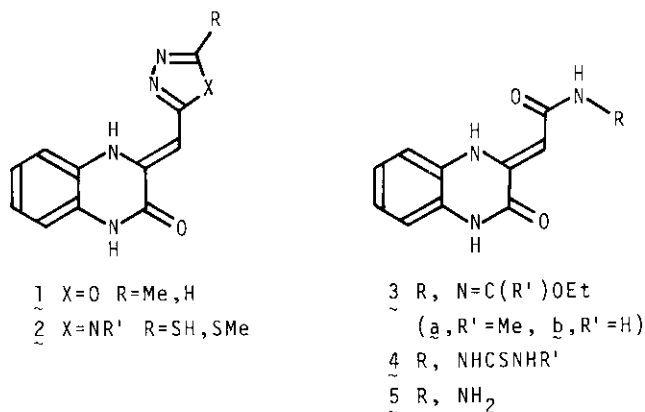


FACILE SYNTHESIS OF NOVEL 3-(4-AMINO-5-METHYL-4H-1,2,4-TRIAZOL-3-YLMETHYLENE)-2-OXO-1,2,3,4-TETRAHYDROQUINOXALINE AND RELATED COMPOUNDS

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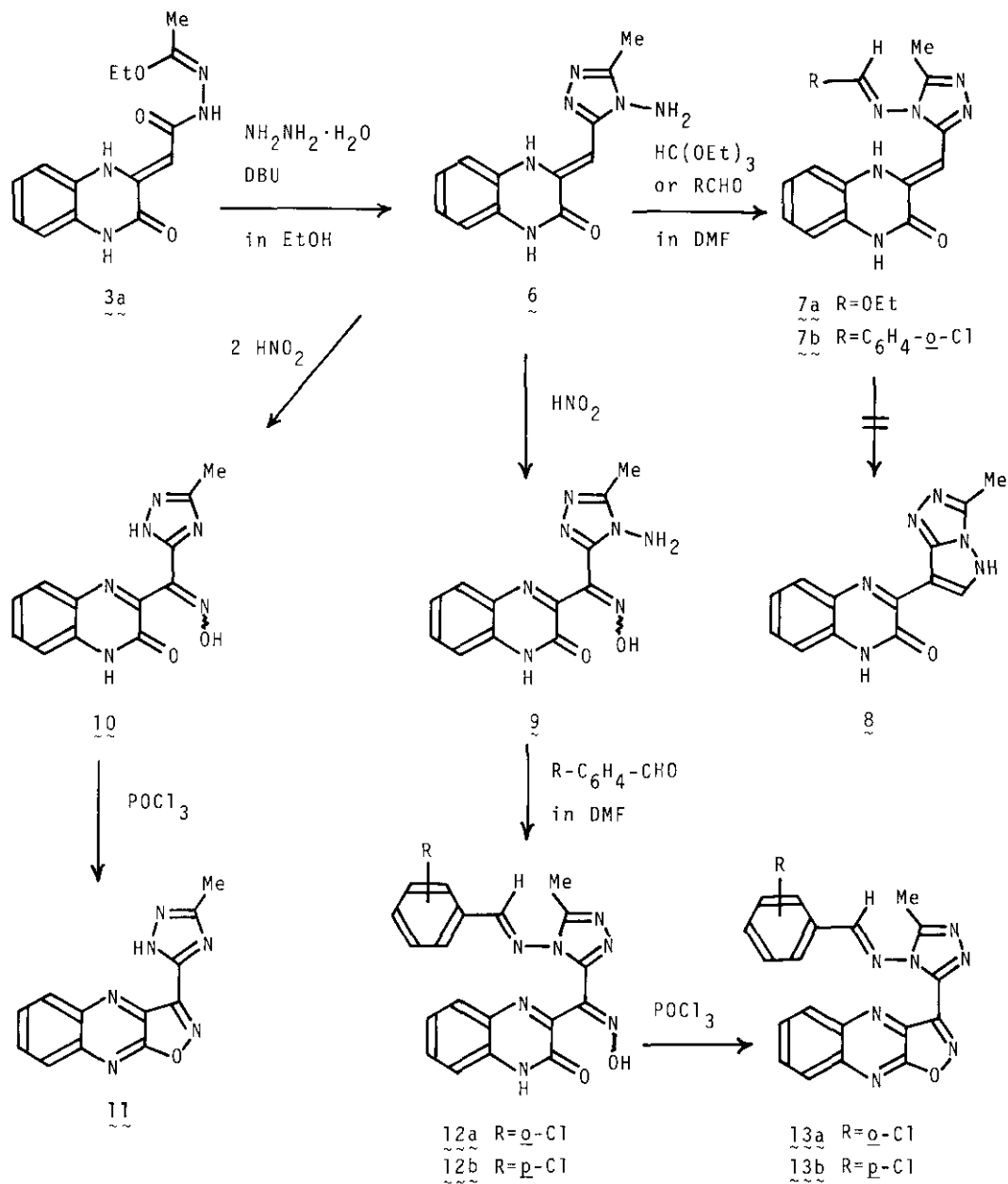
Abstract — The reaction of the hydrazone (3a) with hydrazine hydrate in DBU/EtOH conveniently gave novel 3-(4-amino-5-methyl-4H-1,2,4-triazol-3-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline (6), which was converted into the various new 1,2,4-triazole derivatives (7-13).

From the interest in the various pharmacological activities of 1,3,4-oxadiazoles and 1,2,4-triazoles, we have synthesized a new type of azoles 3-(1,3,4-oxadiazol-2-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines (1)¹ and 3-(1,2,4-triazol-3-yl-



SCHEME 1

methylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines (2)² via the hydrazones (3a,b) and the thiosemicarbazides (4a,b), respectively, from the hydrazide (5) (Scheme 1).

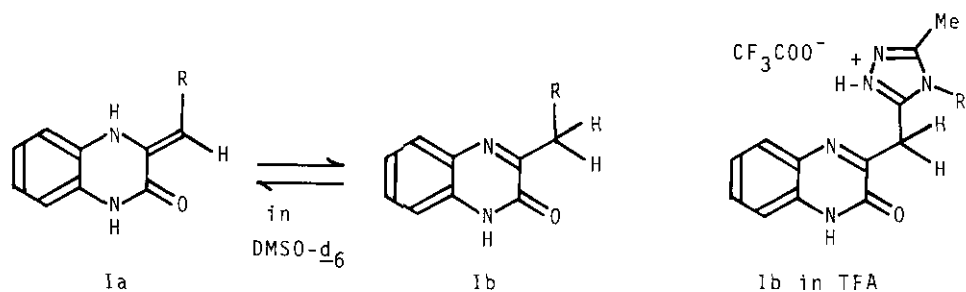


SCHEME 2*

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

However, there was a limitation on derivatization of the above compounds 1 and 2 in the azole nuclei, and hence the synthesis of the 1 and 2 type of 4-amino-4H-1,2,4-triazole was undertaken because of its facile derivatization at the 4-amino group of the triazole ring. As the result, we have found a convenient method for the synthesis of 3-(4-amino-5-methyl-4H-1,2,4-triazol-3-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline (6) from the above hydrazone 3a. This paper describes the synthesis of the novel 1,2,4-triazole 6 and its conversion into the various new compounds (7-13).

The reaction of 3a (10 g) with $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (10 ml) and 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) (2 ml) in EtOH (400 ml) resulted in substitution and cyclization³ to give 6 (7.14 g, 80.3%).⁴ Refluxing of 6 (2 g) in ethyl orthoformate (10 ml)/DMF (40 ml) afforded 3-(4-ethoxymethylamino-5-methyl-4H-1,2,4-triazol-3-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline (7a) (2.04 g, 83.6%),⁵ while the reaction of 6 (2 g, 7.81 mmol) with o-chlorobenzaldehyde (1.65 g, 11.72 mmol) in DMF (50 ml) formed 3-[4-(o-chlorobenzylideneamino)-5-methyl-4H-1,2,4-triazol-3-ylmethylene]-2-oxo-1,2,3,4-tetrahydroquinoxaline (7b) (1.31 g, 44.5%).⁶ Compound 7a hardly cyclized into the 3-quinoxalinylnyl-pyrazolo[3,4-c][1,2,4]triazole compound (8).¹ The reactions of 6 (5 g, 19.5 mmol) with 1.25-fold (1.69 g) and 2.5-fold (3.37 g) molar amount of NaNO_2 in H_2O (100 ml)/AcOH (150 ml) effected hydroxyimination² to provide α -hydroxyimino-3-(4-amino-5-methyl-4H-1,2,4-triazol-3-ylmethyl)-2-oxo-1,2-dihydroquinoxaline (9) (4.42 g, 79.4%)⁷ and α -hydroxyimino-3-(5-methyl-1H-1,2,4-triazol-3-ylmethyl)-2-oxo-1,2-dihydroquinoxaline (10) (5.52 g, 97.4%),^{8,9} respectively. Refluxing of 10 (1 g) in POCl_3 (5 ml)/dioxane (5 ml) resulted in dehydrative cyclization¹⁰ to produce 3-(5-methyl-1H-1,2,4-triazol-3-yl)isoxazolo[4,5-b]quinoxaline (11) (0.82 g, 87.9%).¹¹ The reactions of 9 (4 g, 14.0 mmol) with o- and p-chlorobenzaldehydes (2.96 g, 21.04 mmol) in DMF (100 ml) furnished α -hydroxyimino-3-[4-(o-chlorobenzylideneamino)-5-methyl-4H-1,2,4-triazol-3-ylmethyl]-2-oxo-1,2-dihydroquinoxaline (12a) (4.35 g, 75.5%)¹² and α -hydroxyimino-3-[4-(p-chlorobenzylideneamino)-5-methyl-4H-1,2,4-triazol-3-ylmethyl]-2-oxo-1,2-dihydroquinoxaline (12b) (2.36 g, 41.3%),¹³ respectively. Refluxing of 12a and 12b (1 g) in POCl_3 (5 ml)/dioxane (5 ml) also effected dehydrative cyclization to give 3-[4-(o-chlorobenzylideneamino)-5-methyl-4H-1,2,4-triazol-3-yl]isoxazolo[4,5-b]quinoxaline (13a) (0.73 g, 76.2%)¹⁴ and 3-[4-(p-chlorobenzylideneamino)-5-methyl-4H-1,2,4-triazol-3-yl]isoxazolo[4,5-b]quinoxaline (13b) (0.87 g, 90.9%),¹⁵ respectively.



SCHEME 3

The $^1\text{H-NMR}$ spectrum of 6 in $\text{DMSO-}d_6$ exhibited the vinyl and methylene proton signals at δ 6.28 and 4.28 ppm due to two tautomers 1a and 1b (1a:1b=5:1 at 30 °C, 3:1 at 80 °C), respectively, and its spectrum in trifluoroacetic acid (TFA) represented the methylene proton signal at δ 4.93 ppm due to the tautomer 1b (Scheme 3).^{1,2,16} Compounds 7a and 7b were confirmed as the tautomer 1b, since their methylene proton signals were observed both at δ 4.90 ppm. Moreover, the $^1\text{H-NMR}$ spectrum of 9 in $\text{DMSO-}d_6$ exhibited the one pair of the $\text{C}^{5'}$ -Me, N^1 -H (or =NOH), and $\text{N}^{4'}$ -NH₂ proton signals, presumably due to the syn and anti oxime isomers (1:1 ratio) of 9. On the other hand, 10 was assumed to be the 1H-triazole structure because of its favorable hydrogen bonding between the $\text{N}^{1'}$ -proton and N^4 -atom.¹⁷ 4H-1,2,4-Triazole is less stable than 1H- or 2H-1,2,4-triazole.¹⁷

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4. 6: yellow needles (trituated with hot EtOH), mp 333-334 °C. IR $\nu(\text{KBr})$: 3340, 3175, 1680, 1630, 1610, 1520, 1500 cm^{-1} . NMR ($\text{DMSO-}d_6$) δ : 11.30 (s, 1H, NH), 11.03 (s, 1H, NH), 8.00-6.77 (m, 4H, aromatic), 6.28 (s, 1H, vinyl), 5.93 (s, 2H,

- $N^{4'}$ -NH₂), 4.28 (s, methylene),¹⁶ 2.38 (s, 3H, C^{5'}-Me).
5. 7a: yellow needles (from EtOH), mp 227-228 °C. IR ν (KBr): 3220, 1680, 1640, 1610, 1530, 1500 cm⁻¹. NMR (TFA) δ : 8.80 (s, 1H, N^{4'}-N=CHC₆H₄Et), 8.23-7.00 (m, 4H, aromatic), 4.90 (br s, 2H, methylene), 4.53 (q, $J=7$ Hz, 2H, CH₂ of EtO), 2.83 (s, 3H, C^{5'}-Me), 1.47 (t, $J=7$ Hz, Me of EtO). NH proton signals were not observed.
 6. 7b: yellow needles (from DMF/EtOH), mp 259-260 °C. IR ν (KBr): 1680, 1630, 1610, 1595, 1530, 1500 cm⁻¹. NMR (TFA) δ : 9.44 (s, 1H, N^{4'}-N=CHC₆H₄Cl), 8.50-6.93 (m, 8H, aromatic), 4.90 (br s, 2H, methylene), 2.86 (s, 3H, C^{5'}-Me). NH proton signals were not observed.
 7. 9: colorless needles (from DMF/EtOH), mp 310-311 °C. IR ν (KBr): 3340, 1665, 1600 cm⁻¹. NMR (DMSO-d₆) δ : 13.86 (s, 1/2 H, NH or =NOH), 13.54 (s, 1H, NH or =NOH), 12.13 (s, 1/2 H, NH or =NOH), 8.00-7.17 (m, 4H, aromatic), 6.10 (s) and 5.68 (s) (2H, N^{4'}-NH₂), 2.36 (s) and 2.33 (s) (3H, C^{5'}-Me).
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 9. 10: colorless needles, monohydrate (from DMF/EtOH), mp 285-286 °C. IR ν (KBr): 3440, 3160, 1650, 1605 cm⁻¹. NMR (DMSO-d₆) δ : 13.70 (br s, 1H, NH or OH), 12.53 (br s, 1H, NH or OH), 11.66 (br s, 1H, NH or OH), 8.00-7.20 (m, 4H, aromatic), 3.33 (s, H₂O), 2.33 (s, 3H, C^{5'}-Me).
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 11. 11: colorless needles (from DMF/EtOH), mp 319-320 °C. IR ν (KBr): 3100, 2980, 2890, 2800, 1590, 1580, 1560, 1545, 1500 cm⁻¹. NMR (DMSO-d₆) δ : 14.37 (br, 1H, NH), 8.57-7.83 (m, 4H, aromatic), 2.53 (s, 3H, Me).
 12. 12a: colorless prismic needles (from DMF/EtOH), mp 276-277 °C. IR ν (KBr): 3160, 3100, 2960, 2880, 2820, 2760, 1650, 1605, 1590 cm⁻¹. NMR (DMSO-d₆) δ : 13.00 (br s, 2H, NH and OH), 9.43 (s, 1H, N^{4'}-N=CHC₆H₄Cl), 8.33-7.23 (m, 8H, aromatic), 2.55 (s, 3H, C^{5'}-Me).
 13. 12b: colorless needles (from DMF/EtOH), mp 281-282 °C. IR ν (KBr): 3235, 3190, 3140, 3060, 3030, 2820, 2770, 1660, 1610, 1595 cm⁻¹. NMR (DMSO-d₆) δ : 12.83 (br s, 2H, NH and OH), 9.00 (s, 1H, N^{4'}-N=CHC₆H₄Cl), 8.00-7.33 (m, 8H, aromatic), 2.50 (s, 3H, Me).
 14. 13a: colorless needles (from EtOH), mp 238-239 °C. IR ν (KBr): 3060, 1600,

- 1580, 1555, 1510, 1495 cm^{-1} . NMR (DMSO- d_6) δ : 9.39 (s, 1H, $\text{N}^{4'}$ -N=CHC $_6$ H $_4$ Cl), 8.43-7.27 (m, 8H, aromatic), 2.63 (s, 3H, Me).
15. 13b: colorless needles (from EtOH), mp 235-236 °C. IR ν (KBr): 3060, 1605, 1590, 1575, 1545, 1510, 1495 cm^{-1} . NMR (DMSO- d_6) δ : 9.12 (s, 1H, $\text{N}^{4'}$ -N=CH-C $_6$ H $_4$ Cl), 8.53-7.53 (m, 8H, aromatic), 2.60 (s, 3H, Me).
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