Reactions of Organic Halides with Dimethyl Sulfoxide

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Organic sulfoxides bear some similarity to amine oxides in the methods used for their preparation and in their properties. Both types of compound are basic. Amine oxides react with alkyl halides with formation of the corresponding *N*-alkoxyammonium halides. It seemed possible that sulfoxides would react with alkyl halides with the formation of *S*-alkoxysulfonium halides.

Prior to the publications of Kuhn[1] and Kuhn and Trischmann[2] it had been found in this laboratory that methyl iodide does react with dimethyl sulfoxide but not with the formation of the anticipated *S,S*-dimethyl-*S*-methoxysulfonium iodide but, as was shown by Kuhn and associates,[1,2] of trimethylsulfoxonium iodide, $(CH_3)_3\overset{+}{S}O\cdot I^-$.

Pharmacologic studies made with trimethylsulfoxonium iodide in dogs showed that it possesses the muscarinic and nicotinic activities of acetylcholine. However, it is only $^1/_{1000}$th or $^1/_{10,000}$th as active as acetylcholine in lowering blood pressure and its nicotinic activity is less than that of acetylcholine.[3]

Strangely, it was found that other simple alkyl halides did not react with dimethyl sulfoxide under conditions similar to those observed in the reaction with methyl iodide.

However, it has been found that halides in which a halogen atom is attached to the α-carbon atom to a carbonyl or ester group did react with dimethyl sulfoxide at room temperatures. This reaction, has also been studied recently by Kornblum, Powers, Anderson, Jones, Larson, Levand, and Weaver.[4] We have confirmed the findings of these authors that phenyl glyoxal is found among the products of reaction of α-bromoacetophenone and dimethyl sulfoxide but in only 3% yields, under our conditions. We have also found among the products of this reaction phenylglyoxylic acid in 34% yield and trimethylsulfonium bromide in 50% yields.

Similarly, trimethylsulfonium bromide was found among the products of reaction of dimethyl sulfoxide and ethyl bromoacetate.

The mechanism of these reactions is not clear at this time.

EXPERIMENTAL[5,6]

Reaction between dimethyl sulfoxide and α-bromoacetophenone. Five g. (0.025 moles) α-bromoacetophenone was dissolved in 6 g. (0.077 moles) dimethyl sulfoxide and the mixture kept at room temperature in the darkness. After about 1 hr. the solution became warm and after 2 hr. a crystalline cake was formed, which after addition of ether was put into the deep freezer for 10 hr. Then the sticky crystals were filtered (4 g.) and recrystallized from methanol-ether, m.p. 145° (dec.). Five more recrystallizations yielded 2 g. (50%) of a compound which volatilized completely at about 198°.

Anal. Calcd. for C_3H_9BrS: C, 22.94; H, 5.77. Found: C, 22.99; H, 5.89.

The infrared spectrum was identical with an authentic sample of trimethylsulfonium bromide[7] prepared from $(CH_3)_3\overset{+}{S}I^-$ and Ag_2O followed by neutralization with HBr and crystallization of the salt from methanol-ether.

The filtrate from the crystals and the mother liquors from the recrystallizations were combined, poured into water, and extracted with ether. The ether was removed under reduced pressure, the oily residue treated with sodium bicarbonate solution, and extracted with ether again. The ether was dried as usual, removed, and the remaining brown oil (1.5 g.) warmed with an alcoholic–hydrochloric acid solution containing 4 g. 2,4-dinitrophenylhydrazine. The precipitate yielded after recrystallization from *N,N*-dimethylformamide–ethanol 0.4 g. (3%) phenylglyoxalbis-2,4-dinitrophenylhydrazone, m.p. 288–290°C.

Anal. Calcd. for $C_{20}H_{14}N_8O_8$: C, 48.59; H, 2.85. Found: C, 48.76; H, 3.10.

The bicarbonate solution was made acid with hydrochloric acid and extracted with ether. The ether was dried, removed *in vacuo*, and the residue crystallized in the deep freezer, m.p. 47–57° (1.8 g.); recrystallized from benzene-petroleum ether, m.p. 57–62° (1.3 g.) (34% of theory).

Phenylhydrazone, m.p. 161–162°.[8]

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03. Found: C, 69.81; H, 5.08.

2,4-Dinitrophenylhydrazone, m.p. 189–190°.

Anal. Calcd. for $C_{14}H_{10}N_4O_6$: C, 50.51; H, 3.05. Found: C, 50.36; H, 3.40.

The 2,4-dinitrophenylhydrazone of an authentic sample of phenylglyoxylic acid[9] was prepared; melting point and mixed melting point with above dinitrophenylhydrazone was 189–190°. The infrared spectra of the two 2,4-dinitrophenylhydrazones were identical.

Reaction between dimethyl sulfoxide and ethyl bromoacetate. A mixture of 15.6 g. (0.20 mole) dimethyl sulfoxide and 23.5 g. (0.14 mole) ethyl bromoacetate was kept at room temperature in the darkness. After about five days the solution turned orange, became viscous and crystals were formed. After two weeks (with benzene as a solvent the reaction time is longer), the crystals were separated from the oil, treated with acetone, and recrystallized from methanol-ether. Yield, 10 g. (45%).

Anal. Calcd. for C_3H_9BrS: C, 22.94; H, 5.77; Br, 50.87; S, 20.41. Found: C, 22.76, H, 5.83, Br, 51.19, S, 20.91.

The infrared spectrum was identical with an authentic sample of trimethylsulfonium bromide.[7]

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N^{α},N^{α}-Dimethylhistamine, a Hypotensive Principle in *Casimiroa edulis* Llave et Lex*

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The seeds of *Casimiroa edulis* Llave et Lex., a tree growing in Mexico and Central America, have been used in native medicine as a hypnotic and sedative.[1,2] Ramirez and Rivero[3] have reported that an extract of the seeds is used clinically in insomnia in hypertension; deLille[4] found that intravenous administration of such extracts produced a marked decrease of blood pressure in dogs, and that the material was toxic in higher doses.

A number of chemical investigations of the seeds of *Casimiroa edulis* have been reported.[2,5,6] About a dozen compounds have been isolated, including known coumarins, furanoquinoline alkaloids, and flavones, and some of as yet unknown structure. It was suggested that *N*-benzoyltyramine might be responsible for the pharmacological activity of the plant[6] but no details were given.

The hypotensive action of an extract of *Casimiroa edulis* seeds prepared in this laboratory has been confirmed by Dr. C. A. Stone, of the Merck Institute for Therapeutic Research, West Point, Pa. He found, also, that this effect was not obtained if an antihistamine was also administered, indicating that the hypotensive agent was histamine or a histamine-like compound.

Paper chromatographic analysis of a crude extract of *Casimiroa edulis* seeds by the method of Ames and Mitchell[7] showed that histamine itself was absent. However, at least two other compounds were found which gave positive reactions to the Pauly reagent (diazobenzenesulfonic acid), an agent which gives fairly characteristic reactions with imidazoles. Separation of the imidazoles from the crude extract was then effected by the method of Koessler and Hanke.[8] Eventually, a pure compound was isolated as its hydrochloride and its picrate; it was identical with N^{α},N^{α}-dimethylhistamine which had been produced synthetically;[9] yield of pure compound from seeds was 0.05%. The search for the second compound which gave a positive reaction to Pauly's reagent is being continued.

According to Huebner, Turner, and Scholz, N^{α},N^{α}-dimethylhistamine acts pharmacologically much like histamine,[9,10] in causing a marked lowering of the blood pressure of animals. Apparently, at least part of the pharmacological activity of *Casimiroa edulis* seeds may be attributed to the presence of N^{α},N^{α}-dimethylhistamine. As far as we know, previously this compound has been found in nature only in the sponge *Geodia gigas*, and in this case it was not fully characterized.[11]

EXPERIMENTAL[12]

Seven hundred grams of finely powdered air-dried *Casimiroa edulis* seeds (S. B. Penick, New York) were triturated with five 2500-cc. portions of boiling methanol. The filtered extracts were combined, 250 cc. of water was added and the methanol was removed by distillation. The dark brown residue was extracted thrice with 100-cc. portions of petroleum ether in order to eliminate fats. The petroleum ether extract was discarded since it was negative to Pauly's reagent. The aqueous phase was filtered, alkalinized with cooling to *p*H 11 with sodium hydroxide, and saturated with sodium sulfate. The resulting dark brown liquid was extracted 12 times with 100 cc. of 1-butanol each. The remaining aqueous layer gave no color reaction with Pauly's reagent and was discarded.

The combined butanol extracts were shaken with small portions of diluted hydrochloric acid until all imidazole derivatives, according to Pauly's test, were removed. The acidic aqueous layer was evaporated to dryness in a vacuum desiccator over potassium hydroxide pellets. The black, semisolid residue was dissolved in 50 cc. of absolute ethanol, filtered from sodium chloride, and evaporated again to dryness; yield crude hydrochloride 7.8 g. as a black resin.

By paper chromatography (descending on Whatman No. 1, system 1-propanol/0.2*N* ammonia 2:1, developed with

* It has come to our attention that Hochstein, Ling, and P'an have also noted the presence of dimethylhistamine in *C. edulis* and have observed its marked hypotensive activity. [J. S. L. Ling, S. Y. P'an, and F. A. Hochstein, *J. Pharmacol. Exptl. Therap.*, **122**, 44A (1958)]. No details of the isolation have appeared in print. Dr. Hochstein informs us that the yields they obtained were comparable to those reported here.

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