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The Resolution and Absolute Configuration of "Marcumar" (1)

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Marcumar (3), 3-(α-ethylbenzyl)-4-hydroxycoumarin (I) is a synthetic anticoagulant drug of the class whose first member was the natural product 3,3'-methylenebis(4-hydroxycoumarin), "Dicumarol" (4). Warfarin, 3-(α-acetonylbenzyl)-4-hydroxycoumarin (5), was the first drug of this class to be resolved and related to asymmetric compounds of known configuration (6). We wish to report here comparable studies on Marcumar.

(-)(S)-Marcumar was obtained by fractional crystallization of the quinidine enolate of *rac*-Marcumar. The filtrates from this preparation yielded partially resolved (+)(R)-Marcumar which was purified by crystallization of the quinine enolate. It is interesting that the more potent isomers of both warfarin and Marcumar have the (S) configuration (7).

(-)(S)-Marcumar, (-)(S)-I, was decarboxylated to (-)(R)-*o*-hydroxy-β-phenylvalerophenone. (-)(R)-II, which was *O*-methylated to yield (-)(R)-III. This product was treated with *o*-anisylmagnesium bromide to yield 1,1-di-(*o*-anisyl)-3-phenylpentan-1-ol, (-)(R)-IV. The other enantiomer of IV, (+)(S)-IV, was realized when (+)(S)-methyl-β-phenylvalerate, (+)(S)-V, of known absolute configuration was treated with excess *o*-anisylmagnesium bromide.

The assignment of the (S) configuration to (+)-β-phenylvaleric acid follows from its sterochemical relation to (-)(R)-2-phenylbutane (8) and the assignment of the absolute configuration to the latter by Cram (9).

EXPERIMENTAL

(-)(S)-Marcumar.

rac-Marcumar was prepared by the method of Schroeder *et al.*, (10). Quinidine (52 g., 0.16 mole) and 89.5 g. (0.32 mole) of *rac*-Marcumar were dissolved in a warmed mixture of 250 ml. of chloroform and 500 ml. of acetone. A first crop (51 g.) of Marcumar-quinidine salt was collected after crystallization had proceeded for 24 hours at 25°. The filtrate was concentrated to a syrup. Acetone (250 ml.) was added and the solution was held at -10° for 24 hours, yielding an additional 23 g. of the salt. The first crop was recrystallized once and the second crop twice, then the head fractions were combined and crystallized again. The solvent in each case was 45 ml. per g. of 1:4 (V:V) absolute ethanol - chloroform. Yield 42 g. $[\alpha]_D^{23}$ + 75°±1° (*C* 1, butanone-2). Further recrystallization did not change this rotation (11). The (-)(S)-Marcumar was recovered by stirring the salt with 200 ml. each of chloroform and 5% sodium hydroxide and acidifying the separated aqueous layer with hydrochloric acid. One crystallization from ethanol-water yielded 18 g. of (-)(S)-Marcumar, $[\alpha]_D^{28}$ -122.6°±0.5° (*C* 2, 95% ethanol), m.p. 170-171°.

(+)(R)-Marcumar.

All the filtrates from the Marcumar-quinidine salt were concentrated to a glassy residue which was decomposed by chloroform-alkali partition as above to yield 57 g. of partially resolved (+)(R)-Marcumar; $[\alpha]_D^{25}$ + 39° (*C* 2, 95% ethanol). This product (0.205 mole) and 62.5 g. (0.205 mole) of quinine were dissolved in 950 ml. of ethanol and 360 ml. of warm water was added. Cooling to -10° gave a crystalline product which was recrystallized four times from 11 ml. per g. of 70% (by vol.) ethanol. The terminal rotation was $[\alpha]_D^{24}$ -64±1°, (*C* 1, butanone-2), which did not change on further crystallization. Partition of the salt, acid precipitation and crystallization from ethanol-water yielded 8.5 g. of (+)(R)-Marcumar; $[\alpha]_D^{27}$ +122.8°±0.5° (*C* 2, 95% ethanol), m.p. 170-170.5°. The infrared spectra of chloroform solutions of (+)-, (-)- and *rac*-Marcumar were indistinguishable; λ max ($CHCl_3$): 2.89, 3.37, 5.97, 6.20 μ.

(-)(R)-*o*-Hydroxy-β-phenylvalerophenone, (-)(R)-II.

A solution of 10.2 g. of (-)(S)-Marcumar in 75 ml. of 10% aqueous sodium carbonate was refluxed 5 days. The upper, water insoluble layer of the cooled reaction mixture was separated and distilled to yield 5.5 g. of (-)(R)-II, b.p. 220-225° (15 mm.); α_D^{23} -64.2°±0.1° (neat); λ max (CS_2): 3.45, 6.18 μ: violet color with ferric chloride in dry pyridine.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.3; H, 7.12. Found: C, 80.1; H, 7.41.

The 2,4-dinitrophenylhydrazone was recrystallized from benzene-hexane, m.p. 141-142°.

Anal. Calcd. for $C_{23}H_{22}N_4O_5$: C, 63.6; H, 5.11. Found: C, 63.3; H, 5.00.

(+)(R)-*o*-Methoxy-β-phenylvalerophenone, (+)(R)-III.

A mixture of 2.3 g. of (-)(R)-*o*-hydroxy-β-phenylvalerophenone, 4 ml. of 30% aqueous sodium hydroxide, 5 ml. of dimethyl sulfate, and 20 ml. of dioxane was stirred 12 hours at 25°. The solvents were evaporated and the residue was extracted with a benzene-water mixture. The benzene layer was separated, treated with magnesium sulfate and charcoal, filtered and evaporated. The colorless, oily residue was subjected to a vacuum of 0.1 mm. for 24 hours, yield 2.4 g., α_D^{23} +19.3°±0.1° (neat), no color with ferric chloride-pyridine.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.6; H, 7.52. Found: C, 80.9; H, 7.52.

(-)(R)-1,1-Di-(*o*-anisyl)-3-phenylpentan-1-ol), (-)(R)-IV.

(+)(R)-*o*-Methoxy-β-phenylvalerophenone (2.3 g.) in 30 ml. of ether was added slowly to an ether solution of *o*-anisylmagnesium bromide prepared from 5 g. of *o*-bromoanisole and 3 g. of magnesium. After 4 hours refluxing, 10 ml. of 50% aqueous acetic acid was added. The ether layer was separated, washed with water and with aqueous sodium carbonate, dried (magnesium sulfate) and evaporated to an oil. The oil was dissolved in 25 ml. of warm heptane; cooling to -10° gave a product which was recrystallized from benzene-heptane; yield: 2.7 g. of (-)(R)-1,1-di-(*o*-anisyl)-3-phenylpentan-1-ol, m.p. 100.5-101°; $[\alpha]_D^{22}$ -10.1°±0.2° (*C* 4, benzene).

Anal. Calcd. for $C_{25}H_{28}O_3$: C, 79.8; H, 7.49. Found: C, 80.0; H, 7.31.

(+)(S)-Methyl-β-phenylvalerate, (+)(S)-V.

β-Phenylvaleric acid (VI) was prepared (12) and partially resolved (13). The product, $[\alpha]_D^{24}$ +11.0° (*C* 3, benzene), (3 g.), was esterified with diazomethane and the ester was distilled, yield 2.8 g.; b.p. 152-155° (17 mm.); α_D^{24} +6.4° (neat).

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 75.0; H, 8.93. Found: C, 74.7; H, 8.13.

rac- and (+)(S)-1,1-Di-(*o*-anisyl)-3-phenylpentan-1-ol, *rac*-IV and (+)(S)-IV.

This preparation was exactly analogous to that of (-)(R)-IV except that 2.3 g. of the (+)(S)-V made above replaced the (+)(R)-III. The first crop of crystals from the heptane solution was 1.9 g. of *rac*-IV, m.p. 109-110°, $[\alpha]_D^{24}$ ±0.1° (*C* 2, benzene).

Anal. Found: C, 80.0; H, 7.45.

The filtrate from the *rac*-IV was concentrated to an oil which was dissolved in 1 ml. of heptane. Cooling to 5° gave 0.30 g. of (+)(S)-IV;

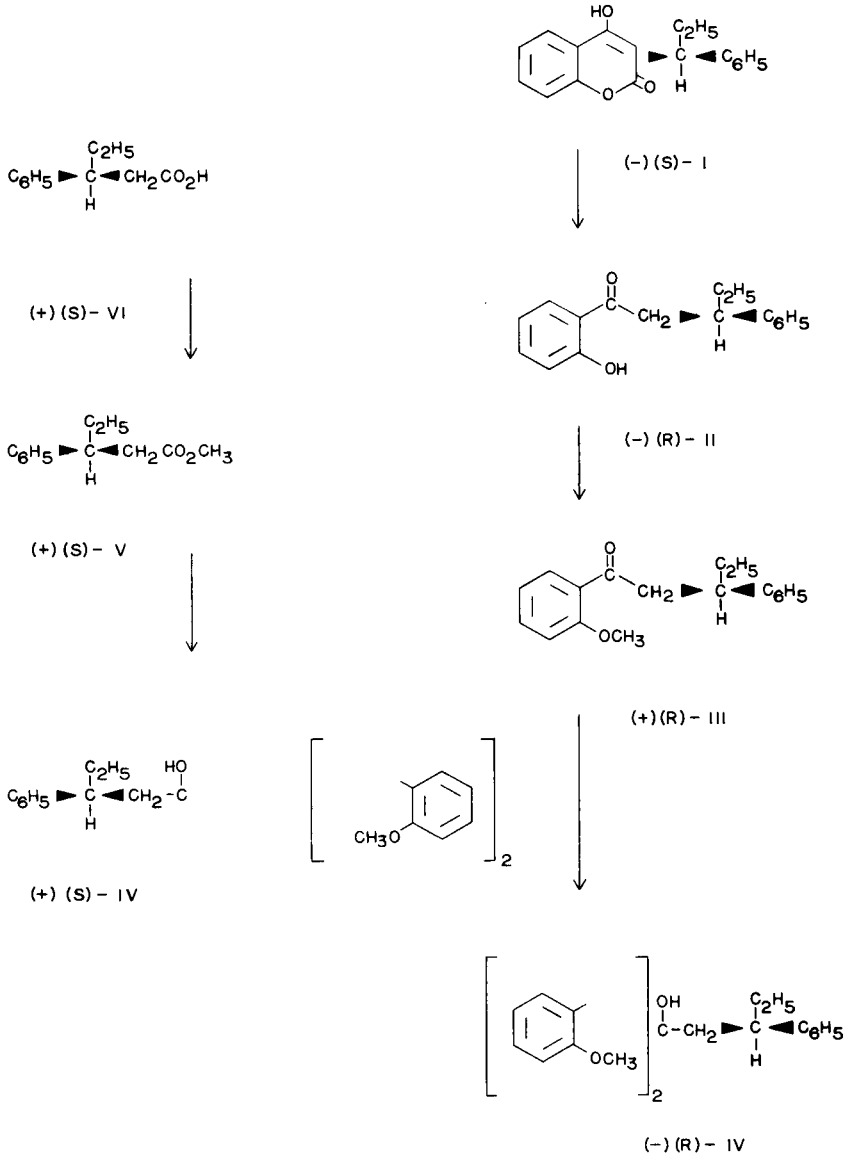

FIGURE 1

m.p. 98-99°; $[\alpha]_D^{24}$ +9.3°± 0.1°.

Anal. Found: C, 80.0; H, 7.25.

The infrared spectra of chloroform solutions of (+)(S)-IV, (-)(R)-IV and *rac*-IV were identical.

REFERENCES

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(7) Unpublished studies (with Dr. J. N. Eble and Dr. W. M. Barker in Dr. Link's laboratory) showed that (-)(S)-Marcumar is about 3 times more potent than its enantiomer in the prothrombin time assay after single doses and about 5 times more potent in divided doses over several days both by prothrombin time and LD_{50} comparisons.

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(11) All Marcumar-alkaloid salt samples were dried at least 12 hours at 0.1 mm and 25°. Rotations were measured in a Schmidt and Haensch model 82-B polarimeter with monochromater; 1=4 dm (solutions) and 1=1 dm (neat).

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