(e) *Component 5*, R_f 0.21–0.22, 417 mg. After drying, the sirup had $[\alpha]_D^{25}$ −15° in water (*c*, 5.2) and +5.7° in methanol (*c*, 5.2). Demethylation of a portion (215 mg.) of the methylated sugar afforded mannose as the only hexose and other partial demethylation products. The mannose was separated from the other components by paper chromatography and readily gave a phenylhydrazone, m.p. and mixed m.p. 198–200°, $[\alpha]_D^{25}$ +33° in pyridine (*c*, 2.0). Treatment of the methylated sugar with *p*-nitrobenzyl chloride and pyridine gave crystalline 1,4,6-tri-*p*-nitrobenzoyl-2,3,-di-*O*-methyl-D-mannose which had m.p. 191–193°, $[\alpha]_D^{25}$ +64° in chloroform (*c*, 3.0): Lit. value for 2,3-di-*O*-methyl-D-mannose, R_f 0.22 in solvent D,[13] $[\alpha]_D$ −15.8° in water[31]; for 1,4,6-tri-*p*-nitrobenzoate, m.p. 194°, $[\alpha]_D$ +65° in chloroform.[5]

A summary of the quantities of the components obtained from the hydrolyzate of the methylated gum and the observed R_f values in solvent D is given below.

Component	R_f, Solvent D	Weight, Mg.	Mmoles
Unknown a	0.82	16	—
1	0.78–0.79	116	0.49
2	0.70–0.71	494	2.09
3	0.55–0.56	21	0.09
4[a]	0.49–0.50	542	2.46
5	0.20–0.21	417	2.00
Unknown b	0.11–0.12	14	—

[a] Contains some methylated galactose derivative, presumably 2,3,6- or 2,4,6- or both.

(31) G. T. Robertson, *J. Chem. Soc.*, 330 (1934).

HONOLULU 14, HAWAII

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY COLLEGE OF FORESTRY AT SYRACUSE UNIVERSITY]

Polymerization of Anhydro Sugar Derivatives. III. 1,6-Anhydro-β-D-galactopyranose and Its 2-*O*-Methyl Ether

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The polymerization of D-galactosan to high molecular weight branched polysaccharides is described. The optical rotation of the product shows the presence of a mixture of α and β linkages. Periodate oxidation indicates a product with forty-three of one hundred units unsubstituted on the secondary hydroxyls, fifty-six substituted on C-2 or C-4 and only one unit resistant to periodate (substituted on C-3 or disubstituted). The 2-*O*-methyl ether is very resistant to polymerization presumably because transformation of the 1,6-anhydro ring to the 1,2-anhydro ring is impossible.

In a reinvestigation[2] of Pictet's[3] polymerization of levoglucosan, it has been shown that highly branched glucosans are produced linked primarily 1,6- and to a lesser degree in the 2,4- and probably 3-positions. Both α and β anomeric forms were shown to be present and these conclusions were generally confirmed and extended by Wolfrom and co-workers in a concurrent research.[4,5] The highest weight average molecular weights achieved in this laboratory were about 20,000 as measured by means of the ultracentrifuge. The products were contaminated by a small percentage of microgel byproduct which was eliminated in the ultracentrifuge determination but which caused molecular weights measured by light scattering to be substantially higher.[6]

In order to explain the presence of α linkages in the polymer, we have proposed a reaction mechanism involving the interaction of the 2-hydroxyl group with the C-1 carbon atom in the transition state. Abe and Prins point out that the molecular weight distribution is most readily explained if, concurrent to our proposed reaction, a more rapid dimerization occurs by the reaction of two anhydro rings. The reactive intermediate is assumed then to attack hydroxyl groups indiscriminately.

In order to gain further perspective on the mechanism of this reaction and to obtain further examples, we now have studied the polymerization of 1,6-anhydro-β-D-galactose and its 2-*O*-methyl ether.

EXPERIMENTAL

Preparation and isolation of monomers and polymers. D-Galactosan and its 2-*O*-methyl ether were prepared respectively by pyrolysis of α-lactose monohydrate[7] and by dimethyl sulfate methylation and hydrolysis of 3,4-isopropylidene-D-galactosan.[8] The physical properties of the former were: m.p. 223–224° $[\alpha]_D^{24}$ −22° (*c* = 1.96) and the latter:

(1) Present address: Section on Carbohydrates, Laboratory of Chemistry, National Institute of Arthritis and Metabolic Diseases, Bethesda 14, Md.

(2) J. daS. Carvalho, W. Prins, and C. Schuerch, *J. Am. Chem. Soc.*, **81**, 4054 (1959).

(3) (a) A. Pictet and J. Sarasin, *Helv. Chim. Acta*, **1**, 87 (1918); (b) A. Pictet, *Helv. Chim. Acta*, **1**, 226 (1918); (c) A. Pictet and J. Pictet, *Helv. Chim. Acta*, **4**, 788 (1921); (d) A. Pictet and J. Pictet, *Compt. rend.*, **173**, 158 (1921); (e) A. Pictet and J. H. Ross, *Compt. rend.*, **174**, 1113 (1922); (f) A. Pictet and J. H. Ross, *Helv. Chim. Acta*, **5**, 876 (1922); (g) Hoffman-LaRoche and Co., A.G., German Pat. **513,126** (Feb. 29, 1928).

(4) A. Thompson and M. L. Wolfrom, *J. Am. Chem. Soc.*, **80**, 6618 (1958).

(5) M. L. Wolfrom, A. Thompson, and R. B. Ward, *J. Am. Chem. Soc.*, **81**, 4623 (1959).

(6) H. Abe and W. Prins, *Makromol. Chem.*, XLII, 216 (1961).

(7) R. M. Hann and C. S. Hudson, *J. Am. Chem. Soc.*, **64**, 2435 (1942).

(8) R. E. Reeves, *J. Am. Chem. Soc.*, **71**, 2118 (1949).

TABLE I

CONDITIONS OF PREPARATION AND RESULTS FOR SELECTED POLYMERS[a]

Polymer	Catalyst	Time, Hr.	Yield, %	$[\alpha]_D^{24}$	$\bar{M}_n$	$\bar{M}_w$	Color
G1	MCA	15	76	+81.8	1,800 3,520[b]	22,500	White
G2	TFA	6	60	+93	—	—	Dark-brown
G3	HYP	15	50	+96.5	—	—	Brown
G4	ZC	4	45	+115.5	—	—	Brown-black
MeG5a	MCA	58	3	+39.5	550	2,230	Brown
MeG5b[c]			*ca.* 95		176	—	

[a] Polymerizations were carried out at 110° at a catalyst/monomer molar ratio 1:50. Monomers were D-galactosan (G) and its 2-*O*-methyl ether (MeG). Catalysts were monochloracetic acid (MCA), trifluoroacetic acid (TFA), hypophosphorus acid (HPA), zinc chloride (ZC). [b] Acetylated. [c] Acetone-soluble fraction.

m.p. 115–116° $[\alpha]_D$ −31.5°. Polymerizations were carried out in somewhat smaller scale than previously[1] but in an identical fashion. The polymer precipitations and isolations also followed the levoglucosan method. In the case of 2-*O*-methyl galactosan, however, alcohol precipitation failed to precipitate a polymer and the aqueous solution was diluted with ten volumes of acetone. The turbid liquor was centrifuged, and the supernatant decanted. Both the residue and the supernatant were freeze dried. Results are described in Table I.

Polygalactosan (400 mg.) was shaken with 5 ml. of pyridine for 30 min. to swell completely and 4 ml. of acetic anhydride was added. The mixture was heated under reflux on a steam bath for 12 hr. The slightly turbid solution was cooled and poured onto crushed ice. The powder was washed to neutrality and dried in vacuo over phosphorus pentoxide. The infrared spectrum showed a very small hydroxyl peak and this substance was used for number average molecular weight determination.

Characterization of products. Oxidations were carried out using 0.10-*M* sodium periodate and botn periodate consumption and formic acid liberation were measured iodometrically as before.[2] Results are given in the text. Weight average molecular weights were determined in aqueous solution by the Archibald approach to equilibrium method in a Spinco Model E ultracentrifuge. Number average molecular weights were determined in aqueous solution in a thermoelectric vapor phase osmometer.[6] The value for polygalactosan (1800) was confirmed by a determination on the acetylated polymer in acetone solution (calculated, 3200; found, 3520).

Infrared spectra were determined in potassium bromide pellets on a Model 11 Baird Infrared Spectrophotometer. D-Galactosan had peaks in the 800 to 900 cm.$^{-1}$ region at 807, 845, 847, 890, 915, and 926. Its 2-*O*-methyl ether had peaks at 752, 804, 850, 880, and 909.

Hydrolysis of polymers and chromatography. A polymer sample (100.0 mg.) was dissolved in 50 ml. of 0.5*N* sulphuric acid and heated on a steam bath for 4 hr. The solution was cooled and neutralized with excess barium carbonate. The solids were filtered off and the filtrate was evaporated to dryness under vacuum. The residue was washed by hot pyridine into a tube and centrifuged. The supernatant was decanted off and concentrated.

A few microliters of the above solution was spotted on Whatman #1 paper, alongside D-galactose, 2-*O*-methyl-D-galactose, lactose, monomers, and polymers. The papers were developed with 1-butanol-water-ethanol (4:5:1) for 18 hr. After drying the paper was sprayed with periodate-benzidine reagent.[9] Results are reported in Table II.

(9) J. H. Cifonelli and F. Smith, *Anal. Chem.*, 26, 1132 (1954).

TABLE II

CHROMATOGRAPHIC RESULTS ON MONOMERS, POLYMERS, AND POLYMER HYDROLYZATES

Substance	R_f[a]	Spot Color[a]
D-Galactosan	0.38	White
D-Galactose	0.18	White
2-*O*-Methyl-D-galactosan	0.61	Yellow brown
2-*O*-Methyl-D-galactose	0.30	White
Lactose	0.07	White
Polymer 1	0.00	—
Polymer 1 hydrolysate	0.18	White
Polymer 5a	0.00	—
Polymer 5a hydrolysate	0.30 (strong) 0.60 (weak)	White Yellow brown
"Polymer" 5b	0.60 (with tailing)	Yellow brown

[a] See Experimental for conditions and reagents.

RESULTS AND DISCUSSION

The polymerization of D-galactosan proceeded in the absence of solvent at 85 to 120° with a mild catalyst, preferably monochloracetic acid, under conditions essentially identical to those used for levoglucosan. This monomer was more prone to decompose and to form dark colored products if the temperature was above this range or if other catalysts were used.

The polygalactosan examined in most detail was a white amorphous powder prepared in 76% yield by heating D-galactosan with one-fiftieth molar ratio of monochloracetic acid for fifteen hours at 110°. The structural interpretations below largely follow the reasoning presented in previous papers in this series. The specific rotation $[\alpha]_D^{24°}$ in water was +81.8°, indicating the presence of both α and β anomeric forms. The number average molecular weight was 1800 and the weight average molecular weight (by ultracentrifuge) was 22,500, showing the wide molecular weight distribution to be expected in this kind of polymerization. The number average molecular weight of the polymer was determined first in water solution (1800) and was confirmed by the value obtained on the acetylated polymer in

acetone solution (experimental 3520, calculated 3200).

Hydrolysis followed by chromatography showed polygalactosan to be completely hydrolyzable to D-galactose; the polymer itself did not move on development of a paper chromatogram. The polymer consumed 1.42 moles of periodate per monomeric unit on oxidation and produced 0.43 moles of formic acid. Thus, of every one hundred anhydrosugar units, forty-three were unsubstituted on the three secondary hydroxyl groups, fifty-six substituted on either C-2 or C-4, and only the one remaining unit was either disubstituted on C-2 or C-4 or singly substituted on the C-3 hydroxyl. The three position is therefore extremely unreactive, but the relative reactivities of C-2, C-4 and C-6 are not known. These calculations are made with the assumption that the unchanged C-1 function (analogous to the reducing end group) is in the form of an anhydro ring. As the number average molecular weight corresponds to a chain of eleven units, some slight error could be introduced if this is not the case.

The infrared spectrum of the polymer was very diffuse and little information could be obtained with surety. Small peaks were probably present around 870 and 882 cm.$^{-1}$ and none was evident in the 830 cm.$^{-1}$ region. Nevertheless the optical rotation we believe to be unequivocal evidence for the presence of both α and β anomeric forms for reasons that have been outlined before for polyanhydroglucose.[1]

The results with 2-*O*-methyl-D-galactosan were in marked contrast to those obtained on the unsubstituted anhydro sugar. The monomer catalyst mixture melted within four hours, but the viscosity of the melt appeared not to change for several days. It was worked up when the melt began to darken (after about sixty hours). Diluting an aqueous solution of the product to give an 85% alcoholic solution failed to precipitate a polymeric fraction, and a separation was only achieved using acetone. The acetone-soluble fraction had a chromatographic behavior similar to that of the starting material with some tailing; the number average molecular weight was 176; the periodate consumption was 0.90. Clearly this fraction consisted of largely unchanged 2-*O*-methyl-D-galactosan.

The acetone-insolubles were a discolored brown powder amounting to only three percent of the starting material. The number and weight average molecular weights were 550 and 2230, respectively. Periodate oxidation indicated that four out of ten units were substituted on C-3 or C-4. Chromatography following hydrolysis showed the presence of 2-*O*-methyl-D-galactose and traces of 2-*O*-methyl-D-galactosan. The latter may have been present as unopened end groups or possibly as a monomeric contaminant. The low specific rotation $[\alpha]$ +39.5° undoubtedly also reflected the presence of unopened 1,6 anhydro rings. A significant peak at 830 cm.$^{-1}$ (and a lesser one near 858 cm.$^{-1}$) in the infrared spectrum appeared to give evidence of the presence of α linkages although infrared spectral data on galactose derivatives may be misleading.[9] Clearly the most remarkable single feature of the polymerization of these two compounds is the great unreactivity of the 2-*O*-methylgalactosan in contrast to the parent compound.

It is apparent that in terms of Abe and Prins' formulation a dimer intermediate can only be formed if conversion of one of the two 1,6-anhydro rings to an 1,2-anhydro ring is possible. In other words, the intermediate which was left unspecified by these authors, is very likely to be a 1,6′-linked dimer with a reactive 1,2-anhydro ring. For the case of galactosan it is found, moreover, that the reactivity of the hydroxyl group in the three position is much lower than in the other positions, so that the assumption of equal reactivity in all B groups in the A-R-B_7 polymerization scheme as used by Abe and Prins is not justified. The reasonable correspondence these authors have found between theory and experiment may be traced to the fact that the distribution does not change appreciably if some hydroxyl groups are less reactive than others. Whether the rapid dimerization which they postulate takes place at all or *via* their proposed mechanism can in principle be determined by a study of the structure of the dimer fraction at low conversions.

It appears that attack by the 2-hydroxyl group on the anhydro ring is an important part of the initiation process. This should not be considered as a means of assisting the ionization of the C-1 position, for Winstein[10,11] has shown that neither a neighboring methoxyl or hydroxyl participate very much in the formation of a carbonium ion. Rather it should be considered as an interconversion of a relatively unreactive protonated 1,6-anhydro ring to a relatively reactive 1,2-anhydro ring. When the 2-position is methylated, this transformation is not possible and the polymerization is severely inhibited. The alternative explanation that the 2-*O*-methyl group merely introduces an additional factor of steric hindrance does not appear to us to be an adequate explanation of the difference in reactivity of the two compounds, after examining the structures with the aid of molecular models. In broad outline the polymerization of 1,6-anhydro-β-D-galactopyranose and its 2-*O*-methyl ether can thus be described in the same terms as that of levoglucosan.[2]

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(9) S. A. Barker, E. J. Bourne, and D. H. Whiffen, "Use of Infrared Analysis" in D. Glick's, *Methods of Biochemical Analysis*, Vol. III, Interscience New York, 1956.

(10) S. Winstein, E. Grunwald, and L. L. Ingraham, *J. Am. Chem. Soc.*, **70**, 821 (1948).

(11) S. Winstein and E. Grunwald, *J. Am. Chem. Soc.*, **70**, 828 (1948).

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SYRACUSE 10, N. Y.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, AND THE DEPARTMENT OF CHEMISTRY, GEORGETOWN UNIVERSITY]

Synthesis of Aminohydrophenanthrene Analogs of Morphine[1]

JAMES G. MURPHY

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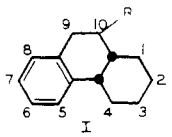
A group of 10-aminohydrophenanthrenes and 10-dimethylaminomethylhydrophenanthrenes, structural analogs of morphine, has been synthesized. The steric relations of the substituent groups on these new aminohydrophenanthrenes has been discussed. A stereoselective Mannich reaction is reported and an unusual epimerization of a benzylic alcohol is presented.

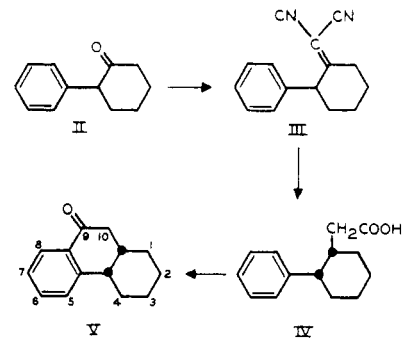
The purpose of the present work was to investigate the hitherto unknown aminohydrophenanthrenes of type I in which R represents an amino group or an aminomethyl group.



I

These phenanthrenes are of interest not only because they retain a large fragment of the morphine molecule but also because they reproduce many of the steric aspects of the natural alkaloid, *i.e.*, in the disposition of the aromatic ring, in the mode of fusion of the alicyclic rings, and in the location of the nitrogen of these substances so that it is close to or identical with that of morphine.

The 10-aminomethyl series. *cis*-1,2,3,4,4a,10a-Hexahydro-9(10H) phenanthrone (V) which had been synthesized by Cook *et al.*[2] appeared to be a highly suitable intermediate for the desired compounds since the carbonyl at position 9 would facilitate modifications at position 10. The stereochemistry of this substance had been corroborated[3,4] by oxidation and nitration to a known diphenic acid derivative. For the preparation of ketone V, 2-phenylcyclohexanone (II) was condensed with malononitrile, a practically quantitative yield of 2-phenylcyclohexylidenemalononitrile (III) being obtained. This unsaturated dinitrile was catalytically reduced, then hydrolyzed, and decarboxylated.



II III IV V

In this way it became possible to secure a 60% yield of the *cis*-acid (IV), which is a marked improvement in yield over the best previously reported procedure (36%[5]). That this reaction sequence led to a satisfactory yield whereas a similar sequence using ethyl cyanoacetate in place of malononitrile gave a low but not specified yield[5] results no doubt from the lower steric requirements of malononitrile for the condensation with 2-phenylcyclohexanone.

Cyclization of the *cis*-acid (IV) to the phenanthrone (V) by heating in sulfuric acid[2] was straightforward. With the phenanthrone (V) at hand, attempts were made to carry out a Mannich reaction. This, under the common reaction conditions of refluxing the components in a solvent[6] failed. Conditions were found (stirring, without solvent, in a 70° bath, under a slow stream of nitrogen) that led to a successful synthesis. In this way it was possible to secure a reproducible 47% yield of the amino ketone (VI). Just as VI was difficult to prepare, so it appeared readily hydrolyzed for it could not be recovered after a relatively short exposure to mineral acid. Although two diastereoisomers of

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(2) J. W. Cook, C. L. Hewett, and C. A. Lawrence, *J. Chem. Soc.*, 71 (1936).

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