could regulate temperatures within ±0.1° for at least 6 hr. Solutions cooled in the cryostat were exposed for 15–60 sec. to the unfiltered radiation from a Hanovia-type 16,200 lamp with a quartz envelope. Uniform coloring of the solutio was observed. The cryostat was quickly transferred to the sample cell compartment of a Cary Model 14 spectrophotometer and the decrease in absorbance of the visible band at $\lambda_{\max}$ was followed with respect to time. A matched cell containing pure ethanol was in the reference beam. In all cases the absorbance of the system ultimately fell to zero. At least two runs were made at each temperature.

Values of the first-order specific rate constant, k, were calculated from the slope of the straight line in plots of log optical density *vs.* time. The reaction was followed for at least two half-lives. Illustrative plots are given in Fig. 1. The Arrhenius activation energy, E_{exp}, was calculated from the slope of the straight line obtained in plots of log k *vs.* $1/T$. The entropy of activation, ΔS^*, was calculated using the following equation.[21]

$$k = e\frac{\bar{k}T}{h}e^{\Delta S^*/R}\,e^{-E_{\text{exp}}/RT}$$

The frequency factor, A, in the Arrhenius equation, $k = Ae^{-E_{\text{exp}}/RT}$ was calculated from the following relationship.

$$A = e\frac{\bar{k}T}{h}e^{\Delta S^*/R}$$

Ultraviolet and Visible Absorption Measurements.—A Cary Model 14 spectrophotometer was used The compounds were dissolved and measured in absolute Spectro Grade ethanol. The ultraviolet absorption spectra were measured in a 1-cm. cell against a reference of pure solvent in a matched cell. The visible irradiation spectra of Fig. 2 were obtained by exposing cryostated solutions at −103.5° for 2 min. to the unfiltered radiation from a Hanovia lamp and measuring against a reference of pure solvent. The anionic spectra of Fig. 2 were obtained at room temperature by adding to the ethanol solutions one drop of 0.01 N potassium hydroxide.

Acknowledgment.—The authors wish to thank Mr. C. DiPietro for the chemical analyses.

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(21) S. Glasstone, K. J. Laidler, and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 199.

The Nuclear Magnetic Resonance Spectra of Heterocyclic Compounds. III. Synthesis and Spectra of Steroids Having 20,21-Bisethylene Dioxide Moieties[1]

E. CASPI,[2a] H. ZAJAC,[2b] AND TH. A. WITTSTRUCK

Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts

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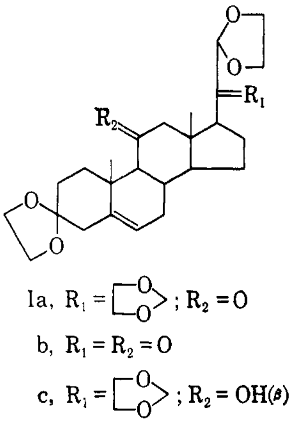
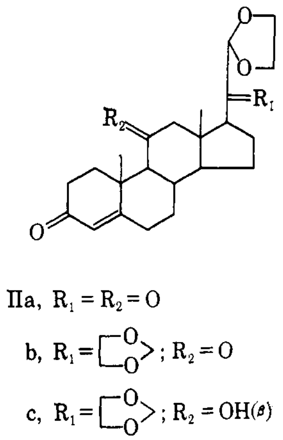
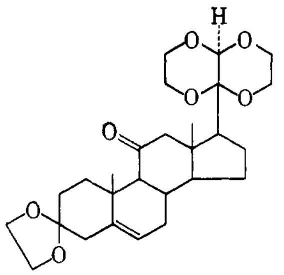
The product of ethylene glycol-*p*-toluenesulfonic acid treatment of the 3,21-bisethylene dioxide (Ib) was found to be identical with the by-product of cortisone ketalization.[3] The previously proposed n.m.r. generalizations for steroidal dioxolanes were confirmed. Compounds with 20,21-bisethylene dioxide (Ia) and 17β-naphthodioxane (III) moieties were isolated as important ketalization by-products of cortisone.[3] Assignment of structures I and II was based largely on n.m.r. evidence. An extension of this work is described in the present article.

In the first paper of this series, studies of the n.m.r. spectra of simple substituted dioxolanes, dioxanes, and naphthodioxanes were presented.[4] It was shown that the single proton on a carbon bearing two oxygens in a five-membered ring gives a resonance at about 5.0–5.2 τ, while a single proton at the bridgehead of *trans*-1,4;5,8-naphthodioxane gives a resonance[5] at 5.35 τ. Furthermore, the signal for the $-O-CH_2-CH_2-O-$ moiety of the dioxolane derivatives in general did not exhibit resolvable splitting from the coupling between the methylene protons, and hence appeared as a relatively narrow signal. In contrast, the corresponding resonance for naphthodioxane was resolvable into a broad multiplet. These observations and reference values were important features in assigning structures I and III. However, since the reference values were obtained for simple dioxolanes and *trans*-1,4;5,8-naphthodioxane, it appeared desirable to verify these for steroids and also to confirm structures Ia and Ic.







III

Our first objective was to prepare a steroidal *aldehydo*-ethylene dioxide and to evaluate the chemical shift for the single proton on the carbon bearing two oxygens. Several routes to such compounds were considered, and the most appropriate appeared to be that described by Tsuda, *et al.*[6] Indeed, when cortisone was

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(2) (a) Recipient of a Public Health Service research career program award CA-K3-16614 from National Cancer Institute; (b) Post Doctoral Fellow (1962-1963) on leave of absence from the Technical University, Lodz, Poland.

(3) E. Caspi, Th. A. Wittstruck, and N. Grover, *J. Org. Chem.*, **28**, 763 (1963).

(4) E. Caspi, Th. A. Wittstruck, and D. M. Piatak, *ibid.*, **27**, 3183 (1962).

(5) Page 3189, line 22 in ref. 3 should read *trans*-1,4;5,8-naphthodioxane.

(6) K. Tsuda, N. Ikekawa, and S. Nozoe, *Chem. Pharm. Bull.* (Tokyo), **7**, 519 (1959).

TABLE I

SUMMARY OF PERTINENT N.M.R. SIGNALS[a]

Compound	-O-CH₂-CH₂-O-			Single protons			CH₃	
(number)	C-3	20	21	4	5	21	18	19
Ib	6.00		6.06		4.65	5.04	9.35	8.79
IIa			6.02	4.31		5.10	9.33	8.58
Ia	6.06	5.91[b]	6.06		4.71	5.17	9.28	8.79
IIb		6.02[b]	6.14[b]	4.25		5.25	9.21	8.57
Ic	6.05	5.88[b]	6.05		4.79	5.12	8.99	8.71
IIc		5.78[b]	5.95[b]	4.23		4.98	8.96	8.55

[a] Values are in τ units. [b] Broad, partially resolved resonance overlapping with the neighboring one. The values quoted are the centers of the signals when not obscured by the C-3 ketals.

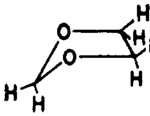
refluxed with ethylmethyldioxolane[7] in presence of *p*-toluenesulfonic acid, Ib was obtained. Mild treatment of Ib with dilute aqueous acetic acid[3,8] gave IIa. The spectroscopic and analytical results were consistent with the assigned structures Ib and IIa. The n.m.r. spectrum of Ib had two signals for single protons at 4.65 and 5.04 τ. Since C-6 protons on Δ^5 double bonds give resonance in the 4.6–4.8-τ region, the 5.04 τ signal must be assigned to the C-21 proton. In addition, there were two narrow signals, each equivalent to four hydrogens, at 6.00 and 6.06 τ. The spectrum of IIa had resonance for single protons at 4.31 and 5.10 τ. The resonance at 4.31 τ obviously arose from the C-4 proton of the 4-en-3-one, and the signal at 5.1 τ was the result of the C-21 hydrogen. The narrow resonance equivalent to four protons, at 6.02 τ was assigned to the –O–CH₂–CH₂–O– moiety at C-21. It seems very likely that the 6.06-τ signal in Ib arose from the C-21 dioxolane group.

Attempts were then made to convert Ib to the 3,20,21-trisethylenedioxide (Ia). When Ib was heated at reflux for 72 hr. in a mixture of benzene, ethylene glycol, and *p*-toluenesulfonic acid and the generated water was removed efficiently, Ia was obtained. The triketal (Ia) on brief treatment with warm aqueous acetic acid gave IIb. Reduction of Ib with lithium aluminum hydride gave the 11β-hydroxytrisethylene dioxide (Ic), which on acid hydrolysis gave IIc. The compounds Ia, IIb, Ic, and IIc were identical with those previously described.[3] Though the presented evidence is consistent with the assigned structures, it should be kept in mind that the *possibility of certain structural rearrangements or fragmentations* initiated by an attack on the heterocyclic moieties during the acid-catalyzed ketalization of Ib cannot be excluded with certainty.

Certain pertinent n.m.r. signals are summarized in Table I. In agreement with previous results, single protons on a carbon bearing two oxygens in a five-membered ring gave signals at 5.0–5.2 τ. The –O–CH₂–CH₂–O– moieties of the C-3 ketals again gave narrow, unsplit resonance at about 6.0 τ, as did the C-21 ketals in the absence of C-20 ketal (Ib, IIa). However, when ketals were present at both C-20 and C-21 (Ia, IIb, Ic, IIc), the signals for these –O–CH₂–CH₂–O– moieties were split into a characteristic multiplet.[3] While the observation was briefly mentioned in the previous communication, the resolution then obtained was not sufficient to clearly discern the multiplicity of the splitting. In the present case it appears that the signals for the C-20 and C-21 ketals consist of two overlapping quartets, centered at about 5.78 and 5.95 for IIc and 6.02 and 6.14 τ for IIb. The high-field quartet probably arises from the C-21 ketal. Both of the ketal systems can be described as A_2B_2 types to a first approximation and, as such, certainly contain more than four lines.[9] Hence, the coupling constants for the –O–CH₂–CH₂–O– protons cannot be readily derived from the spectrum. In Ia and Ic the signal from the C-3 ketal partially obscures that from the C-21 ketal.

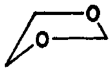
The presence or absence of splitting of the resonance arising from the –O–CH₂–CH₂–O– protons of dioxolane or its derivatives may be rationalized as follows. It is well-documented that five-membered rings exist in puckered conformations where one of the ring atoms is situated outside of the plane of the remaining four.[10] The successive out-of-plane movement of atoms in cyclic compounds is supposed to be transmitted around the ring in a wave-like motion.[11] For the sake of brevity, we shall refer to this motion, in pentacyclic systems, as inversion of the puckered forms.

A fair amount of ring flexibility was observed by the inspection of models of dioxolanes and substituted dioxolanes. There is reason to believe that such molecules will "invert" in a manner similar to cyclopentane unless conditions within the molecules would prevent it. If this assumption is allowed, five conformers can be visualized for dioxolane (IV–VIII). However, only three of these are different from the viewpoint of n.m.r., since the pairs V and VIII, and VI and VII are optical isomers not distinguishable by n.m.r. method.

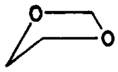


IV

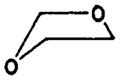
V



VI



VII



VIII

In any given conformation of dioxolane, the protons of the –O–CH₂–CH₂–O– moiety are not equivalent, and hence, a complex pattern would be expected for their resonance. However, dioxolane does not exhibit signal splitting for these protons, although coupling between the protons does exist.[12] It seems reasonable that the chemical shifts average to zero as a result of inversions between the puckered forms. In the case of simple C-2 substituted dioxolanes, whose spectra we

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[7] H. J. Dauben, Jr., G. Loken, and H. J. Ringold, *J. Am. Chem. Soc.*, **76**, 1359 (1954).

[8] R. Antonuci, S. Bernstein, M. Heller, R. Lenhard, R. Littell, and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953).

[9] K. B. Wiberg and B. J. Nist, "The Interpretation of NMR Spectra," W. A. Benjamin, Inc., New York, N. Y., 1962, p. 309.

[10] J. E. Kilpatrick, K. S. Pitzer, and R. Spitzer, *J. Am. Chem. Soc.*, **69**, 2483 (1947).

[11] M. Löw, *Acta Chim. Acad. Sci. Hung.*, **25**, 425 (1960).

[12] R. V. Lemieux, J. D. Stevens, and R. R. Fraser, *Can. J. Chem.*, **40**, 1955 (1962).

have investigated,[4] the signals for the $-O-CH_2-CH_2-O-$ protons appeared either unsplit or split very little.

Let us now consider the steroidal C-21 ketal (IIa). Surveying the molecule from the dioxolane plane indicates that the protons of the $-O-CH_2-CH_2-O-$ portion are oriented either towards or away from the attached steroidal moiety. The effect of a steroidal or any other substituent on these two types of protons is not predictable *a priori.* It is conceivable that inversions of the heterocyclic ring may give an averaging to zero of the chemical shifts. However, unless all protons in question are equivalent in a static sense or on a time average basis, the signal must be split.

Thus present observations that IIa and Ib give an unsplit signal could be interpreted in either of two ways: (a) the dioxolane rings exist in a rigid form in which all of the $-O-CH_2-CH_2-O-$ protons are magnetically equivalent, or (b) the dioxolane rings are rapidly inverting between the possible conformations, and the chemical shifts of the protons in question average out. Of the two alternatives, the latter seems much more likely, especially in view of the observed flexibility on models. In the case of the 2,2′-bis-1,3-dioxolane[4] and analogs Ia, IIa, Ic, and IIc, splitting of the resonance for the $-O-CH_2-CH_2-O-$ protons is seen. This definitely implies a difference in the chemical shifts of the various protons of these moieties. A complex pattern would thus be expected whether the dioxolane rings were inverting or remaining rigid. We believe that the results are better interpreted by assuming that in systems in which two dioxolane moieties are attached to neighboring carbons, the inversion of the heterocyclic rings is restricted. This viewpoint is also consistent with the second mode (b) of interpretation for the spectra of IIa and Ib.

In the course of the previously reported studies on the n.m.r. spectra of substituted 1,4-dioxanes, conformations for *cis-* and *trans*-2,3-diphenyl-1,4-dioxane and 2,3-dichloro-1,4-dioxane were suggested.[4] *For the interpretation of the spectra, and hence the conformations, we have accepted the configurational assignments published in the literature for the cis and trans isomers.*[13,14] We recently had an opportunity to rerun the n.m.r. spectra of *cis-* and *trans*-2,3-diphenyl-1,4-dioxanes and found an error in the reported[4] chemical shifts for the *trans* isomer. The corrected shifts are 5.59 τ (unsplit signal) for C-2,3 protons and 6.03 τ (unsplit signal) for C-5,6 protons and not as previously reported, 5.22 and 5.58 τ, respectively. The correction for the chemical shift for the C-2,3 protons in the *trans* isomer does not alter the conformational argument, provided the configurations were correctly assigned, since the resonance (5.59 τ) is unsplit and remains at higher field than the corresponding resonance (4.88 τ) in the *cis* isomer.

Experimental[15]

Pregn-5-ene-11,20-dione-3,21-bisethylene Dioxide (Ib).—A mixture of cortisone (2 g.), methylethyldioxolane (25 ml.), dioxane (25 ml.), and *p*-toluenesulfonic acid monohydrate (50 mg.) was refluxed for 5 hr. The volatile components were removed in a stream of nitrogen, and the residue was treated with a solution of sodium hydrogen carbonate (90 mg.) in water (15 ml.). The steroids were recovered with benzene, washed with water, dried over sodium sulfate, and concentrated to a residue. The residue was crystallized from ethyl acetate to yield Ib (900 mg.).

A sample was recrystallized several times from ethyl acetate and showed m.p. 148–151°; $\lambda_{\max}$ no specific absorption in the 220–240-mμ region; $\lambda_{\max}^{\text{KBr}}$ 1725, 1700, 1660, 1095 cm.$^{-1}$; n.m.r. spectrum, 4.65, 5.04, 6.00, 6.06, 8.79, and 9.35 τ.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.63; H, 7.89.

Pregn-4-ene-3,11,20-trione-21-ethylene Dioxide (IIa).—A solution of Ib (50 mg.) in aqueous acetic acid (1:1, 3 ml.) was heated at 60° for 30 min. The solution was rendered alkaline with aqueous sodium hydrogen carbonate, and the steroids were extracted with a mixture of methylene chloride–ether (1:3). After washing and drying the extract, the solvents were removed to yield IIa (45 mg.).

A sample was recrystallized from ethyl acetate and showed m.p. 135–140°; $\lambda_{\max}^{\text{MeOH}}$ 238 mμ (ϵ 14,000); $\nu_{\max}^{\text{KBr}}$ 1720, 1700, 1665, 1610, 1080 cm.$^{-1}$; n.m.r. spectrum, 4.31, 5.10, 6.02, 8.58, and 9.33 τ.

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.12; H, 7.84.

Pregn-5-en-11-one-3,20,21-trisethylene Dioxide (Ia).—A mixture of the diketal (Ib, 180 mg.), benzene (100 ml.), ethylene glycol (5 ml.), and *p*-toluenesulfonic acid monohydrate (100 mg.) was refluxed for 72 hr. under a Dean–Stark separator. A funnel was inserted in the separator, and the condensed vapors had to reach the bottom of the adapter prior to returning to the reaction vessel. Solid potassium carbonate was added, then the mixture was diluted with water, and the steroids were recovered with a mixture of benzene–ether (1:1). Following the usual processing a sirup (200 mg.) was obtained. The residue was crystallized from ethyl acetate to yield Ia (170 mg.).

A sample was recrystallized several times from ethyl acetate and showed m.p. 160–162°. The infrared spectrum of the product was indistinguishable from that previously obtained[3]; n.m.r. spectrum, 4.71, 5.17, 5.91 (multiplet), 6.06 (multiplet), 8.79, and 9.28 τ.

Pregn-4-ene-3,11-dione-20,21-bisethylene Dioxide (IIb).—A portion of the triketal (Ia, 10 mg.) was dissolved in aqueous acetic acid (1:1, 2 ml.) and heated at 60° for 30 min. The infrared spectrum of the recovered IIb, m.p. 147–152°, was indistinguishable from that of the previously described sample; n.m.r. spectrum, 4.25, 5.25, 6.02 (multiplet), 6.14 (multiplet) 8.58, and 9.21 τ.

11β-Hydroxypregn-5-ene-3,20,21-trisethylene Dioxide (Ic).—A mixture of Ia (90 mg.), lithium aluminum hydride (340 mg.), dry tetrahydrofuran (25 ml.), and dry ether (25 ml.) was refluxed for 24 hr. After the conventional work-up, crystalline Ic was obtained.

A sample was recrystallized from ethyl acetate and showed m.p. 120–122°; $\nu_{\max}^{\text{KBr}}$ 3575, 1090, 1035 cm.$^{-1}$; n.m.r. spectrum, 4.79, 5.12, 5.88 (multiplet), 6.05 (multiplet) 8.71, and 8.99 τ.

Anal. Calcd. for $C_{21}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 67.92; H, 8.23.

The sample was identical with that previously described.

11β-Hydroxypregn-4-en-3-one-20,21-bisethylene Dioxide (IIc).—A solution of Ic (50 mg.), in aqueous acetic acid (1:1, 3 ml.) was heated for 30 min. at 60°. The volatile components were removed in a stream of nitrogen, and the resulting syrup was chromatographed on t.l.c. (silica gel) using chloroform for development. The major zone was eluted with chloroform to yield IIc. The product was crystallized from ethyl acetate. Its infrared spectrum was identical with that previously described[3]; n.m.r. spectrum, 4.23, 4.98, 5.58 (11α H), 5.78 (multiplet), 5.95 (multiplet), 8.55, and 8.96 τ.

Acknowledgment.—We thank Dr. J. Elks and Dr. A. G. Long of the Glaxo Research Ltd. Greenford, Middlesex, England, for stimulating discussion of the results.

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(13) R. K. Summerbell and D. R. Bergen, *J. Am. Chem. Soc.*, **81**, 633 (1959). The identity of *cis-* and *trans*-2,3-diphenyl-1,4-dioxane with the samples from the collection of the late Professor Summerbell was established by comparison of infrared spectra and mixture melting point. We thank Professor A. S. Hussey for kindly supplying the authentic samples.

(14) We thank Professor N. Allinger, Wayne State University, for independently raising the question of steric assignment in a private communication.

(15) Melting points were taken on a micro hot stage and are corrected. Ultraviolet spectra were taken in methanol with a Cary 11 MS spectrophotometer. Infrared spectra were taken on solids incorporated in potassium bromide blotters with an Infracord 237 spectrometer. N.m.r. spectra were taken in deuteriochloroform as previously described.[3]