

SYNTHESIS OF 4,11-DIMETHYL-2,3,4,5-TETRAHYDRO-2,5-IMINOMETHANO-6H-BENZO[*a*]
[1,4,6]THIADIAZOCINE-3,12-DECANE AND 7,9-DIMETHYL-8,10-DIOXO-2,5-DITHIA-7,9-
DIAZABICYCLO[4.2.2]DECANE

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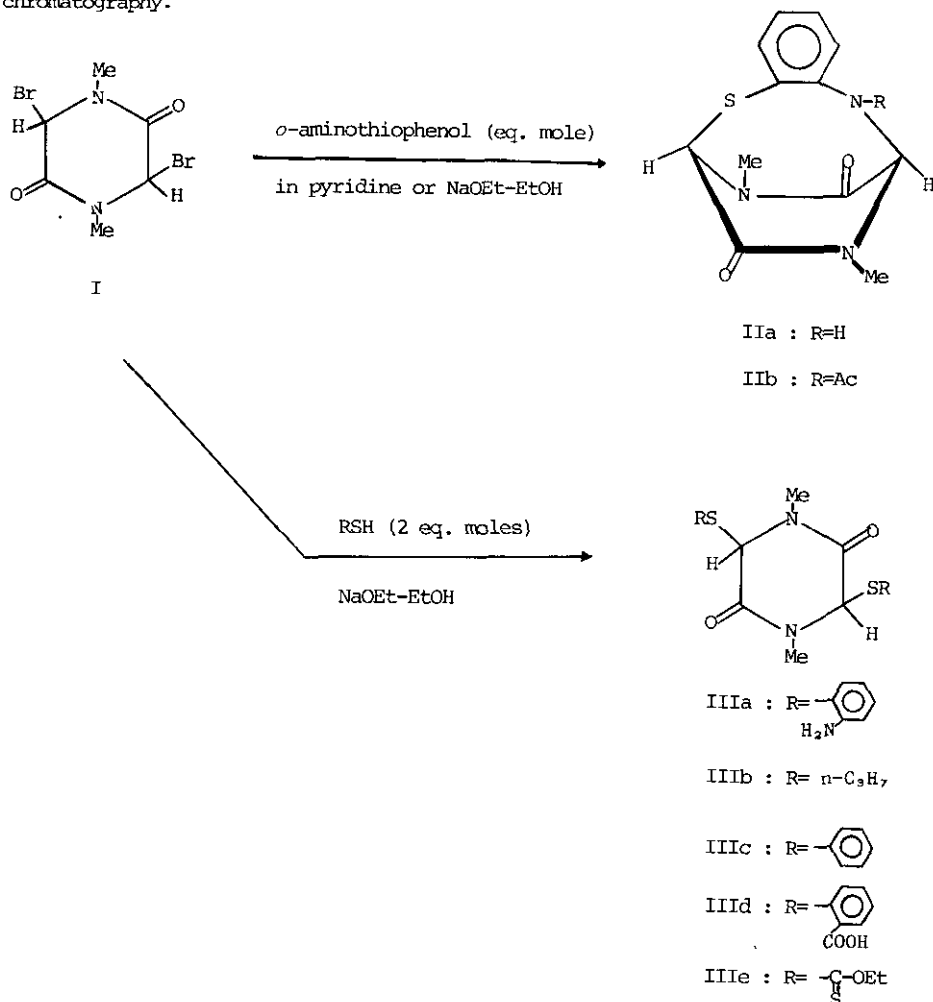
Abstract — Two novel heterocyclic ring systems involving the piperazine ring and the benzothiadiazocine or dithiadiazabicyclodecane skeleton were synthesized: The reaction of 3,6-dibromo-1,4-dimethyl-2,5-piperazinedione (I) with an equivalent mole of *o*-aminothiophenol in ethanol in the presence of sodium ethoxide or in pyridine gave 4,11-dimethyl-2,3,4,5-tetrahydro-2,5-iminomethano-6H-benzo[*a*][1,4,6]thiadiazocine-3,12-decane (IIa), while the reaction of I with two moles of *o*-aminothiophenol gave 3,6-bis(2-aminophenyl)-thio-1,4-dimethyl-2,5-piperazinedione (IIIa). The reaction of I with an equivalent mole of ethanedithiol in ethanol in the presence of sodium ethoxide gave 7,9-diazabicyclo[4.2.2]decane (IV), which was also synthesized from 3,6-dihydroxy-1,4-dimethyl-2,5-piperazinedione (V) and ethanedithiol in dioxane in the presence of zinc chloride.

Fungal metabolites such as gliotoxin,¹ sporidesmin,² and chaetocin³ contain the epidithia-2,5-piperazinedione ring which is an important partial structure to exhibit biological activity. The most simple compound of this ring system is 1,4-dimethyl-3,6-epidithio-2,5-piperazinedione which has been synthesized by Trown.⁴ We have been interested in the syntheses of some new variations of this unique ring system and we now wish to report the syntheses of two novel heterocyclic ring systems; 4,11-dimethyl-2,3,4,5-tetrahydro-2,5-iminomethano-6H-benzo[*a*][1,4,6]thiadiazocine-3,12-decane (II) and 7,9-dimethyl-8,10-dioxo-2,5-dithia-7,9-diazabicyclo[4.2.2]decane (IV).

The reaction of 3,6-dibromo-1,4-dimethyl-2,5-piperazinedione⁴ (I) with thiols (2 equivalent moles) in the presence of sodium ethoxide in ethanol gave the corresponding 3,6-dialkyl(or diaryl)thio-1,4-dimethyl-2,5-piperazinediones (IIIa-e) in 47—78% yields. Whereas the reaction of I with an equivalent mole of *o*-aminothiophenol in pyridine or in the presence of sodium ethoxide in ethanol gave IIa [colorless needles (from EtOH) of mp 246-247°C] in 64% yield. The structural assignment

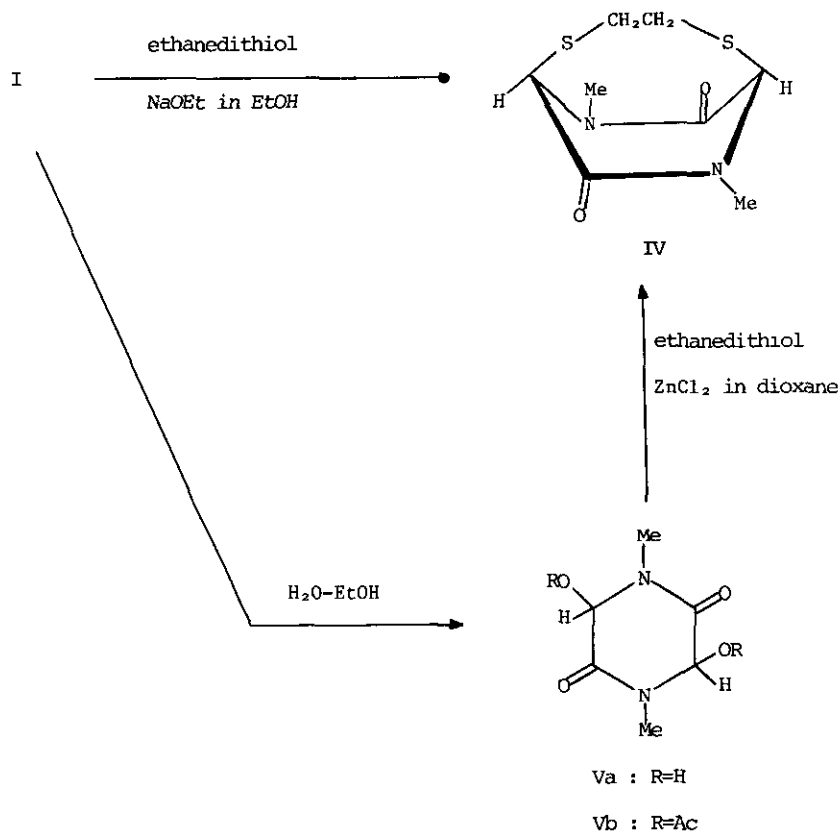
was carried out as follows : The elemental analysis and mass spectrum [$m/e=263(M^+)$] agreed with the formula ($C_{12}H_{13}N_3O_2S$) of IIa. The IR spectrum showed an absorption due to a secondary amine at 3340 cm^{-1} . The NMR spectrum ($\delta_{\text{ppm}}^{\text{CDCl}_3}$) agreed well with the assigned structure ; 2.84 (3H, s, N-Me), 2.92 (3H, s, N-Me), 5.08 (1H, s, one bridgehead proton near the sulfur atom), 5.05 (1H, d, $J=9\text{ Hz}$, another bridgehead proton neighbouring -NH- group), 6.52 (1H, d, $J=9\text{ Hz}$, NH, disappeared on D_2O -exchange), 6.90—7.40 (4H, m, aromatic protons). Acetylation of IIa with acetic anhydride in the presence of pyridine gave IIb [mp $198-199^\circ\text{C}$, 87% yield, NMR (10% solution in CDCl_3) δ : 1.78 (3H, s, $-\text{COCH}_3$), 2.45 (3H, s, N-Me), 3.25 (3H, s, N-Me), 4.92 (1H, s, one bridgehead proton near the sulfur atom), 5.76 (1H, s, another bridgehead proton near the nitrogen atom), 7.00—7.55 (4H, m, aromatic protons)].

Although the stereochemical studies of IIIa-e were not carried out, each of these compounds seems to be either *cis* or *trans* form and is not a mixture of the both forms on the basis of NMR spectra and gas chromatography.



The reaction of I with an equivalent mole of ethanedithiol in ethanol in the presence of sodium ethoxide gave IV in 55% yield; mp 255-257°C, colorless prisms from chloroform-ether (1:1), IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1660 (C=O), NMR (10% solution in CDCl_3) δ : 3.10 (6H, s, $2 \times \text{N-Me}$), 2.98 and 3.08 (each 2H, each d, $J=4$ Hz, $-\text{CHaHbCHaHb}-$), 4.80 (2H, s, two bridghead protons). Mass spectrum: $m/e=232$ (M^+). The elemental analysis agreed with the formula $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_2\text{S}_2$.

Compound (I) was readily converted to 3,6-dihydroxy-1,4-dimethyl-2,5-piperazinedione (Va) [mp 232-234°C, $m/e=174$ (M^+)] by the treatment with water.⁵ The NMR spectrum of Va [2.96 (6H, s, $2 \times \text{N-Me}$), 4.91 (2H, d, $J=7$ Hz, $2 \times \text{CH}$), 6.78 (2H, d, $J=7$ Hz, $2 \times \text{OH}$)] indicated one counterpart of the possible two diastereoisomers, but further stereochemical studies were not carried out. Treatment of Va with an equivalent mole of ethanedithiol and zinc chloride in dioxane gave IV in 50% yield.



ACKNOWLEDGMENT The authors gratefully acknowledge the assistance of Miss K. Yoshida in carrying out this work. Thanks are also due to the members of Microanalytical Center of this Faculty for elementary analyses and measurements of NMR spectra.

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5. T. Sato and T. Hino (Chem. Pharm. Bull., 1976, 24, 285) also obtained Va (8-11.5% yield) from the potassium salt of 3,6-dicarboxy-1,4-dimethyl-2,5-piperazinedione by the reaction with ethanesulfonyl chloride or benzenesulfonyl chloride.

Received, 7th February, 1980