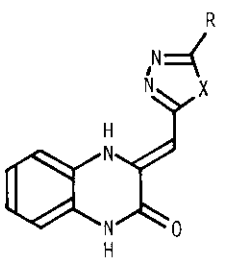
FACILE SYNTHESIS OF NOVEL 3-(4-AMINO-5-METHYL-4H-1,2,4-TRIAZOL-3-YLMETHYLENE)-2-OXO-1,2,3,4-TETRAHYDROQUINOXALINE AND RELATED COMPOUNDS

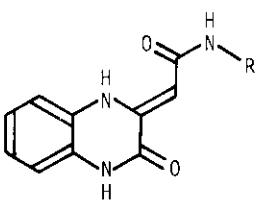
Yoshihisa Kurasawa,* Masayo Ichikawa, Itsuko Kamata,
Yoshihisa Okamoto, and Atsushi Takada
School of Pharmaceutical Sciences, Kitasato University
Shirokane, Minato-ku, Tokyo 108, Japan

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-ylmethylene)-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).

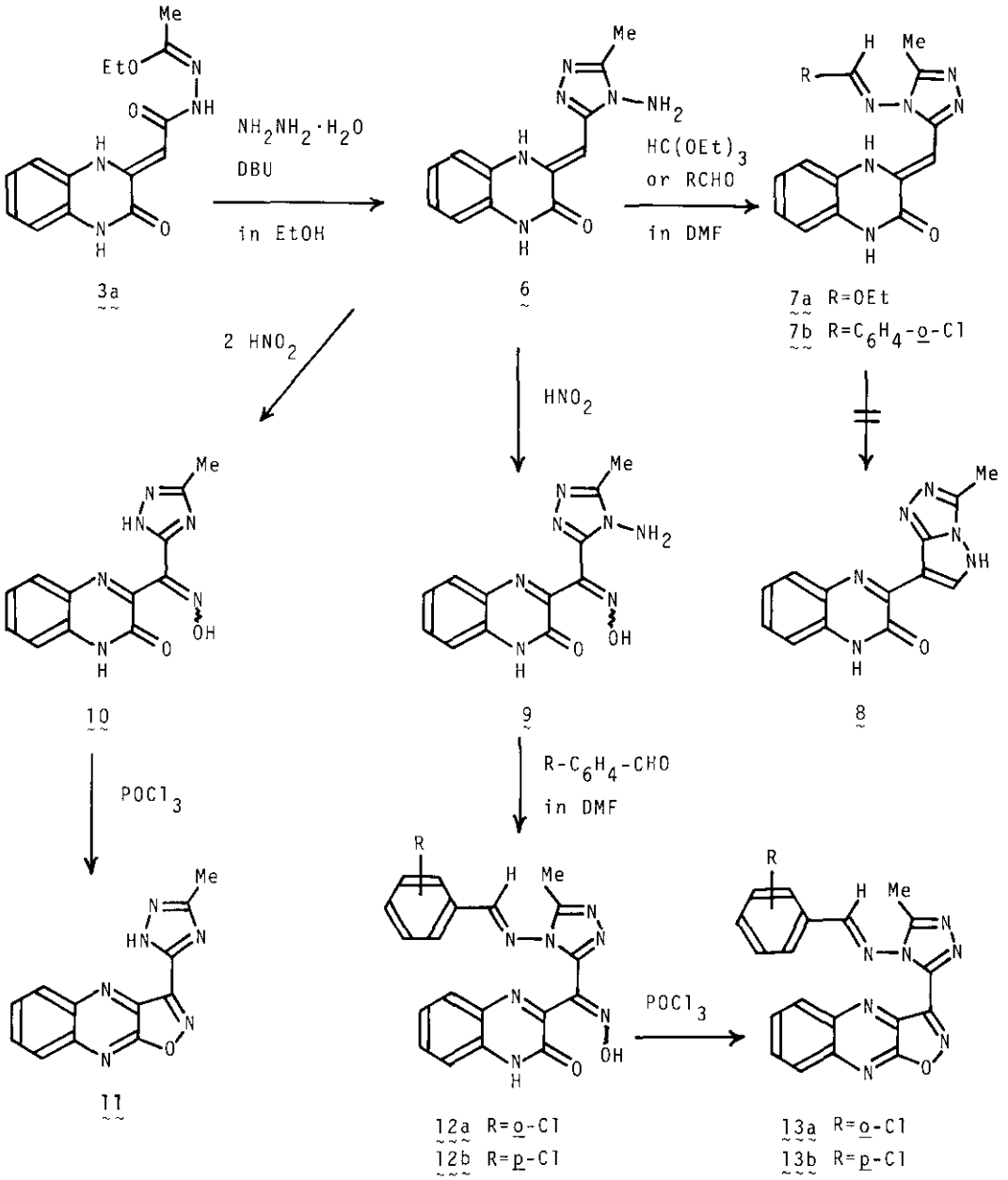


1 X=O R=Me,H
2 X=NR' R=SH,SMe



3 R, N=C(R')OEt
(a, R'=Me, b, R'=H)
4 R, NHCSNHR'
5 R, NH_2

SCHEME 1

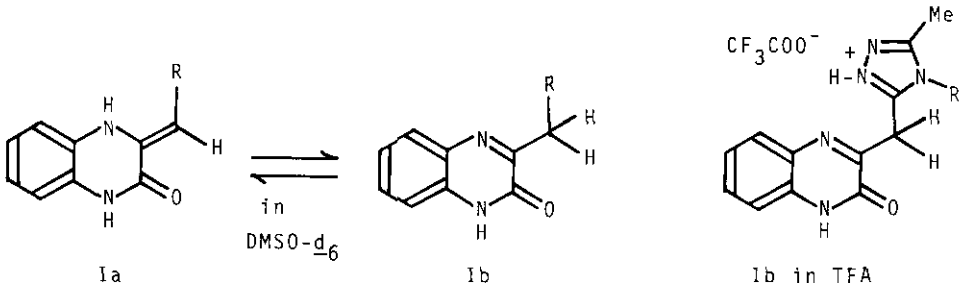


SCHEME 2*

* 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 $NH_2NH_2 \cdot H_2O$ (10 ml) and 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) (2 ml) in EtOH (400 ml) resulted in substitution and cyclization[3] 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-ethoxymethyleneamino-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-quinoxalinyl-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 hydroxyimination[2] 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 cyclization[10] 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) (4.33 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.



Ia Ib Ib in TFA

SCHEME 3

The ^{1}H-NMR spectrum of 6 in DMSO-d_6 exhibited the vinyl and methylene proton signals at δ 6.28 and 4.28 ppm due to two tautomers Ia and Ib (Ia:Ib=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 Ib (Scheme 3).[1,2,16] Compounds 7a and 7b were confirmed as the tautomer Ib, since their methylene proton signals were observed both at δ 4.90 ppm. Moreover, the ^{1}H-NMR spectrum of 9 in DMSO-d_6 exhibited the one pair of the $C^{5'}$-Me, N^1-H (or =NOH), and $N^{4'}$-NH_2 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 $N^{1'}$-proton and N^4-atom.[17] 4H-1,2,4-Triazole is less stable than 1H- or 2H-1,2,4-triazole.[17]

REFERENCES AND FOOTNOTES

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4. 6: yellow needles (triturated with hot EtOH), mp 333-334 °C. IR ν(KBr): 3340, 3175, 1680, 1630, 1610, 1520, 1500 cm^{-1}. NMR (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,

$N^{4'}$-NH_2), 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=CHOEt), 8.23-7.00 (m, 4H, aromatic), 4.90 (br s, 2H, methylene), 4.53 (q, J=7 Hz, 2H, CH_2 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=CHC$_6$H$_4$Cl), 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-d_6) 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, $N^{4'}$-NH_2), 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-d_6) 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, H_2O), 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-d_6) 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-d_6) δ: 13.00 (br s, 2H, NH and OH), 9.43 (s, 1H, $N^{4'}$-N=CHC$_6$H$_4$Cl), 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-d_6) δ: 12.83 (br s, 2H, NH and OH), 9.00 (s, 1H, $N^{4'}$-N=CHC$_6$H$_4$Cl), 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, $N^{4'}$-N=C<u>H</u>C_6H_4Cl), 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, $N^{4'}$-N=C<u>H</u>-C_6H_4Cl), 8.53-7.53 (m, 8H, aromatic), 2.60 (s, 3H, Me).
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