Tetrahedron. Vol. 28, pp. 3583 to 3586. Pergamon Press 1972. Printed in Great Britain

SYNTHESIS OF DIHYDROARBIGLOVIN AND STEREOCHEMISTRY OF ARBIGLOVIN*

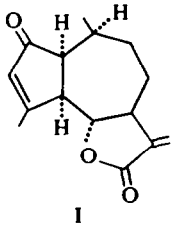
J. N. MARX† and S. M. MCGAUGHEY

Department of Chemistry, Texas Tech University, Lubbock, Texas 79409

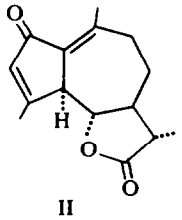
(*Received in USA* 20 *March* 1972; *Received in the UK for publication* 26 *March* 1972)

Abstract—Dihydroarbiglovin (III) has been synthesized by a stereoselective route starting with photolysis of santonin. The synthesis determines the stereochemistry at C-1 and C-10 as shown for arbiglovin (I).

ARBIGLOVIN, a guianolide isolated from *Artemisia biglovii* Gray, was assigned structure I, except for stereochemistry, by Herz and Santhanam.[1] Catalytic hydrogenation gave a tetrahydro product which was shown to be identical to the hydrogenation product of desacetoxymatricarin (leukodin) (II).[1] Our subsequent synthesis of desacetoxymatricarin[2] determined the stereochemistry as shown in formula II, and thus determined the stereochemistry of arbiglovin at all centers except C-1 and C-10. *Cis* hydrogenation of the $\Delta^{1(10)}$ double bond of desacetoxymatricarin could give rise to either III or IV. *A priori*, hydrogenation from the α-side to give III seemed more likely, from inspection of molecular models, but IV could not be excluded since II is an almost planar molecule (see conformational drawing).



I



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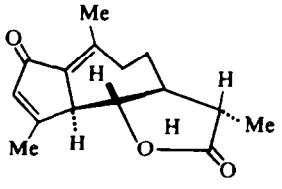
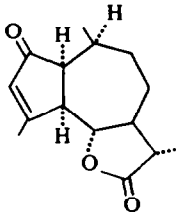
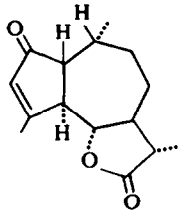


II



III

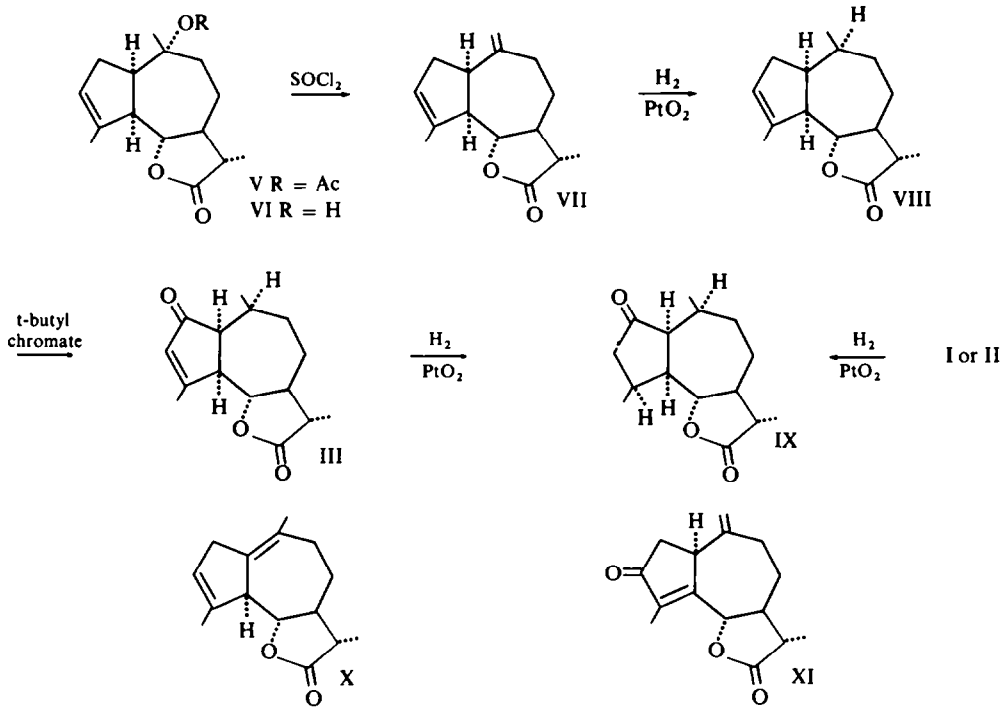


IV

* Presented at the 27th Southwest Regional ACS Meeting, San Antonio, Texas, December 1–3, 1971, Abstract No. 278.

† Author to whom inquiries should be addressed.

We now report a stereospecific synthesis of isomer III and its hydrogenation to a compound which proved to be identical to authentic tetrahydroarbiglovin. This synthesis proved that arbiglovin has stereostructure I.



The Δ^3-olefin acetate V, available in four steps[2] from α-santonin, was converted into the corresponding known[3] hydroxy compound VI with NaOMe in MeOH at reflux or KOBu-t in t-BuOH at room temperature. Although base treatment epimerizes the lactone methyl group at C-11,[3] under the present milder conditions only a small amount of the C-11 epimer was formed. Chromatography on silica gel gave pure VI as the major product. Treatment of VI with $SOCl_2$ in pyridine at $-10°$ for 10 sec gave the exocyclic diene VII as major product. Smaller amounts of the endocyclic double bond isomer, X, were also formed. The two dienes were separated by column chromatography on silica gel impregnated with $AgNO_3$. The endocyclic isomer X, which was the only product under slightly more vigorous conditions (e.g., one minute reaction time with $SOCl_2$ in pyridine at $-10°$), could be oxidized to desacetoxymatricarin (II) with t-butyl chromate, thus proving its structure. The diene mixture could also be obtained directly from olefin acetate V by deacetolysis at 60° on silica gel treated with methanesulfonic acid or similar strong acid. Although the endocyclic isomer X predominated under these conditions, the obtaining of appreciable quantities of VII was surprising, since the isomerization to X is so facile. This deacetolysis reaction required the presence of the silica gel, or only complex decomposition products resulted.

Selective catalytic hydrogenation of the exocyclic double bond of VII occurred

over PtO_2 in EtOH at ambient conditions if the reaction was stopped after one equivalent uptake. The major product, VIII, purified by column chromatography over silica gel, is assigned the stereochemistry shown by inspection of molecular models and by close analogy with compound XI which is known[4] to hydrogenate from the α side. No product from β side hydrogenation could be detected in the present case. The assignment is further strengthened by the fact that the hydrogenation of desacetoxymatricarin was carried out in a manner which is expected to lead to *cis* hydrogenation.[5]

Oxidation of VIII with t-butyl chromate gave the α,β-unsaturated ketone III (18%), after chromatography. All spectral data are in accord with the location of the ketone function at C-2. This compound could correspond to dihydroarbiglovin but since dihydroarbiglovin is not a known compound, III was reduced over PtO_2 in EtOH to give IX (stereochemistry at C-3 assumed), m.p. 155–157°. This compound was identical (m.m.p., IR, NMR, TLC) to a sample of tetrahydroarbiglovin, obtained by reduction of desacetoxymatricarin.[1] Thus, the stereochemistry of arbiglovin is correctly represented by formula I.

Compound III thus corresponds to IIβH, 13-dihydroarbiglovin. It could also conceivably correspond to carpesialactone, a compound isolated from *Carpesium ambrotanoides* L., and assigned structure III without stereochemistry.[6] The IR spectrum of our compound III is much different than the published spectrum[6b] of carpesialactone. No sample of the compound is available for comparison,[7] so the stereochemistry of carpesialactone remains speculative.

EXPERIMENTAL

Hydrolysis of acetate V *to alcohol* VI. Sixty mg V (0·20 mmoles) was stirred for 8 hr in 5·0 ml NaOMe/MeOH solution at room temp. The NaOMe solution was prepared by adding 150 mg Na to 5·0 ml dry MeOH. Ether was added after 8 hr stirring, the solution washed with dilute HCl, H_2O, then dried ($MgSO_4$). The product showed one main spot on TLC (4:1 cyclohexane-EtOAc) which moved more slowly than acetate V and a minor slower moving one due to the C-11 epimer of V.[3] Chromatography over 10 g silica gel gave 35 mg V in fractions (50 ml) 5–10. ν_{CHCl_3} 1770 cm^{-1}; NMR, 4·53 τ (broad s, C-3 H), 5·86 (doublet of doublets, $J_1 = 9$, $J_2 = 10$, C-6 H), 8·17 (broad s, C-4 Me), 8·78 (d, $J = 7$, C-11 Me), 8·85 (s, C-10 Me).

Preparation of the exocyclic/endocyclic diene mixture (VII *and* X) *from acetate* V. A solution of 58·5 mg (0·20 mmoles) of the acetate V in 4·0 ml petroleum ether–ether (9:1) was placed in a 10 ml round bottom flask containing approximately 0·10 silica gel. Two drops 5% HCl were added and the solution taken to dryness on a rotary evaporator with continued heating at 70° for 10 min. The silica gel turned blue then purple. Chromatography over 18 g silica gel with C_6H_6 (100 ml. fractions) gave 21·5 mg of the *exo-endo* diene mixture in fraction 6.

Dehydration of olefin alcohol VI *to diene mixture* (VII *and* X). The alcohol VI (440 mg, 1·7 mmoles) was stirred with 24 ml pyridine and 1·5 ml $SOCl_2$ for 10 seconds at − 10°. Excess (20 ml) water was then added to quench the reaction. Ether was added, shaken, separated, then washed with water and dilute HCl and dried ($MgSO_4$). The ether was evaporated to give 0·35 g of the exocyclic/endocyclic dienes, and by NMR the ratio of the C-3 vinylic hydrogen to the C-15 methylene hydrogen was 1·0 to 1·4 indicating the exocyclic diene to be predominant. Chromatography over silica gel impregnated with $AgNO_3$ (prepared from 12 g $AgNO_3$ and 30 g silica gel in aqueous MeOH and drying at 100°) gave in the 60% benzene − 40% petroleum ether fractions, 0·10 g (23%) of the exocyclic diene VII. ν_{CHCl_3} 1760, 1630, 1600 cm^{-1}; NMR, 8·76 τ (3 H, d, $J = 6$, C-11 Me), 8·13 (3 H, broad s, C-11 Me), 5·98 (1 H, doublet of doublets, $J_1 = 9$, $J_2 = 10$, C-6 H), 5·10 (2 H, broad s, C-15 H's), 4·43 (1 H, broad s, C-3 H). (Calc. for $C_{15}H_{20}O_2$: C, 77·55; H, 8·68. Found: C, 77·03; H, 8·97%).

The endocyclic diene (X) which was eluted from the column with 50% C_6H_6 in petroleum ether, had the

following spectral characteristics: ν_{CHCl_3} 1760, 1630, 1610 cm^{-1}; NMR, 8·77 τ (3 H, d, J = 6, C-11 Me), 8·23 (6 H, broad s, C-4, C-10 Me's) 5·85 (1 H, doublet of doublets, J_1 = 9, J_2 = 10, C-6 H), 4·47 (1 H, broad s, C-3 H).

Preparation of VIII *by hydrogenation of* VII. The exocyclic diene (VII) (100 mg, 0·43 mmoles) in 100 ml EtOH was subjected to hydrogenation by shaking in a H_2 atmosphere with 32 mg prereduced PtO_2 for 2 hr. Total uptake was 10 ml (0·84 equivalents). The solvent was removed after the catalyst was filtered leaving 100 mg clear oil. NMR showed the methylene adsorption at 5·2 τ was gone but the vinyl hydrogen absorption still present. ν_{CHCl_3} 1760, 1610 cm^{-1}, NMR, 9·07 τ (3 H, d, J = 7, C-10 Me), 8·78 (3 H, d, J = 6, C-11 Me), 8·18 (3 H, broad s, C-4 Me), 5·83 (1 H, doublet of doublets, J_1 = 9, J_2 = 10, C-6 H), 4·50 (1 H, s, C-3 H). (Calc. for $C_{15}H_{22}O_2$: C, 76·88, H, 9·96. Found: C, 76·75; H, 9·01%).

Oxidation of VIII *to* III. A solution of 151 mg (0·65 mmoles) VIII in 6·0 ml CCl_4 was refluxed for 12 hr under N_2 with 1·0 ml AcOH, 0·45 mc_2O, and 3·6 ml 1·0 N t-butyl chromate solution (prepared by dissolving 1·36 g CrO_3 in 4·0 ml of t-BuOH with cooling, diluting with 12 ml CCl_4, washing well with water and drying over $MgSO_4$). The resulting mixture was cooled and stirred for 1 hr with 0·30 g oxalic acid in 20 ml water. The almost colorless organic layer was separated, washed with water, dried and solvent removed. The resulting oil was chromatographed on a clean up column yielding 0·098 g of oil containing the impure III. The impure product was then chromatographed over 40 g silica gel. The fractions with 10% ether in petroleum ether contained 27 mg of oily III, which showed one spot by TLC in three solvent systems and had the following spectral data: ν_{CHCl_3} 1750, 1710, 1600 cm^{-1}; NMR, 8·96 τ (3 H, d, J = 5, C-10 Me), 8·77 (3 H, d, J = 6, C-11 Me), 8·00 (3 H, broad s, C-4 Me), 5·95 (1 H, doublet of doublets, C-6 H), 3·92 (1 H, broad s, C-3 H).

Catalytic reduction of dihydroarbiglovin (III) *to tetrahydroarbiglovin* (IX). A solution of 24 mg (0·10 mmoles) III in 50 mg MeOH was hydrogenated over 20 mg PtO_2 at ambient conditions. The hydrogenation uptake was 3·0 ml (1·14 equivalents). After 8 hr the catalyst was filtered and the solvent removed at reduced pressure. Chromatography over 4·0 g of silica gel gave, in the 20% ether–petroleum ether fractions, 21 mg of yellow oil which crystallized from cyclohexane acetone when seeded with a sample of tetrahydrodesacetoxymatricarin, prepared by hydrogen of desacetoxymatricarin.[1] The crystals were recrystallized twice from cyclohexane–acetone and twice from ether to give white crystals m.p. 155–157°. M.m.p. with tetrahydrodesacetoxymatricarin was 155–157°. The samples were also identical by TLC and spectral data: ν_{CHCl_3} 1770, 1740, cm^{-1}; NMR, 9·06 τ (3 H, d, J = 5, C-10 Me), 8·95 (3 H, d, J = 6, C-4 Me), 8·74 (3 H, d, J = 7, C-11 Me), 5·80 (1 H, doublet of doublets, J_1 = 9, J_2 = 10, C-6 H). (Calc. for $C_{15}H_{22}O_3$: C, 71·97; H, 8·86. Found: C, 72·05; H, 8·79%).

Acknowledgements—We wish to thank the Robert A. Welch Foundation for financial support, also Prof. T. A. Geissman for a generous sample of desacetoxymatricarin.

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