# *Notes* A department for short papers of immediate interest.

## The Synthesis of Some New Hydantoin Compounds

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A series of trichloromethylthio compounds were synthesized by Kittleson[1] by the reaction of perchloromethyl mercaptan with the sodium salt of an imide or amide. This group of compounds then was evaluated by Daines[2] against phytopathogens and found to be active. One of these, "SR 406", is now widely used in the agricultural field.

Investigations in these laboratories showed these same compounds to possess high activity against numerous human fungal pathogens *in vitro.* As a result of this study it was decided to prepare a number of N-trichloromethylthiohydantoin derivatives in an attempt to find a compound high in fungicidal activity with a low order of toxicity. The antifungal activities and toxicities of these new derivatives will be reported elsewhere.

### EXPERIMENTAL

The 5-mono- and di-substituted hydantoins were synthesized from the appropriate aldehydes and ketones as described by Henze and Speer.[3] The 3-trichloromethylthiohydantoins were prepared according to the method of Kittleson and Yowell.[4]

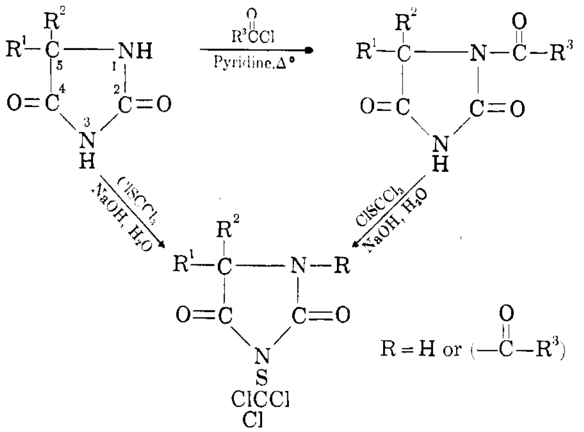

TABLE I

1-Acyl Hydantoins

| Hydantoin | M.P., °C.[a] | Formula | Analyses Nitrogen Calc'd | Analyses Nitrogen Found |
|---|---|---|---|---|
| 1-Acetyl-5,5-diphenyl- | 217 | $C_{17}H_{14}N_2O_3$ | 9.52 | 9.46 |
| 1-Butyryl-5,5-diphenyl- | 163 | $C_{19}H_{18}N_2O_3$ | 8.70 | 8.80 |
| 1-Benzoyl-5,5-diphenyl- | 247 | $C_{22}H_{16}N_2O_3$ | 7.85 | 7.75 |
| 1-Acetyl-5-methyl-5-(carbethoxymethyl)- | 75–77 | $C_{10}H_{14}N_2O_5$ | 11.60 | 11.90 |

[a] Melting points are uncorrected.

TABLE II

3-Trichloromethylthiohydantoins

| Parent Compound | M.P., °C.[a] | Formula | Analyses Nitrogen Calc'd | Analyses Nitrogen Found |
|---|---|---|---|---|
| 5-Methyl-5-*tert*-butyl | 213 | $C_9H_{13}Cl_3N_2O_2S$ | 8.75 | 8.85 |
| 5-Methyl-5-(3-methylbuten-2-yl)- | 158–159 | $C_{10}H_{13}Cl_3N_2O_2S$ | 8.45 | 8.40 |
| 5-Methyl-5-(carbethoxymethyl)- | 173 | $C_9H_{11}Cl_3N_2O_4S$ | 8.03 | 7.85 |
| 5-Methyl-5-(carboxymethyl)- | 189–190 | $C_7H_7Cl_3N_2O_4S$ | 8.72 | 8.80 |
| 5-Methyl-5-(carboxyethyl)- | 153 | $C_8H_9Cl_3N_2O_4S$ | 8.35 | 8.05 |
| 5-*tert*-Butyl-5-(carboxymethyl)- | 234 | $C_{10}H_{13}Cl_3N_2O_4S$ | 7.73 | 7.75 |
| 5-Amyl-5-(carbethoxymethyl)- | 124–125 | $C_{13}H_{19}Cl_3N_2O_4S$ | 6.91 | 7.02 |
| 5-Ethyl-5-isopropyl- | 182 | $C_9H_{13}Cl_3N_2O_2S$ | 8.75 | 8.83 |
| 5-(2,6-Dimethylhepten-6-yl)- | 99–100 | $C_{13}H_{19}Cl_3N_2O_2S$ | 7.52 | 7.31 |
| 5,5-Diphenyl- | 176 | $C_{16}H_{11}Cl_3N_2O_2S$ | 6.98 | 6.90 |
| 1-Acetyl-5,5-diphenyl- | 145–147 | $C_{18}H_{13}Cl_3N_2O_3S$ | 6.35 | 6.15 |
| 1-Butyryl-5,5-diphenyl- | 114 | $C_{20}H_{17}Cl_3N_2O_3S$ | 5.95 | 6.06 |
| 1-Acetyl-5-methyl-5-(carbethoxymethyl)- | 63–66 | $C_{11}H_{13}Cl_3N_2O_5S$ | 7.19 | 7.52 |

[a] Melting points are uncorrected.

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(1) Kittleson, *Science*, **115**, 84 (1952).

(2) Daines, *Am. Fruit Grower*, **73**, 76 (1953).

(3) Henze and Speer, *J. Am. Chem. Soc.*, **64**, 522 (1942).

(4) Kittleson and Yowell, U. S. Patent 2,553,771.

The 1-acylated hydantoins were prepared by a method hitherto unreported for this class of compounds. The reaction time for the synthesis of the acylated hydantoins is much less by using an acid chloride as the acylating agent and carrying out the reaction in pyridine than by the usual method of heating the hydantoin directly with an acid anhydride.[5] A solution of 0.02 mole of the hydantoin in 10 ml. of pyridine was cooled and 0.02 mole of the acid chloride was added slowly. The mixture then was refluxed for 20–30 minutes. The reaction mixture was poured onto crushed ice and the granular material which separated out was filtered off and recrystallized. The position of the acyl group in the products is inferred from their solubility in alkali.

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(5) Biltz, *Ber.*, **41**, 1386 (1908).

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## The Synthesis of Radioactive Diazinon Using P$^{32}$

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Investigations of the mode of action of O,O-diethyl-O-(2-isopropyl-6-methyl-4-pyrimidinyl) thiophosphate (Diazinon) have been difficult because of the lack of suitable analytical techniques. The use of a radioactive label in the Diazinon molecule offers a partial solution to the problems of investigating its distribution and metabolism in both mammals and insects.

It is possible to label Diazinon with C$^{14}$, S$^{35}$, or P$^{32}$. Since the later isotope offers an easy synthetic route and is more readily measured radiometrically, elemental red phosphorus was selected as a starting material. This material was submitted to Oak Ridge National Laboratories for service irradiation to a specific activity of approximately 50 mc. per gram. The synthesis of phosphorus trichloride is based on the method of Forbes, *et al.*[2] The two step chlorination and the use of the powdered antimony[3] were utilized to increase the specific activity and yield of phosphorus trichloride.

No physical constants were obtained on the active products. The $n^{25}_{D}$ of Diazinon from repeated practice runs with inactive materials was 1.4978. The values reported in the literature are 1.4978–1.4881.[4] The specific activity of the product of two active runs ranged from 1.51 to 1.62 mc./g. Bioassays using the common housefly gave an LD$_{50}$ of 2.4 $\mu$ g./g. of flies for the active product compared with a value of 2.5 for a sample of the inactive product. Paper chromatographic analyses of the labeled product, using the methods of *Kaplanis, et al.*[5] gave an $R_f$ of 0.86 using a polar stationary phase and 0.43 using an apolar stationary phase as contrasted with $R_f$'s of 0.86 and 0.42, respectively, for samples of the inactive product. No radioactive contamination of the Diazinon was detected using either system. Determination of the $R_f$ of the labeled O,O-diethyl chlorothiophosphate by radiometric means gave values of 0.87 for the polar stationary system and 0.79 for the apolar stationary system. Paper chromatographic analyses of unreacted diethyl chlorothiophosphate distilled from the final reaction mixture indicated two radioactive spots from the apolar stationary system. The second spot had a value corresponding to that of Diazinon. More careful purification of the unreacted diethyl chlorothiophosphate indicated that some Diazinon was actually being distilled over, under the conditions outlined here.

### EXPERIMENTAL

*Phosphorus trichloride.* Two g. of the irradiated elemental red phosphorus was added to a 25-ml. two-necked flask equipped with a chlorine bubbler, water-cooled condenser, and drying tube. Then 2.5 g. of redistilled phosphorus trichloride was added as a solvent for the chlorination. The flask was heated on an oil-bath to reflux. Dry chlorine then was introduced through the bubbler at a rate sufficient to minimize clogging. After approximately one-half hour of chlorination, the reaction was stopped and cooled in an ice-bath. The remaining 2 g. of irradiated red phosphorus was added, the reaction brought to reflux, and chlorination continued until white specks of phosphorus pentachloride began to appear. The reaction was cooled in an ice-bath and 6.5 g. of powdered antimony was added to convert the phosphorus pentachloride to phosphorus trichloride. After the addition of the antimony, the reaction was allowed to come slowly to room temperature to avoid the violent conversion of phosphorus pentachloride to phosphorus trichloride. The phosphorus trichloride then was distilled (73–75°) into a second reaction vessel at atmospheric pressure. Yields on two active runs ranged from 31 to 62% conversion of P$_4$ to PCl$_3$.

*Thiphosphoryl trichloride.* This compound was synthesized by the method of Knotz.[6] The product was distilled (122–126°) at atmospheric pressure. The yields on two active runs were 87%.

*O,O-Diethyl chlorothiophosphate.* The method for the synthesis of this intermediate was essentially that of Fletcher, *et al.*,[7] modified to minimize radiological hazards. The compound was distilled at 42–45° at 0.25 mm. The yields on two runs ranged from 72–79%.

*Diazinon.* Benzene (90 ml.) containing 13.03 g. of 2-isopropyl-6-methyl-4-hydroxypyrimidine and 11.92 g. of anhydrous potassium carbonate was placed in a round-bottom flask equipped with a water separator and condenser.

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(1) Part of a dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Kansas State College.

(2) Forbes, Roswell, and Maxson, *Inorg. Syntheses*, **2**, 145 (1946).

(3) Baudrimont, *Ann. chem. et phys.*, **4**, 12 (1864).

(4) Gasser, *Z. Naturforsch.*, **8b**, 225 (1953).

(5) Kaplanis, Robbins, and Roan, *J. Agr. Food Chem.*, (Submitted).

(6) Knotz, *Osterr. Chem. Z.*, **50**, 128 (1949).

(7) Fletcher, Hamilton, Hechenbleikner, Hoegberg, Sterl, and Cassady, *J. Am. Chem. Soc.* **70**, 3943 (1948).