dure of Cohn.[6] The by-product, *m*-chlorophenol, was separated from the desired acid by steam distillation and the crude acid recrystallized from water (Norit). The yield was 22% and the white crystals melt at 171.5–172.5°. Cohn[6] reported red crystals which melt at 166°.

Methyl 2-Chloro-6-hydroxybenzoate.—A solution of 1.3 g. (7.6 mmoles) of 2-chloro-6-hydroxybenzoic acid, 11 cc. of methanol and 1 cc. of concentrated sulfuric acid was heated under reflux for seventy-two hours, the reaction mixture concentrated under reduced pressure and then diluted with water. The residual oil was extracted with ether and the ethereal solution washed with freshly prepared sodium bicarbonate solution, dried and the ether distilled. The crude ester was recrystallized from aqueous methanol and the yield of white needles was 1.0 g. (71%), m. p. 47–48°.

Anal. Calcd. for $C_8H_7O_3Cl$: C, 51.49; H, 3.78. Found: C, 51.19; H, 3.92.

N-(4′-Methoxyphenyl)-6-chloroanthranilic Acid (VI).—To a solution of sodium ethoxide prepared from 0.11 g. (4.7 mmoles) of sodium and 10 cc. of absolute ethanol, cooled in an ice-bath, there was added in rapid succession 0.88 g. (4.7 mmoles) of methyl 2-chloro-6-hydroxybenzoate and a solution of 1.14 g. (4.7 mmoles) of N-4-methoxyphenylbenzimidyl chloride[3] in 30 cc. of dry ether. The reaction mixture was shaken vigorously whereupon a precipitate of sodium chloride began to form. The mixture was allowed to stand at room temperature for forty-eight hours, the solvent evaporated and the residue diluted with water. The resulting oily solid was removed by extraction with ether, the ethereal solution dried and the ether distilled.

The crude imido ester was heated in a nitrogen atmosphere at 210–215° for seventy minutes, then dissolved in 10.8 cc. of ethanol and the alcoholic solution diluted with 5.4 cc. of water and 5.4 cc. of a 1 *M* solution of ethanolic sodium ethoxide. The solution was refluxed for one and one-half hours, the alcohol evaporated on a steam-bath and the aqueous solution acidified with dilute hydrochloric acid. The dark oil which formed was separated by decantation and the crude benzoate of the substituted anthranilic acid dissolved in 22 cc. of ethanol. A solution of 7.2 g. of sodium hydroxide in 7.2 cc. of water was added and the mixture refluxed for one hour. The alcohol was evaporated and the solution acidified. The brown solid was extracted *exhaustively* with boiling water to remove the benzoic acid and the remaining brown solid recrystallized from aqueous ethanol. The yellow needle-like crystals melt at 139.5–140.5° (dec.), yield 0.36 g. (27.7%).

Anal. Calcd. for $C_{14}H_{12}O_3NCl$: C, 60.54; H, 4.36; N, 5.04; Cl, 12.76. Found: C, 60.58; H, 4.44; N, 5.63; Cl, 12.65.

2-Methoxy-8,9-dichloroacridine (II).—The ring closure and subsequent chlorination was conducted as described in an earlier publication[1] employing 0.2 g. (0.7 mmole) of acid VI, 1.6 cc. of phosphorus oxychloride and 4 cc. of chlorobenzene. The product was recrystallized from benzene, m. p. 180.3–181.3°, yield 0.08 g. (37.4%). No depression in melting point was noted upon admixture with the previously reported product.[1]

Anal. Calcd. for $C_{14}H_9ONCl_2$: C, 60.45; H, 3.26; N, 5.04; Cl, 25.50. Found: C, 60.80; H, 3.33; N, 5.40; Cl, 25.69.

Summary

Methyl 2-chloro-6-hydroxybenzoate and N-4-methoxyphenylbenzimidyl chloride were condensed in alkaline solution and the resulting imido ester rearranged to N-(4′-methoxyphenyl)-6-chloroanthranilic acid by pyrolysis. Subsequent ring closure and chlorination yielded 2-methoxy-8,9-dichloroacridine which was identical with the product previously reported.

BERKELEY 4, CALIFORNIA RECEIVED FEBRUARY 6, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

Derivatives of the Anomeric Glucopyranosylbenzenes

BY WILLIAM A. BONNER AND JAMES M. CRAIG

In a series of recent papers Hurd and Bonner[1] have developed two methods for the synthesis of acetylated glycosylaromatic hydrocarbons, compounds in which a glycosyl radical is linked directly to an aromatic nucleus. The first of these involved the catalytic glycosylation of aromatic hydrocarbons with polyacetylglycosyl halides or acetates in the presence of aluminum chloride, and produced the desired glycosylaromatic compound in low yield along with a 1,1-diaryl-1-desoxyglycitol. The second synthesis employed the metathetical reaction of the halide function of polyacetylglycosyl halides with Grignard reagents, and permitted the extension of the glycosylation reaction to the aliphatic series. This method had the distinct advantages of high yield, greater generality, and ease of isolation of a pure product. All of the glycosylated hydrocarbons produced above by either method were isolated and characterized as their acetates.

In addition to the crystalline, low-rotating polyacetylglycosylaromatic compounds produced by the Grignard glycosylation, there was usually isolable from the crystallization mother liquors about one-fourth as much of a high-rotating sirup, assumed to be anomeric with the crystalline material. On the basis of their rotations, the crystalline substances were designated as the β-anomers (*e. g.*, tetraacetyl-β-D-glucopyranosylbenzene, m. p. 155–156°, $[\alpha]^{20}D$ −18.6°) and the sirupy by-products as the α-anomers (*e. g.*, "tetraacetyl-α-D-glucosylbenzene," $[\alpha]^{20}D$ 40°). While the sirupy "α-anomers" could not be purified and were therefore not analyzed, their constitutions were supported by the fact that they were readily oxidizable to the predicted aromatic carboxylic acids. The pyranose ring system in the β-anomers has been demonstrated by the periodate oxidation of crystalline β-D-xylopyranosylbenzene[2] which, besides the sirupy β-D-gluco-

(1) Hurd and Bonner, THIS JOURNAL, **67**, 1664, 1759, 1972, 1977 (1945); Bonner, *ibid.*, **68**, 1711 (1946).

(2) Bonner and Hurd, unpublished work presented before the Division of Sugar Chemistry, 110th Meeting of the American Chemical Society, Sept., 1946.

pyranosylbenzene methanolate,[3] is the only compound of this class yet isolated in an unacetylated condition.

The present investigation centers about the "tetraacetyl-α-D-glucosylbenzene," $[\alpha]^{20}D$ 40°, produced as a by-product of the crystalline β-anomer when tetraacetyl-α-D-glucopyranosyl chloride reacts with phenylmagnesium bromide. When this reaction was repeated several times using tetraacetyl-α-D-glucopyranosyl bromide, the rotation of the "α-anomer" was found to vary widely, ranging from 28 to 38°, suggesting that the sirup was not an homogeneous product. All attempts to induce further crystallization of this sirupy material failed. We have also attempted to increase the yield of the sirupy by-product by employing 2-trichloroacetyl-3,4,6-triacetyl-β-D-glucosyl chloride.[4] Indeed, in this experiment the proportion of sirupy "α-anomer" was markedly increased, though the crude yield was somewhat lower. This suggests the possibility that the replacement of the halogen function with a phenyl group occurs with Walden inversion, upon which is superimposed considerable racemization.

When the "α-sirup" obtained by any of these methods was deacetylated with potassium methoxide,[3] the resulting sirup crystallized slowly from 2-propanol to produce prisms, m. p. 186.5–187°, $[\alpha]^{26}D$ 90.5°. Since these analyzed correctly, oxidized quantitatively to benzoic acid, consumed two moles of periodate with liberation of one mole of formic acid, and were strongly dextrorotatory, and since the deacetylated β-anomer had been found[3] to be a weakly dextrorotatory sirup, we believe the new compound to be α-D-glucopyranosylbenzene. This is the first instance of the isolation of a pure α-anomer in this series.

On acetylation of the crystalline α-anomer with acetic anhydride and pyridine, we have obtained tetraacetyl-α-D-glucopyranosylbenzene, m. p. 70–71°, $[\alpha]^{25}D$ 95.1°. It is thus apparent that the previously obtained sirupy "α-anomer" was a mixture containing both the α- and β-anomers. In fact, on reacetylation of the residue obtained on evaporation of the mother liquors from which the α-D-glucopyranosylbenzene was isolated, we have been able to obtain further quantities of tetraacetyl-β-D-glucopyranosylbenzene. Assuming no other components to be present, we estimate from its rotation that the previously designated "α-anomer" was a supercooled mixture containing about equal amounts of the authentic α- and β-anomers. In another connection we have studied the melting point behavior of various mixtures of the anomeric tetraacetyl-D-glucopyranosylbenzenes. These data are given graphically in Fig. 1.

For purposes of comparison with compounds to be reported later, we have also prepared the tetramethyl derivatives of the anomeric glucopyranosylbenzenes. The crystalline α-D-glucopyranosylbenzene yielded tetramethyl-α-D-glucopyranosylbenzene, $[\alpha]^{24}D$ 93.2°, while the sirupy β-anomer produced tetramethyl-β-D-glucopyranosylbenzene, $[\alpha]^{19}D$ 18.0°. Both of the methyl ethers existed as thin, colorless sirups. At an intermediate stage in the methylation of the β-anomer, a crystalline material was isolated, m. p. 106–107°, $[\alpha]^{24}D$ 36.3°. This analyzed correctly for trimethyl-β-D-glucopyranosylbenzene monohydrate, but the location of the three methyl groups has not been determined.

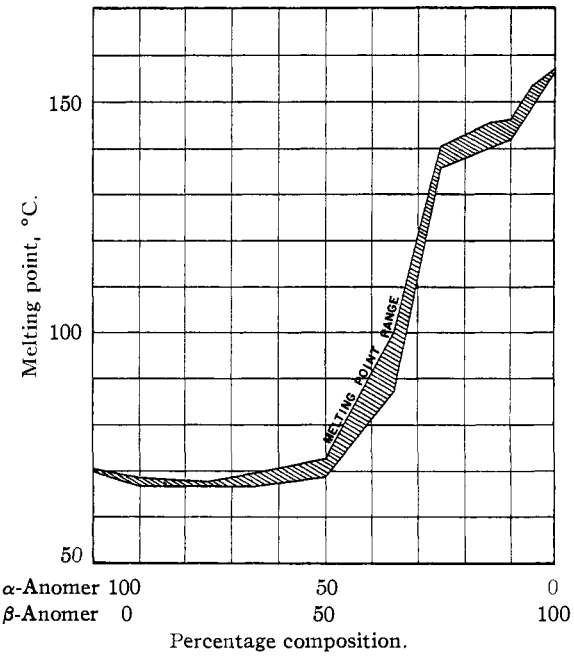


Fig. 1.—Mixed melting point diagram for anomeric tetraacetyl-D-glucosylbenzenes.

Having available several anomeric derivatives of a new class of glycosyl-type compound, it is interesting to apply Hudson's rules of isorotation.[5] The *A*-values, referring to the molecular rotatory contribution of C-1 containing the phenyl group, and the *B*-values, referring to the free or substituted remainder of the molecule, are presented in Table I. For comparative purposes we have included in Table I *B*-values for other appropriately substituted anomeric glucopyranose derivatives.

Table I shows the *A*-values of the glucopyranosylbenzenes and their tetramethyl derivatives to behave about normally, but acetylation of the *B*-portion of the molecule leads to an anomalously high *A*-value in the tetraacetate. The agreement of the *B*-values of the glucopyranosylbenzene derivatives with *B*-values for comparable derivatives is also seen to be normal, with the greatest discrepancies again discernible among the acetates. It is interesting to compare the values A_{Ph} and A_{PhO} for derivatives of glucopyranosylbenzenes and phenyl glucopyranosides, substances

(3) Bonner and Koehler, THIS JOURNAL, **70**, 316 (1948).

(4) Brigl, *Z. physiol. Chem.*, **116**, 1 (1921).

(5) Hudson, THIS JOURNAL, **31**, 66 (1909).

TABLE I

ISOROTATION RULE VALUES FOR ANOMERIC GLUCOPYRANOSE DERIVATIVES[a]

Derivative	$[M]T_D$, °C.	T, °C.	Solvent	Approx. concn., g./100 ml.	A	B
α-D-Glucopyranosylbenzene	21,700	26	MeOH	2	8,370	13,330
β-D-Glucopyranosylbenzene[b,c]	4,960	23	H_2O	3		
α-D-Glucopyranose	20,210	20	H_2O	4	8,420	11,790
β-D-Glucopyranose	3,370	20	H_2O	4		
Methyl α-D-glucopyranoside	30,860	20	H_2O	10	18,750	12,110
Methyl β-D-glucopyranoside	− 6,640	20	H_2O	10		
Phenyl α-D-glucopyranoside	46,100	20	H_2O		32,130	13,970
Phenyl β-D-glucopyranoside	−18,160	20	H_2O	4		
Tetramethyl-α-D-glucopyranosylbenzene[c]	27,600	24	$CHCl_3$	3	11,135	16,465
Tetramethyl-β-D-glucopyranosylbenzene[c]	5,330	19	$CHCl_3$	5		
2,3,4,6-Tetramethyl-α-D-glucopyranose	23,820	20	H_2O	5	3,275	20,545
2,3,4,6-Tetramethyl-β-D-glucopyranose	17,270	20	H_2O	5		
Methyl tetramethyl-α-D-glucopyranoside[c]	36,850	20	H_2O	10	20,595	16,255
Methyl tetramethyl-β-D-glucopyranoside	− 4,340	20	H_2O	4		
Phenyl tetramethyl-α-D-glucopyranoside[c,d]	49,500	22	MeOH	2	35,025	14,475
Phenyl tetramethyl-β-D-glucopyranoside[d]	−20,550	22	MeOH	2		
Tetraacetyl-α-D-glucopyranosylbenzene	38,800	23	$CHCl_3$	4	23,195	15,605
Tetraacetyl-β-D-glucopyranosylbenzene[1]	− 7,590	20	$CHCl_3$	2		
2,3,4,6-Tetraacetyl-α-D-glucopyranose	48,400	20	$CHCl_3$	1	23,815	24,585
2,3,4,6-Tetraacetyl-β-D-glucopyranose	770	20	EtOH	4		
Methyl tetraacetyl-α-D-glucopyranoside	47,280	20	$CHCl_3$	4	26,935	20,345
Methyl tetraacetyl-β-D-glucopyranoside	− 6,590	20	$CHCl_3$	4		
Phenyl tetraacetyl-α-D-glucopyranoside[e]	71,500	20	$CHCl_3$	2	40,525	30,975
Phenyl tetraacetyl-β-D-glucopyranoside[e]	− 9,550	20	$CHCl_3$	2		
Pentaacetyl-α-D-glucopyranose	39,700	20	$CHCl_3$	5	19,110	20,590
Pentaacetyl-β-D-glucopyranose	1,480	20	$CHCl_3$	7		

[a] Values for products other than those reported in this paper or those otherwise specified were obtained from "Polarimetry, Saccharimetry and the Sugars," Nat. Bur. Stand. Circ. C440, U. S. Gov. Printing Office, Washington, D. C., 1942, or from Vogel and Georg, "Tabellen der Zucker und Ihrer Derivate," Julius Springer, Berlin, 1931. [b] Calculated on basis of alcohol-free β-D-glucopyranosylbenzene.[3] [c] Sirup. [d] Voss and Wachs, *Ann.*, **522**, 253 (1936). [e] Montgomery, Richtmyer and Hudson, THIS JOURNAL, **64**, 690 (1942).

differing only in the presence or absence of an oxygen atom at C-1. The A_{PhO} value is seen to be higher than the A_{Ph} by a factor of about two to four. Apparently, the conjugation with the aromatic nucleus of the unshared electrons on the glucosidic oxygen in the phenylglucopyranosides produces a considerably higher partial rotatory contribution of the *A*-portion of the molecule than is the case when the aromatic nucleus is present alone or (as in methyl glucopyranoside derivatives) when the conjugation is lacking.

Experimental Part

Reaction of Tetraacetyl-α-D-glucopyranosyl Bromide with Phenylmagnesium Bromide.—The reaction was performed in the manner described previously,[1] using a six- to eightfold increase in the quantities of starting material. The crude product was isolated, after acetylation, as a thick, amber sirup in 60–80% yield. It was crystallized from a minimum of 2-propanol, yielding tetraacetyl-β-D-glucopyranosylbenzene. The mother liquors were concentrated to dryness, leaving a dextrorotatory sirup. In Table II are tabulated the results of several such preparations.

α-D-Glucopyranosylbenzene.—The entire residual sirup from the fourth run in Table II was deacetylated with potassium in methanol.[3] The potassium-free filtrate was evaporated to a volume of 10 ml. and placed in the refrigerator for twelve hours. There deposited 0.73 g. of crude, tan crystals. Two additional crops totalling 0.20 g. were obtained from the mother liquors. The combined crops were recrystallized from methanol (5 ml.) to give 0.49 g. of colorless prisms, m. p. 184–186°. Further recrystallization gave the pure substance, m. p. 186.5–187°, $[\alpha]^{26}D$ 90.5° (*c*, 2.31, methanol).

TABLE II

YIELDS OF PRODUCTS

Crude yield, Wt., g.	Crude yield, %	Tetraacetyl-β-D-glucopyranosylbenzene, g.	Residual sirup, Wt., g.	Residual sirup, $[\alpha]^{25}D$ ($CHCl_3$), °
19.5	63.6	15.0	4.2	29.5
20.0	65.3	13.5	3.6	37.8
18.3	60.5	11.6	6.7	35.6
34.0	83.2	34.5	5.6	..
7.6	52.3[a]	2.3	4.7	45.3

[a] This run involved the reaction of 2-trichloroacetyl-3,4,6-triacetyl-β-D-glucosyl chloride with phenylmagnesium bromide, and was conducted under similar conditions.

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.26, 59.77; H, 6.98, 6.71. Moles Cpd./Moles $NaIO_4$: Calcd., 0.500. Found, 0.495. Moles Cpd./Moles HCOOH: Calcd., 1.000. Found, 0.966.

When the purified product (76.0 mg.) was oxidized with alkaline potassium permanganate at 100° for forty-five minutes, it was possible to isolate 38.5 mg. (99.8%) of benzoic acid, m. p. 122°, mixed m. p. with an authentic sample 122°.

The mother liquors which produced the original α-D-glucopyranosylbenzene were concentrated to dryness

yielding 3.84 g. of a dark sirup. This was reacetylated with acetic anhydride (35 ml.) containing a drop of sulfuric acid. Isolation of the product in the usual way gave a gummy, semicrystalline mass. This was crystallized from 2-propanol to produce 1.98 g. of tetraacetyl-β-D-glucopyranosylbenzene, m. p. 155–156°, mixed m. p. with a known sample 155–156°. The mother liquors from these crystals yielded 1.66 g. of a dark amber sirup on evaporation. The residual sirups in the remaining Runs of Table I were processed similarly, yielding approximately proportional amounts of α-D-glucopyranosylbenzene.

Tetraacetyl-α-D-glucopyranosylbenzene.—α-D-Glucopyranosylbenzene (256 mg.) was acetylated with acetic anhydride (10 ml.) and pyridine (5 ml.) at 25° for two days. Processing in the usual manner gave 377 mg. (87%) of clear sirup which crystallized spontaneously. Recrystallization from 2-propanol (2 ml.) gave 148 mg. of product, m. p. 68.5–69.5°. Two further recrystallizations gave the pure substance, m. p. 70–71°, $[\alpha]^{23}D$ 95.1° (*c*, 4.43; chloroform).

Anal. Calcd. for $C_{20}H_{24}O_9$: C, 58.70; H, 5.92; CH_3CO, 42.15. Found: C, 58.89, 58.90; H, 5.91, 6.02; CH_3CO, 42.28.

Tetramethyl-α-D-glucopyranosylbenzene.—One gram of α-D-glucopyranosylbenzene was methylated with methyl sulfate (5 ml.) and 30% aqueous sodium hydroxide (14 ml.) according to the procedure of Haworth.[6] There was isolated a sirup, $[\alpha]^{23}D$ 36.5° (*c*, 2.216, chloroform). This was further methylated with methyl iodide (10 ml.) and silver oxide (4.8 g.) according to the method of Purdie and Irvine.[7] There resulted 0.85 g. of a colorless sirup. This was distilled *in vacuo* to yield two fractions, $[\alpha]^{24}D$ 74.7° and 47.2°, suggesting incomplete methylation. The combined fractions were accordingly treated again with methyl iodide and silver oxide. The sirup obtained was distilled (bath temperature 150°, 0.05 mm.) to give 0.44 g. of a colorless, mobile sirup, $[\alpha]^{24}D$ 93.2° (*c*, 3.37, chloroform).

Anal. Calcd. for $C_{16}H_{24}O_5$: C, 64.90; H, 8.15; OCH_3, 41.88. Found: C, 64.64, 64.66; H, 8.18, 8.20; OCH_3, 41.82.

Tetramethyl-β-D-glucopyranosylbenzene.—Tetraacetyl-β-glucopyranosylbenzene (10 g.) was dissolved in methanol (200 ml.) and potassium (0.1 g.) added. After one day the solvent was distilled, and the residue treated with methyl sulfate (50 ml.) and 30% aqueous sodium hydroxide (140 ml.) as before. The product was 6.32 g. of clear, viscous sirup. After drying *in vacuo* over phosphoric anhydride it was remethylated by Purdie and Irvine's procedure to give 5.62 g. of sirup. On standing in a vacuum desiccator this material underwent partial crystallization. The crystalline paste was thinned with absolute ether (3 ml.) and the product filtered and washed with small portions of petroleum ether. The 0.67 g. of solid obtained had m. p. 97–102°. This was recrystallized once from petroleum ether and four times from water to give trimethyl-β-D-glucopyranosylbenzene hydrate, m. p. 106–107°, $[\alpha]^{24}D$ 36.3° (*c*, 2.757, chloroform).

Anal. (of dehydrated substance) Calcd. for $C_{15}H_{22}O_5$: C, 63.90; H, 7.86. Found: C, 64.14, 63.95; H, 7.85, 7.90. Water of hydration: Calcd. 6.0. Found, 7.4.

The ethereal filtrate from these crystals was evaporated at reduced pressure to give a clear sirup, $[\alpha]^{24}D$ 34.5°. This was remethylated again with methyl iodide and silver oxide to yield 4.28 g. of sirup. No further crystalline material was obtained on seeding, so the sirup was distilled. The distillation occurred at 118–120° (0.1 mm.) and 2.86 g. of tetramethyl-β-D-glucopyranosylbenzene was obtained, $[\alpha]^{18}D$ 18.0° (*c*, 5.002, chloroform).

Anal. Calcd. for $C_{16}H_{24}O_5$: C, 64.90; H, 8.15; OCH_3, 41.88. Found: C, 65.00, 64.60; H, 8.30, 8.15; OCH_3, 40.53, 40.40.

(6) Haworth, *J. Chem. Soc.*, **107**, 8 (1915).

(7) Purdie and Irvine, *ibid.*, **83**, 1021 (1903).

Summary

The dextrorotatory sirup obtained as a by-product with tetraacetyl-β-D-glucopyranosylbenzene by the action of phenylmagnesium bromide on tetraacetyl-α-D-glucopyranosyl bromide has been deacetylated to yield α-D-glucopyranosylbenzene. The acetate and methyl ether derivatives of this compound are described, along with tetramethyl-β-D-glucopyranosylbenzene. The application of Hudson's rules of isorotation to the anomeric compounds in this series is discussed.

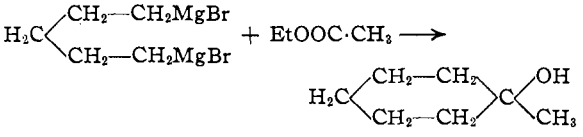
STANFORD, CALIFORNIA RECEIVED JANUARY 27, 1950

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, SCOALA POLITEHNICA]

The Synthesis of Cyclic Alcohols and Olefins by the Interaction of Dimagnesium Halides and Esters

BY COSTIN D. NENITZESCU AND ILEANA NECSOIU

Grignard and Vignon[1] have shown that the dimagnesium derivative of 1,5-dibromopentane reacts with ethyl acetate to give 1-methylcyclohexanol



This type of reaction has received but little attention up to the present, and therefore we have studied the possiblity of its generalization, especially as, today, dibromo derivatives are easily accessible.

(1) V. Grignard and G. Vignon, *Compt. rend.*, **144**, 1358 (1907).

Besides 1,5-dibromopentane, we have studied 1,4-dibromobutane, and made use of esters of saturated monobasic acids, aromatic acids, halogen acids, saturated dibasic acids and 1,2-unsaturated acids. The last three kinds of esters are of special interest, since the corresponding alcohols and/or olefins cannot be prepared by the usual method of treating organomagnesium derivatives with cyclic ketones.

The experimental results are summarized in the tables.

In general the yields exceed 50%, and reach 65% in the case of the esters of saturated acids. Cyclization is preferred over the reaction in which each of the active groups of the dimagnesium