Studies on D-Glucosamine Derivatives. VIII[1]. *1-C-Substituted-1-anilino-1-deoxy-D-arabitols**

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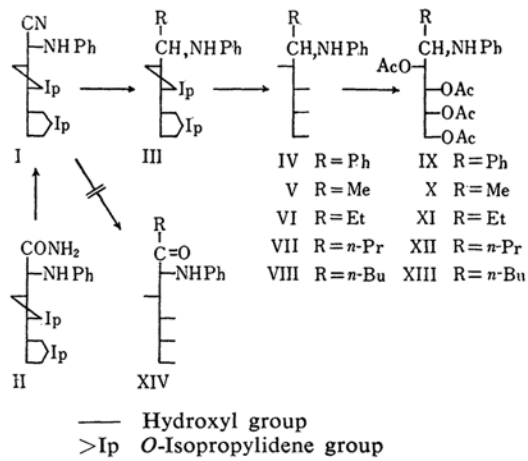
In a previous paper[2], syntheses of 3, 4; 5, 6-di-*O*-isopropylidene-*N*-phenyl-D-glucosaminonitrile (I) and of 3, 4; 5, 6-di-*O*-isopropylidene-*N*-phenyl-D-glucosaminic acidamide (II) have been described. In the present study, the additon of Grignard reagents or alkyl lithiums to the unsaturated function of these compounds is examined, in expectation of obtaining the corresponding 1-*C*-substituted-1-keto-D-glucosamine derivatives (XIV).

Compound I reacted exothermally with Grignard reagents in ether to yield sirupy materials, which on hydrolysis with mineral acid and extraction of the neutrallized hydrolyzate with ethyl acetate gave crystalline materials. These crude crystals were separated into the two diastereoisomers by fractional crystallization from ethyl acetate, of which the one was a dextro-rotating minor product and the other a levo-rotating major product in every case. (In this report, the former is temporarily represented as A-compound and the latter as B-compound.)

The analytical data of these crystals were, however, not consistent with that of XIV. The infrared spectra shown in Fig. 1 indicated the presence of NH and anilino bands at 3300 and 1600 cm^{-1}, but the absence of CN and –CO– bands. It is worthy to note that a few differences between A- and B-compounds in their absorption bands were generally found in the region from 850 to 1050 cm^{-1}. Moreover, the substitution of alkyls to the C-2 of I was deduced from the fact that the diastereoisomers (IV-A and IV-B) obtained from I and phenylmagnesium bromide gave benzoic acid in 70% yield by alkalline permanganate oxidation. The structures of these crystals were, therefore, assigned to the 1-*C*-substituted-1-anilino-1-deoxy-D-arabitols (IV–VIII).



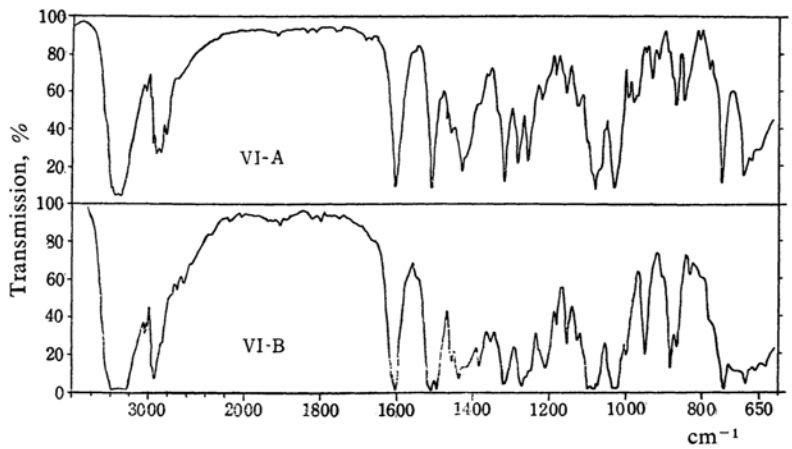


Fig. 1.

* A part of this was presented at the 13th Annual Meeting of the Chemical Society of Japan, Tokyo, 1960.

1) Part VII of this series, This Bulletin, 35, 467 (1962).
2) J. Yoshimura, ibid., 33, 1404 (1960).

These arabitols were converted to the corresponding tetraacetates (IX–XIII) by treating with acetic anhydride in dry pyridine. The melting points, rotation values and analytical data of these diastereoisomeric arabitols and the acetates are listed in Tables I and II.

The reaction products between I and alkyl lithiums were also syrupy, except for 1-*C*-phenyl-1-anilino-1-deoxy-3,4; 5,6-di-*O*-isopropylidene-D-arabitol (III; R=phenyl) obtained from I and phenyl lithium, and each crude syrup was hydrolyzed to the two corresponding diastereoisomers, in a manner similar to that in the case of the Grignard reactions. However, the minor products were the B-compounds and the major, the A in this case. A comparison of the yields of both the A- and B-compounds is made in Table III.

To pursue the whereabouts of the nitrile group in I, the cyano ions in the reaction mixture of I and alkyl lithiums, after having been decomposed with water and extracted with ether, were examined qualitatively and quantitatively. It was found that the water layer showed the positive blue coloration of cyano ions with cupric acetate and benzidine, and that the amount were determined, by volumetric titration using silver nitrate, to correspond to the yields of the arabitols (about 60%) in every case.

The above results indicate that the reaction of I with the Grignard reagents or alkyl lithiums gives rise to the replacement of the nitrile group by the alkyls of these reagents instead of the addition to its unsaturated bond. Although this type of reactions has not been

Table I. 1-*C*-Substituted-1-anilino-1-deoxy-D-arabitols

Compound	Formula (mol. wt.)	M. p., °C	$[\alpha]_D$ in methanol	Carbon, %		Hydrogen, %		Nitrogen, %	
				Found	Calcd.	Found	Calcd.	Found	Calcd.
IV-A	$C_{17}H_{21}O_4N$ (303.3)	191~192	+ 2.7	67.34	67.31	7.17	6.98	4.50	4.62
IV-B	$C_{17}H_{21}O_4N$ (303.3)	164~165	− 4.5	67.57	67.31	7.22	6.98	4.55	4.62
V-A	$C_{12}H_{19}O_4N$ (241.3)	128~129	+84.1	59.52	59.73	7.97	7.94	6.00	5.81
V-B	$C_{12}H_{19}O_4N$ (241.3)	160~161	−41.2	59.83	59.73	8.16	7.94	5.98	5.81
VI-A	$C_{13}H_{21}O_4N$ (255.3)	131~132	+76.9	61.49	61.15	8.39	8.29	5.55	5.49
VI-B	$C_{13}H_{21}O_4N$ (255.3)	161~161.5	−38.5	61.08	61.15	8.39	8.29	5.40	5.49
VII-A	$C_{14}H_{23}O_4N$ (269.3)	134~136	+67.6	62.61	62.43	8.81	8.61	5.17	5.20
VII-B	$C_{14}H_{23}O_4N$ (269.3)	160~161	−18.7	62.24	62.43	8.78	8.61	5.05	5.20
VIII-A	$C_{15}H_{25}O_4N$ (283.4)	126~128	+72.5	63.14	63.58	8.63	8.89	5.06	4.94
VIII-B	$C_{15}H_{25}O_4N$ (283.4)	154~155	−13.0	63.57	63.58	9.14	8.89	4.88	4.94

Table II. 1-*C*-Substituted-1-anilino-1-deoxy-2,3,4,5-tetra-*O*-acetyl-D-arabitols

Compound	Formula (mol. wt.)	M. p., °C	$[\alpha]_D$ in methanol	Carbon, %		Hydrogen, %		Nitrogen, %	
				Found	Calcd.	Found	Calcd.	Found	Calcd.
IX-A	$C_{25}H_{29}O_8N$ (471.5)	56~57	+80.5	63.51	63.68	6.35	6.20	2.80	2.97
IX-B	$C_{25}H_{29}O_8N$ (471.5)	Sirup	+44.6	63.44	63.68	6.47	6.20	2.72	2.97
X-A	$C_{20}H_{27}O_8N$ (409.5)	83~85	+60.3	58.34	58.67	6.92	6.65	3.48	3.42
X-B	$C_{20}H_{27}O_8N$ (409.5)	96~98	+21.7	58.59	58.67	6.53	6.65	3.65	3.42
XI-A	$C_{21}H_{29}O_8N$ (423.5)	81~82	+84.0	59.25	59.56	6.77	6.90	3.35	3.31
XI-B	$C_{21}H_{29}O_8N$ (423.5)	86~87	+42.0	59.61	59.56	6.88	6.90	3.18	3.31
XII-B	$C_{22}H_{31}O_8N$ (437.5)	52~53	+10.2	60.62	60.40	7.31	7.14	3.14	3.20
XIII-B	$C_{23}H_{33}O_8N$ (451.5)	Sirup	+14.0	61.32	61.18	7.30	7.39	3.11	3.10

Table III. Yield (%) of the A- and B-compounds in Grignard and alkyl lithium reactions

1-*C*-Substituted group	Grignard reagent		Alkyl lithium	
	A-Compd.	B-Compd.	A-Compd.	B-Compd.
Phenyl	2.7	51.7	63.0	0
Methyl	3.5	48.2	53.7	3.4
Ethyl	3.8	51.8	58.5	5.6
n-Propyl	4.2	50.2	55.2	4.8
n-Butyl	4.2	52.6	60.5	5.1

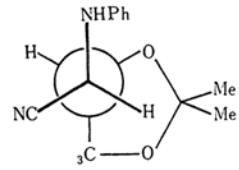
exhaustively investigated, it appears to be fairly general for α,α-disubstituted cyanohydrins[3] and α-aminonitriles[4], among which is I. Kharasch[5] assumed that in all these cases the bond between the nitrile group and the others has a rather high degree of ionic character, with the negative end of the dipole at the cyano group, but the radicals attached to the cyano group are rather weakly electronegative.

On the other hand, the reaction of I with the Grignard reagents led mainly to B-compounds, while alkyl lithiums lead to the A. Although a few examples[6] have been known in which organomagnesium and organolithium compounds showed sterically different behavior, no reports relating to such a characteristic in asymmetric induction has appeared up to the present.

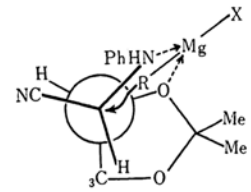
The absolute configuration at C-1 of the diastereoisomers must be determined by another method. However, it seems likely that A-compounds have a glucosamino-structure and the B-compounds a mannosamino-structure, as the former has the same dextro-rotatory character as I. Bonner[7] has already proved that the more dextro-rotatory one of the two diastereoisomers of 1-*C*-phenyl-D-pentitol obtained from 3, 4; 5, 6-diisopropylidene-D-glucosamine and phenylmagnesium bromide, possesses a glucostructure, and the other a manno-structure.

The most stable configuration (XV) of the reaction center of I shown by Newman's representation[8] suggests that it is very reasonable to assume the rigid complex model (XVI) in the transition state, as proposed by Cram et al.[9] as a result of extensive studies on asymmetric induction. Thus, it is concluded that rather polar Grignard reagents reacted smoothly, accompanying Walden inversion[10], to afford a mannosamino-structure.

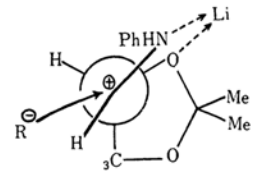
If the nitrile group is eliminated initially through either ionic or free radical mechanism, the alkyl group will predominantly attack from the direction of the previously existing nitrile group on the transition state (XVII), to afford



XV



XVI



XVII

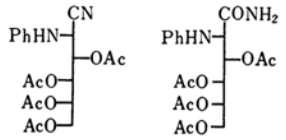
a glucosamino-structure. This mechanism is very suitable to explain the fact that the reaction of I and alkyl lithiums afforded the glucosamino-structure, but the reason for the distinctly different behavior between organomagnesium and organolithium compounds in the reaction described in this paper remains ambiguous. The rather covalent character of the simple organolithium compound, however, has been provided by the non-conductance of solutions of ethyl lithium in benzene[11] and low dipole moment of butyl lithium[12]. This character seems likely to prevent the Walden inversion through the formation of XVI.

The reaction of II with Grignard reagents or alkyl lithiums in ether afforded unchanged II over 80%. Even though the reaction was performed in benzene at 100°C for four hours, 50~56% of II was recovered, and the mother liquor produced a small amount of the D-arabitols when treated in the usual manner. It is interesting that the B-compounds were obtained in the former case and the A-compounds in the latter. From this fact, it can be deduced that the amide II was initially dehydrated to the nitrile[13].

As expected XIV was not obtained in the above-mentioned methods, Hoesch's method[14]

3) T. Asahina et al., *J. Pharm. Soc. Japan*, **494**, 19 (1923); J. Guerden, *Bull. acad. roy. Belg. Classe sci.*, (5), **11**, 701 (1925).
4) P. Bruylants, ibid., (5), **11**. 261 (1925); M. Velghe, ibid., (5), **11**, 301 (1925); A. Christian, *Bull. soc. chim. Belg.*, **33**, 483, (1924); T. S. Stevens et al., *J. Chem. Soc.*, **1931**, 2568; **1932**, 2607; H. M. Taylor and C. R. Hauser, *J. Am. Chem. Soc.*, **82**, 1 (1960).
5) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances", Prentice-Hall, New York (1954).
6) E. P. Kohler, *Am. Chem. J.*, **31**, 655 (1904); **38**, 511 (1907); A. Luttringhaus, *Ber.*, **67**, 1062 (1934).
7) W. A. Bonner, *J. Am. Chem. Soc.*, **73**, 3126 (1951).
8) M. S. Newman, *J. Chem. Educ.*, **32**, 344 (1955).
9) D. J. Cram and K. R. Kopecky, *J. Am. Chem. Soc.*, **80**, 2737, 2748 (1959).
10) C. G. Swain and H. B. Boyles, ibid., **73**, 870 (1951).
11) F. Hein et al., *Z. anorg. u. allgem. Chem.*, **141**, 161 (1924).
12) M. T. Rogers and A. Young, *J. Am. Chem. Soc.*, **68**, 2748 (1946).
13) Ramart-Lucas et al., *Compt rend.*, **185**, 282 (1927); (Mme) Bruzau, *Ann. Chim.*, (11), I, 257 (1934).
14) K. Hoesch, *Ber.*, **60**, 389, 2537 (1927).

for the synthesis of ketones by condensation of a nitrile with phenols was examined with regard to 3, 4, 5, 6-tetra-*O*-acetyl-*N*-phenyl-L-glucosaminonitrile (XVIII)[2]. The mixed solution of XV, fused zinc chloride in chloroform and phenol or catechol in ether was saturated with hydrogen chloride at 0°C and left to stand 2 weeeks in a refrigerator. However, the product obtained was the corresponding acidamide (XIX). This result indicates that the aminonitrile XVIII has a very weak function as a nitrile.



XVIII XIX

Experimental

General Procedure for the Reaction of 3, 4; 5, 6-Di-*O*-isopropylidene-*N*-phenyl-D-glucosaminonitrile (I) with Organometallic Compounds.—To an ice-cold ether solution of the desired Grignard reagents or alkyl lithiums prepared from 0.045 mol. of the corresponding halides and 0.045 mol. of magnesium ribbon or 0.09 mol. of metal lithium was added 5 g. (0.015 mol.) of I in three portions with stirring. After refluxing on a water bath for 3 hr., the cold reaction mixture was cautiously ponred into ice-water, and precipitates were dissolved by the addition of 2 N hydrochloric acid in the case of Grignard reactions.

The aqueous layer was separated from the ether layer and extracted three times with 30 ml. of ether. The combined ether solution was washed with water, dried over anhydrous sodium sulfate, and concentrated in vacuo. The resultant sirup was hydrolyzed in 50% ethanol containing 2 N hydrochloric acid at 60°C for 40 min. and then concentrated in vacuo. The hydrolysis of the isopropylidene group was also accomplished with a small amount of concentrated hydrochloric acid at room temperature for 20 min.

The sirup obtained from acid hydrolyzate was dissolved in water; the small amount of brown oily substance remained was then filtered off through active carbon on filter paper, and the pH of the filtrate was adjusted to 10 with ammonia. The alkaline solution was extracted three times with 50 ml. of ethyl acetate, and the extracts were washed with water and dried with anhydrous sodium sulfate. After evaporation of the solvent under reduced pressure, the crude 1-*C*-substituted-1-anilino-1-deoxy-D-arabitols obtained (IV—VIII) were fractionally crystallized from ethanol or ethyl acetate.

In general, the crude crystals obtained by the Grignard reactions afford the pure B-compound as plates after one recrystallization in ethyl acetate. After repeated separation of the B-compound, a small amount of the A-compound was obtained as needles. In the case of alkyl lithiums, the crude material were dissolved in a suitable amount of hot ethanol, and a small amount of the B-compound was slowly deposited by leaving it to stand at room temperature.

The amounts of A- and B-compounds in the small amount of remaining crystals were determined from its rotational values and were added to each weight of the separated pure substances.

The physical constants of the arabitols are listed in Table I, and a comparison of the yields of the both diastereoisomers is made in Table III.

1-*C*-Phenyl-1-anilino-1-deoxy-2, 3; 4, 5-Di-*O*-isopropylidene-D-arabitol (III, R=Phenyl). — To an ice-cold ether solution of phenyl lithium prepared from 3.9 ml. of bromobenzene was added 4.2 g. of I with stirring. After refluxing 3 hr. on a water bath, the cooled reaction mixture was poured into ice water. The aqueous layer was then separated from the ether layer and extracted with ether. The volumetric titration of cyano ions in the water layer with 5% silver nitrate was shown to be 62.5% of the theoretical value.

The combined ether solution was washed twice with water, dried over anhydrous sodium sulfate and concentrated in vacuo to dryness. The residual sirup (4.7 g.) afforded colorless needless from ethanol-petroleum ether. Yield, 2.0 g., m. p. 88~89°C.

Found: C, 71.60; H, 7.52; N, 3.73. Calcd. for $C_{23}H_{29}O_4N$ (383.5): C, 72.03; H, 7.62; N, 3.65%.

One gram of the above crystal was dissolved in 2 ml. of concentrated hydrochloric acid and diluted with 30 ml. of water after having been left to stand for 20 min. at room temperature. The resultant clear solution was neutralized with an excess amount of ammonia, and the crystalline materials separated were collected and recrystallized from methanol to afford 0.72 g. of pure 1-*C*-phenyl-1-anilino-1-deoxy-D-arabitol (IV-A), m. p. 191~192°C.

The sirup obtained from the mother liquor of III (R=phenyl) was treated in exactly the same manner as described in the general procedure, and afforded 1.1 g. of IV-A (total yield, 63.0%).

Acetylation of 1-*C*-Substituted-1-anilino-1-deoxy-D-arabitols.—A mixture of 2 g. of each arabitol, 10 ml. of acetic anhydride and 10 ml. of dry pyridine was left to stand overnight at room temperature and then poured into ice-water. The solution was extracted with chloroform in the usual manner. The sirup obtained by evaporation of the solvent was crystallized from ethanol-petroleum ether.

The yield was generally 85~90% of the theoretical value. The physical constants of these tetraacetates are presented in Table II.

Reaction of 3, 4; 5, 6-Di-*O*-isopropylidene-*N*-phenyl-D-glucosaminoamide (II) and Organometallic Compounds. — i) To an ice-cold ether solution of ethylmagnesium bromide prepared from 3.5 ml. of ethyl bromide was added 5 g. of II with stirring. After removing the solvent, 50 ml. of dry benzene was added, and the mixture was refluxed for 3 hr. in an oil-bath at 100°C. The cooled reation mixture was poured into ice-water and treated in the usual manner. The sirup obtained was dissolved into a small amount of ethanol,

and light petroleum ether was added just before clouding took place. After keeping it in a refrigerator overnight, the unchanged II (3.0 g.) was filtered off. The mother liquor was concentrated in vacuo, and the residual sirup afforded crystals of VI-B, m. p. 160°C, 150 mg., after treatment in the manner described in the general procedure. These showed no depression on admixture with authentic samples.

ii) A mixture of II (5.0 g.) and phenyl lithium prepared from 5 ml. of bromobenzene in ether was refluxed for 4 hr. on a water-bath and treated in the same manner as has been described above. Four grams of unchanged II and 60 mg. of IV-A, m. p. 190~191°C, were obtained, and the latter showed no depression on admixture with an authentic sample.

iii) A mixture of 2.5 g. of 3,4; 5,6-di-*O*-isopropylidene-*N*-phenyl-L-glucosaminoamide[2] (L-form of II) and phenylmagnesium bromide prepared from 2.4 ml. of bromobenzene in benzene was refluxed on an oil-bath for 3 hr. and then treated in the usual manner. 1.3 g. of unchanged starting material was filtered off, and the residual sirup obtained from the liquor was re-dissolved in dry benzene, and hydrogen chloride passed into it. The resulted precipitates, when treated in the usual manner, afforded crystalline 1-*C*-phenyl-1-anilino-1-deoxy-L-arabitol, (L-form of IV-B), m. p. 163~165°C, 38 mg., $[\alpha]_D^{25}$ +3.5° (*c* 0.55, methanol) and several milligrams of its diastereoisomer, m. p. 189~191°C.

Found of the former: C, 67.02; H, 7.11; N, 4.66. Found of the latter: C, 66.62; H, 7.29; N, 4.69. Calcd. for $C_{17}H_{21}O_4N$: C, 67.31; H, 6.98; N, 4.62%.

An Attempt at Using the Hoesch Synthesis on 3, 4, 5, 6-Tetra-*O*-acetyl-*N*-phenyl-L-glucosaminonitrile (XVIII) and Catechol. — A clear mixed solution of 2,4 g. of XVIII, 0.65 g. of catechol in 10 ml. of chloroform and 0.7 g. of anhydrous zinc chloride in 20 ml. of ether was saturated with hydrogen chloride at 0°C and stored in a refrigerator. The white sirupy materials separated were gradually crystallized. After being left to stand for two weeks, the supernatant liquid was decanted, and the crystals were rinsed twice with ether, then dissolved in chloroform. The chloroform solution was washed with a small amount of diluted ammonia and water and then concentrated to dryness in vacuo. The remaining material was crystallized from ethanol. Yield 1.5 g., m. p. 160~162°C, $[\alpha]_D^{27}$ −18.5° (*c* 0.67, chloroform).

Found: C, 54.42; H, 6.07; N, 6.43. Calcd. for XIX, $C_{20}H_{26}O_9N_2$ (438.4): C, 54.79; H, 5.98; N, 6.39%.

Summary

In the reaction of 3, 4; 5, 6-di-*O*-isopropylidene-*N*-phenyl-D-glucosaminonitrile and Grignard reagents or alkyl lithiums, the nitrile group was substituted for alkyls to yield each pair of diastereoisomers of the 1-*C*-substituted-1-ailino-1-deoxy-D-arabitols. The levo-rotating diastereoisomer was, moreover, exclusively predominant in the former case, and the dextro-rotating one in the latter.

The reaction mechanism for the above asymmetric induction was discussed.

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