Recently Goerdeler and Keuser[3] reported the synthesis of the sulfur analogs of the carbamoyldimedones (dimedone = 5,5-dimethylcyclohexane-1,3-dione). These compounds (B) are readily obtained by treating a β-diketone, such as dimedone, with an isothiocyanate. Since the ability of sulfur to hydrogen bond is a topic of current interest,[4,5] several compounds of type B have been synthesized and their pmr spectra have been determined (Table I).

TABLE I

PROTON MAGNETIC RESONANCE DATA FOR THE CARBOXAMIDES

Compound[a]	Solvent	R, J[b]	NH[c]	OH[c]
B	$CDCl_3$	C_6H_5	13.97	17.37
	CCl_4	C_2H_5 5.0, 7.2	12.2	17.08
	$CDCl_3$	C_2H_5 5.0, 7.2	12.3	17.17
	CCl_4	CH_3 4.8	12.2	17.06
	$CDCl_3$	CH_3 4.85	12.3	17.11
A[d]	$CDCl_3$	C_6H_5	11.7	17.9
	CCl_4	CH_3 5.1	9.6	18.15
	$CDCl_3$	CH_3 5.2	9.7	18.13
C	$CDCl_3$	C_6H_5 5.15[e]	14.2, 14.7	

[a] Since the nomenclature for these compounds is awkward, the letter refers to the figures in the text. [b] J in hertz. [c] In parts per million from tetramethylsilane. [d] Data taken from ref 1. [e] Coupling to methyl.

The data in Table I indicate that substitution of sulfur for the amide oxygen does not greatly alter the nature of the conjugated system. The hydrogen bonds involving the NH are somewhat stronger in the sulfur compounds (B) while the oxygen–sulfur–hydrogen bridges are slightly weaker than in the oxygen derivatives (A). The splitting of 5 Hz resulting from the coupling of the NH to the adjacent methyl (or ethyl) locates the proton on nitrogen with little exchange to the oxygen. Upon lowering the temperature of a chloroform solution of N-methyl-2-thiocarbamoyldimedone (B, R = CH_3) to $-40°$, little change in the pmr spectrum was observed.

An interesting member of the series is formed when the enolic hydroxyl is replaced by a methylamino group as in compound C. The pmr spectra indicate that both NH groups are strongly chelated, but the hydrogen bonds are not as strong as the hydroxyl bridge in compounds A or B. Upon lowering the sample temperature to $-40°$, the broad NH signal at δ = 14.2 ppm gradually assumes the appearance of a poor quartet. This signal can thereby be assigned to the proton residing on the methyl-substituted nitrogen. From the presence of a 5.0-Hz spin coupling of the N-methyl group, it is evident that the proton is on the nitrogen with little exchange to sulfur.

These results suggest that sulfur is as able as oxygen to participate in the unusual cross-conjugation and hydrogen bonding in these systems. This conclusion is in agreement with the studies of Marcus, *et al.*,[4] on simpler compounds.

(3) J. Goerdeler and U. Keuser, *Chem. Ber.*, **97**, 2209 (1964).
(4) S. H. Marcus, W. F. Reynolds, and S. I. Miller, *J. Org. Chem.*, **31**, 1872 (1966).
(5) S. H. Marcus and S. I. Miller, *J. Am. Chem. Soc.*, **88**, 3719 (1966).

Experimental Section

The two compounds, 4,4-dimethyl-2,6-dioxothiocyclohexanecarboxanilide (B, R = C_6H_5) and 4,4-dimethyl-2-(methylamino)-6-oxothio-1-cyclohexene-1-carboxanilide (C) were prepared as described by Goerdeler and Keuser[3] and have the physical properties reported by them.

The compound N-ethyl-4,4-dimethyl-2,6-dioxothiocyclohexanecarboxamide (B, R = C_2H_5) has not been reported. It was prepared similar to the others,[3] and crystallized from hexane. After sublimation, it melted at 54.6–55.4°. *Anal.* Calcd for $C_{11}H_{17}NO_2S$: C, 58.12; H, 7.54; N, 6.16; S, 14.11. Found: C, 58.48; H, 7.51; N, 6.17; S, 14.20.

In a similar manner N-methyl-4,4-dimethyl-2,6-dioxothiocyclohexanecarboxamide (B, R = CH_3) was prepared. It melted at 138.8–139.6°. *Anal.* Calcd for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09; N, 6.57; S, 15.03. Found: C, 56.70; H, 7.07; N, 6.63; S, 15.20.

The determination of spectra has been previously described.[1]

Registry No.—B (R = C_6H_5), 7721-63-3; B (R = C_2H_5), 7721-64-4; B (R = CH_3), 7721-65-5; A (R = C_6H_5), 7721-66-6; A (R = CH_3), 944-53-6; C (R = C_6H_5), 7721-68-8.

Acknowledgments.—This work was supported in part by the National Science Foundation Undergraduate Research Program (Grant GY-354). We thank Miss Margaret Roberts for her assistance in the project.

Preparation of Novel Cyclohexadienonecarboxamides

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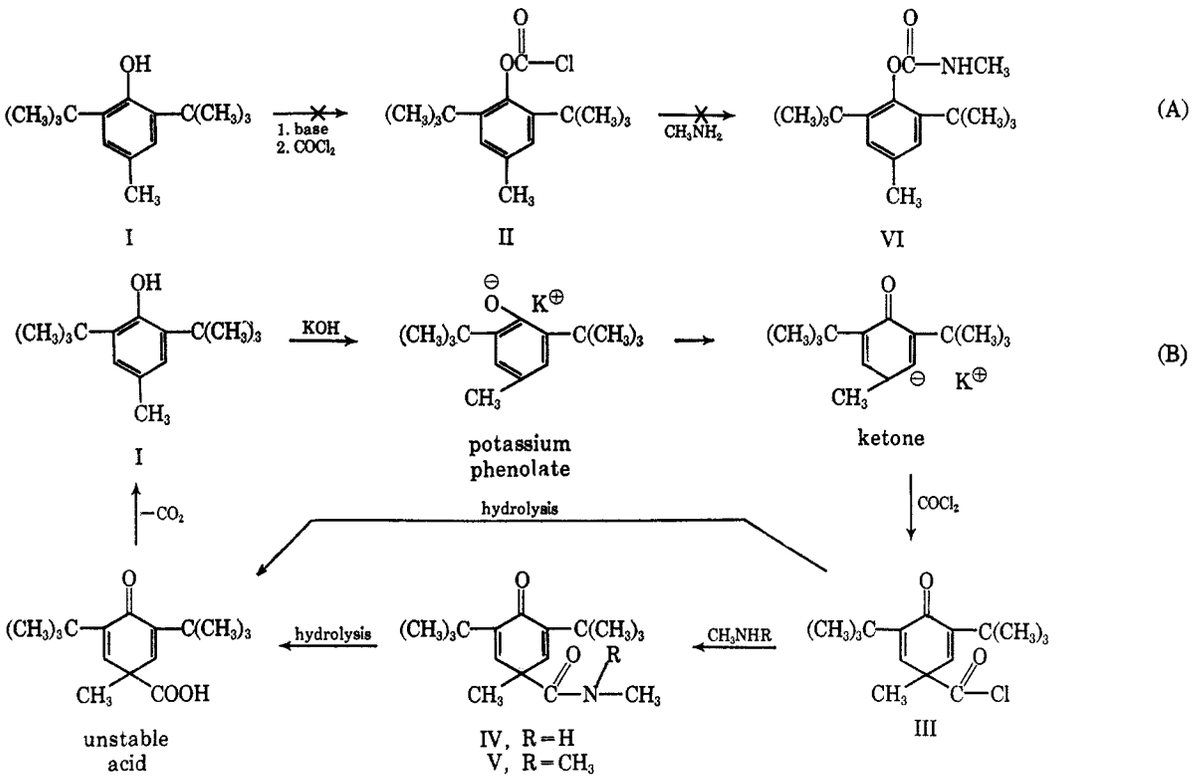
Received September 21, 1966

Phosgene would not react with 2,6-di-*t*-butyl-4-methylphenol (I) under normal conditions to form the corresponding chloroformate (II) because the phenolic hydroxyl group is shielded too much by the adjacent bulky *t*-butyl groups. The chloroformate was desired for subsequent reaction with methylamine to prepare 2,6-di-*t*-butyl-4-methylphenyl methylcarbamate (VI) as illustrated by A. This carbamate, which is a selective herbicide for use on turf grass, is readily produced by reaction of I with methyl isocyanate in the presence of amine catalysts.[1] (See Scheme I.)

Under special conditions and using potassium hydroxide, phosgene reacted to form 3,5-di-*t*-butyl-1-methyl-2,5-cyclohexadien-4-onecarboxylic acid chloride (III). The latter condensed with methylamine and dimethylamine, respectively, to form the corresponding crystalline amides (IV and V) in high purity. Sodium hydroxide did not affect the formation of III even under the conditions successfully used with potassium hydroxide. Tertiary amines, which normally serve as acid acceptors for aryl chloroformate formation,[2] were also ineffective. Only when potassium hydroxide was employed initially to form an anhydrous salt was a significant acidic product

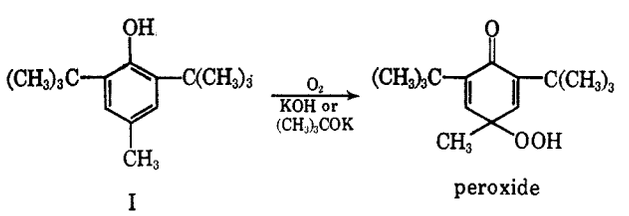
(1) A. H. Haubein, U. S. Patent 3,140,167 (July 7, 1964), assigned to Hercules Powder Co.
(2) M. Matzner, R. P. Kurkjy, and R. J. Cotter, *Chem. Rev.*, **64**, 649 (1964).

SCHEME I



obtained from the reaction with phosgene. However, instead of being the expected chloroformate (II), the product was 3,5-di-*t*-butyl-1-methyl-2,5-cyclohexadien-4-onecarboxylic acid chloride (III). The proposed mechanism for formation of the acid chloride and its derivatives is illustrated by B.

The structures of the crystalline amides (IV and V) were proven by elemental analyses, infrared absorption spectra (which showed they were amides but not carbamates), and nmr studies (which showed they were cyclohexanone derivatives rather than aromatic compounds). Attempts to hydrolyze the acid chloride (III) or the amides (IV and V) to the free acid were unsuccessful. In every case decarboxylation occurred and the isolated product was the starting phenol (I).



A brief search of the literature indicates that the preparation of the acid chloride (III) and amides (IV and V) from the phenol (I) is novel. The only related reactions found in the literature describe[3] oxidative attack at the *para* position to form the peroxide as illustrated below and alkylation of 2,6-di-*t*-butyl-4-methylphenoxide anion in the *para* position.[4]

(3) H. R. Gersmann and A. F. Bickel, *J. Chem. Soc.*, 2356 (1962); 2711 (1959).

(4) B. Miller, *Tetrahedron Letters*, 1727 (1965); B. Miller and H. Margulies, *ibid.*, 1733 (1965); *J. Org. Chem.*, **30**, 3895 (1965); N. Kornblum and R. Seltzer, *J. Am. Chem. Soc.*, **83**, 3668 (1961).

Experimental Section

3,5-Di-*t*-butyl-1-methyl-2,5-cyclohexadien-4-onecarboxylic Acid Chloride (III).—A mixture of 2,6-di-*t*-butyl-4-methylphenol (110 g, 0.5 mole), toluene solvent (700 ml), and potassium hydroxide solution (33 g 85% dissolved in 33 g of water, 0.5 mole contained) was stirred and refluxed through a decanter to remove water from the system. After 4 hr at reflux, 46 ml of water was removed which corresponded to the water charged plus the 0.5 mole expected to form the ketone as illustrated above. The mixture was cooled to 25° and a solution of phosgene (100 g, 1.1 moles) in toluene (100 g) was added. After stirring at 55–60° for 2 hr, the mixture was cooled to 25° and washed with water. The oil layer was dried over Drierite, filtered, and titrated with 0.1 *N* sodium hydroxide using phenolphthalein indicator. The 768 g of oil layer contained 9.9% of acid chloride, which correspond to 53.8% yield based on the phenol. The solution was distilled to obtain a mixture of I and III which distilled at 93–96° (1 mm), and analyzed as 59.8% acid chloride. Infrared studies proved that this fraction was a mixture of I and III. Apparently these compounds are not readily separated by distillation. About 78% of the original acid chloride was found in this distilled fraction. The low yield of III was probably due to its hydrolysis during the washing after the reaction with phosgene. The infrared absorption spectrum of the distilled mixture had the following characteristic bands: hindered OH at 2.75, O=CCl at 5.63, conjugated C=O at 6.05, aliphatic C=C at 6.19, aromatic C=C at 6.75 μ.

Hydrolysis of the acid chloride proceeded as follows. The distilled mixture (55 g, contained 0.11 mole of acid chloride and 0.10 mole of I) was treated with methanol (100 ml) and 20% sodium hydroxide (100 ml, 0.5 mole). After refluxing for 2 hr, the precipitated solid (8 g) was filtered. It was characterized as sodium carbonate by its melting point (375°), insolubility in organic solvents, and effervesence upon treatment with dilute hydrochloric acid. The methanol–water solution was evaporated to dryness under vacuum to obtain 80 g of solid residue. The latter was dissolved in water and ethyl ether and the ether layer was separated. Evaporation of the ether under vacuum gave 45 g of the original phenol (I), which corresponded to 95% total recovery.

3,5-Di-*t*-butyl-1-methyl-2,5-cyclohexadien-4-one-N-methylcarboxamide (IV).—A toluene solution (940 g) of the acid chloride prepared as described above contained 0.688 mole of acid chloride. This solution was stirred at 25° while 40% aqueous methyl-

amine (170 g, 2.2 moles) was added over 30 min. After 2 hr at 25°, the oil layer was separated, washed with water, dried over calcium sulfate, and concentrated under reduced pressure to a residue weight of 400 g. The latter was cooled to −40° and filtered to obtain 190 g of colorless, crystalline IV. This was a quantitative yield based on the acid chloride. An analytical sample was recrystallized from heptane. The infrared absorption spectra of IV and VI were compared to show that VI has characteristic absorption bands for carbamate C=O at 5.74 and 5.84 μ while IV has characteristic absorption bands for conjugated ketone C=O at 5.99 and for secondary amide C=O at 6.05 μ. The nmr spectra for VI and IV were compared to show that the resonance position of the methyl group on the aromatic substrate (VI) was at 2.3 ppm while the methyl group attached to the nonaromatic substrate (IV) appeared at 1.5 ppm. The melting points of VI and IV were 199–200° and 98–99°, respectively.

Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.70; H, 9.81; N, 5.18. Found: C, 73.63; H, 9.56; N, 5.85.

Hydrolysis of IV with potassium hydroxide, concentrated and dilute sulfuric acid, and concentrated hydrochloric acid produced the phenol (I) as the only product isolated.

3,5-Di-*t*-butyl-1-methyl-2,5-cyclohexadien-4-one-N,N-dimethylcarboxamide (V).—A toluene solution of the acid chloride was prepared as previously described except that the washing with water was omitted. After the excess phosgene had been removed under vacuum at 25°, 25% aqueous dimethylamine (149 g, 0.83 mole) was fed at 25°. After 1 hr of stirring at 25° water (300 ml) was added and the oil layer was separated, washed again with water, and dried over Drierite. The solution was concentrated under reduced pressure and crystallized to obtain 122 g of crystalline V. This corresponded to an over-all yield of 84% based on I. An analytical sample was crystallized from acetonitrile to obtain V having mp 84–86°.

Anal. Calcd for $C_{18}H_{29}NO_2$: C, 74.20; H, 10.03; N, 4.81. Found: C, 74.96; H, 9.96; N, 5.16.

The infrared absorption spectrum showed bands at 6.04 μ (tertiary amide C=O).

Summary

Phosgene reacted only under special conditions with 2,6-di-*t*-butyl-4-methylphenol. The product was 3,5-di-*t*-butyl-1-methyl-2,5-cyclohexadien-4-onecarboxylic acid chloride rather than the expected chloroformate of the phenol.

Registry No.—III, 7492-84-4; IV, 7492-85-5; V, 7492-86-6.

Acknowledgment.—The authors gratefully acknowledge the nmr data by A. E. Gabany, Jr., and th einfrared data by C. C. Asbury.

Synthesis and Decarboxylation of Pyridine Carboxylic Acids from Pyridoxol[1]

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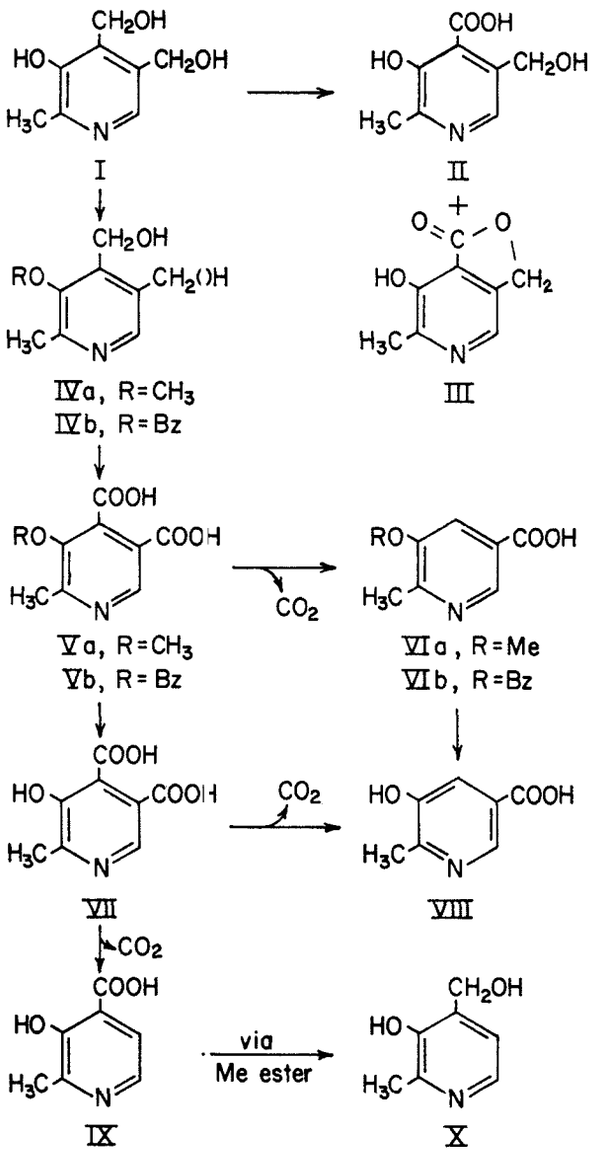
Received September 8, 1966

Bacterial oxidation of pyridoxol (I, Chart I) gives rise to several unusual pyridine derivatives.[4-6] These include 4-pyridoxic acid (II) and its lactone (III),[6] 5-pyridoxic acid,[4] 2-methyl-3-hydroxy-5-formylpyridine-4-carboxylic acid,[6] 2-methyl-3-hydroxypyridine-4,5-dicarboxylic acid (VII),[6] and 2-methyl-3-hydroxypyridine-5-carboxylic acid (VIII).[6] Compound VII is rapidly decarboxylated to VIII by an enzyme isolated from these bacteria.[7] For further study of enzymatic steps in the degradation of vitamin B_6, a source of several of these compounds for use as substrates was required. This paper describes convenient procedures for obtaining VII and VIII from pyridoxol (I), which is commercially available. Both VII[8,9] and VIII[10] have been prepared previously by longer procedures from acyclic precursors. The formation and decarboxylation of VII were also of interest as a possible method for specifically degrading labeled pyridoxol in studies of its biosynthesis.

CHART I



(1) Supported in part by grants (AI-1448 and AM-1575) from the National Institutes of Health, U. S. Public Health Service. Presented in part at the Westdeutsche Chemiedozenten-Tagung, Freiburg, Germany, April 1964 [for an abstract see E. E. Snell and D. Palm, *Angew. Chem.*, **76**, 599 (1964)].

(2) Organisch-Chemisches Institut, Technische Hochschule, München 2, Germany.

(3) Postdoctoral Fellow, National Institute of Arthritis and Metabolic Diseases, 1963–1964.

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(5) M. Ikawa, V. W. Rodwell, and E. E. Snell, *ibid.*, **233**, 1555 (1958).

(6) R. W. Burg, V. W. Rodwell, and E. E. Snell, *ibid.*, **235**, 1164 (1960).

(7) E. E. Snell, A. A. Smucker, A. Ringelmann, and F. Lynen, *Biochem. Z.*, **341**, 109 (1964).

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(10) C. J. Argoudelis and F. A. Kummerow, *J. Org. Chem.*, **26**, 3420 (1961).