Dehydration was accomplished successfully as follows. A solution of 1 g. of the acetate of II in 5 cc. of dry pyridine was cooled in ice and treated with 0.2 cc. of thionyl chloride, added dropwise with shaking. The solution turned yellow and a white solid separated almost at once. After 5 minutes the solid was collected and triturated with water, and after several hours the material was filtered or extracted with ether. One crystallization from methanol gave two crops of methyl-Δ^4-cholestenyl acetate: 0.40 g., m.p. 113.5–115.5°, and 0.12 g., m.p. 112.5–114.5° (total yield, 54%). Each crop on one recrystallization from methanol afforded pure material in the form of glistening leaflets, m.p. 115–116°, $[\alpha]^{22}D$ −25° Di. A mixture of the substance with 6-methylcholesteryl acetate melted at 91–93°.

Anal. Calcd. for $C_{30}H_{50}O_2$ (442.71): C, 81.39; H, 11.38. Found: C, 81.34; H, 11.42.

The pyridine mother liquor was diluted with water, let stand for a few days, and extracted with ether. Evaporation of the acid-washed and dried extract gave an oil that partially solidified on standing, and six crystallizations of the solid fraction from methanol afforded 0.05 g. (5%) of colorless needles of 6-methylcholesteryl acetate, m.p. 115.5–116.5° (mixed m.p.; depression with the acetate of III). The result was the same when acid-washing of the ethereal extract was omitted and all possible contact with acids thus avoided.

Attempted Isomerization.—A solution of 0.09 g. of 6β-methyl-Δ^4-cholestene-3β-ol acetate in 50 cc. of acetic anhydride was treated with 4 drops of 95% sulfuric acid; a series of transient colors was observed, but after two hours at 25° the reaction mixture was largely soluble in water and ether extraction afforded only a negligible amount of amorphous green material. The Δ^4-isomer is also very sensitive to hydrochloric acid: when a solution of 0.03 g. of acetate in 30 cc. of methanol was treated with 3 drops of 36% acid and let stand overnight the only crystalline product isolated melted at 91–93° and depressed the m.p. of both the Δ^4- and Δ^5-isomers.

6β-Methyl-Δ^4-cholestene-3β-ol (III).—Saponification of the acetate (0.2 g.) by refluxing it for one-half hour with 1 *N* alcoholic potassium hydroxide (30 cc.) gave the free alcohol (0.15 g.), m.p. 95–96°, $[\alpha]^{22}D$ +16.6° Di. The substance tends to combine with methanol, although no definite solvate was isolated. Quick cooling of a methanol solution in an ice-bath gives an oil, whereas slow crystallization affords long prismatic needles. Satisfactory analyses were obtained only when the sample had been dried at 66° for 6–10 hr.

Anal. Calcd. for $C_{28}H_{48}O$ (400.66): C, 83.93; H, 12.08. Found: C, 84.20, 84.12; H, 11.94, 12.07.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WASHINGTON UNIVERSITY]

The Condensation of Nitromethane with D-Mannose: Synthesis of D-Manno-D-*gala*-heptose and D-Manno-D-*talo*-heptose

BY JOHN C. SOWDEN AND ROBERT SCHAFFER

D-Mannose has been condensed with nitromethane under the influence of alkali to give 37% of 1-nitro-1-desoxy-D-manno-D-*gala*-heptitol and 10% of 1-nitro-1-desoxy-D-manno-D-*talo*-heptitol. The nitroalcohols were converted to the corresponding aldoheptoses, D-manno-D-*gala*-heptose and D-manno-D-*talo*-heptose, in good yield by treatment of their sodium salts with aqueous sulfuric acid (Nef reaction). The preparation of D-manno-D-*talo*-heptose by this method is a considerable improvement over its preparation by the cyanohydrin synthesis from D-mannose.

The addition of hydrocyanic acid to the D-mannose molecule proceeds almost exclusively to D-manno-D-*gala*-heptonic nitrile and hydrolysis of the latter readily gives 85–90% of D-manno-D-*gala*-heptonic acid, isolated as the barium salt.[1] The epimeric D-manno-D-*talo*-heptonic acid also has been isolated from the reaction in low yield (4–6%) both as the phenylhydrazide[2] and the lead salt.[3] Thus, the yield of D-manno-D-*talo*-heptose obtainable by the Kiliani–Fischer cyanohydrin synthesis from D-mannose is only about 2%. The difficulty of preparing this aldoheptose apparently has discouraged any detailed study of its chemistry and any attempts to prepare from it the related higher-carbon sugars.

In a continuation of our study of the nitromethane synthesis of higher-carbon aldose sugars[4] and in the hope that this method might make D-manno-D-*talo*-heptose more readily available, we have now studied the products of the alkali-induced condensation of D-mannose with nitromethane. Powdered D-mannose is relatively insoluble in a mixture of methanol and nitromethane containing sodium methoxide but, on shaking the suspension, the sugar gradually disappears from the solid phase and is replaced by a precipitate of the amorphous seven-carbon sodium *aci*-nitroalcohols. Removal of the sodium from the latter then gives the mixed nitrodesoxyheptitols in 45–50% combined yield. Subsequent fractional crystallization, which is greatly aided by a marked difference in the solubility of the epimers in water, shows that the ratio of 1-nitro-1-desoxy-D-manno-D-*gala*-heptitol formed to the epimeric 1-nitro-1-desoxy-D-manno-D-*talo*-heptitol is approximately 3.5:1. Since the latter nitroalcohol can be transformed to the corresponding aldoheptose *via* the Nef reaction in excellent yield (80%), D-manno-D-*talo*-heptose is much more easily available by this method than by the previously-known cyanohydrin synthesis. Although the epimeric D-manno-D-*gala*-heptose is obtained in very high yield by the cyanohydrin synthesis, the relative simplicity of the nitromethane synthesis makes it attractive also for the laboratory preparation of this aldoheptose.

D-Manno-D-*talo*-heptose was first obtained in crystalline condition by Peirce,[2] after regeneration from its *p*-nitrophenylhydrazone. He was unable to find a suitable recrystallization solvent and, consequently, did not report any physical constants for the sugar. Later, Ettel[5] reported the preparation of the heptose by the reduction of epimerized D-manno-D-*gala*-heptonic acid. After several re-

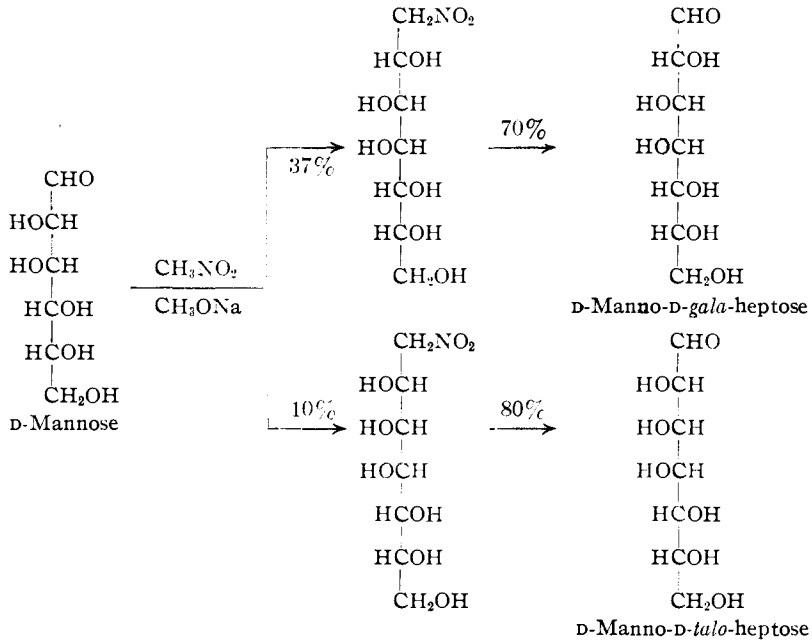
(1) Fischer and Hirschberger, *Ber.*, **22**, 365 (1889).

(2) Peirce, *J. Biol. Chem.*, **23**, 327 (1915).

(3) Isbell, *Bur. Standards J. Research*, **20**, 97 (1938).

(4) Sowden and Fischer, THIS JOURNAL, **66**, 1312 (1944); **67**, 1713 (1945); **68**, 1511 (1946); **69**, 1048, 1963 (1947); Sowden, *ibid.*, **71**, 1897 (1949); **72**, 808 (1950); *Science*, **109**, 229 (1949); *J. Biol. Chem.*, **180**, 55 (1949).

(5) Ettel, *Coll. Czech. Chem. Comm.*, **4**, 504 (1932).



crystallizations, his substance melted at 140° and showed a specific rotation, at equilibrium in water, of 7.61°. No analytical data were recorded. More recently, Isbell[3] repeated the cyanohydrin synthesis from D-mannose, purified the resulting D-manno-D-*talo*-heptonic acid through the lead salt, and reduced the corresponding lactone to obtain a monohydrate of α-D-manno-D-*talo*-heptose ("α-D-β-mannoheptose hydrate") melting at 83° and showing an equilibrium specific rotation in water of 14.5°. In the present work, we have apparently obtained the modification reported by Isbell, since our heptose monohydrate preparation melts at 83–84° and has an equilibrium specific rotation in water of 15.8°. Since the physical constants of Isbell's product and our own show reasonably good agreement yet differ sharply from the values recorded by Ettel for his purified substance, some doubt arises regarding the identity of the latter with *pure* D-manno-D-*talo*-heptose.

It has been noted by Hudson[6] that the preparation of the naturally-occurring heptitol, D-volemitol, by the reduction of D-manno-D-*talo*-heptose, even though the latter arises in poor yield from D-mannose in the cyanohydrin synthesis, is preferable to its isolation from natural sources (the mushroom *Lactarius volemus* and several species of the plant *Primula*). Accordingly, the improvements in preparation of the heptose reported herein also make D-volemitol more readily available.

Experimental

The D-Manno-nitrodesoxyheptitols.—To a suspension of 40 g. of powdered D-mannose in 80 cc. of methanol and 105 cc. of nitromethane was added a solution of sodium methoxide prepared from 10.4 g. of sodium and 250 cc. of methanol. The mixture was shaken mechanically for 18 hours and the resulting precipitated amorphous sodium *aci*-nitroalcohols then were filtered off and washed rapidly with cold methanol, ether and petroleum ether. The moist salts were dissolved in 400 cc. of ice–water and the solution passed immediately through an appropriate column of Amberlite I R-100 to remove sodium. (The passage of the solution over the ion-exchange bed must be carried out fairly rapidly to circumvent crystallization of 1-nitro-1-desoxy-D-manno-D-*gala*-heptitol on the resin.) Concentration of the effluent at reduced pressure produced successive crops of nearly-pure 1-nitro-1-desoxy-D-manno-D-*gala*-heptitol, which were removed by filtration. After complete concentration, crystallization of the sirupy residue from ethanol yielded nearly pure 1-nitro-1-desoxy-D-manno-D-*talo*-heptitol. The combined yield of crystalline nitroalcohols was 29.3 g. (55%). Recrystallization of the higher-melting fractions from water (10 cc./g.) produced 19.6 g. (37%) of 1-nitro-1-desoxy-D-manno-D-*gala*-heptitol, m.p. about 190°, while recrystallization of the lower-melting fractions from 75% ethanol (3 cc./g.) produced 5.6 g. (10%) of 1-nitro-1-desoxy-D-manno-D-*talo*-heptitol, m.p. about 140°. For analysis the nitroalcohols were recrystallized to constant melting point from the respective solvents indicated.

1-Nitro-1-desoxy-D-manno-D-*gala*-heptitol melts, with decomposition, at 197–198° and shows $[\alpha]^{25}D$ 2.4 in water, *c* 1.4.

Anal. Calcd. for $C_7H_{15}O_8N$ (241.2): C, 34.9; H, 6.27. Found: C, 35.1; H, 6.31.

1-Nitro-1-desoxy-D-manno-D-*talo*-heptitol melts at 141–142° and shows $[\alpha]^{25}D$ 3.6 in water, *c* 8.

Anal. Calcd. for $C_7H_{15}O_8N$ (241.2): C, 34.9; H, 6.27. Found: C, 35.0; H, 6.15.

D-Manno-D-*gala*-heptose.—Five grams of 1-nitro-1-desoxy-D-manno-D-*gala*-heptitol was dissolved in 25 cc. of 1 *N* sodium hydroxide and the solution added dropwise to a stirred solution of 3 cc. of sulfuric acid and 4 cc. of water at 20°. The resulting solution was de-ionized by successive passage through appropriate columns of Duolite A-4, Amberlite I R-100 and Duolite A-4. Concentration of the effluent at reduced pressure yielded a partially crystalline residue. This was dissolved in 10 cc. of warm glacial acetic acid and the solution, on cooling, deposited 0.3 g. of unchanged nitroalcohol (m.p. 197–198°). Concentration of the filtrate then produced 2.85 g. (70%) of D-manno-D-*gala*-heptose, m.p. 135–137° and $[\alpha]^{25}D$ 68.1° at equilibrium in water, *c* 3.5. These constants agree well with those reported in the literature for pure D-manno-D-*gala*-heptose.

D-Manno-D-*talo*-heptose Monohydrate.—Five grams of 1-nitro-1-desoxy-D-manno-D-*talo*-heptitol was treated exactly as described above for the D-manno-D-*gala*-epimer. The product in this instance was a colorless sirup. Following the directions of Peirce,[2] a small aliquot of the sirup was converted to the heptose *p*-nitrophenylhydrazone and the latter was cleaved with benzaldehyde. The resulting sirup crystallized readily on addition of ethanol. Seeding of the original sirup then produced 3.8 g. (80%) of D-manno-D-*talo*-heptose monohydrate, m.p. 75–80°, $[\alpha]^{25}D$ 14.7° at equilibrium in water, *c* 4.5. The sugar may be recrystallized readily by dissolving it in a small amount of water, adding isopropyl alcohol to incipient turbidity, and allowing the resulting solution to concentrate by evaporation at room temperature. After two such recrystallizations, the heptose monohydrate showed m.p. 83–84° and $[\alpha]^{25}D$ 15.8° at equilibrium in water, *c* 4. For D-manno-D-*talo*-heptose monohydrate, Isbell[3] records m.p. 83° and $[\alpha]^{20}D$ 14.5° at equilibrium in water.

Anal. Calcd. for $C_7H_{14}O_7 \cdot H_2O$ (228.2): C, 36.8; H, 7.07. Found: C, 36.8; H, 6.88.

1-Nitro-1-desoxy-D-manno-D-*gala*-heptitol Hexaacetate.—Two grams of 1-nitro-1-desoxy-D-manno-D-*gala*-heptitol was treated with 10 cc. of cold (0°) acetic anhydride containing a trace of sulfuric acid. The mixture was warmed to obtain a clear solution and then allowed to stand at room temperature. After two hours, the resulting semicrystalline mass was shaken with ice–water and filtered to produce 3.9 g. (95%) of the hexaacetate. The latter, after recrystallization, first from benzene–petroleum ether and then from

(6) Hudson, *Advances in Carbohydrate Chem.*, **1**, 32 (1945).

ethanol, showed m.p. 150–151° and $[\alpha]^{25}D$ −7.4° in chloroform, *c* 5.2.

Anal. Calcd. for $C_{19}H_{27}O_{14}N$ (493.4): C, 46.2; H, 5.52. Found: C, 46.1; H, 5.34.

D-Manno-pentaacetoxy-1-nitroheptene-1.—Two grams of the above nitroalcohol hexaacetate in 25 cc. of benzene was refluxed for 90 minutes with 2 g. of sodium bicarbonate. Filtration and concentration then produced 1.59 g. (90%) of D-manno-pentaacetoxy-1-nitroheptene-1. After recrystallization from ethanol, the acetylated nitroölefin melted at 111–113° and showed $[\alpha]^{25}D$ 37.3° in chloroform, *c* 4.

The acetylation of 1-nitro-1-desoxy-D-manno-D-*talo*-heptitol with acetic anhydride and sulfuric acid produced a sirupy hexaacetate. The latter, on refluxing in benzene solution with sodium bicarbonate, yielded 58% of D-manno-pentaacetoxy-1-nitroheptene-1, m.p. 111–113°, and $[\alpha]^{25}D$ 38.1 in chloroform, *c* 3.2.

Anal. Calcd. for $C_{17}H_{23}O_{12}N$ (433.4): C, 47.1; H, 5.35. Found: C, 47.1; H, 5.25.

1-Amino-1-desoxy-D-manno-D-*gala*-heptitol Oxalate.—Two grams of 1-nitro-1-desoxy-D-manno-D-*gala*-heptitol in 50 cc. of water was shaken with hydrogen in the presence of 1 g. of Raney nickel at room temperature and atmospheric pressure. The reduction was complete in one and three-quarters hours with the absorption of 3 mole-equivalents of hydrogen. After filtration onto 0.53 g. of oxalic acid dihydrate, concentration of the solution to dryness produced a crystalline residue. Filtration with ethanol then yielded 1.9 g. (90%) of the amine oxalate. After recrystallization from water by the addition of ethanol, the pure salt melted at 193–195°, with decomposition, and showed $[\alpha]^{25}D$ 13.2° in water, *c* 3.4.

Anal. Calcd. for $C_8H_{18}O_8N$ (256.2): C, 37.5; H, 7.08. Found: C, 37.8; H, 7.05.

Reduction of 1-nitro-1-desoxy-D-manno-D-*talo*-heptitol also proceeded smoothly to the amine but the latter failed to yield a crystalline salt with either oxalic acid or *p*-toluenesulfonic acid.

ST. LOUIS, MISSOURI RECEIVED MAY 10, 1951

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

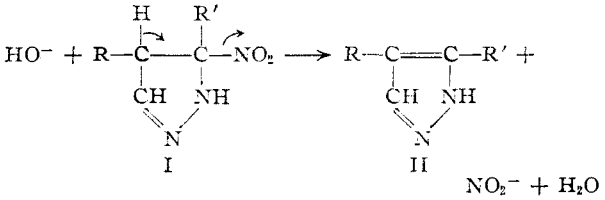
The Condensation of Diazo Compounds with Nitroölefins. II. 3-Bromo- and 3-Nitropyrazoles

BY WILLIAM E. PARHAM AND JAMES L. BLEASDALE[1]

Mechanisms for the decomposition of 3-nitropyrazolines into pyrazoles in acidic and basic media are discussed. The condensation of 1-bromo-1-nitro-2-phenylethylene with diazomethane was effected and the decomposition of the resulting pyrazoline with acid and base was studied. The results were found to follow essentially those anticipated by the mechanisms postulated. The decomposition of 3-bromo-3-nitro-4-phenylpyrazoline with hydrogen chloride was observed to give a 66% yield of 3-bromo-4-phenylpyrazole. The decomposition of the same pyrazoline with sodium carbonate was observed to give a 73% yield of 3-nitro-4-phenylpyrazole. The structure of 3-nitro-4-phenylpyrazole was established by reduction to the corresponding amine and synthesis of the latter from 3-carbethoxy-4-phenylpyrazole by means of a Curtius reaction. The availability of bromonitroölefins suggests that the reaction described might represent a general synthesis for the otherwise difficultly accessible 3-bromo- and 3-nitropyrazoles.

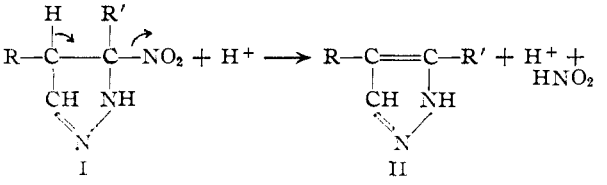
The condensation of diazocompounds with nitroolefins and the decomposition of the resulting nitropyrazolines to give pyrazoles was recently described.[2] The observation that nitropyrazolines could be converted into pyrazoles by the action of either acids or bases prompted us to investigate the decomposition of 3-bromo-3-nitro-4-phenylpyrazoline (IV) with the intention of gaining additional information concerning the mechanism for this elimination reaction.

The decomposition of 3-nitropyrazolines (I)[3a] by alkali probably takes place by the removal of a proton from C_4 followed by a shift of the C_4 electrons into the ring and the simultaneous elimination of the nitro group as an anion[3b] (E_2-mechanism).



The hydrogen atom at C_4 is attached to a carbon–carbon–nitrogen system similar to that found in α-picoline and the increased acidity observed in such systems is usually explained by resonance stabilization[4] of the resulting ion (—C̄—C=N ↔ —C=C—N̈—).

The decomposition of 3-nitropyrazolines (I) by treatment with strong mineral acids may take place by an acid-catalyzed ionization of the nitro group facilitated by the coördination of a proton with subsequent or simultaneous expulsion of a proton at C_4.



A study of the decomposition of 3-bromo-3-nitro-4-phenylpyrazoline (IV) in acidic and basic media was considered of interest to this problem since it was recognized that the decomposition of this pyrazoline could follow a different course depending upon the mechanism of elimination involved. In the presence of base the reaction could proceed by means of an E_1 or E_2 elimination mechanism,[5] and the product would depend upon whether a bromide or nitrite ion is preferentially eliminated from the pyrazoline IV. If the control-

(1) From the Ph.D. Thesis of James L. Bleasdale, July, 1950.

(2) W. E. Parham and J. L. Bleasdale, THIS JOURNAL, **72**, 3843 (1950).

(3) (a) The well established tautomerization of pyrazolines and pyrazoles is assumed during this discussion. (b) *Cf.* M. Kloetzel, *ibid.*, **70**, 3571 (1948), for a similar type of β-elimination in β-nitro esters.

(4) E. Alexander, "Principles of Ionic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 130.

(5) *Cf.* ref. 4, p. 104.