The Chemistry of Some Sterically Hindered Mono- and Diketones

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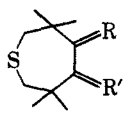
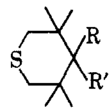
The reaction of 3,3,6,6-tetramethyl-1-thiacycloheptane-4,5-dione (I), under the conditions of the benzilic acid rearrangement, and the reaction of 5-diazo-3,3,6,6-tetramethyl-1-thiacycloheptan-4-one (VII), under the conditions of the Wolff rearrangement, were studied. The results are compared with those of dipivaloyl and its α-diazo derivative in these reactions to show the influence of the cyclic nature of I and VII. The reactivity of diketone I in addition reactions was investigated to study the shielding effect of the two *gem*-dimethyl functions. The same effect was also investigated in the 3,3,5,5-tetramethyl-1-thiacyclohexane system (III–V). The reaction of 4-carboxy-4-hydroxy-3,3,5,5-tetramethyl-1-thiacyclohexane (III) with thionyl chloride to yield 3,3,5,5-tetramethyl-1-thiacyclohexanone (V) appeared interesting.

In connection with studies in this laboratory on highly sterically hindered aromatic[1] and aliphatic compounds[2] we explored the chemistry of the cyclic compounds (I–V).



I, R = R′ = O
II, R = O;
R′ = N–NH$_2$

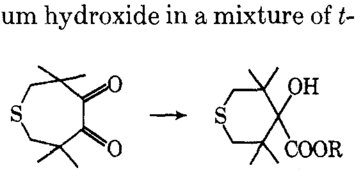


III, R = OH; R′ = COOH
IV, R = OH; R′ = COOCH$_3$
V, R = R′ = O

The factors governing the chemistry of the substituted thiacycloheptane (I and II) and thiacyclohexane derivatives (III–V) are connected with (i) the cyclic nature of these molecules,[1] (ii) the shielding effect due to the two *gem*-dimethyl functions,[3] (iii) the presence of the sulfur atom in the ring,[4] and (iv) the size of the ring.

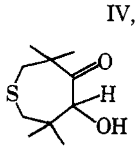
In this paper several interesting aspects of the rearrangement and addition reactions of diketone I are discussed. A comparison with the chemical behavior of the acyclic analog dipivaloyl draws attention to the influence of the cyclic nature of diketone I,[1] especially in rearrangement reactions. Steric effects due to the *gem*-dimethyl functions appear to play an important part in the addition reactions of I and in the chemistry of the thiacyclohexane derivatives III–V. The influence of the sulfur atom in the ring is currently being investigated.[4]

Benzilic Acid Rearrangement.—Dipivaloyl does not give a benzilic acid rearrangement;[5] diketone I gave the hydroxy acid III in 82% yield when it was refluxed with potassium hydroxide in a mixture of *t*-butyl alcohol and water. When a mixture of 1-propanol and water was used as solvent, the yield of III was 52%, and as a by-product the hydroxy ketone VI was isolated in 22% yield. When diketone I was refluxed with sodium methoxide in methanol the hydroxy ester IV was isolated in 82% yield.[6]



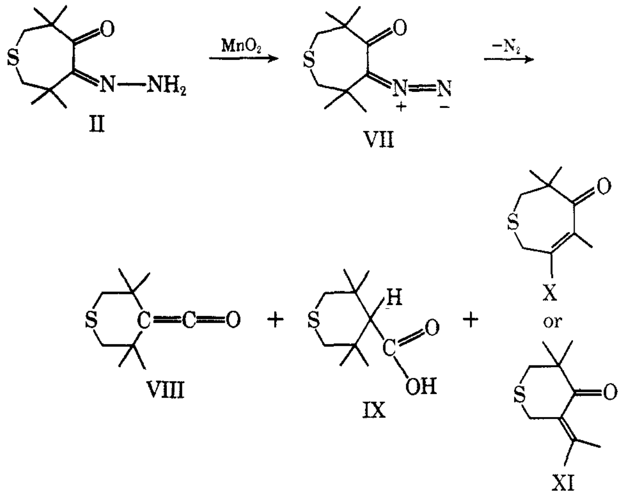
I

III, R = H
IV, R = CH$_3$



VI

Wolff Rearrangement.—A second difference in behavior between dipivaloyl and diketone I is the decomposition of the corresponding α-diazo ketones VII and XII. Oxidation of the ketohydrazone II with manganese dioxide probably gave the α-diazo ketone VII which spontaneously decomposed at room temperature. This α-diazo ketone VII is not stabilized by resonance; the conformation of the seven-membered ring in VII is such that the diazo function and the carbonyl function are orthogonal to one another (skew). This can be seen from the conformation of diketone I and 4,5-dimethylene-3,3,6,6-tetramethyl-1-thiacycloheptane (XVI). Ultraviolet spectra indicate that there is no double-bond resonance in compounds I and XVI.[2] During the decomposition, a Wolff rearrangement takes place and ketene VIII (stable as monomer) and the acid IX are formed in a combined yield of 49%. A third product, isolated in 30% yield, had uv absorption at 246 $m\mu$ (ϵ 4400) and a medium-intensity ir absorption at 1645 cm^{-1}. No decision can be made between structure X or XI for this α,β-unsaturated ketone on the basis of these spectra.[7]



II VII

VIII IX X or XI

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[1] Ae. de Groot and H. Wynberg, *J. Org. Chem.*, **31**, 3954 (1966).

[2] Ae. de Groot, B. Evenhuis, and H. Wynberg, *ibid.*, **33**, 2214 (1968).

[3] Ae. de Groot, J. A. Boerma, and H. Wynberg, *Chem. Commun.*, 347 (1968).

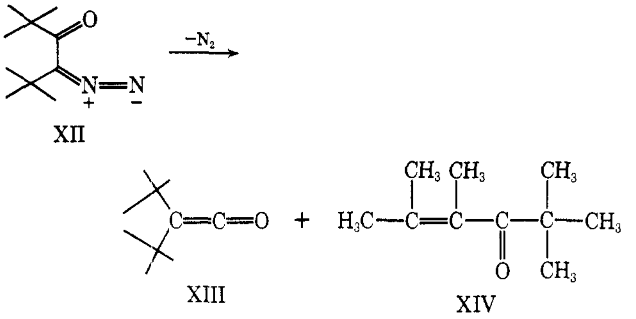
[4] Ae. de Groot, J. A. Boerma, and H. Wynberg, *Tetrahedron Lett.*, 2365 (1968).

[5] F. G. Roberts and P. C. Teague, *J. Amer. Chem. Soc.*, **77**, 6258 (1955).

[6] W. von E. Doering and R. S. Urban, *ibid.*, **78**, 5938 (1956).

[7] Care need be exercised to apply Woodward's rules in this case. Not only a seven-membered ring is involved, and few if any correlations are known for α,β-unsaturated seven-membered ketones, but in addition steric factors can cause appreciable lowering of the ultraviolet maximum in the six-membered α,β-unsaturated ketone XI as well as in the seven-membered ketone X.

Newman[8] isolated in very low yield (0–3%) di-*t*-butyl ketene XIII as the decomposition product of the much more stable diazo ketone XII. The α,β-unsaturated ketone XIV was formed in 80–92% yield in this case. The much higher yield of ketene VIII and acid IX in our case supports the suggestion of Kaplan, *et al.*,[9] that a *cis* position is necessary for the Wolff rearrangement. Our cyclic diazo ketone VII meets this condition better than Newman's diazo ketone XII; the large *t*-butyl groups prevent the *cis* position in XII.[10]



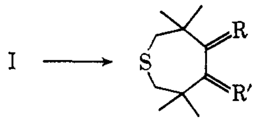
XII

XIII

XIV

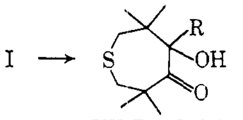
The stable ketene VIII was hydrolyzed to the corresponding acid IX by water and a trace of mineral acid. Reduction of VIII with lithium aluminum hydride gave 4-formyl-3,3,5,5-tetramethyl-1-thiacyclohexane (XV).

Addition Reactions.—Both diketone I and dipivaloyl react similarly to form mainly monoaddition–elimination products.[1,8,11] Several types of Wittig reactions gave monoaddition products except in the formation of diene XVI.[2] Reactions of compounds XVIII[12] and XIX with the corresponding ylides did not give diaddition products; methylene ketone XVII could be converted into diene XVI.

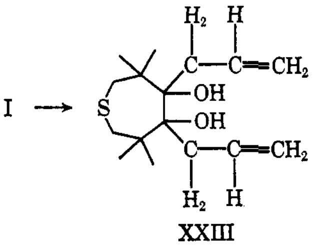


XVI, R = R′ = CH_2
XVII, R = O; R′ = CH_2
XVIII, R = O; R′ = $CHOCH_3$
XIX, R = O; R′ = $CHCOOC_2H_5$

Reaction of diketone I with *t*-butyllithium or with methylmagnesium iodide gave the monoaddition products XX and XXI, respectively; only XXI could be reduced with lithium aluminum hydride to the corresponding diol XXII. Addition of allyllithium to diketone I gave the diaddition product XXIII in 81% yield.



XX, R = $C(CH_3)_3$
XXI, R = CH_3

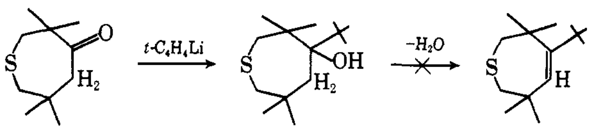


XXIII

Dipivaloyl also gives monoaddition products with organometallic reagents,[13,14] except when treated under forcing conditions.[13] These results indicate that, in general, addition of two molecules of a reagent to diketone I or dipivaloyl does not take place, except when small and reactive reagents are used (see compounds XVI and XXIII).

The steric hindrance due to the *gem*-dimethyl groups is the main reason for this behavior, but some minor points need consideration. For instance, small variations in the size of the ring cause subtle changes in the reactivity of the functional groups. Thus no enediol sulfite was isolated in the reaction of 2-hydroxy-3,-3,5,5-tetramethylcyclohexanone with thionyl chloride.[15] In the reaction of the seven-membered hydroxy ketone VI with thionyl chloride, a stable enediol sulfite was isolated.[3] Under normal reaction conditions, 2,2,5,5-tetramethylcyclohexanone gives a hydrazone,[15,16] but from monoketone XXVII no hydrazone was obtained. Inductive effects (one carbonyl group upon the other) probably play a role, for no hydrazone was obtained in the reaction of monoketone XXIV, hydroxy ketone VI, or methylene ketone XXVII with hydrazine, although the steric hindrance in these compounds is comparable with the hindrance in diketone I.

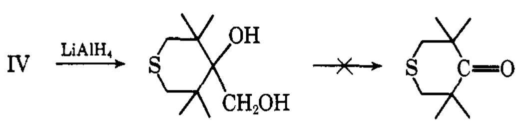
Monoketone XXIV does react with the more reactive *t*-butyllithium to give the adduct XXV in 82% yield.



XXIV XXV XXVI

Attempts to convert the alcohol XXV into alkene XXVI *via* a modified Chugaev reaction[2] were unsuccessful.

Reactions of the Thiacyclohexane Derivatives.—The steric effect of the two *gem*-dimethyl functions is evident in the chemistry of the thiacyclohexane derivatives III–V. The hydroxy ester IV could not be converted into its hydrazide. Reduction of ester IV gave the diol XXVII in 85% yield, but fission of this diol was not possible.



XXVII V

Oxidation of hydroxy acid III with CrO_3 or with lead tetraacetate gave small yields of the ketones XXIX and V, respectively. The bicyclic lactone XXVIII was isolated in 27% yield in the reaction of III with lead tetraacetate.[17] Electrolysis of acid III gave ketone XXIX in 30% yield.

Interestingly, the hydroxy acid III gave the ketone V directly in 76% yield upon treatment with thionyl chloride. Other less hindered hydroxy acids yield

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[8] M. S. Newman and A. Arkell, *J. Org. Chem.*, **24**, 385 (1959).

[9] F. Kaplan and G. K. Meloy, *J. Amer. Chem. Soc.*, **88**, 950 (1966).

[10] N. J. Leonard and P. M. Mader, *ibid.*, **72**, 5388 (1950).

[11] L. Bouveault and R. Loquin, *Bull. Soc. Chim. Fr.*, (3) **35**, 655 (1906).

[12] Ae. de Groot and H. Wynberg, *J. Org. Chem.*, **33**, 3337 (1968).

[13] M. S. Newman and G. R. Kahle, *ibid.*, **23**, 666 (1958).

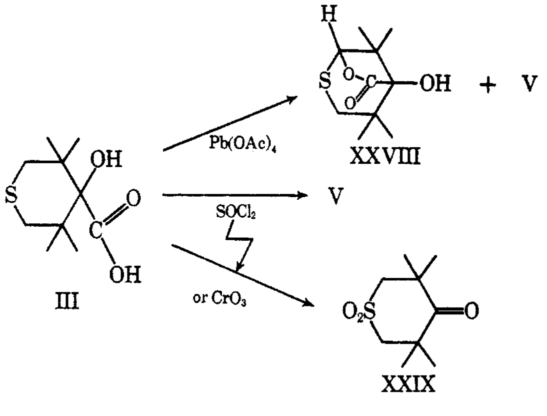
[14] H. J. Backer, *Rec. Trav. Chim. Pays-Bas*, **57**, 967 (1938).

[15] D. E. Gwynn, Ph.D. Thesis, University of Illinois, 1962.

[16] H. A. Bruson, F. W. Grant, and E. Bobko, *J. Amer. Chem. Soc.*, **80**, 3633 (1958).

[17] Analogous reactions of sulfide acids with lead tetraacetate are not known in the literature as far as we know.

stable mixed anhydrides under these conditions.[18,19] These anhydrides decompose to form polyesters instead of ketones.[18] It is evident that steric crowding around the reaction center has once again altered the reaction path.



The cyclic ketones V and XXIX could not be converted into their oximes under normal reaction conditions. Here too the influence of the size of the ring is noticeable. 2,2,5,5-Tetramethylcyclopentanone does not give a 2,4-dinitrophenylhydrazone,[20] but 2,2,4,4-tetramethylcyclobutanone gives an oxime, a semicarbazone, and a 2,4-dinitrophenylhydrazone.[21]

Experimental Section

Infrared spectra were determined in carbon tetrachloride, in potassium bromide discs or neat on a Perkin-Elmer Infracord Model 137 or on a Unicam SP 200. Ultraviolet spectra were recorded on a Zeiss spectrophotometer, Model PMQ II; the solvents are indicated. Nuclear magnetic resonance (nmr) spectra were taken on a Varian A-60 spectrometer with tetramethylsilane as the internal standard and are reported in τ values (parts per million). The solvents used are indicated. Melting points and boiling points are uncorrected. Microanalyses were performed by the analytical department of this laboratory under the supervision of Mr. W. M. Hazenberg.

4-Carboxy-4-hydroxy-3,3,5,5-tetramethyl-1-thiacyclohexane (III).—A solution of 5.0 g (0.025 mol) of diketone I and 30 g of KOH in a mixture of 25 ml of water and 250 ml of 1-propanol was refluxed and stirred for 20 hr. The reaction mixture was concentrated, and water and ether were added. The water solution was extracted with ether. The combined ethereal extracts were dried (Na_2SO_4) and concentrated, giving 1.1 g (22%) of the hydroxy ketone VI. The water layer was acidified with concentrated hydrochloric acid, and the hydroxy acid was filtered and washed with water. Recrystallization from CCl_4 gave 2.7 g (52%) of the hydroxy acid III: mp 174–175°; ir (Nujol) 3600 (OH) and 1690 cm^{-1} (C=C); nmr ($DCCl_3$) τ 6.75, 6.97, 7.60, and 7.83 (d, methylene protons) and 8.72 and 9.92 (s, methyl protons).

Anal. Calcd for $C_{10}H_{18}O_3S$ (218.31): C, 55.01; H, 8.31; S, 14.69. Found: C, 55.4, 55.1; H, 8.3, 8.3; S, 14.2, 14.2.

When a mixture of 25 ml of water and 250 ml of *t*-butyl alcohol was used as a solvent a yield of 82% of the hydroxy acid VI was obtained. No hydroxy ketone was isolated.

4-Carbomethoxy-4-hydroxy-3,3,5,5-tetramethyl-1-thiacyclohexane (IV).—A solution of 10.0 g (0.05 mol) of diketone I and 6.7 g of Na in 200 ml of absolute methanol was refluxed for 20 hr. The reaction mixture was concentrated, and water was added. The water solution was extracted with ether. The ethereal extract was washed with water, dried ($CaCl_2$), and concentrated. The residue was recrystallized from ethanol giving 9.5 g (82%) of the hydroxy ester IV: mp 67–68°; ir (Nujol) 3500 (OH) and 1720 cm^{-1} (C=O); nmr ($DCCl_3$) τ 9.05 and 8.78 (s, methyl protons), 7.89, 7.65 and 7.10, 6.87 (d, methylene protons), 6.30 (s, OH proton), and 6.17 (s, ester methyl protons).

Anal. Calcd for $C_{11}H_{20}O_3S$ (232.34): C, 56.86; H, 8.68; S, 13.80. Found: C, 56.7, 56.8; H, 8.6, 8.6; S, 13.4, 13.5.

Rearrangement of 4-Diazo-3,3,6,6-tetramethyl-1-thiacycloheptan-5-one (VII).—A solution of 4.3 g (0.02 mol) of monohydrazone II in 50 ml of benzene was added to a stirred suspension of 6.0 g of active MnO_2 and 10 g of anhydrous $MgSO_4$ in 50 ml of dry benzene over a period of 30 min. The solution became yellow, and gas evolution started at once. After 48 hr at room temperature no gas evolution was observed, and the reaction mixture was filtered and concentrated. A small portion (500 mg) of the residue was refluxed with dilute hydrochloric acid for 30 min. After cooling to room temperature dilute NaOH solution was added, and the water solution was extracted with ether. The water solution was acidified, and filtration gave 195 mg of the carboxylic acid IX, mp 149–152°. From this amount of acid IX it was concluded that the Wolff rearrangement of diazo ketone VII occurred in 48% yield. Recrystallization of acid IX from absolute ethanol gave an analytical sample: mp 152–153.5°; ir (Nujol) 1700 cm^{-1} (C=O); nmr ($DCCl_3$) τ 7.35, 7.57 7.63, and 7.87 (d, methylene protons), 7.79 (s, α proton), and 8.75 and 8.88 (s, methyl protons).

Anal. Calcd for $C_{10}H_{18}O_2S$ (202.31): C, 59.36; H, 8.97; S, 15.86. Found: C, 59.4, 59.3; H, 9.0, 9.0; S, 15.8, 15.6.

The rest of the residue was chromatographed over silica gel. After elution with dry benzene, 0.55 g (16.5%) of ketene VIII was obtained. Distillation, bp 103–104° (12 mm), gave an analytical sample of X: ir (neat) 2200 cm^{-1} (ketene absorption); nmr (CCl_4) τ 7.65 (s, methylene protons) and 8.73 (s, methyl protons).

Anal. Calcd for $C_{10}H_{16}OS$ (184.29): C, 65.17; H, 8.75; S, 17.40. Found: C, 65.0, 65.0; H, 8.8, 8.9; S, 17.2, 17.4.

After elution with H_2CCl_2, 0.82 g (25%) of ketone X or XI was obtained. Distillation, bp 118–119° (13 mm), gave an analytical sample: uv max (95% EtOH) 246 mμ (ϵ 4400) and 308 (280); ir (neat) 1645 (C=C), 1690 cm^{-1} (C=O); nmr (CCl_4) τ 6.58 and 7.32 (s, methylene protons), 8.22 and 8.30 (s, methyl protons), and 8.83 (s, methyl protons).

Anal. Calcd for $C_{10}H_{16}OS$ (184.29): C, 65.17; H, 8.75; S, 17.40. Found: C, 65.1, 65.3; H, 8.9, 8.8; S, 17.6, 17.5.

After elution with methanol, 0.95 g (26%) of the carboxylic acid IX was isolated.

4-Formyl-3,3,5,5-tetramethyl-1-thiacyclohexane (XV).—A solution of 0.45 g (12 mmol) of ketene VIII in 10 ml of dry ether was added to a stirred suspension of 0.10 g of $LiAlH_4$ in 30 ml of ether. The reaction mixture was refluxed for 1.5 hr, and, after cooling, the excess of the $LiAlH_4$ was destroyed by addition of 2 ml of ethyl acetate. Dilute hydrochloric acid was added and the water solution was extracted with ether. The ethereal extract was washed with Na_2CO_3 solution, dried (Na_2SO_4), and concentrated. Distillation of the residue gave 0.30 g (67%) of the aldehyde XV, bp 120° (13 mm). An analytical sample of XV, mp 71.5–73°, was obtained after three crystallizations from pentane at low temperature: ir (Nujol) 1710 cm^{-1} (C=O); nmr (CCl_4) τ 0.03, 0.10 (d, aldehyde proton), 8.30, 8.38 (d, α proton), 7.43, 7.65 and 7.75, 7.97 (d, methylene protons), and 8.65 and 9.00 (s, methyl protons).

Anal. Calcd for $C_{10}H_{18}OS$ (186.31): C, 64.46; H, 9.74. Found: C, 64.3, 64.3; H, 9.8, 9.9.

4-Carboethoxymethylene-3,3,6,6-tetramethyl-1-thiacycloheptan-5-one (XIX).—A solution of 9.5 g (0.045 mol) of triethyl phosphonoacetate in 10 ml of dry dimethoxyethane was added to a suspension of 2.2 g (0.045 mol) of NaH in 75 ml of dimethoxyethane. This mixture was stirred until no gas evolution was observed (45 min). A solution of 8.0 g (0.04 mol) of diketone I in 10 ml of dimethoxyethane was added, and the reaction mixture was stirred for 2 hr and refluxed for 1 hr. The reaction mixture was poured into 500 ml of water, and the water solution was extracted with pentane. The pentane extract was dried ($MgSO_4$) and concentrated. The residue was distilled, bp 98–128° (0.1 mm), giving 8.4 g (78%) of the keto ester XIX: ir (neat) 1720 (C=O), 1700 (C=O), 1640 (C=C), 1095 cm^{-1} (C—O—C); nmr (CCl_4) τ 8.85, 8.73, 8.62 (t, ester methyl protons), 8.68 (s, ring methyl protons), 7.5 (m, ring methylene protons), 6.07, 5.95, 5.83, 5.70 (q, ester methylene protons), and 4.20 (s, vinyl proton).

Saponification of the ester XIX gave in 60% yield the corresponding carboxylic acid. Crystallization from ethanol gave

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[18] E. E. Blaise and A. Montagne, *Compt. Rend.*, **174**, 1553 (1922).

[19] N. J. Turro, S. S. Edelson, J. R. Williams, and T. R. Darling, *J. Amer. Chem. Soc.*, **90**, 1926 (1968).

[20] L. Eberson, *Tetrahedron Lett.*, 23 (1966).

[21] H. L. Herzog and E. R. Buchman, *J. Org. Chem.*, **16**, 99 (1951).

an analytical sample: mp 184–186°; ir (KBr) 3450 (OH), 1740 (C=O), 1625 cm^{-1} (C=C).

Anal. Calcd for $C_{12}H_{18}O_3S$ (242.32): C, 59.47; H, 7.44; S, 13.22. Found: C, 59.3, 59.2; H, 7.5, 7.6; S, 13.0, 13.2.

5-*t*-Butyl-5-hydroxy-3,3,6,6-tetramethyl-1-thiacycloheptan-4-one (XX).—A solution of 15.5 g (0.17 mol) of *t*-butyl chloride in 20 ml of ether was added over a period of 4 hr to a dispersion of 2.8 g (0.4 g-atom) of Li in 60 ml of ether. The temperature of the reaction mixture was kept below −40°. After the addition of the *t*-butyl chloride, the mixture was stirred for 30 min and then cooled to −70°. At this temperature a solution of 5.0 g (0.02 mol) of diketone I in 40 ml of ether was added, and the reaction mixture was stirred for 2 hr at −70°. The reaction mixture was allowed to come to room temperature, and pieces of unreacted Li were removed. Water was added, and the ether layer was separated, dried (Na_2SO_4), and concentrated. The residue was recrystallized from ethanol giving 3.2 g (59%) of the hydroxy ketone XX: mp 155–156°; ir (Nujol) 3540 (OH), 1685 cm^{-1} (C=O); nmr ($DCCl_3$) τ 8.87 and 8.73 (s, methyl and *t*-butyl protons), 8.37, 8.12 and 7.93, 7.68 (d, methylene protons), 8.90 (s, OH proton), and 6.75, 6.52 and 6.52, 6.30 (d, methylene protons).

Attempted Reduction of Hydroxy Ketone XX.—A solution of 1.0 g of hydroxy ketone XX was refluxed for 4 hr with a suspension of $LiAlH_4$ in ether. Excess $LiAlH_4$ was destroyed, and the reaction mixture was treated as described for aldehyde XV. The ir spectrum and melting point of the residue were identical with those of an original sample of XX.

5-Hydroxy-3,3,5,6,6-pentamethyl-1-thiacycloheptan-4-one (XXI).—A solution of 6.0 g (0.03 mol) of diketone I in 20 ml of ether was added to a solution of 0.035 mol of methylmagnesium iodide in 40 ml of ether. The reaction mixture was refluxed for 1 hr, and then dilute H_2SO_4 solution was added. The ether layer was separated, washed with water and with dilute $NaHCO_3$ solution, dried (K_2CO_3), and concentrated. The residue was recrystallized from petroleum ether (bp 40–60°) giving 5.3 g (82%) of the hydroxy ketone XXI: mp 80–81°; ir (KBr) 3410 (OH), 1700 cm^{-1} (C=O); nmr ($DCCl_3$) τ 9.07, 8.98, 8.79, 8.67, and 8.58 (s, methyl protons), 7.63, 7.38; 7.05, 6.80 and 7.47, 7.25; 7.22, 7.00 (d, methylene protons), and 6.57 (s, OH proton).

Anal. Calcd for $C_{11}H_{20}O_2S$ (216.33): C, 61.08; H, 9.32; S, 14.83. Found: C, 61.1, 61.2; H, 9.2, 9.2; S, 14.9, 14.7.

A reaction of diketone I with a twofold excess methylmagnesium iodide in boiling toluene gave the same hydroxy ketone XXI.

3,3,4,6,6-Pentamethyl-1-thiacycloheptane-4,5-diol (XXII).—A solution of 3.8 g (0.018 mol) of hydroxy ketone XXI in 50 ml of ether was added to a suspension of 0.9 g (0.024 mol) of $LiAlH_4$ in 100 ml of ether over a period of 30 min. The reaction mixture was refluxed for 4 hr and worked up as described for compound XV. The yield of diol XXII, mp 157–158°, was 3.1 g (81%): ir (Nujol) 3470 and 3400 cm^{-1} (OH).

Anal. Calcd for $C_{11}H_{22}O_2S$ (218.36): C, 60.50; H, 10.16. Found: C, 61.1, 60.8; H, 10.5, 10.4.

4,5-Diallyl-3,3,6,6-tetramethyl-1-thiacycloheptane-4,5-diol (XXIII).—A suspension of 64 g (9.1 g-atoms) of Li in 750 ml of ether was cooled to −15°. A solution of 107 g (0.8 mol) of allyl phenyl ether in 375 ml of ether was added over a period of 1 hr, and the reaction mixture was stirred for 15 min at room temperature. The solution was filtered through glass wool in a nitrogen atmosphere to remove the excess Li. A solution of 20 g (0.1 mol) of diketone I in 50 ml of ether was added, and the reaction mixture was stirred for a period of 40 hr at room temperature. The reaction products were hydrolyzed with water; the ether layer was separated; and the water layer was extracted with ether. The ethereal extract was washed with water, dried (Na_2SO_4), and concentrated. The residue was recrystallized from ethanol–water (1:1) giving 23.6 g (83%) of the diol XXIII: mp 82.5–83°; ir (Nujol) 3400 (OH) and 1620 cm^{-1} (C=C).

Anal. Calcd for $C_{16}H_{28}O_2S$ (284.47): C, 67.54; H, 9.92; S, 11.29. Found: C, 67.4, 67.7; H, 9.8, 10.0; S, 11.3, 11.1.

4-*t*-Butyl-3,3,6,6-tetramethyl-1-thiacycloheptan-4-ol (XXV).—A solution of 0.15 mol of *t*-butyllithium in 200 ml of ether was prepared and cooled to −80° (see compound XX). A solution of 12.0 g (0.065 mol) of ketone XXIV in 75 ml of ether was added, and the reaction mixture was stirred for 1 hr at −80°, and then allowed to come to room temperature. Dilute hydrochloric acid was added, and the layers were separated. The ether solution was washed with $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated. The residue was distilled, bp 164–166° (14 mm), giving 13.0 g (82%) of the alcohol XXV: ir (neat) 3500 cm^{-1} (OH); nmr ($DCCl_3$) τ 6.86 (s, OH proton), 7.10, 7.35; 7.63, 7.89; 7.22, 7.45; 7.53, 7.89 (d, methylene protons), 8.79, 8.83, and 9.00 (s, methyl protons), and 8.92 (s, *t*-butyl protons).

Anal. Calcd for $C_{14}H_{28}OS$ (244.43): C, 68.79; H, 11.55. Found: C, 69.1, 69.0; H, 11.4, 11.5.

Attempted Preparation of the Xanthate of XXV.—A suspension of 0.28 g (0.006 mol) of NaH in mineral oil was washed with pentane under nitrogen. After evaporation of the pentane 50 ml of dimethyl sulfoxide was added, and the mixture was heated at 60–70° for 1 hr. After cooling to room temperature 1.2 g (0.005 mol) of alcohol XXV in 10 ml of dimethyl sulfoxide was added. After 30 min, 2 ml of CS_2 was added, and, after another 30 min, 2 ml of CH_3I was added. The reaction mixture was stirred for 1 hr and poured into 150 ml of water. The water solution was extracted with pentane. The pentane extract was dried ($CaCl_2$) and concentrated. A tlc of the residue showed that starting material and one other compound were isolated. After chromatography over silica gel this second compound was isolated, and the ir spectrum suggested that the dithio ester, $CH_3S{=}OCH_2C{=}SSCH_3$, was obtained.

4-Hydroxy-4-hydroxymethylene-3,3,5,5-tetramethyl-1-thiacyclohexane (XXVII).—A solution of 7.0 g (0.03 mol) of hydroxy ester IV in 50 ml of ether was added to a suspension of 1.1 g (0.03 mol) of $LiAlH_4$ in 100 ml of ether. The reaction mixture was refluxed for 4 hr and then worked up as described for compound XV. Recrystallization of the diol XXVII from ethanol gave 5.2 g (82%): mp 180.5–181.5°; ir (Nujol) 3550 cm^{-1} (OH); nmr (CD_3OD) τ 6.35 (s, CH_2OH), 7.01, 7.25, and 7.72, 7.97(d, methylene protons), and 8.95 (s, methyl protons).

Anal. Calcd for $C_{10}H_{20}O_2S$ (204.32): C, 58.78; H, 9.87; S, 15.56. Found: C, 58.9, 58.7; H, 9.9, 9.9; S, 15.6, 15.7.

Oxidation of Hydroxycarboxylic Acid III with $Pb(OAc)_4$.—A solution of 7.0 g (0.032 mol) of acid III and 18.5 g (0.046 mol) of $Pb(OAc)_4$ in 150 ml of acetic acid was stirred for 15 hr at 60–70°. The reaction mixture was concentrated, and water and ether were added. The water solution was extracted with ether, and the ethereal extract was washed with dilute NaOH solution and with water. The ethereal extract was dried (Na_2SO_4) and concentrated. The residue was recrystallized from petroleum ether (bp 40–60°) giving 1.9 g (27.5%) of the lactone XXVIII: mp 95–96°; ir (Nujol) 3480 (OH), 1762 (C=O), and 1100 cm^{-1} (C—O—C); nmr ($DCCl_3$) τ 4.87 (s, S—CH—O), 6.98, 7.22 and 7.55, 7.79 (d, methylene protons), 7.55 (s, OH proton), and 8.53 8.73, 8.83, and 8.93 (s, methyl protons).

Anal. Calcd for $C_{10}H_{16}O_3S$ (216.30): C, 55.52; H, 7.46; S, 14.83. Found: C, 55.6, 55.7; H, 7.5, 7.5; S, 14.7, 14.5; mol wt, 227, 224.

Concentration of the petroleum ether mother liquor gave a liquid residue. Chromatography of this oil over silica gel gave, upon elution with CH_2Cl_2, a small amount (200 mg) of impure ketone V. The ir and nmr spectra were identical with those of an original sample of V.

4-Keto-3,3,6,6-tetramethyl-1-thiacyclohexane 1,1-Dioxide (XXIX).—A solution of 7.0 g (0.032 mol) of hydroxy acid III and 0.1 g of Na in 200 ml of methanol was electrolyzed until the mixture grew dark. The temperature was kept below 35°. The reaction mixture was concentrated, and water and ether were added. The water layer was extracted with ether, and the ethereal extract was dried (Na_2SO_4) and concentrated. The solid residue was recrystallized from hexane giving 2.1 g (31%) of the ketone XXIX: mp 127.5–129°; ir (KBr) 1707, 1692 (C=O), and 1120, 1322 cm^{-1} (SO_2); nmr ($DCCl_3$) τ 6.62 (s, methylene protons) and 8.63 (s, methyl protons).

Anal. Calcd for $C_9H_{16}O_3S$ (204.28): C, 59.90; H, 7.98; S, 15.68. Found: C, 52.9, 52.8; H, 7.9, 7.9; S, 15.5, 15.5.

Ketone XXIX (Second Method).—A solution of 4.0 g (0.018 mol) of hydroxy acid III and 8.0 g of CrO_3 in a mixture of 25 ml of acetic acid and 75 ml of water was stirred for 15 hr at room temperature. Water and ether were added, and the water layer was extracted with ether. The ethereal extract was dried (K_2CO_3) and concentrated, giving 0.60 g (16%) of the ketone XXIX, mp 119–123°. The ir spectrum was identical with that of an original sample of XXIX.

Attempted Reactions with Ketone XXIX.—An attempt to prepare the oxime of ketone XXIX using standard procedures only gave the starting material back. An attempt to prepare the thio ketone of XXIX by heating a mixture of 0.5 g of ketone XXIX and 2.0 g of P_2S_5 in 50 ml of sulfolane at 140° for 30 hr was also unsuccessful. A small amount of ketone XXIX was the only product that was isolated.

3,3,5,5-Tetramethyl-1-thiacyclohexan-4-one (V).—A solution of 5 g (0.023 mol) of hydroxycarboxylic acid III and 2.8 g (0.023 mol) of $SOCl_2$ in 40 ml of benzene was refluxed for 2 hr. The reaction mixture was concentrated, and the residue was chromatographed over silica gel. Upon elution with CH_2Cl_2, 3.0 g (76%) of the ketone V was obtained. Distillation, bp 88 (12 mm), gave an analytical sample: ir (neat) 1690 cm^{-1} (C=O); nmr (CCl_4) τ 7.37 (s, methylene protons) and 8.82 (s, methyl protons).

Anal. Calcd for $C_9H_{16}OS$ (172.30): C, 62.72; H, 9.36; S, 18.61. Found: C, 62.9, 62.8; H, 9.4, 9.4; S, 18.6, 18.5.

Attempts to prepare an oxime of ketone V using standard procedures were unsuccessful. Starting material was recovered almost quantitatively.

Registry No.—III, 17539-59-2; IV, 17539-60-5; V, 17539-61-6; IX, 17539-62-7; X, 17539-63-8; XI, 17539-64-9; XV, 17539-65-0; XIX, 17539-66-1; XIX (free acid), 17539-67-2; XX, 17539-68-3; XXI, 17539-69-4; XXII, 17539-70-7; XXIII, 17605-19-5; XXV, 17539-71-8; XXVII, 17539-72-9; XXVIII, 17539-73-0; XXIX, 17539-74-1.

Synthesis and Nuclear Magnetic Resonance Spectra of 2-Oxazolidones

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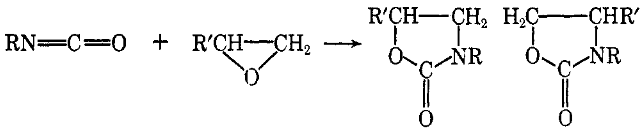
N-substituted 2-oxazolidones have been prepared from isocyanates and epoxides in refluxing DMF with lithium chloride as catalyst. Although the major products are 5-substituted 2-oxazolidones, 4-substituted isomers were also isolated in several cases. The nmr spectra of the 2-oxazolidones were determined, and chemical shift–structure relationships are reported.

The reaction of organic isocyanates with 1,2-epoxides has been reported to yield 2-oxazolidones.[3] A number of catalysts and solvents have been used with varying degrees of success. Most workers reported the formation of only the 5-substituted 2-oxazolidone (I) from the reaction of an isocyanate with an unsymmetrically substituted epoxide. In one case,[3b] however, the product from the reaction of phenyl isocyanate with phenyl glycidyl ether was assigned the structure of the isomeric 4-substituted 2-oxazolidone (II, R′ = $PhOCH_2$; R = Ph). Previous workers had reported the structure I (R′ = $PhOCH_2$; R = Ph) for this reaction product.



I II

Of interest to us were the literature reports that only one isomeric 2-oxazolidone is obtained from the reaction of isocyanates with unsymmetrical 1,2-epoxides despite the relatively vigorous conditions employed (reaction temperatures *ca.* 150° or greater) and possible effects (steric, conjugative, and polar) of substituent groups in the epoxide on the reaction course. We have examined the reaction in more detail and have shown that, although the 5 isomer predominates, some 4 isomer is also formed.

We have also examined the nmr spectra of a variety of N-substituted (I and II) (Table I) and unsubstituted (III and IV) (Table II) 2-oxazolidones, and have made structural assignments on the basis of the results obtained. In one case, that involving **1** (Table I), independent confirmation of the nmr assignments was made by synthesis and hydrolysis studies. The rationale and discussion of the nmr assignments will be given presently. The preparation of the N-unsubstituted 2-oxazolidones and the N-phenyl-5-decyl- and -dodecyl-2-oxazolidones (**8** and **9**) has been described elsewhere.[4] The remaining N-substituted 2-oxazolidones based on *p*-tolyl and *n*-butyl isocyanates were prepared by adding the requisite isocyanate to a solution of the epoxide and lithium chloride catalyst in refluxing N,N-dimethylformamide (DMF). After completing the addition of isocyanate, the reaction mixtures were refluxed for 6 hr and then worked up to give the 2-oxazolidones in good yields (70% or better). These general reaction conditions were arrived at by briefly examining the effect of solvent, catalyst, and mode of addition of reactants on the yield of the 2-oxazolidone prepared from *p*-tolyl isocyanate and styrene oxide.

Weiner[5] has shown that aryl isocyanates react with DMF at elevated temperatures to give formamidines (**11**). To suppress this reaction, we added the isocyanate to a refluxing DMF solution containing the epoxide and catalyst. Initially, using this mode of addition and tetramethyl ammonium iodide as the catalyst, N′-tolyl-N,N-dimethylformamidine (**11**, R = *p*-tolyl), was the only reaction product identified; it accounted for 35% of the starting isocyanate. When the reaction was repeated with lithium chloride as the catalyst, formamidine formation was negligible, and the superiority of lithium chloride as a catalyst for 2-oxazolidone formation was confirmed.

$$RN{=}C{=}O + HC(O)N(Me)_2 \longrightarrow \underset{\textbf{11}}{RN{=}CHN(Me)_2} + CO_2$$

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