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The N-Oxides of New Heterocyclic Systems. Syntheses and Chemical Properties of Thiazolo[4,5-*g*]quinazoline 3-Oxides and Thiazolo[5,4-*f*]quinazoline 3-Oxides

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Thiazolo[4,5-*g*]quinazoline 3-oxides and thiazolo[5,4-*f*]quinazoline 3-oxides, the N-oxides of new heterocyclic systems, were synthesized and their chemical properties were investigated. Namely, the reaction of 7-chloro-1,3-dimethyl-6-nitroquinazoline-2,4(1*H*,3*H*)-dione (**1**) with methyl thioglycolate in the presence of triethylamine gave 7-methoxycarbonylmethylthio-1,3-dimethyl-6-nitroquinazoline-2,4(1*H*,3*H*)-dione (**2**) and subsequent treatment of **2** with pyrrolidine resulted in base-catalyzed dehydrative cyclization to afford 2-methoxycarbonyl-6,8-dimethylthiazolo[4,5-*g*]quinazoline-5,7(6*H*,8*H*)-dione 3-oxide (**3**) and 6,8-dimethyl-2-pyrrolidinocarbonylthiazolo[4,5-*g*]quinazoline-5,7-(6*H*,8*H*)-dione 3-oxide (**5**). On the other hand, the reaction of 5-chloro-1,3-dimethyl-6-nitroquinazoline-2,4(1*H*,3*H*)-dione (**10**) with methyl thioglycolate in the presence of triethylamine directly yielded 2-methoxycarbonyl-6,8-dimethylthiazolo[5,4-*f*]quinazoline-7,9(6*H*,8*H*)-dione 3-oxide (**11**). These N-oxides were confirmed to be useful starting materials for the preparation of a variety of thiazolo[4,5-*g*]- and [5,4-*f*]quinazoline derivatives.

Keywords——7-chloro-6-nitroquinazoline; 5-chloro-6-nitroquinazoline; methyl thioglycolate; triethylamine; pyrrolidine; base-catalyzed dehydrative cyclization; thiazolo[4,5-*g*]quinazoline 3-oxide; thiazolo[4,5-*g*]quinazoline; thiazolo[5,4-*f*]quinazoline 3-oxide; thiazolo[5,4-*f*]quinazoline

Leonard and his colleagues have previously reported the synthesis of benzologs of naturally occurring purines, in which a benzene ring was inserted between the pyrimidine and imidazole portions of the purine ring system,[1] and they found that some of these benzo-separated purines exhibit fluorescence properties and biological activity.[2] Since then, many benzo-separated analogues of biologically important fused pyrimidines have been synthesized.[3-5] In connection with these studies and our continued interest in the thiazolo[4,5-*d*]pyrimidines as potential medicinal agents,[6] we now wish to report the syntheses and chemical properties of new laterally extended and stretched-out benzologs of the thiazolopyrimidine 3-oxides, *i.e.*, thiazolo[4,5-*g*]quinazoline 3-oxides and thiazolo[5,4-*f*]quinazoline 3-oxides.

Thiazolo[4,5-*g*]quinazoline 3-Oxides

As shown in Chart 1, treatment of the 7-chloro-6-nitroquinazoline (**1**)[5c] with methyl thioglycolate in the presence of triethylamine in methanol under reflux for 2 h gave the 7-methoxycarbonylmethylthio-6-nitroquinazoline (**2**) in 89% yield. The structure of **2** was supported by the presence of a signal due to methylenic protons at 4.28 ppm as a singlet in the nuclear magnetic resonace (NMR) spectrum (DMSO-d_6).

Subsequent refluxing of **2** in methanol in the presence of pyrrolidine (pK_a 11.04), a stronger base than triethylamine (pK_a 10.64), for 15 h resulted in base-catalyzed dehydrative cyclization to yield the 2-methoxycarbonyl- and 2-pyrrolidinocarbonylthiazolo[4,5-*g*]-quinazoline 3-oxides (**3** and **5**) in 38 and 12% yields, respectively, along with the deoxygenated 2-pyrrolidinocarbonylthiazolo[4,5-*g*]quinazoline (**6**) in 6% yield. Compound **3**

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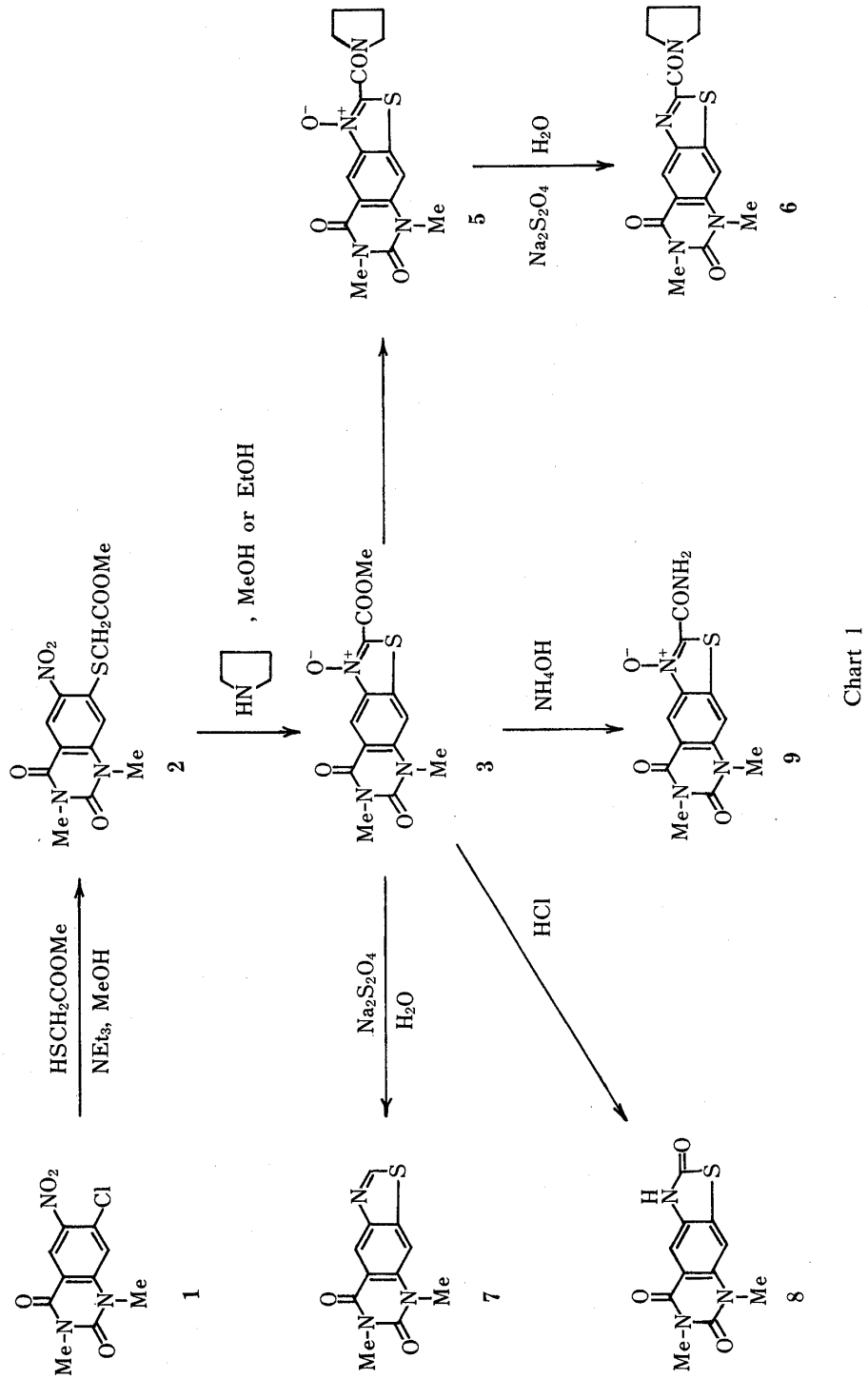

Chart 1

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was readily separated from the reaction mixture, while **5** and **6** were isolated by concentration of the filtrate. These products gave satisfactory analytical and spectral data. In particular, the N-oxides **3** and **5** showed a strong M^+ ion and a remarkable $M^+ - 16$ ion due to the presence of the N-oxide, respectively, in the mass spectrum (MS).

The formation of **5** evidently involves nucleophilic displacement of the methoxycarbonyl group of the pre-formed **3** with pyrrolidine. The use of ethanol instead of methanol caused the exhaustive transesterification of **3** with pyrrolidine to give **5** and **6** in 53 and 15% yields, respectively, probably because of the higher boiling point of ethanol than methanol.

The N-oxide **3** is quite reactive toward various reagents. For example, heating of **3** with sodium dithionite in water unexpectedly gave the 2-unsubstituted thiazolo[4,5-*g*]quinazoline (**7**) in 98% yield presumably by the reductive deoxygenation of the N-oxide and subsequent hydrolytic decarboxylation of the methoxycarbonyl group. Attempts to isolate the deoxygenated 2-methoxycarbonylthiazolo[4,5-*g*]quinazoline (**4**) were found to be unsuccessful even under mild conditions. The proton at the 2 position of **7** was observed at 9.38 ppm as a singlet in the NMR spectrum (DMSO-d_6). In contrast with **3**, treatment of **5** with sodium dithionite readily afforded **6** in 87% yield.

Furthermore, heating of **3** with 10% hydrochloric acid gave the 2-hydroxythiazolo[4,5-*g*]quinazoline (**8**) in 91% yield. Although **8** has two tautomeric forms (keto- and enol-form), the keto-form seems more favorable than the enol-form in the solid state since the infrared (IR) spectrum (KBr) exhibits an additional carbonyl absorption band at 1640 cm^{-1}. The pronounced upfield shifts of the aromatic protons at the 4- and 9-positions of **8** in the NMR spectrum (DMSO-d_6) as compared with other thiazolo[4,5-*g*]quinazolines, *e.g.*, **6** and **7**, also indicated the exclusive contribution of the keto-form in solution. The treatment of **3** with 28% ammonium hydroxide gave the 2-carbamoylthiazolo[4,5-*g*]quinazoline 3-oxide (**9**) in 73% yield. In contrast to the susceptibility of **3** and **5** to deoxygenation, compound **9** was found to be highly stable to reductive deoxygenation using sodium dithionite and oxidative deoxygenation by dimethylformamide (DMF).[7] This stability may be explained in terms of

TABLE I. Thiazolo[4,5-*g*]quinazolines (**3**—**9**)

Compd. No.[a]	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
3	280—282	38[b]	$C_{13}H_{11}N_3O_5S$	48.59	3.46	13.08
				(48.39	3.37	12.97)
5	289—290	12[b]	$C_{16}H_{16}N_4O_4S$	53.31	4.48	15.55
		53[c]		(53.31	4.51	15.79)
6	>300	6[b]	$C_{16}H_{16}N_4O_3S$	55.79	4.69	16.27
		15[c]		(55.65	4.71	16.33)
		87[d]				
7	282—284	98	$C_{11}H_9N_3O_2S$	53.42	3.68	17.00
				(53.18	3.65	16.96)
8	>300	91	$C_{11}H_9N_3O_3S$	50.18	3.45	15.96
				(49.89	3.42	15.87)
9	>300	73	$C_{12}H_{10}N_4O_4S$	47.05	3.30	18.29
				(47.16	3.24	18.39)

a) Compounds **3**, **5**, **6**, **8**, and **9** were recrystallized from DMF and compound **7** was recrystallized from EtOH.
b) The yield in the reaction of **2** with pyrrolidine using MeOH.
c) The yield in the reaction of **3** with pyrrolidine using EtOH.
d) The yield in the reduction of **5** with sodium dithionite.

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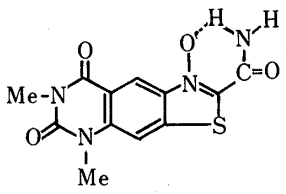
TABLE II. Spectral Data for Thiazolo[4,5-*g*]quinazolines (**3**—**9**)

Compd. No.	IR (KBr) cm^{-1}	NMR[a] δ
3	1730 (CO) 1710 (CO) 1670 (CO)	3.66 (3H, s, NCH_3), 3.83 (3H, s, NCH_3), 4.20 (3H, s, OCH_3), 8.10 (1H, s, 4-H), 9.30 (1H, s, 9-H)
5	1705 (CO) 1650 (CO)	1.79—2.00 (8H, m, pyrrolidine), 3.33 (3H, s, NCH_3), 3.57 (3H, s, NCH_3), 8.25 (1H, s, 4-H), 8.56 (1H, s, 9-H)
6	1700 (CO) 1650 (CO)	2.22 (4H, br, pyrrolidine), 3.70 (3H, s, NCH_3), 3.90 (3H, s, NCH_3), 4.14 (4H, br, pyrrolidine), 8.19 (1H, s, 4-H), 9.22 (1H, s, 9-H)
7	1700 (CO) 1660 (CO)	3.34 (3H, s, NCH_3), 3.57 (3H, s, NCH_3), 8.21 (1H, s, 4-H), 8.62 (1H, s, 9-H), 9.38 (1H, s, 2-H)
8	3250 (NH) 1700 (CO) 1680 (CO) 1640 (CO)	3.28 (3H, s, NCH_3), 3.46 (3H, s, NCH_3), 7.63 (1H, s, 4-H), 7.73 (1H, s, 9-H), 11.94 (1H, br, NH)
9	3270 (NH) 1700 (CO) 1650 (CO)	3.71 (3H, s, NCH_3), 3.89 (3H, s, NCH_3), 7.97 (1H, br, NH), 8.17 (1H, s, 4-H), 9.30 (1H, s, 9-H), 9.97 (1H, br, NH)

a) Compounds **5**, **7**, and **8** were measured in DMSO-d_6 and compounds **3**, **6**, and **9** were measured in CF_3COOH.



9′

intramolecular hydrogen bonding between the carbamoyl group and the N-oxide function as illustrated by the strucrure **9′**. The results on the thiazolo[4,5-*g*]quinazolines are summarized in Tables I and II.

Thiazolo[5,4-*f*]quinazoline 3-Oxides

As shown in Chart 2, the thiazolo[5,4-*f*]quinazoline 3-oxides were synthesized by essentially the same method as used for the thiazolo[4,5-*g*]quinazoline 3-oxides. In contrast to the cyclization of **1**, however, the treatment of the 5-chloro-6-nitroquinazoline (**10**),[5b] with methyl thioglycolate in the presence of triethylamine in ethanol under reflux for 3 h directly gave the desired 2-methoxycarbonylthiazolo[5,4-*f*]quinazoline 3-oxide (**11**) in 58% yield. The presence of the N-oxide moiety was suggested by the observation of a strong M^+ ion and a remarkable $M^+ - 16$ ion in the MS.

Compound **11** serves as a useful starting material for synthesizing of thiazolo[5,4-*f*]-quinazoline derivatives. For example, treatment of **11** with sodium dithionite in water gave the 2-methoxycarbonylthiazolo[5,4-*f*]quinazoline (**12**) in 87% yield as a sole product, and hydrolytic decarboxylation of the methoxycarbonyl group with 10% hydrochloric acid afforded the 2-unsubstituted thiazolo[5,4-*f*]quinazoline (**15**) in 87% yield.

Furthemore, heating of **11** with pyrrolidine in ethanol afforded the 2-

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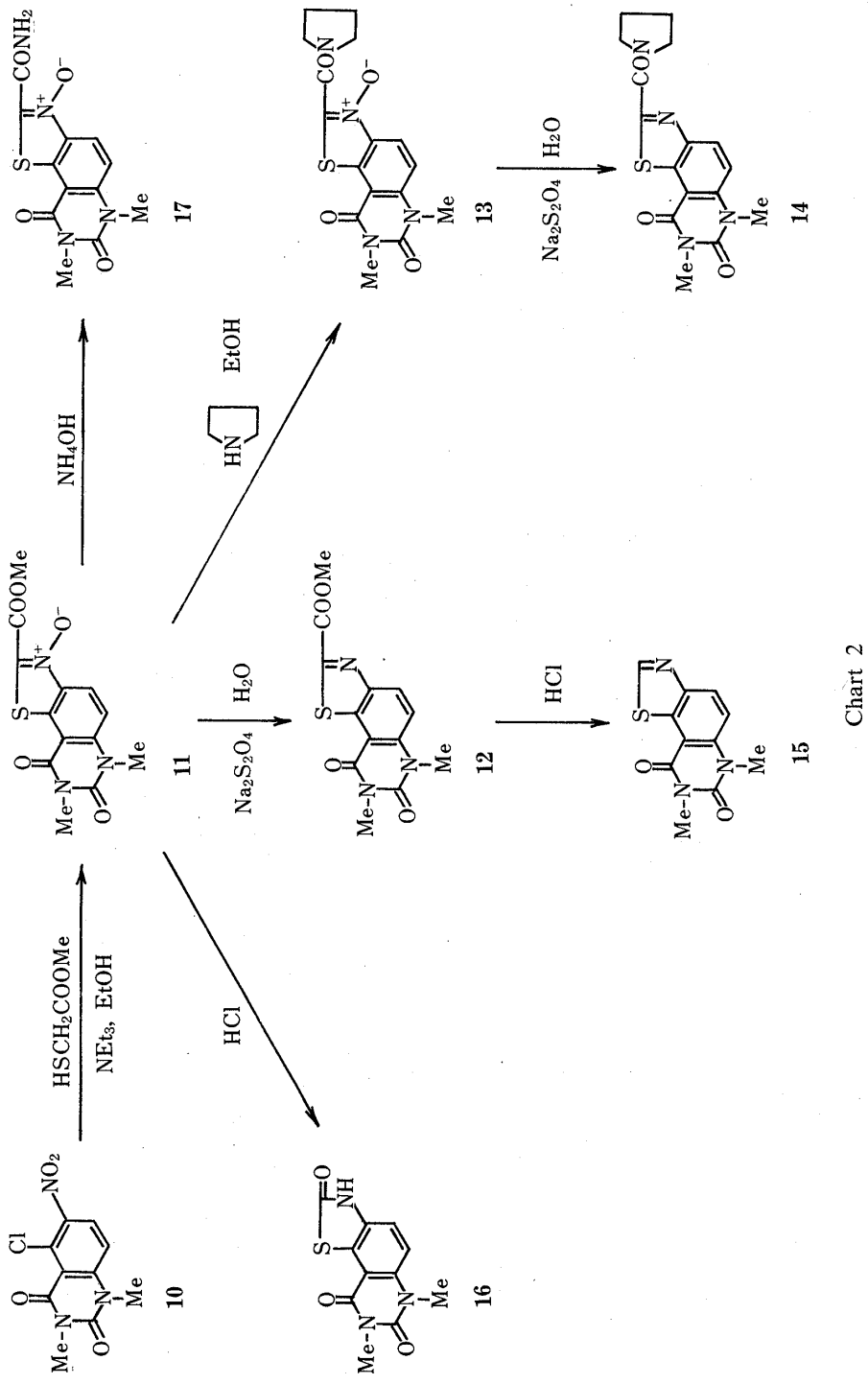

Chart 2

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TABLE III. Thiazolo[5,4-*f*]quinazolines (**11**—**17**)

Compd. No.[a]	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
11	277—279	58	$C_{13}H_{11}N_3O_5S$	48.59	3.46	13.08
				(48.59	3.51	13.00)
12	292—296	87	$C_{13}H_{11}N_3O_4S$	51.13	3.64	13.77
				(51.13	3.69	13.88)
13	272—275	88	$C_{16}H_{16}N_4O_4S$	53.22	4.48	15.55
				(52.98	4.22	15.52)
14	>300	81	$C_{16}H_{16}N_4O_3S$	55.79	4.69	16.27
				(55.78	4.63	16.35)
15	285—287	87	$C_{11}H_9N_3O_2S$	53.42	3.68	17.00
				(53.51	3.67	17.12)
16	>300	78	$C_{11}H_9N_3O_3S$	50.18	3.45	15.96
				(50.03	3.48	15.78)
17	>300	96	$C_{12}H_{10}N_4O_4S$	47.05	3.30	18.29
				(46.87	3.29	18.43)

a) Compounds **11**, **12**, **13**, **14**, **16**, and **17** were recrystallized from DMF and compound **15** was recrystallized from EtOH.

TABLE IV. Spectral Data for Thiazolo[5,4-*f*]quinazolines (**11**—**17**)

Compd. No.	IR (KBr) cm^{-1}	NMR[a] δ
11	1730 (CO) 1700 (CO) 1640 (CO)	3.35 (3H, s, NCH_3), 3.60 (3H, s, NCH_3), 3.88 (3H, s, OCH_3), 7.70 (1H, d, 4-H, J=9 Hz), 8.30 (1H, d, 5-H, J=9 Hz)
12	1705 (CO) 1650 (CO)	3.39 (3H, s, NCH_3), 3.69 (3H, s, NCH_3), 3.97 (3H, s, OCH_3), 7.70 (1H, d, 4-H, J=9 Hz), 8.45 (3H, d, 5-H, J=9 Hz)
13	1700 (CO) 1640 (CO)	1.70—2.17 (8H, m, pyrrolidine), 3.35 (3H, s, NCH_3), 3.62 (3H, s, NCH_3), 7.78 (1H, d, 4-H, J=9 Hz), 8.35 (1H, d, 5-H, J=9 Hz)
14	1695 (CO) 1650 (CO)	2.30 (4H, br, pyrrolidine), 3.74 (3H, s, NCH_3), 3.94 (3H, s, NCH_3), 4.10 (4H, br, pyrrolidine), 8.10 (1H, d, 4-H, J=9 Hz), 8.78 (1H, d, 5-H, J=9 Hz)
15	1700 (CO) 1640 (CO)	3.37 (3H, s, NCH_3), 3.62 (3H, s, NCH_3), 7.63 (1H, d, 4-H, J=9 Hz), 8.42 (1H, d, 5-H, J=9 Hz), 9.40 (1H, s, 2-H)
16	3150 (NH) 1700 (CO) 1680 (CO) 1640 (CO)	3.30 (3H, s, NCH_3), 3.49 (3H, s, NCH_3), 7.32 (1H, d, 4-H, J=9 Hz), 7.45 (1H, d, 5-H, J=9 Hz), 11.93 (1H, br, NH)
17	3300 (NH) 3150 (NH) 1700 (CO) 1660 (CO) 1640 (CO)	3.75 (3H, s, NCH_3), 3.95 (3H, s, NCH_3), 8.00 (1H, d, 4-H, J=9 Hz), 8.75 (1H, d, 5-H, J=9 Hz), 9.87 (2H, br, NH_2)

a) Compounds **11**, **12**, **13**, **15**, and **16** were measured in DMSO-d_6 and compounds **14** and **17** were measured in CF_3COOH.

pyrrolidinocarbonylthiazolo[5,4-*f*]quinazoline 3-oxide (**13**) in 88% yield and treatment of **13** with sodium dithionite yielded the 2-pyrrolidinocarbonylthiazolo[5,4-*f*]quinazoline (**14**) in

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81% yield. Heating of **11** with 3 N hydrochloric acid gave the 2-hydroxythiazolo[5,4-*f*]-quinazoline (**16**) in 78% yield. The exclusive contribution of the keto-form of **16** rather than the enol-form was observed both in the solid state and in solution (DMSO-d_6) in the IR and NMR spectra, respectively. Moreover, the reaction of **11** with 28% ammonium hydroxide at room temperature gave the 2-carbamoylthiazolo[5,4-*f*]quinazoline 3-oxide (**17**) in 96% yield. As expected, by analogy with **9**, compound **17** was stable to both reductive and oxidative deoxygenations.[7] The results on the thiazolo[5,4-*f*]quinazolines are summarized in Tables III and IV.

Experimental

Melting points were taken on a Yanaco micro-hot-stage melting point apparatus and are uncorrected. IR spectra were recorded in KBr pellets on a JASCO IR-A 100 spectrophotometer. NMR spectra were determined at 90 MHz with a Varian EM-390 spectrometer with tetramethylsilane as an internal standard. Ultraviolet (UV) spectra were performed on a Hitachi 124 spectrophotometer in EtOH. The molecular weights for all compounds were confirmed by mass spectroscopy with a JEOL JMS D-300 spectrometer with a direct-inlet system at 70 eV.

7-Methoxycarbonylmethylthio-1,3-dimethyl-6-nitroquinazoline-2,4(1*H*,3*H*)-dione (2)——A mixture of 7-chloro-1,3-dimethyl-6-nitroquinazoline-2,4(1*H*,3*H*)-dione (**1**)[5c] (1.35 g, 0.005 mol), methyl thioglycolate (0.53 g, 0.005 mol), and triethylamine (0.606 g, 0.006 mol) in MeOH (50 ml) was refluxed for 2 h, then allowed to cool. The precipitates were filtered off and recrystallized from toluene to give **2** (1.51 g, 89%), mp 198—200 °C. *Anal.* Calcd for $C_{13}H_{13}N_3O_6S$: C, 46.01; H, 3.87; N, 12.39. Found: C, 45.71; H, 3.79; N, 12.17. NMR (DMSO-d_6) δ: 3.30 (3H, s, NCH_3), 3.57 (3H, s, NCH_3), 3.69 (3H, s, OCH_3), 4.28 (2H, s, $-CH_2-$), 7.28 (1H, s, 5-H), 8.75 (1H, s, 8-H).

2-Methoxycarbonyl-6,8-dimethylthiazolo[4,5-*g*]quinazoline-5,7(6*H*,8*H*)-dione 3-Oxide (3), 6,8-Dimethyl-2-pyrrolidinocarbonylthiazolo[4,5-*g*]quinazoline-5,7(6*H*,8*H*)-dione 3-Oxide (5), and 6,8-Dimethyl-2-pyrrolidinocarbonylthiazolo[4,5-*g*]quinazoline-5,7(6*H*,8*H*)-dione (6)——A mixture of **2** (3.0 g, 0.0088 mol) and pyrrolidine (1.64 g, 0.023 mol) in MeOH (800 ml) was refluxed for 15 h, then allowed to stand overnight at room temperature. The resulting precipitates were filtered off and recrystallized to give **3** (1.07 g). The filtrate was evaporated to dryness *in vacuo*. The residue was collected and recrystallized to give **5** (0.39 g). The mother liquor from this recrystallization was evaporated *in vacuo* and the residue was covered with EtOH. The insoluble crystals were filtered off and recrystallized to give **6** (0.2 g).

6,8-Dimethyl-2-pyrrolidinocarbonylthiazolo[4,5-*g*]quinazoline-5,7(6*H*,8*H*)-dione 3-Oxide (5)——A mixture of **2** (3.0 g, 0.0088 mol) and pyrrolidine (1.64 g, 0.023 mol) in EtOH (200 ml) was refluxed for 15 h. The reaction mixture was evaporated *in vacuo* and the residue was covered with EtOH (30 ml). The insoluble material was filtered off, washed with EtOH, dried, and recrystallized to give **5** (1.7 g). The filtrate was again evaporated *in vacuo* and the residue was covered with EtOH. The insoluble material was filtered off and recrystallized to give **3** (0.46 g). The products were identical with the samples obtained in the above reaction using MeOH.

6,8-Dimethyl-2-pyrrolidinocarbonylthiazolo[4,5-*g*]quinazoline-5,7-(6*H*,8*H*)-dione (6)——A mixture of **5** (0.18 g, 0.0005 mol) and $Na_2S_2O_4$ (0.435 g, 0.0025 mol) in H_2O (10 ml) was refluxed for 10 h, then allowed to cool. The precipitates were filtered off and recrystallized to give **6** (0.15 g), which was identical with the sample obtained in the reaction of **2** with pyrrolidine.

6,8-Dimethylthiazolo[4,5-*g*]quinazoline-5,7(6*H*,8*H*)-dione (7)——A suspension of **3** (0.16 g, 0.0005 mol) in $Na_2S_2O_4$ (0.435 g, 0.0025 mol) in H_2O (20 ml) was refluxed for 10 h, then allowed to cool. The precipitates were filtered off and recrystallized to give **7** (0.12 g).

2-Hydroxy-6,8-dimethylthiazolo[4,5-*g*]quinazoline-5,7(6*H*,8*H*)-dione (8)——A suspension of **3** (0.16 g, 0.0005 mol) in 10% HCl (20 ml) was refluxed for 2 h, then allowed to cool. The precipitates were filtered off, washed well with H_2O, dried, and recrystallized to give **8** (0.12 g).

2-Carbamoyl-6,8-dimethylthiazolo[4,5-*g*]quinazoline-5,7(6*H*,8*H*)-dione 3-Oxide (9)——A suspension of **3** (0.26 g, 0.0008 mol) in 28% NH_4OH (20 ml) was heated at 50 °C for 1 h with stirring. The precipitates were filtered off, washed with H_2O, dried, and recrystallized to give **9** (0.18 g).

2-Methoxycarbonyl-6,8-dimethylthiazolo[5,4-*f*]quinazoline-7,9(6*H*,8*H*)-dione 3-Oxide (11)——A mixture of 5-chloro-1,3-dimethyl-6-nitroquinazoline-2,4(1*H*,3*H*)dione (**10**)[5b] (7.25 g, 0.027 mol), methyl thioglycolate (3.18 g, 0.03 mol), and triethylamine (6.06 g, 0.006 mol) in EtOH (500 ml) was refluxed for 3 h, then allowed to cool. The precipitates were filtered off, washed with EtOH, and recrystallized to give **11** (5.0 g).

2-Methoxycarbonyl-6,8-dimethylthiazolo[5,4-*f*]quinazoline-7,9(6*H*,8*H*)-dione (12)——A mixture of **11** (0.321 g, 0.001 mol) and $Na_2S_2O_4$ (0.87 g, 0.005 mol) in H_2O (40 ml) was refluxed for 3 h, then allowed to cool. The precipitates were filtered off, washed with H_2O, dried, and recrystallized to give **12** (0.265 g).

6,8-Dimethyl-2-pyrrolidinocarbonylthiazolo[5,4-*f*]quinazoline-7,9(6*H*,8*H*)-dione 3-Oxide (13)——A mixture of **11** (0.963 g, 0.003 mol) and pyrrolidine (1.07 g, 0.015 mol) in EtOH (300 ml) was refluxed for 5 h, then allowed to cool.

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The precipitates were filtered off, washed with EtOH, dried, and recrystallized to give **13** (0.95 g).

6,8-Dimethyl-2-pyrrolidinocarbonylthiazolo[5,4-*f*]quinazoline-7,9(6*H*,8*H*)-dione (14)——A mixture of **13** (0.18 g, 0.0005 mol) and $Na_2S_2O_4$ (0.435 g, 0.0025 mol) in water (10 ml) was refluxed for 25 h, then allowed to cool. The precipitates were filtered off, washed well with H_2O, dried, and recrystallized to give **14** (0.14 g).

6,8-Dimethylthiazolo[5,4-*f*]quinazoline-7,9(6*H*,8*H*)-dione (15)——A suspension of **12** (0.153 g, 0.0005 mol) in 10% HCl (10 ml) was refluxed for 5 h. The precipitates were filtered off, washed with H_2O, dried, and recrystallized to give **15** (0.105 g).

2-Hydroxy-6,8-dimethylthiazolo[5,4-*f*]quinazoline-7,9(6*H*,8*H*)-dione (16)——A suspension of **11** (0.161 g, 0.0005 mol) in 3 N HCl (5 ml) was heated at 95 °C for 2.5 h, then allowed to cool. The precipitates were filtered off, washed well with H_2O, dried, and recrystallized to give **16** (0.103 g).

2-Carbamoyl-6,8-dimethylthiazolo[5,4-*f*]quinazoline-7,9(6*H*,8*H*)-dione 3-Oxide (17)——A suspension of **11** (3.21 g, 0.01 mol) in 28% NH_4OH (10 ml) was stirred at room temperature for 3 h. The precipitates were filtered off, washed with H_2O, dried, and recrystallized to give **17** (2.95 g).

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