[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Senecio Alkaloids: Spartioidine, the Alkaloid from Senecio Spartioides; Stereochemical Relationship to Other Senecio Alkaloids

BY ROGER ADAMS AND MAURIZIO GIANTURCO

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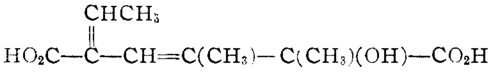
Hydrogenation and hydrolysis of spartioidine from Senecio spartioides yielded products that are typical of those obtained from other Senecio alkaloids by the same procedures. From this information and a comparison of the spectral characteristics of spartioidine with those of related Senecio alkaloids the assignment of a structure to this alkaloid has been possible.

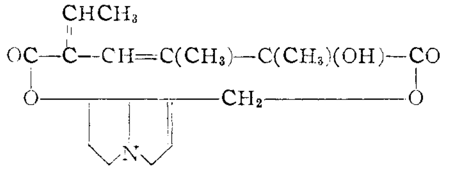
Manske[1] reported the isolation from Senecio spartioides T. G. of senecionine ($C_{18}H_{25}NO_5$) accompanied by two isomeric alkaloids ($C_{18}H_{23}NO_5$). One of them, m.p. 217°, $[\alpha]^{23}\text{D}\ -119.5°$ ($CHCl_3$), was identical with seneciphylline,[2] but the other, spartioidine, m.p. 178° (no rotation reported), was not further investigated.

Konovalova and Danilova[3] noted that seneciphylline upon aqueous alkaline hydrolysis yielded retronecine and isoseneciphyllic acid ($C_{10}H_{14}O_5$), m.p. 105–108° (no rotation reported). The acid is transformed by boiling with ethanolic alkali into an isomer, seneciphyllic acid, m.p. 142–143°, which is also obtained directly from the alkaloid by boiling with ethanolic alkali. The physical properties of isoseneciphyllic acid were redetermined, m.p. 114–115°, $[\alpha]^{28}\text{D}\ -13.25°$, and from degradative studies in this Laboratory[4] the acid was assigned formula I.



$$\overset{\displaystyle CHCH_3}{\overset{\|}{HO_2C—C}}—CH{=}C(CH_3)—C(CH_3)(OH)—CO_2H$$

I



II

The structure for the alkaloid seneciphylline on the basis of the chemical and physical data would then be II.

Dr. Manske kindly provided the authors with a small sample of spartioidine which he had extracted for his original investigation. Spartioidine, like seneciphylline, yields on hydrolysis retronecine and is thus an ester of this base. The infrared spectrum in Nujol mull shows bands for two ester carbonyl groups, one unconjugated (1742 cm.$^{-1}$) and one conjugated (1710 cm.$^{-1}$), and one strong band for a carbon–carbon double bond (1655 cm.$^{-1}$). The presence of an alcoholic hydroxyl group is evidenced by absorption at 3500 cm.$^{-1}$ when the infrared spectrum is determined in chloroform solution.

Quantitative hydrogenation experiments established the presence of three carbon–carbon double bonds. Four mole equivalents of hydrogen were absorbed and the infrared spectrum of the resulting compound indicated the presence of a carboxyl group (zwitterion), a salt structure and an unconjugated ester carbonyl. The hydrogenation of spartioidine had obviously followed the pattern common to the other Senecio alkaloids: hydrogenolysis of the ester linkage at the primary allylic alcohol group of retronecine followed by hydrogenation of the carbon–carbon double bonds. The product is an amino acid. No acid was freed by treatment of its aqueous solution with Dowex 50, indicating that hydrogenation product is not a salt. These data confirm that spartioidine, a pyrrolizidine alkaloid, is of the Senecio type with the two hydroxyl groups of retronecine esterified by a dicarboxylic acid and not by two monocarboxylic acids. The acidic moiety, $C_{10}H_{14}O_5$, of spartioidine is therefore isomeric with that of seneciphylline.

A comparison of the infrared spectra of seneciphylline and spartioidine with those of senecionine and its stereoisomers, integerrimine and usaramoensine,[5] has permitted the formulation of a structure for spartioidine and has also made possible certain deductions concerning the geometric configuration of the carbon–carbon double bond conjugated with the ester carbonyl and of the epimeric form of the asymmetric 2-carbon atom in all five alkaloids.

Integerrimine and usaramoensine have the same configuration about the carbon–carbon double bond (probably *trans*)[5b] as determined by ultraviolet absorption spectra and differ only in the configuration of the asymmetric 2-carbon atom. Since the configuration of the 2-carbon atom is established in integerrimine (III), because integerrinecic acid, its acid moiety, and the corresponding lactone are readily interconverted, and since no change of configuration at the 2-carbon atom during the alkaline hydrolysis of the alkaloids would be expected, the stereochemical formula for usaramoensine may be written as IV.

The configuration at the 3-carbon atom is not shown in the formulas. It is the same in integerrimine, usaramoensine and senecionine because they all lactonize to integerrinecic acid lactone, but its relation to the configuration at the 2-carbon atom is not known.

The infrared spectra of integerrimine and usara-

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[1] R. H. F. Manske, *Can. J. Research*, **17B**, 1 (1939).

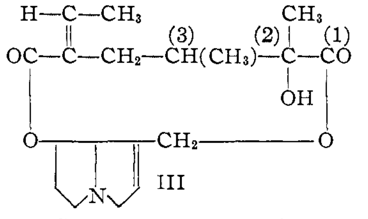
[2] On the basis of optical rotation, it appears that the material contained an impurity of lower optical rotation than seneciphylline, see R. Adams and M. Gianturco, THIS JOURNAL, **78**, 5315 (1956); [m.p. 217°, $[\alpha]\text{D}\ -139°$ ($CHCl_3$)].

[3] R. A. Konovalova and A. Danilova, *J. Gen. Chem. U.S.S.R.*, **18**, 1198 (1948).

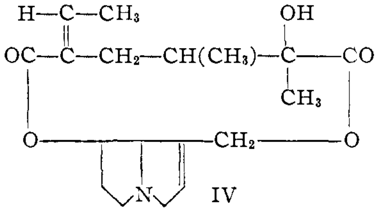
[4] R. Adams, T. R. Govindachari, J. M. Looker and J. D. Edwards, THIS JOURNAL, **74**, 700 (1952); R. Adams and T. R. Govindachari, *ibid.*, **71**, 1180 (1949).

[5] For the infrared spectrum of seneciphylline, see (a) R. Adams and T. R. Govindachari, *ibid.*, **71**, 1180 (1949). For those of senecionine, integerrimine and usaramoensine, see (b) R. Adams and B. L. Van Duuren, *ibid.*, **75**, 4631 (1953). This latter paper furnished the spectral data which are used in this Communication as partial support of the stereochemical conclusions.

moensine determined in Nujol mull are very similar; however, the carbonyl bands are sharp in the former, indicating no hydrogen bonding, and broad in the latter characteristic of hydrogen bonding. This is in agreement with the suggested structures. When the model of the most compact structure possible for usaramoensine (IV) is constructed, the hydrogen of the hydroxyl group is in a position that permits intermolecular hydrogen bonding; in the model for integerrimine (III) it is not.

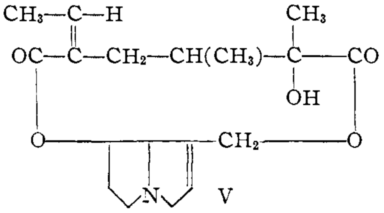


III


IV

Usaramoensenecic and integerrinecic acids obtained by hydrolysis of the respective alkaloids, differ in their configuration at the carbon–carbon double bond as determined by ultraviolet absorption spectra. From a comparison of their spectral characteristics with those of angelic and tiglic acids, they were originally assigned[5b] the *cis* and *trans* configuration, respectively. However, Cason and Kalm[6] have recently questioned the validity of assignment of configurations of $\alpha,\beta$-unsaturated acids with bulky $\alpha$-substituents on this basis. Since in these compounds the *cis*-form would be the less hindered, that is the more planar, it would have a higher extinction coefficient than the corresponding *trans*-form, thus reversing the situation existing in the model pair, angelic and tiglic acids, where the $\alpha$-substituent is a small group. The arguments of Cason and Kalm would probably not apply to the alkaloids, where the interference of the $\alpha$-substituents with the $\beta$-methyl groups should be inhibited by the ring structure, but they may be valid when applied to the corresponding acid moieties. On this assumption the configuration of the carbon–carbon double bond would be *trans* and *cis*, respectively, for usaramoensenecic and integerrinecic acid. This is actually in agreement with the fact that usaramoensenecic acid was obtained under mild hydrolytic conditions while integerrinecic acid was obtained under drastic hydrolytic conditions, which are more apt to convert a less stable into a more stable isomer.[3,7]

The ultraviolet and infrared spectra of senecionine show that the configuration at the carbon–carbon double bond is different (probably *cis*) from that present in integerrimine and usaramoensine. The configuration of the asymmetric 2-carbon atom of senecionine can be assigned on the basis of a comparison of the configuration of the aqueous alkaline hydrolysis products of usaramoensine and senecionine. Since senecic acid has the same configuration at the carbon–carbon double bond as usaramoensenecic acid[8] as determined by ultraviolet spectra and since the configuration at the 3-carbon atom is identical in the two acids because both lactonize to integerrinecic acid lactone, it follows that the 2-carbon atom in senecic acid (and therefore in senecionine) must have a configuration opposite to that existing at the 2-carbon atom of usaramoensenecic acid (and therefore of usaramoensine). The most likely formula for senecionine is shown in V.


V

This is in agreement with the sharp carbonyl bands present in the infrared spectrum of senecionine (Nujol mull) by which no intermolecular hydrogen bonding of the hydrogen atom of the hydroxyl group on the 2-carbon atom is indicated.

Thus, integerrimine (III) and usaramoensine (IV) differ from each other only in the configuration at the asymmetric 2-carbon atom; integerrimine (III) and senecionine (V), differ from each other only in the configuration at the carbon–carbon double bond; senecionine (V) and usaramoensine (IV) differ from each other both in the configuration of the carbon–carbon double bond and the asymmetric 2-carbon atom. A change in configuration at a carbon–carbon double bond causes significant changes in the infrared spectra of such molecules, whereas a change in the configuration of the asymmetric 2-carbon atom has only a minor effect; the spectrum of senecionine differs considerably from those of integerrimine and usaramoensine.

Certain deductions concerning the structure of seneciphylline and spartioidine are now possible. The infrared spectrum of seneciphylline resembles closely that of senecionine and the spectrum of spartioidine resembles equally closely those of integerrimine and usaramoensine but is different

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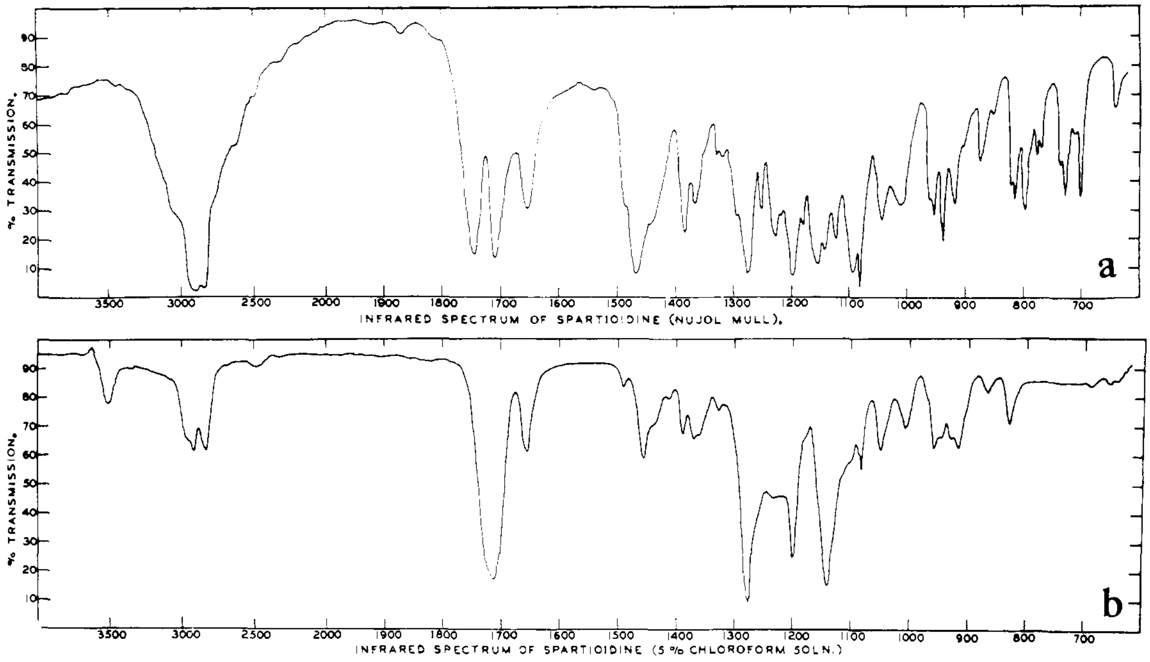
(6) J. Cason and M. J. Kalm, *J. Org. Chem.*, **19**, 1947 (1954).

(7) Platyphylline was reported to yield two different acids on alkaline hydrolysis, depending on the experimental conditions. A scrutiny of the original literature [A. Orekhov and V. Tiedebel, *Ber.*, **68**, 650 (1935) and A. Orekhov, R. A. Konovalova and V. Tiedebel, *ibid.*, **68**, 886 (1935)] leads the authors to believe that Orekhov and co-workers on ethanolic alkaline hydrolysis of platyphylline obtained integerrinecic acid lactone and not senecic acid as reported.[5b] The product of aqueous alkaline hydrolysis may be a mixture of acids, possibly containing isoseneciphyllic acid, since platyphylline was obtained together with seneciphylline and complete separation of the two alkaloids might well have been impossible by the means available at the time of the investigation. Complete separation of mixtures of closely related Senecio alkaloids has only been possible by partition chromatography. See R. Adams and M. Gianturco, THIS JOURNAL, **78**, 398 (1956).

(8) The double bonds in senecionine and usaramoensine have a different configuration; the double bonds in senecic acid and usaramoensenic acid have the same configuration. It appears as though the *trans* configuration of the carbon–carbon double bond (as in usaramoensine and integerrimine) is the more stable in the alkaloids, while the opposite is true for the corresponding acids. It may be possible, then, that mild alkali causes a change in configuration at the carbon–carbon double bond of senecionine (less stable form) prior to hydrolysis. Hydrolysis would then lead to formation of the less stable form of the acid, not further changed under the mild hydrolytic conditions employed.



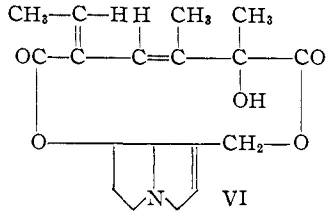
INFRARED SPECTRUM OF SPARTIOIDINE (NUJOL MULL).

INFRARED SPECTRUM OF SPARTIOIDINE (5 % CHLOROFORM SOLN.)

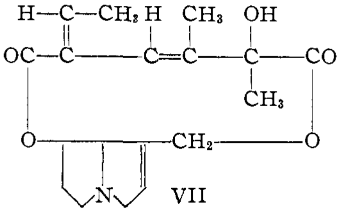
Fig. 1.

from those of seneciphylline and senecionine. Models indicate that the 3-carbon–carbon double bond of the acid moieties in seneciphylline and spartioidine must have the *cis* configuration[9] with respect to the carbon chain and hence it is likely that the same relationship exists between seneciphylline and senecionine (V) and between spartioidine and usaramoensine (or integerrimine) with respect to the configuration at the carbon–carbon double bond conjugated with the ester carbonyl.

It is pertinent that while the infrared spectrum of seneciphylline shows two sharp bands of medium intensity at 1642 and 1660 cm.$^{-1}$, respectively, for the carbon–carbon double bond stretching vibration, the spectrum of spartioidine exhibits only one broad, strong band at about 1655 cm.$^{-1}$. It was observed that when the spectra of senecionine, integerrimine and usaramoensine were determined in chloroform solution, the band for the carbon–carbon stretching vibration in the spectrum of senecionine appeared at 1645 cm.$^{-1}$, but in the spectra of integerrimine and usaramoensine at 1665 cm.$^{-1}$. A change of configuration of the carbon–carbon double bond causes a shift of the band. This fact may explain the difference found in the spectra of seneciphylline and spartioidine in the region of the carbon–carbon stretching vibration. Apparently the band at 1642 cm.$^{-1}$ in the infrared spectrum of seneciphylline, due to the stretching vibration of the carbon–carbon double bond conjugated with the ester carbonyl, has shifted in the spectrum of spartioidine to higher wave numbers. The strong intensity band at 1655 cm.$^{-1}$ is probably due to a combination of the stretching vibration of the carbon–carbon double bond conjugated with the ester carbonyl and the stretching vibration of the second carbon–carbon double bond. Furthermore, the very sharp carbonyl bands in seneciphylline and the broad carbonyl bands in spartioidine are an indication of the probable identity of the configuration at the asymmetric 2-carbon atom in seneciphylline and senecionine on the one hand, and in spartioidine and usaramoensine on the other. This leads to structure VI for seneciphylline and VII for spartioidine.



VI



VII

**Acknowledgment.**—The authors are indebted to Mr. J. Nemeth and Mrs. M. Benassi for the microanalyses and to Mr. J. Brader for the infrared spectra.

## Experimental

**Spartioidine.**—The sample of spartioidine used in this investigation was kindly furnished by Dr. Manske. Its constants were redetermined; ultraviolet spectrum (95% EtOH); $\lambda_{max}$ 215, $\epsilon_{max}$ 10170. The infrared spectrum ($CHCl_3$) shows one broad, strong band at 1655 cm.$^{-1}$ in contrast to two sharp bands of medium intensity at 1642 and 1660 cm.$^{-1}$ in the spectrum of seneciphylline (see Fig. 1). Rotation: 0.0346 g. made up to 2 ml. with 95% ethanol at 25° gave $\alpha_D$ −1.44°; *l* 1, $[\alpha]^{25}_D$ −83.7°.

*Anal.* Calcd. for $C_{18}H_{23}NO_5$: C, 64.86; H, 6.91; N, 4.20. Found: C, 64.91; H, 6.92; N, 4.20.

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(9) F. L. Warren, "The Pyrrolizidine Alkaloids," in "Progress in the Chemistry of Organic Natural Products," Springer Verlag, Wien, 1955, p. 232.

**Hydrogenation of Spartioidine and Seneciphylline.**—A solution of 5.815 mg. of seneciphylline in ethanol absorbed 1.70 cc. of hydrogen at 27.5° and 748.6 mm. This is equivalent to 3.88 moles of hydrogen per mole of alkaloid.

A solution of 5.595 mg. of spartioidine in ethanol absorbed 1.72 cc. of hydrogen at 27.5° and 744.0 mm. This is equivalent to 4.07 moles of hydrogen per mole of alkaloid.

The ethanolic solution of the product of hydrogenation of spartioidine was evaporated to dryness at reduced pressure, the residual oily material was thoroughly dried and its infrared spectrum determined. Bands for a carboxyl group (zwitterion) at 1580 cm.$^{-1}$, for an ester carbonyl at 1730 cm.$^{-1}$ and for a salt-structure at 2340 cm.$^{-1}$ were present. An aqueous solution of the product of hydrogenation of spartioidine had a $p$H value close to neutrality, which did not change after the addition of Dowex 50. This test has been used previously with success for the determination of the inter- or intra-molecular character of salt-like compounds.[10]

**Hydrolysis of Spartioidine.**—Alkaline hydrolysis of 30 mg. of the alkaloid by the usual procedure followed by separation of the acidic and basic fragments yielded retronecine, identified by its infrared spectrum, melting point and a melting point of a mixture with an authentic sample.

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[10] R. Adams and M. Gianturco, THIS JOURNAL, **78**, 4464 (1956).

URBANA, ILLINOIS

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Quinone Imides. XLII. Orientation of Adducts from Substituted $p$-Quinonedimethanesulfonimides

BY ROGER ADAMS AND M. D. NAIR[1]

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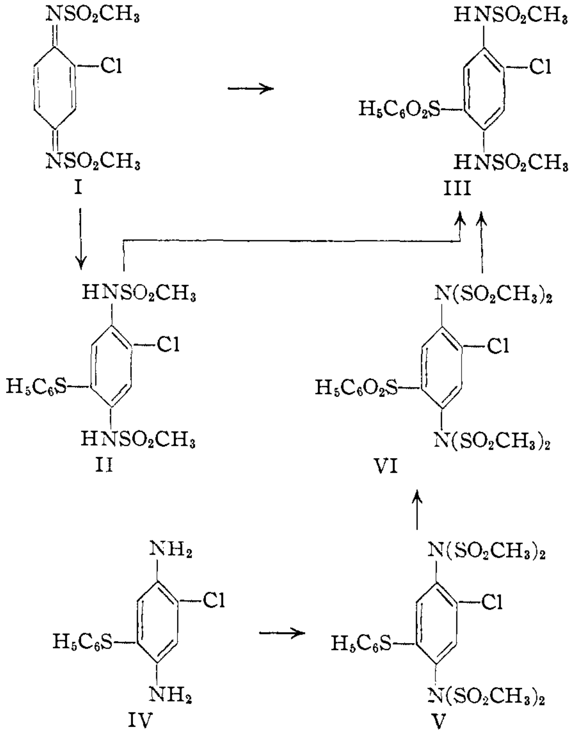
Addition of thiophenol and benzenesulfinic acid to 2-chloro-$p$-quinonedimethanesulfonimide gives 2-chloro-5-phenylmercapto-$p$-phenylenedimethanesulfonamide and 5-benzenesulfonyl-2-chloro-$p$-phenylenedimethanesulfonamide, respectively. Addition of hydrogen chloride to 2-phenylmercapto-$p$-quinonedimethanesulfonamide results in 5-chloro-2-phenyl mercapto-$p$-phenylenedimethanesulfonamide. The 2-benzenesulfonyl-$p$-quinonedimethanesulfonimide, on the other hand, does not give an hydrogen chloride adduct with 1,2,4,5-orientation; by analogy with the corresponding reaction in the benzenesulfonimide series, this compound is assigned a 1,2,3,4-orientation.

Addition of thiophenol and benzenesulfinic acid to 2-chloro-$p$-quinonedibenzenesulfonimide resulted in adducts with 1,2,4,5-orientation[2,3] and addition of hydrogen chloride to 2-phenylmercapto-$p$-quinonedibenzenesulfonimide also yielded 5-chloro-2-phenylmercapto-$p$-phenylenedibenzenesulfonamide.[3] With the strongly electron-attracting benzenesulfonyl group, however, addition of hydrogen chloride resulted in an adduct with 1,2,3,4-orientation.[4]

The orientation in addition of reagents to quinone diimides has been shown to be dependent in part on the character of the groups on the imide nitrogens. The benzoyl and benzenesulfonyl groups had markedly different effects. This suggested a comparison of two sulfonyl groups, one containing an aromatic and the other an aliphatic residue. A few typical addition reactions of $p$-quinonedimethanesulfonimides have now been studied. Thiophenol and benzenesulfinic acid added to 2-chloro-$p$-quinonedimethanesulfonimide (I) to give adducts with identical orientations, since the thiophenol adduct II on oxidation with hydrogen peroxide gives the benzenesulfinic acid adduct III. The orientation of groups in these adducts was shown to be 1,2,4,5 by an unequivocal synthesis. 2-Chloro-5-phenylmercapto-$p$-phenylenediamine (IV)[5] was tetramethanesulfonated to V, oxidized to the benzenesulfonyl derivative VI, and one methanesulfonyl group removed from each nitrogen by means of aqueous alkali, to give III.

Addition of hydrogen chloride to 2-phenylmercapto-$p$-quinonedimethanesulfonimide also resulted in formation of II. These orientations are identical to those observed in the dibenzenesulfonimide series indicating that alteration of the substituted function of the sulfonimide groups does not have any profound effect on the orientation of adducts.



2-Benzenesulfonyl-$p$-quinonedimethanesulfonimide added hydrogen chloride to give an adduct

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[1] An abstract of a portion of a thesis submitted by M. D. Nair to the Graduate College of the University of Illinois, 1956, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] R. Adams, E. F. Elslager and T. E. Young, THIS JOURNAL, **75**, 663 (1953).

[3] R. Adams and T. E. Young, *ibid.*, **75**, 3235 (1953).

[4] R. Adams, T. E. Young and R. W. P. Short, *ibid.*, **76**, 1114 (1954).

[5] R. Adams and M. D. Nair, *ibid.*, **78**, 5932 (1956).