sodium bicarbonate, dilute hydrochloric acid, and water. The organic solvent was removed under reduced pressure and the remaining solid was recrystallized from ethyl acetate–methanol to yield **17β-acetoxy-5-hydroxy-4-oxa-5α-androst-1-en-3-one (11a)**, mp 185–186°. The infrared spectrum of this compound showed bands at 3600–3100 (broad), 1730, 1710, 1690, 1620, 1251, 1040, and 958 $cm^{-1}$; ultraviolet absorption, $\lambda_{max}^{MeOH}$ 217.5 mμ (log ε 3.905); nmr,[7] 0.81 (3 H, singlet, C-18 $CH_3$), 1.25 (3 H, singlet, C-19 $CH_3$), 2.03 (3 H, singlet, C-17 acetate), 4.27 (1 H, broad singlet which disappears upon the addition of $D_2O$, C-5 OH), 4.59 (1 H, triplet, $J$ = 8 cps, C-17 H), AB quartet with doublets[28] centered at 5.93 (1 H, $J$ = 10 cps, C-2 H), and at 6.66 ppm (1 H, $J$ = 10 cps, C-1 H).

*Anal.* Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.82; H, 8.20.

The methyl derivative **11b** was prepared by treating the lactol **11a** with ethereal diazomethane. The product was recrystallized from methanol: mp 115–117°; $\lambda_{max}^{EtOH}$ 215 mμ (log ε 3.887); infrared spectrum bands at 1730 (shoulder), 1720, 1635, 1255, 1213, 1183, 1049, and 830 $cm^{-1}$.

*Anal.* Calcd for $C_{21}H_{30}O_5$: C, 69.59; H, 8.34. Found: C, 69.74; H, 8.47.

**17β-Acetoxy-1-hydroxy-2-oxa-4-androsten-3-one (10).**—For analysis, a sample was recrystallized twice from acetone–*n*-hexane, mp 220–221°. The infrared spectrum showed bands at 3600–3100 (broad), 1740, 1715, 1705 (shoulder), 1630, 1250, 1230, 1041, and 962 $cm^{-1}$; ultraviolet absorption was at $\lambda_{max}^{EtOH}$ 227 mμ (log ε 4.130); nmr[7] peaks were at 0.79 (3 H, singlet, C-18 $CH_3$), 1.17 (3 H, singlet, C-19 $CH_3$), 1.97 (3 H, singlet, C-17 acetate), 4.55 (1 H, unresolved triplet, C-17 H), 5.49 (1 H, singlet, C-1 H), and 5.71 ppm (1 H, singlet, C-4 H).

*Anal.* Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.99; H, 8.10.

**Registry No.**—2, 15266-94-1; **3a**, 15266-95-2; **3b**, 15266-96-3; **4**, 15266-97-4; **5**, 15266-98-5; **6a**, 15266-99-6; **6b**, 15267-00-2; **7a**, 15267-01-3; **7b**, 6224-23-3; **8**, 15292-86-1; **9**, 15292-87-2; **10**, 15292-88-3; **11a**, 15285-89-9; **11b**, 15267-34-2.

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## The Addition of Formaldehyde to Levopimaric Acid and Methyl Levopimarate

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Formaldehyde readily combines with levopimaric acid at low temperatures to give a Diels–Alder adduct in good yield.[2] This is somewhat surprising since formaldehyde is generally considered a poor dienophile.[3-7]

If levopimaric acid and methyl levopimarate are allowed to combine with paraformaldehyde under identical conditions, both give a Diels–Alder adduct. The yields of each adduct, however, differ significantly, the levopimaric acid adduct being formed in almost quantitative yield while the ester adduct is formed in at best 10% yield. From data such as this, it seems reasonable to assume that the free carboxyl group of levopimaric acid in some way enhances the reaction rate.

Because paraformaldehyde added to levopimaric acid only at temperatures above which paraformaldehyde rapidly decomposed to monomeric formaldehyde gas, we surmised that monomeric formaldehyde was the reacting species. This was tested by allowing ethereal and chloroform solutions of monomeric formaldehyde to react with levopimaric acid at low temperature. In both instances levopimaric acid–formaldehyde adduct was formed in yields of 30 and 50%, respectively. Thus, monomeric formaldehyde adds to levopimaric acid under conditions under which paraformaldehyde does not add and paraformaldehyde adds at a significant rate only at temperatures above which it rapidly decomposes; therefore, monomeric formaldehyde is the reacting species.

A carboxyl group could assist in enhancing the reaction rate by polarization of the entering formaldehyde molecule either (1) intramolecularly or (2) intermolecularly. If intermolecular hydrogen bonding causes the increased reaction rate, then one might expect equimolar mixtures of levopimaric acid and methyl levopimarate to give equimolar mixtures of ester and acid adducts. If, on the other hand, an intramolecular process causes the increased rate of reaction, the acid and ester adducts should be formed in the same ratio as if formed from pure acid and ester, respectively.

To test this hypothesis, mixtures of methyl levopimarate, paraformaldehyde, and levopimaric acid were combined and the reaction products were examined by nmr spectroscopy (see Experimental Section). From the nmr spectrum of such a mixture, the amount of methyl levopimarate that has reacted to form adduct can be calculated. Similar experiments were performed with mixtures of methyl levopimarate, paraformaldehyde, and levopimaric acid–formaldehyde adduct. The results of these experiments are reported in Table I.

TABLE I

PER CENT METHYL LEVOPIMARATE THAT REACTED WITH FORMALDEHYDE TO FORM ADDUCT

| Composition | Intensity of A | Intensity of B | Me-LPA reacted, % |
|---|---|---|---|
| 100% Me-LPA | 11 | 70 | 15.7 |
| 100% Me-LPA | 15 | 240 | 6.3 |
| 64% Me-LPA<br>36% LPA | 36 | 45 | 29 |
| 68% Me-LPA<br>32% LPA | 100 | 130 | 33 |
| 49% Me-LPA<br>51% adduct | 48 | 34 | 37 |

From the data in Table I, it is obvious that the percentage of methyl levopimarate which has been consumed is greater when the experiments are run in the presence of levopimaric acid or levopimaric acid–formaldehyde adduct than when only methyl levopimarate is present. This evidence implicates the

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carboxyl group as the functionality responsible for the faster reaction rate of levopimaric acid relative to the rate of reaction of methyl levopimarate. Furthermore, it suggests that intermolecular hydrogen bonding is operative.

Examination of a molecular model of levopimaric acid supports these conclusions. An intramolecular process in which a molecule of levopimaric acid through its equatorial carboxyl forms a hydrogen bond with a formaldehyde molecule which then adds to the diene system of the same molecule would be very unlikely.

As another approach to this problem, we considered a study of the kinetics of the reaction of monomeric formaldehyde with levopimaric acid. However, in ether or chloroform solvent as a result of the polymerization of monomeric formaldehyde it was not possible to obtain reproducible kinetic data to support the contention that the reaction involved either intra- or intermolecular hydrogen bonding.

## Experimental Section

**Isolation and Purification of Levopimaric Acid.**—The method of Harris and Sanderson[8] as modified by Lawrence and coworkers[9] was used isolating and purifying levopimaric acid from pine oleoresin.

**Reaction of Levopimaric Acid with Paraformaldehyde.**—A mixture of 5.6 g of levopimaric acid and 0.06 g of paraformaldehyde was thoroughly ground in a mortar and pestle. A 0.10-g sample of this mixture was placed in an nmr tube, flushed with nitrogen, sealed, and placed in a constant-temperature (130°) oil bath for 15 min. After cooling by placing the tube under running water, the reaction mixture was dissolved in 1 ml of deuteriochloroform and the nmr spectrum was determined. This indicated a 90% yield.

**Reaction of Methyl Levopimarate and Paraformaldehyde.**—A mixture of 0.09 g of methyl levopimarate and 0.01 g of paraformaldehyde was placed in an nmr tube, flushed with nitrogen, and the tube was sealed. The tube was placed in a constant-temperature (130°) oil bath for 15 min. After cooling by placing the tube under running water, the reaction mixture was dissolved in 1 ml of deuteriochloroform and the nmr spectrum was determined. This indicated a 10% yield.

**Preparation of Monomeric Formaldehyde Solutions.**—The formaldehyde generator consisted of a 250-ml erlenmeyer flask (A) with a side arm for carrying the monomeric formaldehyde gas into the receiving flask (B). Flask A was charged with paraformaldehyde and immersed in an oil bath at a constant temperature of 130°. Nitrogen was passed slowly into flask A to flush monomeric formaldehyde out of the generator as it was formed. The side arm of the apparatus was wrapped with a heating tape and maintained at a high enough temperature, at 125–140°, to prevent polymerization on the walls. An appropriate solvent was placed in flask B, which was immersed in a Dry Ice bath, to catch the monomeric formaldehyde. The monomeric formaldehyde concentration was determined by nmr spectroscopy.

**Reaction of Levopimaric Acid with Monomeric Formaldehyde in Ethyl Ether.**—To 50 ml of a solution of monomeric formaldehyde in ethyl ether was added 0.5 g of levopimaric acid. The solution was allowed to stand at room temperature, overnight and the solvent was distilled at reduced pressure. A portion of the residue was extracted with 1 ml of $CDCl_3$ and examined by nmr spectroscopy. Approximately 30% of the levopimaric acid was converted into levopimaric acid–formaldehyde adduct.

**Reaction of Levopimaric Acid with Monomeric Formaldehyde in Chloroform.**—To 250 ml of a solution of monomeric formaldehyde in chloroform ($N_{CH_2O}$ = 0.04) was added 0.3 g of levopimaric acid. The reaction vessel was placed in a water bath at 45° and allowed to cool (a few degrees per hour) to room temperature. Following evaporation of the solvent at reduced pressure, 0.1 g of the solid product was dissolved in 1 ml of $CDCl_3$ and examined by nmr spectroscopy. More than 50% of the levopimaric acid was converted into adduct.

**Reaction of Methyl Levopimarate with Paraformaldehyde in the Presence of Levopimaric Acid–Formaldehyde Adduct.**—A mixture of 0.0936 g of methyl levopimarate, 0.010 of paraformaldehyde, and 0.0925 g of levopimaric acid–formaldehyde adduct was thoroughly mixed in a mortar and pestle. A 0.0999-g sample of this mixture was placed in an nmr tube, flushed with nitrogen, sealed, and placed in a constant-temperature (130°) oil bath for 15 min. After cooling by placing the tube under running water, the reaction mixture was dissolved in 1 ml of deuteriochloroform and analyzed by nmr spectroscopy. The results of this analysis are reported in Table I.

**Reaction of Mixtures of Levopimaric Acid and Methyl Levopimarate with Paraformaldehyde.**—A mixture (A) of 5.6 g of levopimaric acid and 0.60 g of paraformaldehyde was thoroughly mixed in a mortar and pestle. A second mixture (B) containing 0.90 g of methyl levopimarate and 0.10 g of paraformaldehyde was prepared. To 0.0590 g of A was added 0.1137 g of B and after thorough mixing, 0.1010 g of the mixture was transferred to an nmr tube. The tube was flushed with nitrogen, sealed, and placed in a constant-temperature (130°) oil bath for 15 min. After cooling, the reaction mixture was analyzed as usual by nmr spectroscopy. The results of this experiment and a number of similar experiments are reported in Table I.

**Nmr Analysis.**—Nuclear magnetic resonance spectra were obtained from 10% deuteriochloroform solutions using a Varian A-60A spectrometer. Tetramethylsilane was used as internal standard and chemical shifts are reported at $\tau$ values.

The nmr spectrum of the formaldehyde–levopimaric acid adduct showed $\tau$ 9.46, a sharp singlet at intensity of 3, assignable to the C-10 angular methyl group protons. This feature is common to the nmr spectra of all Diels–Alder adducts of levopimaric acid[10,11] and is consistent with the interpretation that formaldehyde adds to the back side of levopimaric acid, placing the double bond in a position to strongly shield the C-10 methyl protons.

The nmr spectrum of the ester adduct is very similar to that of the acid adduct, the primary difference being that the spectrum of the ester adduct contains a sharp singlet (B) centered at $\tau$ 6.36. This absorption also occurs in the spectrum of the methyl levopimarate and is assigned to the protons of the methyl group which is attached to the carboxyl group. The absorption (A) at $\tau$ 9.46 is characteristic of both methyl levopimarate and levopimaric acid Diels–Alder adducts. Thus, from the nmr spectrum of a mixture of methyl levopimarate, methyl levopimarate–formaldehyde adduct and levopimaric acid–formaldehyde adduct, one can compare the total amount of adduct to the total amount of ester plus ester adduct (which is equal to the amount of ester originally present in the reaction mixture described above.) Such a comparison allows one to calculate the minimum amount of methyl levopimarate which has reacted to form adduct.

Based on the above assignments, one may calculate the maximum contribution ($X$) to absorption ($A$) by the formaldehyde–levopimaric acid adduct as

$$\frac{X}{(B)} = \frac{0.9(\text{mole \% LPA})}{\text{mole \% Me-LPA}}$$

$$X = \frac{0.9(\text{mole \% LPA(B)})}{\text{mole \% Me-LPA}}$$

The mole % levopimaric acid is multiplied by 0.9 because only about 90% of the levopimaric acid is converted into adduct under these reaction conditions. The remainder is present as levopimaric acid or as the 12-methylolhydroxy acid which results from opening the ring of the adduct. Now the minimum contribution ($C$) to absorption ($A$) by methyl levopimarate adduct may be calculated

$$C = A - X$$

and the minimum mole % methyl levopimarate that reacted to form adduct may be calculated

$$\% \text{ Me-LPA} = \frac{C}{(B)} \times 100$$

The data from these experiments are reported in Table I.

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