

## SYNTHESIS OF B-*seco* DOISYNOLIC ACIDS

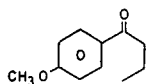
P. CRABBÉ, J. IRIARTE, A. CRUZ and J. H. FRIED

Research Laboratories, Syntex, S.A. Apartado Postal 10-820,  
México 10, D. F., México

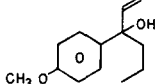
### SUMMARY

The total synthesis of dl-B-*seco*-8-dehydro-*cis*-doisynolic acid 3-methyl ether (XIIIb), dl-B-*seco*-9(11)-dehydro-*cis*-doisynolic acid 3-methyl ether (XVIIIb) and dl-B-*seco*-9(11)-dehydro-*trans*-doisynolic acid 3-methyl ether (XIXb) is described. The assignment of structure and configuration is based on the physical properties presented by these bis-*seco*-steroids.

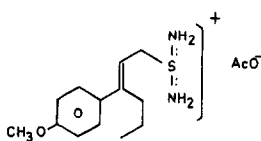
The general synthetic approach which follows is based on the Torgov steroid synthesis [1]. Reaction of p-methoxy-butyrophenone (I) with vinylmagnesium bromide afforded p-methoxy-phenyl-n-propyl-carbinol (II)\* {amorphous,  $\lambda_{\max}$  226, 275 nm ( $\epsilon$  11,100, 1520);  $\nu_{\max}$  3400, 1610, 1585  $\text{cm}^{-1}$ }. Its isothiuronium salt (III) {m.p. 129-131°C (methanol);  $\lambda_{\max}$  260 nm ( $\epsilon$  16,100);  $\nu_{\max}$  3100, 1675, 1595, 1250  $\text{cm}^{-1}$ } was allowed to react with  $\alpha,\gamma$ -dimethyltetronic acid [2] which yielded a mixture of *cis* (IV) {amorphous,  $\lambda_{\max}$  252 nm ( $\epsilon$  11,100);  $\nu_{\max}$  1800, 1755, 1510  $\text{cm}^{-1}$ } and *trans* bicyclic lactone (V) {amorphous,  $\lambda_{\max}$  252 nm ( $\epsilon$  13,400);  $\nu_{\max}$  1800, 1755, 1610  $\text{cm}^{-1}$ } separated by t.l.c.



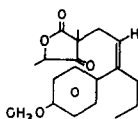
I



II



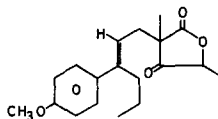
III



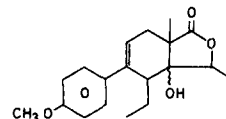
IV

Acid catalyzed ring closure of (V) provided a mixture of the crystalline tricyclic carbinol (VI) {m.p. 177-179°C ( $\text{CH}_2\text{Cl}_2$ -ether);  $\lambda_{\max}$  256 nm ( $\epsilon$  13,500);  $\nu_{\max}$  3370, 1780, 1730, 1600  $\text{cm}^{-1}$ } and the homannular diene (VII) {amorphous,  $\lambda_{\max}$  242 nm ( $\epsilon$  14,100);  $\nu_{\max}$  1770, 1610  $\text{cm}^{-1}$ } separated by t.l.c. Treatment of (VI) with p-toluenesulfonic acid afforded the  $\Delta^{8(9)}$ -enol-lactone (VIII) {m.p. 89-90°C;  $\lambda_{\max}$  270 nm ( $\epsilon$  17,400);  $\nu_{\max}$  1785, 1670, 1610  $\text{cm}^{-1}$ } and in addition,  $\Delta^{8(9)}$ -14 $\alpha$ -carbinol (IX) {amorphous,  $\lambda_{\max}$  264 nm ( $\epsilon$  15,400);  $\nu_{\max}$  3330, 1780, 1610  $\text{cm}^{-1}$ } and  $\Delta^{8(9)}$ -14 $\beta$ -carbinol (X) {amorphous,  $\lambda_{\max}$  270 nm

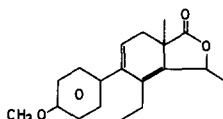
( $\epsilon$  13,200);  $\nu_{\max}$  3330, 1765, 1615  $\text{cm}^{-1}$ ; n.m.r. 1.23 (18-H), 1.33 (t, J 7.5 Hz,  $\text{CH}_2\text{CH}_3$ ), 1.58 (d, J 7 Hz, 15- $\text{CH}_3$ ), 3.83 (Ar-O $\text{CH}_3$ ), 6.83-7.06 ppm (aromatic-H)}. These three compounds were also obtained



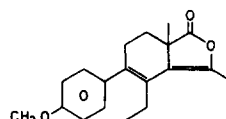
V



VI

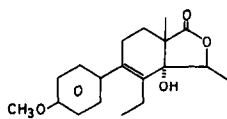


VII

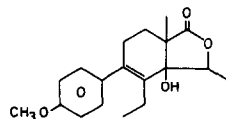


VIII

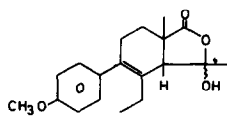
when the bicyclic ketolactone (V) was submitted to similar acid treatment. Alkaline hydrolysis of  $\Delta^{8(9)}$ -enol-lactone (VIII) provided the  $\Delta^{8(9)}$ -lactol (XI) {m.p. 124-128°C ( $\text{CH}_2\text{Cl}_2$ -MeOH);  $\lambda_{\max}$  230 nm ( $\epsilon$  11,500);  $\nu_{\max}$  3300, 1740, 1610  $\text{cm}^{-1}$ }. Methylation of this lactol (XI) with methyl iodide in dimethylformamide afforded the keto-ester (XII) {amorphous,  $\lambda_{\max}$  230, 278 nm ( $\epsilon$  10,900, 2160);  $\nu_{\max}$  1720, 1610  $\text{cm}^{-1}$ } which was reduced electrochemically [3] into the methyl ester (XIIIa) {amorphous,  $\lambda_{\max}$  230, 276 nm ( $\epsilon$  11,200, 1700);  $\nu_{\max}$  1735, 1725, 1610, 1250  $\text{cm}^{-1}$ };



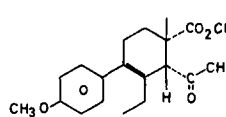
IX



X

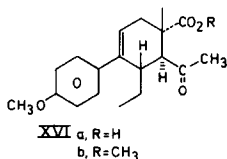
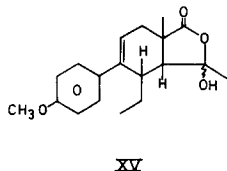
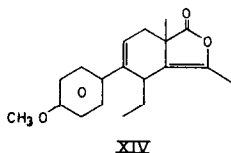
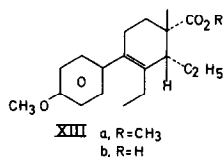


XI

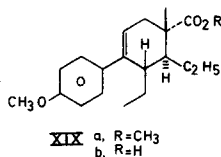
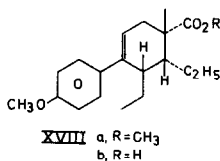
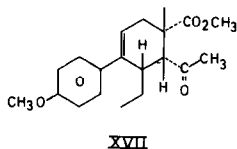


XII

\* Satisfactory analyses or mass spectra were obtained for all new compounds. The n.m.r. spectra were consistent with their structure.



and hydrolyzed with sodium hydroxide in ethylene glycol at reflux temperature to 5,6-*seco*-8-dehydro-dl-*cis*-doisynolic acid methyl ether (XIIIb) {m.p. 113–114°C (methanol);  $\lambda_{\max}$  276 nm ( $\epsilon$  1480);  $\nu_{\max}$  3300, 1695, 1610  $\text{cm}^{-1}$ }. Dehydration of the carbinol (VI) with thionyl chloride in pyridine solution provided an isomer of (VIII), *i.e.* the  $\Delta^{9(11)}$ -lactone (XIV) {m.p. 99–100°C (hexane-ether);  $\lambda_{\max}$  248 nm ( $\epsilon$  17,700);  $\nu_{\max}$  1785, 1720, 1610  $\text{cm}^{-1}$ }. Alkaline hydrolysis of (XIV) yielded a mixture of the expected lactol (XV) {m.p. 128–129°C (ether-hexane);  $\lambda_{\max}$  250 nm ( $\epsilon$  14,000);  $\nu_{\max}$  3350, 1730, 1610  $\text{cm}^{-1}$ } and the *trans*-keto-acid



(XVIa) {144–145°C (ether-hexane);  $\lambda_{\max}$  244 nm ( $\epsilon$  13,700);  $\nu_{\max}$  3330, 1710, 1700, 1690, 1610  $\text{cm}^{-1}$ }. Reaction of (XV) with methyl iodide gave the keto-ester (XVII) {amorphous;  $\lambda_{\max}$  248 nm ( $\epsilon$  13,200);  $\nu_{\max}$  1720, 1705, 1595, 1250  $\text{cm}^{-1}$ }, which was reduced electrochemically into (XVIIIa) {amorphous,  $\lambda_{\max}$  246 nm ( $\epsilon$  13,100);  $\nu_{\max}$  1725, 1610, 1250  $\text{cm}^{-1}$ } and hydrolyzed with base to 5,6-*seco*-9(11)-dehydro-dl-*cis*-doisynolic acid 3-methyl ether (XVIIIb) {m.p. 158–159°C (methanol);  $\lambda_{\max}$  246 nm ( $\epsilon$  13,700);  $\nu_{\max}$  3400, 1730, 1690, 1610  $\text{cm}^{-1}$ }. The *trans*-keto-acid (XVIa) was methylated into the corresponding keto-ester (XVIb) {amorphous,  $\lambda_{\max}$  244 nm ( $\epsilon$  11,800);  $\nu_{\max}$  1730, 1710, 1610, 1250  $\text{cm}^{-1}$ }, which was reduced electrochemically to the ester (XIXa) {amorphous,  $\lambda_{\max}$  244 nm ( $\epsilon$  12,500);  $\nu_{\max}$  1730, 1610, 1250  $\text{cm}^{-1}$ } and finally hydrolyzed with base into 5,6-*seco*-9(11)-dehydro-dl-*trans*-doisynolic acid 3-methyl ether (XIXb) {m.p. 96–98°C (ether-pentane);  $\lambda_{\max}$  242 nm ( $\epsilon$  10,800);  $\nu_{\max}$  3400, 1730, 1690, 1610  $\text{cm}^{-1}$ }.  
The 14 $\alpha$ -H configuration was assigned to (XVIb) on the basis of the 18-H n.m.r. signal which appears at 1.41 ppm (XVIb) vs 1.31 ppm in (XVII).  
Examination of the geometry of the compounds of the *cis*-series (XV, XVII, XVIII) as well as their isomers of the *trans*-series (XVI, XIX) with molecular models indicates that all these  $\Delta^{9(11)}$ -*B-seco*-steroids present the thermodynamically stable 8 $\beta$ -H-stereochemistry, in agreement with similar observations made in analogous substances [4].

## REFERENCES

1. Ananchenko S. N. and Torgov I. V.: *Tetrahedron Lett.*, (1963) 1553–1558.
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3. Throop L. and Tökés L.: *J. Am. chem. Soc.* **89** (1967) 4789–4790.
4. *Inter alia*: Nathan A. H. and Hogg J. A.: *J. Am. chem. Soc.* **78** (1956) 6163–6166, and references cited therein; Smith H., Douglas G. H. and Walk C. R.: *Experientia* **20** (1964) 418–419.