Notes

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Polycyclic N-Hetero Compounds. IV.¹⁾ Reactions of 4-Amino-5-arylpyrimidines with Dimethyl Sulfoxide

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Methylenebis(4-amino-5-arylpyrimidines) (IVa, IVb, VI, VIII) were obtained from 4-acetamido-5-arylpyrimidines (IIa, IIb) and 4-amino-5-arylpyrimidines (Ia, Ib, V, VII) on heating with dimethyl sulfoxide.

Our previous paper³⁾ reported the synthesis of 1,3,10-triazaphenanthrenes from 4-acetamido-5-arylpyrimidines by heating with polyphosphoric acid. However, the Bischler-Napieralski cyclization of 4-acetamido-5-phenylpyrimidine (IIa) itself failed and the resulting product was always deacetylated 4-amino-5-phenylpyrimidine (Ia).

When the cyclization was tried in dimethyl sulfoxide (Me₂SO) solution with phosphoryl chloride as a condensing agent, the isolated product was not 1,3,10-triazaphenanthrene (III), but methylenebis(4-amino-5-phenylpyrimidine) (IVa) with 4-amino-5-phenylpyrimidine (Ia). In the infrared spectrum (IR) of IVa, C=O band disappeared and N-H band appeared at 3320 cm⁻¹. The nuclear magnetic resonance (NMR) spectrum of IVa showed the absorption of CH₂ group at τ 4.88 (2H, t,⁴⁾ $J=6$ Hz) and of two NH groups at τ 3.58 (2H, bt,⁴⁾ $J=6$ Hz), and with D₂O the former changed to singlet and the latter disappeared.

As shown in Chart 1, similar reaction of 4-acetamido-5-(*p*-methoxyphenyl)pyrimidine (IIb) afforded methylenebis(4-amino-5-*p*-methoxyphenyl)pyrimidine (IVb) and deacetylated 4-amino-5-(*p*-methoxyphenyl)pyrimidine (Ib). During the above reaction, dimethyl sulfide (bp 41°) was produced considerably and the reaction temperature did not rise. Isolation of the products was fairly troublesome as there were many by-products (ascertained by a thin-layer chromatography (TLC)). When the reaction was carried out without phosphoryl chloride, that is, IIa with Me₂SO alone, IVa and Ia were obtained from IIa and IVb and Ib from IIb. IVa was hydrolysed to Ia with hot 2N HCl and the ultraviolet (UV) spectra of IVa and Ia were closely similar.

Traynelis and Hergenrother⁵⁾ obtained methylenebisbenzamide and methylenebisacetamide from benzamide and acetamide on heating with Me₂SO respectively and stated that the decomposition of Me₂SO to formaldehyde was prompted with amides, and the resulting formaldehyde built the methylene bridge.

Our present reaction mechanism seems to be similar to that proposed by Traynelis and Hergenrother.⁵⁾ Since the deacetylation always occurred during the reaction, Ia was heated with Me₂SO and the methylenebis compound (IVa) was obtained with a better yield and easier purification. Analogous 4-amino-5-arylpyrimidines (Ib, V, VII) easily gave methylenebis compounds (IVb, VI, VIII) on heating with Me₂SO.

1) Part III: T. Koyama, T. Hirota, Y. Shinohara, S. Fukuoka, and S. Ohmori, *Chem. Pharm. Bull.* (Tokyo), **23**, 494 (1975).

2) Location: *I-1 Tsushima-naka 1-chome, Okayama, 700, Japan.*

3) T. Koyama, T. Hirota, M. Yamato, and N. Ohta, *Yakugaku Zasshi*, **93**, 330 (1973).

4) Refer to experimental part.

5) V.J. Traynelis and W.L. Hergenrother, *J. Org. Chem.*, **29**, 221 (1964).

Experimental

Melting points are uncorrected. NMR spectra were taken on a Hitachi Model R-22 spectrometer (90 MHz) in CDCl_3 with tetramethylsilane as an internal standard (τ value), s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet, b, broad. IR spectra were recorded on a Nihon Bunko Model IR-G spectrometer in KBr disk. UV spectra were taken on a Hitachi EPS-2 spectrophotometer in 99% EtOH. Mass spectra (MS) were taken on a Hitachi RMU-7M spectrometer with a direct inlet system.

Methylenebis(4-amino-5-phenylpyrimidine) (IVa)—a) To a Me_2SO (20 ml) solution of 2.3 g of IIa, 4.5 g of POCl_3 was added dropwise under cooling, exothermic reaction occurred and volatile liquid refluxed vigorously. After 10 hr heating, volatile colorless liquid was collected by distillation, bp 41° , CH_3SCH_3 . NMR (CCl_4): 7.26 (s). These data agree with the bp and chemical shift of authentic sample on NMR. Traynelis and Hergenrother⁵ obtained CH_3SCH_3 by acid catalysed decomposition of Me_2SO . After evaporation of unchanged Me_2SO *in vacuo*, the residue was dissolved in H_2O , made alkaline with Na_2CO_3 , and extracted with ether. The extract was washed with H_2O , dried over Na_2SO_4 , and ether was evaporated. The light brown viscous residue was recrystallized repeatedly from dil. EtOH to 86 mg (7.5%) of IVa as colorless prisms, mp $221\text{--}223^\circ$. Anal. Calcd. for $\text{C}_{21}\text{H}_{18}\text{N}_6$: C, 71.16; H, 5.12; N, 23.72. Found: C, 71.28; H, 5.20; N, 23.61. Mass Spectrum m/e : 354 (M^+). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3320 (N-H). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 249 (4.26), 282 (4.09). NMR: 4.88 (2H, t, $J=6$ Hz, CH_2 , to singlet with D_2O exchange), 3.58 (2H, bt, $J=6$ Hz, 2-NH, disappeared with D_2O exchange), 2.7—2.4 (10H, m, 2- C_6H_5), 1.82 (2H, s, 2-pyrimidine ring $\text{C}_6\text{-H}$), 1.45 (2H, s, 2-pyrimidine ring $\text{C}_2\text{-H}$).

The mother liquid was evaporated, the residue was dissolved in benzene, and chromatographed over alumina. The ether eluate of the column was recrystallized from benzene-cyclohexane to 46 mg (2.5%) of Ia, as pale yellow needles, mp $151\text{--}153^\circ$, identical with the authentic sample (mixed mp, IR, NMR and TLC).

b) A mixture of 2 g of IIa and 20 ml of Me_2SO was heated at $170\text{--}180^\circ$ for 12 hr with stirring. After evaporation of Me_2SO *in vacuo*, benzene-soluble fraction of the tarry residue was purified by preparative TLC (Merck Kieselguhr G, benzene: CHCl_3 : Me_2CO =3: 2: 1). The parts of R_f ca. 0.6 were collected and recrystallized from dil. EtOH to 38 mg (1.4%) of IVa as colorless prisms, identical with the material prepared by the method (a) (mixed mp, IR, NMR, and TLC).

From the parts of R_f ca. 0.5 above preparative TLC, Ia was obtained, identical with the authentic sample (mixed mp, IR, NMR, and TLC).

c) A mixture of 2.1 g of Ia and 20 ml of Me_2SO was heated at $150\text{--}160^\circ$ for 24 hr with stirring. After evaporation of Me_2SO *in vacuo*, the residue was treated with H_2O and extracted with ether. The extract

was washed with H₂O, dried over Na₂SO₄, and the solvent was evaporated. The residue was recrystallized repeatedly from dil. EtOH to 0.34 g (15%) of IVa as colorless prisms, mp 221—223°, identical with the material prepared by method (a) (mixed mp, IR, NMR, and TLC).

Methylenebis (4-amino-5-*p*-methoxyphenylpyrimidine) (IVb)—a) To a solution of 3 g of 4-acetamido-5-(*p*-methoxyphenyl)pyrimidine (IIb) and 30 ml of Me₂SO, 5.7 ml of POCl₃ was added dropwise under cooling and the mixture was refluxed vigorously. After refluxing for 10 hr, the resulting solution was diluted with H₂O, made alkaline with Na₂CO₃, and extracted with ether. The ether layer was washed with H₂O, dried over Na₂SO₄, and the solvent was evaporated. The residue was dissolved in CH₂Cl₂ and chromatographed over alumina. The CH₂Cl₂ eluate afforded a brown powder which was separated by preparative TLC (Merck, Kieselguhr G, acetone: cyclohexane: CHCl₃ = 1: 6: 3), and the parts of *Rf ca.* 0.5 were collected. Recrystallization from dil. EtOH gave 50 mg (1.5%) of IVb as colorless prisms, mp 197—198°. *Anal.* Calcd. for C₂₃H₂₂O₂N₆: C, 66.65; H, 5.35; N, 20.28. Found: C, 66.79; H, 5.28; N, 20.48. Mass Spectrum *m/e*: 414.1847 (M⁺) (Calcd. 414.1844). IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 3310 (N-H). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ϵ): 267.5 (4.69), 227 (4.73). NMR: 6.13 (6H, s, 2-OCH₃), 4.90 (2H, t, *J* = 6 Hz, CH₂), 3.60 (2H, bt, *J* = 6 Hz, 2-NH, disappeared with D₂O exchange and CH₂ signal changed to a singlet), 2.95, 2.74 (each 4H, A₂B₂ q, *p*-OCH₃-phenyl-H), 1.90 (2H, s, pyrimidine ring C₆-H), 1.45 (2H, s, pyrimidine ring C₂-H).

The parts of *Rf ca.* 0.4 above preparative TLC were collected and recrystallized from benzene-cyclohexane to 74 mg (3.5%) of Ib, mp 164—165°, identical with the authentic sample (mixed mp, IR, NMR, and TLC).

b) A mixture of 2 g of IIb and 20 ml of Me₂SO was heated at 180° for 24 hr with stirring. After evaporation of Me₂SO *in vacuo*, the benzene-soluble part of the residue was chromatographed over alumina. The CHCl₃ eluate was rechromatographed over silica gel. The benzene-ether (1: 1) eluate was recrystallized from dil. EtOH to 60 mg (1.7%) of IVb as colorless prisms, mp 197—198°, identical with the material prepared by method (a) (mixed mp, IR, NMR, and TLC).

Ib was obtained from the former chromatography eluted with ether, identical with the authentic sample (mixed mp, IR, NMR, and TLC).

c) A mixture of 1.2 g of Ib and 10 ml of Me₂SO was heated at 150—160° for 24 hr with stirring. After evaporation of Me₂SO, the residue was treated with H₂O and extracted with ether. The extract was washed with H₂O, dried over Na₂SO₄, and the solvent was evaporated. The residue was recrystallized from dil. EtOH to 0.14 g (11%) of IVb as colorless prisms, mp 197—198°, identical with the material prepared by method (a) (mixed mp, IR, NMR, and TLC).

Methylenebis (4-amino-5-(1-naphthyl) pyrimidine) (VI)—A mixture of 1.1 g of 4-amino-5-(1-naphthyl)pyrimidine (V) and 15 ml of Me₂SO was heated at 150—160° for 24 hr with stirring. After evaporation of Me₂SO *in vacuo*, the residue was recrystallized from dil. EtOH to 0.24 g (21%) of VI as colorless needles, mp 192—193°. *Anal.* Calcd. for C₂₉H₂₂N₆: C, 76.63; H, 4.88; N, 18.49. Found: C, 76.39; H, 5.00; N, 18.65. IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 3350 (N-H). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ϵ): 282 (4.46). NMR: 5.18 (2H, t, *J* = 6.5 Hz, CH₂), 4.19 (2H, bt, *J* = 6.5 Hz, 2-NH, disappeared with D₂O exchange and CH₂ signal changed to a singlet), 2.75—2.05 (14H, m, naphthyl-H), 1.83 (2H, s, 2-pyrimidine ring C₆-H), 1.75, 1.71 (each 1H, s, pyrimidine ring C₂-H).

Methylenebis(4-amino-5-(2-naphthyl)pyrimidine) (VIII)—A mixture of 0.40 g of 4-amino-5-(2-naphthyl)pyrimidine (VII) and 10 ml of Me₂SO was heated at 150—160° for 24 hr. After evaporation of Me₂SO *in vacuo*, the residue was recrystallized from dil. EtOH to pale yellow needles, mp 167—170°, which was again recrystallized from benzene to 0.10 g (22%) of VIII as colorless needles, mp 173—174°. *Anal.* Calcd. for C₂₉H₂₂N₆: C, 76.63; H, 4.88; N, 18.49. Found: C, 76.79; H, 4.80; N, 18.40. IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 3350 (N-H). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ϵ): 263 (4.65). NMR: 4.90 (2H, t, *J* = 6 Hz, CH₂), 3.52 (2H, bt, *J* = 6 Hz, 2-NH, disappeared with D₂O exchange and CH₂ signal changed to singlet), 2.65—1.95 (14H, m, 2-naphthyl-H), 1.78 (2H, s, 2-pyrimidine ring C₆-H), 1.45 (2H, s, 2-pyrimidine ring C₂-H).