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

Senecio Alkaloids: the Structure of Trichodesmine

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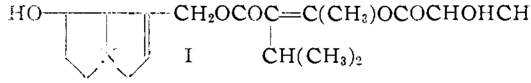
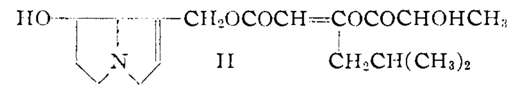
Trichodesmine is hydrolyzed by alkali to methyl isobutyl ketone, *dl*-lactic acid and carbon dioxide. It absorbs in presence of a catalyst four hydrogen atoms with formation of a tetrahydrotrichodesmine, the properties of which indicate it to be a salt. Trichodesmic acid was obtained from this salt. The properties and infrared spectra of trichodesmine, tetrahydrotrichodesmine and trichodesmic acid resemble closely those of monocrotaline, tetrahydromonocrotaline and monocrotalic acid. A structural formula is proposed which satisfies all the properties of this alkaloid.

In a previous communication[1] it was reported that from *Crotalaria juncea* the alkaloids of known structure, seneciphylline, senecionine and riddelline were obtained, as well as trichodesmine, $C_{18}H_{27}NO_6$, a new alkaloid junceine, $C_{18}H_{27}NO_7$, and an optically inactive amino acid, identified as β-hydroxy-N-methyl-DL-norvaline A. This communication concerns the structure of trichodesmine.

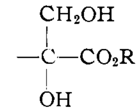
Trichodesmine, m.p. 160–161°, $[\alpha]_D$ +38° (EtOH), was first isolated from *Trichodesma incanum* by Menshikov and Rubinstein[2] who reported that it contained two hydroxyl groups and that on alkaline hydrolysis it yielded (a) an alkanol amine, later shown to be retronecine,[3] (b) methyl isobutyl ketone and (c) *dl*-lactic acid. Menshikov and Rubinstein suggested that the methyl isobutyl ketone, obtained by hydrolysis of the alkaloid, was formed by decarboxylation of either isobutyroacetic acid or isopropylacetoacetic acid. They concluded that trichodesmine is an alkanol amine, containing two hydroxyl groups, combined with two organic acids, one of which is lactic, and the other of which is one of the β-keto acids mentioned above. Since the alkaloid gives no color with ferric chloride, they believed that the *dl*-lactic acid was present as the ester of the enolic hydroxyl form of the β-keto acid. They did not suggest any precise structure for the alkaloid, but two possible formulas designed to fit these facts have been proposed.[4] These structures I and II are untenable since the infrared spectrum of trichodesmine has only a single carbonyl band at 1735 cm.$^{-1}$ indicating an unconjugated ester.[5] Other reactions described below also cannot be explained on the basis of structures I and II.





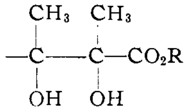
Trichodesmine is reduced with hydrogen and palladium-on-strontium carbonate as catalyst to a tetrahydro derivative, $C_{18}H_{31}NO_6$, m.p. 182°, $[\alpha]_D$ −20.4° (EtOH). The infrared spectrum of tetrahydrotrichodesmine shows complete absence of an ester carbonyl and carbon–carbon double bonds, but the presence of bands at 1615 and 2400 cm.$^{-1}$ that are characteristic of a carboxylate ion and a salt structure, respectively. A band at 1765 cm.$^{-1}$ is attributed to a γ-lactone.

A probable glycol structure in trichodesmine was indicated by the consumption of one mole of periodic acid. A quantitative study of the behavior of several Senecio alkaloids containing glycol functions toward periodic acid permitted certain conclusions concerning configuration. Riddelline[6] and retrorsine,[7] containing the grouping



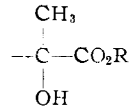
$$\begin{array}{l} \quad CH_2OH \\ \quad | \\ —C—CO_2R \\ \quad | \\ \quad OH \end{array}$$

take up one mole-equivalent of reagent in 3 minutes or less; monocrotaline,[8] which contains the grouping



$$\begin{array}{l} \quad CH_3 \quad CH_3 \\ \quad | \qquad\ | \\ —C——C—CO_2R \\ \quad | \qquad\ | \\ \quad OH \quad OH \end{array}$$

with the two hydroxyls presumably *cis* to each other, reduces one mole-equivalent of reagent in 25 to 30 minutes; trichodesmine under similar conditions requires 45 minutes for the consumption of one mole-equivalent.[9] Seneciphylline, which typifies those Senecio alkaloids containing a



$$\begin{array}{l} \quad CH_3 \\ \quad | \\ —C—CO_2R \\ \quad | \\ \quad OH \end{array}$$

group, was unaffected by periodic acid under the same reaction conditions employed for the alkaloids containing glycol functions.

The relative rates of oxidation of trichodesmine and monocrotaline suggest a difference in configuration of the two hydroxyls in the two molecules. Since it was established in the synthesis of monocrotalic acid that the hydroxyls are *cis* to each other, the same configuration can be assumed to exist in

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(1) R. Adams and M. Gianturco, THIS JOURNAL, **78**, 1919 (1956).

(2) G. M. Menshikov and N. Rubinstein, *Ber.*, **68**, 2039 (1935).

(3) R. A. Konovalova and A. Orekhov, *Bull. soc. chim.*, [5] **4**, 2037 (1937).

(4) N. J. Leonard in "The Alkaloids," Edited by R. H. F. Manske and H. L. Holmes, Vol. I, Academic Press, Inc., New York, N. Y., 1950, p. 160.

(5) Vinyl esters absorb above 1770 cm.$^{-1}$ and conjugated esters below 1730 cm.$^{-1}$; L. J. Bellamy, "Infrared Spectra of Complex Molecules," Methuen and Co., Ltd., John Wiley and Sons, Inc., New York, N. Y., 1954, p. 155.

(6) R. Adams and B. L. Van Duuren, THIS JOURNAL, **75**, 4638 (1953).

(7) E. L. Leisegang and F. L. Warren, *J. Chem. Soc.*, 702 (1950).

(8) R. Adams, P. R. Shafer and B. H. Braun, THIS JOURNAL, **74**, 5612 (1952).

(9) In all these cases, after the primary oxidation had occurred at the relatively rapid rate, further oxidation by periodic acid continued at a very much slower rate. This appeared to be due to gradual oxidation of the initial cleavage products.

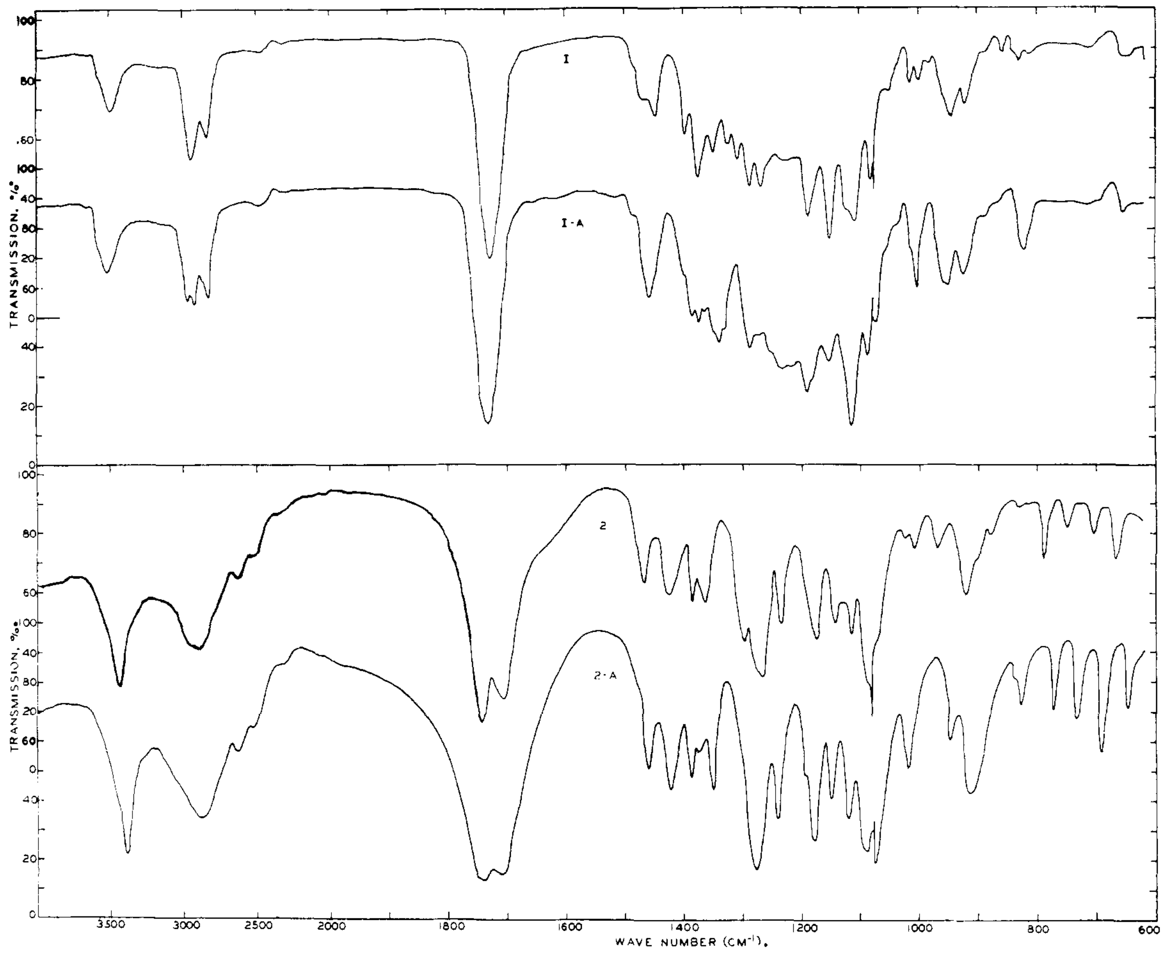

Fig. 1.—Infrared spectra: I, trichodesmine, Nujol mull; I-A, monocrotaline, Nujol mull; 2, trichodesmic acid, KBr; 2-A, monocrotalic acid, KBr.

the alkaloid. The slower rate of oxidation of trichodesmine may be attributed to the *trans* configuration of the hydroxyls. Since trichodesmine contains only two hydroxyl groups,[2] the ones which react with periodic acid, and since the basic moiety of the molecule, retronecine, also contains two hydroxyls, it follows that both alcohol groups in the latter must be esterified in the alkaloid, thus resulting in a postulated structure for trichodesmine very similar to that of monocrotaline.

Trichodesmine and thionyl chloride in the cold gave a white crystalline product, $C_{18}H_{27}NO_8S \cdot HCl$, m.p. 172°, which analyzed for the hydrochloride of an acid sulfite ester of the alkaloid. This compound results from the reaction of one mole-equivalent of thionyl chloride with one hydroxyl group, followed by hydrolysis of the second chlorine atom. The formation of this product, in contrast to the hydrochloride of a neutral cyclic sulfite obtained under the same conditions from monocrotaline, may also be explained by assuming the *trans* configuration of the two hydroxyl groups in trichodesmine. Construction of Fisher–Taylor–Hirschfelder models indicates that a neutral cyclic sulfite can form without strain only if the two hydroxyls are *cis* to each other.

The infrared spectra of trichodesmine and its hydrogenation product showed a striking similarity to those of monocrotaline and its hydrogenation product (Fig. 1).

When monocrotaline was hydrolyzed with barium hydroxide, retronecine, monocrotic acid (α,β-dimethyllevulinic acid) and carbon dioxide, resulted.[10] Menshikov and Rubinstein[2] used sodium hydroxide for the hydrolysis of trichodesmine and isolated methyl isobutyl ketone and lactic acid. It is obvious from these degradation products that, if the two alkaloids are closely related in structure, the alkaline degradation can follow more than one course. This suggestion is further supported by the fact that the maximum yield of α,β-dimethyllevulinic acid from monocrotaline never exceeded 48%. The carbon dioxide evolved by the barium hydroxide degradation of monocrotalic acid was 88% of one mole-equivalent. The alkaline degradation of monocrotaline and monocrotalic acid was therefore effected with aqueous sodium hydroxide under the conditions followed by Menshikov and Rubinstein.[2] From the monocrotaline experiment methyl ethyl ketone was isolated in the form of its dinitrophenylhydrazone. On the other hand, no methyl ethyl ketone resulted from monocrotalic acid; only α,β-dimethyllevulinic acid was formed.

The barium hydroxide hydrolysis of monocrota-

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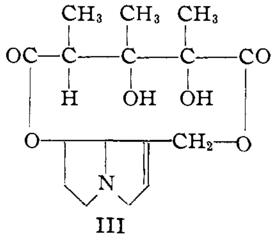
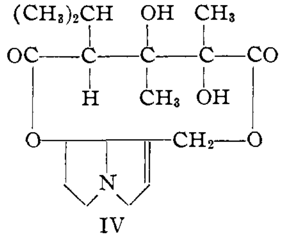
(10) R. Adams, E. F. Rogers and F. J. Sprules, THIS JOURNAL, **61**, 2819 (1939).

line was repeated and indeed methyl ethyl ketone was also formed in this reaction. This ketone, on account of its volatility, had been overlooked in the earlier work, when merely α,β-dimethyllevulinic acid and carbon dioxide were isolated.

Unfortunately the amount of trichodesmine available was too small to attempt to prepare a ketonic acid by barium hydroxide treatment of this alkaloid or its acid moiety, trichodesmic acid.

With the close parallelism of structures indicated between monocrotaline (III) and trichodesmine, the latter may be given structure IV.[11a]

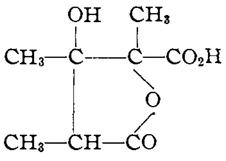

III

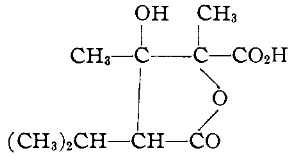

IV

Two features in the trichodesmine molecule IV are uncertain. The two *trans*-hydroxyls might be in the reverse position to each other and the two carboxyls of the acid moiety might be interchanged in their ester formation with the two hydroxyls of retronecine. The representation of the ester linkages as in IV, however, is probably correct since in other alkaloids of similar character[7,12] the carboxyl with the α-carbon holding the hydroxyl has been shown to be esterified with the allylic hydroxyl of retronecine.

When an aqueous solution of tetrahydrotrichodesmine was treated with Dowex-50 in the hydrogen form and then evaporated, a white crystalline, readily purified acid, $C_{10}H_{16}O_5$, m.p. 209–211°, resulted. The infrared spectrum of this compound, which was called trichodesmic acid, was very similar to that of monocrotalic acid and showed the presence of a 5-membered lactone ring, a normal carboxyl and an alcoholic hydroxyl.

The structure of trichodesmic acid, therefore, must be very closely related to that of monocrotalic acid (V), and consequently it is designated by formula VI.

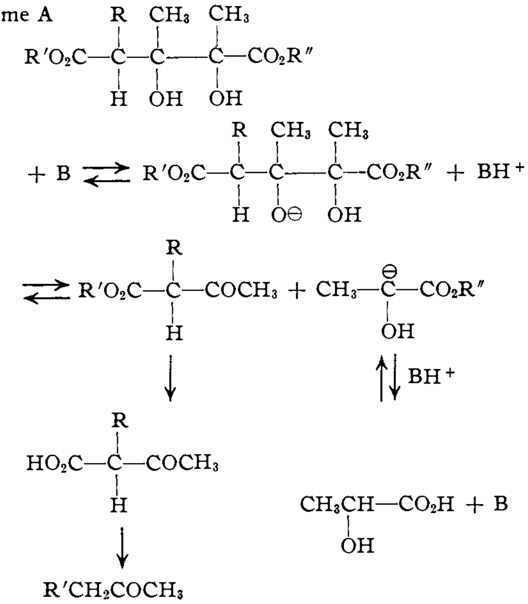

V


VI

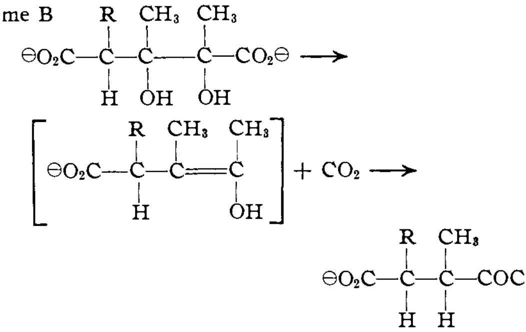
Structure VI is undoubtedly formed from trichodesmine in a manner similar to the formation of monocrotalic acid from monocrotaline—namely, hydrogenolysis of the allylic ester linkage in IV followed by an intramolecular transesterification between the ester linkage at the C_7-carbon atom of the retronecine nucleus and the hydroxyl on the carbon atom alpha to the carboxyl group produced by the hydrogenolysis.

A possible mechanism for the conversion of monocrotaline (III) or trichodesmine (IV) to a simple ketone is shown in A; here it is assumed that the glycol splitting precedes the hydrolysis. A mechanism for the formation of a γ-keto acid from monocrotalic acid or from the alkaloids, shown in B, is based on the assumption that hydrolysis of the alkaloid occurs before the degradation; this coincides with the experimental findings previously mentioned. In presence of alkali both monocrotalic acid and trichodesmic acid will be in the open form as shown in B.

Scheme A

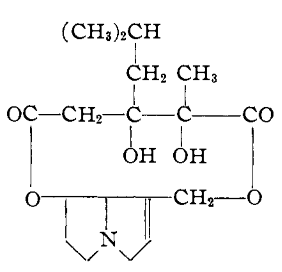


Scheme B



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.

[11a] Another structure for trichodesmine which upon alkaline hydrolysis would probably give methyl isobutyl ketone and lactic acid is represented by



This formula, however, contains an acid moiety which does not obey the isoprene rule. Since every other known C_{10}-acid obtained from the Senecio and Crotalaria alkaloids conforms to the isoprene rule, this formula is rejected on this basis alone.

(12) R. Adams and B. L. Van Duuren, THIS JOURNAL, **75**, 4638 (1953).

Experimental

All melting points are corrected.

Tetrahydrotrichodesmine.—A solution of 0.21 g. of trichodesmine in 20 ml. of ethanol and 5 ml. of glacial acetic acid was hydrogenated at room temperature and atmospheric pressure with 0.02 g. of platinum oxide catalyst. Two mole-equivalents of hydrogen were absorbed in one hour. The solution was filtered from the catalyst which was thoroughly washed with methanol. The combined solvents were eliminated under reduced pressure and the residue was crystallized from acetone containing 5% of methanol. Colorless crystals, weighing 0.17 g. (80%), separated, m.p. 182°. The mother liquors from the crystallization yielded, after partial concentration, an additional crop of 0.025 g. of the material. Rotation: 0.0132 g. made up to 1.50 ml. with ethanol at 25° gave α_D −0.180°, l 1; $[\alpha]^{25}_D$ −20.4°.

Anal. Calcd. for $C_{18}H_{31}NO_6$: C, 60.48; H, 8.74. Found: C, 60.36; H, 8.53.

Trichodesmic Acid.—A solution of 0.15 g. of tetrahydrotrichodesmine in 3 ml. of water was shaken for a few minutes with 1.0 g. of Dowex-50 in the hydrogen phase. The liquid, which became immediately acidic, was filtered and the resin was washed with small volumes of water until the washings reached a practically neutral *p*H value. The water was eliminated under reduced pressure and 0.81 g. (90%) of white material resulted. After crystallization from ether–petroleum ether (b.p. 30-60°) white crystals, m.p. 209–211°, were obtained.

Anal. Calcd. for $C_{10}H_{16}O_6$: C, 55.54; H, 7.46. Found: C, 55.50; H, 7.52.

The specific rotation of this acid is very low and could not be determined accurately with the instrument used.

Tetrahydromonocrotaline.—The hydrogenation of monocrotaline over a platinum oxide catalyst has been described.[13] The resulting salt, however, was not characterized but immediately hydrolyzed to retronecanol and monocrotalic acid. The primary reduction product has now been isolated and purified.

Monocrotaline was hydrogenated as previously reported. The solvent was eliminated under reduced pressure and an oily residue was obtained, which solidified on treatment with dry acetone. It was purified by crystallization from acetone, m.p. 156°; yield quantitative. Rotation: 0.0171 g. made up to 1.5 ml. with ethanol at 25° gave α_D −0.416°, l 1; $[\alpha]^{25}_D$ −36.49°.

Anal. Calcd. for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.26. Found: C, 58.29; H, 8.19.

Periodic Acid Oxidation of Trichodesmine, Monocrotaline, Riddelline, Retrorsine (β-Longilobine) and Seneciphylline.—Solutions of 5 × 10^{-5} mole of the various alkaloids in 10 ml. of 0.02 *M* aqueous periodic acid were prepared at 25°. The course of the reactions was followed by withdrawing 1-ml. aliquots of the solutions and titrating the excess of periodic acid by the arsenite method. The time necessary for the consumption of one mole of reagent varied; less than three minutes for riddelline and retrorsine (containing a primary-tertiary glycol structure); 25 minutes for monocrotaline (containing a ditertiary structure of *cis* configuration); 45 minutes for trichodesmine.[14]

In all cases, after the primary oxidation, periodic acid was very slowly reduced due to the oxidation of the cleavage products. Seneciphylline, which contains only one tertiary hydroxyl group in the α-position to an ester carbonyl, was not attacked at all by the oxidant.

Methyl Ethyl Ketone, a Product of Alkaline Hydrolysis of Monocrotaline.—Two bases were used for the experiments of hydrolysis; barium hydroxide, which is generally used for the hydrolysis of Senecio alkaloids, and sodium hydroxide, which was used by Menshikov and Rubinstein[2] for the hydrolysis of trichodesmine. The two bases gave practically identical results as for the amount of methyl ethyl ketone. A solution of 3 g. of monocrotaline in 30 ml. of 10% aqueous sodium hydroxide was heated under reflux for 1.5 hours using a very efficient condenser. The solvent was boiled off and collected in 3-ml. fractions. The first seven fractions gave a positive sodium nitroprusside test for methyl ketones.[15] An iodoform test indicated that most of the ketone was contained in the first two fractions. 2,4-Dinitrophenylhydrazine reagent[16] was added to the various fractions and yellow products were obtained from the first two, while red material separated from fractions 3–7. The products from fractions 1 and 2 were combined and crystallized from ethanol; m.p. 117°, undepressed on admixture with an authentic sample of the 2,4-dinitrophenylhydrazone of methyl ethyl ketone.

Anal. Calcd. for $C_{10}H_{12}O_4N_4$: C, 47.62; H, 4.80. Found: C, 47.38; H, 4.64.

A papergram of the material from fractions 3–7, according to the procedure of Meigh,[17] indicated the presence of the dinitrophenylhydrazone of methyl ethyl ketone, accompanied by a compound of very low R_f value. Nothing but 2,4-dinitrophenylhydrazine and the derivative of methyl ethyl ketone was obtained by chromatographing the combined fractions 3–7, thus indicating that only one volatile ketone was formed during the hydrolysis of monocrotaline.

Action of Thionyl Chloride on Trichodesmine.—A solution of 0.12 g. of pure trichodesmine in 3 ml. of thionyl chloride was allowed to stand at room temperature for 30 minutes. The excess of thionylc hloride was then evaporated under reduced pressure, the crystalline residue washed thoroughly with benzene and ether and analyzed. The yield of product, m.p. 172°, was 0.145 (94%).

Anal. Calcd. for $C_{18}H_{27}NO_8S \cdot HCl$: C, 47.62; H, 6.17. Found: C, 47.89; H, 6.15.

The hydrolysis of the chlorine in the initial reaction product occurred undoubtedly during the drying after the benzene and ether washings. This drying was achieved by using air freed of dust particles but still containing moisture.

URBANA, ILLINOIS

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[13] R. Adams and E. F. Rogers, THIS JOURNAL, **61**, 2815 (1939).

[14] C. C. Price and H. Kroll, *ibid.*, **60**, 2762 (1938), observed also the much slower oxidation by periodic acid of the tertiary glycol, pinacol, in comparison with the oxidation of ethylene glycol.

[15] F. Feigl, "Spot Tests," Vol. II, Elsevier Publishing Co., New York, N. Y., 1954, p. 160.

[16] R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

[17] D. F. Meigh, *Nature*, **170**, 579 (1952).