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146. Minoru Sekiya, Noboru Yanaihara, and Toshio Masui : Reaction of Amide Homologs. V. Acetamidomethylation of Phenol and Anisole with N,N'-Methylenediacetamide.

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It was outlined in a preliminary communication[1] that α-acylaminoalkylation of aromatic compounds was effected by the interaction of N,N'-alkylidenediamides and phosphoryl chloride. Later, the detailed reports[2] regarding parts of this work were published describing the nature of this reactions with several examples. In continuation of those studies, acetamidomethylation of phenol and anisole was successively examined by the use of the reactants, N,N'-methylenediacetamide and phosphoryl chloride, and this has offered a synthetic procedure for the direct introduction of acetamidomethyl group in these compounds.

I. Acetamidomethylation of Phenol

Acetamidomethylation of phenol was carried out by heating N,N'-methylenediacetamide, and phosphoryl chloride together phenol, under reflux in chloroform. The crude product, obtained by usual treatment of the reaction mixture, was separated by high-vacuum distillation into two kinds of crystals, (A), m.p. 131~132°, and (B), m.p. 139~140°. Both compounds were found on analysis to correspond to a phenol possessing one acetamidomethyl group.

To confirm the position of acetamidomethyl group in each of these compounds, 4- and 2-substituted phenols were synthesized by another route, and (A) was identified with a 4-substituted compound and (B) with a 2-substituted compound by admixture.

Though N-(4- and 2-hydroxybenzyl)acetamide[3,4] (I, II) were previously synthesized through the reduction of 4- and 2-hydroxybenzaldehyde oxime (III, IV), some modifications were adopted in the present route. Following the method of Sekiya,[5] (III) and (IV) were catalytically hydrogenated over Raney nickel, in formamide, under pressure of hydrogen, giving the corresponding N-(4- and 2-hydroxybenzyl)formamide (V, VI) in almost theoretical yield. (V) and (VI) were then hydrolyzed with hydrochloric acid to the corresponding hydroxybenzylamine hydrochlorides (VII, VIII), from which N-(4- and 2-acetoxybenzyl)acetamide (IX, X) were obtained by heating with acetic anhydride in the presence of sodium acetate, followed by partial hydrolysis with dilute sodium hydroxide, giving (I) and (II).

$$\mathrm{HOC_6H_4CHO} \longrightarrow \underset{\text{(III) }(p\text{-comp.}),\ \text{(IV) }(o\text{-comp.})}{\mathrm{HOC_6H_4CH{=}NOH}} \xrightarrow[\mathrm{H_2(Raney\ Ni)}]{\mathrm{HCONH_2}} \underset{\text{(V) }(p\text{-}),\ \text{(VI) }(o\text{-})}{\mathrm{HOC_6H_4CH_2NHCHO}}$$

$$\underset{\text{(VII) }(p\text{-}),\ \text{(VIII) }(o\text{-})}{\mathrm{HOC_6H_4CH_2NH_2HCl}} \longrightarrow \underset{\text{(IX) }(p\text{-}),\ \text{(X) }(o\text{-})}{\mathrm{CH_3COOC_6H_4CH_2NHCOCH_3}} \longrightarrow \underset{\text{(I) }(p\text{-}),\ \text{(II) }(o\text{-})}{\mathrm{HOC_6H_4CH_2NHCOCH_3}}$$

Attempts to convert (I) and (II) into the corresponding amines (VII) and (VIII), by hydrolysis under various conditions were unsuccessful, but the formamidomethyl derivatives

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[1] M. Sekiya, N. Yanaihara : This Bulletin, 7, 746 (1959).

[2] Part III : *Ibid.*, 8, 1120 (1960); Part IV : Chem. Ber., **93**, 2898 (1960).

[3] N.H. Cromwell : J. Am. Chem. Soc., **68**, 2635 (1946); F.W. Holly, *et al.* : *Ibid.* **66**, 1879 (1944).

[4] H. Goldschmitt, *et al.* : Ber., **23**, 2745 (1890).

[5] M. Sekiya : Yakugaku Zasshi, **70**, 545 (1950).

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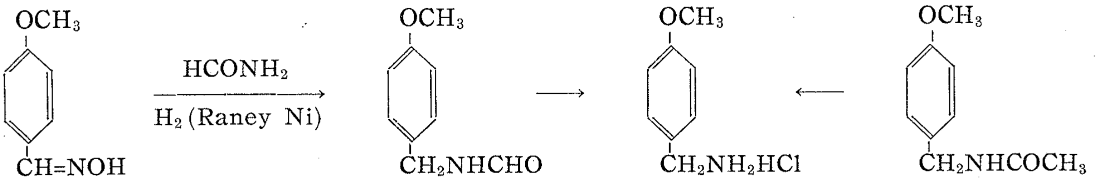
(V and VI), which were not described previously, were easily hydrolyzed as mentioned above.

II. Acetamidomethylation of Anisole

Acetamidomethylation of anisole was carried out by heating anisole, N,N′-methylenediacetamide, and phosphoryl chloride on a boiling water bath. After the reaction mixture was treated as usual, three kinds of substances, (C), m.p. 94~95°, (D), m.p. 135°, and (E), m.p. 52~53°, were obtained by vacuum distillation of the crude oily product. (C) was identified with N-(4-methoxybenzyl)acetamide (XI), by agreement in its melting point with the one reported previously,[6)] and the corresponding amine hydrochloride, 4-methoxybenzylamine hydrochloride (XII), obtained by hydrolysis did not show depression on admixture with the one synthesized by another route.

(D) was found on analysis to correspond to bis(acetamidomethyl)anisole, but no effort was made to confirm its structure. (E) was identified with 4,4′-methylenedianisole by admixture with an authentic sample.

To prepare (XII), the method of Sekiya instead of the previous methods[6)] was also adopted for the reduction of anisaldehyde oxime (XIII). (XIII) was hydrogenated catalytically over Raney nickel in formamide, under high pressure of hydrogen, giving N-(4-methoxybenzyl)formamide (XIV), which was not described previously, in a sufficient yield and (XIV) was hydrolyzed with hydrochloric acid to (XII).



(XIV) (XII) (XI)

Experimental

N-(4-Hydroxybenzyl)acetamide (I) and N-(2-Hydroxybenzyl)acetamide (II) (Condensation of N,N′-Methylenediacetamide with Phenol)——A mixture of 18.8 g. of phenol, 31.2 g. of N,N′-methylenediacetamide, 80 cc. of $CHCl_3$, and 15.4 g. of $POCl_3$ was refluxed for 4 hr. on a water bath. During the reaction HCl evolved and the reaction mixture became homogeneous at the beginning but separated gradually into two layers. The mixture was added with H_2O and neutralized with $NaHCO_3$. The separated oily layer, which did not easily dissolved in $CHCl_3$, was extracted with a considerable amount of $CHCl_3$, which was dried through distillation of $CHCl_3$ from the mixture. The residue was submitted to vacuum distillation to remove unchanged phenol (3.9 g.) and then fractionated by high-vacuum distillation, affording two solid fractions. One fraction of b.p$_{0.02}$ 200~205°, weighing 8.4 g., was recrystallized from Et_2O to needles, m.p. 139~140°, which was found to be identical with (II) by analysis and admixture with an authentic sample synthesized through another route. *Anal.* Calcd. for $C_9H_{11}O_2N$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.45; H, 6.86; N, 8.12.

The other fraction of b.p$_{0.02}$ 221~225°, weighing 6.9 g., was recrystallized from $CHCl_3$ to needles, m.p. 131~132°, which was found to be identical with (I). *Anal.* Calcd. for $C_9H_{11}O_2N$: C, 65.44, H, 6.71; N, 8.48. Found: C, 64.94; H, 6.81; N, 8.38.

4-Hydroxybenzaldehyde Oxime (III)——To a solution of 9 g. of NaOH in 150 cc. of water, 12.2 g. of 4-hydroxybenzaldehyde and 8.3 g. of $NH_2OH \cdot HCl$ were added and the mixture was heated for 3 hr. on a boiling water bath. After cool, the solution was saturated with CO_2, when crude crystals precipitated. This was recrystallized from H_2O to needles, m.p. 68~70°. Yield, 10.8 g.

N-(4-Hydroxybenzyl)formamide (V)——In an autoclave, 13.7 g. of (III), 80 g. of $HCONH_2$, and Raney Ni catalyst (2 g. as 50% alloy) were placed. The mixture was heated at 115° under initial H_2 pressure of 73 atm. (at 18°) and then constant shaking was started. Approximately 0.2 moles of H_2 was absorbed mostly in about 15 min., while the temperature was kept at 115~120°. The reaction

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6) H. Goldschmidt, *et al.*: Ber., **20**, 2409 (1887); W.H. Carothers, *et al.*: J. Am. Chem. Soc., **49**, 2912 (1928).

mixture was filtered to remove the catalyst and $HCONH_2$ was distilled off on a water bath in a reduced pressure. The residue was washed with Me_2CO giving the crude crystals. Yield, 14.5 g. Prisms (from Me_2CO-$CHCl_3$), m.p. 129~130°. *Anal.* Calcd. for $C_8H_9O_2N$: C, 63.56; H, 6.00; N, 9.27. Found : C, 63.33; H, 6.04; N, 9.28.

4-Hydroxybenzylamine Hydrochloride (VII)——To 20 cc. of 10% HCl, 3 g. of (V) was added and the mixture was refluxed for 2 hr. The solution was concentrated to leave crude crystals. Yield, 2.9 g. Needles (from 15% HCl), m.p. 191~192°. *Anal.* Calcd. for $C_7H_{10}ONCl$: C, 52.67; H, 6.32; N, 8.78. Found : C, 52.67; H, 6.37; N, 8.64.

N-(4-Acetoxybenzyl)acetamide (IX)——A mixture of 1 g. of (VII), 4 g. of Ac_2O, and 0.7 g. of AcONa was heated for 1 hr. on a boiling water bath. The reaction mixture was evaporated in a reduced pressure. H_2O was added to the residue and the separated product was extracted with $CHCl_3$. The extract was dried and the solvent was distilled off, giving 0.8 g. of a residue. This was recrystallized from petr. ether to needles, m.p. 77~78°. *Anal.* Calcd. for $C_{11}H_{13}O_3N$: C, 63.75; H, 6.32; N, 6.76. Found : C, 63.51; H, 6.45; N, 6.98.

N-(4-Hydroxybenzyl)acetamide (I)——In 10 cc. of 10% NaOH, 0.4 g. of (IX) was suspended and allowed to stand at room temperature for about 1 hr., when most of the solid went into solution. The solution was saturated with CO_2 and the separated product was extracted with $CHCl_3$. The extract was dried and the solvent was distilled off leaving 0.25 g. of the residue. This was recrystallized from $CHCl_3$-petr. ether to needles, m.p. 130~132°. *Anal.* Calcd. for $C_9H_{11}O_2N$: C, 65.44; H, 6.71; N, 8.48. Found : C, 64.84; H, 6.79; N, 8.27.

2-Hydroxybenzaldehyde Oxime (IV)——To a solution of 12 g. of NaOH in 200 cc. of water, 12.2 g. of salicylaldehyde and 8.3 g. of $NH_2OH \cdot HCl$ were added. The mixture was heated for 3 hr. on a boiling water bath and then treated as in the case of 4-hydroxybenzaldehyde oxime. The product was recrystallized from $CHCl_3$-petr. ether to needles, m.p. 55~57°. Yield, 11.6 g.

N-(2-Hydroxybenzyl)formamide (VI)——In an autoclave, 13.7 g. of (IV), 80 g. of $HCONH_2$ and Raney Ni (2 g. as 50% alloy) were placed and given 68 atm. (at 20°) of initial H_2 pressure. The mixture was shaken at 96~105°. In about 40 min., 88% of the calculated amount of H_2 was absorbed. The reaction mixture was filtered and $HCONH_2$ was distilled off on a water bath in a reduced pressure. The residue crystallized on addition of $CHCl_3$. Yield, 13.2 g. For further purification, its $CHCl_3$ solution was passed through a short column of alumina and gave needles, m.p. 92~93°. *Anal.* Calcd. for $C_8H_9O_2N$: C, 63.56; H, 6.00; N, 9.27. Found : C, 63.52; H, 6.06; N, 9.34.

2-Hydroxybenzylamine Hydrochloride (VIII)——A mixture of 20 cc. of 10% HCl and 3 g. of (VI) was refluxed for 2 hr. and the resultant solution was worked up as for the 4-hydroxy compound. Yield, 2.8 g. Needles (from EtOH), m.p. 127°(decomp.). *Anal.* Calcd. for $C_7H_{10}ONCl$: C, 52.66; H, 6.32; N, 8.78. Found : C, 52.24; H, 6.39; N, 8.45.

N-(2-Acetoxybenzyl)acetamide (X)——A mixture of 1 g. of 2-hydroxybenzylamine hydrochloride, 4g. of Ac_2O, and 0.7 g. of AcONa was heated for 1 hr. on a boiling water bath. After evaporation of the solvent, the mixture was diluted with water and 0.9 g. of crude crystals, so obtained were recrystallized from $CHCl_3$-petr. ether to plates, m.p. 99~100°. *Anal.* Calcd. for $C_{11}H_{13}O_3N$: C, 63.75; H, 6.32; N, 6.76. Found : C, 63.24; H, 6.30; N, 6.72.

N-(2-Hydroxybenzyl)acetamide (II)——To 10 cc. of 10% NaOH 0.4 g. (X) was added and the mixture was worked up as for the 4-hydroxy compound. Plates (from $CHCl_3$-petr. ether), m.p. 140~141°. *Anal.* Calcd. for $C_9H_{11}O_2N$: C, 65.44; H, 6.71; N, 8.48. Found: C, 64.59; H, 6.78; N, 8.08.

N-(4-Methoxybenzyl)acetamide (XI) (Condensation of N,N′-Methylenediacetamide with Anisole)——A mixture of 21.6 g. of anisole, 31.2 g. of N,N′-methylenediacetamide, and 12.3 g. of $POCl_3$ was heated for 3 hr. on a boiling water bath. The viscous reaction mixture was diluted with H_2O, basified with Na_2CO_3, and the separated oily product was extracted with $CHCl_3$. The extract was dried, the solvent was distilled off, and the residue was fractionated by vacuum distillation. A recovery (1 g.) of anisole was obtained as the first fraction. The second solid fraction, b.p$_2$ 135~140°, weighing 5.1 g., was recrystallized from EtOH to plates, m.p. 52~53°, which was found to be 4,4′-methylenedianisole. *Anal.* Calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found : C, 79.08; H, 6.94.

The third solid fraction, b.p$_2$ 160~163°, weighing 16.4 g., was recrystallized from EtOH to plates, m.p. 95~96°, identical with (XI). *Anal.* Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.50; H, 7.14; N, 8.29.

This compound was refluxed with 6 volumes of 10% HCl for 15 hr. and gave 4-methoxybezylamine-hydrochloride, m.p. 230~231°, undepressed on admixture with an authentic sample synthesized through another route.

After removal of the above fractions, the residue was further distilled in higher vacuum and gave a solid fraction of b.p$_{0.0025}$ 195~197°, weighing 13 g. This fraction was recrystallized from benzene-EtOH to needles, m.p. 135°, which corresponded to bis(acetamidomethyl)anisole by analysis, but the position of acetamidomethyl groups was not further investigated. *Anal.* Calcd. for $C_{13}H_{18}O_3N_2$: C, 62.38; H, 7.25; N, 11.19. Found : C, 62.46; H, 7.24; N, 11.53.

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This compound was refluxed with 10% HCl for 15 hr. and gave the corresponding bis(aminomethyl)anisole hydrochloride, m.p. 265°(decomp.). *Anal.* Calcd. for $C_9H_{16}ON_2Cl_2$: C, 45.19; H, 6.74; N, 11.71. Found : C, 45.30; H, 6.86; N, 11.58.

N-(4-Methoxybenzyl)formamide (XIV)——In an autoclave, 7.5 g. of anisaldehyde oxime (XIII), 4.5 g. of $HCONH_2$, 20 cc. of EtOH, and Raney Ni catalyst (1 g. as 50% alloy) were placed and given 96 atm. (at 20°) of initial H_2 pressure. The mixture was shaken at 125~140° and in about 10 min., approximately 0.2 moles of H_2 was absorbed. The reaction mixture was filtered and the filtrate was evaporated. The residue was distilled in a reduced pressure giving a solid distillate of b.p$_2$ 128~131°. Yield, 7.3 g. Plates (from EtOH), m.p. 75~76°. *Anal.* Calcd. for $C_9H_{11}O_2N$: C, 65.44; H, 6.71; N, 8.48. Found : C, 65.62; H, 6.69; N, 8.49.

4-Methoxybenzylamine Hydrochloride (XII)——To 20 cc. of 10% HCl, 3 g. of (XIV) was added and the mixture was refluxed for 2 hr. The solution was concentrated to leave crystals, which were recrystallized form EtOH to needles, m.p. 232~233°.

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Summary

Acetamidomethylation of phenol and anisole was carried out by heating with N,N′-methylenediacetamide and phosphoryl chloride. Formation of N-(2- and 4-hydroxybenzyl)acetamides resulted in the case of phenol and formation of N-(4-methylbenzyl)acetamide in the case of anisole.

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147. Tanekazu Kubota and Hiroshi Miyazaki : Spectrophotometric Studies on Organic Substances. IX.[1] Ultraviolet Absorption Spectra of Derivatives of Heterocyclic N-Oxides. General Properties on the Solvent Effect and the Substituting Effect.

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In a series of previous papers, the ultraviolet absorption spectra[2~7] and electronic structure[8,9] were reported of various basic heterocyclic N-oxides, such as pyridine, quinoline, and acridine N-oxides, and their simple derivatives. From the above investigations it was well established that ultraviolet absorption spectra bands pertinent to heterocyclic N-oxides exhibit a marked blue shift (frequency shift to a shorter wave-length) in polar solvents containing active hydrogen atoms from those in nonpolar solvents. As

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[1] Part VIII. T. Kubota : Yakugaku Zasshi, **77**, 785 (1957).

[2] H. Hirayama, T. Kubota : Ann. Rept. Shionogi Research Lab., **2**, 121 (1952).

[3] *Idem* : Yakugaku Zasshi, **72**, 1025 (1952).

[4] T. Kubota : *Ibid.*, **74**, 831 (1954).

[5] *Idem* : *Ibid.*, **75**, 1540 (1955).

[6] T. Kubota, H. Miyazaki : Nippon Kagaku Zasshi, **79**, 916 (1958).

[7] T. Kubota : *Ibid.*, **79**, 930 (1958).

[8] *Idem* : *Ibid.*, **80**, 578 (1959).

[9] *Idem* : Yakugaku Zasshi, **79**, 388 (1959).

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