Mesoionic Compounds. XXXIII. Thermal Rearrangement of 4*H*-1,3-Thiazinium Betaines to 4-Quinolones[1]

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Condensation of monosubstituted arylthioamides and trisubstituted thioureas with chlorocarbonylphenylketene in anhydrous nonprotic solvents readily gave a variety of *anhydro*-6-hydroxy-4-oxo-2,3,5-trisubstituted 4*H*-1,3-thiazinium hydroxides in excellent yields. At 80° in benzene these underwent ready elimination of carbonyl sulfide to give 4-quinolones, an azetinone and its open-chain iminoketene valence tautomer being implicated as intermediates in the rearrangement. In addition to spectral data, the structures of the quinolones were established by alternative syntheses. These betaines, containing "masked" 1,4 dipoles, did not undergo cycloaddition reactions with a variety of acetylenic and olefinic dipolarophiles, conversion into the 4-quinolones being the preferred reaction pathway.

In the general class of five-membered mesoionic ring systems one of their most interesting, and synthetically useful, properties is their ability to undergo 1,3-dipolar cycloaddition reactions.[2] In six-membered ring systems of this general type both 1,3-dipolar[3] and 1,4-dipolar[4] cycloadditions have been observed, the latter in ring systems in which the "masked" 1,4 dipole results from a suitable arrangement of peripheral heteroatoms and substituent groups. In our previous communications[4] we showed that several pyrimidinium betaines were reactive substrates for 1,4-dipolar cycloadditions. This present communication describes the extension of these concepts to a series of 4*H*-1,3-thiazinium betaines that have an added interest in that they underwent ready thermal elimination of carbonyl sulfide to form 4-quinolones rather than undergo 1,4-dipolar cycloaddition reactions.

The 1,3-thiazine system has been known for several years[5] and recently, independent of our study, a brief report describing the synthesis of several 1,3-thiazinium betaines from thioamides and malonic acid derivatives has appeared.[6] In our study we utilize for the first time in heterocyclic synthesis chlorocarbonylphenylketene (**2**), a versatile 1,3-bielectrophilic species that is prepared from phenylmalonic acid and PCl_5 or $SOCl_2$, followed by distillation under vacuum.[7] Obtained as a crystalline product that can be stored for considerable time, there is no doubt that this is the reactive species in the reactions utilizing phenylmalonyl chloride in the above synthesis of this ring system.[6]

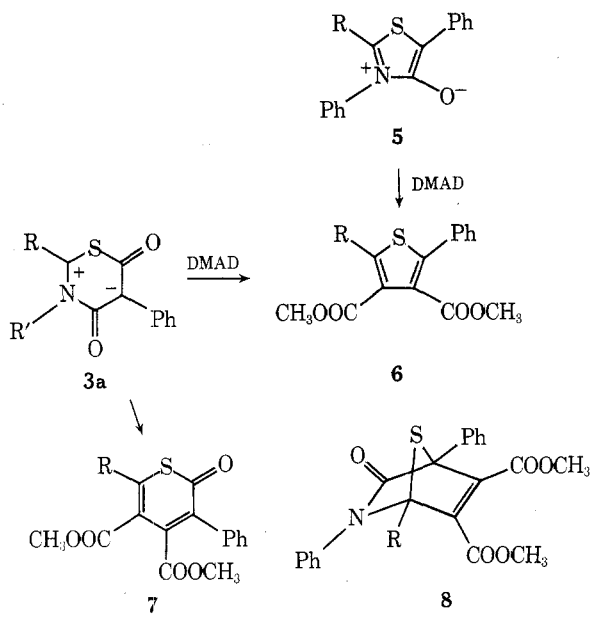
Thiobenzanilide (**1**, R = R′ = Ph) and chlorocarbonylphenylketene (**2**) underwent ready reaction to give *anhydro*-6-hydroxy-4-oxo-2,3,5-triphenyl-4*H*-1,3-thiazinium hydroxide (**3**, R = R′ = Ph), a product that decomposed readily on exposure to moisture. Incorporation of an electron-releasing group in the 2 substituent imparted greater stability to the thiazinium system **3**. Thus, the 2-*p*-chlorophenyl and 2-*p*-methoxyphenyl derivatives of **3** were obtained as high-melting, relatively stable products, and the variety of derivatives of this ring system prepared in this way are described in Table I. In no instance was the molecular ion detected in the mass spectra of these derivatives, whose physical constants, described in Table I, are consistent with the assigned structures. Assuming that the resultant stability of the system is due to some extent to delocalization of the positive charge associated with positions 1–3 of the nucleus, a logical extension would be to incorporate substituents into the 2 position that have appreciable electron-releasing ability. This objective was achieved utilizing disubstituted amino groups, the requisite starting material being the readily available trisubstituted thioureas formed by condensation of an appropriate amine and an isothiocyanate.

N-Methyl-*N*,*N*′-diphenylthiourea (**4**, R = R′ = Ph; R^2 = CH_3), from *N*-methylaniline and phenyl isothiocyanate, and **2** yielded the betaine **3** [R = CH_3(Ph)N; R′ = Ph] as yellow prisms, mp 157° dec, in 88% yield. A single carbonyl absorption was observed in the infrared spectrum of this product at 1600 cm^{-1} and the NMR spectrum indicated an aromatic multiplet at δ 6.8–7.5 in addition to the NCH_3 singlet at δ 3.67. The variety of derivatives of **3** prepared by this route is shown in Table I.

The nature of the substituents in **4** had considerable influence on the basicity of the betaine **3**. Thus, *N*,*N*′-dimethyl-*N*′-phenylthiourea (**4**, R = R′ = CH_3; R^2 = Ph), from dimethylamine and phenyl isothiocyanate, and the ketene **2** gave 6-hydroxy-3-methyl-2-(*N*-methylphenylamino)-4-oxo-5-phenyl-4*H*-1,3-thiazinium chloride as pale yellow prisms (89%), mp 134° dec, which was readily converted into the corresponding betaine **3** [R = CH_3(Ph)N; R′ = CH_3] on treatment with an organic base or on gentle heating under vacuum. Similarly, reaction of *N*,*N*′,*N*′-trimethylthiourea (**4**, R = R′ = R^2 = CH_3) and **2** also resulted in the initial formation of the salt, readily converted into the betaine **3** [R = $(CH_3)_2N$; R′ = CH_3] with triethylamine. As salt formation also was observed with *N*,*N*-dimethyl-*N*′-phenylthiourea (**4**, R = R^2 = CH_3; R′ = Ph), it is clear that the 2 substituent plays an important role both in stabilizing the nucleus and in increasing its basicity.

The betaine **3** may be considered to contain a "masked" 1,4-dipolar system **3a** and, as such, would be anticipated to undergo 1,4-dipolar cycloadditions with acetylenic and olefinic dipolarophiles in analogy to the corresponding pyrimidinium system.[4] With acetylenic dipolarophiles, depending on the fragment extruded from the initial cycloadduct, 2-pyridones or 2-thiapyrones would be formed. The reaction of *anhydro*-3,5-diphenyl-6-hydroxy-2-*p*-methoxyphenyl-4-oxo-4*H*-1,3-thiazinium hydroxide (**3**, R = *p*-$CH_3OC_6H_4$;

R′ = Ph) and dimethyl acetylenedicarboxylate (DMAD) in refluxing xylene resulted in the formation of two major products. The predominant product was ultimately characterized as the quinolone **9** due to thermal rearrangement of the betaine; the minor product (28%) was identified as ethyl 2-*p*-methoxyphenyl-5-phenylthiophene-3,4-dicarboxylate (**6**), synthesized in an alternative way[2b] from DMAD and *anhydro*-3,5-diphenyl-4-hydroxy-2-*p*-methoxyphenylthiazolium hydroxide (**5**). An anticipated product from the



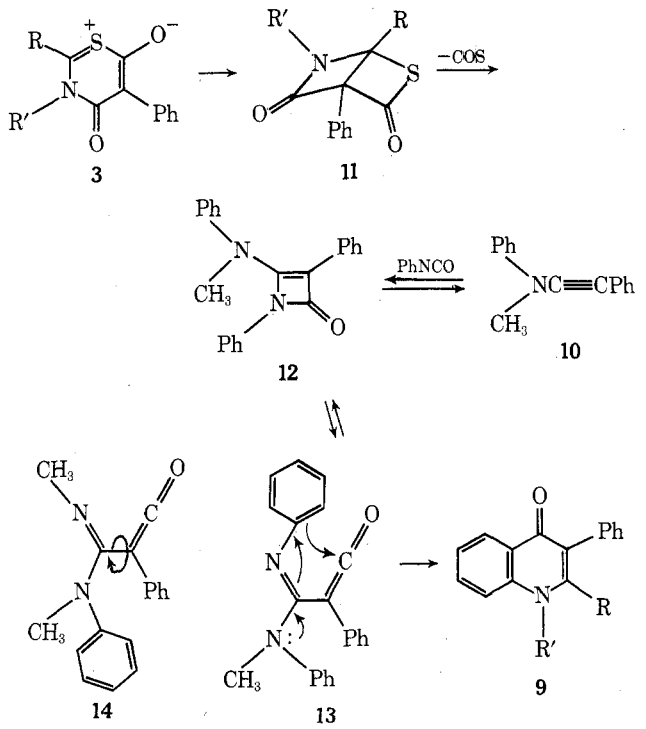
R = *p*-$CH_3OC_6H_4$

reaction of **3** and DMAD was the thiapyrone **7** but the formation of the thiophene may be readily rationalized. Thermal elimination of CO from **7** would afford **6** or, alternatively, elimination of CO from **3** would result in **5**, known to be converted into **8** with DMAD and which, in turn, forms **6**.

The quinolone **9** was also obtained when **3** was heated in xylene or acetonitrile in the absence of DMAD. In the latter solvent a considerably reduced reaction time was required. A gas evolved in the reaction was identified as carbonyl sulfide by reaction with piperidine to give *N,N*-pentamethylenethiocarbamic acid.[8] On the basis of analytical and spectral data (Table II) it was clear that the thermolysis product did not incorporate a molecule of DMAD and its molecular formula indicated that it was derived from the initial betaine by loss of carbonyl sulfide. This product was identified as 2-*p*-methoxyphenyl-3-phenyl-4-quinolone (**9**, R = *p*-$CH_3OC_6H_4$; R′ = H). When the reaction was repeated using variously substituted betaines, it became clear that only those betaines substituted with an aromatic group at N-3 gave the thermolysis product.

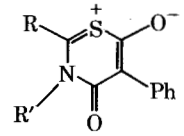
Thermolysis of *anhydro*-2-*p*-chlorophenyl-3,5-diphenyl-6-hydroxy-4-oxo-4*H*-1,3-thiazinium hydroxide (**3**, R = *p*-ClC_6H_4; R′ = Ph) in xylene or in the solid state afforded 2-*p*-chlorophenyl-3-phenyl-4-quinolone (**9**, R = *p*-ClC_6H_4; R′ = H). An unambiguous synthesis of this product was obtained from the fusion of anthranilic acid and benzyl *p*-chlorophenyl ketone.[9] The quinolones obtained by this thermolysis procedure from the thiazinium betaines **3** (R = aryl) had spectral data consistent with the assigned structures and are shown in Table II. That elimination of COS was the preferred reaction, especially in boiling xylene (bp 142°), was shown on attempted reaction of **3** with a variety of dipolarophiles such as fumaronitrile, tetracyanoethylene, *N*-phenylmaleimide, DMAD, diphenylacetylene, ethoxyacetylene, and *n*-butyl vinyl ether; in the majority of cases the thermolysis product was obtained, other products being those derived from hydrolysis of **3**.

Introduction of a more effective electron-releasing group such as a substituted amino group into the 2 position of **3** resulted in a more facile rearrangement to the quinolone and suppression of any 1,4-dipolar cycloaddition characteristics in **3**. *anhydro*-3,5-Diphenyl-6-hydroxy-2-(*N*-methylphenylamino)-4-oxo-4*H*-1,3-thiazinium hydroxide [**3**, R = $N(Ph)CH_3$; R′ = Ph], on reflux in anhydrous benzene, gave 2-(*N*-methylphenylamino)-3-phenyl-4-quinolone [**9**, R = $N(Ph)CH_3$; R′ = H] whose physical characteristics, described in Table II, are in agreement with the assigned structure. The proton at δ 8.9, due to an NH (or OH) proton, was rapidly exchanged with D_2O and the multiplet at δ 8.2 was assigned to the C_5 proton shifted downfield by the 4-oxo group. The ultraviolet data are in accord with data reported[10] in the literature for 4-quinolones of this type, which have also been synthesized from ethyl anthranilate and ynamines.[11] The quinolone **9** [R = $N(Ph)CH_3$; R′ = H] was also prepared by us by condensation of *N*-methyl-*N*,2-diphenylethynylamine[12] (**10**) and phenyl isocyanate, an azetinone intermediate being postulated in the latter reaction.[13] After removal of the solvent and the quinolone from the thermolysis mixture, the infrared spectrum of the residual oil showed strong absorptions at 2000–2200, 1595, and 1640 cm^{-1} and the NMR spectrum aromatic protons at δ 6.6–7.6 and several singlets between δ 3.1 and 3.7. These data were consistent with the presence of the ynamine and phenyl isocyanate in the reaction residue and indicated the likelihood of an azetinone intermediate. The rearrangement may be rationalized in terms of initial loss of COS from a possible valence tautomer **11** with formation of the azetinone **12**. Electrocyclic ring opening of **12**, followed by intramolecular recyclization of the intermediate iminoketone **13** leads readily to the quinolone **9**.



This reaction is analogous to the electrocyclic ring opening of 2,3,4,4-tetraphenyl-2-cyclobuten-1-one to 2,3,4-triphenylnaphthol[14] and 3-ethoxy-2-methyl-4,4-diphenyl-2-cyclobuten-1-one to 3-ethoxy-2-methyl-4-phenyl-1-naphthol,[15] and related ring closures have been observed with arylimidoyl isothiocyanates to quinazolinethiols[16] and the

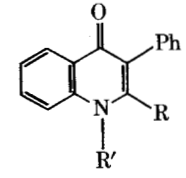
Table I
Some 4*H*-1,3-Thiazinium Betaines Derived from Substituted Thioamides and Thioureas and Chlorocarbonylphenylketene[a]



R	R′	Mp, °C	% yield	Formula	λ_{max} ($CHCl_3$), nm (log ε)	ν_{CO}, cm^{-1}	NMR data, δ ($CDCl_3$)	Registry no.
p-ClC_6H_4	Ph	166–168	94	$C_{22}H_{14}ClNO_2S$	240 (4.27), 315 (3.64)	1680, 1605, 1600	7.25 (m, aromatic)	55712-14-6
p-ClC_6H_4	*p*-$CH_3C_6H_4$	188–189	96	$C_{23}H_{16}ClNO_2S$	270 (3.78), 320 (3.43), 480 (2.55)	1680, 1610	2.25 (s, 3, $ArCH_3$), 6.8–7.8 (m, 13, aromatic)	55712-15-7
p-ClC_6H_4	CH_3	183–185	75	$C_{17}H_{12}ClNO_2S$	252 (4.32), 460 (3.32)	1660, 1610	3.64 (s, 3, NCH_3), 7.20–7.73 (m, 9, aromatic)	55712-16-8
p-$CH_3OC_6H_4$	Ph	172–174	86	$C_{23}H_{17}NO_3S$		1680, 1605	4.05 (s, 3, OCH_3), 7.65 (m, 14, aromatic)	55712-17-9
CH_3(Ph)N	Ph	157	88	$C_{23}H_{18}N_2O_2S$	251 (4.24), 285[b] (3.77)	1600	3.67 (s, 3, NCH_3), 6.8–7.5 (m, 15, aromatic)	55712-18-0
CH_3(Ph)N	CH_3	154	67	$C_{18}H_{16}N_2O_2S$	252 (4.23)	1595	3.02 (s, 3, 2-NCH_3), 3.48 (s, 3, 3-CH_3), 7.0–7.7 (m, 10, aromatic)	55712-19-1
CH_3(Ph)N	CH_3	134[c]	89	$C_{18}H_{17}ClN_2O_2S$[d]	245 (3.83), 283 (4.01)	1665, 1575	3.06 (s, 3, 2-NCH_3), 3.62 (s, 3, 3-CH_3), 7.0–7.6 (m, 10, aromatic)	55712-20-4
$(CH_3)_2N$	CH_3	144	78	$C_{13}H_{14}N_2O_2S$	243 (3.78), 281 (3.96)	1590	3.06, 3.14, 3.46 (s, 9, CH_3), 7.0–7.5 (m, 5, aromatic)	55712-21-5
$(CH_3)_2N$	CH_3	120[c]	83	$C_{13}H_{15}ClN_2O_2S$[d]	240 (3.62), 292 (4.07)	1600	3.12 (br s, CH_3)	55712-22-6
$(CH_3)_2N$	Ph	127[c]	81	$C_{18}H_{17}ClN_2O_2S$	241 (3.91), 287 (4.02)	1675, 1580	3.37 (br s, 6, CH_3), 7.1–7.5 (m, 10, aromatic)	55712-23-7

[a] All obtained as yellow prisms, decomposing at melting point; satisfactory analytical values (±0.4% for C, H, N) were reported for all compounds in table. Ed. [b] Shoulder. [c] HCl. [d] Readily lost HCl during purification.

Table II
Some 4-Quinolones Formed by Thermal Rearrangement of 4*H*-1,3-Thiazinium Betaines[a]



R	R′	Mp, °C	% yield	Formula	$M^{\cdot+}$	λ_{max} (CH_3OH), nm (log ε)	ν_{CO}, cm^{-1}	NMR data, δ	Registry no.
p-ClC_6H_4	H	380–381	47	$C_{21}H_{14}ClNO$	331 (50)	213 (3.72), 260 (3.68), 335 (3.27)	1610, 1605	7.45–8.13 (m, aromatic)[b]	55712-24-8
p-ClC_6H_4	H	384–385[c]	56	$C_{22}H_{16}ClNO$	345 (53)	215 (4.06), 264 (4.01), 340 (3.56)	1615, 1610	2.13 (s, 3, 6-CH_3), 6.8–8.0 (m, 13, aromatic)[b]	55712-25-9

p-$CH_3OC_6H_4$	H	367	40	$C_{22}H_{17}NO_2$	325 (55)	208 (3.54), 273 (3.45), 345 (2.98)	1630, 1610	3.37 (s, 3, OCH_3), 6.7–8.3 (m, 14, aromatic)[b]	55712-26-0
CH_3(Ph)N	H	284	34	$C_{22}H_{18}N_2O$	326 (60)	220 (4.47), 244 (4.34), 285 (4.09), 332 (4.06)	1600, 1550	2.80 (s, 3, CH_3), 6.7–7.4 (m, 13, aromatic), 8.20 (m, 1, C_5 H), 8.9 (br s, 1, OH or NH)[d]	55712-27-1
CH_3NH	CH_3	274	16	$C_{17}H_{16}N_2O$	264 (77)	206 (4.34), 228 (4.44), 242 (4.43), 259 (4.33), 321 (4.18)	1600, 1550	2.75 (d, 3, $NHCH_3$, $J = 6.0$ Hz), 3.78 (s, 3, 1-CH_3), 7.3 (s, 8, aromatic), 8.34 (d, 1, C_5 H, $J_{5,6} = 6.0$ Hz)[d]	55712-28-2
CH_3NH	CH_3	264[e]	36	$C_{17}H_{17}ClN_2O$	264 (18) (M − HCl)	222 (4.63), 249 (4.59), 300 (4.09), 324 (4.14)	1600, 1570	2.60 (s, 3, $^+NH_2CH_3$), 3.98 (s, 3, 1-CH_3), 7.5 (s, 6, aromatic and NH), 7.94 (d, 2, aromatic, $J = 4$ Hz), 8.44 (d, 1, C_5 H, $J_{5,6} = 6$ Hz)[f]	55712-29-3
$(CH_3)_2N$	H	255–256[f]	92	$C_{17}H_{16}N_2O$	264 (65)	206 (4.40), 229 (4.44), 257 (4.43), 275 (4.29),[h] 321 (4.22)	1630, 1587	2.60 (s, 6, NH_3), 7.23 (br s, 9, aromatic and NH), 8.2 (d, 1, C_5 H, $J_{5,6} = 6$ Hz)[d]	25083-38-9
$(CH_3)_2N$	H	252–253[e,i]	43	$C_{17}H_{17}ClN_2O$	264 (14) (M − HCl)	224 (4.63), 257 (4.60), 297 (3.98), 334 (4.18)	1640, 1600	2.80 (s, 6, NCH_3), 7.35 (s, 9, aromatic and NH), 8.2 (d, 1, C_5 H, $J_{5,6} = 6$ Hz)[f]	25083-39-0

[a] All colorless prisms; those with 2-aryl substituents crystallized from acetic acid, others from ethanol; satisfactory analytical values (±0.4% for C, H, N) were reported for all compounds in table. [b] Ed. [c] CF_3COOH. [c] 6-Methyl product, from the betaine derived from 4-chloro-4′-methylthiobenzanilide. [d] $CDCl_3$. [e] HCl. [f] DMSO-d_6. [g] Lit.[11] mp 256°. [h] Shoulder. [i] Lit.[11] mp 244–248°.

photodesulfurization of dibenzoylstilbene episulfide to 2,3-diphenyl-4-phenoxy-1-naphthol.[17]

The presence of one aromatic nucleus in the initial thiourea is essential for the rearrangement of the thiazinium betaine to the quinolone. Thus, thermolysis of *anhydro*-6-hydroxy-3-methyl-2-(*N*-methylphenylamino)-4-oxo-5-phenyl-4*H*-1,3-thiazinium hydroxide [**3**, R = CH_3(Ph)N; R′ = CH_3] readily gave 1,4-dihydro-1-methyl-2-methylamino-3-phenyl-4-quinolone (**9**, R = CH_3NH; R′ = CH_3). In this case the iminoketene intermediate **13** must undergo a 180° rotation about the C_2–C_3 bond as in **14** since there is no 3-phenyl substituent. The corresponding thiazinium chloride also underwent this rearrangement, in this case the quinolinium chloride being isolated. As anticipated, *anhydro*-2-dimethylamino-6-hydroxy-3-methyl-4-oxo-5-phenyl-4*H*-1,3-thiazinium hydroxide [**3**, R = $(CH_3)_2N$; R′ = CH_3] did not undergo rearrangement under the above conditions. An interesting feature of the NMR spectrum of this betaine was the nonequivalency of the *N*-methyl groups at the 2 position (δ 3.14, 3.06), indicating some double bond character in the C_2–N bond owing to delocalization of the positive charge over the thiourea partial structure.

Experimental Section[18]

General Procedure for the Synthesis of the 1,3-Thiazinium Betaines. Preparation of *anhydro*-3,5-Diphenyl-6-hydroxy-2-(*N*-methylphenylamino)-4-oxo-4*H*-1,3-thiazinium Hydroxide [3, R = CH_3(Ph)N; R′ = Ph]. *N*-Methyl-*N*,*N*′-diphenylthiourea (2.4 g, 10 mmol) was added with stirring to chlorocarbonylphenylketene (2.0 g, 11 mmol) in dry benzene (50 ml). After stirring at room temperature for 1 hr, the solid product was collected and washed well with dry benzene (50 ml), yielding yellow prisms, 3.4 g (88%), mp 157° dec (Table I). When the product separated as the thiazinium chloride it was converted into the betaine by treatment with Et_3N in THF followed by pouring the reaction mixture into water. Alternatively, the chloride was heated to ca. 40° (0.1 mm) for approximately 48 hr.

General Procedure for the Thermolysis of the 1,3-Thiazinium Betaines. Formation of 2-(*N*-Methylphenylamino)-3-phenyl-4-quinolone [9, R = CH_3(Ph)N; R′ = H]. The betaine **3** [R = CH_3(Ph)N; R′ = Ph] (2.2 g, 5.7 mmol) was refluxed for 12 hr in dry benzene (50 ml). Upon cooling, the separated solid was collected and recrystallized from ethanol, forming colorless needles, 0.63 g (34%), mp 284° (Table II).

Alternative Synthesis of 2-(*N*-Methylphenylamino)-3-phenyl-4-quinolone [9, R = CH_3(Ph)N; R′ = H]. *N*-Methyl-*N*,2-diphenylethynylamine (0.5 g, 2.5 mmol) and phenyl isocyanate (0.29 g, 2.5 mmol) in dry benzene (50 ml) were refluxed for 12 hr. Upon cooling, the separated solid was collected and recrystallized from benzene, forming colorless needles, 0.15 g (18%), mp 284°.

Reaction of *anhydro*-2,3-Diphenyl-6-hydroxy-2-(*p*-methoxyphenyl)-4-oxo-4*H*-1,3-thiazinium Hydroxide (3, R = *p*-$CH_3OC_6H_4$; R′ = Ph) and Dimethyl Acetylenedicarboxylate. The thiazinium betaine (0.3 g, 10 mmol) and DMAD (1.0 g, 5 mmol) were refluxed in dry xylene (50 ml) for 3 hr. After removal of the solid that separated on cooling, the mother liquor was evaporated and the crude residue was chromatographed on silica gel using $CHCl_3$ as eluent. The first fraction eluted from the column crystallized from $CHCl_3$–hexane as colorless prisms and was identified as methyl 2-*p*-methoxyphenyl-5-phenylthiophene-3,4-dicarboxylate (**6**): 0.07 g (28%), mp 107–109° dec; ir (KBr) ν_{CO} 1730 cm^{-1}; λ_{max} (CH_3OH) 300 nm (log ε 3.95), 240 (4.10), 255 (4.17); NMR ($CDCl_3$) δ 3.72 (s, 3, OCH_3), 3.75 (s, 3, $COOCH_3$), 3.76 (s, 3, $COOCH_3$), 7.0–7.5 (m, 9, aromatic); $M^{\cdot+}$ 382 (100).

Anal. Calcd for $C_{21}H_{18}O_5S$: C, 65.95; H, 4.75. Found: C, 66.22; H, 4.85.

The solid separated from the initial reaction mixture crystallized from acetic acid as colorless prisms and was identified as 2-(*p*-methoxyphenyl)-3-phenyl-4-quinolone, 0.1 g (40%), mp 367° (Table II).

Alternative Synthesis of Methyl 2-(*p*-Methoxyphenyl)-5-phenylthiophene-3,4,-dicarboxylate. *p*-Methoxythiobenzanilide (10.0 g, 0.041 mol), α-bromophenylacetic acid (5.0 g, 0.023 mol), and NEt_3 (6.0 g, 0.085 mol) in benzene were refluxed for 2 hr. After

cooling, Et_3NHBr was filtered off and the benzene was removed in vacuo. Ac_2O (6.0 g, 0.059 mol) was added to the resulting red oil and the solution was shaken. Ether was added after crystallization started; the product was collected, washed with ether, and dissolved in dry benzene (100 ml). DMAD (3.0 g, 0.013 mol) was added and, after 24-hr reflux, removal of solvent, and chromatography on silica gel with $CHCl_3$ as eluent, methyl 2-(*p*-methoxyphenyl)-5-phenylthiophene-3,4-dicarboxylate, mp 107–109° (80%), was obtained identical with that isolated above.[19]

Registry No.—**2**, 17118-70-6; **6**, 20851-14-3; **10**, 32907-84-9; *N*-methyl-*N*,*N*′-diphenylthiourea, 4949-93-3; phenyl isocyanate, 103-71-9; dimethyl acetylenedicarboxylate, 762-42-5; *p*-methoxythiobenzanilide, 26060-23-1; α-bromophenylacetic acid, 4870-65-9.

References and Notes

(1) (a) Support of this work by U.S. Public Health Service Research Grant HL 15021, National Heart and Lung Institute, is gratefully acknowledged. (b) Abstracted from the Ph.D. Thesis of R.E., 1975, and M.S. Thesis of M.N., 1973, Rensselaer Polytechnic Institute. (c) Part XXXII: K. T. Potts, J. Baum, and E. Houghton, *J. Org. Chem.*, **39**, 3631 (1974).

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Bridgehead Nitrogen Heterocycles. IX. Fused-Ring Systems Derived from Fusion of the 1,2,4-Thiadiazole System with the Isoxazole, 1,3,4-Oxadiazole, Thiazole, 1,2,4-Thiadiazole, and 1,3,4-Thiadiazole Systems[1]

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Amino derivatives of the title heterocycles containing the amino group as part of a partial amidine structure reacted with trichloromethanesulfenyl chloride via an isolable trichloromethanesulfenamide intermediate to yield the 3*H*-isoxazolo[3,2-*c*]-, 3*H*-thiazolo[2,3-*c*]-, 3*H*-1,3,4-thiadiazolo[2,3-*c*]-, and the 3*H*-1,2,4-thiadiazolo[4,3-*d*][1,2,4]thiadiazole as well as the 3*H*-1,2,4-thiadiazolo[3,4-*b*][1,3,4]oxadiazole systems. These were characterized by spectral and chemical properties.

In contrast to the large number of substituted, monocyclic 1,2,4-thiadiazoles described in the literature,[2] examples of ring-fused 1,2,4-thiadiazole derivatives remain relatively few. Conceptually there are two general methods for the synthesis of systems containing the ring-fused 1,2,4-thiadiazole moiety. The most direct method involving fusion of an appropriately substituted 1,2,4-thiadiazole has attained only limited usage.[3] The second method, involving ring closure of a 2-amino heterocycle containing a partial amidine structure with a sulfur-containing cyclization agent[4] or by oxidation of an appropriately substituted thiourea,[5] constitutes the most commonly encountered route to these fused ring systems. In earlier publications[6] we have shown that trichloromethanesulfenyl chloride is a particularly efficacious cyclization agent for the synthesis of a variety of six-membered ring systems fused to the 1,2,4-thiadiazole nucleus. This present communication describes the extension of this synthetic route to the preparation of a variety of 5,5-fused ring systems, to a large part unavailable by earlier procedures.

3*H*-Isoxazolo[3,2-*c*][1,2,4]thiadiazole System (4). Reaction of trichloromethanesulfenyl chloride with 2 equiv of 3-amino-5-methylisoxazole (**1**) and 4 equiv of Et_3N proved to be extremely exothermic and resulted in an intractable complex mixture of at least seven components over a range of reaction temperatures (0–20°). However, addition of an aqueous solution of **1** to a stirred, aqueous suspension of trichloromethanesulfenyl chloride, potassium carbonate, Alconox, and crushed ice afforded a cream-colored solid which crystallized from ethanol as colorless needles. Analytical and spectral data (ν_{NH} 3180, $\nu_{C=N}$ 1620 cm^{-1}) supported the product's formulation as the sulfenamide **2**, which was confirmed by the following transformations. Reaction with 2-amino-5-methylpyridine in the presence of Et_3N produced a complex reaction mixture which could be partially resolved using preparative layer chromatography. The major component isolated from this mixture was identified[6] as 6-methyl-3-(5-methyl-2-pyridylimino)-3*H*-1,2,4-thiadiazolo[4,3-*a*]pyridine (**3**, R = 5-CH_3-2-C_5H_3N; R_1 = 6-CH_3) and presumably occurs via a transamination reaction such as was observed in the reactions of 1,1,1-trichloro-*N*-(2-pyrimidyl)methanesulfenamide and 2-aminopyridines.[6] The second component isolated from the mixture crystallized from acetone as cream needles and was