Method B.—A 2-Gm. quantity of Ib was added to hot paraffin oil and heated to 230° for 30 min. After cooling, the paraffin oil was decanted and the solid residue was triturated with petroleum ether to remove traces of paraffin oil. Then it was recrystallized from chloroform, m.p. 185°, and mixed melting point proved to be recovered starting material.

REFERENCES

(1) Nabih, I., and ElSheikh, M., Abstracts of Papers, 150th Meeting, American Chemical Society, Atlantic City, N. J., September 1965.
(2) Swingle, M., Phillips, M., and Gehan, J., *U. S. Dept. Agr., Bur. Entomol. Plant Quaranline*, July 1944, 621.
(3) Paramentier, R., *Compt. Rend. Soc. Biol.*, **143**, 585 (1949).
(4) Block, H., *et al.*, *Helv. Chim. Acta*, **30**, 539(1947).
(5) Knorr, L., *Ber.*, **17**, 541(1884).
(6) Backeberg, O., *J. Chem. Soc.*, **1935**, 1568.
(7) Jacini, G., and Bertulli, N., *Gazz. Chim. Ital.*, **69**, 111(1939).
(8) Heiduschha, A., and Goldstein, E., *Arch. Pharm.*, **254**, 584(1916).
(9) Szent-Gyorgyi, A., *Biochem. Z.*, **150**, 195(1924).
(10) Bangdiwala, B., and Desai, C., *J. Indian Chem. Soc.*, 31, 688(1954); through *Chem. Abstr.*, **50**, 1008g(1956).
(11) Mann, F., and Saunders, B., "Practical Organic Chemistry," Longmans, London, England, 1960, p. 520.
(12) Blicke, F. F., *Org. Reactions*, **1**, 303(1947).

Synthesis of Two 4,5-Dialkyl Isosydnones

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The syntheses of two new dialkyl isosydnones are described. These represent the first nonbenzenoid derivatives to be reported. Spectral data for each compound are also given.

THIS LABORATORY has been interested in the study of *meso*-ionic compounds as possible therapeutic agents for several years. The first *meso*-ionic sydnone system I was synthesized in 1935 by Earl and Mackney (1). The authors have previously reported (2–6) the synthesis and pharmacological activity of a number of 3-monosubstituted and 3,4-disubstituted derivatives of this system. Both the monoalkyl and the dialkyl substituted syndnones exhibited potent central nervous system stimulatory properties (2–4). Further work on a possible mechanism of action and important medicinal chemical features of this system is currently underway in this laboratory.

As a logical extension of these investigations, a study of the medicinal aspects of a system isomeric with the sydnones was warranted.

The synthesis of ψ-2,4-dihydro-4,5-diphenyl-2-keto-1-oxa-3,4-diazole (II*a*) has been reported by Hashimoto and Ohta (7). (The system II shall be referred to by the name *isosydnone*.) This system is isomeric with the sydnone ring I in that the pseudolactone function has been reversed in structure II. An earlier report by Hoegerle (8) disclosed the synthesis of a fused ring *meso*-ionic system III from the reaction of *N*-aminopyridone-(2) with phosgene. This system contains the isosydnone nucleus which was first obtained as a monocyclic system II*a* in 1961(7).

Hashimoto (7) achieved the synthesis of compound II*a* by the method of Hoegerle (8), in which 1-benzoyl-1-phenylhydrazine was treated with phosgene in chloroform solution in the presence of potassium carbonate. The product was characterized through its infrared spectrum and degradative reactions in both acid and base. Further attempts to prepare other derivatives of this nucleus (II) were unsuccessful, with the exception of preparing a small amount of compound II*b*. However, the amount obtained was insufficient to afford complete characterization.

Recently, Ainsworth (9) has reported the preparation of 4-methyl-5-phenylisosydnone II*b* in good yield, as well as a study of the nature of the reaction. The method of synthesis differed from that employed by Hashimoto (7) in that the hydrochloride salt of the acylhydrazine was used in solution in dioxane, and the reaction was completed under reflux conditions rather than at -7 to $-10°$.

Both of the isosydnone derivatives, II*a* and II*b*, reported contain a phenyl ring which can aid in stabilizing the *meso*-ionic system through π-electron delocalization. For the purpose of studying the medicinal chemical aspects of the isosydnones (II), it was desirable to synthesize derivatives in which both R and R′ are alkyl substituents. This was also necessary for correlation with the medicinal activity of the alkyl-sydnones (2–6). With this purpose in mind, this preliminary report discloses the synthesis of two new dialkyl isosydnones, II*c* and II*d*.

The problem of obtaining 1-acylated hydrazines was overcome to a large degree by acylating the alkylhydrazine in a high dilution of ether with the appropriate acid anhydride (10). This procedure gives a mixture of 1-acylhydrazine and 1,2-di-acylhydrazine which can be separated by fractional distillation to provide the 1-acylhydrazine in good yield.

EXPERIMENTAL

4,5-Dimethylisosydnone (IIc).—1-Acetyl-1-methylhydrazine (IV) (0.19 mole) was dissolved in 2 L. of cold chloroform containing 300 Gm. of anhydrous potassium carbonate. The mixture was cooled to $-10°$ in a propylene glycol–dry ice bath. With vigorous stirring, a steady stream of phosgene was introduced into the mixture for a period of 15 min. The mixture was allowed to warm to room temperature while stirring. After refluxing for 0.5 hr. to expel the excess phosgene, the insoluble solids were filtered out, and the chloroform solution was concentrated *in vacuo* to give a red oil. Vacuum distillation of the oil yielded 4 Gm. of a colorless oil

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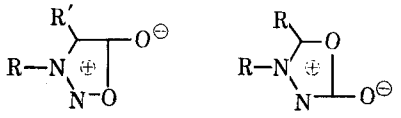
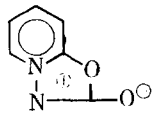
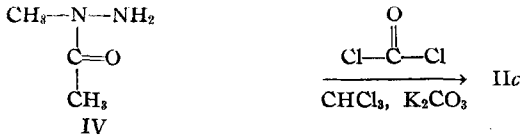


I II

a, R = R′ = ϕ
b, R = CH_3, R′ = ϕ
c, R = R′ = CH_3
d, R = $CH(CH_3)_2$, R′ = CH_3

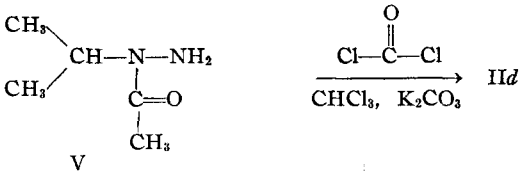


III



IV IIc

Scheme I



V IId

Scheme II

(II*c*) at a boiling point of 50–52°/0.5 mm. (See Scheme I.)

Anal.—Calcd. for $C_4H_6N_2O_2$: C, 42.10; H, 5.30; N, 24.60; O, 28.00. Found: C, 41.95; H, 5.73; N, 24.53; O, 27.79.

4-Isopropyl-5-methylisosydnone (II*d*).—1-Acetyl-1-isopropylhydrazine (V) (0.09 mole) was reacted with phosgene under the same conditions specified above. Evaporation of the solvent yielded a yellow oil which would not distil. Addition of benzene to the oil resulted in the precipitation of a solid which on recrystallization from benzene gave 2 Gm. of white crystals II*d* which melted at 111–112°. (See Scheme II.)

Anal.—Calcd. for $C_6H_{10}N_2O_2$: C, 50.70; H, 7.00; N, 19.70; O, 22.60. Found: C, 51.08; H, 7.03; N, 19.75; O, 22.14.

DISCUSSION

The infrared spectrum of isosydnone II*c* contained an absorption in the pseudocarbonyl region (7) at 1785 cm.$^{-1}$. Also noted was the disappearance of the amide I band at 1650 cm.$^{-1}$ which was present in the starting acylhydrazine (IV).

Compound II*c* is not stable in hydroxylic solvents, which led to problems in obtaining ultraviolet absorption data. An absorption was detected in the 200 to 220-mμ region, but the molar extinction coefficient could not be ascertained.

The infrared spectrum of isosydnone II*d* contained an absorption at 1750 cm.$^{-1}$ representing the pseudocarbonyl group, and was devoid of the amide I band at 1675 cm.$^{-1}$ from the starting acylhydrazine (V).

This derivative II*d* was more stable in solution than compound II*c*. The ultraviolet spectrum indicated that an aqueous solution was stable for 36–48 hr. at room temperature. The spectrum shows a $\lambda_{max.}^{H_2O}$ 235 mμ, ϵ 4000.

It is evident that the synthesis of other dialkyl isosydnones may be achieved with this general procedure with the appropriate 1-acyl-1-alkylhydrazines.

REFERENCES

(1) Earl, J. C., and Mackney, A. W., *J. Chem. Soc.*, **1935**, 899.
(2) Kier, L. B., *et al.*, *Nature*, **195**, 817(1962).
(3) Kier, L. B., and Dhawan, D., *J. Pharm. Sci.*, **51**, 1058 (1962).
(4) Dhawan, D., and Kier, L. B., *ibid.*, **53**, 83(1964).
(5) Kier, L. B., Dhawan, D., and Fregly, M. J., *ibid.*, **53**, 677(1964).
(6) Fregly, M. J., Kier, L. B., and Dhawan, D., *Toxicol. Appl. Pharmacol.*, **6**, 529(1964).
(7) Hashimoto, M., and Ohta, M., *Bull. Chem. Soc. Japan*, **34**, 668(1961).
(8) Hoegerle, K., *Helv. Chim. Acta*, **41**, 548(1958).
(9) Ainsworth, C., *Can. J. Chem.*, **43**, 1607(1965).
(10) Sugarman, G., *Dissertation Abstracts*, **24**, 526(1963).