

unsuccessful. Titration revealed that the sample was only 69.7% pure, and probably contaminated by succinic acid.

*N-Hydroxymaleamic acid** was synthesized in a similar manner from maleic anhydride. There was obtained a 48.5% yield of tan triangular plates, melting at 121–128° (dec.). Ferric chloride in aqueous solution produced an intense reddish purple color. According to titration data, this material is 72.5% pure, but attempts to improve it by recrystallization were unsuccessful.

Anal. Calcd. for $C_4H_3NO_4$: C, 36.7; H, 3.8; N, 10.7. Found: C, 35.1; H, 3.8; N, 10.2.

*N-Hydroxyoxalamic acid** (oxalomonohydroxamic acid). Although this compound has not been prepared previously, the sodium, copper, barium, and lead salts have been reported.²⁶ The copper salt, however, was probably the mixed copper-sodium salt $(NaOCCONHO)_2Cu$, since upon treatment with hydrogen sulfide it produced the monosodium salt $NaOCCONHOH$.

The potassium salt $KOCCONHOH$ was prepared by the action of hydroxylamine in ethanol on potassium ethyl oxalate. This compound is unchanged on heating to 250°, but decomposes suddenly when held near a flame. Aqueous ferric chloride yields a deep red-brown colored complex, and aqueous cupric acetate a bright green precipitate, probably $(KOCCONHO)_2Cu$.

The free hydroxamic acid is believed to have been isolated in low yield as follows. The pH of a solution of the potassium salt was lowered to 0.19 by the addition of dilute hydrochloric acid, at which point 90% of the carboxyl groups should be in the undissociated form, assuming that the pK of the carboxyl group of oxalomonohydroxamic acid is the same as the first pK of oxalic acid (1.19). Addition of cupric chloride to this solution yielded a cupric salt, probably $(HOCCONHO)_2Cu$, which liberated the hydroxamic acid on treatment with hydrogen sulfide.

14.3 g. (0.1 mole) of the potassium salt was dissolved in 150 ml. of water, and the pH lowered to 0.19 by the drop-

(26) O. Dimroth and O. Dienstbach, *Ber.*, 41, 4077 (1908).

wise addition of 3*N* hydrochloric acid with vigorous stirring. At this point there was added dropwise a solution of 25.6 g. (0.15 mole) of cupric chloride dihydrate in 50 ml. of water, which had been adjusted to pH 0.15 with concentrated hydrochloric acid. The light green precipitate of copper salt began to separate, and the mixture was allowed to stand in the refrigerator overnight. The copper salt was then filtered off under suction, washed with water and then methanol, and dried on the filter, weight 7.57 g. This was suspended in 150 ml. of methanol and hydrogen sulfide was passed in with occasional shaking. When it was judged that all of the copper salt had reacted, the copper sulfide was filtered off and washed with methanol. The combined filtrate and washings were evaporated under reduced pressure to produce a moist white solid, which was redissolved in 25 ml. absolute ethanol, filtered, and treated with several volumes of petroleum ether (34.5–55°). Since only a very small amount of material had appeared after standing for 3 days in the refrigerator, the solvents were evaporated once more to yield an oil, which on trituration with petroleum ether produced a solid. After filtration, washing with petroleum ether and drying, there was obtained 0.22 g. (2% yield) of a white product melting with vigorous decomposition at 130.5–134° to a white solid residue, which in turn melted at about 195° (dec.). The color produced with aqueous ferric chloride seemed to depend on the concentrations used and the pH, ranging from intense violet to red-brown. Although a satisfactory elemental analysis was not obtained, the titration curve was in good agreement with theory. Neutral equivalents: monobasic, 106 (calcd., 105); dibasic, 53.6 (calcd., 52.5).

Anal. Calcd. for $C_2H_3NO_4$: C, 22.9; H, 2.9; N, 13.3. Found: C, 20.3; H, 2.4; N, 12.1.

Acknowledgment. It is a pleasure to acknowledge the assistance of Mr. R. Proper in the synthetic work.

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[CONTRIBUTION FROM THE R. B. WETHERILL LABORATORY OF CHEMISTRY, PURDUE UNIVERSITY, LAFAYETTE, INDIANA]

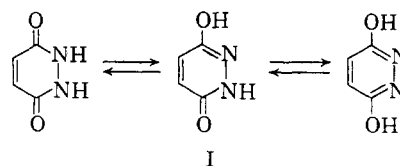
The Reaction of Maleic Hydrazide with Formaldehyde and Alcohols in Acidic Medium^{1,2}

HENRY FEUER AND RONALD HARMETZ

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Maleic hydrazide reacts in the presence of acid with formaldehyde and ethanol or methanol to give 2-ethoxymethyl-6-hydroxy-3(2H)-pyridazinone and 2-methoxymethyl-6-hydroxy-3(2H)-pyridazinone respectively. A structure determination is presented which unambiguously proves that these products are *N*-substituted maleic hydrazide derivatives.

Maleic hydrazide (I) has been reported to undergo a number of reactions with substitution on oxygen or nitrogen. Feuer and Rubinstein³ recently reported that acylation and benzenesulfonation of compound I resulted in the exclusive



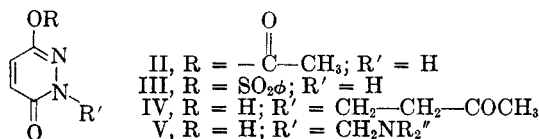
formation of 3-(1H-6-pyridazinonyl) acetate (II) and 3-(1H-6-pyridazinonyl) benzenesulfonate (III) respectively. The present authors established⁴ that compound I underwent the Michael type reaction

(1) Paper VI in the series, "The Chemistry of Cyclic Hydrazides."

(2) (a) From the Ph.D. thesis of Ronald Harmetz; (b) presented before the Division of Organic Chemistry at the New York City Meeting of the American Chemical Society, September, 1957.

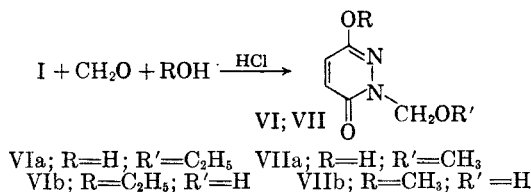
(3) H. Feuer and H. Rubinstein, *J. Am. Chem. Soc.*, 80, 5873 (1958).

(4) H. Feuer and R. Harmetz, *J. Am. Chem. Soc.*, 80, 5877 (1958).



with methyl vinyl ketone and other activated double bonded compounds to afford *N*-substituted products (IV), and Hellmann and Löschmann⁵ claimed to have obtained *N*-substituted Mannich products (V) by treating compound I with various amines and formaldehyde.

When compound I was treated with formaldehyde and dimethylamine hydrochloride in an ethanolic solution containing a small quantity of hydrochloric acid, the expected Mannich-type product was not obtained. Instead, a small amount of product was isolated, the neutralization equivalent

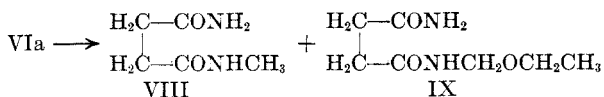


and elemental analysis of which were consistent with structures VIa and VIb. The same compound was obtained in an 82% yield (23% conversion), when dimethylamine hydrochloride was omitted from the reaction mixture.

When an analogous reaction was carried out with methanol, a white crystalline solid was secured in 34% yield (7% conversion). The elemental analysis of this material was in agreement with structures VIIa and VIIb.

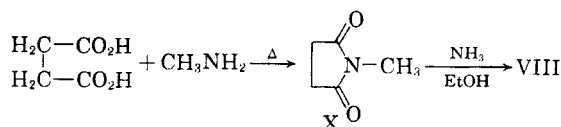
The presence of an alkoxy group in compounds VI and VII was indicated by their infrared spectra, which showed a characteristic ether band at 9.15 μ . Further confirmation of an ether linkage was secured when both compounds gave a positive Zeisel alkoxy test.

In order to determine its structure unambiguously, compound VI was treated with Raney nickel in refluxing ethanol, because it has been recently established⁴ that *N*-substituted maleic hydrazides were converted by this procedure to substituted succinamides. When compound VI was subjected to these hydrogenolysis conditions, two compounds VIII and IX, m.p. 160–161° and 142–144°, were obtained. They were identified as amides by their infrared spectra. Compound

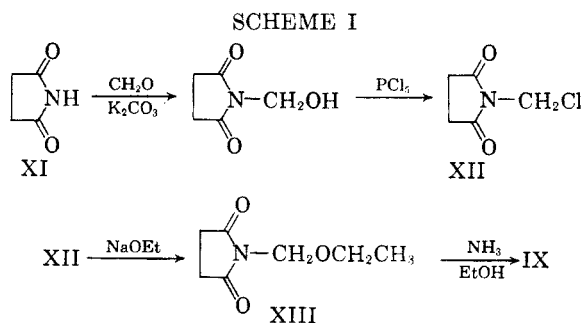


VIII was identified as *N*-methylsuccinamide by its elemental analysis and comparison with an authentic sample. Authentic *N*-methylsuccinamide

(VIII) was prepared by the ammonolysis of *N*-methylsuccinimide (X).



Compound IX could not be sufficiently purified for elemental analysis, but was definitely identified as *N*-ethoxymethylsuccinamide (IX), by comparison with an authentic sample which was prepared as shown in Scheme I.



N-Ethoxymethylsuccinimide (XIII) was prepared in a 75% yield from succinimide (XI) by following the procedure of Cherbuliez and Sulzer.⁶ The desired compound *N*-ethoxymethylsuccinamide (IX) was obtained in a 47% yield by heating compound XIII at 100° in a sealed tube containing 95% ethanol saturated with ammonia. It was identified by its elemental analysis and infrared spectrum, which was identical with that of compound IX obtained from the hydrogenolysis of compound VIa. Also, a mixed melting point determination of these two products did not show a depression.

The above data unambiguously established that maleic hydrazide reacted in the presence of hydrochloric acid with formaldehyde and ethanol or methanol to afford the *N*-substituted maleic hydrazide derivatives VIa and VIIa.

The ultraviolet spectra of compounds VIa and VIIa showed absorption maxima at 315 $m\mu$, which is in agreement with our previous findings⁴ that *N*-substituted maleic hydrazide derivatives show absorption maxima in the region 316–318 $m\mu$, while the *O*-substituted compounds absorb in the region 306–308 $m\mu$.

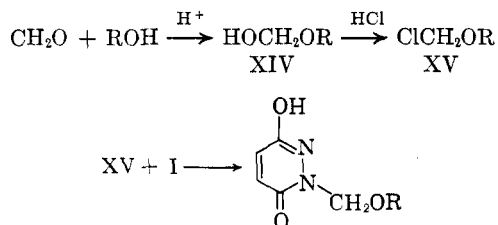
PROPOSED REACTION PATH

Two possible reaction paths leading to the formation of compounds VIa and VIIa may be postulated.

The first involves an initial condensation between formaldehyde and the alcohol to produce a hemiacetal (XIV), which in turn reacts with the

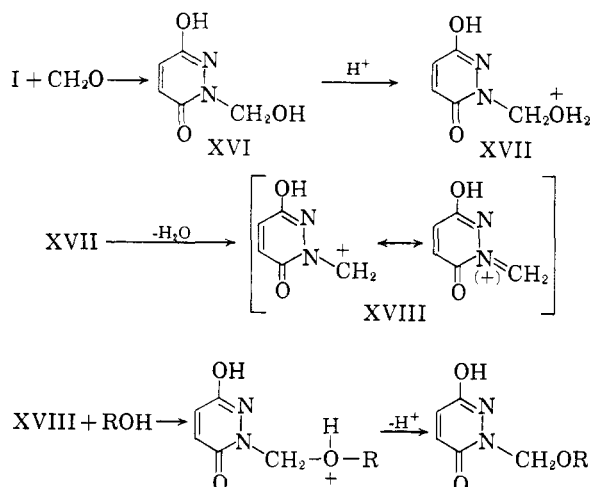
(5) H. Hellmann and I. Löschmann, *Angew. Chem.*, **67**, 110 (1955); *Chem. Ber.*, **89**, 594 (1956).

(6) E. Cherbuliez and G. Sulzer, *Helv. Chim. Acta*, **8**, 567 (1925).



hydrochloric acid to yield a chloromethyl alkyl ether (XV). The latter then reacts with maleic hydrazide to give the final product. The postulated formation of a chloromethyl alkyl ether (XV) as an intermediate receives support from the reports of Farren⁷ and Reychler⁸ that chloromethyl ethyl ether and chlorodimethyl ether can be prepared by treating ethanol or methanol with paraformaldehyde and hydrogen chloride. Additional support for intermediate XV was obtained when the reaction of maleic hydrazide with chloromethyl ethyl ether gave a 67% yield (12% conversion) of VIa.

The other reaction path for the formation of compounds VIa and VIIa involves an initial reaction between maleic hydrazide (I) and formaldehyde to yield *N*-hydroxymethylmaleic hydrazide



(XVI) which, after protonation and loss of a molecule of water, is converted to the carbonium ion XVIII. This intermediate is then transformed, by nucleophilic attack of the alcohol and subsequent loss of a proton, to the final product.

EXPERIMENTAL

2-Ethoxymethyl-6-hydroxy-3(2H)-pyridazinone (VIa). (a) *Using Hydrochloric Acid.* In a 200 ml. flask were placed 11.2 g. (0.1 mole) of maleic hydrazide, 3.3 g. (0.11 mole) of paraformaldehyde, 125 ml. of absolute ethanol, and 10 ml. of concd. hydrochloric acid. The mixture was refluxed for 24 hr. and then kept at 5° for several more hr. Filtration afforded 6.3 g. of unreacted maleic hydrazide. The filtrate was evaporated to one half its volume and kept at 5° overnight. Three g. of product, m.p. 138–139° was obtained

(7) J. W. Farren, H. R. Fife, F. E. Clark and C. E. Garland, *J. Am. Chem. Soc.*, **47**, 2419 (1925).

(8) A. Reychler, *Bull. soc. chim.*, [4] **1**, 1195 (1907).

which was recrystallized from benzene, m.p. 142–143°. The filtrate was evaporated to approximately 20 ml. and placed at –15° for several hr. Upon filtration a solid was obtained which was extracted with hot benzene until no precipitate formed on cooling the extract. By this method an additional 1.0 g. (82% yield, 23% conversion) of *2-ethoxymethyl-6-hydroxy-3(2H)-pyridazinone* (VIa) was obtained.

Anal. Calcd. for $\text{C}_7\text{H}_{10}\text{O}_3\text{N}_2$: C, 49.40; H, 5.92; N, 16.46; neut. equiv., 170. Found: C, 49.44; H, 5.98; N, 17.04; neut. equiv., 168.

(b) *Employing Chloromethyl Ethyl Ether.* A mixture of 5.6 g. (0.05 mole) of maleic hydrazide, 4.7 g. (0.05 mole) of chloromethyl ethyl ether, and 50 ml. of absolute ethanol was refluxed for 24 hr. and then kept at 10° for several more. Upon filtration 2.1 g. of unreacted maleic hydrazide was obtained. Evaporation of the filtrate afforded 4.5 g. of solid, m.p. 140–300°, which was subsequently extracted with 200 ml. of hot benzene, which yielded on cooling 1.0 g. (67% yield, 12% conversion) of *2-ethoxymethyl-6-hydroxy-3(2H)-pyridazinone* (VIa), m.p. 135–136°. Recrystallization from benzene raised the melting point to 141–142°.

The infrared spectra of compound VIa prepared by methods "a" and "b" were superimposable and showed a band at 9.15 μ for the ether linkage and a medium band at 6.00 μ (ring carbonyl). λ_{max} 95% EtOH 315 (log ϵ 4.48).

2-Methoxymethyl-6-hydroxy-3(2H)-pyridazinone (VIIa). In a 200 ml. round-bottom flask, equipped with a stirrer and reflux condenser, were placed 11.21 g. (0.1 mole) of maleic hydrazide, 3.0 g. (0.1 mole) of paraformaldehyde, 10 ml. of concd. hydrochloric acid, and 125 ml. of methanol. The mixture was refluxed for 22 hr. and then filtered to remove 2.1 g. of unreacted maleic hydrazide. An additional 7.0 g. of maleic hydrazide was recovered by cooling the filtrate to 5°. The filtrate was concentrated to 20 ml. and cooled to 10° for several hours. Subsequent filtration yielded 1.0 g. (34% yield, 7% conversion) of *2-methoxymethyl-6-hydroxy-3(2H)-pyridazinone* (VIIa) m.p. 149–153°. After recrystallization from toluene the melting point was raised to 153–154°. The infrared spectrum showed a strong band at 9.15 μ for the ether linkage and a medium band at 6.02 μ (ring carbonyl). λ_{max} 95% EtOH 315 (log ϵ 3.52).

Anal. Calcd. for $\text{C}_8\text{H}_9\text{O}_3\text{N}_2$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.13; H, 5.08; N, 18.18.

Hydrogenolysis of 2-Ethoxymethyl-6-hydroxy-3(2H)-pyridazinone (VIa). In a 500 ml. round-bottom flask, equipped with a reflux condenser, were placed 70 ml. of settled Raney nickel,⁹ 250 ml. of 70% ethanol and 3.4 g. (0.02 mole) of compound VIa. The mixture was refluxed for 5 hr., centrifuged, and decanted while still hot. The Raney nickel was washed with 500 ml. of boiling 95% ethanol, centrifuged, and the supernatant liquid decanted. Combination and subsequent evaporation of the ethanolic solutions afforded 2.3 g. of a mixture, m.p. 95–125°, containing *N*-methylsuccinamide and *N*-ethoxymethylsuccinamide. The mixture was extracted with 100 ml. of warm ethylene dichloride and upon evaporation of the solvent a solid was obtained which was wastefully recrystallized twice from ethylene dichloride, and four times from acetonitrile to afford *N-ethoxymethylsuccinamide*, m.p. 142–144°. Further purification of this compound was unsuccessful. Recrystallization of the solid, which remained after the ethylene dichloride extraction, from acetonitrile yielded pure *N-methylsuccinamide*, m.p. 160–161°.

Anal. Calcd. for $\text{C}_8\text{H}_{10}\text{O}_2\text{N}_2$: C, 46.16; H, 7.75; N, 21.53. Found: C, 46.16; H, 7.94; N, 21.67.

N-Methylsuccinamide (VIII). *N*-Methylsuccinimide¹⁰ (11.3 g., 0.1 mole), and 50 ml. of 95% ethanol were placed in a combustion tube and ammonia was bubbled into the mixture until the solution was saturated. The tube was then

(9) R. Mozingo, D. E. Wolf, S. A. Harris, and K. Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1943).

(10) N. Menshutkin, *Ann.*, **182**, 92 (1877).

sealed and heated for 6 hr. at 100°. The mixture was evaporated to dryness and the solid obtained was treated with 50 ml. of cold acetonitrile. Filtration afforded 3 g. (23% conversion) of *N*-methylsuccinamide, m.p. 154–156°, and evaporation of the filtrate yielded unreacted *N*-methylsuccinimide. Recrystallization of the product from acetonitrile raised the melting point to 160–161° (lit. value,¹¹ m.p. 158–162°).

A mixed melting point between this compound and the higher melting product obtained by the hydrogenolysis of compound VIa gave no depression. The infrared spectra of these two substances were superimposable and showed strong characteristic amide bands at 3.08, 3.21, and 6.10 μ .

Anal. Calcd. for $C_8H_{10}O_2N_2$: C, 46.16; H, 7.75; N, 21.53. Found: C, 46.15; H, 7.83; N, 21.46.

N-Ethoxymethylsuccinamide (IX). In a combustion tube were placed 12.5 g. (0.079 mole) of *N*-ethoxymethylsuccin-

(11) F. S. Spring and J. C. Woods, *J. Chem. Soc.*, 628 (1945).

imide⁶ and 50 ml. of 95% ethanol. After saturating the solution with liquid ammonia, the tube was sealed and heated for 6 hr. at 100°. Subsequent evaporation of the solvent afforded a mixture of solid product and liquid starting material which was separated by filtration. Recrystallization of the solid from acetonitrile afforded 6.5 g. (47% conversion) of *N*-ethoxymethylsuccinamide, m.p. 138–145°. Two additional recrystallizations raised the melting point to 146–146.5°.

A mixed melting point determination between this compound and the lower melting product obtained from the reduction of compound VIa showed no depression (m.p. 144–146°). The infrared spectra of these two substances were superimposable and showed strong characteristic amide bands at 2.95, 3.01, 3.12 and 6.08 μ and an aliphatic ether band at 9.05 μ .

Anal. Calcd. for $C_7H_{14}O_3N_2$: C, 48.26; H, 8.10; N, 16.08. Found: C, 48.17; H, 8.09; N, 16.34.

LAFAYETTE, INDIANA

[CONTRIBUTION FROM THE ENTOMOLOGY RESEARCH DIVISION, AGRICULTURAL RESEARCH SERVICE,
U. S. DEPARTMENT OF AGRICULTURE]

Synthesis of Methylenedioxyphenyl Compounds from Isosafrole and Sesamol

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During a search for compounds with improved insecticidal activity, 31 new ethers and esters were synthesized from sesamol and isosafrole. Methods of preparation, physical constants, and some biological information are reported herein.

As part of our search for new compounds with improved insecticidal activity, 3,4-methylenedioxyphenyl compounds containing a halogen in the 6-position of the phenyl group were synthesized. Their preparation and that of their intermediates, totaling 31 new compounds, are given. Most were obtained in good or high yield.

Some of the compounds are related to the insecticide 6-chloropiperonyl chrysanthemumate (barthrin)¹; *i.e.*, they contain a bromine instead of a chlorine atom in the 6-position of the 3,4-methylenedioxyphenyl group. Unfortunately, no substantial improvement in insecticidal activity over barthrin was attained. The addition of bromine usually increased insecticidal activity over the unbrominated analog, but it also decreased activity in several instances.

The derivatives of isosafrole (1,2-methylenedioxy-4-propenylbenzene), given in Table I, were prepared essentially as outlined by Pond and co-workers² with one improvement. These investigators brominated isosafrole in ether and reported no yields; we used both ether and glacial acetic acid as solvents and obtained higher yields and a purer product with the latter.

Derivatives of sesamol (3,4-methylenedioxyphenol), given in Table II, were prepared according to published procedures.³ The shift of the double bond (conversion of an allyl to a propenyl group) and the preparation of allylmethylenedioxyphenol from its ether precursor, by the Claisen rearrangement, were carried out in the usual way.⁴ Bromination of the double bond took place readily in a solution of glacial acetic acid at 10°.

Results of screening the compounds as chigger and body louse toxicants, mosquito larvicides, and mosquito repellents are given in Table III. The methods of test and classification of activity are the same as those given by King.^{5a} Some of the ethers (I–X) of Table I showed excellent activity as mosquito larvicides; however, the corresponding activity of the esters (XI–XVIII) was nil. Good larvicidal and pediculocidal activities were shown by the sesamol ethers (XX–XXVI); one of these (XX) is a positional isomer of myristicin (3,4-methylenedioxy-5-methoxy-1-allylbenzene), a natural product known to be synergistic with pyrethrin.⁶ The best pediculocide (XXIII) differs

(1) W. F. Barthel and B. H. Alexander, *J. Org. Chem.*, **23**, 1012 (1958); W. A. Gersdorff and P. G. Piquett, *J. Econ. Entomol.*, **62**, 85 (1959).

(2) F. J. Pond, E. S. Erb, and A. G. Ford, *J. Am. Chem. Soc.*, **24**, 327 (1902); F. J. Pond and C. R. Siegfried, *J. Am. Chem. Soc.*, **25**, 262 (1903).

(3) L. Claisen and O. Eisleb, *Ann.*, **401**, 36 (1913); C. F. H. Allen and J. W. Gates, Jr., *Org. Syntheses, Coll. Vol. III*, 140 (1955).

(4) D. S. Tarbell, *Org. Reactions*, **2**, 26 (1944).

(5a) W. V. King, *U. S. Dept. Agr. Handbook*, No. 69, 397 pp. (1954). (b) p. 2.

(6) R. Kerr, Australia, *Commonwealth Sci. and Ind. Res. Bull.* **261** (1951).