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PYRROLIZIDINE ALKALOIDS.
THE TOTAL SYNTHESIS OF RETUSAMINIC ACID

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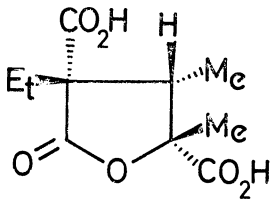
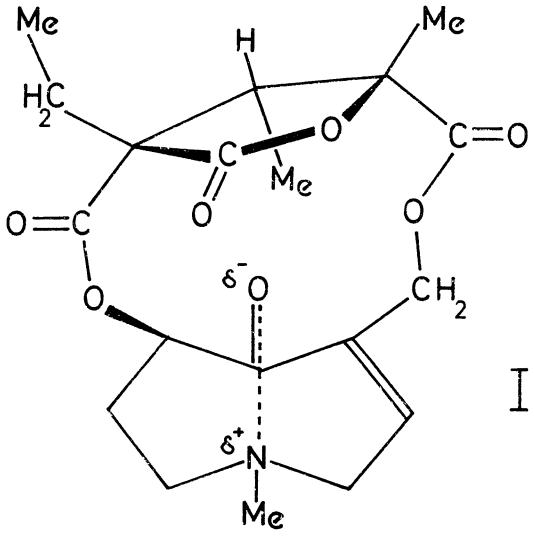
(±)-Retusaminic acid has been synthesized from diethyl 1-methylacetonylmalonate and resolved by means of cinchonidine. The synthesized enantiomer was shown to be identical with natural retusaminic acid.

Retusamine was isolated from Crotalaria retusa L. by Culvenor and Smith[1], and shown by an X-ray crystallographic study[2] of its bromocamphor sulphonate to have the structure (I). The hydrogenolysis of (I) gave a new dicarboxylic acid $C_{10}H_{14}O_6$, named retusaminic acid (II)[3]. In this communication, we wish to report a total synthesis of retusaminic acid.



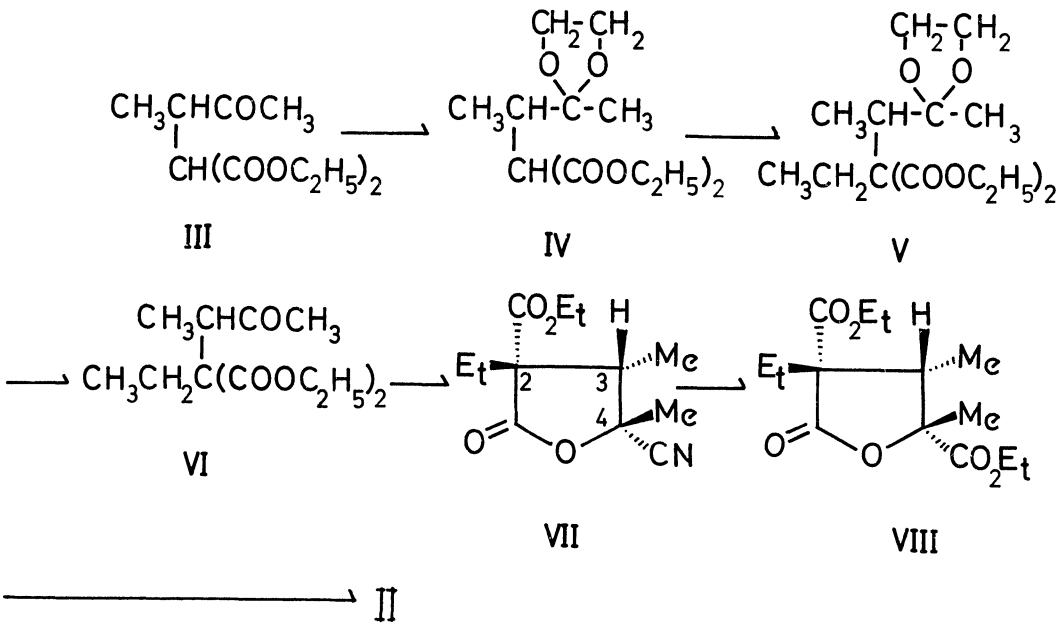
II

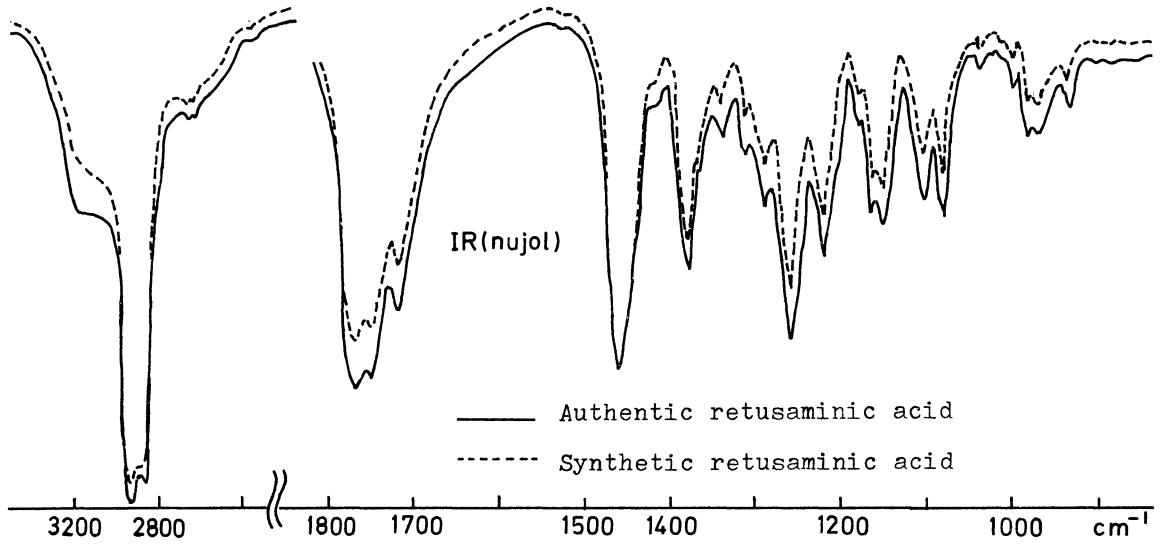


I

Diethyl 1-methylacetonylmalonate (III) was used as a starting material. The ketalization of the keto-ester (III) in Dean-Stark trap with ethylene glycol, benzene and a minimum quantity of concentrated sulfuric acid gave a ketal-ester (IV) ; bp 167 - 170°C (20 mmHg) ; IR (neat) : 1735, 1160, 1045 cm^{-1} ; NMR in $CDCl_3$ (δ) : 1.15 (t, $-COOCH_2C\underline{H}_3$), 1.32 (s, $-\overset{|}{C}-C\underline{H}_3$), 1.35 (d, $-\overset{|}{C}H-C\underline{H}_3$), 2.75 (m, $-\overset{|}{C}H-C\underline{H}-CH_3$), 3.42 (d, $-C\underline{H}-CH-CH_3$), 3.90 (s, $-O-C\underline{H}_2-C\underline{H}_2-O-$), 4.15 (q, $-COOC\underline{H}_2CH_3$). The treatment of the ketal-ester (IV) in dry benzene, which was exchanged for dry dimethyl formamide after 1 hr, with sodium hydride, and followed by the ethylation with ethyl bromide at 50°C under nitrogen atmosphere gave a ethyl-ketal-ester (V) ; bp 135 - 145°C (3 mmHg) ; IR (neat) : 1735, 1240, 1140 cm^{-1}. The deketalization of the ethyl-ketal-ester (V) in dry acetone with a small amount of p-toluenesulfonic acid gave a ethyl-keto-ester (VI) ; bp 160 - 165°C (24 mmHg) ; IR (neat) : 1730, 1255, 1135 cm^{-1} , NMR in $CDCl_3$ (δ) : 0.77 (t, $-\overset{|}{C}-CH_2C\underline{H}_3$), 1.13 (d, $-\overset{|}{C}H-C\underline{H}_3$), 1.15 (t, $-COOCH_2C\underline{H}_3$) 2.01 (q, $-\overset{|}{C}-C\underline{H}_2CH_3$), 2.25 (s, $-COC\underline{H}_3$), 3.20 (q, $-C\underline{H}-CH_3$), 4.20 (q, $-COOC\underline{H}_2CH_3$). The treatment of the ethyl-keto-ester (VI) in sealed flask with dry hydrogen cyanide and calcium oxide at 50°C gave colored oily product, which was purified by means of column chromatography on silica gel to give a cyano-lactone (VII) ; mp 43°C ; IR (nujol) : 1800, 1745, 1250 cm^{-1} ; NMR in $CDCl_3$ (δ) : 1.05 (t, $-\overset{|}{C}-CH_2C\underline{H}_3$), 1.25 (t, $-COOCH_2C\underline{H}_3$), 1.27 (d, $-\overset{|}{C}HC\underline{H}_3$), 1.75 (s, $-\overset{|}{C}(CN)-C\underline{H}_3$), 1.98 (q, $-\overset{|}{C}-C\underline{H}_2CH_3$) 2.72 (q, $-C\underline{H}CH_3$), 4.12 (q, $-COOC\underline{H}_2CH_3$). The cyano-lactone (VII) in dry ether was treated at 0°C with dry ethanol, which was saturated with dry hydrogen chloride and gave a ester-lactone (VIII) ; bp 140 -145°C (3 mmHg) ; IR (neat) : 1790, 1745, 1250 cm^{-1} NMR in $CDCl_3$ (δ) : 1.00 (t, $-\overset{|}{C}-CH_2C\underline{H}_3$), 1.07 (d, $-\overset{|}{C}HC\underline{H}_3$), 1.25 (t, $-COOCH_2C\underline{H}_3$) 1.60 (s, $-\overset{|}{C}(COOC_2H_5)-C\underline{H}_3$), 1.92 (q, $-\overset{|}{C}-C\underline{H}_2CH_3$), 2.75 (q, $-\overset{|}{C}HC\underline{H}_3$), 4.10 (q, $-COOC\underline{H}_2CH_3$). The hydrolysis of the ester-lactone (VIII) with 10 % sodium hydroxide solution at 50°C overnight gave, after chromatographic purification, (±)-retusaminic acid (II) ; mp 163°C. The IR ($CHCl_3$) of the racemate (II) was superimposable with that of natural retusaminic acid. As the natural acid, known in absolute configuration, could be derived from the cyano-lactone (VII), the stereochemistry of C_3-methyl group relative to C_4-methyl group in (VII) was assigned as trans-configuration. Therefore, the hydrogen cyanide addition reaction of (VI) was stereospecific.

The racemate was resolved with cinchonidine and the diastereoisomer isolated, gave, on decomposition, an acid (mp 166 - 167°C, $[\alpha]_D$ -45°) identical with natural retusaminic acid.





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REFERENCES

1) Culvenor C. C. J., and Smith L. W., Aust. J. Chem., 10, 464 (1957).

2) Wunderlich J. A., Chemy. Ind., 2089 (1962).

3) Culvenor C. C. J., O'Donovan G. M., and Smith L. W., Aust. J. Chem., 20, 801 (1967).

4) Satisfactory elemental analyses were obtained for all new compounds.

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