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THE ABSOLUTE CONFIGURATIONS OF (+)-MARMESIN AND (-)-HYDROXYTREMETONE

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On careful examination of white snakeroot tremetol, Bonner et al.[1)2)] succeeded in isolating three ketones: (-)-tremetone, dehydrotremetone and (-)-hydroxytremetone (VI). (-)-Tremetone also has been found together with (-)-toxol[3)] in crude rayless-goldenrod tremetol.

Although the absolute configurations of (-)-toxol and (-)-tremetone have been established by the elaborate studies of Zalkow and Bonner[4)5)], the absolute configuration of (-)-hydroxytremetone remained unsolved in spite of the synthesis of its racemic modification[6)].

We have been interested in determining the absolute configurations of the isoprenoid[7)] side chains of natural phenolic compounds, and in this communication we report the syntheses of (-)-hydroxytremetone (-)-(VI) and (+)-marmesin (+)-(Vb) from (R) and (S)-6-benzyloxycoumaran-2-carboxylic acid (IIa) respectively. These synthetic approaches eventually led to successful assignment of their absolute configurations.

Treatment of 6-benzyloxycoumarone-2-carboxylic acid (I) with 2% sodium amalgam furnished the racemic coumarancarboxylic acid (IIa), m.p. 127.5-128.5° which was then converted into (-)-α-phenylethylamine salt. Several recrystallizations from acetone gave a homogeneous salt, m.p. 172-173°, $[\alpha]_D^{23}$ -72.4° (c, 1.70 in MeOH) and the decomposition of the salt with diluted hydrochloric acid

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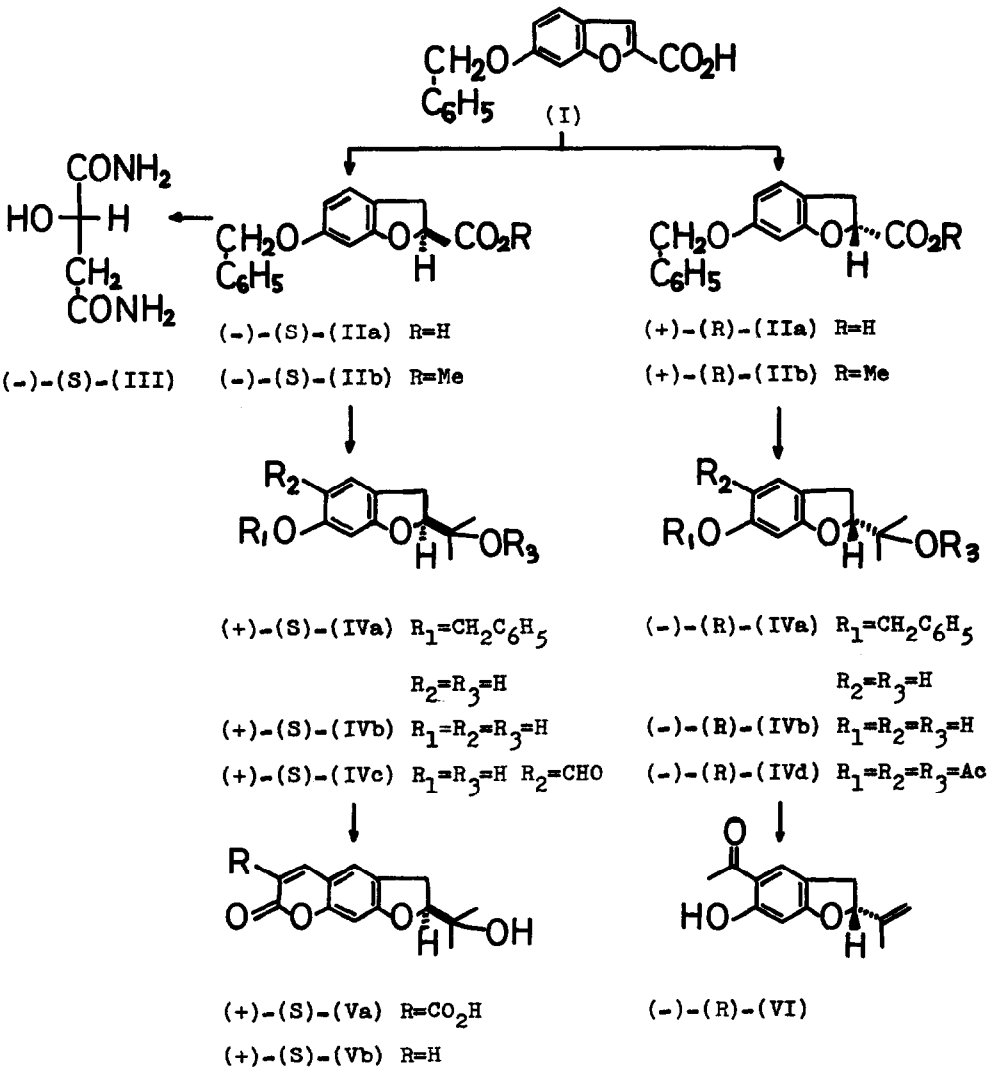
yielded the coumarancarboxylic acid (-)-(IIa) as needles with m.p. 116°, $[\alpha]_D^{21}$ -64.8° (c, 1.0 in MeOH). After exhaustive ozonolysis of (-)-(IIa) in acetic acid, the resulting malic acid was converted into (-)-(S)-malamide (III), m.p. 156-158°, $[\alpha]_D^{18}$-36.7° (c, 3.08 in H_2O), via methyl ester. The S-configuration of (-)-(IIa) was thus established.



Synthesis of (+)-Marmesin (Vb)[9]*

Refluxing with methanol and p-toluenesulfonic acid converted (-)-(IIa) into the methyl ester (-)-(IIb), b.p. 158-175°/0.02 mmHg, $[\alpha]_D^{25}$-50.7° (c, 0.6 in MeOH). Grignard reaction with methylmagnesium bromide modified the side chain of (-)-(IIb) yielding the tertiary alcohol (+)-(IVa), b.p. 160-164°/0.02 mmHg, $[\alpha]_D^{24}$ +7.02° (c, 1.5 in MeOH), whose hydrogenolysis with 5% Pd/C in methanol afforded the phenol, (+)-(IVb), m.p. 129-130°, $[\alpha]_D^{24}$+21.3° (c, 1.3 in MeOH). Gattermann formylation (modification by Adams) of the phenol (+)-(IVb) furnished the aldehyde (+)-(IVc), m.p. 106-107°, $[\alpha]_D^{22}$+79.7° (c, 0.85 in MeOH), which was heated with malonic acid in the presence of aniline. From the reaction mixture the coumarinecarboxylic acid (+)-(Va) was obtained as yellow needles, m.p. 244-245°, $[\alpha]_D^{24}$+51.8° (c, 0.55 in pyridine)[10].

Boiling with Adkins catalyst in quinoline decarboxylated (+)-(Va) to yield (+)-marmesin (Vb), m.p. 186-186.5°, $[\alpha]_D^{23}$+20.3° (c, 1.2 in $CHCl_3$) (Found: C, 68.26; H, 5.72%), (Reported:[11] m.p. 189.5°, $[\alpha]_D$+26.8° (in $CHCl_3$)), indicating the S-configuration of (+)-marmesin and the R-configuration of (-)-nodakenetin[12], the enantiomer of (+)-marmesin, obtained from Peucedanum decursivum Maxim.

Synthesis of (-)-Hydroxytremetone (VI)

The coumarancarboxylic acid (IIa) with the R-configuration, m.p. 114-115°, $[\alpha]_D^{17}$+60.3° (c, 1.13 in MeOH), was obtained from the mother liquor of the above-mentioned optical resolution. The same sequence of reactions described in the S-series was followed in the R-series giving (+)-(IIb), b.p. 180-200°/1 mmHg, $[\alpha]_D^{21}$+45.7° (c, 1.01 in MeOH); (-)-(IVa), b.p. 160-165°/1 mmHg, $[\alpha]_D^{20}$-6.12° (c, 1.39 in MeOH); and (-)-(IVb), m.p. 128.5-129.5°, $[\alpha]_D^{22}$-22.3° (c, 1.77 in MeOH). Acetylation of (-)-(IVb) with acetic anhydride and stannic chloride afforded (-)-(IVd), m.p. 102.5-103.5°, $[\alpha]_D^{21}$-77.3° (c, 1.64 in MeOH), whose side chain could be converted into the requisite isopropenyl type by heating at 330° for 1 and 1/4 min.

After hydrolysis with 5% potassium hydroxide, the product was purified by

* The racemic series of compounds were prepared by the same procedures, and all new compounds reported in this communication have the requisite spectral and analytical characteristics.

chromatography on silica gel to give (-)-hydroxytremetone (VI), m.p. 70-71°, $[\alpha]_D^{21}$-46.4° (c. 0.89 in EtOH) (Found: C, 71.55; H, 6.53%). (Reported[1)2)]: m.p. 70-71°, $[\alpha]_D^{24}$-50.7° (in EtOH)).

These findings established the R-configuration of (-)-hydroxytremetone, showing this family of compounds, (-)-tremetone, (-)-toxol and (-)-hydroxytremetone isolated from "tremetol", all have the same configuration pertinent to their biogenetic origins.

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