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Shun-ichi Yamada, Tozo Fujii, Keijiro Takagi, Yasuo Gomi, and Seishi Matsushita : Preparation of Tyrosol and 4-Methoxyphenethyl Alcohol.

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The investigation of inhibitors against monoamine oxidase in this laboratory prompted us to take an interest in testing tyrosol (V) and 4-methoxyphenethyl alcohol (X), and led us to preparing them from the corresponding amines (I and VI) which were available in some quantities in our laboratory.

Among several methods for the syntheses of tyrosol (V)[1] and 4-methoxyphenethyl alcohol (X),[2] the deamination of the corresponding amines with nitrous acid[1b] did not seem to be preferable owing to unsatisfactory yield of the resulting alcohols. Whitemore *et al.* reported that reaction of aliphatic amines with nitrous acid resulted in the formation of alcohols in poor yield, which were contaminated with isomers.[3]

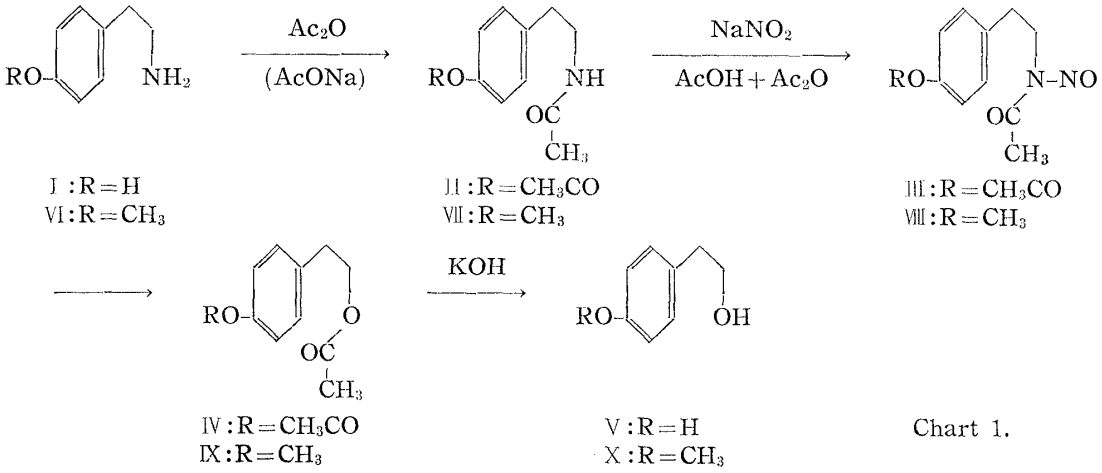

Chart 1.

Several years ago, a new elegant method for deamination of aliphatic amines was developed by White.[4] 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. This method was applied successfully to 3,4-dimethoxy- and 3,4-methylenedioxyphenethylamine and hydrolysis of the resultant esters led to the corresponding alcohols in good overall yield.[5]

The application of the White's method to the preparation of the alcohols (V and X)

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1) *a*) J. v. Brown : Ber., **45**, 1277 (1912). *b*) F. Ehrlich, P. Pistschimuka : *Ibid.*, **45**, 2430 (1912). *c*) E. Ferber : *Ibid.*, **62**, 189 (1929). *d*) C. S. Cheng, C. Ferber, R. I. Bashford, Jr., G. F. Grillot : J. Am. Chem. Soc., **73**, 4082 (1951).

2) *a*) V. Grignard : Compt. rend., **141**, 45 (1905). *b*) L. Bouveault, G. Blanc : D. R. P. 164, 294 (Chem. Zentr. **1905**, II, 1701). *c*) M. Tiffeneau : Ann. Chim. Phys., [8], **10**, 350 (1907). *d*) F. B. LaForge, W. F. Barthel : J. Org. Chem., **9**, 250 (1944). *e*) J. Colonge, P. Rochas : Compt. rend., **223**, 403 (1946). *f*) I. Wender, H. Greenfield, S. Metlin, M. Orchin : J. Am. Chem. Soc., **74**, 4079 (1952). *g*) K. H. Slotta, H. Heller : Ber., **63**, 3029 (1930). *h*) W. H. Saunders, Jr., R. A. Williams : J. Am. Chem. Soc., **79**, 3712 (1957). *i*) K. Ishikawa, S. Fukushima, H. Ouchi, M. Tsuchida : *Ibid.*, **80**, 6005 (1958).

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

4) *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).

5) T. Fujii, M. Tashiro, K. Ohara, M. Kumai : This Bulletin, 8, 266 (1960).

from the amines (I and VI) is illustrated in Chart 1. Acetylation of the amine (I) with a mixture of acetic anhydride and anhydrous sodium acetate, and that of VI with acetic anhydride were carried out at 80~85° for 2 hours. The acetamides (II and VII), without being isolated, was immediately nitrosated with a mixture of acetic acid, acetic anhydride and sodium nitrite. The resultant N-nitrosoamides (III and VIII) were extracted with benzene and heated in the same solvent under reflux for 18 hours to give the esters (IV and IX) in good yield. Hydrolysis of the distilled esters (IV and IX) with methanolic potassium hydroxide gave the corresponding alcohols (V and X) in a good yield, which were respectively identified with the authentic samples by comparison of the infrared absorption spectra, mixed melting point test (for tyrosol (V)), and conversion into the phenylurethan (for 4-methoxyphenethyl alcohol (X)). The overall yields of V and X were 62.5% and 76%, respectively.

Examination of inhibitory action of these alcohols (V and X) against monoamine oxidase is now in progress.

Experimental*2

Identification of the Amides (II and VII)——Acetylation of the amines (I*3 and VI[6]) was carried out under the same reaction condition as described in the preparation of IV and IX and the amides (II, VII) were isolated in the usual way.

N-(4-Acetoxyphenethyl)acetamide (II): Colorless needles, m.p. 101.5~102° (reported[7] m.p. 103°) (from hexane-benzene (2 : 1)). Yield, 95.5%. *Anal.* Calcd. for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.22; H, 6.55; N, 6.30. IR ν_{max}^{KBr} cm^{-1}: 3311 (NH), 1765 (COOAr), 1639 (CONH), 1547 (amide II), 1239 (COOAr).

N-(4-Methoxyphenethyl)acetamide (VII): Colorless needles, m.p. 85~86° (reported as an oil of $b.p_{15}$ 195~200°)[8] (from hexane-benzene (2 : 1)). Yield, quantitative. *Anal.* Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.34; H, 7.38; N, 7.44. IR ν_{max}^{KBr} cm^{-1}: 3307 (NH), 2843, 2803 (CH_3O), 1640 (CONH), 1560 (amide II), 1262, 1040 (CH_3O).

4-Acetoxyphenethyl Acetate (IV)——To an intimate mixture of tyramine*3 (I: 3.25 g.) and anhyd. AcONa (3.25 g.) was added dropwise Ac_2O (14.5 g.) with ice cooling and the mixture was heated in a water bath at 80~85° for 2 hr. and then cooled. To this solution was added a mixture of glacial AcOH (24 cc.) and Ac_2O (120 cc.) and the whole was cooled to 0°, and treated with granular $NaNO_2$ (36 g.) under stirring during 5 hr. After being kept at 0° for 15 hr. with stirring, the temperature was allowed to rise to 15° during 30 min. and the mixture was poured onto a mixture of ice and water (ca. 400 cc.).[4b] The pale yellow, crystalline N-nitrosoamide (III) separated was extracted with ca. 300 cc. of benzene, and the benzene solution was washed with H_2O, 5% Na_2CO_3 solution, and H_2O, dried over anhyd. Na_2SO_4, and then heated under reflux for 18 hr. The resultant solution was concentrated to ca. 100 cc., washed with H_2O, satd. $NaHCO_3$ solution, and H_2O, dried, and evaporated *in vacuo* to leave a brown oil (5.18 g.). When this oil was distilled, IV was obtained as a colorless oil of $b.p_5$ 153° (reported[9] $b.p_{18}$ 187°) in a yield of 4.25 g. or 80.7% based on the amine (I) used. *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.38; H, 6.37. IR $\nu_{max}^{Capil.}$ cm^{-1}: 1770 (COOAr), 1745 (COOR), 1247 (COOR), 1193 (COOAr).

4-Methoxyphenethyl Acetate (IX)——To 4-methoxyphenethylamine[6] (VI: 4.52 g.) was added dropwise Ac_2O (9.20 g.) with ice cooling and the whole was heated in a water bath at 80~85° for 2 hr., cooled, and then treated with a mixture of glacial AcOH (30 cc.) and Ac_2O (150 cc.). The solution was cooled to 0° and treated with granular $NaNO_2$ (45 g.) in the same way as in the case of IV. The pale yellow, oily N-nitrosoamide (VIII) separated was extracted with benzene (300 cc.) and decomposed thermally as in the case of III. Distillation of the crude oil (IX: 5.66 g.) thus obtained gave the pure acetate (IX) as a colorless oil of $b.p_3$ 119° (reported[2c] $b.p_{11}$ 156~157°) in a yield of 4.80 g., or 82.3% based on the amine (VI) used. *Anal.* Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.56; H, 7.44. IR $\nu_{max}^{Capil.}$ cm^{-1}: 2810 (CH_3O), 1750 (COOR), 1255 (broad, strong) (COOR, CH_3O), 1035 (CH_3O).

Tyrosol (V)——A solution of the diacetate (IV: 4.16 g.) in a mixture of 50% KOH solution (8.0 g.)

*2 All melting and boiling points are uncorrected.
*3 A commercially available sample was used.
6) J.C. Robinson, Jr., H.R. Snyder: Org. Syntheses, Coll. Vol. III, 721 (1955).
7) M. Cloetta, F. Wünsche: Chem. Zentr., **1923**, III, 88.
8) G.S. Walpole: J. Chem. Soc., **97**, 943 (1910).
9) Beilstein, **6**, I, 443.

and MeOH (20 cc.) was heated under reflux for 4 hr., and the MeOH was distilled off from this solution. The residual solution was made acid to Congo red with conc. HCl under cooling, then made basic to litmus with K_2CO_3, and the crystals separated were extracted with ether (ca. 170 cc.). The ethereal solution was dried over anhyd. K_2CO_3, and evaporated to leave a slightly yellowish solid (2.27 g.) of m.p. 83~89°. When this solid was distilled, the phenolic alcohol V was obtained as a colorless oil of $b.p_4$ 158° (reported[1b] $b.p_{18}$ 195°) in a yield of 2.06 g. or 77.4% based on the diacetate IV used. It solidified on standing at room temperature, m.p. 91~92°. Recrystallization from $CHCl_3$ gave colorless needles, m.p. 91~92°(reported m.p. 92°,[1d] m.p. 92~93°,[1c] m.p. 93°[1a,1b]). *Anal.* Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found : C, 69.53; H, 7.01. IR ν_{max}^{KBr} cm^{-1} : 3467, 3182 (OH), 1242 (ArOH), 1053 (ROH). This sample produced a pink color on a freshly cut end of potatoes,[1d,10] and showed no depression on admixture with an authentic specimen prepared from 4-methoxyphenethyl alcohol.[1d] The IR absorption spectrum of this sample in KBr disc was also superimposable with that of the authentic specimen mentioned above.

4-Methoxyphenethyl Alcohol (X)——A mixture of the acetate (IX : 4.68 g.), 50% KOH solution (6.6 g.) and MeOH (20 cc.) was heated under reflux for 4 hr. The MeOH was distilled off from this solution to separate an oil, which was extracted repeatedly with benzene (ca. 130 cc.). After drying, the benzene solution was evaporated *in vacuo* to leave a brown oil (3.69 g.). When this oil was distilled, the alcohol (X) was obtained as a colorless oil of $b.p_5$ 121° (reported[2a] $b.p_{13}$ 143~144°) in a yield of 3.39 g. or 92.4% based on IX used. *Anal.* Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found : C, 69.45; H, 7.76. IR $\nu_{max}^{Capil.}$ cm^{-1} : 3460 (broad) (OH), 2810 (CH_3O), 1259 (CH_3O), 1040 (broad) (OH, CH_3O). The IR absorption spectrum of this sample in a liquid film phase was superimposable with that of a specimen prepared by reduction of ethyl 4-methoxyphenylacetate with $LiAlH_4$.

Phenylurethan : Colorless needles, m.p. 126~127° (from hexane) (reported m.p. 127.0~128.6°,[2f] m.p. 125°[11]). *Anal.* Calcd. for $C_{16}H_{17}O_3N$: C, 70.83; H, 6.32; N, 5.16. Found : C, 70.76; H, 6.22; N, 5.16. IR ν_{max}^{KBr} cm^{-1} : 3376 (NH), 1702 (NHCOOR).

This sample was found to be identical with the phenylurethan prepared from an authetic sample of X by mixed melting point test and comparison of their IR absorption spectra in KBr disc.

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Summary

Tyrosol (V) and 4-methoxyphenethyl alcohol (X) were prepared from the corresponding amines (I and VI) in good yield. The steps involved are formation of the acetamides (II and VII), N-nitrosoamides (III and VIII), and acetic esters (IV and IX) by application of the White's method, and hydrolysis of the resultant esters to form the alcohols (V and X).

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10) M. W. Onslow, M. E. Robinson : Biochem. J., **19**, 421 (1925).
11) R. Crigee, P. Dimroth, K. Noll, R. Simon, C. Weis : Chem. Ber., **90**, 1070 (1957).