The Synthesis of 1,3,4-Oxadiazolo[3,2-*b*]isoquinoline and 1,3,4-Thiadiazolo-[3,2-*b*]isoquinoline Derivatives from Homophthalic Anhydride

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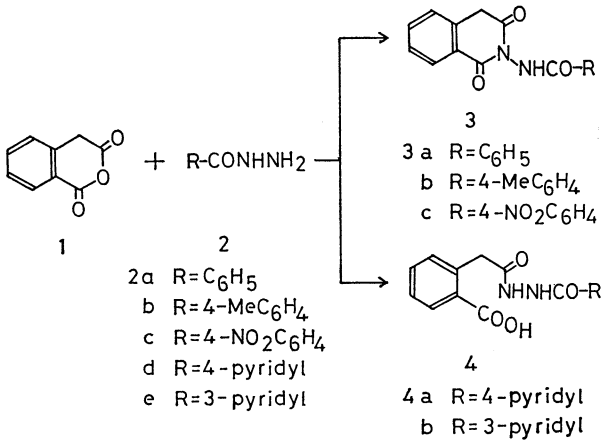
The synthesis of 1,3,4-oxadiazolo[3,2-*b*]isoquinoline and 1,3,4-thiadiazolo[3,2-*b*]isoquinoline derivatives is described. The reaction of homophthalic anhydride (**1**) with acylhydrazines (**2**) afforded 2-acylamino-1,2,3,4-tetrahydroisoquinoline-1,3-diones (**3**) or 1-(*o*-carboxyphenylacetyl)-2-acylhydrazines (**4**). The treatment of **3** or **4** with polyphosphoric acid gave 2-substituted 1,3,4-oxadiazolo[3,2-*b*]isoquinolin-5(5*H*)-ones (**5**) in quantitative yields. The treatment of **3** or **4** with phosphorus pentasulfide gave 2-substituted 1,3,4-thiadiazolo[3,2-*b*]-isoquinoline-5(5*H*)-thiones (**6**). 2-Phenyl-1,3,4-oxadiazolo[3,2-*b*]isoquinoline-5(5*H*)-thione (**9**) was obtained by the reaction of **5a** with phosphorus pentasulfide.

Homophthalic anhydride is a readily-available cyclic anhydride,[1] which is considered to be a useful starting material for the synthesis of various condensed isoquinoline derivatives. Homophthalic anhydride (**1**) has been condensed with *o*-phenylenediamine to give benzimidazo[1,2-*b*]isoquinoline derivatives.[2–5] On the other hand, *o*-aminobenzenethiol has been treated with 5-substituted homophthalic anhydride to form 2-substituted benzylbenzothiazoles, which were then cyclized to 9-substituted isoquinolino[3,2-*b*]benzothiazolones.[6] Thiazolo[3,2-*b*]isoquinoline derivatives[7] were similarly obtained from 2-aminoethanethiol and **1**. In the reaction of **1** with 1,2-dimethylhydrazine, 2,3-dimethyl-1,2,3,4-tetrahydro-5*H*-2,3-benzodiazepine-1,4-dione[8] has been isolated. The reaction of **1** with *S*-alkylisothiosemicarbazides has been reported to give 2-alkylthio-*s*-triazolo[1,5-*b*]isoquinolin-5-ones, and their reactions have been studied.[9] *s*-Triazolo[1,5-*b*]isoquinolin-5-ones[10,11] have also been synthesized from **1** and amidrazones.

In this paper we wish to report the synthesis of two groups of heterocycles which have new ring systems.

Results and Discussion

When **1** was treated with acyl hydrazines (**2**) in boiling acetic acid, the products isolated were 2-acylamino-1,2,3,4-tetrahydroisoquinoline-1,3-diones (**3**) or 1-(*o*-carboxyphenylacetyl)-2-acylhydrazines (**4**).



Scheme 1.

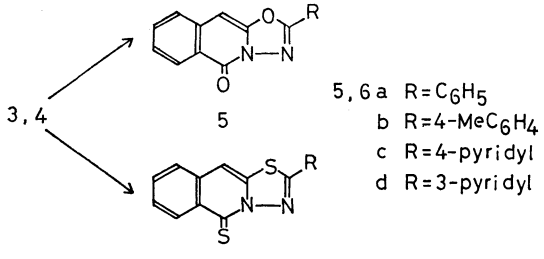
Thus, the reaction of **1** with benzohydrazide (**2a**) gave 2-benzamido-1,2,3,4-tetrahydroisoquinoline-1,3-dione (**3a**) in a 92% yield. The IR spectrum of **3a** showed an NH absorption at 3250 cm^{-1} and three carbonyl absorptions at 1735, 1695, and 1660 cm^{-1}. The reaction of **1** with (**2b**) and (**2c**) proceeded in a similar manner to give (**3b**) and (**3c**). However, the products obtained from (**2d**) and (**2e**) were 1-(*o*-carboxyphenylacetyl)-2-acylhydrazines (**4a**) and (**4b**). The physical properties and spectral data, shown in Table 1, are consistent with the structure assigned.

TABLE 1. PHYSICAL PROPERTIES AND SPECTRAL DATA OF **3** AND **4**

Compound	Reaction time (hr)	Yield (%)	Mp (°C) Solvent	Found (%) (Calcd (%)) C	H	IR (KBr, cm^{-1})	UV (λ_{max}^{MeOH} nm (log ε))
3a	4	92	190—191 MeOH	68.54 (68.56	4.48 4.32)	3250, 1735, 1695, 1660	238(4.13), 280(sh, 3.36) 290(sh, 3.23), 310(sh, 2.93)
3b	4	74	206—208 AcOH	69.19 (69.37	4.61 4.80)	3220, 1730, 1695, 1650	243(4.43), 282(sh, 3.51) 292(sh, 3.41), 310(sh, 3.30)
3c	10	76	210—211 MeOH	58.94 (59.08	3.67 3.41)	3280, 1743, 1700, 1665	251(4.33)
4a	5	66	112—115 MeOH	60.06 (60.19	4.56 4.38)	3430, 3160, 2920, 2820, 1735, 1700 1663	242(4.20), 310(sh, 3.49)
4b	16	35	166—169 EtOH	60.27 (60.19	4.66 4.38)	3540, 3160, 2980, 1730, 1670	243(4.21), 290(sh, 3.24) 310(sh, 2.86)

The dehydration of **3** with polyphosphoric acid proceeded smoothly to give the desired products (**5**) in quantitative yields. Thus, **3a** was heated with polyphosphoric acid at 125—130 °C, and the reaction mixture was treated in the usual manner to give 2-phenyl-1,3,4-oxadiazolo[3,2-*b*]isoquinolin-5(5*H*)-one (**5a**). The IR spectrum of **5a** showed no NH absorptions, only one C=O absorption at 1685 cm^{-1} and a new C=N absorption at 1652 cm^{-1}. The olefinic proton resonance of **5a** in the NMR spectrum was observed at δ 6.49 ppm. The elemental analysis and the mass-spectral molecular ion at *m/e* 262 also supported the assigned structure. A similar cyclization by polyphosphoric acid occurred in one step in the case of **4**. The **5** compounds showed characteristic IR absorptions at 1683—1685 (C=O) and 1648—1652 (C=N) cm^{-1}. The physical properties and spectral data are summarized in Table 2. The **5** compounds are heterocycles with a new ring system.

When **3** or **4** was heated with phosphorus pentasulfide in refluxing pyridine, 2-substituted 1,3,4-thiadiazolo[3,2-*b*]isoquinoline-5(5*H*)-thiones (**6**) were obtained; these heterocycles also belong to a new ring system. 2-Phenyl-1,3,4-thiadiazolo[3,2-*b*]isoquinoline-5(5*H*)-thione (**6a**) showed no NH or C=O absorptions in the IR spectrum. The NMR spectrum exhibited a signal of an olefinic proton at δ 7.31 ppm. The molecular-ion peak at *m/e* 294 and the other fragment-ion peaks in the mass spectrum were also consistent with the structure. The physical properties and spectral data of the other compounds of **6** are summarized in Table 2. These compounds show similar absorption maxima in the UV and visible spectra.



Scheme 2.

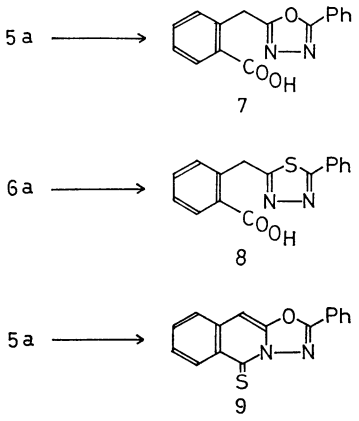
Some reactions of these new heterocycles **5** and **6** were attempted. The hydrolysis of **5a** in refluxing aqueous methanol containing sodium hydroxide afforded a crystalline product (**7**). The characteristic absorptions of the carboxyl group were observed at 2620—3340 (OH) and 1705 (C=O) cm^{-1} in the IR spectrum. The NMR spectrum of **7** indicated the presence of a methylene group at δ 4.13 ppm. From the above data, the structure of **7** was assigned to 2-(*o*-carboxybenzyl)-5-phenyl-1,3,4-oxadiazole. A similar treatment of **6a** with alkaline afforded a product (**8**). The characteristic absorption of the carboxyl group were observed at 2340—3440 and 1688 cm^{-1} in the IR spectrum. **8** was also shown to be the ring-opened product 2-(*o*-carboxybenzyl)-5-phenyl-1,3,4-thiadiazole.

When **5a** was treated with phosphorus pentasulfide

TABLE 2. PHYSICAL PROPERTIES AND SPECTRAL DATA OF 5 AND 6

Compound	Reaction time	Yield (%)	Mp (°C) Solvent	Found (%) (Calcd (%)) C	H	IR (KBr, cm^{-1})	UV (λ_{max}^{MeOH} nm (log ε))
5a	40 min	100	236—238 Pyridine	73.50 (73.27	3.78 3.84)	3040, 1685, 1652, 1610	245(sh, 4.51), 256(sh, 4.59), 263(4.61), 290(sh, 4.13), 354(sh, 3.83), 370(3.92), 385(sh, 3.79)
5b	40 min	100	290—292 Pyridine	73.72 (73.90	4.14 4.38)	3040, 1685, 1652, 1610	251(sh, 4.47), 268(4.63), 354(sh, 3.88), 368(3.95), 385(sh, 3.80)
5c	40 min	100	267—269 Pyridine	68.57 (68.43	3.46 3.45)	3045, 1685, 1650, 1620	255(4.60), 290(sh, 4.11), 380(3.73)
5d	40 min	100	249—250 MeOH	68.65 (68.43	3.66 3.45)	3060, 1683, 1648, 1620	244(sh, 4.51), 253(4.58), 261(sh, 4.55), 290(sh, 4.13), 372(3.82)
6a	4 hr	48	217—218 Pyridine	65.34 (65.30	3.65 3.43)	3040, 1600, 1530, 1472	230(4.45), 270(4.61), 294(4.51), 347(sh, 3.87) 443(4.01), 465(3.97)
6b	5 hr	49	178—180 Pyridine	66.55 (66.23	4.11 3.92)	3040, 1665, 1605, 1532	232(4.53), 274(4.57), 299(4.60), 348(sh, 3.87), 440(4.06), 463(4.03)
6c	5 hr	39	269—273 Pyridine	61.27 (61.02	3.28 3.07)	3030, 1603, 1530, 1475	225(4.42), 266(4.65), 290(4.37), 330(3.99), 350(sh, 3.93), 467(3.92)
6d	5 hr	50	251—252 Pyridine	61.12 (61.02	3.04 3.07)	3030, 1600, 1533, 1469	227(4.39), 266(4.58), 292(4.45), 326(3.94), 349(sh, 3.90), 450(3.96), 470(3.92)

in refluxing pyridine, yellow needles (**9**) were obtained in a quantitative yield. The IR spectrum of **9** showed no C=O absorption, but the C=N absorption band which was characteristic of the **5** compounds remained at 1652 cm^{-1}. The absorption maxima observed in the UV and visible spectrum were similar to those of **5a**. These spectral data and the satisfactory analytical value accorded with the structure of **9** as 2-phenyl-1,3,4-oxadiazolo[3,2-*b*]isoquinoline-5(5*H*)-thione.



Scheme 3.

Experimental

All the melting points are uncorrected. The IR, UV, and NMR spectra were measured with a JASCO Model IRA-2, a Shimadzu Model MPS-501, and a Hitachi Model R-20 spectrometer respectively. A Shimadzu Model UM-3B apparatus was used for the elemental analysis.

*2-Benzamido-1,2,3,4-tetrahydroisoquinoline-1,3-dione (**3a**).* A mixture of **1** (724 mg, 4.5 mmol) and **2a** (618 mg, 4.5 mmol) in acetic acid (10 ml) was refluxed for 4 hr. After the concentration of the solution *in vacuo* and subsequent cooling, the crystals were filtered to give **3a** (1.15 g, 92% yield). Recrystallization from methanol afforded white crystals; mp 190—191 °C.

The other derivatives, **3b**, **3c**, **4a**, and **4b** were obtained according to methods similar to those described in the case of **3a**.

*2-Phenyl-1,3,4-oxadiazolo[3,2-*b*]isoquinolin-5(5*H*)-one (**5a**).* A mixture of **3a** (840 mg, 3.0 mmol) and polyphosphoric acid (2.7 g) was heated at 125—130 °C with gentle stirring for 40 min. After cooling, the mixture was poured into water (30 ml) and the resulting precipitates were filtered to give **5a** in a quantitative yield. Recrystallization from pyridine afforded yellow plates; mp 236—238 °C. NMR ($CDCl_3$): δ 6.49 (s, 1H, =CH–), 7.2—8.7 (m, 9H, aromatic H). Mass *m/e* (%): 262 (M^+, 100), 131 (57), 103 (57).

The other derivatives, **5b**—**5d**, were obtained from **3** or **4** according to methods similar to those described in the case of **5a**.

*2-Phenyl-1,3,4-thiadiazolo[3,2-*b*]isoquinoline-5(5*H*)-thione(**6a**).* A mixture of **3a** (560 mg, 2.0 mmol) and finely powdered phosphorus pentasulfide (450 mg. 2.0 mmol) in pyridine (3.0 ml) was refluxed for 4 hr. The insoluble materials were then filtered off from the hot solution, and the filtrate was cooled. The precipitates were filtered to give **6a** (227 mg, 48% yield). Recrystallization from pyridine afforded orange needles; mp 217—218 °C. NMR ($CDCl_3$): δ 7.31 (s, 1H, =CH–) 7.5—8.2 (m, 9H, aromatic H). Mass *m/e* (%): 294 (M^+, 100), 266 (17), 250 (44), 191 (23), 159 (40), 147 (98), 146 (65), 121 (63).

*2-(o-Carboxybenzyl)-5-phenyl-1,3,4-oxadiazole (**7**).* A solution of **5a** (262 mg, 1.0 mmol) in a mixture of aqueous sodium hydroxide (1 M, 5.0 ml) and methanol (5.0 ml) was refluxed for 5 hr. After the removal of the solvent, water (15 ml) was added to the residue, and the solution was neutralized with dilute hydrochloric acid. The resulting precipitates were filtered to give **7** (191 mg, 68% yield). Recrystallization from methanol afforded white needles; mp 174—175 °C. Found: C, 68.76; H, 4.37%. Calcd for $C_{16}H_{12}O_3N_2$: C, 68.56; H, 4.32%. IR (KBr): 3360, 3040, 2960, 2740, 2620, 1705, 1608, 1555 cm^{-1}. UV λ_{max}^{MeOH} nm (log ε): 280 (4.32). NMR (DMSO-d_6): δ 4.13 (s, 2H, $-CH_2-$), 7.4—8.3 (m, 9H, aromatic H).

*2-(o-Carboxybenzyl)-5-phenyl-1,3,4-thiadiazole (**8**).* A solution of **6a** (147 mg, 0.50 mmol) in a mixture of aqueous sodium hydroxide (1 M, 2.5 ml) and methanol (15 ml) was refluxed for 24 hr. After the subsequent evaporation of the solvent, water (15 ml) was added to the residue; the small amount of insoluble materials was then filtered off. The filtrate was neutralized with dilute hydrochloric acid, and the resulting precipitates were filtered to give **8** (111 mg, 75% yield). Recrystallization from methanol afforded white needles; mp 193—194 °C. Found: C, 64.87; H, 4.04%. Calcd for $C_{16}H_{12}O_2N_2S$: C, 64.87; H, 4.08%. IR (KBr): 3440, 2860, 2760, 2680, 2455, 2370, 1688, 1597, 1459 cm^{-1}. UV λ_{max}^{MeOH} nm (log ε): 272 (4.22).

*2-Phenyl-1,3,4-oxadiazolo[3,2-*b*]isoquinoline-5(5*H*)-thione (**9**).* A mixture of **5a** (500 mg, 2.0 mmol) and phosphorus pentasulfide (440 mg, 2.0 mmol) in pyridine (10 ml) was refluxed for 8 hr. The insoluble materials were filtered off from the hot solution, and then the filtrate was concentrated *in vacuo* to one-half volume. After cooling, the precipitates were filtered to give **9** (542 mg, 100% yield). Recrystallization from ethanol afforded yellow needles; mp 205—206 °C. Found: C, 69.44; H, 3.62%. Calcd for $C_{16}H_{10}ON_2S$: C, 69.06; H, 3.62%. IR (KBr): 3040, 1652, 1610, 1572, 1535, 1472 cm^{-1}. UV λ_{max}^{MeOH} nm (log ε): 218 (4.34), 259 (4.64), 282 (4.61), 310 (sh, 4.02), 415 (4.02), 436 (4.03).

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