

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

The Alkaloid of *Crotalaria Grantiana*. I. Grantianine

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*Spectabilis* is the species of the genus *Crotalaria* most commonly used as a leguminous plant in the Southern States. It contains a large amount of toxic alkaloid and hence investigations are under way to find other *Crotalaria* species which might be used for the same purpose and which contain no or only small amounts of poisonous principles.

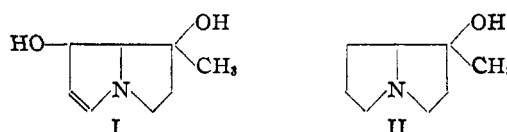
The only alkaloid thus far isolated and characterized from the various species of *Crotalaria* is monocrotaline. Its extraction from *Crotalaria spectabilis* and a description of experiments designed to determine its constitution have been reported in previous papers.<sup>1</sup> It proved to be analogous to the alkaloids obtained from the genera *Heliotropium*, *Senecio* and *Trichodesma*. This class of natural bases will undoubtedly prove to be one of the most widely distributed. The substances are esters, each formed from a different aliphatic or alicyclic acid and the bicyclic base retronecine or a closely related base, heliotridine, platynecine, rosmarinine,<sup>2</sup> etc.

A preliminary study has now been completed on an alkaloid extracted by ethanol from *Crotalaria grantiana*. The name, grantianine, is proposed for it. It is readily isolated in a pure state and has the empirical formula  $C_{18}H_{28}O_7N$ , as determined by analysis of the base, its methiodide and picrate. Saponification with methanolic potassium hydroxide resulted in formation of retronecine (about 45% of the theoretical was isolated), identified by comparison with an authentic sample. The acid portion of the molecule has not yet been obtained in a pure state.

A reaction which proved very helpful in the study of monocrotaline was treatment with hydrogen in the presence of a catalyst. Hydrogenolysis takes place upon absorption of the first molecule of hydrogen followed by reduction of the double bond with the second molecule. By this means, it was possible to isolate monocrotalic acid which, in the presence of the alkaline reagents employed for saponification of the alkaloid, is

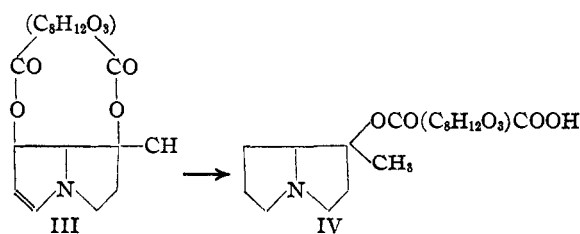
decomposed. The base isolated in the hydrogenolysis reaction is retronecanol derived from retronecine by replacement of a hydroxyl by hydrogen and reduction of the double bond.

Formulas for retronecine (I) and retronecanol (II) have been proposed which agree reasonably well with the experimental facts available.



Whether these structures are correct is for the present discussion of minor significance. The fact has been established definitely that one hydroxyl is less reactive than the other and that the more reactive one is usually removed by hydrogenolysis before the double bond is reduced.

Upon hydrogenation of grantianine with platinum oxide catalyst in a mixture of acetic acid and ethanol, two moles of hydrogen were rapidly absorbed. A product crystallized from the reaction mixture. Monocrotaline under these conditions is cleaved to retronecanol (II) and monocrotalic acid, but grantianine absorbed two molecules of hydrogen without cleavage. The tetrahydrograntianine has the empirical formula  $C_{18}H_{27}O_7N$ . Since the alkaloid is a derivative of retronecine, it may be a cyclic diester of retronecine, with one molecule of a dibasic acid (III). The first molecule of hydrogen probably cleaves the less stable ester grouping and the second molecule reduces the double bond in the nucleus of the base. The tetrahydro product would then be an amino acid of the type shown in IV. Its solubility characteristics—slightly soluble in



(1) Neal, Rusoff and Ahmann, *THIS JOURNAL*, **57**, 2560 (1935); Adams and Rogers, *ibid.*, **61**, 2815 (1939); Adams, Rogers and Sprules, *ibid.*, **61**, 2819 (1939); Adams, Rogers and Long, *ibid.*, **61**, 2822 (1939); Adams and Long, *ibid.*, **62**, 2289 (1940); Adams and Rogers, *ibid.*, **63**, 228, 537 (1941).

(2) De Waal, *Nature*, **146**, 777 (1940); de Waal, *Onderstepoort J. Vet. Sci. and Animal Ind.*, **12**, 155 (1939); **14**, 433 (1940).

water, essentially insoluble in hot and cold ethanol, soluble in hot glacial acetic acid, soluble in cold dilute hydrochloric acid and cold dilute

aqueous ammonia—tend to confirm this assumption. On this basis, the acid, grantianinic acid, in grantianine would have the structure  $C_8H_{12}O_3(COOH)_2$ , which resembles closely that of monocrotalic acid,  $C_7H_{11}O_3COOH$ . In fact it would not be surprising if the skeleton structure of grantianinic acid might represent replacement of a hydrogen by a  $-CH_2COOH$  group in the monocrotalic acid nucleus.

In the reduction of grantianine, a by-product was isolated as a picrate from the filtrate after removal of the tetrahydro compound. It has not yet been identified on account of the small amount available; it appears, however, to be a picrate of a derivative of tetrahydrograntianine in which one less oxygen atom is present, or from which one molecule of water has been eliminated.

### Experimental

**Grantianine.**—About 700 g. of finely ground seed of *Crotalaria grantiana* was extracted by percolation for a total of seventy hours with 95% ethanol at room temperature. The extracts were worked up as described for monocrotaline.<sup>1</sup> The first crop of crystalline alkaloid from absolute ethanol consisted of 2.07 g. of practically colorless prisms and a second crop of 0.33 g. brought the total to 2.40 g. (0.34%). Removal of the ethanol from the filtrate left 3.5 g. of viscous red liquid which did not crystallize. Several recrystallizations from absolute ethanol gave a pure white product of constant m. p. 204–205° (cor.) with decomposition.

*Anal.* Calcd. for  $C_{13}H_{23}O_7N$ : C, 59.17; H, 6.34; N, 3.83. Found: C, 59.20, 58.97; H, 6.20, 6.31; N, 3.83, 4.15.

*Rotation.* 0.1013 g. made up to 5 cc. with chloroform at 27° gave  $\alpha_D +2.05^\circ$ ;  $l$ , 2;  $[\alpha]^{27}_D +50.6^\circ$ .

**Grantianine Methiodide.**—A solution of 0.1 g. of grantianine in a mixture of 0.5 cc. of chloroform and 4 cc. of acetone was treated with 0.2 cc. of methyl iodide and refluxed for forty-five minutes. The methiodide separated and was purified by recrystallization from the same mixed solvent. It formed fine white platelets, m. p. 242–243° (cor.) in an evacuated tube.

*Anal.* Calcd. for  $C_{13}H_{23}O_7NI$ : C, 44.98; H, 5.17; N, 2.76. Found: C, 45.06; H, 5.46; N, 2.73.

**Grantianine Picrate.**—Equivalent weights of grantianine and picric acid dissolved in minimum amounts of hot absolute ethanol were mixed. The picrate precipitated immediately and was purified from the same solvent. It formed fine yellow rhombic crystals whose melting point varied with the mode of heating. Taken in the usual way the compound began to darken at about 210–215° and melted with complete decomposition at 225–228°.

*Anal.* Calcd. for  $C_{13}H_{23}O_7N \cdot C_6H_3O_7N_3$ : C, 48.48; H, 4.41; N, 9.44. Found: C, 48.58, 48.90; H, 4.71, 4.61; N, 9.29.

Grantianine could be converted into a hydrochloride by mixing the alkaloid with a little aqueous hydrochloric acid

containing a few drops of ethanol and evaporating to dryness. The residue crystallized on scratching and was recrystallized from hot absolute ethanol to which dry ether was added to turbidity. It formed rosetts of rhombic platelets, m. p. 221–222° (cor.) in an evacuated tube with decomposition.

**Saponification of Grantianine.**—A mixture of 0.3 g. of grantianine and 0.33 g. of potassium hydroxide in 3 cc. of methanol was refluxed for fifty minutes. The alkaloid dissolved at once; within five minutes a solid salt began to precipitate. The solution containing suspended potassium salt was cooled and most of the methanol evaporated in an air current. About 0.5 cc. of water was added and the mixture again evaporated in air. Finally, the solution was evaporated in vacuum until salts began to appear. The viscous residue was extracted five times with 2-cc. portions of ether. The ether solution after drying was evaporated and the oily residue inoculated with a tiny crystal of retronecine. Crystals formed. These were taken up in a little acetone and filtered; colorless prisms were obtained which after a recrystallization had a m. p. 118.5–120° (cor.) and showed no depression when mixed with authentic retronecine; yield, 0.012 g.

Additional extractions of the alkaline mixture with ether and evaporation of the solvent gave an oil which upon treatment with hydrochloric acid produced crystals of retronecine hydrochloride. The solution was evaporated and triturated with ethanol. The hydrochloride was recrystallized from absolute ethanol, m. p. 164–165° (cor.); yield, 0.015 g. It gave no depression in a mixed melting point with retronecine hydrochloride.

The aqueous alkaline solution after ether extraction was acidified with concentrated hydrochloric acid, extracted with chloroform, evaporated to dryness and triturated with ethanol. Retronecine hydrochloride separated; yield, 0.04 g.

The total yield amounted to 44% of the theoretical.

**Tetrahydrograntianine.**—A solution of 0.289 g. of pure grantianine in 3 cc. of glacial acetic acid and 5 cc. of 95% ethanol was hydrogenated at room temperature in the presence of 0.05 g. of platinum oxide. Two moles of hydrogen were absorbed in eight minutes, although shaking was continued for one hour. After filtration of the catalyst, and addition of 5 cc. of absolute ethanol, well-formed polyhedra began to separate. After several hours at 2°, the tetrahydro derivative was filtered. Additional material separated from the filtrate. In all, 0.094 g. was obtained. The product was recrystallized by dissolving in hot glacial acetic acid and adding absolute ethanol in which it is very insoluble giving white crystals, m. p. 242.5° (cor.), with evolution of gas in an evacuated tube.

*Anal.* Calcd. for  $C_{13}H_{27}O_7N$ : C, 58.52; H, 7.37; N, 3.79. Found: C, 58.47; H, 7.44; N, 4.04.

The product is slightly soluble in water, practically insoluble in cold or hot ethanol, soluble in hot glacial acetic acid, cold dilute hydrochloric acid and aqueous ammonia.

The original filtrate from which the crude tetrahydrograntianine was obtained, was evaporated to dryness and yielded 0.2 g. of residue. This was taken up in boiling 50% ethanol, the solution filtered and treated with a warm solution of 0.1 g. of picric acid in water. A picrate separated rapidly in the form of yellow platelets; yield, 0.076 g.

It was purified by recrystallization from water, m. p. 156–157° (cor.) with decomposition.

*Anal.* Calcd. for  $C_{18}H_{27}O_6N \cdot C_8H_5O_7N_3$ : C, 49.48; H, 5.19; N, 9.62. Found: C, 49.73; H, 5.37; N, 9.76.

### Summary

1. A new alkaloid grantianine has been isolated from *Crotalaria grantiana*.
2. It is saponified by methanolic potassium

hydroxide to retronecine and an acid not yet isolated in a pure state.

3. Reduction gives tetrahydrograntianine which is postulated as an amino acid.

4. Preliminary results thus indicate that grantianine may be retronecine esterified on both hydroxyls with one molecule of a dibasic acid.

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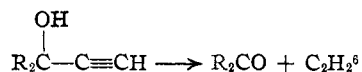
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## The Decomposition of Certain Acetylenic Carbinols

BY A. F. THOMPSON, JR., AND CHARLES MARGNETTI<sup>1</sup>

Various catalysts are available for the vapor phase dehydration of tertiary acetylenic carbinols to yield vinylacetylene derivatives. Anhydrous magnesium sulfate,<sup>2</sup> basic aluminum sulfate,<sup>3</sup> and aluminum phosphate,<sup>4</sup> have all been used successfully for this dehydration reaction. Activated alumina has been shown by Vaughn<sup>5</sup> to be a satisfactory dehydration catalyst for tertiary ethynyl carbinols only if the alkaline ingredients present, principally sodium oxide, are removed by suitable treatment, which he has devised. It has long been known that in the presence of alkali the decomposition of tertiary ethynyl carbinols proceeds to form ketones and acetylenic hydrocarbons according to the reaction



Recently, it was shown<sup>7</sup> that hexynyl carbinols, in contrast to the ethynyl carbinols studied by Vaughn, were smoothly dehydrated over ordinary alumina, only relatively small amounts of hexyne being produced. A number of ethynyl and hexynyl carbinols were compared and these results confirmed in all cases. It seemed worthwhile to investigate more fully the effect of the

group  $\text{R}^1$ , in the general formula  $\text{R}_2\text{C}-\text{C}\equiv\text{CR}^1$ , upon the relative extent of the two predominant decomposition reactions, cleavage and dehydration.

(1) From the thesis submitted by Charles Margnetti to the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Bachelor of Science.

(2) Zakharova, *Sci. Repts. Leningrad State Univ.*, **2**, 162 (1936).

(3) Carothers and Coffman, *This Journal*, **54**, 4074 (1932).

(4) Thompson and Powers, unpublished results.

(5) Vaughn, U. S. Patent 2,197,956.

(6) Moureu, *Bull. soc. chim.*, [3] **33**, 151 (1905).

(7) Thompson, Burr and Shaw, *This Journal*, **63**, 186 (1941).

A number of acetylenic tertiary carbinols were accordingly prepared, by condensation of the appropriate acetylenic Grignard reagent with the ketone in ethereal solution. Table I summarizes the properties of the carbinols obtained. The substances were analyzed for unsaturation by quantitative catalytic hydrogenation, which served to check the purity of the samples.

TABLE I

Acetylenic carbinol	Yield, %	B. p., °C.	mm.	$n_D^{20}$	Double bonds (cat. H <sub>2</sub> )
Methylethylpropynyl	70	132–135	760	1.4308	2.08
Methylethylisopropylethynyl	76	128–130	35	1.4169	2.05
Methylethyl- <i>t</i> -butylethynyl	58	137–140	35	1.4211	1.92
Methylethylphenylethynyl	65	138–140	15	1.5469	2.06
Methylethyl-(1,2-dimethyl)-vinylethynyl <sup>8</sup>	79	117–120	15	1.4611	3.08
Methylamylpropynyl	71	105–108	15	1.4400	2.05
Methylamylphenylethynyl	78	114–117	2	1.5522	2.11
Methylamyl-(1,2-dimethyl)-vinylethynyl <sup>8</sup>	79	115–118	5	1.4941	3.13
Diisopropylhexynyl	68	130–133	15	1.4565	2.14

The decomposition reactions of the carbinols so obtained were then studied by heating them with alumina as previously described.<sup>7</sup> The less volatile of the carbinols were distilled through the apparatus under diminished pressure and the decomposition products collected in a dry-ice trap. Separation was accomplished by careful fractionation of the liquid mixture. The ketones were identified by preparation of derivatives, and the hydrocarbons by catalytic hydrogenation. The acetylenic nature of the hydrocarbons formed was indicated by obtaining heavy precipitates of the

(8) The two vinylacetylenic carbinols were prepared from the dimethylvinylacetylene fraction obtained by dehydration of methylethylethynylcarbinol. This fraction should consist essentially of 3-methylpentyne-1-ene-3, but there is no proof that a small amount of the alternative dehydration product, 2-ethylbutene-1-yne-3, is not also present.