[Chem. Pharm. Bull. 15(1) 108～110 (1967)] UDC 547.562.07.04

15. Minoru Sekiya and Noboru Yanaihara: Reaction of Amide Homologs. XVI.[*1] α-Acetamidoalkylation of β-Naphthol and 2,6-Xylenol.

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Direct introduction of higher α-acetamidoalkyl groupings into the nuclei of β-naphthol and 2,6-xylenol was accomplished by their reactions with the corresponding N,N′-alkylidenebisamides in the presence of phosphoryl chloride.

(Received April 18, 1966)

The reaction of N,N′-alkylidenebisamides with aromatic compounds in the presence of phosphoryl chloride, leading to aromatic α-acylaminoalkyl compounds, has been reported in a number of papers[1～4] from this laboratory. Most of the reactions with a variety of aromatic compounds, described in these papers, involved acetamidomethylation with N,N′-methylenebisacetamides and α-acetamidobenzylation with N,N′-benzylidenebisacetamide, and a few involved α-acetamidoethylation with N,N′-ethylidenebisacetamide; the last was worked up with 2,4-xylenol,[1] β-naphthol[2] and 4-cresol.[2] Among these reactions, α-acetamidoethylation appears worthy of particular mention, as few has been reported on direct introduction of the α-acylaminoethyl grouping to aromatic nucleus by any of the other methods,[5] *i.e.*, Einhorn-Tscherniac reaction, Stefanovic's method and the others, which are only for acylaminomethylation or α-acylaminobenzylation. Even a few examples were for the α-acetamidoethylation, the similar method appeared to be capable of further extension to higher analogs. The present paper deals with the extension to aromatic α-acetamidoalkylation, of which alkyl involves not only ethyl, but also some higher alkyls.

The improved method,[6] lately establised in this laboratory, for the preparation of higher alkylidene analogs of the N,N′-alkylidenebisacetamide (alkylidene: ethylidene, propylidene, *n*-butylidene, *n*-heptylidene, and 3-phenylpropylidene) was available for supplying them as reactants to the reaction. As model substrates for the reaction, were elected β-naphthol and 2,6-xylenol, which are relatively susceptible to electrophilic substitution and the attacking position of which is limited. For β-naphthol, 1-acetamidopropylation, 1-acetamidobutylation, 1-acetamidoheptylation, and 1-acetamido-3-phenylpropylation, and for 2,6-xylenol, 1-acetamidoethylation and 1-acetamidopropylation were successfully performed to give a series of unknown α-acetamidoalkyl-substituted compounds. General reaction procedure is nearly the same as that reported previously for acetamidoethylation of β-naphthol. In brief, this is to carry out the reaction in refluxing chloroform solution of β-naphthol or 2,6-xylenol, N,N′-alkylidenebisacetamide and phosphoryl chloride in 1.0 : 1.6 : 0.8 molar proportion. On referring to the work previously reported,[1] general reaction equation could be written as shown in Chart 1.

The compositions and the infrared spectra of the products obtained indicated the assigned α-acetamidoalkyl phenols. Then, NMR was selected for gaining more reliable evidence regarding the structures of α-acetamidoalkyl groupings, as there would be a fear as to the C-position of the alkyl group attached to the aromatic nucleus, if in

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[*1] Part XV: This Bulletin, **15**, 128 (1967).

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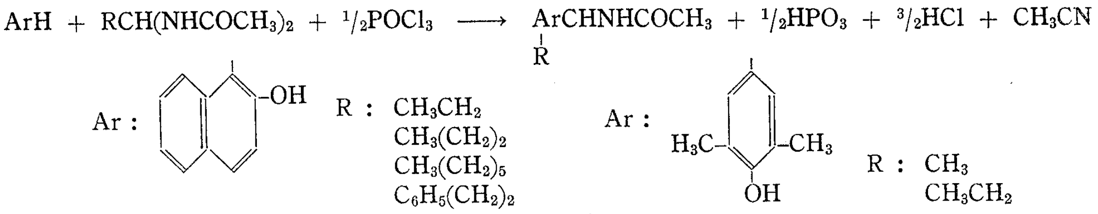

$$ArH + RCH(NHCOCH_3)_2 + {}^{1}/_{2}POCl_3 \longrightarrow \underset{R}{ArCHNHCOCH_3} + {}^{1}/_{2}HPO_3 + {}^{3}/_{2}HCl + CH_3CN$$

Chart 1.

this series of the reaction electrophile would be carbonium ion that might undergo isomerization. We elected two representative samples, α-(1-acetamidopropyl)-β-naphthol and α-(1-acetamidoethyl)-β-naphthol for the NMR measurement, because exact measurements for others were not possible, as difficult solubility in any solvent and complexity of the spectra were encountered. The latter compound, which was one described in a previous paper[2] as a product of α-acetamidoethylation of β-naphthol and not confirmed by NMR measurement, was again prepared as an analogous product by the same procedure as that described in the foregoing. Table I shows the observed spectra of the two samples. Clear informations for the 1-acetamidopropyl and 1-acetamidoethyl structures were obtained by the defined splitting patterns for their terminal C-methyls, which appeared respectively as triplet at τ8.97 (3-3H) and doublet at 8.33 (2-3H). The signals for the 2-methylene protons of the 1-acetamidopropyl grouping were in part overlapped with that of the methyl protons of the acetyl. The low intensity multiplets expected for 1-methine protons of the two 1-acetamidoalkyl groupings could not be clearly observed because of the poor signal-to-noise ratio. Then, these ascertainments for the two samples would serve as evidence also for the structures of α-acetamidoalkyl groupings of the other analogous products.

While the higher α-acetamidoalkylations of β-naphthol and 2,6-xylenol were successully exemplified as shown above, the similar method would appear to be capable for extension to other phenols or aromatic compounds relatively susceptible to electrophilic substitution.

TABLE I. NMR Spectra[a] of α-(1-Acetamidoalkyl)-β-naphthols

α-Substituent	τ-Value (multiplicity[b]) (J in c.p.s.)			
	3-3H	2-2H	1-H	acetyl-CH_3
$CH_3CH_2\dot{C}HNHCOCH_3$	8.97(t)(7.0)	7.30~7.97	3.71~4.16(m)[c]	7.42(s)
	2-3H	1-H		
$CH_3\dot{C}HNHCOCH_3$	8.33(d)(7.0)	3.69~4.15(m)[c]		7.68(s)

a) Spectra were measured in trifluoroacetic acid with a JNM-3H-60 spectrometer at 60 Mc. Values are given in p.p.m. relative to tetramethylsilane as internal standard.
b) s=singlet, d=doublet, t=triplet, m=multiplet.
c) Complex signal of uncertain multiplicity.

Experimental

General Procedure——In 30 ml. of $CHCl_3$ 0.025 mole of β-naphthol or 2,6-xylenol and 0.04 mole of N,N'-alkylidene-bisacetamide were dissolved on heating on a water bath and then 0.02 mole of $POCl_3$ was added. The mixture was refluxed for 3 hr. During the course of the reaction, gentle evolution of HCl was observed. To the mixture roughly 50 ml. of ice water was added and, with stirring, $NaHCO_3$ was sufficiently added to neutralize. The $CHCl_3$ layer was separated, if desired, an additional $CHCl_3$ was used, and dried over Na_2SO_4. After removal of $CHCl_3$, the residue was crystallized by means of addition of ether or petr. ether, or of column chromatography. Yields, based on the starting β-naphthol or 2,6-xylenol, and assignments of the products are indicated in the following.

α-(1-Acetamidopropyl)-β-naphthol——Was obtained in 62% yield. Recrystallization from ether gave prisms, m.p. 194~195°. *Anal.* Calcd. for $C_{15}H_{17}O_2N$: C, 74.05; H, 7.04; N, 5.76. Found : C, 73.92; H, 7.31; N, 5.91. IR λ_{max}^{KBr} cm^{-1} : 1641, 1522 (-CONH-).

α-(1-Acetamidobutyl)-β-naphthol——Was obtained in 70% yield. Recrystallization from EtOH gave prisms, m.p. 223~224°. *Anal.* Calcd. for $C_{16}H_{19}O_2N$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.38; H, 7.26; N, 5.50. IR $\lambda_{\max}^{\text{KBr}}$ cm^{-1}: 1639, 1530 (-CONH-).

α-(1-Acetamidoheptyl)-β-naphthol——Was crystallized by chromatography on a silicagel column using $CHCl_3$ as an eluent. Yield, 41%. Recrystallization from ether gave prisms, m.p. 98~100°. *Anal.* Calcd. for $C_{19}H_{25}O_2N$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.35; H, 8.29; N, 4.48. IR $\lambda_{\max}^{\text{KBr}}$ cm^{-1}: 1627, 1526 (-CONH-).

α-(1-Acetamido-3-phenylpropyl)-β-naphthol——Was obtained in 37% yield. Recrystallization from MeOH gave prisms, m.p. 184~185°. *Anal.* Calcd. for $C_{12}H_{21}O_2N$: C, 78.97; H, 6.68; N, 4.39. Found: C, 78.53; H, 6.72; N, 4.38. IR $\lambda_{\max}^{\text{KBr}}$ cm^{-1}: 1639, 1523 (-CONH-).

4-(1-Acetamidoethyl)-2,6-dimethylphenol——Was obtained in 23% yield. Recrystallization from EtOH gave plates, m.p. 177~178°. *Anal.* Calcd. for $C_{12}H_{17}O_2N$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.33; H, 8.21; N, 6.82. IR $\lambda_{\max}^{\text{KBr}}$ cm^{-1}: 1634, 1560 (-CONH-).

4-(1-Acetamidopropyl)-2,6-dimethylphenol——Was crystallized by chromatography on a silicagel column using $CHCl_3$ as an eluent. Yield, 25%. Recrystallization from $CHCl_3$-ether gave prisms, m.p. 131~132°. *Anal.* Calcd. for $C_{13}H_{19}O_2N$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.45; H, 8.56; N, 6.62. IR $\lambda_{\max}^{\text{KBr}}$ cm^{-1}: 1640, 1559 (-CONH-).

Thanks are due to Mr. K. Narita and Miss N. Yamazaki for elemental analyses.

[Chem. Pharm. Bull. 15(1) 110~118 (1966)]

UDC 615.74-011 : 547.964.4.07

16. Noboru Yanaihara, Minoru Sekiya*1, Keijiro Takagi, Hitoshi Kato, Masamichi Ichimura, and Taku Nagao*2 :

Syntheses of Bradykinin Analogs Containing Sarcosine Residues and Their Biological Activities.*3

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Five sarcosine-containing bradykinin analogs such as 2-, 3-, and 7-sarcosine, 2,3-disarcosine, and 2,3,7-trisarcosine bradykinins were synthesized Biological activities of these analogs were compared with those of synthetic bradykinin.

(Received April 25, 1966)

Schröder[1)] has recently reported the syntheses of bradykinin analogs in which proline residue in position 2, 3, or 7 of the molecule was replaced by alanine, and he described that 3-alanine bradykinin possesses the full activity both on the guinea-pig ileum and on the blood pressure of rabbit, whereas the replacement of proline residue in position 2 or 7 causes a considerable decrease of the biological activity.

On the basis of the evidences[2~6)] presently available, including the above observation, it seemed that proline residues in positions 2 and 7 play an important role in

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