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 paper[3] 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 (Me_2SO) 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 CH_2 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 D_2O 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 Me_2SO 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 Hergenrother[5] obtained methylenebisbenzamide and methylenebisacetamide from benzamide and acetamide on heating with Me_2SO respectively and stated that the decomposition of Me_2SO 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 Me_2SO 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 Me_2SO.

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

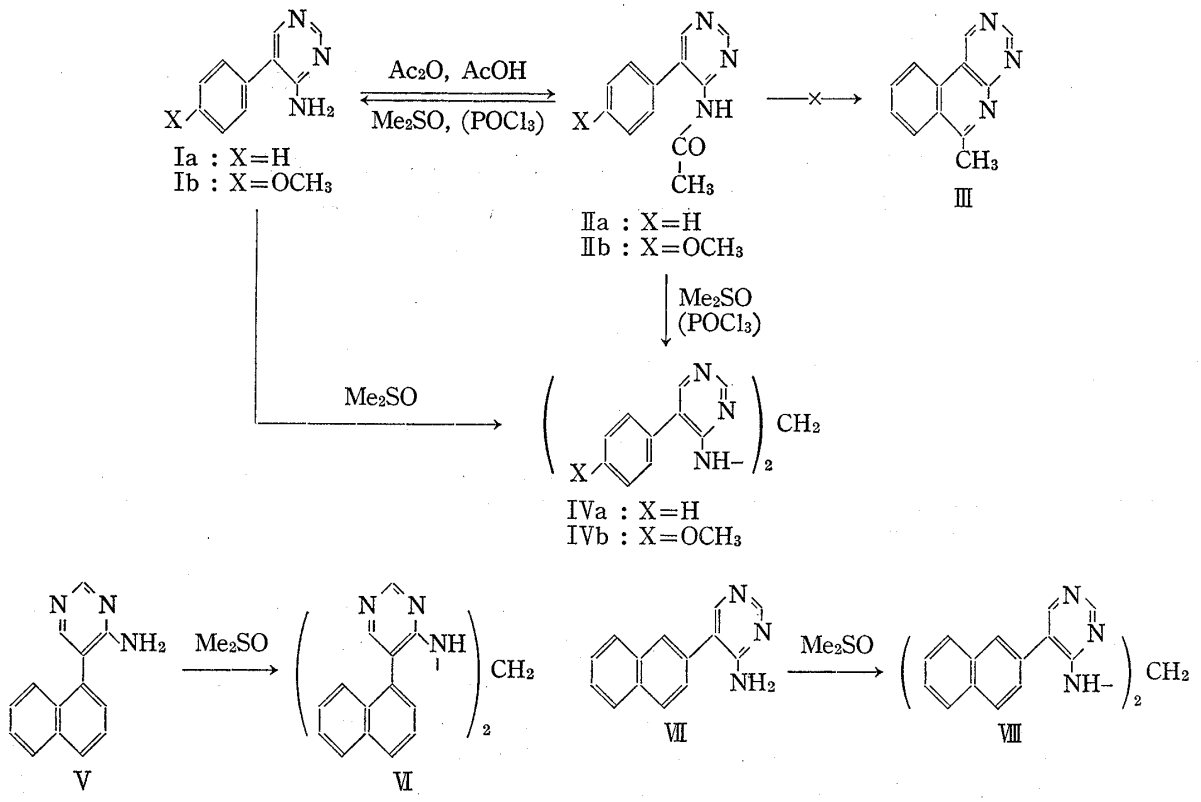

Chart 1

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 Hergenrother[5] 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—223°. *Anal.* Calcd. for $C_{21}H_{18}N_6$: 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 ν_{max}^{KBr} cm^{-1}: 3320 (N–H). UV λ_{max}^{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 C_6–H), 1.45 (2H, s, 2-pyrimidine ring C_2–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—153°, 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—180° 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 *Rf 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 *Rf 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—160° 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 H_2O, dried over Na_2SO_4, 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 Me_2SO, 5.7 ml of $POCl_3$ was added dropwise under cooling and the mixture was refluxed vigorously. After refluxing for 10 hr, the resulting solution was diluted with H_2O, made alkaline with Na_2CO_3, and extracted with ether. The ether layer was washed with H_2O, dried over Na_2SO_4, and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 and chromatographed over alumina. The CH_2Cl_2 eluate afforded a brown powder which was separated by preparative TLC (Merck, Kieselguhr G, acetone: cyclohexane: $CHCl_3$=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 $C_{23}H_{22}O_2N_6$: 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 ν_{max}^{KBr} cm^{-1}: 3310 (N–H). UV λ_{max}^{EtOH} nm (log ε): 267.5 (4.69), 227 (4.73). NMR: 6.13 (6H, s, 2-OCH_3), 4.90 (2H, t, J=6 Hz, CH_2), 3.60 (2H, bt, J=6 Hz, 2-NH, disappeared with D_2O exchange and CH_2 signal changed to a singlet), 2.95, 2.74 (each 4H, A_2B_2 q, *p*-OCH_3-phenyl-H), 1.90 (2H, s, pyrimidine ring C_6–H), 1.45 (2H, s, pyrimidine ring C_2–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 Me_2SO was heated at 180° for 24 hr with stirring. After evaporation of Me_2SO *in vacuo*, the benzene-soluble part of the residue was chromatographed over alumina. The $CHCl_3$ 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 samlpe (mixed mp, IR, NMR, and TLC).

c) A mixture of 1.2 g of Ib and 10 ml of Me_2SO was heated at 150—160° for 24 hr with stirring. After evaporation of Me_2SO, the residue was treated with H_2O and extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4, 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 Me_2SO was heated at 150—160° for 24 hr with stirring. After evaporation of Me_2SO *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 $C_{29}H_{22}N_6$: C, 76.63; H, 4.88; N, 18.49. Found: C, 76.39; H, 5.00; N, 18.65. IR ν_{max}^{KBr} cm^{-1}: 3350 (N–H). UV λ_{max}^{EtOH} nm (log ε): 282 (4.46). NMR: 5.18 (2H, t, J=6.5 Hz, CH_2), 4.19 (2H, bt, J=6.5 Hz, 2-NH, disappeared with D_2O exchange and CH_2 signal changed to a singlet), 2.75—2.05 (14H, m, naphthyl-H), 1.83 (2H, s, 2-pyrimidine ring C_6–H), 1.75, 1.71 (each 1H, s, pyrimidine ring C_2–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 Me_2SO was heated at 150—160° for 24 hr. After evaporation of Me_2SO *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 $C_{29}H_{22}N_6$: C, 76.63; H, 4.88; N, 18.49. Found: C, 76.79; H, 4.80; N, 18.40. IR ν_{max}^{KBr} cm^{-1}: 3350 (N–H). UV λ_{max}^{EtOH} nm (log ε): 263 (4.65). NMR: 4.90 (2H, t, J=6 Hz, CH_2), 3.52 (2H, bt, J=6 Hz, 2-NH, disappeared with D_2O exchange and CH_2 signal changed to singlet), 2.65—1.95 (14H, m, 2-naphthyl-H), 1.78 (2H, s, 2-pyrimidine ring C_6–H), 1.45 (2H, s, 2-pyrimidine ring C_2–H).