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Pyrimido-1,4-benzothiazines and -1,4-benzothiazepines. I. Oxidative Coupling and Pummerer Rearrangement of Pyrimido-1,4-benzothiazine and Its Sulfoxide

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Pyrimido-(1,4)-benzothiazinedione (I) underwent oxidative coupling with water, alcohols and morpholine at the 4*a*-angular position in the presence of iodine and base such as triethylamine or morpholine. The facile Pummerer rearrangement of its sulfoxide also give 4*a*-substituted derivatives. The mechanisms of these reaction are also discussed.

A recent article[2] from our laboratory has described a convenient preparative method of 1,3-dimethyl-10*H*-pyrimido(5,4-*b*)-1,4-benzothiazine-2,4-(1*H*,3*H*)-dione (I), which is of interest from the pharmacological and chemical viewpoints. Goldman[3] and Fenner[4,5] have reported the synthesis of derivatives of I *via* alternate routes and the unusual chemical natures of this intriguing system, *i.e.*, the formation of stable radicals and ylides, and occurrence of the reverse Pummerer–type rearrangement of 4*a*-chloro derivative to the corresponding sulfoxide.

The present paper describes our own findings on the reactivity of I and its sulfoxide (II), involving a novel oxidative coupling of I with water, methanol, ethanol or morpholine at the angular 4*a*-position and the Pummerer–type rearrangement of II leading to 4*a*-substituted derivatives. The mode of the reactions are also discussed in connection with that of the phenothiazine system.

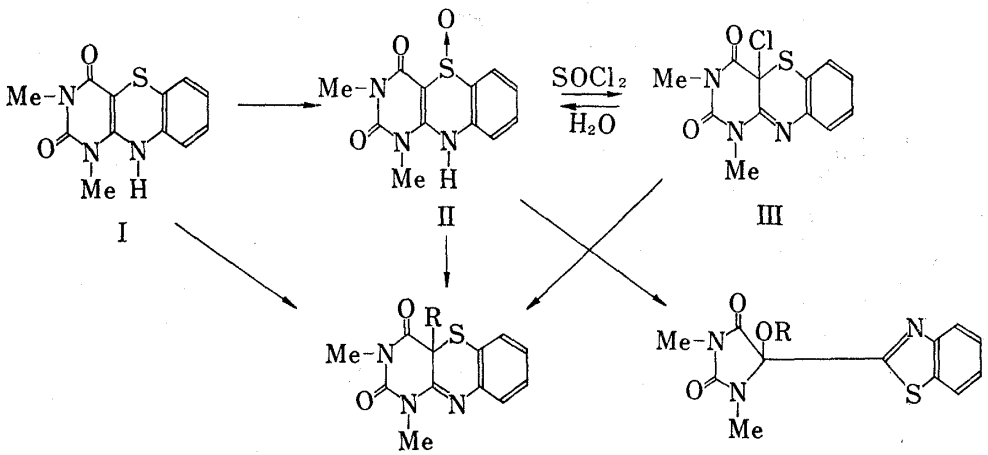

Chart 1

1) Location: *6–1, Higashi 5-Chome, Mitahora, Gifu, 502, Japan.*
2) Y. Maki, T. Hiramitsu, and M. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **22**, 1265 (1974).
3) J.M. Goldman and E.G. Andrews, as quoted in "Chem. Eng. News," July 10, 1967, p. 44; Abstract of Papers, "1st International Congress of Heterocyclic Chemistry, New Mexico, 1967; US Patent 3483198.
4) H. Fenner, *Arzneim. Forsch.*, **20**, 1815 (1970).
5) H. Fenner, *Tetrahedron Letters*, **1970**, 617.

When a solution of I in methanol was heated under reflux in the presence of iodine and excess triethylamine, 4*a*-methoxy derivative (IVb) was obtained in 70% yield. The reaction mixture developed initially an intense green color and then a brown color at the end.

The nuclear magnetic resonance spectrum (NMR) of IVb showed the presence of a methoxy group (3H, singlet, δ 3.17). Absence of an NH grouping in the molecule was confirmed by infrared (IR) and NMR spectra. The ultraviolet spectrum (UV) of IVb (λ_{max}^{EtOH} mμ (ε): 225(35500), 251(28500), 313(21000)) was different from that of I (λ_{max}^{EtOH} mμ (ε): 218(14500), 251(16400), 286(7830)). One of two carbonyl stretching bands in its IR spectrum (1730 cm^{-1}) was observed in the higher frequency than that of I (1680 cm^{-1}). Analogously, 4*a*-ethoxy derivative (IVc) was obtained in 70% yield. Treatment of I with morpholine in the presence of iodine afforded 4*a*-morpholino derivative (IVd) in 84% yield.

These compounds (IVb—d) were identical in every respect with the samples prepared by Goldman's procedure which involves the reaction of 4*a*-chloro derivative (III) with methanol, ethanol and morpholine.

Unstable 4*a*-hydroxy derivative (IVa) was isolated when I was treated with iodine and triethylamine in wet chloroform or benzene at room temperature. Goldman has suggested that the smooth conversion of sulfoxide (II) or 4*a*-chloro derivative (III) into 2-(1,3-dimethyl-5-hydroxy-5-hydantoinyl)benzothiazole (Va) could proceed *via* an intermediate (IVa). In agreement with his aspect, the formation of Va was observed upon heating IVa with or without solvent.

The presence of triethylamine seems to be requisite for the coupling of I with alcohols. In fact, prolonged heating of a mixture of I and iodine in ethanol without triethylamine resulted in the almost recovery of I. Employment of other oxidizing agents such as lead dioxide and potassium ferricyanide did not give satisfactory results.

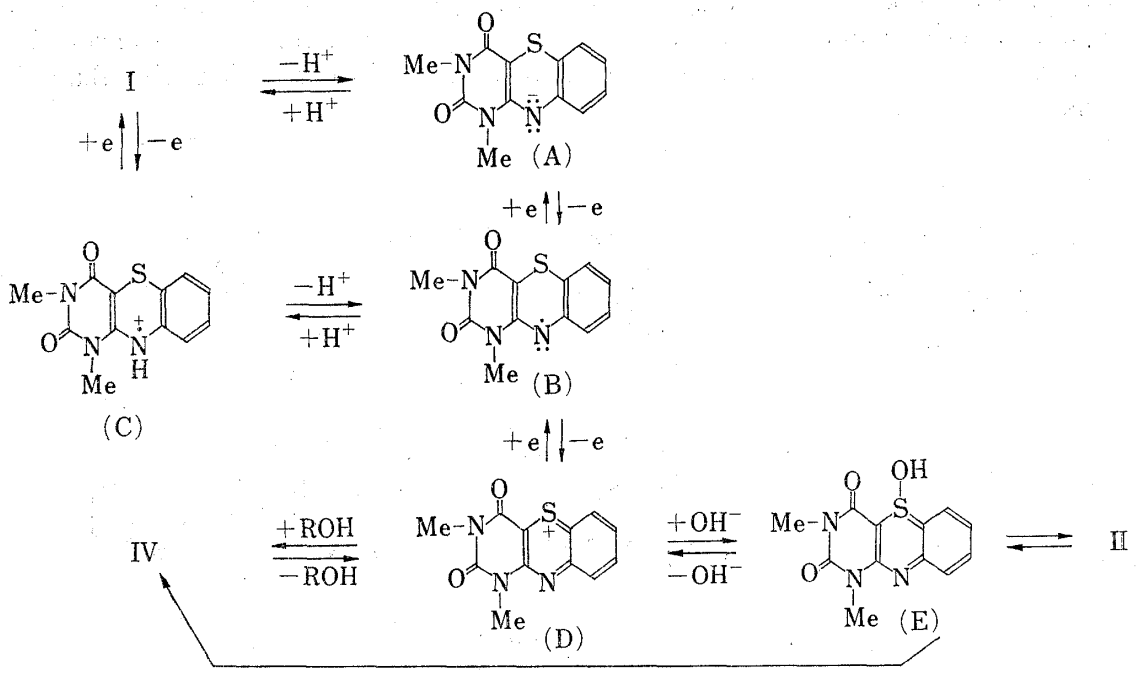

Chart 2

Phenothiazines have long been known to undergo one electron oxidation to give radicals and cationic species.[6,7] Analogously, I could easily form radical (B), radical cation (C) and thiazinium ion (D) which play significant roles in the reaction of I. Goldman[3] has reported isolation of the radical (B) by reduction of 4*a*-chloro derivative (III) with ferrous ion. The

6) For a review, see C. Bodea and I. Silberg, "Advance in Heterocyclic Chemistry," Vol. 9, ed. by A.R. Katritzky and A.J. Boulton, Academic Press, New York and London, 1968, p. 321.
7) P. Hansen and R.O.C. Norman, *J. Chem. Soc. Perkin II*, **1973**, 264 and cited references.

formation of (B) has been also proved on the basis of electron spin resonance spectrum (ESR) when biacetyl was added to the solution of I in dimethyl sulfoxide.[5]

The green solution obtained initially in the oxidative coupling leading to IV showed a well-defined ESR signal (triplet, a_N 4.9 gaus) identical with that of the radical (B) previously observed by Fenner.[5]

Treatment of IVb with borontrifluoride etherate resulted in the formation of an unstable purple powder which appears to be the thiazinium ion (D) tetrafluoroborate (NMR (CD_3NO_2) δ: 3.45 (3H, s, N-C$\underline{H}_3$), 3.85 (3H, s, NC$\underline{H}_3$), 7.25—8.00 (m, aromatic protons)). Addition of ethanol to the salt thus obtained gave easily IVc.

On the basis of above observations, the coupling of I in the presence of iodine as an oxidizing agent with water, alcohol or amine leading to IVa—d can be explained in terms of a reaction sequence of I→A→B→D→IV. The presence of base seems to be necessary for the facile formation of the radical (B) *via* one-electron oxidation of the N-anion (A) formed by deprotonation of I. However, an alternative formation of (B) involving deprotonation of the radical cation (C) generated directly from I cannot be excluded.

Analogous oxidative coupling has been observed when 2-phenyl-phenathro(9,10-*d*)-imidazoles were treated with potassium ferricyanide in alcohols containing caustic alkali.[8]

Goldman[3] has pointed out that sulfoxide (II) undergoes the Pummerer rearrangement upon treatment with thionyl chloride to give 4*a*-chloro derivative which curiously reproduces II in contact with water. We found that the reaction of II with methanol and ethanol takes place the Pummerer-type rearrangement leading to 4*a*-methoxy or ethoxy derivatives (IVb, c).

Oxidation of I with an equimolar amount of *m*-chloroperbenzoic acid in chloroform gave II in 87% yield. A suspension of the sulfoxide (II) in methanol or ethanol was heated under reflux for 20 hr, IVa, b were obtained in 43% and 50% yields, respectively. Under these conditions, the presence of 4*a*-hydroxy derivative (IVa) and the ring-contracted product (Va) in the reaction mixture were often detected by thin-layer chromatography (TLC).

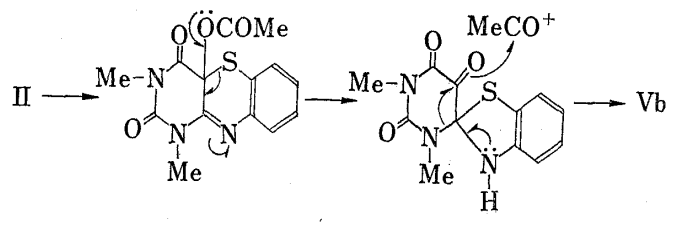

Chart 3

A similar type of the rearrangement[9] has been observed in 1,3-dialkyl-1*H*-pyrimido(5,4-*b*)-1,4-thiazine-2,4,7(3*H*,5*H*,8*H*)-trionsulfoxide, in which the solvent molecule is incorporated exclusively at the C_6-position (the methylene carbon), but not at the 4*a*-angular position. The rearrangement may involve a nucleophilic attack of alcohols or water at the angular 4*a*-position of a hydroxy tautomeric form of the sulfoxide (E) in a concerted fashion (see Chart 2).

Upon treatment of II with hot acetic anhydride, 2-(1,3-dimethyl-5-acetoxy-5-hydantoinyl)benzothiazole (Vb) was obtained in 80% yield. The structure of Vb was confirmed on the basis of spectral data, microanalytical result and its synthesis by acetylation of Va.[3]

The formation of Vb from II may be outlined in Chart 3, involving the Pummerer rearrangement, followed by a double ring contraction.

Experimental

All melting points are uncorrected. IR spectra were run on a Hitachi R-215 spectrometer. NMR spectra were recorded at 60 MHz with a Hitachi R-20B using TMS as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet.

4*a*-Methoxy and 4*a*-Ethoxy -1,3-dimethyl-1,2,3,4-tetrahydro-4*a*(*H*)-pyrimido-(5,4-*b*)-1,4-benzothiazine-2,4-dione (IVb and IVc)——To a well stirred suspension of I (0.2 g) and I_2 (1.0 g) in MeOH (100 ml) was added

8) Y. Sakaino, H. Kakisawa, K. Arita, M. Kouno, and H. Morishima, *Tetrahedron*, **29**, 1185 (1973).
9) B.F. Schroder and R.M. Dodson, *J. Am. Chem. Soc.*, **84**, 1904 (1962).

$(Et)_3N$(5.0 g) in portions at room temperature. The resulting green solution was refluxed until the color of the reaction mixture changes to brown at the end. After removal of the solvent, the residue was dissolved in $CHCl_3$ and washed with 10% aqueous solution of $Na_2S_2O_3$. The organic layer was dried over anhyd. Na_2SO_4 and concentrated to dryness. The residue was chromatographed on silica gel (solvent: $CHCl_3$) to isolate IVb (0.15 g), mp 121° (from ether), as colorless prisms. IR ν_{max}^{KBr} cm^{-1}: 1730, 1670 (CO). NMR (DMSO-d_6) δ: 3.17 (3H, s, OCH_3), 3.25 (3H, s, NCH_3), 3.50 (3H, s, NCH_3), 7.10—7.70 (4H, m, aromatic protons). UV λ_{max}^{EtOH} $m\mu(\varepsilon)$: 225 (35500), 251 (28500), 313 (21000). *Anal.* Calcd. for $C_{13}H_{13}O_3N_3S$: C, 53.61; H, 4.50; N, 14.43. Found: C, 53.61; H, 4.72; N, 13.91. Mass Spectrum *m/e*: 291 (M^+), 260 (M^+-OCH_3).

4*a*-Ethoxy derivative (IVc) was analogously prepared by employing EtOH as a solvent in 70% yield. Colorless prisms (from *n*-hexane), mp 112—113°. IR ν_{max}^{KBr} cm^{-1}: 1720, 1680 (CO). NMR (DMSO-d_6) δ: 0.83 (3H, t, $J=7$ Hz, OCH_2CH_3), 3.24 (3H, s, NCH_3), 3.50 (3H, s, NCH_3), 3.63 (2H, q, $J=7$ Hz, OCH_2CH_3), 7.05—7.65 (4H, m, aromatic protons). *Anal.* Calcd. for $C_{14}H_{15}O_3N_3S$: C, 55.08; H, 4.95; N, 13.77. Found: C, 55.03; H, 5.12; N, 13.61. Mass Spectrum *m/e*: 305 (M^+), 260 ($M^+-OCH_2CH_3$).

4*a*-Morpholino-1,3-dimethyl-1,2,3,4-tetrahydro-4*a*(*H*)-pyrimido-(5,4-*b*)-1,4-benzothiazine-2,4-dione (IVd)——To a well stirred suspension of I (0.26 g) in morpholine (20 ml) was added I_2 (2.0 g) in portions at room temperature. The solution was heated at 100° for 1 hr. After evaporation of the solvent, the residue was washed with H_2O and recrystallized from MeOH to give IVd (0.22 g) as colorless needles, mp 186°. IR ν_{max}^{KBr} cm^{-1}: 1710, 1670 (CO). NMR (DMSO-d_6) δ: 2.00—2.80 (4H, m, N $(CH_2)_2$), 3.23 (3H, s, NCH_3), 3.34 (4H, t $O(CH_2)_2$), 3.50 (3H, s, NCH_3), 7.00—7.60 (4H, m, aromatic protons). UV λ_{max}^{EtOH} $m\mu(\varepsilon)$: 225 (32500), 258(20100), 301 (8600), 312 (8400). *Anal.* Calcd. for $C_{16}H_{18}O_3N_4S$: C, 55.48; H, 5.24; N, 16.18. Found: C, 55.29; H, 5.27; N, 16.11.

4*a*-Hydroxy-1,3-dimethyl-1,2,3,4-tetrahydro-4*a*(*H*)-pyrimido-(5,4-*b*)-1,4-benzothiazine-2,4-dione(IVa)——A mixture of I (0.2 g), $(Et)_3N$ (5.0 g) and H_2O (1.0 g) in $CHCl_3$ (50 ml) was stirred at room temperature for 20 hr. The reaction mixture was washed with 10% aqueous $Na_2S_2O_3$ and dried over anhyd. Na_2SO_4. The solvent was evaporated under reduced pressure at room temperature and the residue was carefully recrystallized from $CHCl_3$–*n*-hexane to give IVa (0.16 g) as colorless needles, mp 125—126°. IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 1720, 1660 (CO). NMR (DMSO-d_6) δ: 3.25 (3H, s, NCH_3), 3.49 (3H, s, NCH_3), 7.10—7.65 (4H, m, aromatic protons), 8.20 (1H, broad, OH). UV λ_{max}^{EtOH} $m\mu(\varepsilon)$: 225 (28500), 252 (14700), 311 (8100). *Anal.* Calcd. for $C_{12}H_{11}O_3N_3S$: C, 51.99; H, 4.00; N, 15.16. Found: C, 52.00; H, 4.01; N, 15.21.

After heating of IVa at 100° for 1 hr in an NMR sample tube using DMSO-d_6 as a solvent, the NMR spectrum of the reaction mixture showed that the conversion of IVa into Va occurred quantitatively.

Thiazinium Cation Tetrafluoroborate (C)——Excess borontrifluoride etherate was added to IVb (0.58 g) in absolute ether (30 ml) with stirring at room temperature. Precipitated purple powder (C) (0.45 g) was collected. Attempts to purify this powdery substance were failure because of its instability.

Its NMR spectrum (in CD_3NO_2) showed the presence of two N-methyl signals at δ 3.45 and δ 3.85, and aromatic protons in the region δ 7.20—8.00.

The salt (C) (0.35 g) was added to 10 ml of H_2O, MeOH, EtOH or morpholine. The resulting solution was poured dropwise into 1% aqueous NaOH (50 ml) on ice-cooling with stirring for 1 hr. After standing for 30 min, the solution deposited IVa, b, c, d in 70—80% yields, respectively. IVa-d thus obtained were identical in every respect with the samples prepared by above mentioned procedure.

1,3-Dimethyl-1,2,3,4-tetrahydro-10*H*-pyrimido(5,4-*b*)-1,4-benzothiazine-2,4(1*H*,3*H*)-dione Sulfoxide (II)——To a stirred suspension of I (1.31 g) in $CHCl_3$ (50 ml) was added 85% *m*-chloroperbenzoic acid (1.00 g) in $CHCl_3$ (10 ml) by portions at room temperature. The stirring was continued until the color of the reaction mixture turns from yellow to colorless. The precipitated solid was collected and washed with $CHCl_3$ and then ether. Thus, II (1.20 g) was obtained as a colorless powder in the nearly pure state. IR ν_{max}^{KBr} cm^{-1}: 3330 (NH), 1700 (CO), 1000 (SO). NMR (DMSO-d_6) δ: 3.28 (3H, s, NCH_3), 3.63 (3H, s, NCH_3), 7.3—8.1 (4H, m, aromatic protons), 10.75 (1H, broad, NH).

Pummerer Rearrangement of Sulfoxide (II)——A solution of II (0.55 g) in MeOH (100 ml) was refluxed for 20 hr. After evaporation of the solvent, the residue was submitted to silica gel chromatography (solvent: $CHCl_3$) to isolate IVb (0.25 g). Analogously, IVc (0.30 g) was obtained when II (0.55 g) was refluxed in EtOH for 20 hr.

Ring contraction of Sulfoxide (II) to 2-(1,3-Dimethyl-5-acetoxy-5-hydantoinyl)benzothiazole (Vb)——Sulfoxide (II) (0.28 g) was heated with Ac_2O (20 ml) at 100° for 2 hr. After removal of Ac_2O under reduced pressure, the residue was recrystallized from MeOH to give Vb (0.25 g), as colorless needles, mp 146°. IR ν_{max}^{KBr} cm^{-1}: 1800, 1770, 1730 (CO). NMR ($CDCl_3$) δ: 2.30 (3H, s, $COCH_3$), 2.96 (3H, s, NCH_3), 3.17 (3H, s, NCH_3), 7.45—7.60, 7.90—8.25 (4H, m, aromatic protons). UV λ_{max}^{EtOH} $m\mu(\varepsilon)$: 219 (18500), 263 (9600), 290 (2700), 300 (1800). *Anal.* Calcd. for $C_{14}H_{13}O_4N_3S$: C, 52.66; H, 4.10; N, 13.16. Found: C, 52.47; H, 3.95; N, 13.02.

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