

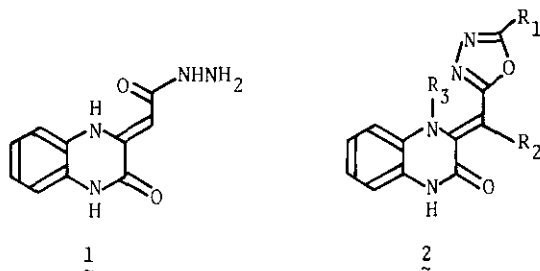
A FACILE SYNTHESIS OF NOVEL 3-(1,2,4-TRIAZOL-5-YL)METHYLENE-2-
OXO-1,2,3,4-TETRAHYDROQUINOXALINES AND THEIR RELATED COMPOUNDS

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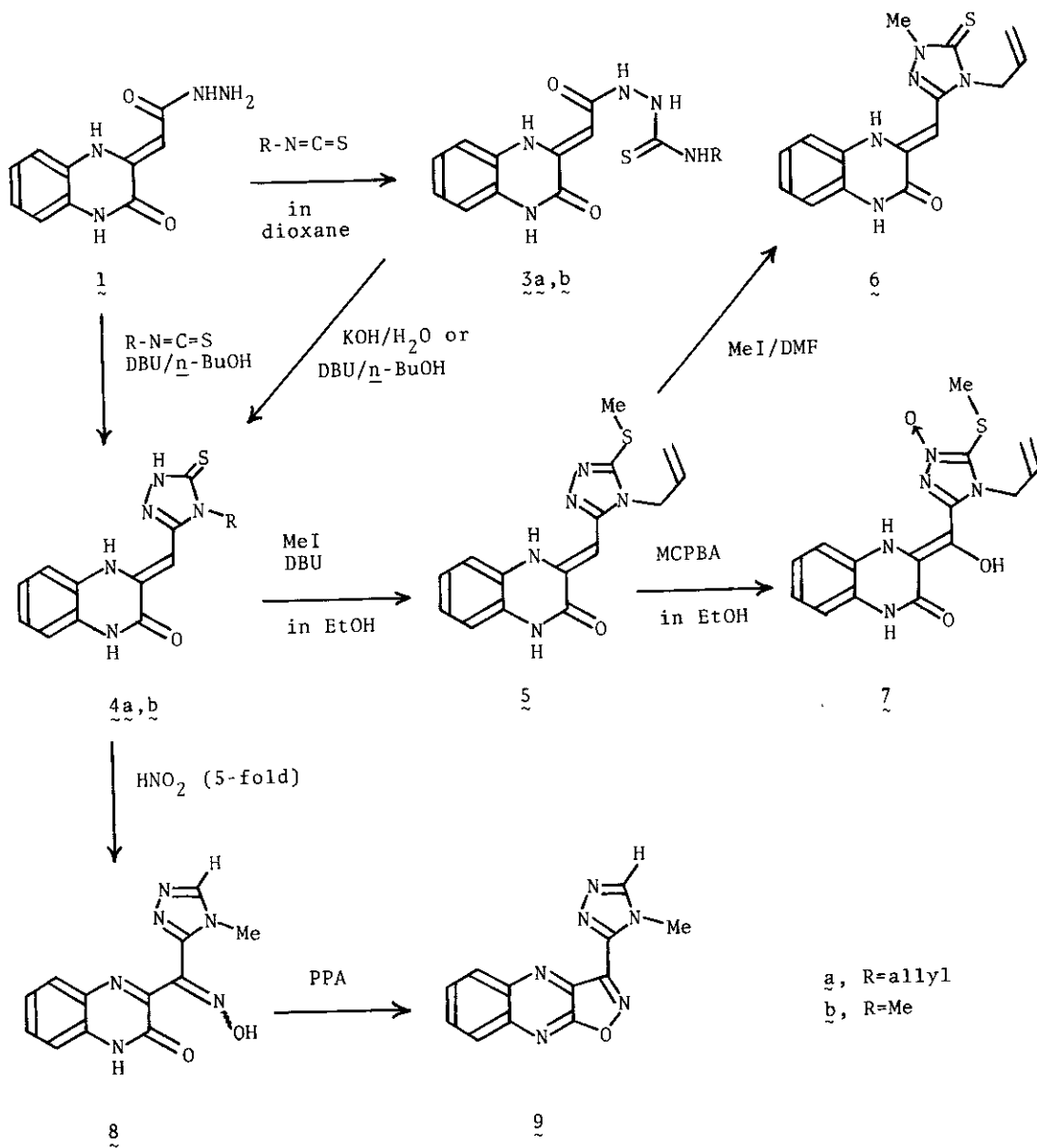
Abstract — Various new type of triazoles, 3-(1,2,4-triazol-5-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxalines (4-7) and related compounds (8,9), were synthesized from 3-hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (1).

Various 1,3,4-oxadiazoles have been known to possess fungicidal, herbicidal, and bactericidal activities,¹ and we have previously synthesized the new type of 1,3,4-oxadiazoles, 3-(1,3,4-oxadiazol-2-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxalines (2), from 3-hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (1) in order to evaluate the above activities.^{1,2} Moreover, many 1,2,4-triazoles have been also reported to possess bactericidal,³ fungicidal,⁴ pesticidal,⁵ and plant growth regulatory⁶ activities, but there have been few reports concerning the synthesis and biological evaluation of 1,2,4-triazoles having a quinoxalinylmethylene moiety in the 3- or 5-position. This paper describes a convenient synthesis of the above novel type of 1,2,4-triazoles.

The reaction of 1 (10 g, 45.9 mmol) with allyl or methyl isothiocyanate (46.1 mmol) in dioxane (200 ml) afforded the thiosemicarbazide (3a)⁷ (13.73 g, 94.4%) or (3b)⁸



Scheme 1



Scheme 2 *

(12.91 g, 96.7%), respectively. Refluxing of 3a or 3b (1 g) with KOH (1.5 eq.) in H₂O (30 ml) effected cyclization⁹ to provide 3-(4-allyl-2H-1,2,4-triazoline-3-thion-5-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (4a)¹⁰ (0.76 g, 81%) or 3-(4-methyl-2H-1,2,4-triazoline-3-thion-5-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (4b)¹¹ (0.28 g, 29.9%), respectively. Refluxing of 3a or 3b (10 g) in 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) (2 ml) and *n*-BuOH (400 ml) also afforded 4a (8.02 g, 85.5%) or 4b (8.74 g, 93.2%), respectively, in improved yields. In addition, the reaction of 1 (5 g, 22.9 mmol) with allyl or methyl isothiocyanate (equimolar amount) in DBU (1 ml) and *n*-BuOH (200 ml) directly produced 4a (4.74 g, 69.1%) or 4b (5.1 g, 81.5%), respectively.

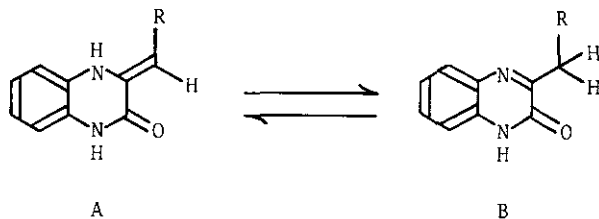
Methylation of 4a (4.22 g, 16.7 mmol) with MeI (2.61 g, 18.4 mmol) in DBU (2.80 g, 18.4 mmol) and EtOH (250 ml) provided 3-(4-allyl-3-methylthio-s-triazol-5-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (5)¹² (3.37 g, 76.2%). Further refluxing of 5 (2 g, 6.39 mmol) with MeI (1.5 eq.) in DMF (50 ml) induced N₂-methylation¹³ to result in the formation of 3-(4-allyl-2-methyl-1,2,4-triazoline-3-thion-5-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (6)¹⁴ (0.91 g, 45.5%). Moreover, the reaction of 5 (5 g, 16.0 mmol) with *m*-chloroperbenzoic acid (MCPBA) (2 eq.) in EtOH (200 ml) caused methylenic C-hydroxylation¹⁵ and N-oxidation to furnish 3-[1-(4-allyl-3-methylthio-s-triazol-5-yl)-1-hydroxy]methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline 2'-oxide (7)¹⁶ (940 mg, 18%), but the allyl group was not epoxidized. The N₂-oxide assignment was based on the following mass and NMR spectral data. The fragmentary [M⁺-16 (O)] ion peak was observed together with the [M⁺-17 (OH)] ion peak, which was presumably due to the presence of the SMe group.¹⁷ The methyl and allylic proton signals of 7 appeared in a lower magnetic field than those of 5.

The reaction of 4b (5 g, 18.3 mmol) with NaNO₂ (3.79 g, 54.9 mmol) in H₂O (100 ml) and AcOH (200 ml) effected hydroxyimination¹⁸ and sulfur extrusion to afford 3-[1-hydroxyimino-1-(4-methyl-s-triazol-5-yl)]methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (8)¹⁹ (3.25 g, 65.7%). Heating of 8 (5 g) in polyphosphoric acid (PPA) [H₃PO₄ (20 ml), P₂O₅ (10 g)] produced 3-(4-methyl-s-triazol-5-yl)isoxazolo[4,5-b]quinoxaline (9)²⁰ (1.86 g, 39.8%).

REFERENCES AND FOOTNOTES

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3. G. Mazzone, F. Bonina, and G. Blandino, Farmac. Ed. Sci. (Ital.), 1981, 36, 1004 (C. A., 96, 122698m).
4. Eur. Pat. Appl. EP 40345 (C. A., 96, 104256m); Brit. UK Pat. Appl. GB 2075004 (C. A., 96, 104257n); Brit. UK Pat. Appl., GB 2075005 (C. A., 96, 104258p).
5. Ger. Offen. DE 3020500 (C. A., 96, 142863q).
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7. 3a: colorless powder, mp 230-232 °C. $\nu(\text{KBr})$: 3300, 1690, 1640 cm^{-1} . $\delta(\text{DMSO-}d_6)$: 12.43 (s), 11.43 (s), 10.13 (s), 9.63 (s), 9.40 (s), and 9.15 (s) (4H, NH), ²¹ 8.10 (t, $J=4.5$ Hz, 1H, CSNHCH₂CH=CH₂), 8.00-6.70 (m, 4H, aromatic), 5.83 (m, 1H, -CH₂-CH=CH₂), 5.68 (s, C₃=CH-), ²¹ 5.30-4.87 (m, 2H, -CH₂-CH=CH₂), 4.10 (m, 2H, -CH₂-CH=CH₂), 3.72 (s, C₃-CH₂-). ²¹
8. 3b: colorless powder, mp 256-258 °C. $\nu(\text{KBr})$: 3300, 3160, 3010, 1670, 1630 cm^{-1} . $\delta(\text{DMSO-}d_6)$: 11.50 (s), 10.00 (br.s), 9.33 (s), and 9.10 (s) (4H, NH), ²¹ 7.90 (q, $J=4.5$ Hz, 1H, CSNHMe), 7.83-6.67 (m, 4H, aromatic), 5.68 (s, C₃=CH-), ²¹ 3.73 (s, C₃-CH₂-), ²¹ 2.94 (d, $J=4.5$ Hz) and 2.88 (d, $J=4.5$ Hz) (3H, CSNHMe). ²¹ The Me proton signals became two lines on addition of D₂O.
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10. 4a: yellow powder, mp 334-336 °C. $\nu(\text{KBr})$: 3120, 3060, 3010, 1680, 1640, 1610 cm^{-1} . $\delta(\text{DMSO-}d_6)$: 13.81 (s), 13.57 (s), 12.40 (s), and 11.46 (s) (2H, N₁- and N₄-H), ²¹ 10.03 (s, 1H, N₂-H), 7.77-6.67 (m, 4H, aromatic), 5.88 (s, C₃=CH-), ²¹ 5.86 (m, 1H, -CH₂-CH=CH₂), 5.30-4.83 (m, 2H, -CH₂-CH=CH₂), 4.68 (dd, $J=4.5$ Hz, 2H, -CH₂-CH=CH₂), 4.18 (s, C₃-CH₂-). ²¹
11. 4b: yellow powder, mp above 340 °C. $\nu(\text{KBr})$: 3120, 3060, 3010, 1680, 1640, 1610 cm^{-1} . $\delta(\text{DMSO-}d_6)$: 13.78 (s), 13.47 (s), 12.40 (s), and 11.43 (s) (2H, N₁- and N₄-H), ²¹ 10.00 (s, 1H, N₂-H), 7.77-6.77 (m, 4H, aromatic), 5.93 (s, C₃=CH-), ²¹ 4.27 (s, C₃-CH₂-), ²¹ 3.50 (s) and 3.53 (s) (3H, N₄-Me). ²¹
12. 5: yellow needles, mp 213-214 °C. $\nu(\text{KBr})$: 1675, 1635, 1615 cm^{-1} . $\delta(\text{DMSO-}d_6)$: 11.33 (s) and 11.13 (s) (2H, N₁- and N₄-H), ²¹ 7.23-6.73 (m, 4H, aromatic), 5.97 (s, C₃=CH-), ²¹ 5.92 (m, 1H, -CH₂-CH=CH₂), 5.30-4.53 (m, 4H, -CH₂=CH=CH₂), 4.23 (s, C₃-CH₂-), ²¹ 2.63 (s) and 2.58 (s) (3H, SMe). ²¹

13. P. Molina and M. Alajarin, Synthesis, 1983, 414.
14. 6: yellow needles, mp 285-287 °C. $\nu(\text{KBr})$: 1680, 1640, 1610 cm^{-1} . $\delta(\text{DMSO-}d_6)$: 12.37 (s), 11.40 (s), and 10.08 (s) (2H, N_1 - and N_4 -H), ²¹ 7.60-6.70 (m, 4H, aromatic), 5.90 (m, 1H, $-\text{CH}_2-\text{CH}=\text{CH}_2$), 5.87 (s, $C_3=\text{CH}-$), ²¹ 5.27-4.57 (m, 4H, $-\text{CH}_2-\text{CH}=\text{CH}_2$), 4.18 (s, $C_3-\text{CH}_2-$), ²¹ 3.79 (s) and 3.76 (s) (3H, N_2 , -Me). ²¹
15. Y. Kurasawa, Y. Moritaki, and A. Takada, Heterocycles, 1982, 19, 1619.
16. 7: yellow needles, mp 229-231 °C. $\nu(\text{KBr})$: 3220, 1650, 1610 cm^{-1} . $\delta(\text{DMSO-}d_6)$: 12.03 (s, 1H, N_1 -H), 11.22 (s, 1H, N_4 -H), 9.85 (s, 1H, OH), 7.30-6.53 (m, 4H, aromatic), 6.00 (m, 1H, $-\text{CH}_2-\text{CH}=\text{CH}_2$), 5.40-4.92 (m, 4H, $-\text{CH}_2-\text{CH}=\text{CH}_2$), 3.20 (s, 3H, SMe).
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19. 8: colorless needles, mp 295-297 °C. $\nu(\text{KBr})$: 3140, 1690, 1610 cm^{-1} . $\delta(\text{DMSO-}d_6)$: 12.53 (s) and 12.18 (s) (2H, N_1 -H and OH), 8.57 (s, 1H, C_3 , -H), 7.90-7.20 (m, 4H, aromatic), 3.87 (s, 3H, Me).
20. 9: yellow needles, mp 303-305 °C. $\nu(\text{KBr})$: 1590, 1555, 1515, 1500 cm^{-1} . $\delta(\text{DMSO-}d_6)$: 9.91 (s, 1H, C_3 , -H), 8.70-8.00 (m, 4H, aromatic), 4.62 (s, 3H, Me).
21. R. Mondelli and L. Merlini, Tetrahedron, 1966, 22, 3253; Y. Kurasawa and A. Takada, Heterocycles, 1983, 20, 1917. The NMR spectra of 1, ² 2, ² 3-7 in $\text{DMSO-}d_6$ exhibit the following tautomers A and B, and hence the extra NH and $C_3-\text{CH}_2-$ protons peaks are observed.



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

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