# A New Synthon in Heterocycle Synthesis (1)

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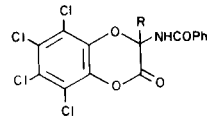
A tetrachlorobenzodioxinone, prepared from 2-phenyl-4-benzyl-2-oxazolin-5-one and *o*-chloranil was found to react with ethanol to give the ester **6**. This compound reacted readily with various bis-nucleophiles to form five- and six-membered heterocyclic compounds.

*J. Heterocyclic Chem.*, 14, 149 (1977).

In a recent report (2), the synthesis of a series of tetrachlorodioxinones (**1**) by the addition of *o*-chloranil to azlactones was described. As discussed in that communication, basic nucleophiles convert **1** into α-substituted amino acid derivatives (**2**) with the simultaneous formation of tetrachlorocatechol. This was an indication to us that **1** might be used as a synthon (**4**) useful in the synthesis of heterocycles, since bifunctional nucleophiles (**3**) should convert **1** into novel heterocyclic carbonyl compounds (**5**)



1 a, R = H

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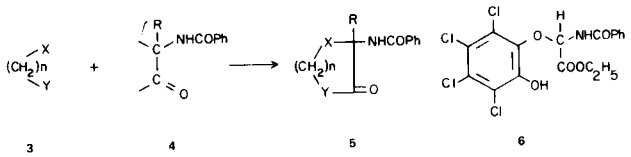
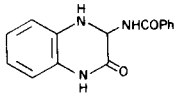
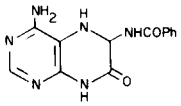
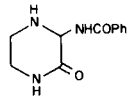
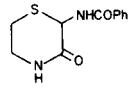
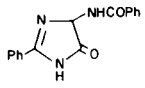
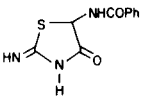


3 4 5 6

Table I

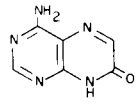
| | | Yield (%) | M.p. | Reaction Solvent (time, temperature) | Recrystallization Solvent |
|---|---|---|---|---|---|
| 7 |  | 75 (81 (a) | 223-228 dec. | Dichloromethane (Ethyl acetate) (b) (48 hours, TR) (c) | Methanol |
| 8 |  | 91 | > 350 dec. | DMSO (48 hours, RT) | Methanol |
| 9 |  | 68 | 187-199 | Chloroform (96 hours, RT) | Methanol |
| 10 |  | 28 | 203-205 | DMSO | Ethyl acetate |
| 11 |  | 65 | 293-296 dec. | Ethyl acetate | Methanol |
| 12 |  | 34 | 240-244 dec. | Ethyl acetate | Ethyl acetate |

(a) Yield as prepared from **6** (**1a**). (b) Solvent for reaction using **1a**. (c) RT = room temperature.

having a quaternary carbon with a ketone or aldehyde oxidation state. This report describes our efforts in this area.

Indeed, heterocycles were formed when **1a** was treated with **3**, but even in the presence of two equivalents of nucleophile only small isolable yields of product were obtained. The α-phenoxy ester (**6**), formed by treatment of **1a** with excess ethanol, was a much better source of the synthon (**4**) and led to heterocycles of the type **5** in good to excellent yields. Only *o*-phenylene diamine reacted cleanly with both **1** and **6** to give the 3-benzamidoquinoxalinone (**7**); the other heterocycles in Table I were all prepared from the ester **6**.

The hydroquinoxalinone (**7**) was readily oxidized to the known (3) 3-benzamido-2-quinoxalinone confirming the structure. The structure of the highly insoluble pteridinone (**8**) was shown to be a 7- rather than a 6-ketopteridine by its ultraviolet spectrum (4) and the fact that it was quickly converted into the known 4-amino-7-quinoxalinone (**13**) on standing in trifluoroacetic acid. We feel that this kind of elimination giving a more aromatic



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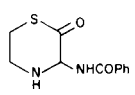

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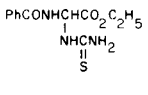

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product may be responsible (where possible) for the difficulties observed in some of this work. While the monocyclic piperidone (**9**) was formed in good yield uneventfully, the 3-thiomorpholinone (**10**) was not readily isolated in good yield. A mixture of products was obtained when the free mercaptoethylamine was treated with **6**, but the amine hydrochloride gave the small isolable yield of **10**. No attempt was made to maximize the yield. The alternative 2-thiomorpholinone structure **14** was ruled out by the infrared, $^{13}C$ and $^{1}H$ nmr spectra. All attempts to prepare aminomorpholinones using ethanolamine under a variety of conditions failed to yield pure identifiable products.

Two five-membered ring compounds (**11** and **12**) were also prepared from **6** using benzamidine and thiourea. The latter reaction, carried out at room temperature, also gave a small yield of **15**, the product of attack by nitrogen at the reactive α-carbon of **6**. In all the cases examined by us, the most nucleophilic hetero atom has attacked the α-carbon of **6** to give the predominant product.

## EXPERIMENTAL

General Method.

The reactions were carried out on a 1-2 mmolar scale maintaining a 2:1 molar ratio of nucleophile: **6** in every case in 10-25 ml. of the appropriate (Table I) solvent. All the products except **8** and **10** precipitated directly from the cooled reaction mixtures. Compound **8** was precipitated after dilution with 20-30 ml. of water. After filtration of **12**, evaporation of the filtrate gave 50 mg. of crude **15** which was obtained in 18% yield, m.p. 185-188°; ir (Nujol): 3450, 3330 and 3290 (NH/SH), 1745 ($CO_2Et$), 1650 $cm^{-1}$ (CONH); $^{1}H$ nmr (DMSO-$d_6$): δ 1.3 (t, 3H, $OCH_2CH_3$), 4.3 (q, 2H, $OCH_2CH_3$), 6.4 (d of d, 1H, NH-CHNH), 7.4-8.2 (m, 7H, $C_6H_5$ and $NH_2$), 8.8 (d, 1H, -NH-), 9.9 (d, 1H, -NH-).

*Anal.* Calcd. for $C_{12}H_{15}N_3O_3S$: C, 51.24; H, 5.38; N, 14.94. Found: C, 51.14; H, 5.35; N, 14.89.

2-Oxo-3-benzamido-1,2,3,4-tetrahydroquinoxaline (**7**).

This compound was prepared by the general method described above: ir (Nujol): 3290, 3250, 3170 (NH), 1665 (amide C=O); nmr (DMSO-$d_6$): δ 10.52 (s, 1H, NH), 9.36 (d, 1H, J = 8 Hz, CH-NH), 7.86 (m, 2H, *ortho* H's of $C_6H_5$), 7.44 (m, 3H, *meta* and *para* H's of $C_6H_5$), 6.78 (m, 5H, NH, 5,6,7,8 H's of quinoxalinone), 5.81 ppm (d, 1H, J = 8 Hz, CH-NH).

*Anal.* Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.25; H, 4.99; N, 15.66.

4-Amino-6-benzamido-7-oxo-5,6,7,8-tetrahydropteridine (**8**).

This compound was prepared by the general method described above: ir (Nujol): 3480, 3340, 3320, 3200 (NH), 1700, 1650 $cm^{-1}$ (C=O); $^{1}H$ nmr (DMSO-$d_6$): δ 5.86 (1H, d, d, J = 2 Hz, J = 8 Hz, NH-CH-NH), 6.09 (d, 1H, J = 2 Hz, -NH-CH-NH), 6.36 (s, 2H, $-NH_2$), 7.30-7.60 (m, 3H, $C_6H_5$), 7.74 (s, 1H, pyrimidine ring H), 7.80-7.90 (m, 2H, $C_6H_5$), 9.44 ppm (d, 1H, J = 8 Hz, -NH-CO-$C_6H_5$).

*Anal.* Calcd. for $C_{13}H_{12}N_6O_2$: C, 54.92; H, 4.25; N, 29.56. Found: C, 54.78; H, 4.33; N, 29.52.

3-Benzamido-2-piperazinone (**9**).

This compound was prepared by the general method described above: ir (Nujol): 3320, 3240, 3200 (N-H), 1695 (CONH), 1640 $cm^{-1}$ (CONH); $^{1}H$ nmr (DMSO-$d_6$): δ 2.7-3.4 (m, $-CH_2CH_2-$, NH), 5.16 (1H, d, NH-CH-NH), 7.4-7.6 (m, 3H, $C_6H_5$), 7.8-8.0 (m, 3H, $C_6H_5$ and NHCO), 9.16 (d, 1H, NH-COPh).

*Anal.* Calcd. for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.21; H, 6.00; N, 19.22.

2-Benzamidoperhydro-1,4-thiazin-3-one (**10**).

A solution of **6** (453 mg., 1 mmole) and 2-aminoethanethiol hydrochloride (150 mg., 1.3 mmoles) in 5 ml. of DMSO was warmed at 70-80° for 30 minutes. The reaction mixture was diluted with 30 ml. of water, and the precipitate was filtered. The filtrate was diluted with 5% sodium carbonate solution and extracted twice with ethyl acetate. The dried extracts were evaporated *in vacuo* giving a solid which was washed with ether and recrystallized from ethyl acetate to afford 65 mg. (28%) of **10** as colorless needles, m.p. 203-205°; ir (Nujol): 3320 (NH), 1690 (CONH), 1650 (CONH) $cm^{-1}$; $^{1}H$ nmr (DMSO-$d_6$): δ 2.80-3.20 (m, 2H, S-$CH_2$), 3.40-3.60 (m, 2H, $-NCH_2-$), 5.70 (d, 1H, J = 8.4 Hz, S-CH-NH), 7.40-7.60 (m, 3H, Ph), 7.80-8.00 (m, 2H, Ph), 8.15 (s, 1H, NH-$CH_2$-), 9.02 (d, 1H, J = 8.4 Hz, -NH-CH-); $^{13}C$ NMR (DMSO-$d_6$): δ 165.9 (C=O), 165.3 (C=O), 127.8-133.0 ($C_6H_5$), 47.9 (C-2), 42.06 (C-5), 25.7 (C-6).

*Anal.* Calcd. for $C_{11}H_{12}N_2O_2S$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.87; H, 5.15; N, 11.80.

2-Phenyl-4-benzamido-2-imidazolin-5-one (**11**).

This compound was prepared by the general method described above: ir (Nujol): 3340, 3200-2500 (NH/OH), 1750, 1670 $cm^{-1}$

(CONH); $^1$H nmr (DMSO-$d_6$): δ 7.6-8.2 (m, 11H, 2 $C_6H_5$, N*H*), 9.0 (s, 1H, N*H*), 12.5 (s, 1H, O*H*).

*Anal.* Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.04. Found: C, 68.84; H, 4.71; N, 15.01.

2-Imino-5-benzamidothiazolidin-4-one (**12**).

This compound was prepared by the general method described above: ir (Nujol): 3240 (NH), 3100-2500 (OH/NH), 1690 (CONH), 1650 cm$^{-1}$ (CONH); $^1$H nmr (DMSO-$d_6$): δ 6.3 (d, 1H, -C*H*-NH-), 7.4-8.2 (m, 5H, $C_6H_5$), 9.1 (s, 1H, N*H*), 9.3 (s, 1H, N*H*), (d, 1H, -N*H*-CH-).

*Anal.* Calcd. for $C_{10}H_9N_3O_2S$: C, 51.07; H, 3.86; N, 17.87. Found: C, 50.85; H, 3.93; N, 17.92.

4-Amino-8*H*-dihydropteridin-7-one (**13**).

A solution of 38 mg. of **8** in 0.5 ml. of trifluoroacetic acid was allowed to stand at room temperature for 1 hour and was then evaporated *in vacuo*. The residue was dissolved in water and the solution was neutralized with sodium bicarbonate. The crystals were collected on a filter, washed with water and dried to afford 20 mg. (91%) of **13**, m.p. 350° (lit. (4) m.p. 350°). The uv spectrum of **13** in water under neutral, acidic and basic conditions were consistent with those reported (4). The aqueous layer was extracted with chloroform and evaporation of the combined ex- gave 10 mg. of benzamide as shown by its infrared spectrum.

Oxidation of **7**.

A solution of 267 mg. of **7** in 20 ml. of warm dioxane containing 272 mg. of DDQ was stirred for 1 hour at room temperature. The reaction mixture was evaporated *in vacuo;* the residue was dissolved in 50 ml. of chloroform and the solution was washed with 5% sodium bicarbonate solution. Evaporation of the organic layer gave crystals, which were recrystallized from methanol to afford 190 mg. (72%) of 3-benzamido-2-quinoxalinone as colorless needles, m.p. 263-267° dec., (lit. (3) m.p. 255°); ir (Nujol): 3360, 3200 (NH/OH), 1670 cm$^{-1}$ (CONH); $^1$H nmr (DMSO-$d_6$): δ 7.2-8.0 (m, 9H, Ar*H*), 10.2 (s, 1H, N*H*), 12.7 (s, 1H, O*H*).

Acknowledgment.

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## REFERENCES AND NOTES

(1) Presented at the Fifth Symposium on the Chemistry of Heterocyclic Compounds, Bratislava, Czechoslovakia, July 1975.

(2) J. M. Riordan and C. H. Stammer, *Tetrahedron Letters*, 1247 (1976).

(3) D. Shiho and S. Tagani, *Chem. Pharm. Bull.*, 5, 45 (1957).

(4) D. Soll and W. Pfleiderer, *Chem. Ber.*, **96**, 2977 (1963).