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Reaction of Amide Homologs. III. α-Acylamidoalkylation of 2,4-Xylenol with Bisamides.

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It has already been reported by Stefanovic, *et al.*[1] that N,N′-benzylidenebisamide reacts with aromatic phenols or phenol esters such as acetate and benzoate, resulting in the formation of aromatic α-acylamidobenzyl compounds, when heated together at a high temperature (140∼250°).

On the other hand, the authors found that various aromatic compounds reacted smoothly at lower temperatures with N,N′-alkylidenebisamide in the presence of phosphoryl chloride, affording α-acylamidoalkyl compounds. A brief outline of this reaction was published as Communication to the Editor in this Bulletin.[2] The present paper is a detailed report describing the nature of the reaction in the case of 2,4-xylenol as the aromatic compound.

When 2,4-xylenol is reacted, in the presence of phosphoryl chloride, respectively with N,N′-methylenebisacetamide, N,N′-ethylidenebisacetamide, and N,N′-benzylidenebisacetamide, as one kind of N,N′-alkylidenebisamide, the corresponding α-acetamidoalkyl compounds, i.e. N-(2-hydroxy-3,5-dimethylbenzyl)acetamide, N-(2-hydroxy-α,3,5-trimethylbenzyl)acetamide, and N-(α-phenyl-2-hydroxy-3,5-dimethylbenzyl)acetamide, were obtained in a good yield as shown in the Table I.

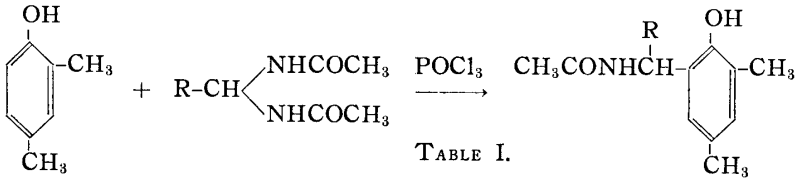

TABLE I.

R	Reaction Temp. (°C)	Reaction Time (hr.)	Solvent	Yield (%)
H	94∼96	1	—	94
〃	80∼85	1.5	Benzene	92
CH_3	80∼85	3	〃	74
C_6H_5	94∼96	1.5	—	98
〃	65∼68	1.5	Chloroform	83

For carrying out the reaction, a mixture of 2,4-xylenol, N,N′-alkylidenebisamide, and phosphoryl chloride, in a molar ratio of 1:1.2:0.5, was heated on a boiling water bath, when the reaction took place in homogeneous system with evolution of hydrogen chloride. It was also practicable to use inert solvents, such as benzene, chloroform, and carbon tetrachloride, for the reaction. In these cases, the reaction mixture became homogeneous after a short time and then gradually separated into two layers, the lower layer of which contained salts of producing mineral acids with the product, α-acetamidoalkyl compound.

In view of Stefanovic's report, N-(α-phenyl-2-hydroxy-3,5-dimethylbenzyl)acetamide was obtained in the lower yield of 74.4% by simply heating together 2,4-xylenol and N,N'-benzylidenebisacetamide. An attempt was made to extend Stefanovic's α-acylamidobenzyl-

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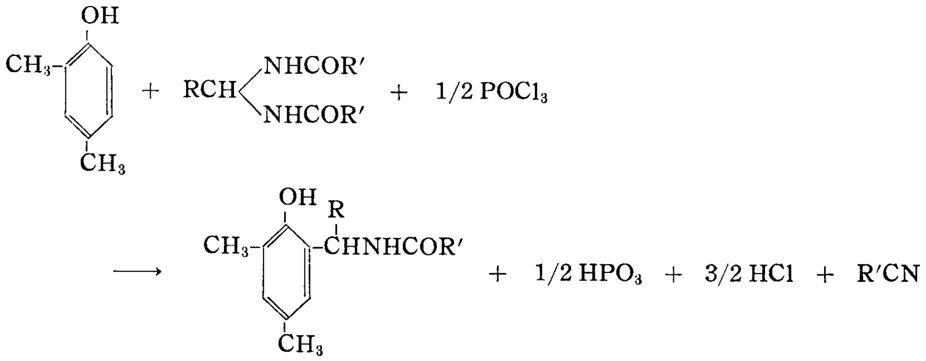
[1] G.J. Stefanovic, *et al.* : Rec. trav. chim., **76**, 249(1957).
[2] M. Sekiya, N. Yanaihara : This Bulletin, **7**, 746(1959).

ation to other N,N′-alkylidenebisamide such as N,N′-methylenebisacetamide and N,N′-ethylidenebisacetamide, but the desired acetamidoalkylation did not occur and in the former, 6,6′-methylene-bis-2,4-xylenol alone was obtained. Hence, it will be recognized that the combination of N,N′-alkylidenebisamide-phosphoryl chloride is the exclusively effective agent for the α-acylamidoalkylation of 2,4-xylenol.

Further studies showed that this reaction is characterized by the formation of a by-product nitrile which corresponded to the one produced from one amide residue of N,N′-alkylidenebisamide. This was confirmed by the experimental results of the following two cases. In the case of the reaction of 2,4-xylenol, N,N′-methylenebisbenzamide, and phosphoryl chloride, benzonitrile was obtained in 90% of theoretical yield from the reaction mixture together with the corresponding amount of the main product, N-(2-hydroxy-3,5-dimethylbenzyl)benzamide. In another case, the reaction of 2,4-xylenol, N,N′-methylenebisacetamide, and phosphoryl chloride was carried out in benzene. In this case, the formation of acetonitrile as a by-product was also presumed, ammonia and acetic acid being confirmed by hydrolysis of its benzene solution obtained by distillation of the reaction mixture.

In all cases of the reaction, hydrogen chloride was evolved; taking account of this fact, the reaction would reasonably be represented by the following general sequence.



It is apparent that in the reaction mixture, α-acylamidoalkyl compound forms unstable salt with metaphosphoric acid and a part of hydrogen chloride.

Furthermore, the effect of two amide residues of N,N′-alkylidenebisamide on the reaction was examined by comparison of the yields between the reactions of 2,4-xylenol with those containing different amide residues such as N,N′-methylenebisformamide, N,N′-methylenebisacetamide, N,N′-methylenebispropionamide, and N,N′-methylenebisbenzamide. The results obtained are summarized in Table II. As is shown, the yield increased in the order of stability of the amide group ($HCONH- < CH_3CH_2-CONH- < CH_3CONH-, C_6H_5-CONH-$). As the order corresponds to that of stability of the nitriles expected to be produced in the reaction, it appears that the reaction tends to produce the more stable nitrile.

In order to search for condensation agents other than phosphoryl chloride, the reaction between 2,4-xylenol and N,N′-methylenebisacetamide was examined by the use of phos-

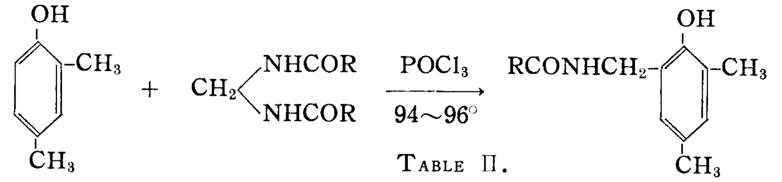


Table II.

R	Yield (%)	2,4-Xylenol recovered (%)
H	38	44
CH_3	94	0
CH_3CH_2	89	5
C_6H_5	93	0

phorus trichloride, phosphorus pentachloride, sulfuryl chloride, and thionyl chloride, but the yield of acetamidomethyl compound did not go higher than 37% (92% in the case of phosphoryl chloride).

The products, N-(2-hydroxy-3,5-dimethylbenzyl)amide homologs, obtained in the foregoing experiments have not previously been described, except for its acetamide.[3] They were hydrolysed with dil. hydrochloric acid giving 2-hydroxy-3,5-dimethylbenzylamine hydrochloride. The reactivity toward hydrolysis was in the descending order of formamide, propionamide, and acetamide, or benzamide, which corresponded to the order of the instability of amides. The other products obtained, N-(2-hydroxy-α,3,5-trimethylbenzyl)acetamide, which was not previously described, and N-(α-phenyl-2-hydroxy-3,5-dimethylbenzyl)acetamide[1] were also hydrolysed to the corresponding amine hydrochlorides, but the latter was relatively resistant to hydrolysis and formed a considerable amount of unknown by-product. These two amine hydrochlorides were also not described previously.

Experimental

Condensation with N,-N′Methylenebisacetamide; Formation of N-(2-Hydroxy-3,5-dimethylbenzyl)acetamide—a) A mixture of 12.2 g. (0.1 mole) of 2,4-xylenol, 15.6 g. (0.12 mole) of N,N′-methylenebisacetamide, and 7.7 g. (0.05 mole) of $POCl_3$ was heated for 1 hr. on a boiling water bath, when evolution of HCl was observed. A homogeneous, viscous, condensation mixture was obtained. This was diluted with H_2O and neutralized with $NaHCO_3$. The resultant precipitate was collected. Yield, 18.1 g. (94%). Needles (from EtOH), m.p. 146~147°. *Anal.* Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.23; H, 7.78; N, 7.29.

b) A mixture of 12.2 g. of 2,4-xylenol, 15.6 g. of N,N′-methylenebisacetamide, 50 cc. of benzene, and 7.7 g. of $POCl_3$ was refluxed for 1.5 hr. on a water bath. The reaction mixture became homogeneous after a short time and then gradually separated into two layers. After being treated with H_2O and $NaHCO_3$, the benzene layer was dried and evaporated. The residue soon crystallized. Yield, 17.8 g. (92%). Needles (from EtOH), m.p. 146~147°. This compound was proved to be identical with the one obtained in (a) by mixed m.p. test.

c) In order to ascertain the formation of acetonitrile which might be expected as one of the reaction products, the reaction mixture obtained in the same manner as described in (b) was treated as in the following. The mixture was distilled to give the benzene fraction, which was redistilled and refluxed for 2 hr. with 30 cc. of 10% HCl. The aqueous layer was basified with NaOH and evaporated to dryness, when NH_3 was proved in the distillate. The residue was extracted with EtOH to remove NaCl. The extract was weakly acidified and treated with 4-phenylphenacyl bromide in the usual manner to give 4-phenylphenacyl acetate, m.p. 108~109°, undepressed on admixture with an authentic sample. *Anal.* Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found : C, 75.15; H, 5.43.

Thus NH_3 and AcOH were confirmed as the saponification products and the possibility of acetonitrile formation in the reaction cannot be excluded.

Condensation with N,N′-Methylenebisbenzamide; Formation of N-(2-Hydroxy-3,5-dimethylbenzyl)benzamide—A mixture of 12.2 g. (0.1 mole) of xylenol, 30.5 g. (0.12 mole) of N,N′-methylenebisbenzamide, and 7.7 g. (0.05 mole) of $POCl_3$ was heated on a boiling water bath for 1 hr. and then treated with H_2O and $NaHCO_3$. The separated product was extracted with benzene. After removal of benzene, the residue was distilled with steam and the steam distillation residue crystallized. Yield, 23.8 g. (93%). Prisms (from petr. ether), m.p. 119~120°. *Anal.* Calcd. for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71; N, 5.49. Found : C, 74.85; H, 6.77; N, 5.67.

The oily substance in the distillate of the foregoing distillation was washed with NaOH solution to remove a small quantity of 2,4-xylenol, taken up with benzene, and dried. After removal of benzene, the residue was distilled under a reduced pressure giving an oily substance of b.p.$_{20}$ 84~85°. Yield, 9.3 g. (90%). This was shown to be identical with benzonitrile by analysis and by being hydrolyzed to benzamide by alkaline H_2O_2. *Anal.* Calcd. for C_7H_5N : C, 81.53, H, 4.89; N, 13.58. Found : C, 81.78; H, 5.10; N, 13.51.

Condensation with N,N′-Methylenebispropionamide; Formation of N-(2-Hydroxy-3,5-dimethylbenzyl)propionamide—A mixture of 6.1 g. (0.05 mole) of 2,4-xylenol, 9.5 g. (0.06 mole) of N,N′-methylenebispropionamide, and 3.8 g. (0.025 mole) of $POCl_3$ was heated on a boiling water bath for 1 hr. and then treated with H_2O and $NaHCO_3$. The separated product was extracted with benzene. The benzene layer was distilled with steam to separate the recovery of xylenol (0.3 g.) and benzene. The

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[3] G. Zigeuner, *et al.* : Monatsh., **81**, 1108(1950).

steam distillation residue soon crystallized. Yield, 9.2 g. (89%). Needles (from benzine), m.p. 106°. *Anal.* Calcd. for $C_{12}H_{17}O_2N$: C, 69.54; H, 8.27; N, 6.76. Found : C, 69.28; H, 8.41; N, 6.91.

Condensation with N,N′-Methylenebisformamide; Formation of N-(2-Hydroxy-3,5-dimethylbenzyl)formamide—A mixture of 6.1 g. (0.05 mole) of 2,4-xylenol, 9.5 g. (0.06 mole) of N,N′-methylenebisformamide, and 3.8 g. (0.025 mole) of $POCl_3$ was heated on a boiling water bath for 1 hr. In this case, evolution of HCl was violent and weakened in a few min. The condensation mixture was treated as in the case of N-(2-hydroxy-3,5-dimethyl)propionamide. Recovery of 2,4-xylenol, 2.7 g. Yield, 3.4 g. (38%). Needles (from petr. benzine), m.p. 116.5~117°. *Anal.* Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.82. Found : C, 66.80; H, 7.59; N, 7.85.

Condensation with N,N′-Benzylidenebisacetamide; Formation of N-(α-Phenyl-2-hydroxy-3,5-dimethylbenzyl)acetamide—a) A mixture of 6.1 g. (0.05 mole) of 2,4-xylenol, 11.5 g. (0.06 mole) of N,N′-benzylidenebisacetamide, and 3.8 g. (0.025 mole) of $POCl_3$ was heated on a boiling water bath for 1.5 hr. and then treated with H_2O and $NaHCO_3$. The separated product was steam distilled and the residue crystallized. Yield, 13.2 g. (98%). Needles (from EtOH), m.p. 153~155°. *Anal.* Calcd. for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11; N, 5.20. Found : C, 75.89; H, 7.20; N, 5.27.

b) A mixture of 6.1 g. of 2,4-xylenol, 11.5 g. of N,N′-benzylidenebisacetamide, 30 cc. of $CHCl_3$, and 3.8 g. of $POCl_3$ was refluxed on a water bath for 1.5 hr. and then treated with H_2O and $NaHCO_3$. The $CHCl_3$ layer was evaporated. The residue solidified, when the impurity was removed by steam distillation. Yield, 11.2 g. (83%). Needles, m.p. 150~151°. This compound was proved by mixed m.p. test to be identical with the one obtained by method (a).

Condensation with N,N′-Ethylidenebisacetamide; Formation of N-(2-Hydroxy-α,3,5-trimethylbenzyl)acetamide—A mixture of 6.1 g. (0.05 mole) of 2,4-xylenol, 8.6 g. (0.06 mole) of N,N′-ethylidenebisacetamide, 20 cc. of benzene, and 3.8 g. (0.025 mole) of $POCl_3$ was refluxed on a water bath for 3 hr. and then treated with H_2O and $NaHCO_3$. The benzene layer was dried and evaporated. The residue was distilled under reduced pressure, giving oily substance, $b.p_1$ 142~152°. Yield, 7.6 g. (74%). After standing for about 2 weeks, this solidified, which was recrystallized from petr. ether-Et_2O to plates, m.p. 105~106°. *Anal.* Calcd. for $C_{12}H_{17}O_2N$: C, 69.54; H, 8.27; N, 6.76. Found : C, 69.25; H, 8.25; N, 6.73.

Hydrolysis of N-(2-Hydroxy-3,5-dimethylbenzyl)amide Homologs—N-(2-Hydroxy-3,5-dimethylbenzyl)amide homologs such as -acetamide, -benzamide, -propionamide, and -formamide all underwent hydrolysis to give 2-hydroxy-3,5-dimethylbenzylamine hydrochloride, when each substance was refluxed for 2 hr. with 6 times its weight of 10% HCl. The reactivity toward hydrolysis was in the descending order of -formamide, -propionamide, and -acetamide or -benzamide, and, among these, -formamide was particularly easily hydrolysed. The product (hydrochloride) was recrystallized from 10% HCl to needles, m.p. 249~250° (decomp.). This was shown to be identical with 2-hydroxy-3,5-dimethylbenzylamine hydrochloride by analysis and by mixed m.p. test. *Anal.* Calcd. for $C_9H_{14}ONCl$: C, 57.58; H, 7.51; N, 7.46. Found : C, 57.44; H, 7.54; N, 7.45.

Hydrolysis of N-(2-Hydroxy-α,3,5-trimethylbenzyl)acetamide—A mixture of N-(2-hydroxy-α,3,5-trimethylbenzyl)acetamide and 6 times its weight of 10% HCl was refluxed for about 2 hr., when a small amount of oily product remained undissolved. Filtration and evaporation gave a crystalline residue, which was recrystallized from dil. HCl to needles, m.p. 214~215°. This was shown to be 2-hydroxy-α,3,5-trimethylbenzylamine hydrochloride by analysis. *Anal.* Calcd. for $C_{10}H_{16}ONCl$: C, 59.57; H, 7.99; N, 6.94. Found : C, 59.56; H, 8.04; N, 7.02.

Hydrolysis of N-(α-Phenyl-2-hydroxy-3,5-dimethylbenzyl)acetamide—A mixture of N-(α-phenyl-2-hydroxy-3,5-dimethylbenzyl)acetamide and 6 times its weight of 10% HCl was refluxed for about 4 hr., when oily substance remained undissolved. It formed crystals (from EtOH), m.p. 116~118°, which were not further investigated. On cooling the HCl solution, a crystalline substance deposited which was recrystallized from 10% HCl to needles, m.p. 191.5~193°, and were shown to be α-phenyl-2-hydroxy-3,5-dimethylbenzylamine hydrochloride by analysis. *Anal.* Calcd. for $C_{15}H_{18}ONCl$: C, 68.30; H, 6.49; N, 5.31. Found : C, 68.31; H, 6.76; N, 5.36.

Summary

N,N′-Alkylidenebisacetamide, such as N,N′-methylenebisacetamide, N,N′-ethylidenebisacetamide, and N,N′-benzylidenebisacetamide, reacted smoothly with 2,4-xylenol by the interaction of phosphoryl chloride, affording N-(α-alkyl-2-hydroxy-3,5-dimethylbenzyl)acetamide by substitution of α-acetamidoalkyl group, in a good yield. Effect of the amide residues in N,N′-alkylidenebisamide on the reaction was examined with N,N′-methylenebisformamide, -acetamide, -propionamide, and -benzamide. The general reaction sequence was presumed and found to be characterized by the formation of a nitrile as a by-product corresponding to the one amide residue in N,N′-alkylidenebisamide.

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