57% yield; mp 199–202 °C; mass spectrum, $m/e$ 584 ($M^+$) (octamethyl derivative); $^1H$ NMR $\delta$ 4.16 (s, 2, S-$CH_2$), 7.73 (s, 1, $C^7$ H), 7.6 and 8.06 (q, 4, $C_6H_4$), 8.8 (d, 1, CONH); UV $\lambda_{max}$ ($\epsilon_{max}$) (pH 1) 258 (35000), 281 (18000); (pH 7) 256 (31000), 281 (17600); (pH 11) 257 (26500), 289 (18000).

Anal. Calcd for $C_{20}H_{20}N_6O_6S\cdot 1.0H_2O$: C, 48.90; H, 4.52; N, 17.12. Found: C, 48.82; H, 4.76; N, 17.21.

**Acknowledgment.** This study was supported by Research Grant CH-125 from the American Cancer Society and by Training Grant CA09038 from the National Cancer Institute.

**Registry No.** **5**, 74332-03-9; **6**, 74346-17-1; **7**, 74332-04-0; **8**, 36707-45-6; **9**, 74332-05-1; **9** sulfene, 74332-10-8; **9** sulfoxide, 74332-11-9; **10**, 74332-06-2; **11**, 74332-07-3; **12**, 13726-52-8; **13**, 2378-95-2; **15**, 74332-08-4; **16**, 74332-09-5; **17**, 74346-18-2; tetraethyl 4,4-dithiobis(*N*-benzoyl-L-glutamate), 56527-28-7.

# Heterocyclic Ring-Closure Reactions. 6.[1] Preparation and Further Cyclization Reactions of 5-Imino-1,3-diphenyl-4-thioxo-2-imidazolidinone and 5-Imino-1,3-diphenyl-2,4-imidazolidinedithione

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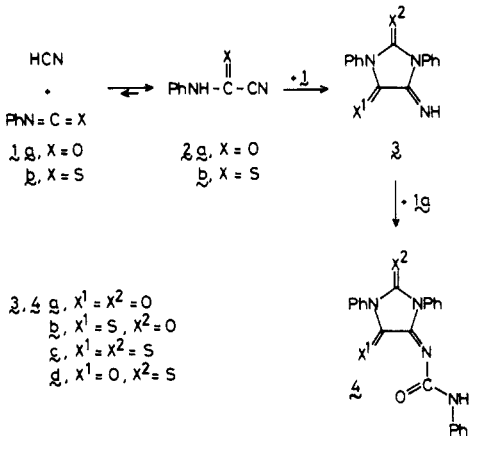
Phenyl isocyanate (**1a**) and phenyl isothiocyanate (**1b**) react with cyanothioformanilide (**2b**) to give the title compounds **3b** and **3c**. With additional **1a**, **3b,c** provide the 5-(*N*-phenylcarbamoyl) derivatives **4b,c**. With hydrochloric acid, **3b,c** afford the 4-oxo compounds **5a,b**, whereas excess hydrochloric acid converts **3c** into the 2,5-thiazolidinedione **6**. With hydrogen sulfide, **3c** gives phenyldithiooxamide (**7**) and **3b** the 4-thiohydantoin **8**. With benzaldehyde, **3b,c** furnish 4,6-dihydro-2,4,6-triphenyl-5*H*-imidazo[4,5-*d*]thiazol-5-one (**9a**) and -5-thione (**9b**). When boiled in phenol at 180 °C, **3b,c** cyclize to 5,7-dihydro-1,3,5,7-tetraphenyldiimidazo[4,5-*b*:4′,5′-*e*]-pyrazine-2,6(1*H*,3*H*)-dione (**10a**) and -dithione (**10b**).

Our interest in the ring-closure reactions of oxalic acid derivatives such as dithiooxamide[1,4] and cyanogen[5] on the one hand and of heterocumulenes[6] on the other led us to investigate the possible cyclization reactions of cyanothioformanilide (**2b**) with phenyl isocyanate (**1a**) and phenyl isothiocyanate (**1b**). The feasibility of such reactions was anticipated from the earlier work of Dieckmann and Kämmerer on the base-catalyzed reactions of **1a** with hydrogen cyanide to give **2a**, 1,3-diphenyl-5-imino-2,4-imidazolidindione (**3a**), and 1,3-diphenyl-5-(*N*-phenylcarbamoyl)-imino-2,4-imidazolidindione (**4a**), the 1:1, 1:2, and 1:3 products of hydrogen cyanide with **1a**[7] (Scheme I).

Scheme I




Of particular interest were the reaction products **3b** and **3c** which possess a thiocarbonyl group at $C_4$ and an imino function at $C_5$ since they might be capable of further cyclization reactions in which these sulfur and/or nitrogen functions could be incorporated into an additional fused ring.

The cyanothioamide **2b** reacts rapidly with **1a**[8] to give **3b** in high yield under a variety of conditions. Not unexpectedly, at elevated temperatures in the absence of a base, the only product is **4b**. With phenyl isothiocyanate (**1b**) and **2b** formation of **3b** proceeds more slowly, and deeply colored side products reduce the yield. It was not

(1) Part V: R. Ketcham, T. Kappe, and E. Ziegler, *J. Heterocycl. Chem.*, **10**, 223 (1973).

(2) On leave from the University of California. Work done at University of Hamburg. Supported in part by grants from the Academic Senate, University of California, and the German Academic Exchange Service.

(3) Inquiries may be directed to either author.

(4) (a) J. R. Johnson and R. Ketcham, *J. Am. Chem. Soc.*, **82**, 2719 (1960); (b) R. Ketcham and S. Mah, *J. Med. Chem.*, **14**, 743 (1971).

(5) S. C. Mutha and R. Ketcham, *J. Org. Chem.*, **34**, 2053 (1969).

(6) E. Schaumann, H. Mrotzek, and F. Assmann, *Liebigs Ann. Chem.*, 334 (1979), and previous papers of the series.

(7) W. Dieckmann and H. Kämmerer, *Ber. Dtsch. Chem. Ges.*, **38**, 2977 (1905); **40**, 3737 (1907).

(8) E. P. Papadopoulos, *J. Org. Chem.*, **44**, 3858 (1979). We had completed our work on compounds **3b**, **4b**, and **5a** when this paper appeared.

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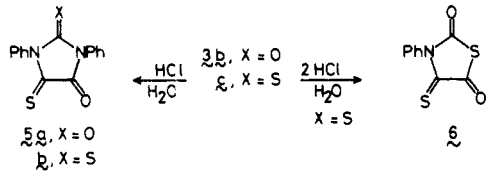
possible to isolate a 2:1 reaction product by using excess **1b** or by reaction of **1b** with **3c**. However, the imino group of **3c** reacts with phenyl isocyanate (**1a**) to give **4c** in high yield. The reaction of **1b** with **2a** gave a mixture of products which included **3a–c** and **2b** but none of the desired product **3d**. This may be explained on the basis of the lower reactivity of both **2a** and **1b** together with the instability of **2a** with respect to HCN and **1a**. Interestingly, **2a** could be prepared in high yield from **2b** by using dimethyl sulfoxide and iodine.[9] The success of this reaction in spite of the low stability of **2a** demonstrates the utility of this method.

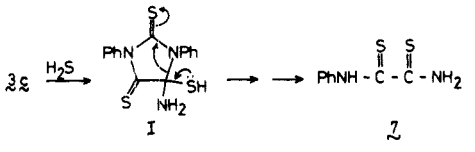
The imino dithione **3c**, like **3a**[7] and **3b**,[8] reacts with hydrochloric acid with conversion of the imino group to a carbonyl group. However, the thioxo group at $C_2$ apparently makes the system more susceptible to ring cleavage. Thus, using the conditions that had been used to convert **3a**[7] and **3b**[8] to their carbonyl analogues, we obtained not **5b** but 3-phenyl-4-thioxo-2,5-thiazolidinedione (**6**). However, with 1 equiv of hydrochloric acid the desired conversion of **3c** to **5b** was achieved.




**5a**, X = O
**b**, X = S

**6**

The reactions of **3b** and **3c** with hydrogen sulfide in the presence of triethylamine were studied in the hope of obtaining the 4,5-dithiones. However, **3c** reacts with hydrogen sulfide in the presence of triethylamine to give phenyldithiooxamide (**7**) in low yield, another example of

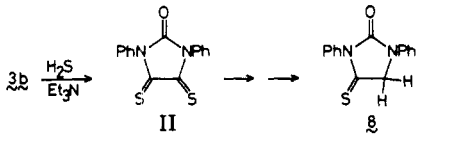



I

**7**

ring cleavage apparently facilitated by the thiocarbonyl group at $C_2$. The imino nitrogen of **3c** is not lost but has become the unsubstituted amide nitrogen in **7**. These observations can best be explained by recognizing the thioamide group in the tetrahedral intermediate I as a better leaving group than the oxygen analogues from **3a** and **3b**.

**3b** reacts rapidly with an excess of hydrogen sulfide at room temperature to give the hydantoin derivative **8** which, surprisingly, has not yet been described. These observations suggest that in this case the dithione II is formed but that it reacts futher to produce **8**.[10]

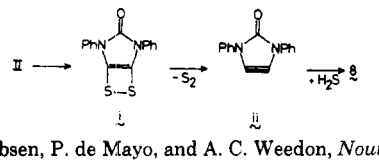



II

**8**

(9) M. Mikolajczyk and J. Luczak, *Synthesis*, 114 (1975).

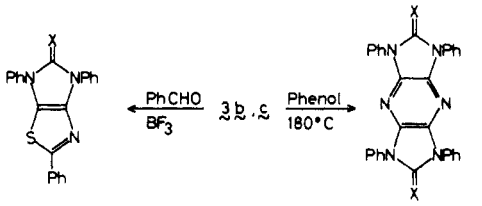
(10) It is tempting to speculate on the mechanism of this reduction. The work of de Mayo[11] on 1,2-dithiones suggests a path involving ring closure of II to a dithiete (i) followed by loss of $S_2$ to produce a benzyne-type intermediate (ii) which then adds $H_2S$ to give **8**. Further studies on this and other reactions of **3b** and **3c** with $H_2S$ are planned.




i ii

(11) N. Jacobsen, P. de Mayo, and A. C. Weedon, *Nouv. J. Chim.*, 2, 331 (1978).

Potentiometric studies[12] indicated that **3b** and **3c** are reducible with half-wave potentials of −1.15 and −1.35 V, respectively. In both cases the reaction involved a one-electron transfer and was irreversible as shown by cyclic voltametry. This suggests that the 4,5-thioxoimino system behaves qualitatively like an *o*-quinone and as such might be capable of reductive cyclization reactions. In fact, the $BF_3$-catalyzed redox cyclizations of **3b** and **3c** with benzaldehyde provided the imidazolinothiazoles **9a** and **9b** in modest yields.




**3b**, **c**

**9a**, X = O
**b**, X = S

**10a**, X = O
**b**, X = S

When heated, preferably in the presence of phenol, **3b** and **3c** undergo a thermal condensation with loss of the elements of $H_2S_2$ to give the remarkably stable, high-melting triheterocyclic system **10**.

## Experimental Section[13]

**Cyanothioformanilide (2b)** was prepared according to the method of Reissert and Brüggemann.[14]

**Cyanoformanilide (2a). 2b** (1.62 g) was heated at 80 °C for 4 h in 4 mL of $Me_2SO$ with 40 mg of iodine.[9] The reaction mixture was diluted with water, treated with sodium thiosulfate, and extracted with ether. The ether extract was dried, the solvent removed, and the residue crystallized from benzene: yield 1.25 g (86%); mp 132–136 °C. In later experiments we used the more convenient procedure of Papadopoulos.[8]

**5-Imino-1,3-diphenyl-4-thioxo-2-imidazolidinone (3b).** To a solution of 3.24 g (20 mmol) of **2b** and 2 mL of triethylamine in 10 mL of THF was added slowly 2.2 mL (22 mmol) of **1a**. The reaction mixture became warm, and the conversion appeared to be complete almost immediately. The solvent and the amine were removed under reduced pressure, and the product was crystallized from $CHCl_3$–EtOH to give 4.0 g (70%) of orange product, mp 122–123 °C (lit.[8] mp 122–122.5 °C).

**5-Imino-1,3-diphenyl-2,4-imidazolidinedithione (3c).** To a solution of 3.24 g (20 mmol) of **2b** and 2.4 mL (22 mmol) of **1b** in 25 mL of 95% EtOH was added 0.65 mL of triethylamine. After the mixture was allowed to stand at 5 °C for 2 h, 2 mL of water was added, and the mixture was seeded with **3c** and allowed to stand overnight at 5 °C. The yellow crystals were collected, washed with 75% EtOH, and crystallized from $CHCl_3$–petroleum ether: yield 3.30 g (56%); mp 119–122 °C. The analytical sample melted at 123–124 °C: IR 3195, 1662, 1590 and 1488 $cm^{-1}$. Anal. Calcd for $C_{15}H_{11}N_3S_2$: C, 60.58; H, 3.73; N, 14.13; S, 21.56. Found: C, 60.67; H, 3.71; N, 14.17; S, 21.38.

**1,3-Diphenyl-5-[(*N*-phenylcarbamoyl)imino]-4-thioxo-2-imidazolidinone (4b).** Equilvalent amounts of **1a** and **3b** were heated under reflux in toluene to afford an almost quantitative yield of **4b**, mp 222–224 °C (lit.[8] mp 217.5–218.5 °C).

The same product was obtained by heating **2b** with **1a** in toluene at 110 °C.

**1,3-Diphenyl-5-(*N*-phenylcarbamoyl)imino-2,4-imidazolidinedithione (4c).** Equivalent amounts of **1a** and **3c** were heated under reflux in toluene for 3 h. The yellow product which started to crystallize after 1 h was filtered and washed with

(12) J. Voss and G. Wiegand, private communication.

(13) Reactants and products were weighed to the nearest 10 mg. Melting points were taken on a hot stage, except for **10b**, and are uncorrected. IR spectra were determined on a Perkin-Elmer 297 spectrometer in KBr. The mass spectra were measured on a Varian MAT CH 7 spectrometer. The $^1H$ NMR spectrum was taken on a Varian T-60 in $CDCl_3$ and the $^{13}C$ NMR spectrum on a Bruker WP-60 spectrometer.

(14) A. Reissert and K. Brüggemann, *Ber. Dtsch. Chem. Ges.*, **57**, 981 (1924).

EtOH to give an almost quantitative yield: mp 255–260 °C dec; IR 3290, 1650, 1595, 1530 $cm^{-1}$. Anal. Calcd for $C_{22}H_{16}N_4OS_2$: C, 63.44; H, 3.87; N, 13.45; S, 15.40. Found: C, 63.64; H, 3.81; N, 13.39; S, 15.33.

**1,3-Diphenyl-5-thioxo-2,4-imidazolidinedione (5a).** Treatment of **3b** in hot ethanol with an excess of concentrated HCl and dilution with water afforded **5a**: 70% yield; mp 159–162 °C (lit.[8] mp 156–158 °C).

This product can also be obtained from **4b** by the same procedure.

**1,3-Diphenyl-2,5-dithioxo-4-imidazolidinone (5b).** To a hot solution of 300 mg (1 mmol) of **3c** in 6 mL of 95% EtOH and 1 mL of $H_2O$ was added 0.1 mL of 10 N HCl. The mixture was diluted with 10 mL of $H_2O$ to give 250 mg of product (83%); mp 133–137 °C, resolidified and melted at 152–155 °C. Recrystallization from $CHCl_3$–petroleum ether provides 200 mg of product: mp 154–157 °C; IR 1731 $cm^{-1}$. Anal. Calcd for $C_{15}H_{10}N_2OS_2$: C, 60.38; H, 3.38; N, 9.39; S, 21.49. Found: C, 60.19; H, 3.21; N, 9.32; S, 21.25.

**3-Phenyl-4-thioxo-2,5-thiazolidinedione (6).** To a hot solution of 220 mg of **3c** in 5 mL of 95% EtOH was added 1 mL of 10 N HCl. A transient red color was observed. The reaction mixture was diluted with water, and the crystals were collected: yield 120 mg (72%); mp 180–183 °C. This was crystallized from $CHCl_3$–petroleum ether: mp 184–186 °C; IR 1750, 1725, 1590, 1490 $cm^{-1}$; $^{13}C$ NMR [$(CD_3)_2CO$] $\delta$ 129.2–135.3 (aromatic C), 157.1 (C-2), 183.4 (C-5), 192.8 (C-4). Anal. Calcd for $C_9H_5NO_2S_2$: C, 48.42; H, 2.26; N, 6.27; S, 28.72. Found: C, 48.14; H, 1.98; N, 6.24; S, 28.68.

**Phenyldithiooxamide (7) from 3c.** Through a suspension of 150 mg of **3c** in 5 mL of EtOH containing 0.07 mL of triethylamine was passed a stream of $H_2S$. The reaction mixture became clear and darkened slightly. Dilution with an equal volume of water gave a mixture of substances which contained mostly sulfur. Further dilution with water gave a small amount of orange needles (mp 84–86 °C), which after crystallization melted at 98–99 °C and were identical in all respects with **7** prepared from **2b** and $H_2S$ in the presence of triethylamine (lit.[14] mp 98 °C).

**1,3-Diphenyl-4-thiohydantoin (8).** Through a suspension of 560 mg (2 mmol) of **3b** in 30 mL of absolute EtOH and 0.2 mL of triethylamine was passed a stream of $H_2S$ until the system became clear. Soon thereafter a precipitate began to form. The precipitate was collected after a few minutes and washed with EtOH. The almost colorless crystals weighed 490 mg and melted at 155–175 °C. Sulfur was detected by TLC and was obtained in crystalline form from the mother liquor. Recrystallization of the product from chloroform–petroleum ether gave fine needles: mp 195–197 °C; IR 1755, 1600, 1500 $cm^{-1}$; $^1H$ NMR $\delta$ 7.0–7.7 (m, 10 H, arom), 4.75 (s, 2 H, $CH_2$). Anal. Calcd for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44; S, 11.95; mol wt 268.34. Found: C, 67.07; H, 4.50; N, 10.38; S, 12.22; mol wt 268, 271 (osmometric, $CHCl_3$).

**4,6-Dihydro-2,4,6-triphenyl-5*H*-imidazo[4,5-*d*]thiazol-5-one (9a).** To 280 mg (1 mmol) of **3b** and 110 mg (1 mmol) of benzaldehyde in 2 mL of dioxane was added 6 drops of $BF_3$·$Me_2O$. The reaction mixture warmed slightly, and the reddish precipitate of the $BF_3$ salt of **3b** formed rapidly. The mixture was heated under reflux for 8 h. A small amount of white, water-soluble crystals separated during this time. The reaction mixture was diluted with EtOH and filtered after being allowed to stand 1 h to give the product: 140 mg (38%); mp 154–158 °C. Recrystallization from $CHCl_3$–petroleum ether gave pale yellow crystals: mp 157–161 °C; IR 1715, 1598, and 1500 $cm^{-1}$; mass spectrum, $m/e$ (relative intensity) 369 (97, $M^+$), 340 (51), 121 (100). Anal. Calcd for $C_{22}H_{15}N_3SO$: C, 71.52; H, 4.09; N, 11.37; S, 8.68. Found: C, 71.69; H, 3.92; N, 11.28; S, 8.75.

When **3b** was heated at 180 °C with benzaldehyde, **10a** was formed.

**4,6-Dihydro-2,4,6-triphenyl-5*H*-imidazo[4,5-*d*]thiazole-5-thione (9b).** When 300 mg (1 mmol) of **3c** was reacted with a twofold excess of benzaldehyde in the same way as described above, there was obtained 200 mg (61%) of **9b** (mp 262–265 °C), which after recrystallization melted at 261–263 °C: IR 1595, 1496 $cm^{-1}$; mass spectrum, $m/e$ (relative intensity) 385 (97, $M^+$), 103 (100). Anal. Calcd for $C_{22}H_{15}N_3S_2$: C, 68.54; H, 3.92; N, 10.90; S, 16.63. Found: C, 68.47; H, 3.85; N, 10.92; S, 16.77.

The same product can be obtained in about 35% yield by heating **3c** with benzaldehyde at 180 °C for a few minutes.

**5,7-Dihydro-1,3,5,7-tetraphenyldimidazo[4,5-*b*:4′,5′-*e*]pyrazine-2,6(1*H*,3*H*)-dione (10a).** A mixture of 600 mg (2 mmol) of **3b** and 2 g of phenol was heated for 45 min in an oil bath at 180 °C. The reaction mixture was diluted with ethanol, and after the mixture cooled the crystals were collected: yield 160 mg (23%); mp 350–355 °C. Recrystallization from DMF gave pale yellow crystals: mp 353–355 °C; IR 1705, 1603, 1502 $cm^{-1}$; mass spectrum, $m/e$ (relative intensity) 496 (100, $M^+$), 248 (19, $M^{2+}$ or $M/2^+$). Anal. Calcd for $C_{30}H_{20}N_6O_2$: C, 72.57; H, 4.06; N, 16.93. Found: C, 71.92, H, 4.09; N, 16.93.

The same product was obtained by heating **3b** at 170 °C for 0.5 h.

**5,7-Dihydro-1,3,5,7-tetraphenyldiimidazo[4,5-*b*:4′,5′-*e*]pyrazine-2,6(1*H*,3*H*)-dithione (10b).** When **3c** was heated in phenol at 180 °C as described above, a product melting above 365 °C was obtained in 11% yield. Recrystallization from DMF gave yellow crystals which decomposed around 440 °C: IR 1595, 1498, 1422 $cm^{-1}$; mass spectrum, $m/e$ (relative intensity) 528 (100, ($M^+$), 264 (26, $M^{2+}$ or $M/2^+$). Anal. Calcd for $C_{30}H_{20}N_6S_2$: C, 68.16; H, 3.81; N, 15.90; S, 12.13. Found: C, 68.46; H, 3.79; N, 16.01; S, 12.16.

**Registry No. 1a**, 103-71-9; **1b**, 103-72-0; **2a**, 6784-22-1; **2b**, 4955-82-2; **3b**, 71342-25-1; **3c**, 74331-41-2; **4b**, 71342-37-5; **4c**, 74346-13-7; **5a**, 71342-31-9; **5b**, 74331-42-3; **6**, 74331-43-4; **7**, 17270-94-9; **8**, 74331-44-5; **9a**, 74331-45-6; **9b**, 74331-46-7; **10a**, 74331-47-8; **10b**, 74331-48-9; benzaldehyde, 100-52-7.

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# New Synthesis of 1,2,4-Thiadiazoles

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A new synthesis of 1,2,4-thiadiazoles has been developed. *N*′-(Thioaroyl)- (and *N*′-arylthiocarbamoyl-) *N*,*N*-dimethylamidines, which were prepared in excellent yields by reactions of thioamides (and thioureas) with *N*,*N*-dimethylalkanamide dimethyl acetals, reacted with *O*-(mesitylenesulfonyl)hydroxylamine in dichloromethane or hydroxylamine-*O*-sulfonic acid in a mixture of absolute ethanol and methanol to give 1,2,4-thiadiazoles in excellent yields.

Recently, we reported a general method[2] for the synthesis of 1,2,4-triazoles **3** and 1,2,4-oxadiazoles **4** in which the (dimethylamino)alkylidene moiety was utilized as a masked acyl function.[2-5] This method involved the re-

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