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A NEW RING TRANSFORMATION OF THIAZOLO[4,5-*g*]QUINAZOLINE 3-OXIDES INTO
[1,4]THIAZINO[3,2-*g*]QUINAZOLINES BY THE 1,3-DIPOLAR CYCLOADDITION
REACTION

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1,3-Dipolar cycloaddition reaction of thiazolo[4,5-*g*]quinazoline 3-oxides with ethyl phenylpropiolate resulted in a ring transformation of the thiazole nucleus to give [1,4]thiazino[3,2-*g*]quinazolines, a new class of heterocycles.

KEYWORDS — thiazolo[4,5-*g*]quinazoline 3-oxide; ethyl phenylpropiolate; 1,3-dipolar cycloaddition reaction; ring transformation; [1,4]thiazino[3,2-*g*]quinazoline

We have recently reported that the 1,3-dipolar cycloaddition reaction of a thiazolo[5,4-*d*]pyrimidine 3-oxide with acetylenic dipolarophiles causes a new ring transformation of the thiazole nucleus to give pyrimido[4,5-*b*] [1,4]thiazines as primary reaction products.¹⁾ In connection with these findings and with current stimulated medicinal interest in benzologs of purine and pteridine,²⁾ we have now investigated the reaction of the laterally extended benzolog of thiazolo[5,4-*d*]pyrimidine, *i.e.*, 2-substituted 6,8-dimethylthiazolo[4,5-*g*]quinazoline-5,7(6H,8H)-dione 3-oxides (1a, 1b),³⁾ with ethyl phenylpropiolate (EPP).

As shown in Chart 1, heating 1a (0.8 mmol) with EPP (1.6 mmol) in toluene (10 ml) at 130°C for 50 h gave the expected [1,4]thiazino[3,2-*g*]quinazoline (6a; 34%),⁴⁾ along with the deoxygenation product of 1a (13%)⁵⁾ after chromatographic separation on activated alumina with CHCl₃. The characterization of 6a was based on satisfactory analytical and spectral data (IR, ¹H-NMR, MS). Of particularly interest is the occurrence of a secondary amino group in both the IR (3280 cm⁻¹) and the ¹H-NMR (δ 9.41, D₂O exchangeable) spectra, which indicates the formation of a 1,4-thiazine nucleus.

On the other hand, heating of 1b (0.5 mmol) with EPP (1.5 mmol) in toluene (50 ml) at 130°C for 25 h afforded not only the thiazinoquinazoline (6b; 16%)⁶⁾ corresponding to 6a but also the 4-benzoylthiazinoquinazoline (5b; 25%)⁷⁾ together with the deoxygenation product of 1b (12%).³⁾ The structure of 6b was supported by its spectral analogy to 6a, while that of 5b was indicated by the lack of a secondary amino group in both the IR and the ¹H-NMR spectra and by the presence of a characteristic M⁺-105 fragment ion due to the liberation of a benzoyl radical. The structure was confirmed by hydrolytic conversion to 6b (55%) with ethanolic HCl.

Chart 1

Chart 2

As depicted in Chart 2, the ring transformation can be explained theoretically in terms of the initial formation of the adduct (2) by 1,3-dipolar cycloaddition. The cleavage of the N-O and C-S bonds of 2 to form 3, followed by the recyclization, would give 4 as the primary product. It seems likely that 4 is rather unstable and readily converts to the 4-benzoyl derivative 5, although the detailed mechanism is not yet clear. The hydrolytic cleavage of the benzoyl group of 5 would yield 6 as a final product. The deoxygenation of 1 would proceed by the thermal process.⁸⁾

Further work is in progress to elucidate the mechanism and extend the scope of the reaction.

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- 3) H. Kanazawa, K. Senga, and Z. Tamura, Chem. Pharm. Bull., 33, 618 (1985).
- 4) Compound 6a: mp 246-247°C. IR (Nujol): 3280 cm⁻¹(NH), 1740 (CO), 1695 (CO), 1640 (CO), 1620 (CO). ¹H-NMR (400 MHz, DMSO-d₆) δ: 1.17 (3H, t, Me, J=6 Hz), 3.21 (3H, s, Me), 3.37 (3H, s, Me), 3.77 (3H, s, Me), 4.21 (2H, q, CH₂, J=6 Hz), 6.85 (1H, s, 5-H), 7.03 (1H, s, 10-H), 9.42 (1H, s, NH, D₂O exchangeable). MS m/z: 391 (M⁺), 331, 318, 287, 259.
- 5) 2-Methoxycarbonyl-6,8-dimethylthiazolo[4,5-g]quinazoline-5,7(6H,8H)-dione: mp 281-282°C. IR (Nujol): 1700cm⁻¹(CO), 1660 (CO). MS m/z: 305 (M⁺), 249, 220, 162, 120.
- 6) Compound 6b: mp >300°C. IR (Nujol): 3300cm⁻¹(NH), 1690 (CO), 1675 (CO), 1620 (CO). ¹H-NMR (400 MHz, DMSO-d₆) δ: 1.14 (3H, t, Me, J=6 Hz), 1.78-1.92 (4H, m, pyrrolidine), 3.23 (3H, s, Me), 3.39 (3H, s, Me), 3.27-3.41 (4H, m, pyrrolidine), 4.03 (2H, q, CH₂, J=6 Hz), 9.38 (1H, s, NH, D₂O exchangeable). MS m/z: 430 (M⁺), 384, 359, 331, 287, 259.
- 7) Compound 5b: mp 243-245°C. IR (Nujol): 1710sh cm⁻¹(CO), 1705 (CO), 1665 (CO), 1640sh (CO). ¹H-NMR (400 MHz, DMSO-d₆) δ: 1.21 (3H, t, Me, J=6 Hz), 1.76-1.84 (4H, m, pyrrolidine), 3.18-3.38 (4H, m, pyrrolidine), 3.21 (3H, s, Me), 3.30 (3H, s, Me), 4.21 (2H, q, CH₂, J=6 Hz), 7.35-7.48 (5H, m, Ph), 7.51 (1H, s, 5-H), 7.71 (1H, s, 10-H). MS m/z: 534 (M⁺), 430, 429, 384, 359, 331, 287, 260, 259.
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