2) The dye which combined with sample reaches maximum value at a certain pH value.

3) Dissociation constants of a sample and of a dye should preferably be as large as possible.

4) The calibration curve is linear.

5) In general, the ratio of combination of a sample and a dye is nearly in integral ratio, such as 1 : 1.

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Yoshio Ban and Takeshi Oishi: The Preparation of 2-(Substituted phenyl)ethanols.

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As the 2-(substituted phenyl)ethanols (Va, b, c in Chart 1) are very useful starting compounds for the syntheses of benzoquinolizine derivatives, several routes for the preparation of these alcohols have been described.[1~3]

Of these, the best one has been to reduce the (substituted phenyl)acetic acid ester with lithium aluminum hydride, but this process involves many steps and the reagent is rather expensive to use on a preparative scale.

Now it was found that veratraldehyde (Ia) can be converted to 3,4-dimethoxyphenethyl alcohol (Va) in a four-step process involving Darzens reaction with an over-all yield of about 45~50%.

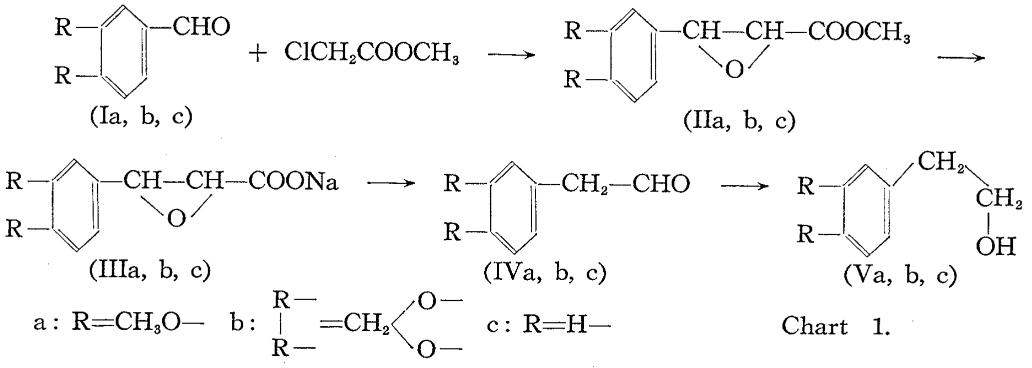

Chart 1.

As illustrated in Chart 1, veratraldehyde (Ia) was condensed with methyl chloroacetate, giving methyl 3-(3,4-dimethoxyphenyl)glycidate (IIa) in a yield of about 85% by applying Henecka's conditions,[4] which used sodium methoxide in methanolic solution as a condensing agent.

Methyl glycidate (IIa) thus obtained was hydrolysed to give its sodium salt (IIIa), which was converted to the corresponding aldehyde (IVa) very smoothly by carrying out the decarboxylation under anhydrous condition. Sodium glycidate (IIIa) suspended in a solution of just one molar equivalent of acetic acid in benzene was stirred and heated gently until the evolution of carbon dioxide ceased. Although the aldehyde (IVa) could be isolated in a pure state in 70% yield by this procedure, it was more convenient in most instances to subject the crude reaction product directly to hydrogenation without distillation.

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1) C. Schöpf, G. Göttmann, E. Meisel, L. Neuroth: Ann., **563**, 86(1949).

2) S. Sugasawa, Y. Suzuta: Yakugaku Zasshi, **71**, 1159(1951).

3) M. Pailer, K. Schneglberger, W. Reifschneider: Monatsh., **83**, 513(1952).

4) H. Henecka: Ann., **583**, 110(1953).

In quite the same way, piperonal (Ib) gave 3,4-methylenedioxyphenethyl alcohol (Vb) in almost the same yield. With the benzaldehyde series (R=H), however, the decarboxylation of sodium 3-phenylglycidate (IIIc) was not effected under the anhydrous condition as described above, but (IVc) was obtained in 50% yield, when (IIIc) was heated in a solution of one molar equivalent of 15% acetic acid (85% water) in benzene which was similar to Shin-ya's procedure.[5]

As phenethyl alcohol can be prepared with better yields in other ways, this route seems not to be recommended for its preparation. The effect of electron-releasing substituents such as methoxyl or methylenedioxy on the ease of decarboxylation should be pointed out here. The over-all yield of the alcohols thus obtained is shown in Table I.

TABLE I.

Starting Compound	Product	Over-all yield (%)
(Ia)	(Va)	45.3∼49
(Ib)	(Vb)	47
(Ic)	(Vc)	38.4∼42

The authors are grateful to Prof. S. Sugasawa for his kind encouragement throughout this work, and wish to thank Messrs. I. Murakami, Y. Shimizu, S. Yokoyama, H. Kaneshima, and Miss M. Nakagawa for their technical cooperation in this work. Thanks are also due to Mr. K. Narita of this Institute for microanalytical data.

Experimental[6]

Methyl 3-(3,4-Dimethoxyphenyl)glycidate (IIa)—To a solution of 62 g. (2.7 gram-atoms) of Na in 900 cc. of dehyd. MeOH, chilled to −10° in an ice-salt bath, a solution of 299 g. (1.8 moles) of veratraldehyde (Ia) and 293 g. (2.7 moles) of methyl chloroacetate was added during a period of 3 hrs., during which time the reaction mixture was vigorously stirred, and finally the whole became a thick white paste. After the addition was completed, the mixture was stirred at −5° for 2 hrs., and then at room temperature for 3 hrs. The mixture was poured into 3.5 L. of ice water containing 20 cc. of AcOH. Methyl glycidate (IIa) precipitated as a white crystalline powder, which was collected by filtration, washed well with cold water, and dried in a desiccator. The crude glycidate weighed 343∼371 g. (80∼86.5%), and was pure enough for the next reaction. Recrystallized from MeOH, it gave colorless blades, m. p. 65∼66°. *Anal.* Calcd. for $C_{12}H_{14}O_5$: C, 60.49; H, 5.92. Found: C, 60.76; H, 6.00.

This is the general procedure for the condensation of methyl chloroacetate with (Ib) and (Ic).

Methyl 3-(3,4-Methylenedioxyphenyl)glycidate (IIb)—The crude reaction product (yield, 90.9%), obtained by applying the general procedure, melted at 65° and after a single recrystallization from MeOH had the same melting point. *Anal.* Calcd. for $C_{11}H_{10}O_5$: C, 59.46; H, 4.53. Found: C, 59.31; H, 4.47.

Methyl Phenylglycidate (IIc)—Separated as an oil and purified in the usual way, b.p$_{6}$ 115∼116°; yield, 90%[7].

Sodium 3-(3,4-Dimethoxyphenyl)glycidate (IIIa)—To a solution of 343 g. (1.44 moles) of methyl glycidate (IIa) in 1.8 L. of benzene was slowly added a solution of 34 g. (1.48 gram-atoms) of Na in 480 cc. of dehyd. MeOH at 5°. Then to the colorless viscous mixture 30 cc. (1.67 moles) of water was added in one portion, white powder precipitating. To make it easy to filter the product by suction, 1 L. of ether was added to the mixture, which was allowed to stand at 5∼10° for 3 hrs. There was obtained 316 g. (89.1%) of crude (IIIa), which was used for the next step without further purification. Similarly, (IIb) and (IIc) were prepared in the yield of 97% and 98%, respectively.

(3,4-Dimethoxyphenyl)acetaldehyde (IVa)—To a suspension of 100 g. (0.41 mole) of (IIIa) was added 25 g. (0.41 mole) of AcOH, the mixture was stirred and refluxed gently on a steam bath for 2.5 hrs. until the evolution of CO_2 ceased. Water was added to the cooled reaction mixture and the aqueous layer was extracted with benzene. The benzene extract was washed with water, dried over Na_2SO_4, and benzene was removed by distillation, leaving a pale yellow oil (yield, 57.5 g. 78.5%), which could be used directly for the next hydrogenation.

The pure substance has b.p$_{0.1\sim0.2}$ 113∼116° (yield, 70%) and affords a semicarbazone, m.p. 160∼161°.[8]

This modified procedure can be used for the preparation of (IVb), b.p$_{1\sim2}$ 126° (crude yield, 80%);

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[5] S. Shin-ya: Nippon Nogei Kagakkaishi **24**, 281 (1950) [C. A. **47**, 6374 (1953)].

[6] All melting points are uncorrected.

[7] S. Ishikawa, H. Yamamoto: Kagaku Kenkyusho Hôkoku. (Tokyo) **26**, 170 (1950).

[8] E. Kaufman, E. Eliel, J. Rosenkranz: Ciencia (Mex.), **7**, 136 (1946) [C. A., **41**, 2398 (1947)].

semicarbazone, m.p. 176°.[9] (IVc) could not be obtained by the same procedure and the following procedure was conducted:

To a stirred suspension of 70 g. (0.376 mole) of (IIIc) in 200 cc. of benzene, 144 cc. (0.36 mole) of 15% AcOH (85% water) was added at room temperature, and the reaction mixture was heated to 70~80° for ca. 1 hr. until the evolution of CO_2 ceased. Water was added, the mixture was extracted with benzene, and the benzene layer was treated in the usual way to give ca. 35 g. of crude phenylacetaldehyde, which was used for the hydrogenation. The pure aldehyde: b.p_7 73° (yield, 50%)[5]; oxime,[10] m.p. 98°.

3,4-Dimethoxyphenethyl Alcohol (Va)—A solution of 47.5 g. of crude (IVa) in 200 cc. of EtOH was hydrogenated over 15 g. of Raney Ni (W-2) at an initial pressure of 40 atm. of hydrogen at 40° for 3 hrs. until more than the calculated amount of H_2 was taken up. The filtered solution was evaporated *in vacuo*, the remaining oil was dissolved in benzene, washed with satd. NaCl solution, dried over Na_2SO_4, and benzene was removed. The residual oil was distilled, giving a colorless oil of b.p_4 145~150°. Yield, 38 g. (62.3% from (IIIa)). The purified alcohol solidified on standing at room temperature, m.p. 48°.[1]

In a similar way, 3,4-methylenedioxyphenethyl alcohol (Vb)[2] of b.p_4 135~136° was obtained in the yield of 54.7% from (IIIb), and phenethyl alcohol (Vc)[11] of b.p_{12} 98~100° in the yield of 48% from (IIIc).

Summary

3,4-Dimethoxyphenethyl alcohol and 3,4-methylenedioxyphenethyl alcohol were respectively prepared from veraltraldehyde and piperonal in a four-step process involving Darzens reaction with the over-all yield of 45~50%.

(Received May 15, 1958)

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[9] C. Harries, H. Adam: Ber., **49**, 1032 (1916); H. Erdtman, R. Robinson: J. Chem. Soc., **1933**, 1530; C. Schöpf, W. Salzer: Ann., **544**, 1 (1940).

[10] W. Dollfus: Ber., **25**, 1917 (1892).

[11] H. Soden, W. Rojahn: Ber., **33**, 1723 (1900).

UDC 577.164.11

Shigeru Yoshida and Mitsuru Kataoka: Studies on the Allied Compounds of Vitamin B_1. XXIII.[1] Synthesis of N-Acyl-O,S-dibenzoylthiamines.

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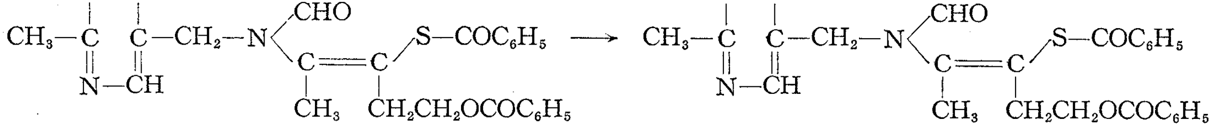
N-Acylation of thiothiamine and tetrahydrofurothiothiamine was described in the preceding paper[1] and for the same purpose of preparing N-acylated thiamine derivatives, the same reaction as before was carried out on O,S-dibenzoylthiamine[2] (I), from which N-acyl-O,S-dibenzoylthiamines (II) were obtained. Of the various acylated derivatives, only N-acetyl derivative (IIa: $R=CH_3$) was obtained in crystalline state, and N-propionyl (IIb: $R=C_2H_5$) and N-butyroyl (IIc: $R=C_3H_7$) were characterized as their crystalline picrates, respectively melting at 148° and 160°. Repeated recrystallization of the picrate resulted in deacylation, with increasingly higher melting point, and the final product was identified with O,S-dibenzoylthiamine picrate.



(I)

(II) a: $R=CH_3$
b: $R=C_2H_5$
c: $R=C_3H_7$

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[1] Part XXII: This Bulletin, **6**, 527 (1958).

[2] S. Yoshida: Yakugaku Zasshi, **74**, 993 (1954); T. Matsukawa, H. Kawasaki: *Ibid.*, **73**, 705, 709 (1953).