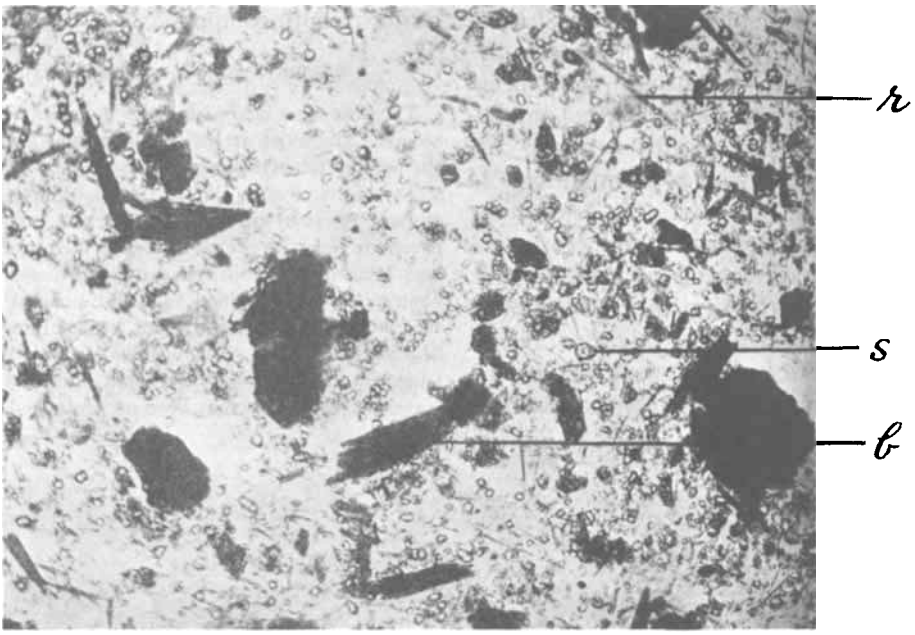

Fig. 3.—Powdered *Mirabilis Jalapa* Root. Photomicrograph X 100. *r*, raphides of calcium oxalate; *s*, starch; *b*, bundle of acicular crystals of calcium oxalate.

SUMMARY

1. A fraudulent substitute for Jalap has appeared on the American market which is identified as the tuberous root of *Mirabilis Jalapa* L.

2. The physical characteristics, histology, and the powdered root of *Mirabilis Jalapa* are described.

3. It is found that the non-lignified character of the cork, the presence of numerous raphides of calcium oxalate, the relatively small amount of resin, the presence of characteristic starch grains, some of which appear in spherical and oval aggregates, and the absence of rosette aggregates of calcium oxalate, bordered pored tracheæ and absence of lignified fibers and stone cells readily distinguish it from Jalap.

4. An assay showed this substitute to contain 2.78% of total resins.

5. It has been determined that the powdered root of *Mirabilis Jalapa* is an irritant to the skin and mucous membrane.

6. A description of the plant yielding the substitute is given.

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A Study of *p*-Nitrosothymol and *p*-Aminothymol*,†

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Thymol because of its availability, therapeutic activity and lack of toxicity has re-

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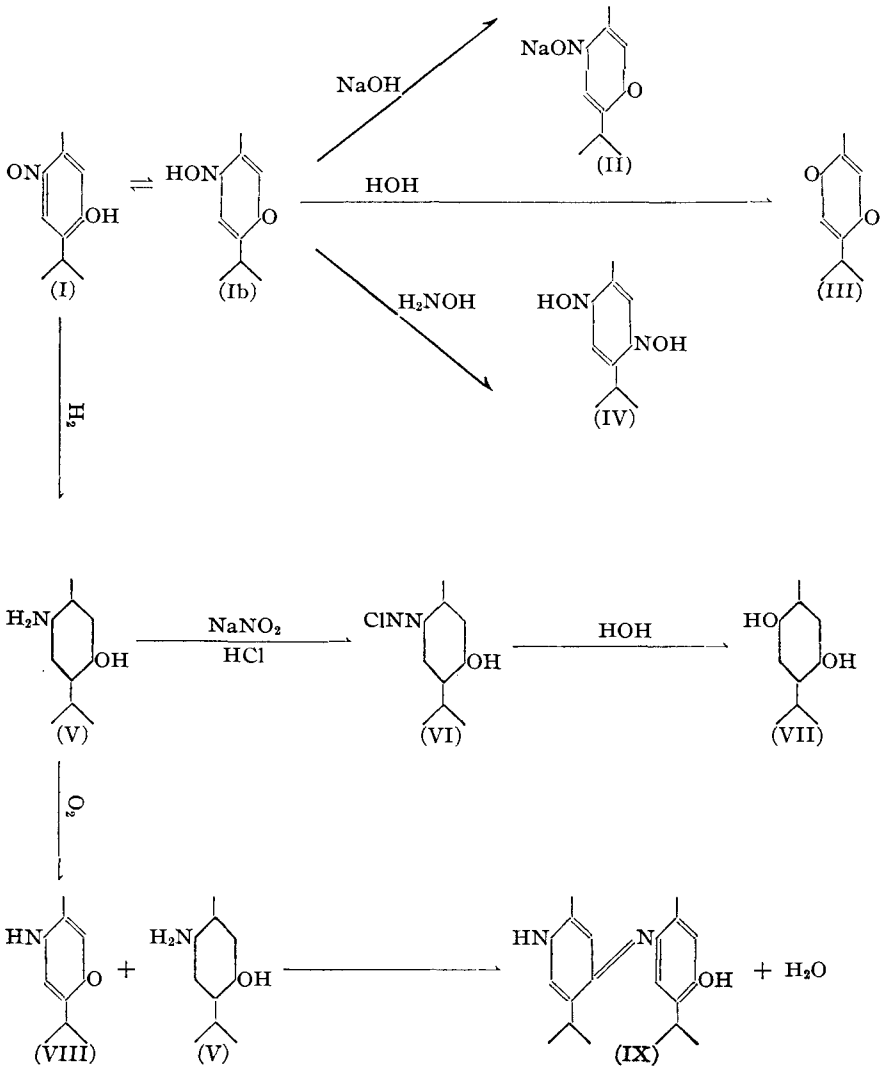
ceived a good deal of attention from pharmacists, chemists and pharmacologists. As a result of this work a number of medicinally important thymol derivatives have been prepared. While nitrosating thymol and reducing the resulting *p*-nitrosothymol by means of hydrogen sulfide to *p*-aminothymol, which compound was needed in connection with another study, the writers became interested in certain aspects of the chemical behavior of *p*-nitrosothymol and *p*-aminothymol. The present investigation represents an effort to facilitate the reduction of *p*-nitrosothymol to *p*-aminothymol and to learn something more of the chemical behavior of both compounds.

THEORETICAL AND EXPERIMENTAL

The flow sheet below indicates the reactions which received the most attention and shows graphically the compounds which resulted from these reactions.

Tautomerism of p-Nitrosothymol.—The *p*-nitrosothymol (I) used in these studies was prepared in excellent yields by the method described by Kremers and Wakeman (1) in "Organic Syntheses." The compound was obtained as a buff-colored powder which was recrystallized from benzol in the form of practically white, short needles melting at 162° C. (uncorr.). *p*-Nitrosothymol was found to repel water so effectively that even on prolonged tritura-



Flow sheet

tion with aqueous liquids the compound could not be wetted. It was slowly but completely volatile with steam.

p-Nitrosothymol is freely soluble in pyridine and in solutions of the hydroxides of alkali metals producing in both instances a very dark brown solution. By the careful addition of hydrochloric acid the color of the dark brown solution was discharged and the light-colored *p*-nitrosothymol reprecipitated. These color changes may be explained on the basis that the practically colorless *p*-nitrosothymol obtained by the action of nitrous acid on thymol is tautomeric with the more highly colored thymoquinonemonoxime (Ib) which is obtained by condensing hydroxylamine with thymoquinone. The product in each case may be represented by the tautomeric equilibrium (I $\rightleftharpoons$ Ib). It is generally agreed that the nitroso-benzenoid structure prevails in a neutral medium whereas the oxime-quinonoid form predominates in alkaline and acid solutions (2). The intense brown color of the alkaline solution is presumably due to the anions from the highly ionized salt (II) formed from thymoquinonemonoxime (Ib) and the alkali (3). It is interesting to note that either a 0.15% aqueous solution of calcium hydroxide or a 20% aqueous solution of sodium carbonate is capable of effecting this tautomeric transformation while a 20% aqueous solution of sodium bicarbonate was without effect in this respect.

Hydrolysis of Thymoquinonemonoxime.—Although thymoquinone (III) may be obtained by oxidizing *p*-aminothymol (V) with ferric chloride (4) and by a number of other methods described in the literature (5), (6) it is still listed at 55 cents a Gm. (7).

Since the readily available *p*-nitrosothymol (I) is a tautomer of thymoquinonemonoxime (Ib) it seemed worth while to determine, whether it would be possible to bring about the tautomeric rearrangement of *p*-nitrosothymol into its quinonoid-oxime modification and then effect the hydrolysis of the oxime thereby directly obtaining thymoquinone (III). The following factors indicated that thymoquinone could be prepared by these reactions. (1) An acid medium would tend to convert the tautomeric compound to its quinonoid-oxime form (8). (2) The chemical behavior of the quinones indicate that the 6-membered ring has lost its aromaticity and is essentially an unsaturated diketone (9). (3) The monoximes of ketones may often be hydrolyzed by aqueous acids to yield the original ketone and hydroxylamine (10).

Recently Tseng, *et al.* (11), (12), claim to have obtained good yields of thymoquinone and phenanthraquinone by hydrolyzing thymoquinonemonoxime and phenanthraquinonemonoxime, respectively, by the use of 8% hydrochloric acid and in the case of the latter compound with the addition of formaldehyde as a catalyst. The results of Tseng, *et al.*, could not be reproduced with thymoquinonemonoxime although their procedure was followed and in one trial formaldehyde was used for its catalytic effect. It was observed during these reactions that the admixture of the *p*-nitrosothymol with the acid was very poor even after 15 hours of refluxing. Finally, with the knowledge that certain organic solvents facilitated the admixture of *p*-nitrosothymol with aqueous liquids and upon the assumption that the carbonyl group in formaldehyde was responsible for its catalytic property in hydrolyzing ketoximes this effort was made toward bringing about the desired reaction.

Three and a half grams (0.02 mole) of *p*-nitrosothymol was triturated with 2.5 cc. (0.04 mole) of acetone to form a paste. To this was added 50 cc. of 7% hydrochloric acid and the entire mixture was refluxed for twenty-four hours over an asbestos gauze by means of a direct flame. After about ten hours of refluxing the appearance of an appreciable quantity of yellow oil around the cooler portion of the boiling flask indicated that a fair amount of thymoquinonemonoxime had been hydrolyzed into thymoquinone. Steam distillation of the reaction mixture yielded 1.2 Gm. of thymoquinone which was obtained in the form of orange-colored, plate-shaped crystals which without further purification melted at 45° C. (corr.). The melting point of thymoquinone is given in the literature as 45.5° C. (13). This yield represents 36% of the theoretical.

A sample of thymoquinonedioxime (IV) was prepared by treating *p*-nitrosothymol with hydroxylamine but an attempt to hydrolyze this compound by means of 2% hydrochloric acid was not successful.

Reduction of p-Nitrosothymol.—There are several methods described in the literature for the reduction of *p*-nitrosothymol to *p*-aminothymol (14), (15). However, only one attempt to use catalytic hydrogenation for this purpose has been reported (16) and in this instance only about half the theoretical amount of *p*-aminothymol was obtained. The production of *p*-aminothymol by the catalytic reduction of *p*-nitrosothymol was therefore undertaken.

Following the procedure of Ott and Schroter (17) a palladium catalyst was prepared by shaking 0.05 Gm. of palladous chloride with 2 Gm. of animal charcoal in 100 cc. of distilled water in an atmosphere of hydrogen until no more hydrogen was absorbed. Eighteen grams (0.1 mole) of *p*-nitrosothymol were dissolved in 350 cc. of absolute ethyl alcohol by mechanical agitation. Dry hydrogen chloride was passed into the solution until 4 Gm. or 1.1 equivalents was absorbed. The palladiumized charcoal was added to the solution of *p*-nitrosothymol and the entire mixture was placed in a 500-cc. round-bottom flask which was attached by means of a ground glass connection to a hydrogen delivery train, assembled according to the directions of Hartung (18). Hydrogen was led into the flask through a large graduated cylinder and supplied throughout the reaction at a pressure of approximately 20 inches of water. Mechanical agitation of the flask was begun and continued until the

calculated quantity, 4500 cc. (0.2 mole), of hydrogen had been absorbed which usually required about four hours. The catalyst was filtered off by suction and the alcohol evaporated from the filtrate by means of a steam-bath. The *p*-aminothymol hydrochloride thus obtained was colored but after being washed by suction with several small portions of ethyl acetate a practically white compound resulted which weighed 19.5 Gm. representing 97% of the theoretical yield. (In another experiment, using a different type of hydrogenation apparatus, the Adams platinum catalyst (19) was found to be equally as efficient for this particular reduction.) The *p*-aminothymol hydrochloride melted at 252° C. (uncorr.) and could be obtained as extremely fine, needle-shaped, white crystals by dissolving in ethyl alcohol and allowing solvent to evaporate spontaneously.

Analyses:

Calculated for $C_{10}H_{16}ONCl$ Cl = 17.60
Found Cl = 17.90

This determination was made by the well-known Parr bomb method.

Unless at least an equivalent of hydrogen chloride was present to convert the freshly reduced *p*-aminothymol to its hydrochloride a considerable amount of oxidation took place before the compound could be isolated which resulted in the formation of a relatively large amount of a purple compound possessing the properties of a dye. This not only decreased the yield of the desired compound but made purification most difficult. The formation of the purple dye may be accounted for by assuming that the first product formed by the oxidation of *p*-aminothymol is the thymoquinone monoimine (VIII) which condenses with the unoxidized *p*-aminothymol (V) to form the anil (IX) which might be termed an indothymol. This explanation is supported by an experiment of Schwob (20) in which it was found that charcoal catalyzes the oxidation of a mixture of an aromatic diamine and a phenol to the corresponding indophenol and moreover the oxidation of *p*-aminothymol took place in absolute ethyl alcohol, an ideal medium for anil formation. The indothymol-like compound dissolved in alcohol to give a purple solution which was decolorized by the addition of hydrogen sulfide or ascorbic acid (21). The purple alcoholic solution was susceptible to color changes on the addition of an acid or a base (22). These properties of the purple compound likewise bear out its relationship to the indophenols.

Diazotization of p-Aminothymol.—An attempt to diazotize *p*-aminothymol was deemed worth while since the resulting diazonium salt, by virtue of its replaceable diazo group, would constitute an intermediate from which it might be possible to prepare medicinally important derivatives of thymol. It was found that attempts to replace the diazo group in the thymoldiazonium chloride (VI) by the usual method of warming the aqueous solution resulted in the formation of a red tar from which only a small amount of thymohydroquinone (VII) could be isolated. Since the formation of the highly colored tar is presumably due to a coupling reaction the method finally used to replace the diazo group with a hydroxyl group was based on the observation of Zeigler, *et al.* (23), that the chance of inter-molecular reaction is considerably diminished if the solution of the reacting substances is made sufficiently dilute.

Two grams (0.01 mole) of *p*-aminothymol hydrochloride were added to 50 cc. of water containing 4 cc. of concentrated hydrochloric acid. The mixture was cooled by means of an ice-bath to 3° C. and to it was slowly added under constant stirring 0.69 Gm. (0.01 mole) of sodium nitrite previously dissolved in 10 cc. water. As the nitrite solution was added the undissolved *p*-aminothymol hydrochloride disappeared and a brown foam began to appear on the surface of the solution. The foam soon became a dark-colored flocculent precipitate which was removed by filtration and discarded since its weight was found to be negligible. After removing the brown precipitate, the green solution of the diazonium salt was poured into 2 L. of strongly agitated boiling water. The solution was allowed to cool to room temperature and then evaporated under reduced pressure to about 1/20 of its original volume. The solution was cooled to 0° C. whereupon a crop of short, needle-shaped, yellowish crystals of thymohydroquinone precipitated. These crystals melted at 138° C. (uncorr.) and weighed 0.7 Gm. which represented a yield of 43% of the theoretical.

SUMMARY

1. The tautomerism of the *p*-nitrosothymol–thymoquinonemonoxime system has been studied with a view toward determining the effect of this on the hydrolysis of the compound.

2. Thymoquinone was obtained in fair yields by hydrolyzing *p*-nitrosothymol by means of a catalyst in an acid solution.

3. *p*-Nitrosothymol was quantitatively reduced to *p*-aminothymol by the use of hydrogen in the presence of a palladium catalyst and in a different experiment by the use of a platinum catalyst.

4. An explanation for the color changes involved in the oxidation of *p*-aminothymol has been offered and supported.

5. *p*-Aminothymol was diazotized and thymohydroquinone was obtained from the resulting diazonium salt by means of a new method.

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The Glycosides of Asclepias Cornuti or the Common Milkweed*

By A. E. Rihn† and H. G. DeKay‡

The common milkweed has been studied for its caoutchouc content (1), fibers, seed hairs, seed oil (2) and constituents in its lactiferous sap (3). A number of papers on these topics have been published since 1910.

The common milkweed was official in the U. S. P. from 1820 to 1864. The related species, *A. tuberosa* was official in the U. S. P. until 1916 when it was placed in the N. F. In 1936, it was deleted from the N. F.

Both species are members of the genus, *Asclepias*, and belong to the *Asclepiadaceæ* family. The common species has two botanical names, *Asclepias syriaca* (Linné, 1753) and *Asclepias Cornuti* (Decaisne, 1844). It may be differentiated from other species by its erect follicles which are covered with short soft processes and mounted on recurved pedicles. The leaf is broad and rounded at the apex, and different in other minor respects (4).

The sugars of the plant were studied by Gerhardt (6).

The related species native to Europe had been studied as far back as 1825 (5). Harnack (7), Gram (8), Tanret (9), Kubler (10) studied the glycoside from *Vincetoxicum officinale*. Gram also studied the glycosides from *A. curassavica* and *A. tuberosa* and found that they possessed a similar pharmacological activity.

Kubler assigned the formula, $C_{46}H_{70}(OCH_3)_4O_{16}$, to the glycoside obtained from *V. officinale*. It has since been determined that two forms of the compound exist, one water-soluble and the other water-insoluble.

Masson (11) isolated a saponid from *V. officinale* and found that it resembled the glycoside, vincetoxin. Van Rijn (12) states that vincetoxin is apparently identical with asclepiadin, the compound obtained from *A. tuberosa* and *A. curassavica* by Gram. A number of bulletins of the United States Department of Agriculture report the isolation of toxic gycosides from species of *Asclepias* native to the West.

Asclepias Cornuti has been used in dropsy, and as an emetic and cathartic. Gram's study on the pharmacological action of the glycoside showed that it affected the respiration, causing the heart to stop in diastole. No report of a thorough study on the glycosides of *A. Cornuti* was found in the literature.

EXPERIMENTAL

STUDIES ON ASCLEPIAS CORNUTI

The plants were gathered in Tippecanoe County,

* An abstract of a thesis presented to the faculty of Purdue University in partial fulfilment of the requirements for the degree of Master of Science.

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