THE JOURNAL OF Organic Chemistry

VOLUME 49, NUMBER 25

DECEMBER 14, 1984

Synthesis of Substituted 2-Imidazolidinones and Annelated Hydantoins via Amidoalkylation Transformations

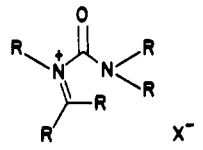
Zeng-Kun Liao and Harold Kohn*[1]

Department of Chemistry, University of Houston—University Park, Houston, Texas 77004

Received June 5, 1984

The synthetic utility of 4-hydroxy-2-imidazolidinone amidoalkylation reactions is limited by the propensity of the carbon-5 unsubstituted and carbon-5 monosubstituted adducts to undergo dehydration to yield 2-imidazolones. Two techniques are reported which avoided this competitive side reaction. The first approach utilized reactive allyl silanes. Treatment of substituted 4-hydroxy-2-imidazolidinones **16** with allyltrimethylsilane (**17**) under Lewis acid mediated conditions led to high yields of the intermolecular alkylation product **18**. The second technique examined the use of parabanic acid substrates as starting materials for the preparation of annelated hydantoins. Treatment of **22** with $NaBH_4$ led to preferential reduction of the 5-carbonyl moiety to give **23**. Cyclization of **23** with trifluoroacetic anhydride and trifluoroacetic acid gave the fused ring hydantoin, which was selectively reduced with $LiAlH_4$ in the final step to yield the corresponding annelated 2-imidazolidinone.

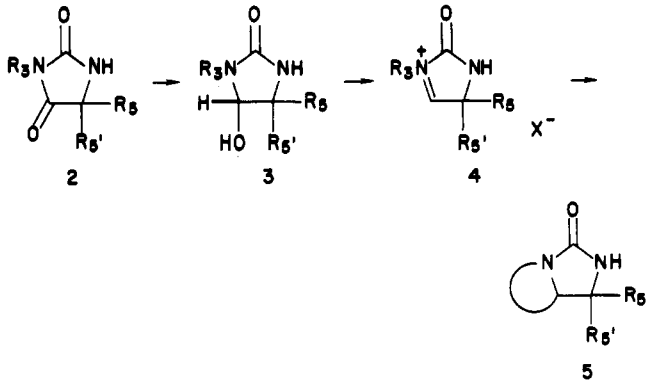
Reactions initiated by *N*-carbamoyliminium ions **1** provide a powerful new technique for the synthesis of substituted vicinal diamines.[2-6] In previous studies, we



1

have demonstrated the versatility of these species for the construction of annelated imidazolidinones. Specifically, we have shown that N_3-alkenyl[3] and N_3-aromatic[2] side chains undergo efficient cyclization to yield six- and seven-membered ring adducts. In the former case, the reaction proceeded with a high degree of stereospecificity.

In this paper, we examine the applicability of this method to carbon-5 unsubstituted (**2**, R_5, $R_{5'}$ = H) and carbon-5 monosubstituted (**2**, $R_{5'}$ = H) hydantoins. It was observed that the desired amidoalkylation transformation did not proceed in these cases but rather competitive dehydration of the 4-hydroxy adducts **3** occurred. Two modifications of this approach are elaborated that circumvented this elimination process and which proved useful for the synthesis of substituted 2-imidazolidinones and annelated hydantoins.



2 **3** **4** **5**

Results and Discussion

Compounds **8** and **12** were synthesized to test the suitability of the previous annelation technique to carbon-5 monosubstituted hydantoins. Both substrates were prepared by the alkylation (KOH, Me_2SO) of the corresponding hydantoins **6**[7] and **11**[8] with (*m*-methoxy-

(1) Camile and Henry Dreyfus Teacher-Scholar Grant Recipient, 1977-1982.

(2) Kohn, H.; Liao, Z. K. *J. Org. Chem.* **1982**, *47*, 2787-2789, and references therein.

(3) Liao, Z. K.; Kohn, H. *J. Org. Chem.* **1984**, *49*, 3812-3819.

(4) Zaugg, H. E. *Synthesis* **1984**, *2*, 85-110, and references therein.

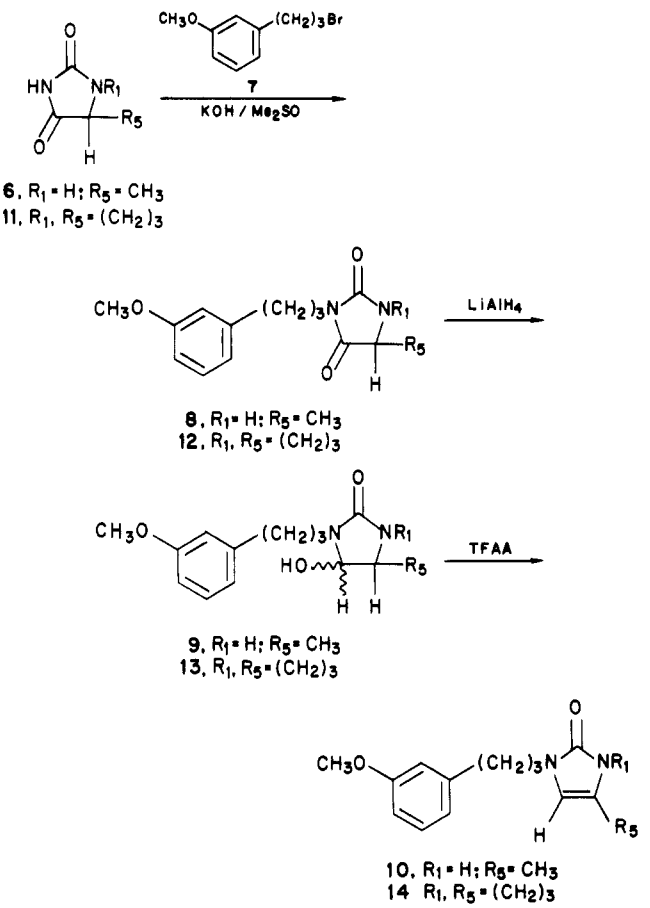
(5) Zaugg, H. E.; Arendsen, D. L. *J. Heterocycl. Chem.* **1974**, *11*, 803-806.

(6) (a) Zaugg, H. F.; Leonard, J. E.; Arendsen, D. L. *J. Heterocycl. Chem.* **1974**, *11*, 833-834. (b) Ben-Et, G.; Ben-Ishai, D. *J. Chem. Soc., Chem. Commun.* **1969**, 376. (c) Ben-Ishai, D.; Ben-Et, G. *Ibid.* **1969**, 1399. (d) Goldstein, E.; Ben-Ishai, D. *Tetrahedron Lett.* **1969**, 2631-2634. (e) Ben-Ishai, D.; Ben-Et, G.; Warshawsky, A. *J. Heterocycl. Chem.* **1970**, *7*, 1289-1293. (f) Ben-Ishai, D.; Goldstein, E. *Tetrahedron* **1971**, *27*, 3119.

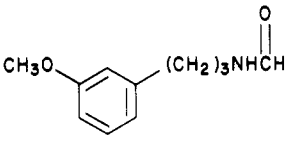
(7) Finkbeiner, H. *J. Org. Chem.* **1965**, *30*, 3414-3419.

0022-3263/84/1949-4745$01.50/0

Scheme I



phenyl)propyl bromide[9] (7). Reduction of each hydantoin (8 and 12) with $LiAlH_4$ yielded a mixture of cis and trans 4-hydroxy adducts 9 and 13, respectively. As expected the cis adducts were the predominant products in both reactions.[10] Treatment of 9 and 13 with trifluoroacetic anhydride gave the corresponding imidazolones 10 (55% yield) and 14 (44% yield), respectively.[11] A small amount (14% yield) of formamide 15 was isolated in the latter reaction. The origin of this compound is unknown. This dehydration process was not observed in the corresponding *N*-acyliminium transformations.[12]

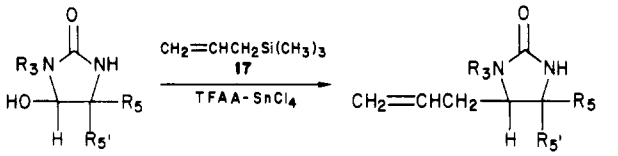


15

Imidazolones 10 and 14 exhibited a carbonyl absorption band in the infrared spectrum between 1670 and 1690 cm^{-1}.[13] Moreover, in the ^1H NMR spectra, a characteristic signal was observed between δ 5.76 and 5.80 for the ring methine proton.[13]

Since the overall utility of this amidoalkylation methodology hinged upon the ability to prepare substituted or annelated imidazolidinones independent of the substitution pattern at carbon-5, two modifications of the technique were examined. The first approach employed the use of reactive olefinic compounds. These substrates should permit amidoalkylation to compete effectively with dehydration.

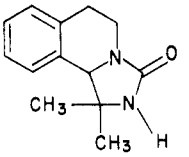
Use of Allyl Silanes. In recent years, several investigators have demonstrated the high nucleophilicity of allyl silanes toward Lewis acid activated electrophilic centers.[14] We initially evaluated this methodology with the 5,5′-dimethyl-substituted 4-hydroxy-2-imidazolidinone **16a**.[2]



a, R_3 = 3-(OCH_3)$C_6H_4CH_2$; R_5, R_5' = CH_3
b, R_3 = $C_6H_5(CH_2)_2$; R_5, R_5' = CH_3
c, R_3 = $C_6H_5CH_2$; R_5 = H, R_5' = CH_3
d, R_3 = $C_6H_5CH_2$; R_5, R_5' = H

Treatment of **16a** with allyltrimethylsilane (17) (1.6 equiv), $SnCl_4$, and trifluoroacetic anhydride gave a 66% yield of the *inter*molecular alkylation product **18a**. A key signal in the proton-coupled ^{13}C NMR spectrum for **18a** was the doublet at 63.9 ppm for carbon-4.

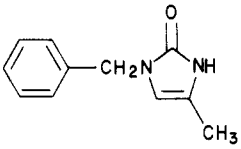
The overall reactivity of this activated alkene 17 was gauged by performing a comparable experiment with **16b**.[2] This adduct has been shown to undergo *intra*molecular cyclization to give the tetrahydroisoquinoline 19 in the



19

absence of any other nucleophilic species.[2] Under acid-mediated conditions, a 94% yield of the intermolecular addition product **18b** was obtained. No evidence for **19** was detected by thin-layer chromatographic analysis of the crude product mixture.

The success of these reactions prompted the examination of the reactivity of **16c**[10] with 17. The reaction was initiated at −20 °C with 1.9 equiv of 17. After workup and purification **18c** and **20**[13,15] were isolated in 67% and 18%



20

yields, respectively. The observation of a small coupling constant (J = 2 Hz) in the ^1H NMR spectrum for the methine hydrogens in **18c** supported the proposed trans configurational assignment.[16] The stereochemical preference of this reaction paralleled that observed for the

(8) Stark, G. R.; Smyth, D. G. *J. Biol. Chem.* **1963**, *238*, 214–226.
(9) Available from ICN Pharmaceuticals, Inc.
(10) Cortes, S.; Kohn, H. *J. Org. Chem.* **1983**, *48*, 2246–2254.
(11) A similar result was observed when compounds 9 and 13 were treated with trifluoroacetic acid and trifluoroacetic anhydride.
(12) Schoemaker, H. E.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 163–172, and references therein.
(13) Cortes, S.; Liao, Z.-K.; Watson, D.; Kohn, H. *J. Med. Chem.*, in press.
(14) (a) Overman, L. E.; Malone, T. C.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6993–6994. (b) Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1983**, *24*, 1407–1410. (c) Kraus, G. A.; Neuenschwander, K. *J. Chem. Soc., Chem. Commun.* **1982**, 134–135. (d) Takano, S.; Numata, H.; Ogasawara, K. *Ibid.* **1982**, 769–770. (e) Danishefsky, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 3803–3805. (f) Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1983**, *24*, 1563–1566, and references therein.
(15) Chupp, J. P. *J. Heterocycl. Chem.* **1971**, *8*, 557–563.
(16) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Elmsford, NY, 1969; p 286 and references therein.

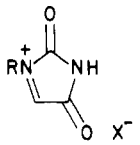
amidoalkylation reactions of substituted pyrrolidines.[14c] Presumably, steric factors are responsible for the stereochemical results in both cases.

This series of experiments was completed by examining the reactivity of the unsubstituted 4-hydroxy-2-imidazolidinone **16d**[10] with **17**. Addition of trifluoroacetic anhydride and $SnCl_4$ to a CH_2Cl_2 mixture containing **16d** and **17** (1.4 equiv) at −35 °C gave an 82% yield of the desired alkylated product **18d**. No imidazolone was detected in this reaction.

These results demonstrated that the undesired dehydration process from iminium ion **4** can be effectively circumvented by the use of reactive allylsilanes. On the basis of these observations, the strategic placement of an allylsilane unit in the N_3 side chain of hydantoins **2** should allow access to annelated 2-imidazolidinones independent of the substitution pattern at carbon-5.

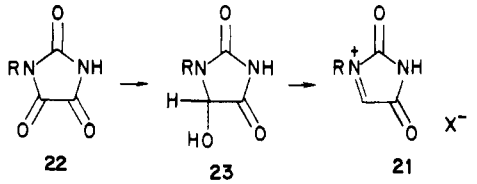
Use of Parabanic Acid Substrates. An alternative approach to carbon-5 unsubstituted 2-imidazolidinones is to place a group at carbon-5 which cannot undergo elimination during the amidoalkylation transformation but which can be subsequently converted to the perhydro derivative. The carbonyl moiety satisfied these criteria. In this case, the projected iminium ion is **21**. Complete reduction of the 5-carbonyl group after alkylation can be accomplished with $LiAlH_4$ provided the adjacent nitrogen atom is unsubstituted.[10,17]

Limited studies have appeared on the use of these ions (**21**) for intra-[5] and intermolecular[6b-d] amidoalkylation of



21

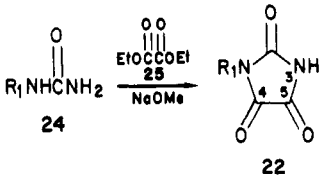
aromatic substrates to afford substituted hydantoins.[18] In some cases, however, iminium ion **21** was generated from the carbon-5 halide derivatives.[5] Our previous hydantoin reductive studies[10] suggested that parabanic acid substrates **22** might prove to be versatile starting materials for the



22 **23** **21**

5-hydroxy adduct **23**. Moreover, **23** was expected to display enhanced stability vs. the corresponding 5-halo derivative,[19] and also to lead to iminium ion **21** formation upon treatment with Lewis acids.

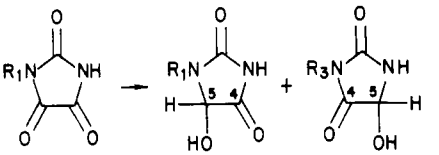
This concept has been examined. Parabanic acids **22a–d** were prepared from the corresponding substituted ureas[20-22] (**24a–d**) and diethyl oxalate (**25**) in the presence of sodium methoxide (34–52% yield).[23] Reduction of



24 **22**

a, R_1 = $C_6H_5(CH_2)_2$
b, R_1 = $3,4\text{-}(OCH_3)_2C_6H_3(CH_2)_2$
c, R_1 = $C_6H_5(CH_2)_3$
d, R_1 = $3\text{-}(OCH_3)C_6H_4CH_2$

22a–d with $NaBH_4$ in methanol[24] gave both monohydroxy adducts **23a–d** and **26a–d**, respectively in 33–58% yield.



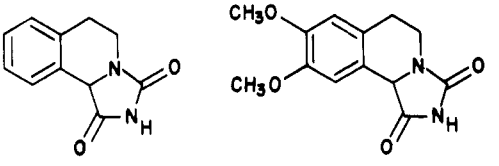
22 **23** **26**

a, $R_1(R_3)$ = $C_6H_5(CH_2)_2$
b, $R_1(R_3)$ = $3,4\text{-}(OCH_3)_2C_6H_3(CH_2)_2$
c, $R_1(R_3)$ = $C_6H_5(CH_2)_3$
d, $R_1(R_3)$ = $3\text{-}(OCH_3)C_6H_4CH_2$

In the four systems examined, preferential reduction (1.4–2.8:1) occurred at the carbonyl-5 moiety vs. the carbonyl-4 group in **22**.[25] Both regioisomers **23** and **26** were crystalline materials which showed no decomposition over several months.

Isomers **23** and **26** could be differentiated by several NMR parameters. First, introduction of chirality at carbon-5 in **22** gave rise to a pronounced coupling interaction between the diastereotopic methylene hydrogens attached to the N-1 nitrogen in **23**. This phenomenon was not observed in **26** where the distance between the chiral center at carbon-5 and the N_3-methylene protons is too large to distinguish these diastereotopic hydrogens. Second, the ^{13}C NMR chemical shift value for the carbon-5 resonance in **23** uniformly appeared between 78.5 and 78.8 ppm, while the corresponding resonance in **26** was observed between 75.0 and 76.1 ppm.

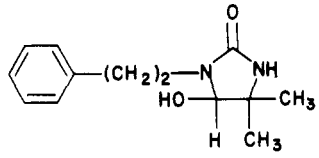
Each 1-substituted 5-hydroxyimidazolidine-2,4-dione **23** was treated with trifluoroacetic anhydride and trifluoroacetic acid in an effort to initiate the intramolecular amidoalkylation transformation. Compounds **23a** and **23b** gave the desired cyclized products **27** (87% yield) and **28**



27 **28**

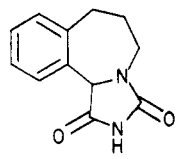
(71% yield), respectively. In the case of **28**, the detection of two aromatic singlets at δ 6.61 and 7.23 in the ^1H NMR spectrum verified the 1,2,4,5-tetrasubstitution pattern in the aromatic ring. The excellent yield for the cyclization of **23a** provided strong support for the employment of parabanic acid substrates in amidoalkylation transformations. In a previous study,[2] only a 40% yield was noted for the conversion of the corresponding dimethyl derivative **29** to **19** with trifluoroacetic anhydride and trifluoroacetic acid.

(17) Marshall, F. J. *J. Am. Chem. Soc.* **1956**, *78*, 3696–3697.
(18) The Diels–Alder reaction of the conjugated base of iminium ion **21** (R_1 = H) and 1,3-dienes has been described.[6d,f]
(19) Abblard, J.; Meynaud, A. *Bull. Soc. Chim. Fr.* **1971**, 942–946.
(20) Green, A. L.; Willey, G. L. *J. Pharm. Pharmacol.* **1969**, *21*, 366–373.
(21) Buck, J. S. *J. Am. Chem. Soc.* **1934**, *56*, 1607–1608.
(22) Hjort, A. M.; de Beer, E. J.; Buck, J. S.; Ide, W. S. *J. Pharmacol.* **1935**, *55*, 152; *Chem. Abstr.* **1936**, *30*, 3095.[7]
(23) Todd, A. R.; Whittaker, N. *J. Chem. Soc.* **1946**, 628–633. Murray, J. I. "Organic Synthesis"; Wiley: New York, 1963; Collect. Vol. IV, pp 744–746 and references therein.
(24) For a similar reductive procedure, please see ref 19.
(25) Reduction of **22a** with $LiAlH_4$ (0.53 equiv) in THF (room temperature, 20 h) led to a mixture of monohydroxy adducts **23a** and **26a** (20% yield) and the corresponding dihydroxy derivative (15% yield).

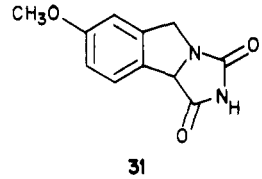


29

This methodology was extended to the formation of the corresponding fused seven-membered ring system. Treatment of **23c** with trifluoroacetic anhydride and trifluoroacetic acid (CH_2Cl_2, reflux, 10 days) gave a 39% yield of **30**. We were not able, however, to generate the related



30



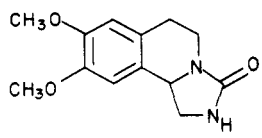
31

five-membered ring annelated adduct **31**. Only starting material was recovered when **23d** was subjected to trifluoroacetic anhydride and trifluoroacetic acid (CH_2Cl_2, reflux, 10 days). A comparable result has been previously observed.[2]

Several key features in the ^1H and ^{13}C NMR spectra for **27**, **28**, and **30** were diagnostic of structure. The methine hydrogen on the annelated hydantoin ring appeared as a distinct singlet in the ^1H NMR between δ 5.03 and 5.35. The corresponding carbon resonance was located between 59.1 and 64.3 ppm. Furthermore, resonances were observed between 156.4 and 156.8 and 172.0 and 172.4 ppm in the ^{13}C NMR spectrum of each adduct, consistent with the presence of a hydantoin ring.[10]

The possibility that the 3-substituted 5-hydroxyimidazolidine-2,4-diones **26** might serve as viable precursors to the annelated hydantoins was briefly examined. No detectable conversion of **23b** in Me_2SO-d_6 to **26b** was observed by ^{13}C NMR both in the absence of acid (room temperature, 1 month) and in the presence of trifluoroacetic acid (room temperature, 18 h). Furthermore, treatment of **26b** with trifluoroacetic anhydride and trifluoroacetic acid (CH_2Cl_2, reflux, 40 h) led to a 65% recovery of starting material. Thin-layer chromatographic analysis of the crude reaction mixture showed no evidence of **28**.

The viability of this synthetic strategy for the preparation of carbon-5 unsubstituted 2-imidazolidinones was demonstrated in the case of compound **28**. Reduction of this substrate with excess $LiAlH_4$ at room temperature gave the perhydro derivative **32** in 30% yield. Imidazolidinone **32** exhibited a characteristic carbonyl absorption at 1700 cm^{-1}.[2] The carbonyl carbon resonance in the ^{13}C NMR spectrum was detected at 161.5 ppm.



32

Conclusions

The synthetic utility of the 4-hydroxy-2-imidazolidinone amidoalkylation reactions[2,3] has been restricted by the propensity of the carbon-5 unsubstituted (**3**, R_5, $R_{5'}$ = H) and carbon-5 monosubstituted (**3**, R_5 = alkyl, $R_{5'}$ = H) adducts to undergo dehydration to yield 2-imidazolones. Two techniques have been successfully developed that have circumvented this competitive side reaction. The first method employed a highly reactive alkene in the alkylation step. The second methodology strategically placed a carbonyl unit on the heterocyclic ring, thus blocking the dehydration process.

Experimental Section

General Methods are the same as those described in ref 3.

Preparation of 3-[3-(*m*-Methoxyphenyl)propyl]-5-methylimidazolidine-2,4-dione (8). A Me_2SO solution (80 mL, stored over 4-Å molecular sieves, and then freshly distilled from CaH_2) containing 5-methylimidazolidine-2,4-dione (**6**) (5.00 g, 44 mmol) and KOH (2.50 g, 44 mmol) was heated to 100–110 °C (1 h). The solution was cooled, and 3-(*m*-methoxyphenyl)propyl bromide (**7**) (10.00 g, 44 mmol) in 30 mL of Me_2SO was slowly added. The reaction was kept at room temperature (2 days). The reaction was quenched by the addition of H_2O (25 mL), and the solution was extracted with Et_2O (3 × 400 mL). The Et_2O layers were combined, washed with H_2O (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, 65% benzene–ethyl acetate) to give 3-[3-(*m*-methoxyphenyl)propyl]-5-methylimidazolidine-2,4-dione (**8**) in 87% yield (10.00 g): R_f 0.38 (65% benzene–ethyl acetate); mp 76–78 °C; IR (KBr) 3230, 1780, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (d, 3 H, J = 8 Hz), 1.69–2.13 (m, 2 H), 2.63 (t, 2 H, J = 8 Hz), 3.52 (t, 2 H, J = 8 Hz), 3.78 (s, 3 H), 3.97 (q, 1 H, J = 8 Hz), 6.19 (br s, 1 H), 6.73–6.82 (m, 3 H), 7.17 (dd, 1 H, J = 8, 8 Hz); ^{13}C NMR ($CDCl_3$) 17.6 (q), 29.3 (t), 33.1 (t), 38.5 (t), 52.8 (d), 55.2 (q), 111.5 (d), 114.0 (d), 120.7 (d), 129.4 (d), 142.6 (s), 157.6 (s), 159.7 (s), 174.7 (s) ppm; MS, m/e (relative intensity) 262 (100), 148 (43), 135 (80), 122 (100), 121 (27), 105 (14), 91 (28); M_r 262.1313 (calcd for $C_{14}H_{18}N_2O_3$, 262.1317).

Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.09; H, 6.83; N, 10.61.

Preparation of *cis*/*trans*-3-[3-(*m*-Methoxyphenyl)-propyl]-4-hydroxy-5-methylimidazolidin-2-one (9). Using the method previously reported,[10] an equimolar amount of $LiAlH_4$ (0.76 g, 20 mmol) was slowly added in increments to a THF (100 mL of THF/0.10 g of $LiAlH_4$) solution of the 3-[3-(*m*-methoxyphenyl)propyl]-5-methylimidazolidine-2,4-dione (**8**) (5.19 g, 20 mmol) at room temperature. The reaction was allowed to stir at room temperature (2 days), and then excess $LiAlH_4$ was destroyed with H_2O and aqueous 15% NaOH.[26] The reaction mixture was filtered, and the filtrate dried ($MgSO_4$) and concentrated in vacuo. The crude product was recrystallized from benzene to give 3.07 g (59% yield) of **9** (^{13}C NMR analysis[10] indicated that the cis/trans ratio of the recrystallized product was approximately 6:1): mp 109–112 °C; IR (KBr) 3300, 3200, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (d, 3 H, J = 7 Hz), 1.89 (tt, 2 H, J = 8, 8 Hz), 2.60 (t, 2 H, J = 8 Hz), 3.13–3.69 (m, 3 H), 3.75 (s, 3 H), 4.80–5.06 (m, 3 H), 6.48–6.80 (m, 3 H), 7.16 (dd, 1 H, J = 8, 8 Hz) (Addition of D_2O to the ^1H NMR sample simplified the multiplet at δ 4.80–5.06 to a doublet (J = 6 Hz). The area under this signal integrated for one proton); ^{13}C NMR ($CDCl_3$) 14.1 (q), 29.7 (t), 33.3 (t), 39.7 (t), 51.0 (d), 55.2 (q), 81.9 (d), 111.3 (d), 114.1 (d), 120.8 (d), 129.3 (d), 143.4 (s), 159.7 (s), 161.0 (s) ppm; MS, m/e (relative intensity) 264 (6), 247 (100), 148 (42), 121 (33), 112 (82), 98 (30), 91 (23).

Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.61; H, 7.63; N, 10.60. Found: C, 63.63; H, 7.39; N, 10.49.

Preparation of 1-[3-(*m*-Methoxyphenyl)propyl]-4-methyl-2-imidazolone (10). A CH_2Cl_2 (60 mL) solution of *cis*/*trans*-3-[3-(*m*-methoxyphenyl)propyl]-4-hydroxy-5-methylimidazolin-2-one (**9**) (1.30 g, 5 mmol) and trifluoroacetic anhydride (0.48 mL, 6 mmol) was heated to reflux (5 days). The solution was hydrolyzed with H_2O (10 mL), then neutralized with aqueous 15% NaOH, washed with H_2O (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 50% ethyl acetate–methanol) to give 0.67 g (55%) of **10**: R_f 0.19 (50% benzene–ethyl acetate); IR (neat, NaCl) 3240, 3050, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80–2.10 (m, 2 H), 2.00

(26) Micovic, V. M.; Mihailovic, M. L. J. *J. Org. Chem.* **1953**, *18*, 1190–1200.

(s, 3 H), 2.61 (t, 2 H, J = 8 Hz), 3.54 (t, 2 H, J = 8 Hz), 3.70 (s, 3 H), 5.76 (s, 1 H), 6.60–6.85 (m, 3 H), 7.12 (dd, 1 H, J = 8, 8 Hz), 9.15 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 10.8, 32.9, 33.1, 42.5, 55.1 107.0, 111.5, 114.2, 118.0, 120.8, 129.4, 142.9, 154.0, 159.8 ppm; MS, m/e (relative intensity) 246 (33), 245 (100), 125 (25), 121 (52), 120 (63), 112 (80), 111 (55), 91 (46); M_r 246.1364 (calcd for $C_{14}H_{18}N_2O_2$, 246.1368).

Preparation of 3-[3-(*m*-Methoxyphenyl)propyl]-1,3-diazabicyclo[3.3.0]octane-2,4-dione (12). A Me_2SO (60 mL, stored over 4-Å molecular sieves, and then freshly distilled from CaH_2) solution containing 1,3-diazabicyclo[3.3.0]octane-2,4-dione (**11**) (6.60 g, 47 mmol) and KOH (3.36 g, 60 mmol) was heated to 100–110 °C (1 h) and then cooled to 70 °C. A Me_2SO (15 mL) solution of 3-(*m*-methoxyphenyl)propyl bromide (10.00 g, 44 mmol) was then added, and the solution was maintained at 70–80 °C (10 h), and then kept at room temperature (2 days). After using the same workup procedure previously described for **8**, the crude product was purified by flash chromatography (SiO_2, 65% benzene–ethyl acetate) to give 3-[3-(*m*-methoxyphenyl)-propyl]-1,3-diazabicyclo[3.3.0]octane-2,4-dione (**12**) as a liquid in 50% yield (6.81 g): R_f 0.75 (65% benzene–ethyl acetate); IR (neat, NaCl) 1775, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.80–2.20 (m, 6 H), 2.60 (t, 2 H, J = 7 Hz), 3.00–3.40 (m, 2 H), 3.50 (t, 2 H, J = 7 Hz), 3.80 (s, 3 H), 4.00 (t, 1 H, J = 8 Hz), 6.60–6.80 (m, 3 H), 7.00–7.30 (m, 1 H); ^{13}C NMR ($CDCl_3$) 27.0 (t), 27.5 (t), 29.2 (t), 33.1 (t), 38.8 (t), 45.5 (t), 55.1 (q), 63.3 (d), 111.5 (d), 113.9 (d), 120.8 (d), 129.4 (d), 142.6 (s), 159.7 (s), 160.9 (s), 174.0 (s) ppm; MS, m/e (relative intensity) 288 (72), 218 (7), 154 (13), 148 (42), 135 (61), 122 (100), 105 (14), 91 (33); M_r 288.1478 (calcd for $C_{16}H_{20}N_2O_3$, 288.1474).

Preparation of *cis*-3-[3-(*m*-Methoxyphenyl)propyl]-4-hydroxy-1,3-diazabicyclo[3.3.0]octan-2-one (13). The procedure employed for the preparation of **9** was repeated with **12** (6.00 g, 20 mmol) and $LiAlH_4$ (0.76 g, 20 mmol) in THF at room temperature (2 days). After workup a mixture of *cis*- and *trans*-3-[3-(*m*-methoxyphenyl)propyl]-4-hydroxy-1,3-diazabicyclo-[3.3.0]octan-2-one (**13**) was obtained in 30% yield (1.34 g, ^{13}C NMR analysis[10] indicated that the cis/trans ratio was 3:1). Separation of the binary mixture by flash chromatography (SiO_2, 25% benzene–ethyl acetate) gave the cis adduct as a liquid: R_f 0.58 (25% benzene–ethyl acetate); IR (neat, NaCl) 3350, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.85–1.94 (m, 6 H), 2.49–2.68 (m, 2 H), 3.20–3.54 (m, 5 H), 3.78 (s, 3 H), 5.50 (br s, 2 H), 6.68–6.79 (m, 3 H), 7.08–7.26 (m, 1 H) (Addition of D_2O to the ^{1}H NMR sample led to a reduction in the relative area of the signal at δ 5.50 from two protons to one hydrogen); ^{13}C NMR ($CDCl_3$) 25.0 (t), 28.4 (t), 29.6 (t), 33.2 (t), 40.1 (t), 45.5 (t), 55.2 (q), 66.9 (d), 82.6 (d), 111.3 (d), 114.1 (d), 120.8 (d), 129.4 (d), 143.3 (s), 159.7 (s), 163.4 (s) ppm; MS, m/e (relative intensity) 290 (2), 272 (52), 193 (30), 148 (40), 138 (100), 122 (70), 121 (45), 109 (34), 91 (60), 77 (40); M_r 290.1630 (calcd for $C_{16}H_{22}N_2O_3$, 290.1630).

Preparation of 3-[3-(*m*-Methoxyphenyl)propyl]-1,3-diazabicyclo[3.3.0]oct-4-en-2-one (14). A solution of *cis*-3-[3-(*m*-methoxyphenyl)propyl]-4-hydroxy-1,3-diazabicyclo[3.3.0]octan-2-one (**13**) (0.49 g, 2 mmol) and trifluoroacetic anhydride (0.18 mL, 2 mmol) in CH_2Cl_2 (40 mL) was kept at room temperature for 2 days. The solution was hydrolyzed with H_2O (10 mL), then neutralized with aqueous 15% NaOH, washed with H_2O (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2). The initial product, *N*-[3-(*m*-methoxyphenyl)propyl]formamide (**15**), was obtained from the column in 14% yield (50 mg), with EtOAc as the eluent: R_f 0.42 (EtOAc); IR (neat, NaCl) 3300, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.73–1.93 (m, 2 H), 2.63 (t, 2 H, J = 8 Hz), 3.15–3.42 (m, 2 H), 3.77 (s, 3 H), 6.00 (br s, 1 H), 6.70–6.80 (m, 3 H), 7.09–7.29 (m, 1 H), 8.12 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 31.0, 33.2, 37.8, 55.2, 111.3, 114.2, 120.8, 129.5, 142.9, 159.8, 161.4 ppm; MS, m/e (relative intensity) 193 (28), 148 (52), 135 (54), 122 (100), 105 (35), 91 (38); M_r 193.1108 (calcd for $C_{11}H_{15}NO_2$, 193.1103).

The second adduct, 3-[3-(*m*-methoxyphenyl)propyl]-1,3-diazabicyclo[3.3.0]oct-4-en-2-one (**14**), was recovered in 44% yield (0.20 g) from the column by the use of MeOH as the eluent: R_f 0.22 (EtOAc); IR (neat, NaCl) 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.80–2.80 (m, 8 H), 3.50–3.80 (m, 4 H), 3.78 (s, 3 H), 5.80 (t, 1 H, J = 1 Hz), 6.60–6.82 (m, 3 H), 7.15 (dd, 1 H, J = 8, 8 Hz); ^{13}C NMR ($CDCl_3$) 22.8, 28.1, 31.2, 33.0, 42.2, 43.2, 55.2, 101.6, 111.4, 114.1, 120.8, 126.1, 129.3, 143.0, 150.3, 160.0 ppm; MS, m/e (relative intensity) 272 (80), 151 (100), 138 (98), 137 (60), 124 (75), 121 (45), 109 (55), 91 (38); M_r 272.1535 (calcd for $C_{16}H_{20}N_2O_2$, 272.1525).

Preparation of 3-(*m*-Methoxybenzyl)-4-[3-(prop-1-enyl)]-5,5-dimethylimidazolidin-2-one (18a). To a CH_2Cl_2 solution (25 mL) of 3-(*m*-methoxybenzyl)-4-hydroxy-5,5-dimethylhydantoin[2] (**16a**) (1.25 g, 5 mmol) and trifluoroacetic anhydride (0.8 mL, 10 mmol) were added allyltrimethylsilane (**17**) (0.91 g, 8 mmol) and $SnCl_4$ (0.6 mL, 5 mmol) successively at room temperature. The reaction solution was kept at room temperature (84 h) and then quenched with an aqueous 1 N HCl solution (10 mL). The organic layer was successively washed with H_2O (15 mL), aqueous 15% NaOH (20 mL), and H_2O (15 mL), dried (Na_2SO_4), and concentrated in vacuo. Compound **18a** was isolated as an oil in 66% yield (0.90 g) by flash chromatography (SiO_2, 25% benzene–ethyl acetate): R_f 0.80 (25% benzene–ethyl acetate); IR (neat, NaCl) 3250, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21 (s, 6 H), 2.29–2.38 (m, 2 H), 3.06–3.31 (m, 1 H), 3.78 (s, 3 H), 4.07 (d, 1 H, J = 15 Hz), 4.80 (d, 1 H, J = 15 Hz), 4.86–5.25 (m, 3 H), 5.36–6.00 (m, 1 H), 6.83–7.31 (m, 4 H); ^{13}C NMR ($CDCl_3$) 23.3 (q), 29.1 (q), 33.1 (t), 45.2 (t), 55.4 (q), 55.6 (s), 63.9 (d), 112.9 (d), 113.4 (d), 117.8 (t), 120.2 (d), 129.5 (d), 134.4 (d), 139.2 (s), 159.9 (s), 161.2 (s) ppm; MS, m/e (relative intensity) 234 (11), 233 (71), 121 (100), 91 (12).

Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.98; H, 8.01; N, 10.15.

Preparation of 3-(2-Phenethyl)-4-[3-(prop-1-enyl)]-5,5-dimethylimidazolidin-2-one (18b). Utilizing the procedure described for **18a**, 3-(2-phenethyl)-4-hydroxy-5,5-dimethylimidazolidin-2-one[2] (**16b**) (1.32 g, 6 mmol) and trifluoroacetic anhydride (0.72 mL, 9 mmol) in CH_2Cl_2 (50 mL) were treated with **17** (1.10 g, 9 mmol) and $SnCl_4$ (0.65 mL, 6 mmol) at room temperature. The reaction solution was kept at room temperature (1 day). After workup, **18b** was isolated in 94% yield (1.36 g) by flash chromatography (SiO_2, 20% benzene–ethyl acetate): R_f 0.50 (20% benzene–ethyl acetate); mp 117–120 °C; IR (KBr) 3320, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 6 H), 2.25 (t, 2 H, J = 6 Hz), 2.67–3.83 (m, 5 H), 4.43 (br s, 1 H), 4.83–5.25 (m, 3 H), 7.25 (s, 5 H); ^{13}C NMR ($CDCl_3$) 23.0 (q), 28.8 (q), 33.2 (t), 34.1 (t), 42.6 (t), 55.7 (s), 64.4 (d), 117.9 (t), 126.3 (d), 128.4 (d), 128.9 (d), 134.6 (d), 139.2 (s), 160.9 (s) ppm (The signals at 128.4 and 128.9 ppm were approximately twice the intensity of neighboring peaks.); MS, m/e (relative intensity) 217 (66), 167 (81), 125 (23), 113 (100), 105 (58); MS (CI) 259 (P + 1); M_r 258.1735 (calcd for $C_{16}H_{22}N_2O$, 258.1732).

Preparation of *trans*-3-Benzyl-4-[3-(prop-1-enyl)]-5-methylimidazolidin-2-one (18c). The preceding method was utilized for the preparation of *trans*-3-benzyl-4-[3-(prop-1-enyl)]-5-methylimidazolidin-2-one (**18c**). Beginning with a CH_2Cl_2 solution (25 mL) containing both 3-benzyl-4-hydroxy-5-methylimidazolidin-2-one[10] (**16c**) (0.26 g, 1.3 mmol) and allyltrimethylsilane (**17**) (0.29 g, 2.5 mmol), trifluoroacetic anhydride (0.20 mL, 2.5 mmol) and $SnCl_4$ (0.18 mL, 1.5 mmol) were added at −20 °C. The reaction solution was maintained at −20 °C (2 h) and then gradually raised to room temperature and kept at this temperature for 8 h. After workup, the ^{1}H NMR spectrum of crude product showed the presence of both *trans*-3-benzyl-4-[3-(prop-1-enyl)]-5-methylimidazolidin-2-one (**18c**) and 1-benzyl-4-methylimidazolone (**20**) in a 4:1 ratio. Compound **18c** was isolated by flash chromatography (SiO_2, 30% benzene–ethyl acetate) in 67% yield (0.20 g): R_f 0.83 (30% benzene–ethyl acetate); IR (neat, NaCl) 3250, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.12 (d, 3 H, J = 7 Hz), 2.19 (dd, 2 H, J = 10, 6 Hz), 3.07 (qd, 1 H, J = 7, 2 Hz), 3.47 (td, 1 H, J = 10, 2 Hz), 3.93 (d, 1 H, J = 15 Hz), 4.77 (d, 1 H, J = 15 Hz), 5.00–5.80 (m, 4 H), 7.28 (s, 5 H); ^{13}C NMR ($CDCl_3$) 21.6 (q), 36.1 (t), 44.8 (t), 50.2 (d), 61.4 (d), 118.6 (t), 127.3 (d), 128.0 (d), 128.6 (d), 132.9 (d), 137.4 (s), 161.5 (s) ppm (The signals at 128.0 and 128.6 ppm were approximately twice the intensity neighboring peaks.); MS, m/e (relative intensity) 189 (27), 91 (100); MS (CI), 231 (P + 1).

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.10; H, 7.88; N, 12.17. Found: C, 72.77; H, 7.77; N, 12.30.

The second product isolated by flash chromatography (SiO_2, EtOAc) was identified as 1-benzyl-4-methylimidazolone (**20**) (45 mg, 18% yield): R_f 0.43 (30% benzene–ethyl acetate); mp 160–162 °C (lit.[15] mp 162–165 °C).

Preparation of 3-Benzyl-4-[3-(prop-1-enyl)]imidazolidin-2-one (18d). The procedure described for the preparation of **18a** was adopted for the synthesis of **18d**. Accordingly, trifluoroacetic anhydride (0.88 mL, 11 mmol) and $SnCl_4$ (1 mL, 10 mmol) were added to a mixture of 3-benzyl-4-hydroxy-imidazolidin-2-one[10] (**16d**) (1.63 g, 8.5 mmol) and **17** (1.37 g, 12 mmol) in CH_2Cl_2 (100 mL) at −35 °C. The reaction solution was maintained between −30 and −40 °C for 2 h and then at room temperature for an additional 10 h. After workup, **18d** was isolated by flash chromatography (SiO_2, EtOAc) in 82% yield (1.50 g): mp 45–48 °C; R_f 0.52 (20% benzene–ethyl acetate); IR (KBr) 3240, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.21–2.31 (m, 2 H), 3.08–3.48 (m, 3 H), 4.04 (d, 1 H, J = 15 Hz), 4.76 (d, 1 H, J = 15 Hz), 4.98–5.45 (m, 3 H), 6.52 (br s, 1 H), 7.26 (s, 5 H); ^{13}C NMR ($CDCl_3$) 36.5 (t), 43.3 (t), 45.0 (t), 54.2 (d), 118.6 (t), 127.4 (d), 128.0 (d), 128.6 (d), 132.5 (d), 137.3 (s), 162.8 (s) (The signals at 128.0 and 128.6 ppm were approximately twice the intensity of neighboring peaks.); MS (CI), 217 (P + 1); M_r 216.1257 (calcd for $C_{13}H_{16}N_2O$, 216.1263).

Preparation of 1-(2-Phenethyl)imidazolidine-2,4,5-trione (22a). To a methanolic sodium methoxide solution [9.00 g of Na (390 mmol) in 400 mL of methanol] was added *N*-(2-phenethyl)urea[20] (**24a**) (27.21 g, 165 mmol) at room temperature. After dissolution of the urea, diethyl oxalate (**25**) (21.93 g, 150 mmol) was slowly added at room temperature. The reaction solution was kept at room temperature (24 h) and aqueous concentrated HCl (15 mL) was added at 0–5 °C, leading to the formation of a precipitate. The solid was filtered and washed with methanol (2 × 75 mL), and the methanol solutions were combined, neutralized with an aqueous 15% NaOH solution, dried (Na_2SO_4), and concentrated in vacuo. The residue was washed with H_2O (2 × 25 mL) and recrystallized from EtOH to give 1-(2-phenethyl)imidazolidine-2,4,5-trione (**22a**) in 43% yield (14.00 g): mp 188–190 °C; IR (KBr) 3300, 1780, 1750, 1730 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.77 (t, 2 H, J = 7 Hz), 3.36 (t, 2 H, J = 7 Hz), 7.25 (s, 5 H), 10.42 (br s, 1 H); ^{13}C NMR (Me_2SO-d_6) 33.2, 39.3, 126.5, 128.4, 128.5, 137.9, 154.1, 157.8, 158.7 ppm (The signals at 128.4 and 128.5 ppm were approximately twice the intensity of neighboring peaks.); MS, m/e (relative intensity) 218 (5), 104 (100), 91 (80); M_r 218.0693 (calcd for $C_{11}H_{10}N_2O_3$, 218.0691).

Preparation of 1-[2-(3,4-Dimethoxyphenethyl)]-imidazolidine-2,4,5-trione (22b). Utilizing the same procedure described for the preparation of **22a**, diethyl oxalate (**25**) (7.30 g, 50 mmol) was slowly added to a methanolic sodium methoxide solution [2.99 g (130 mmol) of Na in 300 mL of methanol] containing *N*-[2-(3,4-dimethoxyphenethyl)]urea[21] (**24b**) (11.20 g, 50 mmol). The reaction solution was maintained at room temperature for 20 h. After workup, the residue was recrystallized from EtOH or separated by flash chromatography (SiO_2, 10% benzene–ethyl acetate) to give pure **22b** in 52% yield (9.00 g): R_f 0.44 (30% benzene–ethyl acetate); mp 174–176 °C; IR (KBr) 3260, 1805, 1765, 1745 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.79 (t, 2 H, J = 8 Hz), 3.46–3.73 (m, 2 H), 3.71 (s, 3 H), 3.73 (s, 3 H), 6.75–6.82 (m, 3 H), 11.76 (br s, 1 H, D_2O exchangeable) (The signal at δ 3.46–3.73 was partially obscured by the HOD signal in this region.); ^{13}C NMR (Me_2SO-d_6) 32.7 (t), 39.5 (t), 53.4 (q), 112.0 (d), 112.5 (d), 120.5 (d), 130.3 (s), 147.5 (s), 148.7 (s), 154.2 (s), 157.9 (s), 158.7 (s) ppm (The signal at 53.4 ppm was approximately twice the intensity of nearby peaks.); MS, m/e (relative intensity) 278 (23), 164 (29), 151 (100); M_r 278.0908 (calcd for $C_{13}H_{14}N_2O_5$, 278.0902).

Preparation of 1-(3-Phenylpropyl)imidazolidine-2,4,5-trione (22c). Using the previously described procedure, diethyl oxalate (**25**) (7.30 g, 50 mmol) was slowly added to a methanolic sodium methoxide solution [2.76 g (130 mmol) of Na in 200 mL of methanol] containing *N*-(3-phenethyl)urea[20] (**24c**) (8.90 g, 50 mmol). The solution was maintained at room temperature for 3 days. After workup, **22c** was isolated by flash chromatography (SiO_2, 50% benzene–ethyl acetate) in 34% yield (3.90 g): R_f 0.85 (50% benzene–ethyl acetate); mp 112–114 °C; IR (KBr) 3225, 1780, 1750, 1700 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.66–2.03 (m, 2 H), 2.41 (t, 2 H, J = 8 Hz), 3.47 (t, 2 H, J = 9 Hz), 7.23 (s, 5 H), 11.89 (br s, 1 H); ^{13}C NMR (Me_2SO-d_6) 29.0, 32.2, 37.8, 125.8, 128.1, 128.2, 141.2, 154.5, 158.2, 158.9 ppm (The signals at 128.1 and 128.2 ppm were approximately twice the intensity of the neighboring peaks.); MS, m/e (relative intensity) 232 (30), 128 (20), 105 (37), 104 (14), 91 (100); M_r 232.0856 (calcd for $C_{12}H_{12}N_2O_3$, 232.0848).

Preparation of 1-(*m*-Methoxybenzyl)imidazolidine-2,4,5-trione (22d). Beginning with *m*-methoxybenzyl urea[22] (**24d**) (9.00 g, 50 mmol) and a methanolic sodium methoxide solution [2.76 g (120 mmol) of Na in 200 mL of methanol], diethyl oxalate (**25**) (7.50 g, 51 mmol) was slowly added at room temperature, and the reaction solution was kept at this temperature for 15 h. After utilization of the workup procedure described for the preparation of **22a**, crude 3-(*m*-methoxybenzyl)imidazolidine-2,4,5-trione (**22d**) was recrystallized from MeOH to give 4.50 g (39% yield) of product: mp 135–137 °C; IR (KBr) 3250, 1800, 1760, 1725 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.73 (s, 3 H), 4.61 (s, 2 H), 6.81–7.26 (m, 4 H), 8.50 (br s, 1 H); ^{13}C NMR (Me_2SO-d_6) 42.2 (t), 54.9 (q), 112.8 (d), 113.0 (d), 119.4 (d), 129.4 (d), 137.0 (s), 154.5 (s), 158.2 (s), 159.0 (s), 159.2 (s) ppm; MS, m/e (relative intensity) 234 (100), 163 (58), 148 (62), 121 (56); M_r 234.0639 (calcd for $C_{11}H_{10}N_2O_4$, 234.0640).

Reduction of 1-(2-Phenethyl)imidazolidine-2,4,5-trione (22a). To a methanolic solution (30 mL) containing 1-(2-phenethyl)imidazolidine-2,4,5-trione (**22a**) (2.20 g, 10 mmol) was added $NaBH_4$ (0.21 g, 6 mmol) in increments at room temperature, and the reaction was kept at this temperature for 20 h. The reaction was quenched by the addition of H_2O (0.20 mL), then carefully neutralized with concentrated aqueous HCl, dried (Na_2SO_4), and concentrated in vacuo. The crude mixture was purified by flash chromatography (SiO_2, 60% benzene–ethyl acetate). The initial product isolated in 28% yield (0.62 g) was 1-(2-phenethyl)-5-hydroxyimidazolidine-2,4-dione (**23a**): R_f 0.52 (50% benzene–ethyl acetate); mp 174–175 °C; IR (KBr) 3370, 3200, 1780, 1725 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.83 (t, 2 H, J = 8 Hz), 3.35–3.59 (m, 2 H), 4.99 (d, 1 H, J = 8 Hz), 6.92 (d, 1 H, J = 8 Hz, D_2O exchangeable), 7.25 (s, 5 H), 10.76 (br s, 1 H, D_2O exchangeable); ^{13}C NMR (Me_2SO-d_6) 33.6, 40.5, 78.7, 126.2, 128.3, 128.5, 138.8, 155.1, 172.4 ppm (The signals at 128.3 and 128.5 ppm were approximately twice the intensity of the neighboring peaks.); MS, m/e (relative intensity) 220 (18), 129 (41), 104 (100), 91 (56).

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.03; H, 5.49; N, 12.64.

The second adduct (0.21 g, 10% yield) recovered from column chromatography was identified as 3-(2-phenethyl)-5-hydroxyimidazolidine-2,4-dione (**26a**): R_f 0.37 (50% benzene–ethyl acetate); mp 147–149 °C; IR (KBr) 3420, 3300, 1780, 1720 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.60–3.00 (m, 2 H), 3.30–3.80 (m, 2 H), 5.20 (d, 1 H, J = 8 Hz), 6.90 (d, 1 H, J = 8 Hz), 7.30 (s, 5 H), 8.45 (br s, 1 H) (The signals at δ 2.60–3.00 and 3.30–3.80 were partially obscured by the HOD peak in this region.); ^{13}C NMR (Me_2SO-d_6) 33.6, 38.4, 75.0, 126.2, 128.3, 128.5, 137.3, 156.1, 172.4 ppm (The signals at 128.3 and 128.5 ppm were approximately twice the intensity of neighboring peaks.); MS, m/e (relative intensity) 220 (34), 104 (100), 91 (92).

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.78; H, 5.37; N, 12.53.

Reduction of 1-[2-(3,4-Dimethoxyphenethyl)]-imidazolidine-2,4,5-trione (22b). To a MeOH (50 mL)–THF (50 mL) solution containing 1-[2-(3,4-dimethoxy)phenethyl]-imidazolidine-2,4,5-trione (**22b**) (1.00 g, 4 mmol) was added $NaBH_4$ (91 mg, 2.4 mmol) in increments at room temperature, and the reaction solution was stirred at this temperature for 15 h. The workup procedure described in the previous reaction was utilized. The initial product (0.30 g, 30% yield) isolated by flash chromatography (SiO_2, 40% benzene–ethyl acetate) was identified as 1-[2-(3,4-dimethoxyphenethyl)]-5-hydroxyimidazolidine-2,4-dione (**23b**): R_f 0.38 (50% benzene–ethyl acetate); mp 171–173 °C; IR (KBr) 3350, 3260, 1785, 1730 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.75 (t, 2 H, J = 7 Hz), 3.09–3.68 (m, 3 H), 3.57 (s, 3 H), 3.58 (s, 3 H), 4.98 (d, 1 H, J = 8 Hz), 6.67–7.05 (m, 3 H), 10.53 (br s, 1 H); ^{13}C NMR (Me_2SO-d_6) 33.1 (t), 40.5 (t), 55.3 (q), 55.4 (q), 78.7 (d), 112.0 (d), 112.4 (d), 120.4 (d), 130.1 (s), 147.3 (s), 148.6 (s), 155.1 (s), 172.4 (s) ppm; MS, m/e (relative intensity) 280 (12), 164 (42), 151 (100); Mr 280.1052 (calcd for $C_{13}H_{16}N_2O_5$, 280.1059).

The second adduct eluted from the column was 3-[2-(3,4-dimethoxyphenethyl)]-5-hydroxyimidazolidine-2,4-dione (**26b**) and

was obtained in 16% yield (0.16 g): R_f 0.31 (50% benzene–ethyl acetate); mp 157–159 °C; IR (KBr) 3400, 3280, 1785, 1725 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.74 (t, 2 H, J = 8 Hz), 3.38–3.63 (m, 3 H), 3.89 (s, 3 H), 3.93 (s, 3 H), 5.13 (d, 1 H, J = 8 Hz), 6.75–6.91 (m, 3 H), 8.59 (br s, 1 H); ^{13}C NMR (Me_2SO-d_6) 32.9, 39.0, 55.3, 55.4, 75.6, 111.9, 112.4, 120.5, 130.5, 147.4, 148.6, 155.9, 172.3 ppm; MS, m/e (relative intensity) 280 (12), 164 (87), 151 (100); M_r 280.1065 (calcd for $C_{13}H_{16}N_2O_5$, 280.1059).

Reduction of 1-(3-Phenylpropyl)imidazolidine-2,4,5-trione (22c). The procedure employed for the preparation of **23a** and **26a** was repeated with **22c** (3.19 g, 14 mmol) and $NaBH_4$ (0.30 g, 7 mmol) in methanol (50 mL) at room temperature (5 h). After workup, the binary mixture was separated by flash chromatography (SiO_2, 50% benzene–ethyl acetate). The initial isomer isolated was identified as 1-(3-phenylpropyl)-5-hydroxyimidazolidine-2,4-dione (**23c**) and was isolated in 22% yield (0.72 g): R_f 0.49 (50% benzene–ethyl acetate); mp 128–130 °C; IR (KBr) 3350, 3170, 1775, 1720 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.70–1.90 (m, 2 H), 2.59 (t, 2 H, J = 8 Hz), 3.14–3.33 (m, 2 H), 5.07 (d, 1 H, J = 9 Hz), 6.86 (d, 1 H, J = 9 Hz, D_2O exchangeable), 7.23 (s, 5 H), 10.74 (br s, 1 H, D_2O exchangeable); ^{13}C NMR (Me_2SO-d_6) 29.3 (t), 32.4 (t), 38.9 (t), 78.8 (d), 125.7 (d), 128.2 (d), 128.5 (d), 141.5 (s), 155.3 (s), 172.6 (s) ppm (The signals at 128.2 and 128.5 ppm were approximately twice the intensity of neighboring peaks.); MS, m/e (relative intensity) 234 (16), 216 (18), 118 (25), 117 (70), 104 (45), 103 (45), 91 (100); M_r 234.1011 (calcd for $C_{12}H_{14}N_2O_3$, 234.1004).

The second adduct eluted from the column was 3-(3-phenylpropyl)-5-hydroxyimidazolidine-2,4-dione (**26c**) and was obtained in 11% yield (0.35 g): R_f 0.42 (50% benzene–ethyl acetate); mp 107–109 °C; IR (KBr) 3380, 3300, 1785, 1720 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.32–1.50 (m, 2 H), 2.21 (t, 2 H, J = 8 Hz), 2.99 (t, 2 H, J = 8 Hz), 4.77 (d, 1 H, J = 9 Hz), 6.38 (d, 1 H, J = 9 Hz, D_2O exchangeable), 6.85 (s, 5 H), 8.22 (br s, 1 H, D_2O exchangeable); ^{13}C NMR (Me_2SO-d_6) 29.2, 32.2, 37.3, 75.7, 125.7, 128.1, 128.2, 141.2, 156.0, 172.5 ppm (The signals at 128.1 and 128.2 ppm were approximately twice the intensity of neighboring peaks.); MS, m/e (relative intensity) 234 (9), 217 (20), 216 (36), 118 (30), 117 (100), 91 (47); M_r 234.1007 (calcd for $C_{12}H_{14}N_2O_3$, 234.1004).

Reduction of 1-(*m*-Methoxybenzyl)imidazolidine-2,4,5-trione (22d). Following the procedure described for the reduction of **22a**, compound **22d** (4.20 g, 18 mmol) in MeOH (200 mL) was treated with $NaBH_4$ (0.42 g, 11 mmol) at 5–10 °C (5 h) and then allowed to remain at room temperature for 10 h. After workup, a pair of isomers were separated by flash chromatography (SiO_2, 50% benzene–ethyl acetate). The initial isomer eluted was identified as 1-(*m*-methoxybenzyl)-5-hydroxyimidazolidine-2,4-dione (**23d**) (1.44 g, 34% yield): R_f 0.49 (50% benzene–ethyl acetate); mp 98–100 °C; IR (KBr) 3350, 3200, 1775, 1725 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.74 (s, 3 H), 4.13 (d, 1 H, J = 15 Hz), 4.75 (d, 1 H, J = 15 Hz), 4.94 (br s, 1 H, D_2O exchangeable), 5.02 (br s, 1 H), 6.70–7.22 (m, 4 H), 10.90 (br s, 1 H, D_2O exchangeable); ^{13}C NMR (Me_2SO-d_6) 42.5 (t), 54.9 (q), 78.7 (d), 112.6 (d), 113.1 (d), 119.6 (d), 129.5 (d), 138.6 (s), 155.5 (s), 159.3 (s), 172.4 (s) ppm; MS, m/e (relative intensity) 236 (19), 163 (11), 162 (50), 136 (48), 122 (100), 121 (52).

Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.76; H, 5.02; N, 11.78.

The second adduct was identified as 3-(*m*-methoxybenzyl)-5-hydroxyimidazolidine-2,4-dione (**26d**) and was obtained in 24% yield (1.01 g): R_f 0.40 (50% benzene–ethyl acetate); mp 132–134 °C; IR (KBr) 3400, 3240, 1780, 1725 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.73 (s, 3 H), 4.49 (s, 2 H), 5.13 (br s, 1 H, D_2O exchangeable), 5.25 (br s, 1 H), 6.80–7.36 (m, 4 H), 8.70 (br s, 1 H, D_2O exchangeable); ^{13}C NMR (Me_2SO-d_6) 40.6, 54.9, 75.9, 112.5, 113.2, 119.4, 129.5, 138.1, 155.8, 159.3, 172.3 ppm; MS, m/e (relative intensity) 236 (100), 121 (62), 91 (76).

Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 56.03; H, 5.01; N, 11.83.

Preparation of 4,5-Benzo-1,8-diazabicyclo[4.3.0]nonane-7,9-dione (27). A CH_2Cl_2 solution (30 mL) containing 1-phenethyl-5-hydroxyimidazolidine-2,4-dione (**23a**) (0.19 g, 0.9 mmol), trifluoroacetic anhydride (1 mmol, 0.14 mL), and trifluoroacetic acid (3 mL) was heated to reflux (70 h). The reaction was quenched by the addition of H_2O (10 mL), and the organic phase was successively washed with an aqueous 15% NaOH solution (10 mL) and H_2O (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The desired product **27** was isolated by flash chromatography (SiO_2, 50% benzene–ethyl acetate) in 87% yield (0.13 g): R_f 0.70 (50% benzene–ethyl acetate); mp 178–180 °C; IR (KBr) 3190, 1780, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.88–3.25 (m, 3 H), 4.12–4.36 (m, 1 H), 5.12 (s, 1 H), 7.19–7.34 (m, 4 H), 8.75 (br s, 1 H, D_2O exchangeable); ^{13}C NMR ($CDCl_3$) 28.1 (t), 37.5 (t), 59.4 (d), 126.0 (d), 127.2 (d), 128.1 (d), 128.3 (s), 129.3 (d), 133.4 (s), 156.4 (s), 172.0 (s) ppm; MS, m/e (relative intensity) 202 (100), 131 (59), 130 (88); M_r 202.0745 (calcd for $C_{11}H_{10}N_2O_2$, 202.0742).

Preparation of 4,5-(3,4-Dimethoxybenzo)-1,8-diazabicyclo[4.3.0]nonane-7,9-dione (28). A CH_2Cl_2 solution (50 mL) containing 1-(3,4-dimethoxyphenethyl)-5-hydroxyimidazolidine-2,4-dione (**23b**) (0.46 g, 1.6 mmol), trifluoroacetic anhydride (1.6 mmol, 0.25 mL), and trifluoroacetic acid (5 mL) was stirred at room temperature (24 h) and then heated to reflux (5 h). After hydrolysis with H_2O (10 mL), the organic phase was neutralized with aqueous 15% NaOH solution, washed with H_2O (2 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. Pure **28** was obtained in 71% yield (0.30 g) by flash chromatography (SiO_2, 40% benzene–ethyl acetate) of the product residue: R_f 0.40 (50% benzene–ethyl acetate); mp 192–194 °C; IR (KBr) 3200, 1765, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.67–3.16 (m, 3 H), 3.85 (s, 3 H), 3.90 (s, 3 H), 4.17–4.58 (m, 1 H), 5.03 (s, 1 H), 6.61 (s, 1 H), 7.23 (s, 1 H), 9.03 (br s, 1 H, D_2O exchangeable); ^{13}C NMR ($CDCl_3$) 27.5 (t), 37.6 (t), 55.9 (q), 56.1 (q), 59.1 (d), 108.4 (d), 111.7 (d), 120.1 (s), 125.5 (s), 148.3 (s), 148.9 (s), 156.5 (s), 172.4 (s) ppm; MS, m/e (relative intensity) 262 (89), 231 (46), 177 (15), 176 (100), 164 (19).

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.43; H, 5.35; N, 10.57.

Preparation of 5,6-Benzo-1,9-diazabicyclo[5.3.0]decane-8,10-dione (30). A CH_2Cl_2 solution (50 mL) containing 1-(3-phenylpropyl)-5-hydroxyimidazolidine-2,4-dione (**23c**) (0.55 g, 2.3 mmol), trifluoroacetic anhydride (3 mmol, 0.42 mL), and trifluoroacetic acid (4 mL) was heated to reflux (10 days). After workup according to the procedure described for the preparation of **27**, pure **30** was obtained in 39% yield (0.20 g) by flash chromatography (SiO_2, 50% benzene–ethyl acetate): R_f 0.58 (50% benzene–ethyl acetate); mp 177–179 °C; IR (KBr) 3200, 1775, 1725 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.69–1.88 (m, 2 H), 2.69–4.38 (m, 4 H), 5.35 (s, 1 H), 7.25 (m, 4 H), 10.93 (br s, 1 H); ^{13}C NMR (Me_2SO-d_6) 26.2, 32.2, 42.6, 64.3, 126.3, 126.4, 128.2, 130.0, 133.1, 141.2, 156.8, 172.2 ppm; MS, m/e (relative intensity) 216 (50), 145 (43), 144 (30), 129 (30), 117 (100), 105 (22), 91 (20); M_r 216.0894 (calcd for $C_{12}H_{12}N_2O_2$, 216.0899).

Room Temperature Reduction of 4,5-(4,5-Dimethoxybenzo)-1,8-diazabicyclo[4.3.0]nonane-7,9-dione (28). Preparation of 4,5-(4,5-Dimethoxybenzo)-1,8-diazabicyclo[4.3.0]nonan-9-one (32). 4,5-(4,5-Dimethoxybenzo)-1,8-diazabicyclo[4.3.0]nonane-7,9-dione (**28**) (0.30 g, 1 mmol) was dissolved in THF (50 mL) and treated with $LiAlH_4$ (0.11 g, 3 mmol). The mixture was allowed to stir at room temperature (20 h), and then the excess $LiAlH_4$ was destroyed by the successive addition of H_2O (0.15 mL), 15% aqueous NaOH (0.15 mL), and H_2O (0.4 mL).[26] The inorganic precipitate was filtered, and the solution was dried (Na_2SO_4) and then concentrated in vacuo. The desired 4,5-(4,5-dimethoxybenzo)-1,8-diazabicyclo[4.3.0]nonan-9-one (**32**) was separated in 30% yield (80 mg) by flash chromatography (SiO_2, 90% EtOAc–EtOH): R_f 0.50 (90% EtOAc–EtOH); mp 158–161 °C; IR (KBr) 3260, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.56 (dd, 1 H, J = 3, 16 Hz), 2.91–3.03 (m, 1 H), 3.01–3.11 (m, 1 H), 3.38 (dd, 1 H, J = 7, 11 Hz), 3.86 (s, 6 H), 3.90–3.97 (m, 1 H), 4.07–4.15 (m, 1 H), 4.86 (dd, 1 H, J = 7, 9 Hz), 5.04 (br s, 1 H), 6.51 (s, 1 H), 6.60 (s, 1 H); ^{13}C NMR ($CDCl_3$) 27.1, 38.1, 46.4, 54.8, 56.0, 56.2, 108.0, 112.2, 126.0, 128.0, 148.4, 148.6, 161.5 ppm; MS (CI), 249 (P + 1); M_r 248.1168 (calcd for $C_{13}H_{16}N_2O_3$, 248.1161).

Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.41; H, 6.47; N, 10.83.

Acknowledgment. We thank the Robert A. Welch Foundation for their generous support of this research.

Registry No. **6**, 616-03-5; **7**, 6943-97-1; **8**, 92763-90-1; *cis*-**9**, 92763-91-2; *trans*-**9**, 92763-92-3; **10**, 92763-93-4; **11**, 5768-79-6; **12**, 92763-94-5; *cis*-**13**, 92763-95-6; *trans*-**13**, 92763-96-7; **14**, 92763-97-8; **15**, 92763-98-9; **16a**, 81572-18-1; **16b**, 81572-16-9; **16c**, 92764-01-7;

16d, 85369-80-8; 17, 762-72-1; 18a, 92763-99-0; 18b, 92764-00-6; 18c, 92764-02-8; 18d, 92764-03-9; 20, 33542-53-9; 22a, 92764-04-0; 22b, 92764-05-1; 22c, 92764-06-2; 22d, 92764-08-4; 23a, 92764-09-5; 23a (dihydroxy deriv), 92764-19-7; 23b, 92764-11-9; 23c, 92764-13-1; 23d, 92764-15-3; 24a, 2158-04-5; 24b, 25017-47-4; 24c, 25017-27-0; 24d, 92764-07-3; 25, 95-92-1; 26a, 92764-10-8; 26b, 92764-12-0; 26c, 92764-14-2; 26d, 92764-16-4; 27, 54608-40-1; 28, 92764-17-5; 32, 92764-18-6.

Reactions of Monothiobenzil and Its Dimer

Richard C. Hartnedy and Donald C. Dittmer*

Department of Chemistry, Syracuse University, Syracuse, New York 13210

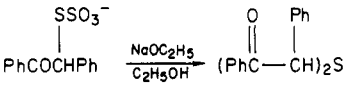
Received July 6, 1984

In contrast to the usual formation of monothiobenzil from desyl thiosulfate in a two-phase system involving aqueous sodium hydroxide and methylene chloride, the dimer, 2,4-dibenzoyl-2,4-diphenyl-1,3-dithietane, is obtained in the absence of methylene chloride; and didesyl sulfide is obtained in ethanolic sodium hydroxide–methylene chloride. Thermolysis of monothiobenzil or monothioanisil gives 1,2,3,4-tetraaryl-2-butene-1,4-diones which may be accompanied by benzil or anisil. Monothiobenzil forms an unstable adduct with cyclopentadiene which can be converted to a stable dibromo derivative; it is converted to benzil by treatment with peracids or nitric acid. Dibenzoylstilbene is obtained by thermolysis of the dimer of monothiobenzil or by treatment of the dimer with triphenylphosphine. Treatment of the dimer with Cleland's reagent (2,3-dihydroxy-1,4-butanedithiol) gives didesyl sulfide, and treatment with cyanide ion gives 2-benzoyl-2,4,5-triphenyl-1,3-oxathiole.

Monothiobenzil was first obtained[1] by photolysis of the *S*-oxide of 2-benzoyl-2,4,5-triphenyl-1,3-oxathiole, which was originally incorrectly identified as the episulfoxide of 2,3-dibenzoyl-2,3-diphenylthiirane largely because the parent sulfide gave dibenzoylstilbene on desulfurization with triphenylphosphine.[2] Norin and co-workers revised this thiirane structure[2,3] to that of an oxathiole.[4a,b] A convenient preparation of monothiobenzil is the elimination of sulfite ion from desyl thiosulfate in aqueous sodium hydroxide–methylene chloride,[5] which is related to early investigations of the elimination of hydrogen cyanide from desyl thiocyanate (1,2-diphenyl-2-thiocyanatoethanone) which gave oxathiole instead of monothiobenzil.[2a] Treatment of desyl thiocyanate with excess sodium hydride in dimethoxyethane gives 2,4,5-triphenyl-2*H*-1,3-oxathiole,[4c] and monothiobenzil is converted to 2-benzoyl-2,4,5-triphenyl-1,3-oxathiole by azibenzil.[6] A dimer of monothiobenzil, 2,4-dibenzoyl-2,4-diphenyl-1,3-dithietane, undergoes photochemical cycloreversion to monothiobenzil.[7] This paper reports some new relationships between monothiobenzil, the dimer, and the oxathiole.

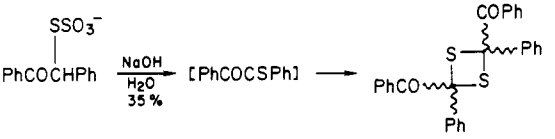
Results and Discussion

Monothiobenzil and Monothioanisil. These two monothio-1,2-diketones are prepared from the appropriate desyl thiosulfate as described previously.[5] The two-phase system of aqueous sodium hydroxide and methylene chloride is essential because if the monothiobenzil is not efficiently removed from the aqueous medium by methylene chloride, other reactions intervene. In ethanolic sodium hydroxide–methylene chloride, didesyl sulfide, **1**, is obtained, possibly by hydrolysis of the thiosulfate to the mercaptan, the latter then displacing a thiosulfate ion from a second molecule of desyl thiosulfate. Alternatively, the mercaptan might be formed by a Meerwein–Ponndorf–Verley reduction of the thiocarbonyl group of monothiobenzil. Although the dimer, **2**, of monothiobenzil is a side



1

product in the preparation of the latter, a better yield of dimer is obtained by treatment of desyl thiosulfate with aqueous sodium hydroxide in the absence of methylene chloride.



2

Thermolysis of monothiobenzil or monothioanisil gives mainly the 1,2-diaroyl-1,2-diarylethylene analogous to other reactions, especially those involving thiones.[8,9] The reaction may proceed via a 1,2-dithietane intermediate of the kind previously proposed to account for alkene formation from thiocarbonyl compounds,[9c,10] or it may proceed via the 1,3-dithietane, **2**. The predominance of cis alkene may be due to secondary orbital or electrostatic interactions which favor a cis configuration in the transition state. If the 1,3-dithietane is the precursor and if it is puckered, the bulkier phenyl groups would prefer the

(1) (a) Dittmer, D. C.; Levy, G. C.; Kuhlmann, G. E. *J. Am. Chem. Soc.* **1967**, *89*, 2793. (b) Dittmer, D. C.; Kuhlmann, G. E.; Levy, G. C. *J. Org. Chem.* **1970**, *35*, 3676. (c) Dittmer, D. C.; Kuhlmann, G. E. *J. Org. Chem.* **1970**, *35*, 4224.

(2) (a) Dittmer, D. C.; Levy, G. C. *J. Org. Chem.* **1965**, *30*, 636. (b) For desulfurization of oxathioles to alkenes by triphenylphosphine, see: Oka, K.; Dobashi, A.; Hara, S. *Tetrahedron Lett.* **1980**, *21*, 3579.

(3) Dittmer, D. C.; Levy, G. C.; Kuhlmann, G. E. *J. Am. Chem. Soc.* **1969**, *91*, 2097.

(4) (a) Jacobsson, U.; Kempe, T. Norin, T. *J. Org. Chem.* **1974**, *39*, 2722. (b) Kempe, U.; Kempe, T.; Norin, T. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1547. (c) Kuhlmann, G. E.; Dittmer, D. C. *J. Org. Chem.* **1969**, *34*, 2006.

(5) (a) Saville, B.; Steer, M. *J. Chem. Soc., Chem. Commun.* **1972**, 616. (b) Bak, C.; Praefeke, K. *Chem. Ber.* **1979**, *112*, 2744.

(6) Bak, C.; Praefeke, K. *Chem. Ztg.* **1978**, *102*, 456; *Chem. Abstr.* **1979**, *90*, 137716.

(7) (a) Bak, C.; Praefeke, K. *Z. Naturforsch, B: Anorg. Chem., Org. Chem.* **1980**, *35B*, 372. (b) deMayo, P.; Weedon, A. C.; Wong, G. S. K. *J. Org. Chem.* **1979**, *44*, 1977.

(8) Ireland, C. J.; Pizey, J. S. *J. Chem. Soc., Chem. Commun.* **1972**, 4.

(9) (a) Behr, A. *Chem. Ber.* **1872**, *5*, 970. (b) Gattermann, L. *Chem. Ber.* **1895**, *28*, 2869. (c) Schonberg, A.; Brosowski, K.-A.; Singer, E. *Chem. Ber.* **1962**, *95*, 2144.

(10) (a) Schmidt, U.; Kabitzke, K. H. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 641. (b) Schmidt, U.; Kabitzke, K. H.; Boie, I.; Osterroht, C. *Chem. Ber.* **1965**, *98*, 3819. (c) Jahn, R.; Schmidt, U. *Chem. Ber.* **1975**, *108*, 630.

0022-3263/84/1949-4752$01.50/0