UDC 547.314.07

151. Issei Iwai and Kazuo Tomita : Studies on Acetylenic Compounds. XIX. A New Method for Synthesis of DL-Arabinose.*1

(*Takamine Research Laboratory, Sankyo Co., Ltd.**2)

In the previous papers,[1,2] Iwai and Iwashige reported the total synthesis of four DL-pentoses from 1,1-diethoxy-5-tetrahydropyran-2-yloxypent-3-yn-2-ol. It was anticipated that DL-ribose and DL-arabinose would be obtained as the final products from 5-ethoxy-4-penten-2-yn-1-ol by catalytic hydrogenation, followed by *cis*-hydroxylation, but only *dl*-arabinose was obtained.

The route for the synthesis of DL-arabinose was planned as shown in Chart 1.

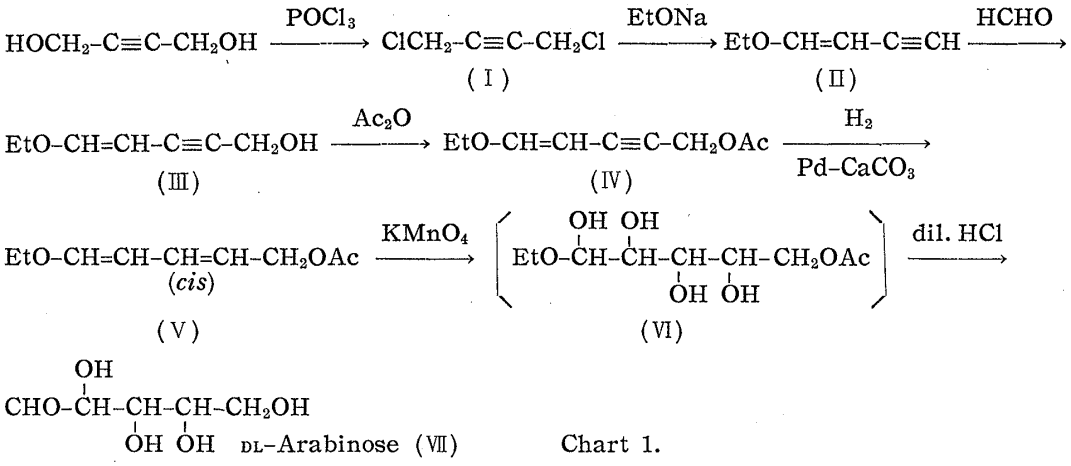

Chart 1.

First, 1,4-dichloro-2-butyne[3] (I) was obtained by the chlorination of 2-butyne-1,4-diol with phosphoryl chloride in a good yield. The formaldehyde regenerated from paraform aldehyde was introduced into the dry tetrahydrofuran solution of 4-ethoxy-3-buten-1-yn-1-yl magnesium bromide[4] (II) and formed 5-ethoxy-4-penten-2-yn-1-ol (III) as a viscous oil. The alcohol is easily polymerized even at room temperature. The partial hydrogenation of the alcohol did not give the corresponding diene-alcohol even when using a large amount of the Lindlar catalyst. Therefore, the reaction residue containing the alcohol (III) was acetylated by the usual method with acetic anhydride and pyridine to give 5-ethoxy-4-penten-2-yn-1-ol acetate (IV), b.$p_{0.03}$ 72~75° (bath temp.), and the infrared spectrum of (IV) showed absorptions at 2230 (-C≡C-), 1630 (-CH=CH-), 1760 (-OAc), and 1110 (-O-) cm^{-1}. Partial hydrogenation of the acetylenic acetate (IV), using palladium-calcium carbonate as catalyst, furnished the corresponding 2-*cis*-diene compound (V), b.$p_{0.03}$ 78~83° (bath temp.), in a good yield. The analytical result and the infrared absorptions at 1650 and 1610 cm^{-1}, due to conjugated diene structure, agreed well with those of 2-*cis*-5-ethoxy-2,4-pentadien-1-ol acetate.

The compound (V) was hydroxylated with the aqueous solution of potassium permanganate. After filtration, potassium ion was removed by passing through a cation exchange resin column (Amberlite IRC-50). The neutral solution was hydrolyzed with

---

*1 Part XVIII: This Bulletin, **9**, 492 (1961).

*2 Nishi-shinagawa, Shinagawa-ku, Tokyo (岩井一成, 富田和男).

1) I. Iwai, T. Iwashige: This Bulletin, **9**, 316 (1961).
2) I. Iwashige: *Ibid.*, **9**, 492 (1961).
3) N. Sampei, Y. Endo: Ann. Report Takamine Lab., **11**, 41 (1959).
4) A.W. Johnson: J. Chem. Soc., **1946**, 1012.

hydrochloric acid, the solution was passed through Amberlite IR-4B, and evaporated to dryness in a reduced pressure. A red brown syrupy residue was obtained, which was strongly possitive to orcinol, the typical test for pentose. By paper partition chromatography,*3 it showed only one spot at Rf 0.24, while a mixture of D-arabinose and the residue showed the same Rf value (0.24) and D-arabinose showed a different Rf value (0.27). The crude pentose was chromatographed on a Dowex-1 column (borate form)[5] and only one fraction showing positive orcinol test was obtained. From this fraction, a pentose showing the same Rf value (0.28) as that of D-arabinose was obtained by the method of Zill and Khym.[6] Furthermore, the infrared spectrum of this pentose tetrapropionate[7] was identical with that of D-arabinose tetrapropionate in chloroform solution as shown in Fig. 1.

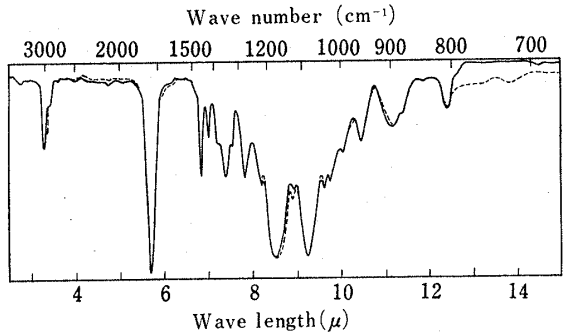

Fig. 1. Infrared Absorption Spectra of DL-Arabinose Tetrapropionate and D-Arabinose Tetrapropionate ($CHCl_3$ solution)

—— DL-Arabinose tetrapropionate
------ D-Arabinose tetrapropionate

From these results, the pentose obtained was confirmed as DL-arabinose.

Theoretically, it is possible to consider formation of C-3-OH/C-4-OH *erythro* and *threo* by the *cis*-hydroxylation of (V). The formation of DL-ribose for the former and DL-arabinose for the latter may be expected. The fact that only DL-arabinose has been obtained is very interesting.

Hockett, *et al.*[8] reported that D-arabinal was hydroxylated mainly to D-arabinose by hydrogen peroxide in *tert*-butanol, in the presence of osmium tetroxide. Bergmann, *et al.*[9] also obtained mannose from glucal by *trans*-hydroxylation using perbenzoic acid. In these cases, it may be expected that D-ribose and D-glucose would also be produced but they did not obtain these compounds. Therefore, it was concluded that a similar stereospecific reaction proceeded and only DL-arabinose was produced.

Experimental

1,4-Dichloro-2-butyne (I)——N,N-Dimethylaniline (420 g.) was added dropwise into the benzene (200 cc.) solution of butynediol (200 g.) and $POCl_3$ (420 g.), with stirring, keeping the temperature below 40° with ice cooling. After the cooling-bath was removed, the temperature was raised slowly to 70° and the mixture was stirred for 1 hr. at this temperature. The reaction mixture was poured into water (600 cc.) and the organic layer was separated. The aqueous layer was extracted with benzene. The combined organic layer was washed, dried, and distilled to give 1,4-dichloro-2-butyne (I) as an almost colorless oil (194 g.), b.p_{29} 74~75°.

1-Ethoxy-1-buten-3-yne (II)——1,4-Dichloro-2-butyne (73.5 g.) was added to a solution of EtONa prepared from Na (30 g.) and dehyd. EtOH (550 cc.). The mixture was refluxed for 1 hr. with stirring. The solution was poured into ice-water (2.5 L.) and extracted with Et_2O. The extract was

*3 Toyo Roshi No. 50. Solvent: BuOH-AcOH-H_2O (4:1:5). Temp.: 20°. Time: 16 hr. Detection: Partridge reagent.

5) J.X. Khym, L.P. Zill: J. Am. Chem. Soc., **74**, 2090 (1952); K. Mori, M. Nakamura: Nippon Nogei-Kagaku Kaishi, **34**, No. 4, A5 (1960).
6) L.P. Zill, J.X. Khym, G.M. Cheniae: J. Am. Chem. Soc., **75**, 1339 (1953).
7) C.D. Hurd, K.M. Gordon: *Ibid.*, **63**, 2657 (1941).
8) R.C. Hockett, S.R. Millman: *Ibid.*, **63**, 2587 (1941).
9) M. Bergmann, H. Schotte: Ber., **54**, 440 (1921).

washed, dried over Na_2SO_4, and evaporated. The Et_2O residue was distilled in a reduced pressure to give 1-ethoxy-1-buten-3-yne (II) (31.7 g.), b.p_{35} 56~58°, n_D^{18} 1.4738 (Johnson reported b.p_{15} 42°, n_D^{19} 1.4759). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3370, 2120(-C≡CH), 1650(-CH=CH-), 1120(-O-).

5-Ethoxy-4-penten-2-yn-1-ol (III)——A solution of 1-ethoxy-1-buten-3-yne (17 g.) in dry tetrahydrofuran (100 cc.) was added dropwise with stirring into a Grignard reagent prepared from Mg (4.3 g.) and EtBr (20 g.) in tetrahydrofuran (120 cc.). The mixture was kept at about 40°. After 1 hr.'s stirring at room temperature, HCHO gas, which was generated from dry paraformaldehyde (8 g.) by heating at 180°, was introduced into the reaction mixture with a stream of N_2 under ice-cooling. After stirring at room temperature for 2 hr., the resulting complex was decomposed with saturated aqueous NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layer was washed, dried over K_2CO_3, and the solvent was distilled off in a reduced pressure. The residue (IIIa) was distilled *in vacuo* to give 5-ethoxy-4-penten-2-yn-1-ol (III) (3.5 g.), b.$p_{0.01}$ 63~73° (bath temp.), n_D^{19} 1.5207. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3500(-OH), 2220(-C≡C-), 1660(-CH=CH-), 1110(-O-).

If the bath temperature was raised up to 120°, the residue suddenly turned into charcoal-like mass. The compound (III) easily polymerized in the air. It was hard to purify by distillation and a large amount of brown resin remained, which did not distill out even at 0.001 mm. Hg pressure at 110°.

Hydrogenation of (III)——A solution of 5-ethoxy-4-penten-2-yn-1-ol (730 mg.) in AcOEt (30 cc.) was shaken in H_2 at atmospheric pressure, in the presence of a large amount of Lindlar catalyst (1.5 g.) until 1 mole of H_2 had been absorbed (6 hr.) The solution was filtered to remove the catalyst and evaporated in a reduced pressure to leave a brown syrup. The syrup was distilled *in vacuo* to give a pale yellow liquid, b.$p_{0.01}$ 65~75° (bath temp.) (25 mg.) and a large amount of resin remained. The distillate turned to a brown syrupy oil in the air and its IR spectrum showed no characteristic absorption band for diene structure.

5-Ethoxy-4-penten-2-yn-1-ol Acetate (IV)——The residue (IIIa) (15.6 g.) containing (III), prepared from (II) (14.4 g.) as mentioned above, was added to a solution of Ac_2O (15.6 g.) in dry pyridine (40 cc.), the mixture was allowed to stand for 3 days at room temperature, and then poured into ice-water containing HCl. The separated oil was extracted with Et_2O, the Et_2O extract was washed with 5% $NaHCO_3$ and water, and dried over Na_2SO_4. After evaporation of Et_2O, the brown syrupy residue was ditsilled *in vacuo* to give 5-ethoxy-4-penten-2-yn-1-ol acetate, b.$p_{0.03}$ 72~75° (bath temp.) (6.7 g.), n_D^{26} 1.4872. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2230(-C≡C-), 1630(-CH=CH-), 1760(OAc), 1110(-O-).

The pale yellow oil turned gradually brown in the air.

2-*cis*-5-Ethoxy-2,4-pentadien-1-ol Acetate (V)——A solution of 5-ethoxy-4-penten-2-yn-1-ol acetate (IV) (3.20 g.) in AcOEt (100 cc.) was hydrogenated in the presence of Lindlar catalyst (6.5 g.) at atmospheric pressure. When 1 molar equivalent of H_2 was absorbed, the reaction was stopped. The solution was filtered to remove the catalyst and the solvent was evaporated in a reduced pressure at room temperature. The residue was distilled *in vacuo* to give 2-*cis*-5-ethoxy-2,4-pentadien-1-ol acetate (V), (2.80 g.) as a pale yellow oil, b.$p_{0.03}$ 78~83° (bath temp.). n_D^{27} 1.4762. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1650, 1610(-CH=CH-), 1745(-OAc), 1110(-O-). *Anal.* Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.78; H, 8.23.

DL-Arabinose (VII)——2-*cis*-5-Ethoxy-2,4-pentadien-1-ol acetate (2.55 g.) was suspended in water (50 cc.) by vigorous stirring. A cold solution of $KMnO_4$ (3.16 g.) in H_2O (160 cc.) was added dropwise to the suspension during 1.5 hr. at 0° to 1° under ice-salt cooling. The mixture was then allowed to rise to room temperature. After the precipitated MnO_2 had coagulated, it was filtered off and washed with a small amount of water. The combined aqueous solution was passed through a cation-exchange resin (Amberlite IRC-50) to remove K ion. The effluent (260 cc.) was treated with conc. HCl (2.6 cc.) and hydrolysis was allowed to proceed at room temperature for 2 days. The acidic solution was passed through an anion exchange resin (Amberlite IR-4B) and the neutral solution obtained was evaporated to dryness at room temperature in a reduced pressure to leave a red brown syrup (0.95 g.), which gave a positive orcinol test, showing the presence of pentose. By paper partition chromatography, the substance showed one spot (Rf 0.24), while D-arabinose and D-ribose employed as control showed different Rf values (0.27 and 0.32, respectively).

The residue (0.90 g.) was dissolved in 0.1 *M* $K_2B_4O_7$ (25 cc.) and passed through a column (0.9 $cm.^2$ × 15 cm.), filled with ion-exchange resin, Dowex-1 (borate form), and the column was eluted with 0.025 *M* $K_2B_4O_7$. When about 1.3 L. of 0.025*M* eluting agent had flowed, a fraction showing a positive orcinol test was not obtained. The eluting agent was switched to 0.05*M* $K_2B_4O_7$. After about 1.4 L. of the eluting agent (0.05*M*) had been used, a fraction showing positive orcinol test came out. The fractions (ca. 1.5 L.) were collected and treated with Dowex-50 to remove K ion. When the solution was concentrated *in vacuo* at room temperature, a white crystalline residue was obtained. The residue was dissolved in MeOH (400 cc.) and evaporated *in vacuo* at room temperature. An almost colorless syrupy residue (130 mg.) was obtained. The paper partition chromatography of the

residue showed only one spot (Rf 0.28) and *d*-arabinose employed as control gave a spot with the same Rf value (0.28).

A solution of the residue (120 mg.) and propionic anhydride (630 mg.) dissolved in pyridine (860 mg.) was left at room temperature for 5 days. The reaction mixture was poured into ice-water and extracted with Et_2O. The Et_2O extract was washed successively with 10% HCl and water, dried over Na_2SO_4, and evaporated. The residue was distilled *in vacuo* and gave a colorless viscous oil (200 mg.), b.$p_{0.0003}$ 160~165° (bath temp.), whose analytical values agreed with those for arabinose tetrapropionate. The infrared spectrum of this oil in $CHCl_3$ solution was identical with that of D-arabinose tetrapropionate prepared analogously. *Anal.* Calcd. for $C_{17}H_{26}O_9$: C, 54.54; H, 7.00. Found: C, 54.59; H, 6.96.

The authors wish to express their deep gratitude to Prof. K. Tsuda, The Institute of Applied Microbiology, University of Tokyo, and to Mr. M. Matsui, Director of this Laboratory, for their kind guidance and encouragement throughout the course of this investigation. The measurement of infrared spectra was carried out by Messrs O. Amakasu and H. Higuchi, and by Miss N. Sawamoto, and microanalyses were made by Messrs. T. Onoe and H. Nagashima, and Misses C. Furukawa and H. Ohtsuka.

Summary

DL-Arabinose was stereospecifically synthesized starting from 5-ethoxy-4-penten-2-yn-1-ol, which was prepared by the Grignard reaction of formaldehyde with 4-ethoxy-3-buten-1-yn-1-yl magnesium bromide.

(Received January 23, 1961)

UDC 547.94 : 582.675

152. Tohru Hino: Synthetic Approaches to Calycanthaceae Alkaloids. II.*1 A Synthesis of 1,1′-Dimethyl-3,3′-bis(2-aminoethyl)-3,3′-bioxindole.

(*Faculty of Pharmaceutical Sciences, University of Tokyo**2)

The structure of calycanthine,[1] the main alkaloid of Calycanthaceae plants, has been investigated by Barger,[1a] Manske,[1b] Späth,[1c] and others, since its first isolation by Eccles in 1888. In 1954, Robinson and Teuber[2] pointed out that the previously suggested structure for the alkaloid appeared to be unnecessarily complicated and proposed its structure as (I), an N-methyltryptamine dimer, by clarifying the structure of calycanine, a degradation product of the alkaloid, and by the biogenetic consideration. Recently, Woodward, Harley-Mason, *et al.*[3] proposed a new structure (II), derived from β,β-coupling of N-methyltryptamine as in the case of Robinson's structure, by the synthetic proof of calycanine and conformational consideration with biogenetic speculation. The structure (II) was proved by X-ray work by Glasgow group.[4]

---

*1 The paper by T. Hino and T. Shioiri (This Bulletin, 8, 839 (1960)) is designated as Part I of this series.

*2 Hongo, Tokyo (日野 亨).

1) *a*) G. Barger, *et al.*: J. Chem. Soc., **1939**, 510; *b*) R.H.F. Manske, *et al.*: Can. J. Research, **B16**, 432 (1938); **B17**, 293 (1939), **B24**, 224 (1946); *c*) E. Späth, K. Eiter, *et al.*: Monatsh. **79**, 11, 17, 22 (1948); **80**, 607 (1949); **81**, 404 (1950); **83**, 916 (1952). cf. Léo Marion; R.H.F. Manske, H.L. Holmes: "The Alkaloids," Vol. II, Chapter XIII, pp. 434 (1952). Academic Press Inc., New York. J.E. Saxton: Quart. Rev., **10**, 108 (1956).

2) R. Robinson, H.J. Teuber: Chem. & Ind. (London), **1954**, 783.

3) R.B. Woodward, J. Harley-Mason, *et al.*: Proc. Chem. Soc., **1960**, 76.

4) T.A. Hamor, J.M. Robertson, *et al.*: *Ibid.* **1960**, 78.