[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

FURTHER STUDIES ON 4-QUINOLIZONE DERIVATIVES[1]

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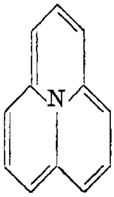
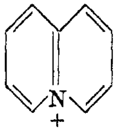
In a recent publication (1), we reported on the preparation of 4-quinolizone (4*H*-quinolizin-4-one) and 4-thioquinolizone (4*H*-quinolizin-4-thione). One of the points of interest in these molecules was the possibility of employing them for the synthesis of the tricyclic structure shown by I. This molecule, for which we propose the trivial name tricyclazine, is desired in order to obtain experimental evidence regarding current theories and methods of calculating resonance energies of aromatic molecules. In the present paper we are reporting the results of preliminary studies along these lines.



I



II

When 4-thioquinolizone (III) was treated with methyl iodide, it readily formed a quaternary salt whose properties are in agreement with those to be expected for a compound having structure IV. As shown in Fig. 1 the ultraviolet absorption spectrum of IV is rather similar to that of the dehydroquinolizinium ion (II) although it lacks the fine structure exhibited by this more symmetrical ion (2). Furthermore, when IV was treated with diethyl malonate in the presence of triethylamine, it steadily evolved methyl mercaptan and formed the substitution product, V. The evolution of methyl mercaptan proves the attachment of the methyl group to sulfur and establishes the correctness of IV as the structure of the quaternary salt.

The formation of V was carried out following the same general procedure used by Brooker, Keyes, and Williams (3) in their preparations of cyanine dyes. Since the dehydroquinolizinium ion (II) might be a desirable nucleus for preparing such dyes, it was of interest to further characterize IV by treating it with one of the typical reagents used in the preparation of cyanine dyes. The reaction of IV with lepidine methiodide occurred readily in good yield to give VI, a red-purple dye having λ_{max} at 545 mμ (log ϵ 4.5).

The isolation of V was accomplished through the formation of its hydrochloride salt. The physical properties and melting point behavior of this hydro-

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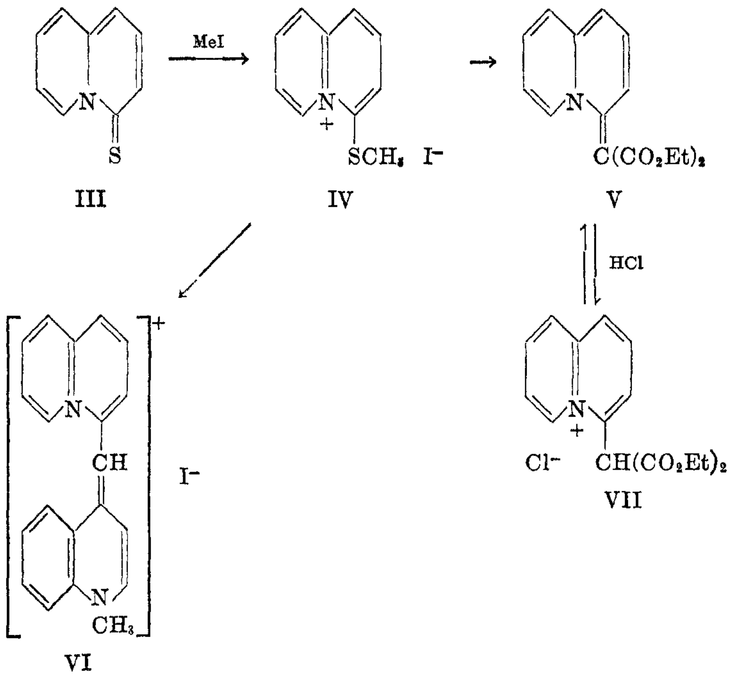
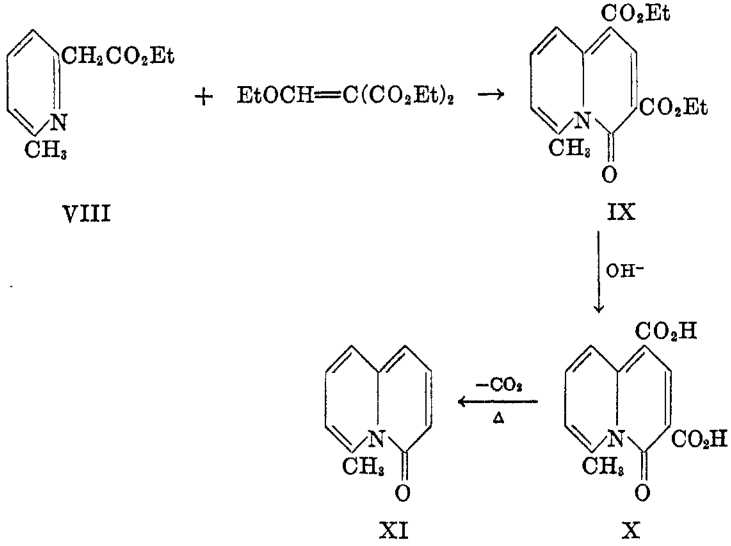
chloride would indicate that dissociation of the salt occurs very readily. That the hydrochloride exists as the dehydroquinolizinium ion (VII) is strongly indicated from its ultraviolet absorption spectrum which is similar to that of IV. It would appear, as shown in Fig. 1, that solutions of the hydrochloride are stable only in the presence of added hydrogen chloride; in its absence dissociation to the methine base (V) must be virtually complete since such solutions show spectra similar to that of 4-quinolizone (1).



If the 6-methyl analog of V could be prepared, it would be expected that cyclization would readily occur to give the carbon skeleton present in tricyclazine (I). The synthesis of 6-methyl-4-quinolizone was therefore investigated, following the same general procedure worked out previously for 4-quinolizone (1). The formation of the necessary starting material, ethyl 6-methyl-2-pyridylacetate (VIII), was carried out as described by Kornfeld (4). Condensation of this with diethyl ethoxymethylenemalonate gave the desired 1,3-dicarbethoxy-6-methyl-4-quinolizone (IX) in 80% yield. However, attempts to remove the carbethoxyl groups by acid hydrolysis, as was done in the previous series, failed completely. In the case of the 6-methyl homolog, cleavage of the quinolizone ring system apparently occurs under the conditions necessary to effect acid hydrolysis of the ester linkage. Adams and Pachter (5) encountered similar difficulties in their studies of the closely related pyrido[1,2-*a*]pyrimidones and found that under the conditions of basic hydrolysis the heterocyclic ring system was stable. This proved to be true in the present case as well and, by a modification of their procedure, it was possible to effect removal of the carbethoxyl groups in good yield.



In view of the ready availability of 6-methyl-4-quinolizone by this reaction scheme, its conversion to 6-methyl-4-thioquinolizone was carefully investigated using a variety of reaction conditions and many different preparations of phosphorus sulfides. Unfortunately, all of these attempts resulted in tarry products from which it was not possible to isolate any of the desired 6-methyl-4-thioquinolizone.

EXPERIMENTAL[3]

4-Methylmercaptodehydroquinolizinium iodide (IV). When 500 mg. of 4-thioquinolizone (2) was treated with 3 ml. of methyl iodide and the mixture was warmed a short while on the steam-bath, crystals separated from the solution. These were collected and recrystallized from an ethanol-ethyl acetate mixture to give 900 mg. (95%) of light yellow crystals, m.p. 171–173°.

Anal. Calc'd for $C_{10}H_{10}INS$: C, 39.61; H, 3.32.

Found: C, 40.08; H, 3.65.

4-(Dicarbethoxymethyl)dehydroquinolizinium chloride (VII). A solution of 400 mg. of 4-methylmercaptodehydroquinolizinium iodide, 350 mg. of diethyl malonate, and three drops of triethylamine in 3 ml. of ethanol was boiled under reflux for five hours. Methyl mercaptan was steadily evolved during this period. The solution was then concentrated under reduced pressure, and the residue was taken up in chloroform, washed with water, and dried. After removal of the chloroform, the residual oil was dissolved in ether giving a yellow solution. When dry hydrogen chloride was passed into the ether solution, the color was discharged and a white solid was precipitated. Recrystallization of the solid from an ethanol-ether mixture gave white crystals, m.p. 125–130° dec. The crystals became yellow with loss of hydrogen chloride on heating and the sample for analysis was dried at room temperature.

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[3] Analyses by Miss Viola Williams. All melting points are corrected.

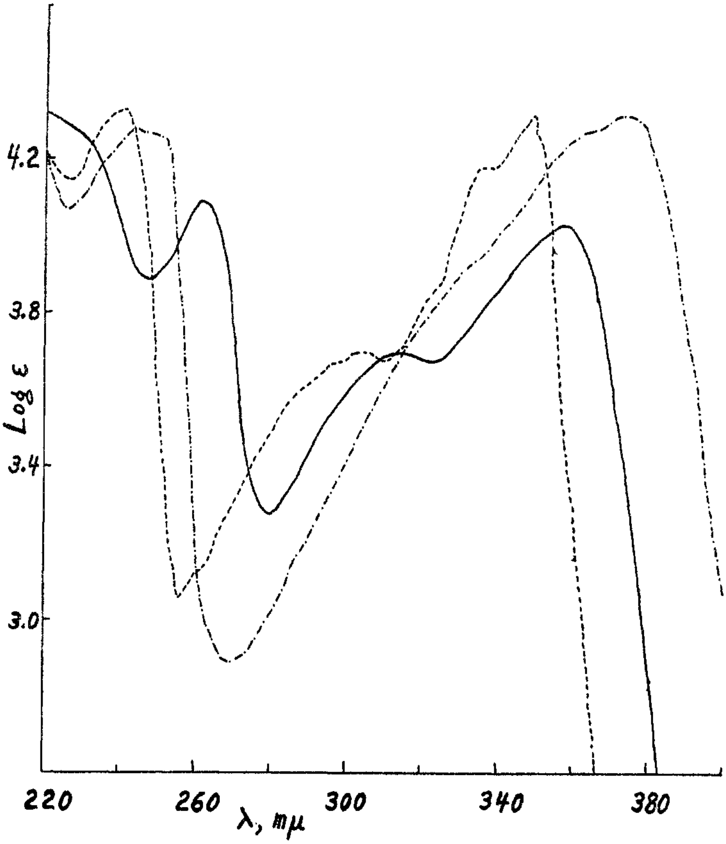

FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA OF 4-METHYLMERCAPTODEHYDROQUINOLIZINIUM IODIDE (IV, ————) in water and 4-(dicarbethoxymethyl)dehydroquinolizinium chloride (VII) in ethanol (—•—•) and in concentrated hydrochloric acid (- - -).

Anal. Calc'd for $C_{16}H_{18}ClNO_4$: C, 59.35; H, 4.98.

Found: C, 59.12; H, 4.74.

Conversion of IV to the cyanine dye (VI). A solution of 270 mg. of 4-methylmercaptodehydroquinolizinium iodide (IV), 270 mg. of lepidine methiodide, and 150 mg. of piperidine in 8 ml. of ethanol was boiled under reflux for four hours. When the solution was cooled, a reddish-purple dye separated. This was collected and recrystallized twice from methanol to give 150 mg. (41%) of a deep red solid, m.p. 270–272°.

Anal. Calc'd for $C_{20}H_{17}IN_2$: C, 58.26; H, 4.16.

Found: C, 58.00; H, 4.20.

1,3-Dicarbethoxy-6-methyl-4-quinolizone (IX). A mixture of 54.2 g. of ethyl 6-methyl-2-pyridylacetate[4] and 72.0 g. of diethyl ethoxymethylenemalonate (6) was heated at 180–185° until 85% of the expected quantity of ethanol had distilled (2–3 hrs.). The warm solution was then poured into 100 ml. of acetone and cooled to 0°. The yellow crystals, which separated, were collected and washed with cold acetone. This gave 73.5 g. (80%) of yellow

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[4] The best yield (40%) of this product was obtained following the general procedure of Woodward and Kornfeld [*Org. Syntheses*, **29**, 44 (1949)] rather than that described in reference 4. It was obtained as a colorless oil, b.p. 132° at 18 mm., whose hydrochloride salt melted at 112–115°.

crystals, m.p. 117–119°, sufficiently pure for use in the next step. On further recrystallization from acetone there was obtained a sample of yellow crystals, m.p. 124–128°.

Anal. Calc'd for $C_{16}H_{17}NO_5$: C, 63.35; H, 5.65.

Found: C, 63.22; H, 5.71.

6-Methyl-4-quinolizone-1,3-dicarboxylic acid (X). To a cold solution of 73.5 g. of 1,3-dicarbethoxy-6-methyl-4-quinolizone in 500 ml. of warm ethanol there was added 450 ml. of a 5% aqueous sodium hydroxide solution and the mixture was allowed to stand at 5° for 45 hours. The mixture was then acidified with hydrochloric acid, keeping the temperature of the mixture below 20°. The precipitate was collected and washed thoroughly with water. This gave 46.0 g. (77%) of an amorphous yellow solid. Since it could not be recrystallized from any of the usual solvents, it was purified for analysis by taking it up in alkali and reprecipitating it with acid. The resulting pale yellow solid melted with decomposition over a range from 263 to 275°.

Anal. Calc'd for $C_{12}H_9NO_5$: C, 58.30; H, 3.67.

Found: C, 57.98; H, 3.78.

6-Methyl-4-quinolizone (XI). When 23.0 g. of 6-methyl-4-quinolizone-1,3-dicarboxylic acid was heated at 250–265° under 1 mm. pressure, it rapidly evolved carbon dioxide and a red semi-solid distilled into the receiver. This was purified by sublimation under reduced pressure to give 8.0 g. (54%) of light yellow crystals, m.p. 48.5–50.5°.

Anal. Calc'd for $C_{10}H_9NO$: C, 75.45; H, 5.70.

Found: C, 75.59; H, 5.87.

Attempted conversion of 6-methyl-4-quinolizone to 6-methyl-4-thioquinolizone. When 6-methyl-4-quinolizone was treated with phosphorus pentasulfide following the procedure formerly employed with 4-quinolizone (1), none of the desired 6-methyl-4-thioquinolizone sublimed from the reaction mixture and attempts to recover a product from the mixture gave only tars. Similar experiences were encountered with tetraphosphorus heptasulfide or mixtures of phosphorus pentoxide and phosphorus pentasulfide.

SUMMARY

The synthesis of 6-methyl-4-quinolizone and related derivatives is described. It is shown that 4-methylmercaptodehydroquinolizinium iodide is a useful reagent for preparing compounds containing the dehydroquinolizinium nucleus.

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REFERENCES

(1) BOEKELHEIDE AND LODGE, *J. Am. Chem. Soc.*, **73**, 3681 (1951).
(2) BOEKELHEIDE AND GALL, *J. Am. Chem. Soc.*, In press.
(3) BROOKER, KEYES, AND WILLIAMS, *J. Am. Chem. Soc.*, **64**, 199 (1942).
(4) KORNFELD, Ph.D. Thesis, Harvard University, 1945.
(5) ADAMS AND PACHTER, *J. Am. Chem. Soc.*, **74**, 5491 (1952).
(6) PARHAM AND REED, *Org. Syntheses*, **28**, 60 (1948).