Crystals recovered from the distillation head, m.p. (sealed tube) 129–143°, were analyzed by dissolving in 50% v./v. aqueous ethanol and titrating with 0.1*N* sodium hydroxide to the phenolphthalein end point, to determine the thiophenyl content. Mannitol was added and the boron content estimated by again titrating with sodium hydroxide to the phenolphthalein end point.

*Anal.* Calcd. for $C_{18}H_{15}BS_3$: B, 3.20; $C_6H_5S$, 96.8. Found: B, 3.09; $C_6H_5S$, 96.2.

The infrared absorption spectrum, determined with 10% w./v. solutions in carbon tetrachloride and carbon disulfide, exhibited peaks at the following wave numbers (cm.$^{-1}$): 685vs, 697vs, 740vs, 897vs, 916vs, 947s (broad), 1001w, 1024m, 1066m, 1093w, 1443s, 1452s, 1484s, 1587s, 3030m.

CONTRIBUTION NO. 20
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## Intramolecular Hydrogen Bonding to Sulfur

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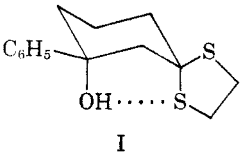
Although sulfur has not been well recognized as a base participating in hydrogen bonding, several reports have appeared implicating this atom as a proton acceptor.[1] Intermolecular hydrogen bonding between methanol' and di-*n*-butyl sulfide was shown to give a shift of 155 cm.$^{-1}$ which was of the same magnitude as the shift found when oxygen was the proton acceptor in di-*n*-butyl ether.[2] This indicated that a high electronegativity was not the predominating factor in determining the hydrogen bonding ability of a base.[3] Evidence for intramolecular hydrogen bonding involving sulfur has been reported in 2,2′-thiodiphenol.[4] In this example the authors noted a decrease in frequency of a 149 cm.$^{-1}$ which is comparable to that found in intermolecular hydrogen bonding between methanol and di-*n*-butyl sulfide.

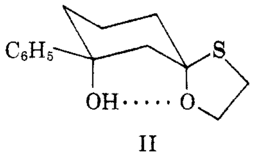
An example of intramolecular hydrogen bonding involving sulfur was examined in 7-phenyl-1,4-dithiospiro[4.5]-7-decanol (I). The evidence was derived from the absorption characteristics of I, 7-phenyl-1,4-oxathiospiro[4.5]-7-decanol (II), and 7-phenyl-1,4-dioxaspiro[4.5]-7-decanol (III) in the fundamental O—H stretching region and the first overtone in the near infrared. For additional verification of the assigned absorption peaks 8-phenyl-1,4-dioxaspiro[4.5]-8-decanol (IV) was examined.

Compound IV being a 1,4 system would have to assume the boat conformation prior to formation of intramolecular hydrogen bonding. Stolow[5] has demonstrated the existence of such bonding in a *cis*-1,4-cyclohexanediol forced into a twist conformation by interaction with *t*-butyl groups in positions 2 and 5. No evidence for intramolecular hydrogen bonding was found in IV. Two concentration-dependent peaks were found; one at 3604 cm.$^{-1}$ increased on dilution in nonpolar solvent and is assigned to unassociated hydroxyl.[6] Intermolecular hydrogen bonding was evident from a broad band at 3449 cm.$^{-1}$ which disappeared on dilution.

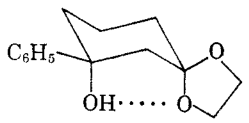
As expected compound III had a concentration independent band at 3503 cm.$^{-1}$, a shift of 101 cm.$^{-1}$ from the unassociated hydroxyl in IV. The magnitude of the shift, an increase of 26 cm.$^{-1}$ over that reported for *cis*-1,3-cyclohexanediol[7] indicates a stronger hydrogen bond which arises from the restriction of the hydroxyl and ether oxygen thereby decreasing the O......O distance.



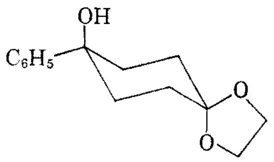
I



II



III



IV

The thioketal I showed two concentration independent bands, one at 3581 cm.$^{-1}$ and the other at 3446 cm.$^{-1}$ The former is a shift of 23 cm.$^{-1}$ indicating a weak bond. This spectral shift is in agreement with that reported for OH....$\pi$ bonding.[8] The peak of 3446 cm.$^{-1}$ is a shift of 158 cm.$^{-1}$ from the position assigned for unassociated hydroxyl. This indicated a slightly stronger bond than that reported for 2,2′-thiodiphenol.[4]

The determination of the conformation of the hemithioketal was made by comparison of models of compounds I, II, and III and their absorption in the hydroxyl stretching region. Measurements made on stereo models indicate that if II has both oxygens *cis*, the O.....O distance is slightly greater than found in III due to the sulfur and the corresponding increase in bond lengths in the oxathiolane ring. Thus, the spectral shift should be less than 101 cm.$^{-1}$ found in III. Similarly if

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[1] G. C. Pimetel and A. L. McCellan, *The Hydrogen Bond*, W. H. Freeman and Co., San Francisco, Calif., 1960, p. 201.

[2] P. von R. Schleyer and R. West, *J. Am. Chem. Soc.*, **81**, 3164 (1959).

[3] L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, Ithaca, N. Y., 1960, ed. 3, p. 452.

[4] A. W. Baker and A. T. Shulgin, *J. Am. Chem. Soc.*, **80**, 5388 (1958).

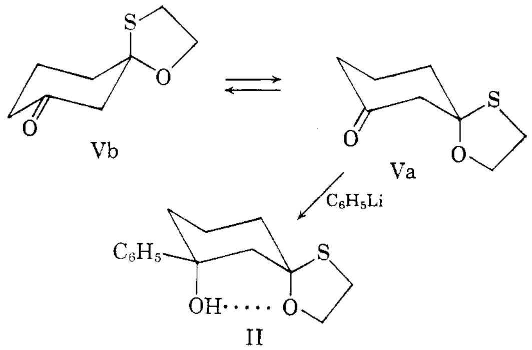
[5] R. D. Stolow, *J. Am. Chem. Soc.*, **83**, 2592 (1961).

[6] R. West, J. J. Korst, and W. S. Johnson, *J. Org. Chem.*, **25**, 1976 (1960).

[7] L. P. Kuhn, *J. Am. Chem. Soc.*, **74**, 2492 (1952).

[8] F. A. L. Anet and D. M. G. Bavin, *Can. J. Chem.*, **34**, 1756 (1956). D. C. Kleinfelter and P. von R. Schleyer, *J. Am. Chem. Soc.*, **83**, 2329 (1961).

the hydroxyl and sulfur are *cis* in II the O. . . .S distance would be greater than that found in I. Therefore the magnitude of the shift should be less than 158 cm.$^{-1}$ From steric considerations compound V would be expected to assume thermodynamic equilibrium (Va) prior to reaction with phenyllithium[9] which is kinetically controlled giving structure II. The hydrogen bond in II is to the ether oxygen the band appearing at 3519 cm.$^{-1}$ The shift of 85 cm.$^{-1}$ as expected is less than that in III by 16 cm.$^{-1}$ indicating a weaker hydrogen bond due to increased O. . . . .O distance. The conformation of the hemithioketal is as shown in structure II.[10]



Additional evidence for strong hydrogen bonding in compounds I, II, and III was demonstrated by the near-infrared spectra. The 1,4 system (IV) absorbed strongly at 7037 cm.$^{-1}$ ($\epsilon$ = 2.54) indicating the absence of strong intramolecular hydrogen bonding.[11] Compound II, the hemithioketal, showed weak and diffuse absorption at 6920–6892 cm.$^{-1}$; maximum absorption is at 6906 cm.$^{-1}$ ($\epsilon$ = 0.5). The ketal III (7143–6983 cm.$^{-1}$, max 7124 cm.$^{-1}$, $\epsilon$ = 0.34) and the thioketal I (6906 cm.$^{-1}$, $\epsilon$ = 0.8) both had weak absorption in the overtone region. Thus, the absence of intense absorption is further evidence for strong intramolecular hydrogen bonding between O-H . . . .O in II and III and between O-H. . . .S in I.

## EXPERIMENTAL

The infrared spectra were obtained using a Perkin-Elmer Model 21 spectrophotometer equipped with NaCl optics. Solutions varied in concentration from 0.1 to 0.005*M* in spectrograde carbon tetrachloride. Cells varied from 0.5-mm. sodium chloride liquid cells to 1-cm. silica cells. The instrument was calibrated against water vapor and benzyl alcohol. Assignments are accurate to ±5 cm.$^{-1}$ The $\Delta\nu$, being relative, difference is assumed to be accurate to ±2 cm.$^{-1}$

A Cary Model 14 was used for examination of the 1–1.5 $\mu$ region. Carbon tetrachloride solutions were examined in 10-cm. optical glass cells. The instrument was calibrated against methanol and the reported frequencies are accurate to ±2 cm.$^{-1}$ for sharp peaks.

*7-Phenyl-1,4-dithiospiro[4.5]-7-decanol* (I). A solution of 12.5 g. of 1,3-cyclohexanedione (0.11 mole), 7.0 g. of ethanedithiol (0.075 mole), and 100 mg. of *p*-toluenesulfonic acid in 100 cc. of anhydrous benzene was refluxed for 3 hr. Slightly more than the theoretical amount of water collected in a Dean-Stark trap. The benzene solution was washed successively with 25 cc. of 5% sodium bicarbonate and two 25-cc. portions of water. After drying the solution over anhydrous sodium sulfate the solvent was removed and the product 1,4-dithiospiro[4.5]-7-decanone was collected at 130–136°/0.6 mm. yielding 6.0 g. (48%).

A solution of ether containing 0.07 mole of phenyllithium was treated with an ether solution of 5.5 g. of 1,4-dithio-[4.5]-7-decanone (0.03 mole). After the addition was completed the suspension was decomposed with water; the ether layer was separated and dried over anhydrous sodium sulfate. The solvent was distilled and the residue was recrystallized from ether to give 4.0 g. (45%) of 7-phenyl-1,4-dithiospiro [4.5]-7-decanol (I), m.p. 96–97°; ultraviolet absorption[12] $\lambda_{\max}^{\mathrm{CH_3OH}}$ 241 m$\mu$, $\epsilon$ = 457.

*Anal.* Calcd. for $C_{14}H_{18}OS_2$: C, 63.11; H, 6.81; S, 24.07. Found: C, 63.29; H, 6.71; S, 23.90.

*7-Phenyl-1,4-oxathiospiro[4.5]-7-decanol* (II). Mercaptoethanol (5.2 g., 0.067 mole) and 12.5 g. of 1,3-cyclohexanedione (0.11 mole) were refluxed in benzene containing a catalytic amount of *p*-toluenesulfonic acid. After washing with sodium bicarbonate solution and water the solution was dried. Distillation of the residue gave 2.8 g. of 1,4-oxathiospiro[4.5]-7-decanone, (V) 24%, collected at 98–110°/0.2 mm.

*Anal.* Calcd. for $C_8H_{12}O_2S$: C, 55.81; H, 7 03; S, 18.63. Found: C, 55.53; H, 6.83; S, 18.60.

Treatment of an ether solution of 0.07 mole of phenyllithium with 2.3 g. of 1,4-oxathiospiro[4.5]-7-decanol (0.013 mole) and subsequent work-up gave 0.95 g. of solid. After three recrystallizations from ether 0.60 g. (18%) of 7-phenyl-1,4-oxathiospiro[4.5]-7-decanol (II) was collected, m.p. 94–96°.

*Anal.* Calcd. for $C_{14}H_{18}O_2S$: C, 67.16; H, 7.25; S, 12.80. Found: C, 67.15; H, 7.30; S, 13.01.

*7-Phenyl-1,4-dioxaspiro[4.5]-7-decanol* (III). A mixture of 12.5 g. of 1,3-cyclohexanedione (0.11 mole), 6.2 g. of ethylene glycol (0.1 mole) and 100 mg. of *p*-toluenesulfonic in 100 cc. of benzene was efficiently stirred and refluxed for 3 hr. After treating the mixture as described in I the residue was fractionally distilled. The first fraction consisted of 8.0 g. of 1,4-dioxaspiro[4.5]-7-decanone (51%) collected at 103–108°/4.5 mm.

*Anal.* Calcd. for $C_8H_{12}O_3$: C, 61.53; H, 7.75. Found: C, 61.37; H, 8.08.

The second fraction collected at 108–112°/4.5 mm. had no carbonyl absorption. This fraction analyzed for the diketal, 1,4,8,11-tetraoxadispiro[4.1.4.3]tetradecane.

*Anal.* Calcd. for $C_{10}H_{16}O_4$: C, 59.99; H, 8.05. Found: C, 59.89; H, 7.85.

An ether solution of 0.07 mole of phenyllithium was treated with 6.8 g. of 1,4-dioxaspiro[4.5]-7-decanone (0.043 mole) in ether. The mixture was treated as described in I and the residue fractionated to give 3.9 g. of 7-phenyl-1,4-dioxaspiro-7-decanol III (39%) collected at 124–129°/0.5 mm.

*Anal.* Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.54; H, 7.85.

*8-Phenyl-1,4-dioxaspiro[4.5]-8-decanol* (IV). A benzene solution of 10.0 g. of 1,4-cyclohexanedione (0.089 mole), 5.5 g. of ethylene glycol (0.089 mole) and a catalytic amount of *p*-toluenesulfonic acid was refluxed and stirred for 6 hr. during which slightly less than the theoretical amount of water collected in a Dean-Stark trap. After treatment as described in I the residue was distilled. The product, 1,4-dioxaspiro[4.5]-8-decanone, was collected at 67–70°/0.45 mm. (9.0 g., 65%). Recrystallization from petroleum ether

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[9] A. H. Beckett, N. J. Harper, A. D. Balon, and T. H. Watts, *Tetrahedron*, **6**, 319 (1959).

[10] C. Djerassi and M. Gorman, *J. Am. Chem. Soc.*, **75**, 3704 (1953). C. Djerassi, M. Shamma, and T. Y. Kan, *J. Am. Chem. Soc.*, **80**, 4723 (1958).

[11] See. Ref. 3, p. 485.

[12] E. A. Fehnel and W. Carmack, *J. Am. Chem. Soc.*, **71**, 84 (1959).

(b.p. 60–70°) gave white crystals melting at 65–73° (reported[13] m.p. 73–74°).

A second fraction collected at 75–85°/0.5 mm. did not absorb in the carbonyl region. Analysis indicated the diketal, 1,4,9,12-tetraoxadispiro[4.2.4.2]tetradecane.

*Anal.* Calcd. for $C_{10}H_{16}O_4$: C, 59.99; H, 8.05. Found: C, 60.13; H, 7.96.

Treatment of an ether solution containing 0.07 mole of phenyllithium with 7.0 g. of 1,4-dioxaspiro[4.5]-8-decanone (0.045 mole) and subsequent work-up as described in I gave an oily residue. This was distilled and 3.90 g. of 8-phenyl-1,4-dioxaspiro[4.5]-8-decanol (37%) was collected at 150–155°/1 mm. The product solidified and was recrystallized from ether-heptane, m.p. 94–96°.

*Anal.* Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.96; H, 7.57.

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[13] P. D. Gardner, G. R. Haynes, and R. L Brandon, *J. Org. Chem.*, 22, 1206 (1957).

## 3-Substituted 2,4-Quinazolinediones

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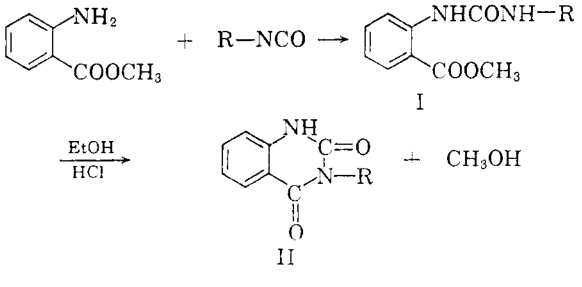
The known methods for the preparation of 3-substituted 2,4-quinazolinediones are complicated and result in relatively low yields. For example, 3-methyl and 3-ethyl-2,4-quinazolinedione are prepared by treating *N*-methyl and *N*-ethyl phthalamide with potassium hypobromite[1] in yields of 48% and 53%, respectively. Another method of synthesizing 3-substituted quinazolinediones involves heating aromatic isocyanates or their dimers with a molten mixture of aluminum chloride and sodium chloride.[2] Yields by this procedure are in the order of 49–64%. It has been reported also[3] that 3-phenyl-2,4-quinazolinedione is obtained when 1,3-diphenylurea is heated with potassium carbonate at 260° under 50 atm. of carbon dioxide pressure. Staiger and Wagner[4] report a synthesis of quinazolinediones by treating isatoic anhydride with primary amines followed by ring closure of the resulting ω-substituted uramidobenzoic acids with dilute sulfuric acid. The latter method has two major drawbacks: the formation of varying amounts of substituted anthranilamides and the failure of some of the uramidobenzoic acids to ring-close.

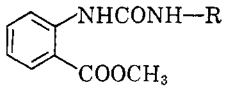
We have now found that a convenient method, and one that produces 3-substituted 2,4-quinazolinediones (II) in excellent yields, involves treating methyl anthranilate with an isocyanate to yield the corresponding ω-substituted methyl uramidobenzoate (I) which in turn is cyclized by treatment with a solution of hydrochloric acid in ethanol. The following equation illustrates the course of the reaction.



The preparation of the ω-substituted methyl uramidobenzoates (I) is most conveniently carried out by treating methyl anthranilate with an isocyanate in the presence of a solvent; *e.g.*, petroleum ether, toluene, diethyl ether, *etc.* Triethylamine is added to facilitate the reaction. Table I lists several ω-substituted methyl uramidobenzoates prepared by this procedure.

TABLE I

ω-SUBSTITUTED METHYL URAMIDOBENZOATES



| R | Yield, % | M.P.[a] | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|
| *n*-Propyl | 91 | 97–99 | 11.86 | 11.44 |
| *n*-Butyl | 88 | 79–80 | 11.19 | 11.00 |
| Cyclohexyl | 94 | 163–164 | 10.14 | 9.97 |
| Phenyl | 93 | 144–145 | 10.36 | 10.14 |
| *p*-Tolyl | 78 | 151–152 | 9.85 | 9.70 |
| α-Naphthyl | 90 | 190–191 | 8.75 | 8.87 |

[a] Melting points are uncorrected.

The cyclization of the ω-substituted methyl uramidobenzoates listed in Table I was accomplished by refluxing the disubstituted urea esters with an ethanol–hydrochloric acid solution (1:1 by volume). Dilute sulfuric acid, of 10% or 20% concentration, gave varied results; the propyl and butyl derivatives cyclized readily, while the other urea esters were recovered unchanged even after prolonged heating at elevated temperatures. However, by increasing the acid concentration to 37% sulfuric acid, the formation of the quinazoline derivative could be accomplished.

Table II lists the 3-substituted 2,4-quinazolinediones prepared by the cyclization of the ω-substituted methyl uramidobenzoates with ethanolic hydrochloric acid.

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(1) F. S. Spring and J. C. Woods, *J. Chem. Soc.*, 625–28 (1945).

(2) N. S. Dokunikhin and L. A. Gaera, *Zhur. Obshcheĭ Khim.*, 23, 606–10 (1953).

(3) A. I. Kizber and A. S. Glagoleva, *Doklady Akad. Nauk S.S.S.R.*, 83, 89–92 (1952).

(4) R. P. Staiger and E. C. Wagner, *J. Org. Chem.*, 18, 1427–39 (1953).