen chloride. The solid salt that separated was collected and leached with hot acetone. There was obtained 6.7 g. of crude hydrochloride, the infrared spectrum of which revealed that it was substantially free of 3α-tropanylnitrile hydrochloride. After recrystallization there was obtained 3.40 g. of the pure salt, m.p. 301–302° dec., whose infrared spectrum was indistinguishable from that of the previous sample of 3β-tropanylnitrile hydrochloride.

The purified salt was converted to the base in the usual way. Pure **3β-tropanylnitrile** (1.76 g.) boiled at 74° (0.4 mm.) and melted at 15–16°.

Anal. Calcd. for $C_9H_{14}N_2$: C, 71.95; H, 9.39; N, 18.65. Found: C, 72.19; H, 9.65; N, 18.59.

When 186 mg. of the 3β-nitrile hydrochloride, m.p. 303–306°, was refluxed in 5 ml. of methanol with 81 mg. of sodium methoxide, the hydrochloride that was isolated after the above processing gave an infrared spectrum identical with the starting material.

However, when 150 mg. of 3α-tropanylnitrile was refluxed with 27 mg. (half molar quantity) of sodium methoxide in 5 ml. of ethanol under conditions comparable to those described above, the hydrochloride isolated was that of 3β-tropanylnitrile. No bands in the infrared spectrum corresponding to hydrochloride of starting material were present.

Methyl Tropane-3β-carboxylate from 3α-Tropanylnitrile.—Twenty-four grams of 3α-tropanylnitrile was dissolved in 250 ml. of methanol containing 3.1 ml. of water, and a stream of hydrogen chloride was passed through the solution for one hour. The temperature rose to 55° and ammonium chloride started to separate. After four hours at room temperature the mixture was filtered and the filtrate concentrated to leave an oil. This was dissolved in ice-water, neutralized with concentrated sodium hydroxide and made strongly alkaline with an excess of solid potassium carbonate. The ester was removed with ether, dried over Drierite and distilled to give a fraction boiling at 83° (0.2 mm.), wt. 15.1 g., $n^{25}D$ 1.4799 and another fraction, b.p. 78–80° (0.2 mm.). A portion of the ester was converted to the oxalate in acetone solution and after recrystallization from ethanol it melted at 150–152°. We found that Zirkle's oxalate melted at 149–151° and on admixture did not depress the melting point of our material.[11]

From 3β-Tropanylnitrile.—A quantity of 186 mg. of 3β-tropanylnitrile hydrochloride, m.p. 303–306°, was dissolved in 18 ml. of methanol and the solution was saturated with dry hydrogen chloride during 1.3 hours and then left overnight. The solution was concentrated to dryness and processed as before. The basic oil that remained after removal of ether was converted to the oxalate in ethanol, wt. 120 mg., which after one crystallization from ethanol melted at 148–151° and did not depress the melting point of an authentic sample.

Tropane-3β-carboxamide.—Seven grams of methyl tropane-3β-carboxylate was dissolved in 10 ml. of absolute methanol and at 0° was mixed with a saturated methanolic solution of ammonia containing 0.2 g. of sodium methoxide. The solution was placed in a pressure flask and left for six days. The solution was then taken to dryness and the residue was dissolved in chloroform. Hexane was added to the point of turbidity and the solution was cooled overnight. The crop of crystals, m.p. 151–152°, was filtered and dried; wt. 3.22 g. A second crop, wt. 0.62 g., obtained from the filtrate was slightly less pure. The infrared spectrum of the first crop revealed the presence of a strong carboxamide band.

Anal. Calcd. for $C_9H_{16}N_2O$: N, 16.65. Found: N, 16.34.

3β-Aminotropane.—A sodium hypobromite solution was prepared by adding 1.2 ml. of bromine to a solution of 4.8 g. of sodium hydroxide in 40 ml. of water at −5°. To this solution at 0°, 3.36 g. of the above amide was added in one portion. The solution was allowed to warm to room temperature and then it was heated for two hours on the steam-bath. The cooled reaction mixture was then saturated with potassium carbonate and extracted with four 50-ml. portions of ether. The extract was dried for 2 hours over potassium carbonate, filtered and concentrated to leave an oil which weighed 2.10 g. This was dissolved in 5 ml. of ethyl acetate and treated with 2.5 ml. of phenyl isothiocyanate. The mixture warmed spontaneously to 75°. It was cooled and filtered. The solid was washed with ethyl acetate and then hexane. It weighed 3.70 g., m.p. 169–172°. After recrystallization from ethyl acetate the phenylthioureide melted at 174.5–175°. A mixture with the phenylthioureide of 3β-aminotropane, m.p. 175–176°, obtained from sodium–alcohol reduction of tropinone oxime, melted at 174.5–175°. The infrared spectra of the two derivatives were identical.

8-Benzyl-3α-chloronortropane Methobromide.—Seventeen grams of 3α-tropanyl chloride was dissolved in 75 ml. of dry acetonitrile and 21.2 g. of benzyl bromide in 25 ml. of the same solvent was added. The solution warmed and crystals soon appeared. The mixture was kept in ice for 1 hour and then was allowed to stand for 3 hours at room temperature. The crystals were filtered, washed with acetonitrile and acetone, wt. 33.0 g. (94%), m.p. 213°. The analytical sample melted at 213° after recrystallization from methanol.

Anal. Calcd. for $C_{15}H_{21}BrClN$: C, 54.47; H, 6.40; Br, 24.17. Found: C, 54.46; H, 6.12; Br, 24.28.

A solution of 33 g. of this salt and 10.2 g. of potassium cyanide in 50 ml. of ethanol and 10 ml. of water was refluxed for 18 hours. The mixture turned very dark. It was cooled and filtered. The solid was boiled with methanol and filtered. The filtrate was reserved. The ethanol filtrate was concentrated to dryness and the residue was dried azeotropically with benzene. The solid was boiled with methanol and filtered. The methanol filtrates were combined and concentrated to yield in three crops 11.7 g. of the starting salt.

3-Benzoyltropane.—To a solution of phenylmagnesium bromide prepared from 13.3 g. of bromobenzene and 2.3 g. of magnesium in ether there was added dropwise a solution of 10 g. of 3α-tropanyl in 50 ml. of ether. A gummy precipitate formed almost immediately. The apparatus was set for downward distillation and the ether was replaced with dry benzene. The mixture was refluxed for 3 hours and then was decomposed by the addition of 70 ml. of 6 *N* hydrochloric acid. The mixture was warmed on the steam-bath and then cooled. The layers were separated. The aqueous layer was washed with benzene and then made alkaline with ammonia. The oil that separated was taken up in ether and dried. Distillation afforded 5.5 g. of 3-benzoyltropane, b.p. 130–134° (0.2 mm.) $n^{25}D$ 1.5540.

Anal. Calcd. for $C_{15}H_{19}NO$: N, 6.11. Found: N, 6.05.

Diphenyl-3-tropanylcarbinol.—The above ketone (5.5 g.) was stirred with 20 ml. of ether and under nitrogen at −35° while a filtered ethereal solution of phenyllithium prepared from 4.7 g. of bromobenzene and 0.45 g. of lithium was added dropwise. A cloudy solution resulted. The reaction mixture was stirred at −20° for 2 hours and then

---

[11] Zirkle (ref. 5) reported that methyl tropane-3β-carboxylate boiled at 81–82° (3.5 mm.), $n^{25}D$ 1.4792, and gave an oxalate, m.p. 145–147°. The corresponding 3α-ester boiled at 74–77° (2.0 mm.), $n^{25}D$ 1.4822, and gave an oxalate, m.p. 165–167°.

treated with 50 ml. of water. The organic layer was separated and the gaseous phase was washed with ether. The combined organic layers were dried over sodium sulfate, filtered and evaporated to leave an oil which crystallized when triturated under pentane. The solid, m.p. 178–182°, weighed 2.0 g. and melted at 185–186° after crystallization from aqueous alcohol.

Anal. Calcd. for $C_{21}H_{25}NO$: N, 4.56. Found: N, 4.53.

RENSSELAER, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL BIOCHEMISTRY, UNIVERSITY OF MINNESOTA]

Reduction of the Products of Periodate Oxidation of Carbohydrates. VI. Methylation Studies on the Monoaldehyde Formed by Catalytic Reduction of D'-Methoxy-D-hydroxymethyldiglycolic Aldehyde[1]

BY I. J. GOLDSTEIN AND F. SMITH

RECEIVED MARCH 18, 1958

The monoaldehyde III or IV obtained upon mild catalytic reduction of D'-methoxy-D-hydroxymethyldiglycolic aldehyde (I), reacting as II, has been subjected to methylation studies. Structures are proposed for the cyclic methylated derivatives (V and VI) as a result of the finding that hydrolysis of V and VI gives racemic 1-*C*-methylglyceritol and glyoxal.

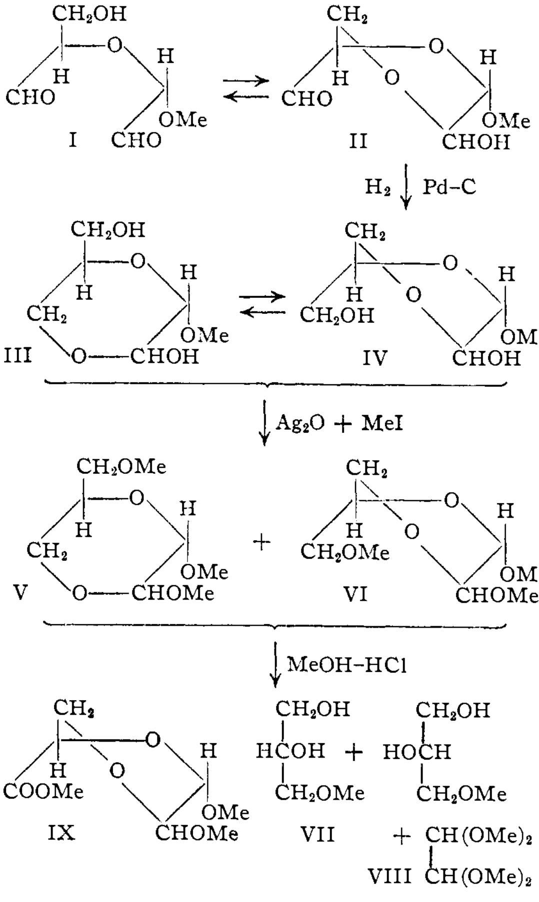
In a previous communication[2] it was shown that hydrogenation in the presence of a palladium–charcoal catalyst of the so-called dialdehyde I, obtained by periodate oxidation[3,4] of methyl α-D-glucopyranoside, effects preferential reduction of the aldehydic group at C_4 of the parent glycoside. The half-aldehyde so formed is shown herein by methylation studies to consist of the two tautomeric forms III and IV.

Treatment of the monoaldehydes III and IV with silver oxide and methyl iodide afforded a sirupy product containing a mixture, A, of the diastereoisomers V and VI. The structures V and VI assigned to the isomers in the methylated product (A) are supported by the following evidence.

The methylated product A derived from II showed $[\alpha]^{25}\mathrm{D}$ +132° (ethanol), a value comparable with that, $[\alpha]^{28}\mathrm{D}$ +125° (ethanol), of the parent monoaldehyde II which suggests a structural similarity and indicates[5] that the two isomers V and VI in A possess a cyclic structure. The methoxyl content of A revealed that two methoxyl groups had been introduced into III and IV during the methylation. Although showing a formal resemblance to the glycosides, the methylated mixture A proved to be much more stable than the average methyl glycopyranoside, five days treatment with boiling *N* sulfuric acid being required for complete hydrolysis.

Methanolysis of the mixture A containing V and VI gave racemic 1-*O*-methylglyceritol and glyoxal tetramethylacetal. Since L-1-*O*-methylglyceritol does not suffer racemization under the conditions used to methanolize V and VI, the formation of racemic 1-*O*-methylglyceritol (VII) reveals the presence of the two diastereoisomers V and VI. Support for the structure of V and VI also is provided by the characterization of glyoxal tetramethylacetal (VIII).

The methanolyzate of A also was found to contain a small amount of methyl glycerate which is most probably derived from the crystalline methyl ester IX, formed by the simultaneous oxidation and methylation of the dialdehyde I reacting as II. The aldehyde II is present as an impurity in the mixture of III and IV unless the monoaldehyde is purified by distillation.



These results indicate that the monoaldehyde consists of a mixture of diastereoisomeric dioxane compounds, one (IV) in which the ring engages the hydroxyl group at C_6 of the original glucoside and the aldehydic group at C_2 and the second (III) in

---

[1] Paper No. 3917, Scientific Journal Series, Minnesota Agriculture Experiment Station. This paper forms part of a thesis submitted by I. J. Goldstein to the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph. D. (1956). The work was sponsored by the Office of Ordnance Research, U. S. Army.

[2] J. E. Cadotte, G. G. S. Dutton, I. J. Goldstein, Bertha A. Lewis, F. Smith and J. W. Van Cleve, THIS JOURNAL, **79**, 691 (1957).

[3] H. Hérissey, P. Fleury and M. Joly, *J. pharm. chim.*, **20**, 199 (1934).

[4] E. L. Jackson and C. S. Hudson, THIS JOURNAL, **59**, 944 (1937).

[5] I. J. Goldstein, Bertha A. Lewis and F. Smith, *ibid.*, **80**, 939 (1958).