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SYNTHESIS OF 4,11-DIMETHYL-2,3,4,5-TETRAHYDRO-2,5-IMINOMETHANO-6*H*-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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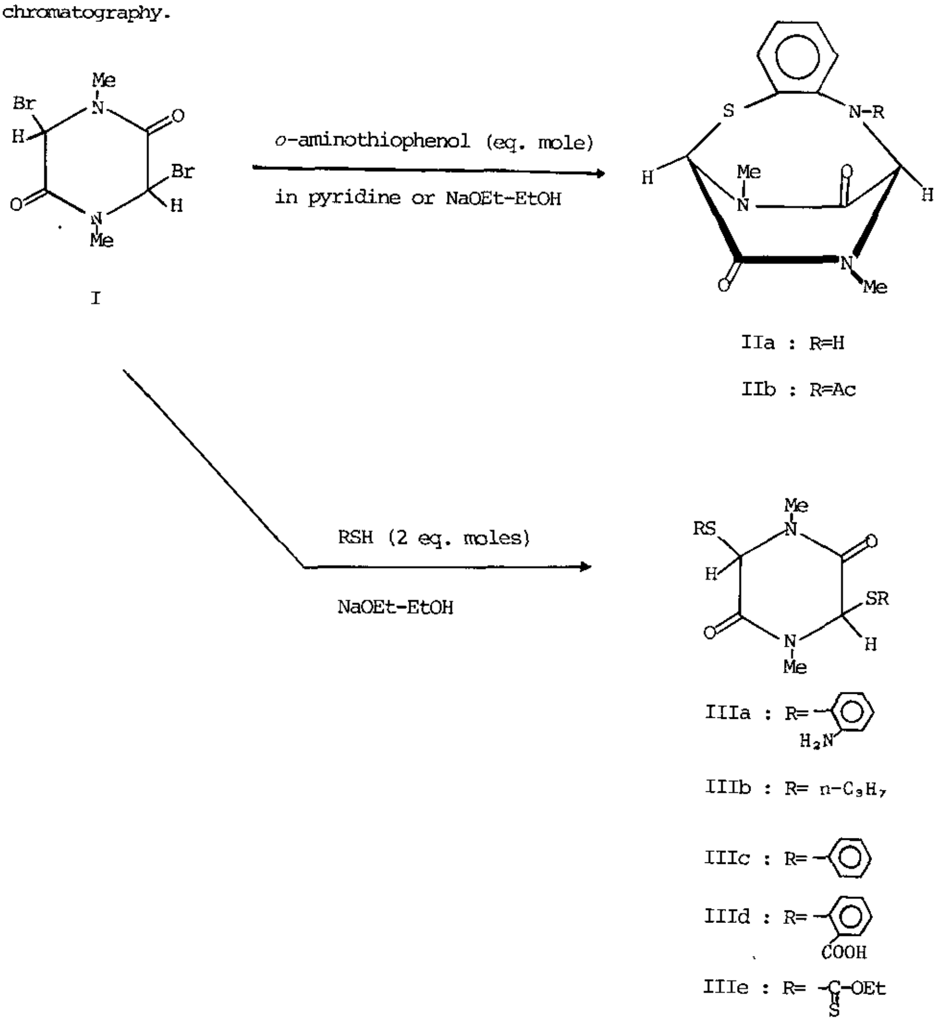
Abstract —— Two novel heterocyclic ring systems involving the piperazine ring and the benzothiadiazocine or dithiadiazabicyclodecane skeleton were synthesized : The reaction of 3,6-dibromo-1,4-dimethyl-2,5-piperazinedione (I) with an equivalent mole of *o*-aminothiophenol in ethanol in the presence of sodium ethoxide or in pyridine gave 4,11-dimethyl-2,3,4,5-tetrahydro-2,5-iminomethano-6*H*-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 chaetocin[3] 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-6*H*-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-piperazinedione[4] (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 structual 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 ($\delta_{ppm}^{CDCl_3}$) agreed well with the assigned structure ; 2.84 (3H, s, N-Me), 2.92 (3H, s, N-Me), 5.08 (1H, s, one brigehead proton near the sulfur atom), 5.05 (1H, d, J=9 Hz, another brigehead proton neighbouring -NH- group), 6.52 (1H, d, J=9 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°C, 87% yield, NMR (10% solution in $CDCl_3$) δ : 1.78 (3H, s, $-COCH_3$), 2,45 (3H, s, N-Me), 3.25 (3H, s, N-Me), 4.92 (1H, s, one brigehead proton near the sulfur atom), 5.76 (1H, s, another brigehead 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.



I

IIa : R=H

IIb : R=Ac

IIIa : R=

IIIb : R= n-C_3H_7

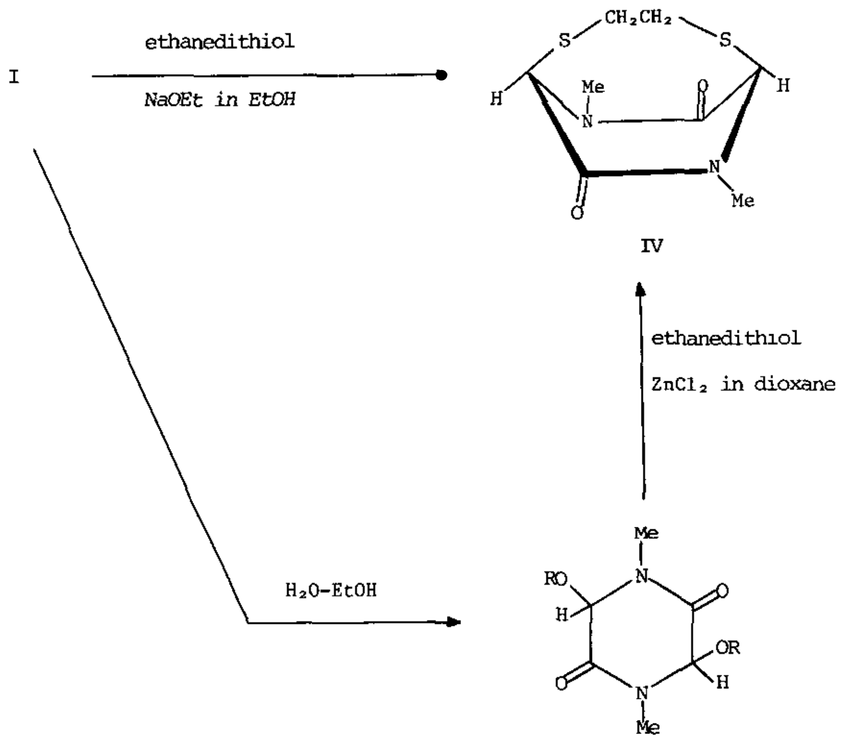
IIIc : R=

IIId : R=

IIIe : R= -C(=S)-OEt

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 ν_{max}^{KBr} cm^{-1} : 1660 (C=O), NMR (10% solution in $CDCl_3$) δ : 3.10 (6H, s, 2× N-Me), 2.98 and 3.08 (each 2H, each d, J=4 Hz, -CHaHbCHaHb-), 4.80 (2H, s, two bridghead protons). Mass spectrum : m/e=232 (M^+). The elemental analysis agreed with the formula $C_8H_{12}N_2O_2S_2$.

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× N-Me), 4.91 (2H, d, J=7 Hz, 2× CH), 6.78 (2H, d, J=7 Hz, 2× 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.



Va : R=H

Vb : R=Ac

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REFERENCES AND NOTES

1. M. R. Bell, J. R. Johnson, B. S. Wildi, and R. B. Woodward, J. Am. Chem. Soc., 1958, 80, 1001.
2. S. Safe and A. Taylor, J. Chem. Soc.(C), 1970, 432.
3. D. Hauser, H. P. Weber, and H. P. Sigg, Helv. Chim. Acta, 1970, 53, 1061.
4. P. W. Trown, U. S. Patent, 3562253 (1971).
5. T. Sato anf 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 ethanesulfenyl chloride or benzenesulfenyl chloride.

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