A FACILE SYNTHESIS OF NOVEL HETEROCYCLE-CONJUGATED QUINOXALINES

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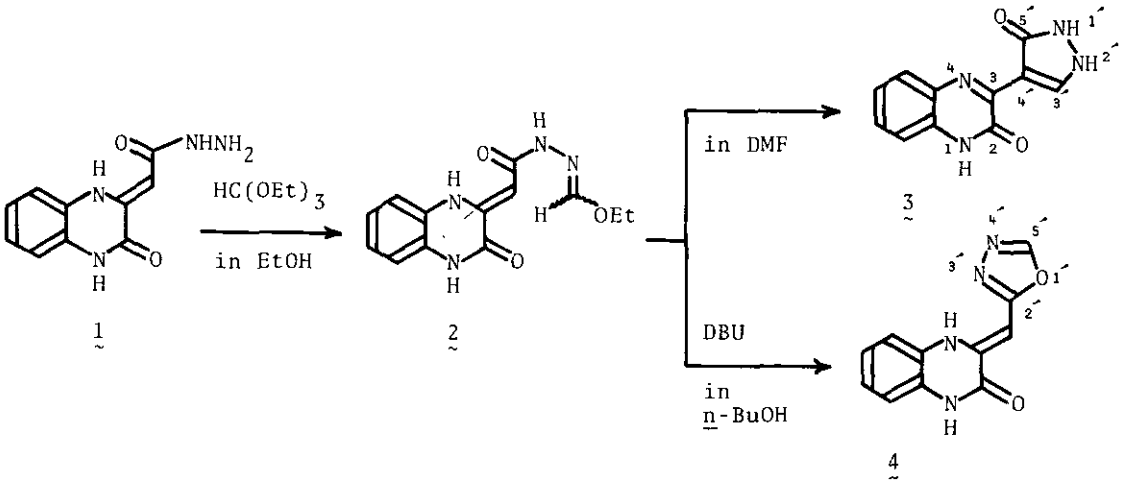
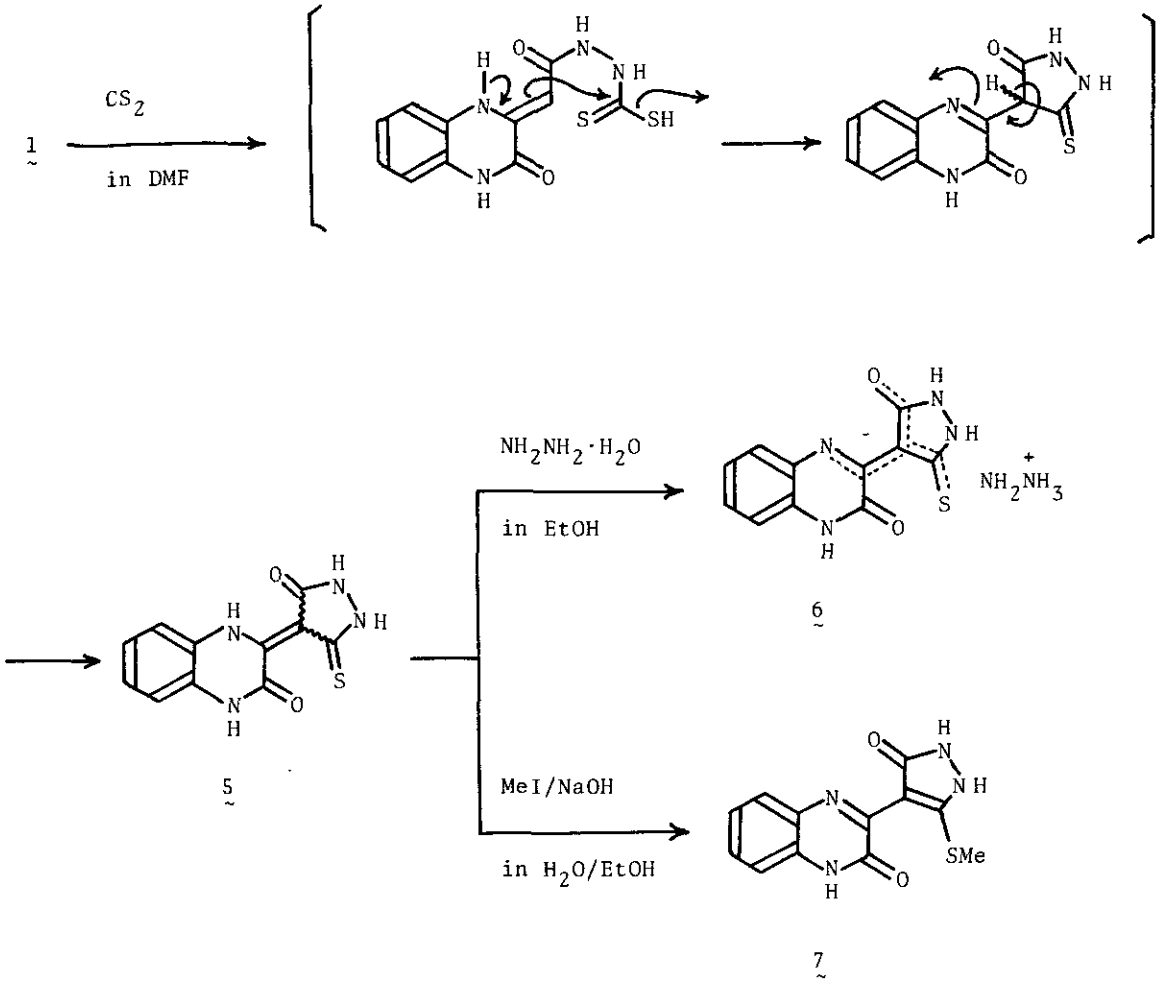
Abstract —— Novel pyrazole- and 1,3,4-oxadiazole-conjugated quinoxalines (5-9) were synthesized selectively from 3-hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (1).

In previous papers,[1,2] we reported that the reaction of 3-hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (1) with ethyl orthoformate gave the hydrazone (2), which was regioselectively cyclized to 3-(5-oxo-3-pyrazolin-4-yl)-2-oxo-1,2-dihydroquinoxaline (3) and 3-(1,3,4-oxadiazol-2-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (4), as shown in Scheme 1. Since pyrazolones[3] and 1,3,4-oxadiazoles[2] have been known to possess various pharmacological activities, several mod-



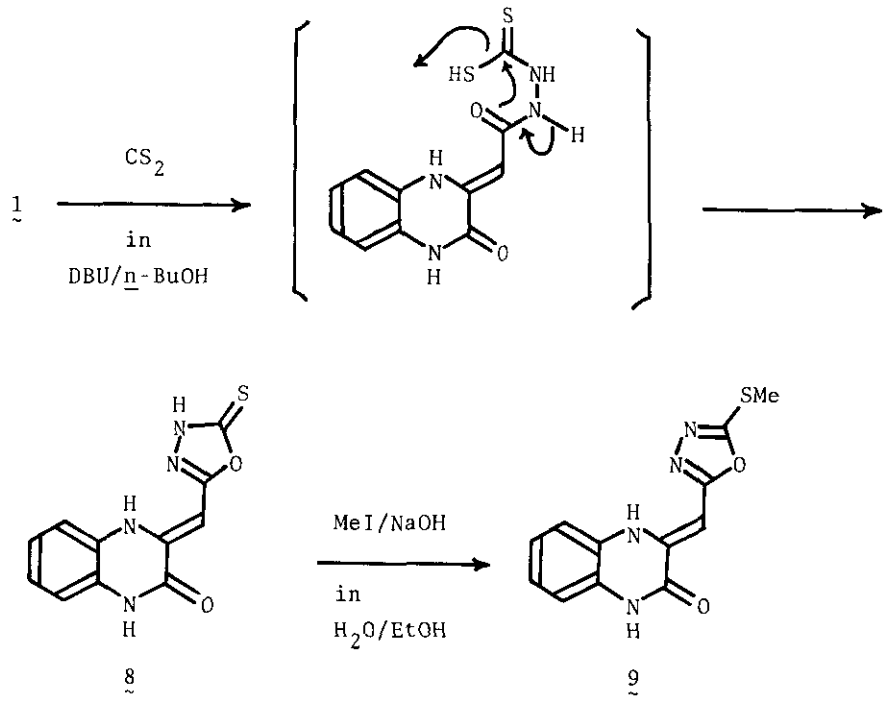
1 2 3 4

Scheme 1



Scheme 2*

ifications for 3[4] and 4[2] have been carried out in order to search for useful agents. However, the respective 3'- and 5'-positions of 3 and 4 were not functionalized easily by the above method, and hence it was necessary to select a one-carbon reagent to be incorporated into 1. Among the one-carbon reagents, carbon disulfide (CS_2) was found to be suitable to furnish the 3'- and 5'-thio compounds. This paper describes the synthesis of the novel heterocycle-conjugated quinoxalines by the above regioselective cyclizations.



8 9

Scheme 3*

EXPERIMENTAL

Formation of Pyrazole Ring (Scheme 2)

The reaction of 1 (10 g, 45.9 mmol) with CS_2 (17.46 g, 230 mmol) in DMF (500 ml) afforded 3-(5-oxo-3-thioxopyrazolidin-4-ylidene)-2-oxo-1,2,3,4-tetrahydroquinoxaline (5)[5] (8.64 g, 72.4%). The reaction of 5 (5 g, 19.2 mmol) with hydrazine hydrate (5.77 g, 115.4 mmol) formed the hydrazinium salt (6)[6] (5.18 g, 92.3%), but not 3'-hydrazino derivative. Methylation of 5 (5 g, 19.2 mmol) with MeI (4.09 g, 28.8 mmol)/NaOH (0.84 g, 21.08 mmol) in H_2O (50 ml)/EtOH (150 ml) provided 3-(3-methylthio-5-oxo-3-pyrazolin-4-yl)-2-oxo-1,2-dihydroquinoxaline (7)[7] (4.79 g, 90.9%), while the 3'-SMe group of 7 was not replaced with amines or hydrazines.

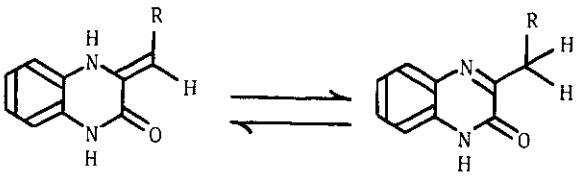
Formation of 1,3,4-Oxadiazole Ring (Scheme 3)

The reaction of 1 (10 g, 45.9 mmol) with CS_2 (5.23 g, 68.8 mmol) in 1,8-diazabicyclo-[5,4,0]-7-undecene (DBU) (7 ml)/n-BuOH (600 ml) gave 3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (8)[8] (9.95 g, 83.4%). Methylation of 8 (5 g, 19.2 mmol) with MeI (4.09 g, 28.8 mmol)/KOH (1.29 g, 23.04 m-

mol) in H_2O (50 ml)/EtOH (100 ml) afforded 3-(5-methylthio-1,3,4-oxadiazol-2-yl)-methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (9)[9] (4.23 g, 80.3%).

REFERENCES AND FOOTNOTES

1. Y. Kurasawa, Y. Moritaki, and A. Takada, Synthesis, 1983, 238.
2. Y. Kurasawa, Y. Moritaki, T. Ebukuro, and A. Takada, Chem. Pharm. Bull., 1983, 31, 3897.
3. D. Lednicer and L. A. Mitscher, "The Organic Chemistry of Drug Synthesis," John Wiley and Sons, Inc., New York, London, Sydney, Toronto, 1977, pp 234-238.
4. Y. Kurasawa and A. Takada, Heterocycles, 1980, 14, 281; Idem, Chem. Pharm. Bull., 1981, 29, 2871.
5. 5: brown powder, mp 310-311 °C. ν(KBr): 1685, 1640, 1615 cm^{-1}. δ(DMSO-d_6): 13.17 (s, 1H, NH), 12.80 (s, 1H, NH), 12.66-11.33 (br, 2H, NH), 7.90-6.80 (m, 4H, aromatic).
6. 6: red needles, mp 321-322 °C. ν(KBr): 3280, 1650, 1635, 1620 cm^{-1}. δ(DMSO-d_6): 12.00-6.67 (br, 8H, NH), 7.73-7.00 (m, 4H, aromatic).
7. 7: yellow needles, mp 331-332 °C. ν(KBr): 1670, 1620, 1600 cm^{-1}. δ(DMSO-d_6): 13.97 (br s, 1H, NH), 13.00 (br s, 1H, NH), 12.45 (br s, 1H, NH), 7.67 (m, 1H, C_5-H), 7.50-7.10 (m, 3H, aromatic), 2.39 (s, 3H, Me).
8. 8: yellow needles, mp 220-222 °C. ν(KBr): 1680, 1640, 1610 cm^{-1}. δ(DMSO-d_6): 12.46 (s, NH),[10] 11.60 (s, 1H, NH), 9.63 (s, 1H, N_4,-H), 7.77-6.80 (m, 4H, aromatic), 5.86 (s, C_3=C<u>H</u>-),[10] 4.29 (C_3-C<u>H</u>$_2$-).[10]
9. 9: yellow needles, mp 228-230 °C. ν(KBr): 1680, 1635, 1615 cm^{-1}. δ(DMSO-d_6): 12.47 (s), 11.53 (s), and 10.33 (s) (2H, N_1- and N_4-H),[10] 7.80-6.77 (m, 4H, aromatic), 6.00 (s, C_3=C<u>H</u>-),[10] 4.39 (s, C_3-C<u>H</u>$_2$-),[10] 2.71 (s) and 2.66 (s) (3H, Me).[10]
10. R. Mondelli and L. Merlini, Tetrahedron, 1966, 22, 3253; Y. Kurasawa and A. Takada, Heterocycles, 1983, 20, 1917. The NMR spectra of 8 and 9 in DMSO-d_6 exhibit the following two tautomers A and B, and hence the extra NH and C_3-C<u>H</u>$_2$- proton peaks are observed.



A B

* Satisfactory mass spectral and microanalytical data were obtained for all new samples.

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