Note

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Tozo Fujii, Minoru Tashiro, Kenji Ohara, and Makio Kumai : The Preparation of 3,4-Dimethoxy- and 3,4-Methylenedioxy-phenethyl Alcohol.

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Several methods are known in the literature[1,2] for the preparation of 3,4-dimethoxy- and 3,4-methylenedioxy-phenethyl alcohol (X and XV), which are useful starting materials for the introduction of homoveratryl and homopiperonyl groups in organic syntheses, for example, in benzoquinolizine chemistry.

Of these methods, the deamination of 3,4-dimethoxy- and 3,4-methylenedioxy-phenethylamine (VI and XI) with nitrous acid[1d,e,2a] does not seem preferable owing to unsatisfactory yield and the quality of the resulting alcohols.[1b] This is reminiscent of the fact that the conversion of aliphatic amines into alcohols with nitrous acid results in low yield of alcohols contaminated with isomers.[3,5c]

It has been reported that heating of N-benzyl-N-nitrosobenzamide (IIIb) with ethanol yielded benzyl benzoate (IVb) with other products.[4] A few years ago, a new elegant method for the deamination of aliphatic amines was developed by White.[5] The steps involved are acylation of the amine, nitrosation of the amide, and thermal elimination of nitrogen from the resulting N-alkyl-N-nitrosoamide to form the corresponding ester.

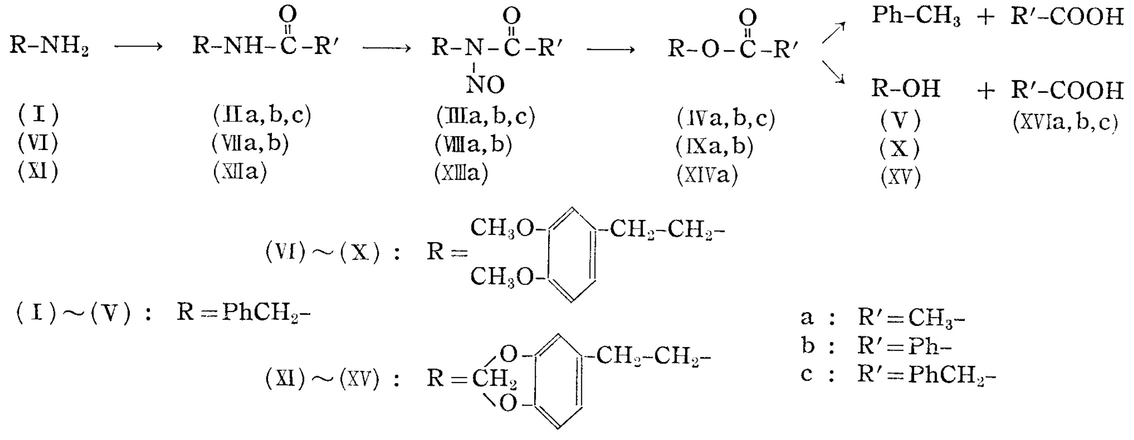

Chart 1.

[*1] Hongo, Tokyo (藤井澄三, 田代　実, 小原賢治, 熊井巻夫).

1) For 3,4-dimethoxyphenethyl alcohol : *a*) J. D. Fulton, R. Robinson : J. Chem. Soc., **1933**, 1463. *b*) C. Schöpf, G. Göttmann, E.-M. Meisel, L. Neuroth : Ann., **563**, 86(1949). *c*) R. S. Livshits, M. S. Bainova, A. I. Gurevich, N. A. Preobrazhenskii : Zhur. Obschei Khim., **23**, 525(1953) (C. A., 48, 3368(1954)). *d*) J. S. Buck : J. Am. Chem. Soc., **53**, 2192(1931). *e*) M. Pailer, K. Schneglberger, W. Reifschneider : Monatsh., **83**, 513(1952). *f*) Y. Ban, T. Oishi : This Bulletin, **6**, 574 (1958). *g*) M. Lora-Tamayo, R. Madronero, G. G. Munoz : Chem. & Ind. (London), **1959**, 657. *h*) M. Barash, J. M. Osbond : J. Chem. Soc., **1959**, 2157.

2) For 3,4-methylenedioxyphenethyl alcohol : *a*) P. Medinger : Monatsh., **27**, 245(1906). *b*) F. W. Semmler, K. Bartelt : Ber., **41**, 2751(1908). *c*) S. Sugasawa, Y. Suzuta : Yakugaku Zasshi, **71**, 1159(1951). *d*) Y. Ban, T. Oishi : This Bulletin, **6**, 574(1958).

3) F. C. Whitmore, D. P. Langlois : J. Am. Chem. Soc., **54**, 3441(1932); M. L. Henry : Compt. rend., **145**, 899(1907).

4) H. v. Pechmann : Ber., **31**, 2640(1898).

5) *a*) E. H. White : J. Am. Chem. Soc., **76**, 4498(1954). *b*) *Idem* : *Ibid.*, **77**, 6008(1955). *c*) *Idem* : *Ibid.*, **77**, 6011(1955). *d*) *Idem* : *Ibid.*, **77**, 6014(1955).

The preparation of benzyl alcohol (V), and 3,4-dimethoxy- and 3,4-methylenedioxyphenethyl alcohol (X and XV) from the corresponding amines (I, VI, and XI) was examined by applying White's method as shown in Chart 1. In the case of (a) series (R′=Me), the nitrosation of the amides (II, VII, and XII) was carried out with a mixture of acetic acid, acetic anhydride, and sodium nitrite, while in the case of (b)(R′=Ph) and (c) (R′=PhCH$_2$) series, nitrogen tetroxide was used to avoid transacylation of the amide during the reaction. The resultant N-nitroso compounds (III, VIII, and XIII), without being isolated, were respectively heated in a solvent such as hexane or benzene under reflux for 18 hours to give the esters (IV, IX, and XIV) in a good yield and in a practically pure state. Hydrolysis of the distilled esters (IV, IX, and XIV) with methanolic potassium hydroxide gave the corresponding alcohols (V, X, and XV) in a good yield, which were respectively identified with the authentic samples by comparison of the infrared absorption spectra and by converting them to the corresponding phenylurethans. In the case of (XV), the oily product thus obtained was slightly contaminated with a trace of some crystalline impurities which could not be removed by redistillation.

In the case of the benzyl esters (IVb,c), their structures were also proved by converting them to the corresponding acids (XVIb,c) by hydrogenolysis over palladium-carbon.

When the reaction mixture of (VI) with acetic anhydride was immediately nitrosated in the same solvent and followed by elimination of nitrogen, the overall yield of (IXa) was nearly equal to that of the procedure which involved isolation of the acetamide (VIIa).

Experimental[*2]

Preparation of Amides—The amides (IIa,b,c, VIIa,b, and XIIa[6]) were obtained by heating the corresponding amines (I, VI,[7] and XI[7]) for 2 hr. with an excess of Ac$_2$O or by treating the amines with acid chloride under the Schotten-Baumann condition. In all cases, the yield was 95~97%. The m.p.s of the following amides were higher than the reported values:

N-(3,4-Dimethoxyphenethyl)acetamide (VIIa): Colorless needles, m.p. 98~99° (reported[6] m.p. 94~95°), as recrystallized from hexane-benzene (2:1). *Anal.* Calcd. for $C_{12}H_{17}O_3N$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.89; H, 7.40; N, 6.45. IR ν_{max}^{Nujol} cm^{-1}: 3286 (NH), 1630 (CONH$_2$). When this sample was treated with POCl$_3$ as usual, 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline, m.p. 105~106°,[6] was obtained.

Sometimes, (VIIa) was obtained as crystals which melted partially at 95° and then wholly at 99°. It solidified on cooling and this sample melted sharply at 98~99°. It is assumed that a sample of m.p. 98~99° and reported one of m.p. 94~95° are probably dimorphs, though it was not investigated further.

N-(3,4-Dimethoxyphenethyl)benzamide (VIIb): Colorless needles, m.p. 97~98° (reported[8] m.p. 90~91°) from hydr. EtOH. *Anal.* Calcd. for $C_{17}H_{19}O_3N$: N, 4.91. Found: N, 4.90. This sample gave 1-phenyl-6,7-dimethoxy-3,4-dihydroisoquinoline as colorless prisms, m.p. 120~121°,[8] by the usual treatment with POCl$_3$.

3,4-Dimethoxyphenethyl Acetate (IXa)—A solution of the amide (VIIa: 6.7 g.) in a mixture of glacial AcOH (30 cc.) and Ac$_2$O (150 cc.) was treated with 45 g. of granular NaNO$_2$ in the same way as that of White.[5b] The resulting mixture was poured into a mixture of ice and H$_2$O. The crystalline N-nitrosoamide (VIIIa) separated was extracted with ca. 300 cc. of benzene, the benzene solution was washed with H$_2$O, 5% Na$_2$CO$_3$ solution, and H$_2$O, dried over Na$_2$SO$_4$, and then refluxed on a steam bath for 18 hr. The resultant solution was concentrated to ca. 60 cc., washed with satd. NaHCO$_3$ solution, followed by H$_2$O, dried, and evaporated *in vacuo* to leave a brownish yellow oil. When this oil was distilled, (IXa) was obtained as a slightly yellowish oil of b.p$_{0.01}$ 120~123° in a yield of 6.0 g. or 89.3% based on the amide used. *Anal.* Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.15; H, 7.75. IR $\nu_{max}^{Capil.}$ 1736 cm^{-1} (COOR).

[*2] All melting and boiling points are uncorrected.

6) E. Späth, N. Polgar: Monatsh., **51**, 190(1929).

7) J.C. Robinson, Jr., H.R. Snyder: Org. Syntheses, Coll. Vol. III, 721(1955).

8) H.J. Harwood, T.B. Johnson: J. Am. Chem. Soc., **56**, 468(1934); S. Sugasawa: Yakugaku Zasshi, **55**, 224(1935).

When 3,4-dimethoxyphenethylamine (VI) was heated with Ac_2O for 2 hr. and the resultant mixture was immediately treated as described above, (IXa) was also obtained in a yield of 86.5% based on (VI).

In a similar way, benzyl acetate (IVa), b.p$_{1.5}$ 62~64°, and 3,4-methylenedioxyphenethyl acetate (XIVa), b.p$_{0.025}$ 110~112°,[*3] were obtained from (IIa) and (XIIa) in respective yield of 80% and 90.7%.

3,4-Dimethoxyphenethyl Benzoate (IXb)—To a suspension of an intimate mixture of the amide (VIIb : 6.6 g.) and anhyd. AcONa (5.7 g.) in hexane (50 cc.), N_2O_4 9) (4.6 g.) was added at 0° by fractionally distilling the latter from the calculated amount of its 10% solution in CCl_4. After being kept at 0° for 2.5 hr. under occasional shaking, the whole was poured into ice-water. The crystalline N-nitrosoamide (VIIIb) that separated was collected on a filter and then dissolved in benzene (ca. 200 cc.). The benzene solution was combined with the hexane layer which was separated from the filtrate and worked up as in the case of (VIIIa). Thus, (IXb) was obtained as a slightly yellowish syrup, b.p$_{0.65}$ 210~215°, in a yield of 5.56 g. or 84% based on the amide used. Though it solidified on standing (m.p. 32~40°), the compound (IXb) was not analyzed and used directly in the following hydrolysis.

In a similar way, benzyl benzoate (IVb), b.p$_3$ 142~144°, and benzyl phenylacetate (IVc), b.p$_5$ 155~157°, were respectively prepared from (IIb) and (IIc) in yields of 87.9% and 84.8%. When (IVb) and (IVc) thus obtained were respectively hydrogenated over 20% Pd-C in EtOH solution at room temp. under atmospheric pressure, one molar equivalent of H_2 was smoothly absorbed to afford BzOH (XVIb) and phenylacetic acid (XVIc) in yields of 90% and 91%, which were respectively identified by admixture with authentic specimens.

3,4-Dimethoxyphenethyl Alcohol (X)—i) A solution of the acetate (IXa : 5.96 g.) in a mixture of 50% KOH solution (3.0 g.) and MeOH (20 cc.) was refluxed on a steam bath for 5 hr., and MeOH was distilled off from this solution to separate an oil, which was extracted repeatedly with benzene. After drying, the benzene solution was evaporated *in vacuo* to leave a yellowish oil which solidified on standing at room temperature. When this oil was distilled, (X) was obtained as a nearly colorless oil of b.p$_{1.5}$ 127~129° in a yield of 4.63 g. or 95.7%. It solidified on standing at room temperature, m.p. 40~43° (reported 1a) m.p. 47~48°). No m.p. depression occurred on admixture with a specimen prepared by the method (iii). The IR absorption spectrum of this sample was also well superimposable with that of an authentic specimen mentioned above.
Phenylurethan : Colorless needles, m.p. 99~100° (from hydr. EtOH), was identified with an authentic sample 1a) by admixture.

In a similar way, benzyl alcohol (V), b.p$_{10}$ 82~83°, was obtained from (IVa) in 60% yield. Phenylurethan : Colorless needles, m.p. 75~76° (from hexane), was identified with an authentic specimen 10) by admixture.

Similarly, 3,4-methylenedioxyphenethyl acetate (XIVa) gave an oily product, b.p$_{2.5}$ 120~122°, in 96.2% yield. However, the product was slightly contaminated with a trace of some crystalline impurities which could not be removed by redistillation. In spite of this contamination, this oil solidified on being kept at 0° to 3° overnight and melted at room temperature (ca. 20°) as does the authentic specimen[*4] of (XV). Its IR absorption spectrum was superimposable with that of an authentic specimen of (XV). Therefore, it is supposed that the product (XV) thus obtained is practically pure.
Phenylurethan : Colorless needles, m.p. 98~99°; yield, 80.6% after one recrystallization from hydr. EtOH. It was identified by admixture with the phenylurethan prepared from an authentic (XV). *Anal.* Calcd. for $C_{16}H_{15}O_4N$: C, 67.36; H, 5.30; N, 4.91. Found : C, 67.03; H, 5.55; N, 5.07. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3344 (NH), 1709 (-HNCOOR).

ii) When the benzoate (IXb) (4.50 g.) was hydrolyzed as in the case of (IXa), (X) and BzOH (XVIb) were obtained in yields of 90% and 92%, which were respectively identified with authentic samples by admixture.

iii) 1h) To a suspension of powdered $LiAlH_4$ (7.5 g.) in dehyd. ether (400 cc.) a solution of ethyl 3,4-dimethoxyphenylacetate (59.5 g.) in dehyd. ether (180 cc.) was added dropwise with stirring and cooling (−10° to −5°) during 1.5 hr. After stirring for 2 hr. at room temperature, the mixture was gently refluxed on a steam bath with stirring for 4 hr. Wet ether, H_2O, followed by dil. HCl, were added under effective cooling. The ether layer was separated, the aqueous layer was salted out with NaCl, and repeatedly extracted with benzene. The benzene solution was combined with the ether layer, dried, and evaporated. The resultant residue was distilled *in vacuo* to form a colorless oil (X), b.p$_{5.5}$ 155~158°, which solidified on cooling, m.p. 45~46°. 1a) Yield, 46.9 g. or 97%. Phenylurethan : Color-

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[*3] *Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found : C, 62.97; H, 5.53. IR $\nu_{\max}^{\text{Capil.}}$ 1732 cm^{-1} (COOR).

[*4] The authors are grateful to Mr. T. Kato for a donation of this specimen prepared from ethyl 3,4-methylenedioxyphenylacetate by reduction with $LiAlH_4$.

9) L. Vanino : "Handbuch der Präparativen Chemie," I, 127(1913). Ferdinand Enke, Stuttgart.

10) F. Straus, H. Grindel : Ann., **439**, 311(1924).

less needles, m.p. 99~100°1a) (from hydr. EtOH).

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Summary

3,4-Dimethoxy- and 3,4-methylenedioxy-phenethyl alcohol (X and XV) were respectively prepared from the corresponding amines (VI and XI) in a good overall yield. The steps involved are formation of the esters (IXa, b and XIVa) by applying White's method5) to the amines, and hydrolysis of the resultant esters to form the alcohols (X and XV). Similarly, benzyl alcohol (V) and benzyl esters (IVa, b, c) were also prepared from benzylamine (I).

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