Gas-Solid Reactions: Photochemical Oxidation of Thioketones in the Crystalline State†

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Photochemical oxidation of 11 diaryl thioketones (1–11) was conducted in the solid state. Quite interestingly, of these only six were oxidized to the corresponding carbonyl compound whereas the rest were photostable. However, in solution all were readily oxidized. The difference in behavior between the thioketones in the solid state has been rationalized on the basis of molecular arrangement in the crystal. X-ray crystal structure analyses of four thioketones were carried out in this connection.

Reactions of organic compounds are more selective when performed in the solid state rather than in solution. Results presented here on the solid-state photooxidation of thioketones lend credence to this widely held belief. One of the factors that contributes toward the poor stability of thioketones is their ready oxidizability by the atmospheric oxygen in the presence of light.[1] It has been reported from our laboratory that thioketones in general are readily oxidized in solution to the corresponding *S*-oxides and/or ketones upon exposure to visible light.[2] A number of examples are known in which a substance vulnerable to attack by oxygen in solution or in the melt is indefinitely stable as the crystalline solid. Therefore, it was of interest to investigate the photooxidizability of thioketones in the solid state. In this connection photooxidation of diaryl thioketones 1–11 in the solid state was conducted and the results are presented here.

Results

Thioketones 1–11 investigated are listed in Figure 1. Finely pulverized crystals of 2–11 were exposed to UV radiation in aerated atmosphere in Pyrex petri dishes. Several of these thioketones readily changed their color and were converted quantitatively to the corresponding ketones; no other products were identified. Surprisingly, some of these thioketones were found to be stable to UV radiation under these conditions. Results are summarized in Table I. Solid-state photooxidation of thiobenzophenone (1) has been conducted as early as 1896 by Gatterman and Schulze and is reported to give benzophenone and a cyclic trisulfide.[3] In none of these cases investigated here did we isolate any cyclic trisulfides. As found in solution oxidation, sulfur dioxide is identified as the gaseous product during the solid-state photooxidation of 2–4, 7, and 8. Photochemical behavior of thioketones 1–11 in the solid state is truly interesting when compared to that in solution. Benzene solutions of thioketones 1–11 were readily (≤3 h) photooxidized to the corresponding ketones. In fact, 4,4′-dimethoxythiobenzophenone (5) is the most reactive of all, requiring only 30 min of irradiation, in solution.[4] Therefore, it was indeed surprising to observe this to be stable in the crystalline state. This indicated that the electronic properties of the thioketones are not controlling their reactivity in the solid state. It is known in other systems that reactivity in the solid state is much dependent on the molecular packing in the crystal lattice rather than on the inherent electronic properties of the molecule.

In order to understand the reactivity difference between these thioketones based on their molecular packing, a systematic crystallographic investigation of a few of these thioketones was undertaken. Single-crystal X-ray analyses of thioketones 3, 5, 6, and 7 (Figure 1) were carried out as representative examples of reactive and unreactive thioketones. The X-ray structure of thiobenzophenone (1) is already reported in the literature[5] and the results are utilized to understand its chemical reactivity in the solid state. Space groups and cell constants of these five thioketones are included in Table I.[6] The molecular crystal packing along the channel axis for the above five thioketones are shown in Figures 2 and 3.

Discussion

A comparison of the molecular packing of the above five thioketones is quite revealing in rationalizing their photoreactivity in the solid state. Of the five thioketones under consideration, three are photooxidizable (1, 3, and 7) and two are inert (5 and 6). It may be observed from Figure 2 that in reactive thioketones there is a channel along the shortest crystallographic axis with the thiocarbonyl chromophore directed along the channel. Further, thiocarbonyl S···S intermolecular distances between adjacent planes in all these cases are ≤3.9 Å. On the other hand, in the case of stable thioketones 5 and 6, the packing arrangement does not reveal any such channel passing through any of the crystallographic axis (Figure 3). Further, the thiocarbonyl S···S contact distance between the adjacent layers are 4.83 and 6.05 Å for 5 and 6, respectively, much larger than in reactive thioketones. It may be hypothesized that the channel is essential for oxygen to diffuse into the crystal and to effect oxidation. If this be the case, a knowledge of the channel cross sectional area is essential. The cross sectional areas of the channels calculated according to the method outlined in the experimental section for these thioketones are recorded in Table I. As typical examples, projections of the crystal packing on a plane perpendicular to the channel axis for 6 and 7 are shown in Figure 4. For the unreactive thioketones 5 and 6 either there is no channel (5) or the channel is too small (≃2.3 Å for 6). For the reactive thioketones (1, 3, and 7) the channel cross sectional area

† Respectfully dedicated to Professor J. D. Dunitz on the occasion of his 60th birthday.

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Table I. Photooxidation of Diaryl Thioketones 1-11 in the Solid State and Crystal Properties of a Few Selected Thioketones

crystal studied	mp, °C	duration of irradiation	nature of rxn: in soln[b]	nature of rxn: in solid state[b]	crystal data	channel axis	cross section of the channel, Å²
1[c]	53	1 day	yes	yes	$P2_1/n$, a = 14.042 Å, b = 5.863 Å, c = 13.402 Å, β = 106.4°, z = 4	b	9
2	75	7 days	yes	yes			
3	120	15 days	yes	yes	Pbca, a = 7.443 Å, b = 32.691 Å, c = 11.828 Å, z = 8	a	3.7
4		12 days	yes	yes			
5	117	30 days	yes	no	$P\bar{1}$, a = 9.810 Å, b = 9.635 Å, c = 15.015 Å, α = 7.11, β = 102.30, γ = 107.76°, z = 4		
6	201	30 days	yes	no	$P2_1/c$, a = 17.029 Å, b = 6.706 Å, c = 14.629 Å, β = 113.5°, z = 4	b	2.3
7	110	17 days	yes	yes	$P2_12_12_1$, a = 5.873 Å, b = 13.677 Å, c = 15.668 Å, z = 4	a	8.3
8	184	20 days	yes	yes			
9	258	30 days	yes	no			
10	142	30 days	yes	no			
11	141	30 days	yes	no			

[a] Crystals were irradiated at room temperature using a 450-W medium-pressure mercury lamp. [b] Product of oxidation was the corresponding ketone. [c] X-ray data taken from Rindorf, G.; Carlsen, L. *Acta Crystallogr. Sect. B* **1979**, *35*, 1179.

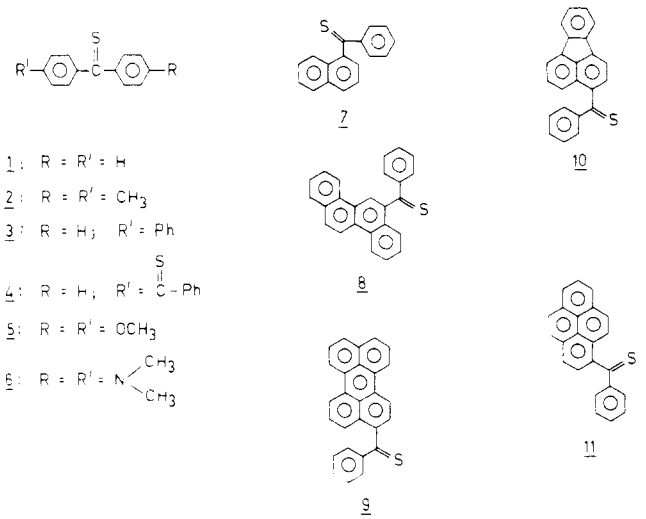

Figure 1. Thioketones investigated in the solid state.

is fairly large. It is noteworthy that for **3**, the cross sectional area is considerably smaller than for **1** and **7**. This may be attributed to the significant difference in the packing mode close to the region of the reactive thiocarbonyl group, whereas the adjacent thiocarbonyl chromophores are one above the other in **3**; these groups are displaced from one another in **1** and **7** (Figure 2). From the nature of the packing modes it is to be anticipated that the reaction is initiated on the (010) face in the case of compound **1** whereas in the other two cases, **3** and **7**, the initiation is on the (100) face. However, no attempt was made to identify crystal faces from optical goniometry and to investigate the anisotropic nature of the reaction rates in different directions of the crystal.

There remains the question of the mechanism of the oxidation of thioketones in the solid state. It is established that both light and oxygen are essential for this process. In solution, oxidation is believed to occur through the interaction of singlet oxygen with thioketones, the former being generated by the energy transfer process from excited thioketone.[2] However, direct oxidation involving the excited thioketone and triplet oxygen has been observed in di-*tert*-butyl thioketone.[7] Therefore, in the solid state oxidation might involve either a singlet or a triplet oxygen. In any case, the primary step requires an interaction between an excited thioketone and a ground-state oxygen. Therefore, for the oxidation to be efficient oxygen should be able to diffuse into the successive layers of thioketones. As discussed above, absence of a channel in **5** and **6** might then be responsible for their photostability. On the other hand, presence of a channel in **1**, **3** and **7** makes them susceptible for oxidation.

A simple mechanism that could be visualized for this oxidation involves attack of oxygen at the exposed excited thiocarbonyl chromophore at the crystal surface to form a monolayer of the carbonyl compound. As the carbonyl compound is formed, disorientation of the reacted layer may occur so as to allow the oxygen to diffuse into the next layer where the process is repeated. However, the presence of thiocarbonyl chromophore at the crystal surface is not the sole condition for the oxidation to occur. It is also necessary that the thiocarbonyl groups be so arranged that oxidation of one molecule exposes another close neighbor to an oxygen molecule. This is evident from the difference in reactivity between the five thioketones being considered. Although, in all the five cases, the presence of a thiocarbonyl chromophore at the crystal surface could be identified; the above required arrangement of reactive chromophores is present only in reactive thioketones.

The general mechanism outlined here for the oxidation of thioketones correlates well with the various gas–solid reactions reported in the literatures. Reaction of ammonia gas with crystalline benzoic acids and benzoic anhydrides studied extensively by Paul, Curtin, and co-workers has been established to require a similar type of arrangement of reactive centers.[8] Most recently, photooxidation of 21-cortisol *tert*-butylacetate has been rationalized on the basis of molecular packing in the crystal lattice.[9] Quite

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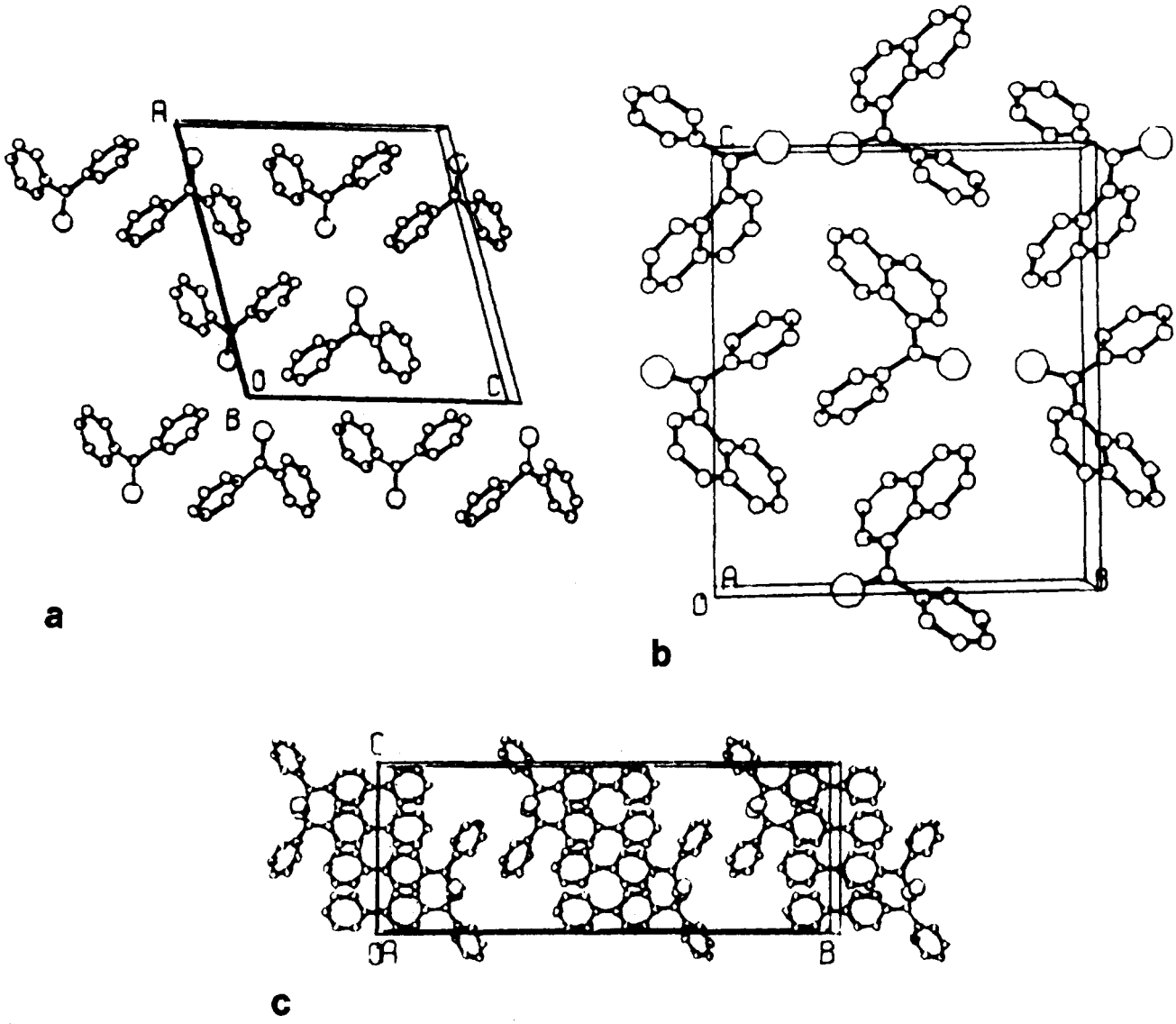

Figure 2. The molecular crystal packing of reactive thioketones (1, 3, and 7). (a) 1, view along b axis. (b) 7, view along a axis. (b) 3, view along a axis.

interestingly, a channel of the cross sectional area $\simeq 3.5$ Å^2 through which oxygen diffuses into the crystal has been identified in this system. Differences in reactivity of oxygen toward radicals produced in a number of crystalline amides has once again been rationalized on the basis of the ability to diffuse into the site of reaction which is controlled by crystal structure.[10] Interestingly, although tetramethylrubrene is readily photooxidized in the crystalline state, the parent rubrene is photostable.[11] This difference in reactivity has been attributed to the possible differences in permeability of the two crystals to oxygen. Oxidation of *trans*-stilbene and diethylstilbesterol by ozone in the crystalline state has been understood in terms of molecular packing and defects in the crystal lattice.[12] Thus the present study as well as the earlier reports support the notion that the permeability of the crystals toward the reacting gas is essential for efficient gas–solid reaction.

In conclusion, the reactivity difference between the various thioketones in the solid state has been understood on the basis of molecular arrangement in the crystal lattice. Details of solid-state photooxidation, namely, the pathway to the corresponding ketones after the initial interaction of oxygen with excited thioketone, awaits further investigation.

Experimental Section

Preparation of Thioketones. Thioketones 1–11 were prepared from the corresponding ketones by standard procedures.[13] The general procedure involved simultaneous bubbling of dry hydrogen chloride and hydrogen sulfide gases through an alcoholic solution of ketone (500 mg/20 mL) at −5 °C for 24 h. The dark blue or green solution was concentrated and the crystals were filtered out and recrystallized at least thrice from benzene, toluene, or methanol. Spectral data of thus obtained thioketones were identical with literature reports.

Difficulties were encountered in obtaining pure thioketones in the case of 1 and 2. Normal purification in aerated atmosphere resulted in the formation of the corresponding ketones. Therefore, recrystallization and isolation of products were conducted in a nitrogen atmosphere. Even under these conditions thioketones 1 and 2 obtained were found to contain at least 10% ketones and

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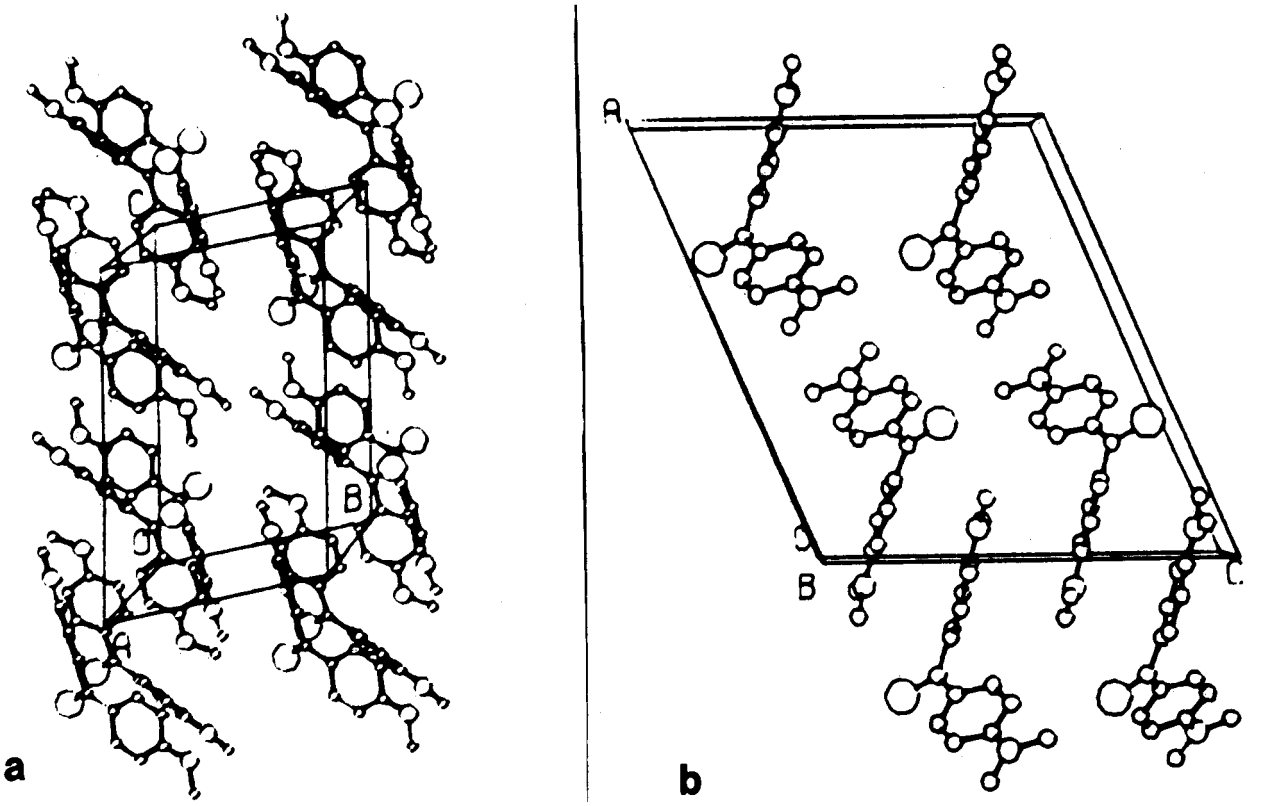

Figure 3. The molecular crystal packing of unreactive thioketones (5 and 6). (a) 5, view along a axis. (b) 6, view along b axis.

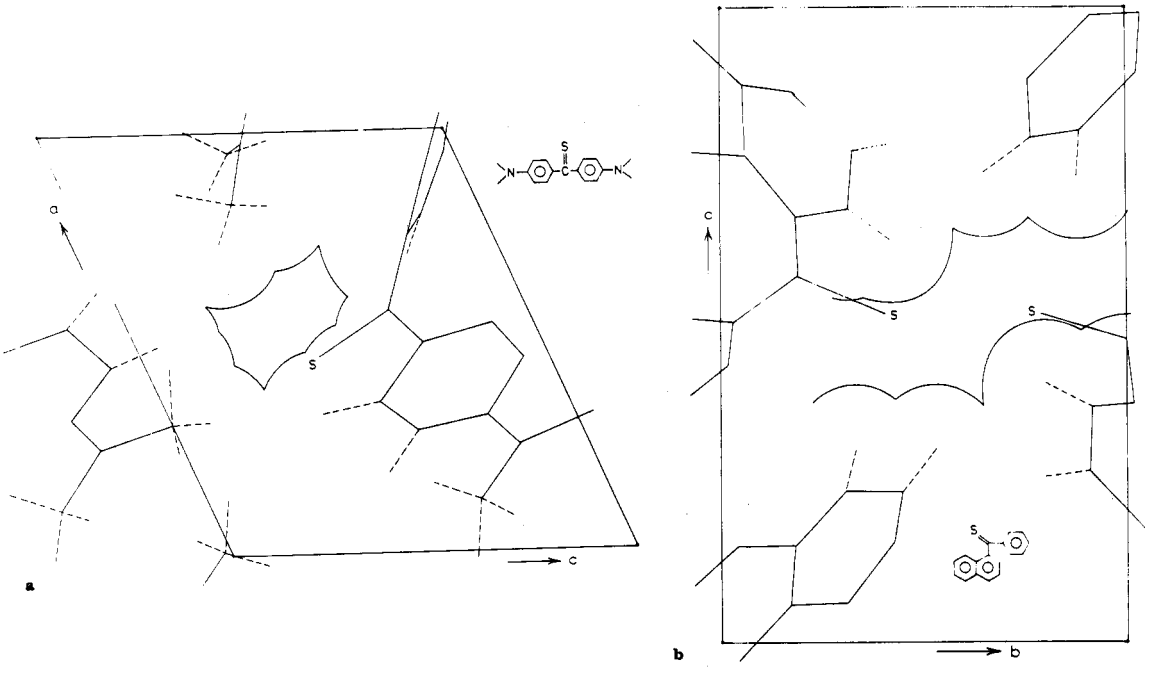

Figure 4. Projection of the crystal packing on a plane perpendicular to the channel axis. (a) Michler's thioketone (6). (b) 1-Phenylnaphtyl thioketone (7).

were used as such for photooxidation studies.

Photooxidation of Thioketones. Finely pulverized crystals of 1–11 were spread over a Pyrex petri dish and covered with a Pyrex watch glass. These were irradiated using a 450-W medium-pressure mercury lamp from a distance of approximately 2 ft. The temperature of the irradiation vessels did not rise above 30 °C and none of the thioketones investigated vaporized at this temperature. Progress of the irradiation was monitored by micro TLC and after complete decolorization products were isolated by preparative TLC. Of the eleven thioketones investigated only five underwent ready oxidation to the corresponding ketones (Table I) and the rest remained unchanged even after one month of irradiation. Thioketones 2–4 and 7 gave the corresponding ketone as the sole product in quantitative yield. Formation of ketones were confirmed by comparison with authentic samples. Thioketones 5, 6 and 8–11 did not show any reaction and thioketones were quantitatively recovered after one month of exposure to UV radiation.

Reactive thioketones 1–4 and 7 were found to be indefinitely stable in crystalline form under sealed conditions. Only 1 and 2 were found to decay when left in an aerated atmosphere in the dark whereas the rest remained unchanged in the dark under aerated conditions. Thus the need for light and oxygen was established.

X-ray Crystallographic Analysis of Thioketones 3, 5, 6, and 7. X-ray structural investigations of four thioketones (3, 5,

6, and 7) were carried out in our laboratory whereas that for 1 has already been reported. Good single crystals of thioketones were obtained upon recrystallizing the crude reaction products from suitable solvents. Full details of the X-ray crystal analyses of these compounds are published separately[6] and only the essential information needed for our discussion is provided here.

Reactive thioketones 3 and 7 were taken inside a Lindeman capillary and 5 and 6 were used as such for intensity data collection. Intensity data were collected on an Enraf-Nonius CAD-4 diffractometer using either a monochromated Cu K_α radiation (for 3, 5, and 7) or a monochromated Mo K_α radiation (for 6) in $\omega/2\theta$ scan mode. Two standard reflections were measured for every sixty reflections and no significant changes in the intensities of these reflections were observed.

All the structures were solved via the direct method program (MULTAN-80).[14] For thioketone 7, the first E map gave only the naphthalene ring and after Karle recycling all non-hydrogen atoms were identified. In the case of the other three thioketones, the first E map itself revealed the positions of all the non-hydrogen atoms. Hydrogen atoms were fixed from geometrical considerations and verified from difference map. Space group and cell constants of the four thioketones as well as those of 1 taken from the literature are provided in Table I.

Channel Cross Section Area.[15] For each thioketone (1, 3, 5, 6, and 7), the packing of the molecules viewing down the shortest crystal axis was drawn. It may be mentioned that the channel direction in all the cases was also the shortest crystal axis. The channel boundaries were delimitated by drawing circles centered on the atom positions with their corresponding van der Waal's radii. Since the sulfur atom is involved in the reaction, no circles were drawn around the thiocarbonyl sulfur atom. The cross sectional area is determined by integration. In the case of 4,4′-dimethoxythiobenzophenone (5) no channel was evident. The measured channel cross sectional areas for the other four thioketones are tabulated in Table I.

Powder Diffraction. X-ray powder photographs were taken only in the case of reactive thioketones 3 and 7. Thiobenzophenone 1 was too reactive to carry out any measurements. X-ray powder diffraction patterns were recorded using a Phillips powder diffractometer employing monochromated Cu K_α radiation. Powder patterns taken before irradiation and after complete oxidation of the samples were different and it could be concluded that the product ketone is formed as an aggregate of microcrystals.

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Registry No. 1, 1450-31-3; 2, 1141-08-8; 3, 1450-32-4; 4, 17435-08-4; 5, 958-80-5; 6, 1226-46-6; 7, 33083-79-3; 8, 40812-80-4; 9, 40812-81-5; 10, 58508-75-1; 11, 40812-79-1.

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Total Synthesis of Two Furanomycin Stereoisomers

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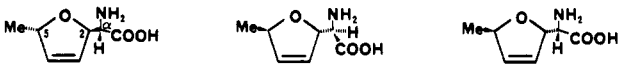
D-Glucosamine hydrochloride (3), an inexpensive, commercially available reagent, has been transformed stereoselectively into two new stereoisomers of furanomycin, (αR,2S,5R)-furanomycin (**2a**) and its isomer with the opposite configuration at the amino acid functionality, (αS,2S,5R)-furanomycin (**2b**).

The antibiotic (+)-furanomycin or (+)-α-amino-2,5-dihydro-5-methylfuran-2-acetic acid (1) was isolated from

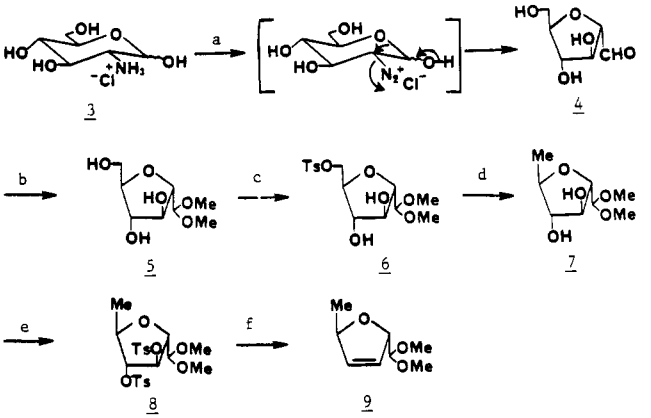


1 2a 2b

a culture filtrate of *Streptomyces* L-803 (ATCC 15795) by Katagiri and co-workers.[1] Compound 1 shows considerable activity against a number of Gram-negative bacteria and other microorganisms such as T_2, T_3 phage, and its activity is antagonized by L-isoleucine. The total synthesis of 1 from α-D-glucose showed its molecular configuration to be αS,2R,5S.[2] This assignment was confirmed by the X-ray crystal structure analysis of its *N*-acetyl derivative.[3]

The first total synthesis of (±)-furanomycin was reported by Masamune and Ono.[4] The four stereoisomeric cis forms of 1 were synthesized by us[5] and by Parker and Robins,[6] and two of the trans forms, including 1, were also prepared in our laboratory.[5] We now wish to report the total synthesis of the other two trans forms. As a continuation of our studies using carbohydrates as "chiral templates", we have developed a stereocontrolled synthesis

Scheme I[a]



[a] a, N_2O_3 (g), H_2O; b, CH_3OH, $(CH_3O)_3CH$; c, *p*-TsCl, pyridine–chloroform (2:1); d, $LiAlH_4$, THF, Δ; e, *p*-TsCl, pyridine; f, NaI, Zn, DMF, Δ.

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