column) showed two peaks in the ratio 80:20. This mixture was separated by preparative TLC (silica gel, hexane) to give 3-butyl-3,7-dimethyl-1,6-octadiene as the major product and (6*E*)-2,6-dimethyl-2,6-dodecadiene. The latter product [bp 65 °C (0.1 mm)] had IR and H^1NMR data identical with those reported by Normant.[6]

Acknowledgment. This research was supported by grants from the Ministry of Education, and National Research Council of Italy.

Registry No. 2a, 73969-14-9; **2b**, 72737-52-1; **2b**·CuBr, 82434-18-2; (*E*)-**2c**, 82679-45-6; (*Z*)-**2c**, 82679-48-9; (*Z*)-**2c**·CuBr, 82434-17-1; **2d**, 82679-46-7; *n*-C_4H_9MgBr, 693-03-8; $PhCH_2MgCl$, 6921-34-2; $ClMgOCH_2(CH_2)_2CH_2MgBr$, 82679-47-8; *n*-$C_8H_{17}MgBr$, 17049-49-9; CuBr, 7787-70-4; 3-butyl-3,7-dimethyl-1,6-octadiene, 69747-29-1; *trans*-3-nonene, 20063-92-7; *trans*-1-phenyl-3-hexene, 60669-38-7; *trans*-6-nonen-1-ol, 31502-19-9; 4-phenyl-3-methyl-1-butene, 1647-06-9; 3-methyl-1-undecene, 18435-37-5.

Favorsky Rearrangements of α-Halogenated Acetylcycloalkanes.[1-3] 3

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The rearrangement of 21-bromopregnenolone acetate with sodium methoxide in dimethoxyethane leads to an epimeric mixture of 17-methylated etio esters in which the 17α-methyl derivative prevails, in contradistinction to the rearrangement under identical conditions of 17-bromopregnenolone acetate which affords predominantly the 17β-methyl 17α-etio ester. This excludes the possibility that in *every* cyclopropanonic Favorsky rearrangement a dipolar species is formed as the primary *intermediate* from the originally produced enolate ion. All the results of cyclopropanonic Favorsky rearrangements may be explained by the assumption of a competition between a concerted and a nonconcerted cyclopropanone formation, the protic and polar character of the medium exerting an important influence on the concertedness and the nonconcertedness of the mechanism. As a possible alternative, a gradient of mechanisms could be considered. The competition between reactions leading to rearrangement and substitution products and the dependence of their relative importance on the medium are also discussed.

Some years ago we suggested [1,6,7] that the complex stereochemical results of Favorsky rearrangements of α-halogenated acetylcycloalkanes, in particular of α-halogenated 20-keto steroids, in which cyclopropanones are considered to be intermediates, can be explained by the assumption that two mechanistic pathways may be operative, in some cases simultaneously: one, corresponding to a "Loftfield-type" mechanism,[8] in which the initially formed enolate is converted directly, concertedly, and stereospecifically to a cyclopropanone which is then opened to rearrangement products with a unique stereochemistry at the originally halogenated carbon atom (cf. pathway *a* in Scheme I) and another one, corresponding to a "Dewar-type" mechanism,[9] in which the enolate is first transformed into a dipolar intermediate which may lead to two epimeric cyclopropanones which are opened to epimeric rearrangement products (pathway b in Scheme I).[10] We further suggested that a polar and protic medium would favor the formation of a dipolar intermediate (cf. **3**) and a nonprotic and mildly polar medium a "concerted" ring closure[11] and that, in the case of the nonconcerted pathway, steric factors could result in a marked stereoselectivity of the conversion of the dipolar intermediate to one of the epimeric cyclopropanones and thus result in a stereoselective formation of rearrangement products with one of the two possible configurations.[15]

We have already presented arguments[1] against suggestions[16,17] that in *all* cyclopropanonic Favorsky rearrangements the cyclopropanones had to be formed in a concerted fashion. Certain authors, in particular Bordwell and his collaborators,[18] suggested for *all* cyclopropanonic Favorsky rearrangements a nonconcerted pathway, implying the formation, prior to the cyclopropanone cyclization, of a dipolar intermediate or, at least, a dipolar ion-like transition state.[18a,c,19,20] We relate here the results of the rearrangement of 21-bromopregnenolone acetate (**10a**) with

(1) Part 2: Engel, Ch. R.; Roy, S. K.; Capitaine, J.; Bilodeau, J.; McPherson-Foucar, C.; Lachance, P. *Can. J. Chem.* **1970**, *48*, 361.

(2) This publication represents paper 49 in our series on "Steroids and Related Products". Paper 48: Engel, Ch. R.; Lourdusamy, M. M.; Mukherjee, D.; Le-Van, Chau, *Pol. J. Chem.*, in press.

(3) Reported in part at the 46th Congress of the French-Canadian Association for the Advancement of Sciences (ACFAS), Ottawa, May 1978, and contained in part in a paper presented to the 28th Congress of the International Union of Pure and Applied Chemistry, Vancouver, Aug 1981.

(4) Abbreviated from part of the doctoral thesis of Y.M., Université Laval, Quebec, Canada, 1976.

(5) Abbreviated in part from the M.Sc. thesis of J. C., Université Laval, Quebec, Quebec, Canada, 1973.

(6) Engel, Ch. R.; Roy, S. K.; Bilodeau, J.; Lachance, P. "Abstracts of Papers", 19th International Congress of Pure and Applied Chemistry, London, 1963; Section A, pp 53–54.

(7) Engel, Ch. R. *Chimia*, **1965**, *19*, 507.

(8) Loftfield, R. B. *J. Am. Chem. Soc.* **1951**, *73*, 4707.

(9) Burr, J. C.; Dewar, M. J. S. *J. Chem. Soc.* **1954**, 1201.

(10) For reasons of simplicity, we have depicted in Scheme I only rearrangement products arising from the principal mode of opening of the cyclopropanone rings.

(11) Similar suggestions have been made by House and Gilmore[12] and, subsequently to our preliminary reports,[6,7] by Tchoubar and co-workers.[13,14]

(12) House, H. O.; Gilmore, F. *J. Am. Chem. Soc.* **1961**, *83*, 3980.

(13) Gaudemar, A.; Parello, J.; Skrobek, A.; Tchoubar, B. *Bull. Soc. Chim. Fr.* **1965**, 2405.

(14) Skrobek, A.; Tchoubar, B. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1966**, *263*, 80.

(15) For an added verification of this hypothesis, cf. a subsequent paper of this series.

(16) Smissman, E. E.; Lemke, T. L.; Kristiansen, O. *J. Am. Chem. Soc.* **1966**, *88*, 334.

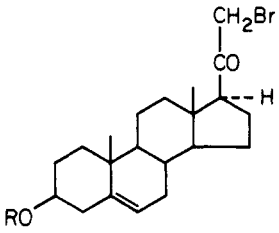
(17) House, H. O.; Frank, G. A. *J. Org. Chem.* **1965**, *30*, 2948.

(18) (a) Bordwell, F. G.; Scamehorn, R. G. *J. Am. Chem. Soc.* **1971**, *93*, 3410. (b) Bordwell, F. G.; Strong, J. C. *J. Org. Chem.* **1973**, *38*, 579. (c) Cf. also: Bordwell, F. G.; Carlson, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 3370.

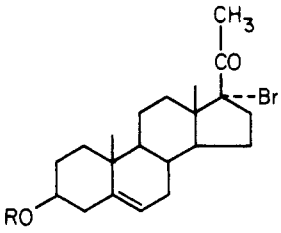
(19) (a) Bordwell, F. G.; Scamehorn, R. G. *ibid.* **1968**, *90*, 6751. (b) Bordwell, F. G.; Scamehorn, R. G.; Springer, W. R. *ibid.* **1969**, *91*, 2087. (c) Cf. also: Bordwell, F. G.; Frame, R. R.; Scamehorn, R. G.; Strong, J. C.; Meyerson, S. *Ibid.* **1967**, *89*, 6704. (d) Bordwell, F. G.; Almy, J. *J. Org. Chem.* **1973**, *38*, 575.

(20) Cf. also: Hunter, D. H.; Stothers, J. B.; Warnhoff, E. W. In "Rearrangements in Ground and Excited States"; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. I, pp 391 ff.

0022-3263/82/1947-4485$01.25/0



10 , R = H
10a , R = Ac



11 , R = H
11a , R = Ac

sodium methoxide in absolute dimethoxyethane which, in conjunction with those of the rearrangement with the same reagents, under identical conditions, of 17-bromopregnenolone acetate (**11a**) and of other rearrangements of α-halogenated 20-keto steroids,[1] show that the hypothesis postulating for *all* such rearrangements the intervention of a true dipolar *intermediate* is not tenable.

The rearrangement of analytically pure 21-bromo-3β-acetoxy-5-pregnen-20-one (21-bromopregnenolone acetate, **10a**) with sodium methoxide in absolute dimethoxyethane was carried out exactly as described for 17-bromo-3β-acetoxy-5-pregnen-20-one (**11a**).[1] The neutral and acid components of the reaction product were separated, the neutral fraction was reacetylated, and the acid fraction methylated and acetylated. The complex mixtures were separated primarily by preparative thin-layer chromatography by using the continuous elution technique.[21] The results are summarized in Scheme II.

We isolated from the acetylated neutral fraction the epimeric Favorsky rearrangement products methyl 3β-acetoxy-17α-methyl-5-etienate (**12b**) and methyl 3β-acetoxy-17β-methyl-17α-eti-5-enate (**13b**), the substitution products 3β,21-diacetoxy-5-pregnen-20-one (**14a**) and 3β-acetoxy-21-methoxy-5-pregnen-20-one (**15a**), and the products of oxidative degradation methyl 3β-acetoxy-5-etienate (**16b**) and methyl 3β-acetoxy-7-oxo-5-etienate (**17b**). From the methylated and acetylated acid fraction the 17α-methyletienate **12b** and the acetoxyetienate **16b** were separated. The structures of these products were confirmed by infrared, NMR, and combustion analyses (cf. Experimental Section), and those of the known products were also confirmed by comparison with authentic samples or with values reported in the literature. The quantitative yields of these products were determined gas chromatographically,[22] separately for the acetylated neutral fraction and for the far less abundant methylated and acetylated acid fraction of the original reaction product.[23] Together, these two fractions contained 3.8% of the 17α-methyl Favorsky ester **12b**, 2.4% of the 17β-methyl Favorsky ester **13b**, 10.7% of 3β,21-diacetoxy-5-pregnen-20-one (**14a**), 3.4% of 3β-acetoxy-21-methoxy-5-pregnen-20-one (**15a**), 11.3% of methyl 3β-acetoxy-5-etienate (**16b**), and small amounts of methyl 3β-acetoxy-7-oxo-5-etienate (**17b**).

Discussion

Origin of the Etienates 16b and 17b. We suggest that the etienic esters **16a** and **17a**, isolated as the acetates **16b** and **17b**, or the corresponding acids **16** and **17**, originate from one of the substitution products, the 21-hydroxy 20-ketone **14**. It is well-known that 21-hydroxy 20-ketones are labile in basic media, in the presence of oxygen,[24] and that they are degraded under such conditions to etianic acids.[25] The majority of ester **16b** indeed originates from the acid fraction (cf. Experimental Section).[26] The formation of 5-unsaturated 7-ketones (cf. **17**, **17a**, and **17b**) from 5-olefinic 7-unsubstituted steroids, in the presence of oxygen in a basic medium is not surprising.[27]

Stereochemistry and Mechanism of the Rearrangement. The here-described results, in conjunction with those previously obtained,[1] clearly rule out that in *each* cyclopropanonic Favorsky rearrangement a true dipolar *intermediate* is formed prior to the cyclopropanone(s). Indeed, an identical dipolar intermediate would have to be formed from the two α-halogenated ketones, isomeric with respect to the position of the halogen substituent (cf. sequences **1** → **2** → **3** and **5** → **4** → **3**, in Scheme I). Thus, from 21-bromopregnenolone acetate (**10a**) and from 17-bromopregnenolone acetate (**11a**) there should be obtained, with the same reagents under identical conditions, the same mixture of rearrangement products. This is essentially true (cf. Table I) when the reaction is carried out in the highly protic and polar medium bicarbonate–methanol–water, which should indeed favor the formation of a dipolar intermediate,[1] but diametrically opposed stereochemical results were now obtained upon rearrangement in the aprotic medium sodium methoxide–dimethoxyethane, the ratio of 17α-methylated and 17β-methylated etio acid derivatives amounting to 1:19 in the case of the 17-bromide **11a**[1] and to 1.6:1 in the case of the 21-bromo ketone **10a**.[28]

The discrepancy of the results in different media is, however, compatible with the assumption[1,6,7,12-14] that the reaction in an aprotic and mildly polar medium is concerted, that in a protic and polar medium a delocalized intermediate is involved, and that in media of intermediate protonocity and polarity a concerted and nonconcerted pathway may be operative simultaneously. We have clearly shown[1] that this assumption is born out by the results of the rearrangement in various media of 17α-brominated 21-methyl 20-ketones. Together with previously reported findings,[1,29,30] the here-reported results confirm that this is likewise true in the case of the rearrangement of 21-halogenated 20-keto steroids.[31] Results

(21) Cf.: Randerath, K. "Thin-layer Chromatography"; Academic Press: New York, 1966; pp 51–52.

(22) We sincerely thank Professor G. Just, McGill University, Montreal, for kindly putting his facilities and advice at our disposal for the gas chromatographic determinations.

(23) The crude mixtures also contained other products which could not be obtained in the pure state but none of which represented Favorsky rearrangement products.

(24) Blomeyer, F. In Lettré, H.; Inhoffen, H.; Tschesche, R. "Über Sterine, Gallensäuren und verwandte Naturstoffe"; Ferdinand Enke Verlag: Stuttgart, 1959; Vol. II, p 278.

(25) Cf.: (a) Barton, D. H. R.; Holness, N. J.; Klyne, W. *J. Chem. Soc.* **1949**, 2456. (b) Engel, Ch. R. D.Sc. Thesis, Swiss Federal Institute of Technology, Zurich, **1951**, pp 28, 55.

(26) The recuperation of relatively small amounts of esters **16b** and **17b** from the acetylated neutral fraction may be explained by the consideration that in the presence of methoxide, methyl esters of type **16a** and **17a** may be formed directly from aldehydo ketones, primary oxidation products.

(27) Cf.: (a) Wintersteiner, O.; Bergström, S. *J. Biol. Chem.* **1941**, *137*, 785. (b) Bergström, S.; Wintersteiner, O. *Ibid.* **1941**, *143*, 597. (c) Bergström, S.; Wintersteiner, O. *Ibid.* **1942**, *143*, 503.

(28) In Table I we also included the results of the rearrangement of the isomeric α-halogenated 20-ketones **10** and **11** in a medium of intermediate polarity and protonicity: potassium methoxide–methanol. As can be seen, a small difference in the ratio of the two isomeric rearrangement esters is observed upon the reaction of the 17-bromide (**11a**) and the 21-halide (**10**). This difference, less apparent in our previous publication[1] in which the results with 21-halides[29] had been rounded up, is small but probably significant, because it corresponds to the results of several experiments.

(29) (a) Heusser, H.; Engel, Ch. R.; Plattner, Pl. A. *Helv. Chim. Acta* **1950**, *33*, 2237. (b) Engel, Ch. R. D.Sc. Thesis, Swiss Federal Institute of Technology, Zurich, 1951, pp 16, 17, 39–41.

(30) Personal communication of Dr. N. L. Wendler from the Merck Sharp & Dohme Laboratories, Rahway, NJ, quoted in ref 1.

Table I. Proportions of 17α- and 17β-Methyl Etio Acid Derivatives Formed in Favorsky Rearrangements of α-Halogenated 3β-Acetoxy- and 3β-Hydroxy-5-pregnen-20-ones in Relation to the Position of the Halogen Substituent and the Medium

halide	medium	proportion of 17α-methyl and 17β-methyl etio acid derivatives	ref[a]
17α-bromide (11a)	$KHCO_3$, CH_3OH, H_2O	23:1	1
21-bromide (10a)		1:~0	1
17α-bromide (11a)	$KOCH_3$, CH_3OH	1.8:1	1
21-halide[b] (10)		2.5:1	29
17α-bromide (11a)	$NaOCH_3$, $CH_3OCH_2CH_2OCH_3$	1:19	1
21-bromide (10a)		1.6:1	E

[a] The letter "E" refers to experiments described in the Experimental Section of this paper. [b] Bromide or chloride.

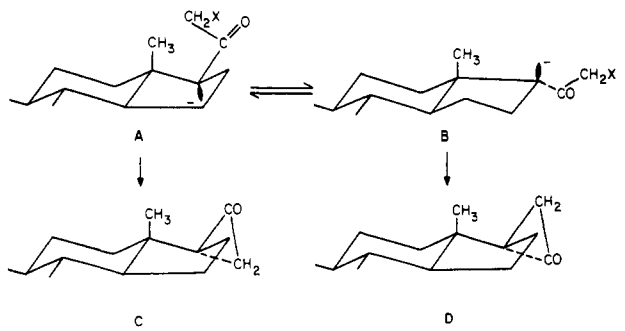
of rearrangements of other α-halogenated acetylcycloalkane[12-14] are also in agreement with this hypothesis.

In a review article,[20] Hunter et al., developing a hypothesis already taken into consideration by Bordwell,[19a,b,32] pointed out that the stereoelectronic objections to a concerted S_N2 cyclization of the halogenated enolate ion to a cyclopropanone can be avoided if one assumes that in an aprotic and nonpolar medium the "disrotatory closure of the developing oxyallyl (dipolar intermediate) commences before the bond to the leaving (halogen) group is completely broken". The stereochemical spectrum of Favorsky rearrangements of α-halogenated 20-keto steroids could thus be explained by the assumption of a competition between such a reaction, *stereochemically* equivalent to an S_N2 displacement, and a reaction involving the intervention of a true dipolar *intermediate*, one of the determining factors influencing the choice between these mechanisms, or the preponderance of one of them, being again the polarity and protonicity of the medium. One could possibly also consider, alternatively, gradients of mechanisms corresponding to the degree to which the departure of the halogen substituent is effectively completed at the onset of the disrotatory ring closure.[33]

Origin of the Substitution Products. In agreement with the generally accepted view,[1,16,17,19b,d,20,34,35] substantiated by new findings of our laboratory,[36] we suggest that the 21-hydroxy 20-ketone **14** and, indirectly, its degradation products **16** and **17** are essentially formed via an alkoxy epoxide (cf. Scheme III).[37]

The formation in not negligible amounts of the methoxy ketone **15** is of interest, since Bordwell and Carlson[38] have stated that "α-alkoxy ketone byproducts have seldom, if ever, been observed in Favorsky rearrangements of primary α-halo ketones". On the other hand, in agreement with Bordwell and Carlson,[38] who expressed the opinion that in aprotic media α-alkoxy ketone byproducts of Favorsky

(31) We have explained[1] the predominant formation of 17α-methylated etio acid derivatives upon rearrangement of both 17- and 21-halogenated 20-keto steroids in the presence of the 18-methyl group in polar and protic media by the stereoselective transformation of the dipolar intermediate into the cyclopropanone whose methylene group has the α configuration. The almost exclusive formation of 17β-methyl 17α-etio acid derivatives upon the rearrangement of 17α-halogenated 20-ketones in mildly polar and aprotic media may be explained by a concerted cyclopropanone ring closure, involving inversion in position 17. Evidently, in the case of a 21-halogenated 20-ketone, whose 21-position is achiral, a concerted cyclopropanone formation cannot be expected to lead stereospecifically to a single epimer. One could now have considered the enolate ion, formed by abstraction of the α'-proton from a 21-halogenated 20-ketone, to have a "flat" geometry in positions 17–20 and thus to give rise stereoselectively, similarly to a dipolar intermediate, to a 17α-methylated etio acid derivative. We have tentatively taken into consideration[1] that the lack of marked stereoselectivity in a concerted cyclopropanone formation from such an enolate ion could be due to hindrance experienced by the 21-halogen ion, parting toward the β face of the molecule, this hindrance resulting in a diminution of the stereoselectivity of the formation of the cyclopropanone with an α configuration of its methylene group. However, as suggested to us by Dr. D. N. Kirk from the University of London, such a hindrance, which would be primarily exerted by the 18-methyl group, should not be appreciable. In agreement with Dr. Nguyen Trong Anh from the University of Paris-South, we now tentatively suggest that the lack of marked stereoselectivity of Favorsky rearrangements of 21-halogenated 20-keto steroids in aprotic and mildly polar media may be rationalized by the consideration that although the negative charge of enolate ions is strongest on the oxygen atom, they also have carbanionic character. It has indeed been suggested that if an α-halogenated enolate ion is converted to a cyclopropanone by a concerted reaction, a rehybridization toward an authentic carbanion had to occur.[19a] If one now considers limit structures A and B, it can be seen that in the latter (B), leading to the cyclopropanone with



a β configuration of its methylene group (D), the interaction between the angular 18-methyl group and the 21-CH_2X group is smaller than in the case of the former (A). This should partly counterbalance the greater stability of the cyclopropanone with an α configuration of its methylene group (derived from limit structure A). Thus, the relatively small stereoselectivity in favor of the 17α-methyl etio acid derivatives in the case of the here-described rearrangement would be explained, as well as the higher stereoselectivity in the more polar and more protic medium methoxide–methanol, in which part of the reaction would proceed *via* a dipolar intermediate and thus highly stereoselectively.

(32) Cf., however, ref 18a, wherein Bordwell et al. present arguments not favoring the hypothesis under discussion.

(33) A referee cautioned against this last hypothesis which we propose as an alternative to a competition between concerted and nonconcerted mechanisms, since it would "raise the vexed question of front-side displacement in S_N2-like reactions". However, if one accepts Professor Warnhoff's proposal, only the *stereochemistry* of certain cyclopropanonic Favorsky rearrangements would be S_N2-like. One could rather compare the rearrangements proceeding with inversion with those S_N1 displacements which also proceed with inversion and in which the stereochemical course of the reaction is explained by the close association of the ion pair formed by the cationic species and the leaving anion. In the case of a reaction in a more polar and more protic medium, the ion pair would be less strongly associated, but its anionic component could still be sufficiently close to disturb to some extent one of the two possible disrotatory ring closures. In the case of a highly protic medium, the leaving group would be completely removed, giving rise to a "free" dipolar intermediate, so that the ring closure could occur both ways, except if other steric factors are responsible for a marked stereoselectivity of the reaction.

(34) Bordwell, F. G.; Almy, J. *J. Org. Chem.* **1973**, *38*, 571.

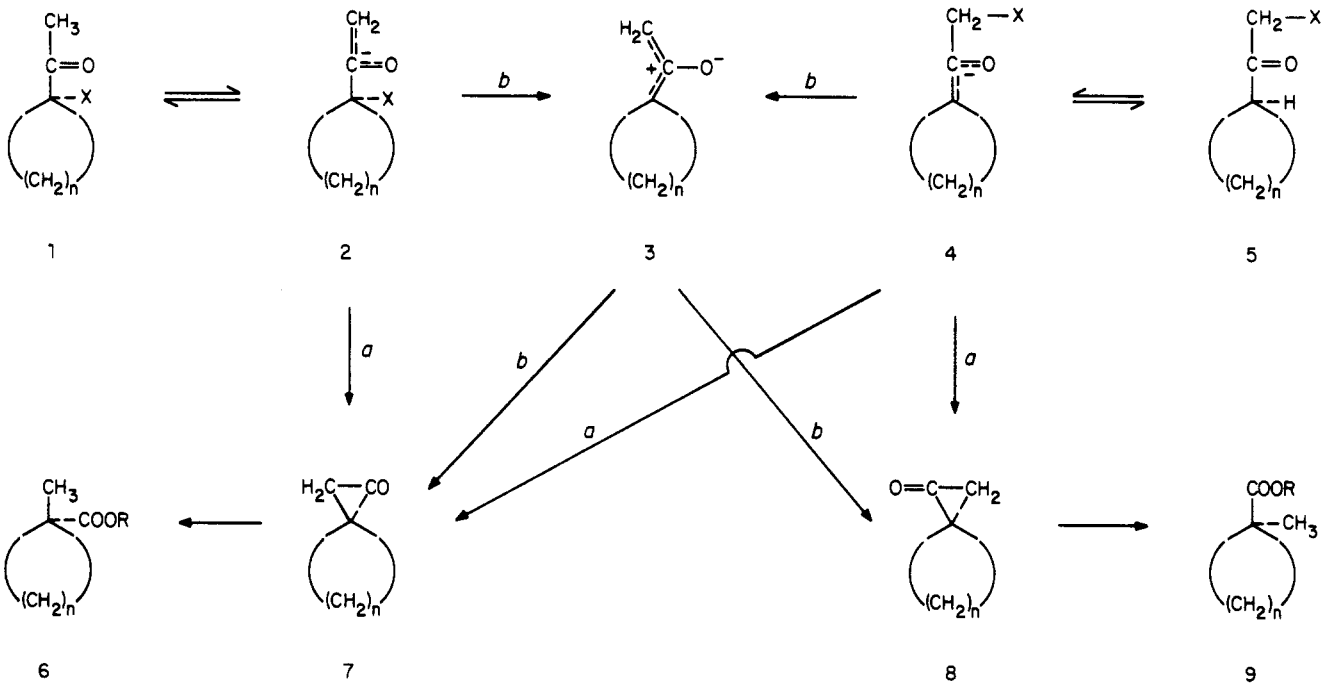
(35) Kende, A. S. *Org. React.* **1960**, *11*, 261 and literature quoted therein.

(36) Cf. the following paper of this series; submitted for publication in *J. Org. Chem.*

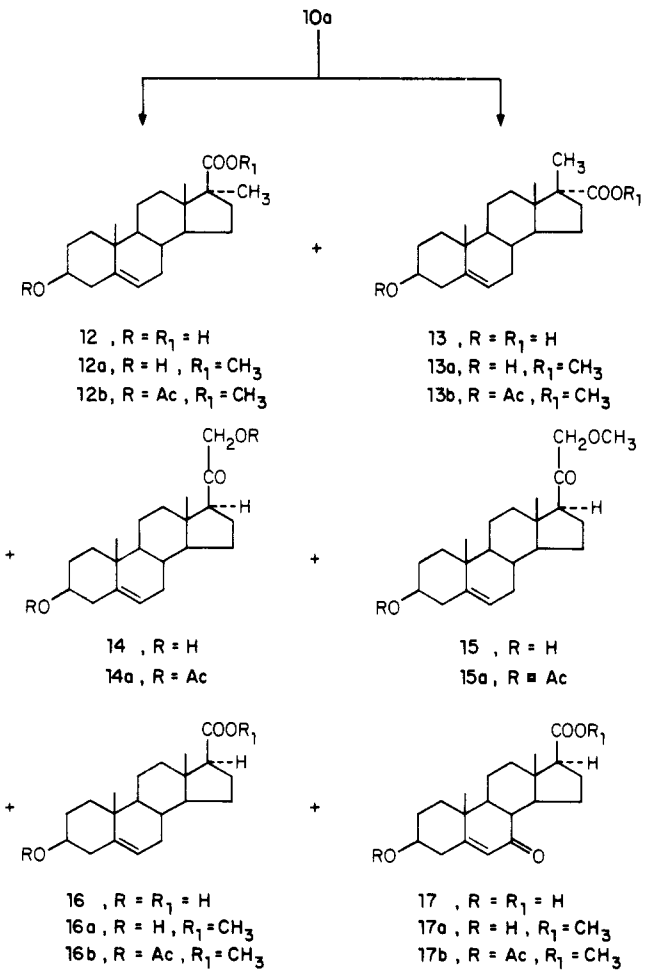
(37) Cf., however, also Bordwell and Carlson's suggestion[38] that they may arise from intermediate enol allylic halides.

(38) Bordwell, F. G.; Carlson, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 3377.

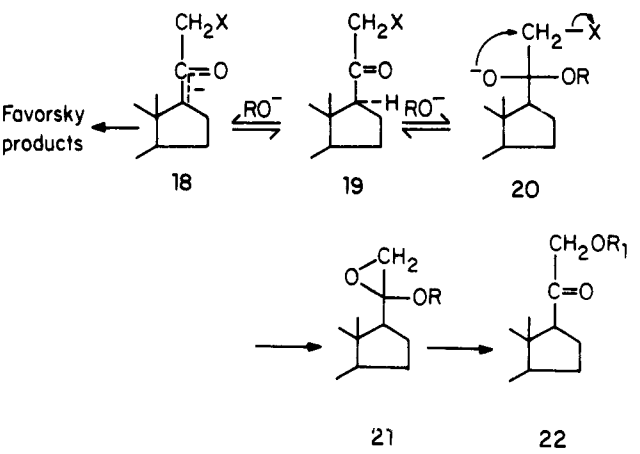
Scheme I



Scheme II



Scheme III



rearrangements are not formed by solvolysis of an intermediate enol allylic halide, we can indeed exclude such a pathway for our primary halo ketone, because in the same medium no 21-methoxy 20-ketone is formed from the isomeric 17-bromo 20-ketone **11a**.[1,39] An S_N2 mechanism, tentatively proposed by Bordwell and Carlson[38] for the formation of α-alkoxy ketones in aprotic media, cannot be ruled out for the formation of the 21-methoxy 20-ketone **15**, in spite of the general reservations toward such a pathway for reactions with alkoxy nucleophiles,[18c,38] but neither can a reaction involving an epoxy ether intermediate, because the main argument against such a mechanism, the formation in various instances of the same alkoxy ketone from positionally isomeric α-halo ketones, does clearly not apply to α-halogenated 20-keto steroids.[39]

Proportion of Rearrangement and Substitution Products. The high proportion of substitution products obtained in the here-described rearrangement in dimethoxyethane may seem surprising since in general their formation is favored in protic media,[41] as substantiated by the virtual absence of substitution products in the rearrangement of 21-halogenated 20-ketones with methoxide in absolute methanol,[29] in contradistinction to their rearrangement with bicarbonate in aqueous methanol.[1] Now,

(39) The only α-methoxy 20-ketone ever isolated (in 0.5–2% yield) from a 17-bromo 20-ketone has been a 17α-methoxy derivative.[40]

(40) Deghenghi, R.; Schilling, G.; Papineau-Couture, G. *Can J. Chem.* **1966**, *44*, 789.

(41) Compare, among many reports to this effect, ref 1, 17, and 19a.

in the aprotic solvent dimethoxyethane, the proportion of substitution products was even higher than in aqueous methanol (cf. Table I).

This result could be rationalized if one considered in its entirety the equilibrium which will establish itself when a 21-halogenated 20-ketone is treated with base *and the reactions which the species in equilibrium undergo* (cf. Scheme III, in which the competition between the formation of Favorsky products arising from cyclopropanones and of substitution products formed from epoxy ethers is considered). The halo ketone **19** is in equilibrium both with its enolate ion (**18**) which yields the Favorsky products and with the oxy anion (**20**), formed by attack of the carbonyl function and transformed into an epoxy ether (**21**) which, in turn, leads irreversibly to substitution products (cf. **22**). While in the equilibrium between the enolate ion **18** and the oxy anion **20** the former should indeed be favored in an aprotic and strongly basic medium and the latter in a less basic and protic medium, the final result of the reaction will also depend on the rate of the reactions of each of these intermediates. Thus, in the medium methoxide–dimethoxyethane the negatively charged oxygen atom of the oxy anion **20**, formed alongside the favored enolate **18**, is not solvated and will close fast to the epoxy ether **21**, contrary to the situation in a protic medium in which solvation should result in a slower epoxide formation. Therefore the epoxy ether formation can be favored in an aprotic medium in spite of the assistance of a protic medium in the breaking of the carbon–halogen bond. This can explain the formation of an appreciable proportion of substitution products in the reaction of halo ketone **10a** with methoxide in dimethoxyethane, although this medium favors the formation of an enolate of type **18**.[42] Conversely, in the medium bicarbonate–methanol–water the low rate of the reaction of the solvated oxy anion **20**, now favored in the original equilibrium, may result in the formation of appreciable amounts of rearrangement products. Finally, in the medium methoxide–absolute methanol, in which enolate **18** is favored and in which the competitively formed solvated oxy anion **20** reacts slowly, the almost exclusive formation of rearrangement products is plausible.

This explanation is not in contradiction to the observation that in the case of certain α-halogenated ketones in which the halogen atom is tertiary,[17] the proportion of Favorsky esters is favored in dimethoxyethane, contrary to the situation of a reaction in methanol. Indeed, the interplay of the reactions schematically depicted in Scheme III could be changed by the fact that an enolate forms more readily by abstraction of a proton from a methylene or methyl group than from a tertiary carbon atom. In the case of α-halogenated 20-keto steroids, the difference of the reactions involving on one hand the 21-methyl-halogenated 20-ketone (cf. **10**) and, on the other hand, the ketone with a tertiary 17-halogen substituent (cf. **11**) is particularly striking, not only because of the relative ease of the proton abstraction but also, and importantly, because in the case of the 17-halogenated 20-ketone the epoxy ether formation, competing with the enolate formation, is sterically impeded by the 18-methyl group, in contradistinction to the situation prevailing with a 21-halogenated 20-ketone.[1,36] One may indeed ascribe the practically complete absence of substitution products in the case of rearrangements of 17-brominated 20-ketones in all investigated media primarily to the steric hindrance exerted by the angular methyl group.[1,36]

(42) As pointed out above, an S_N2 mechanism for the formation of the 21-methoxy 20-ketone **15**, representing only 15% of the substitution products, cannot be ruled out. It is evident that for such a displacement reaction the medium methoxide–dimethoxyethane should be more favorable than a protic medium, so that the fact that such a product has not been isolated in reactions in protic media would be understandable.

Experimental Section

General Methods. The melting points were taken in evacuated capillaries, and the temperatures were corrected. For column chromatography, neutral aluminum oxide (Woelm, activity III) and Davison's silica gel 923 were used. Thin-layer chromatographies were performed with silica gel GF-254 (EM reagents). Gas chromatographic separations were performed in Professor G. Just's laboratory at McGill University with a Hewlett-Packard F&M Scientific instrument with an incorporated recorder, Model 5750. The separation of each of the identified components of the mixtures was obtained with 3% OV-17 as liquid phase on Chromosorb W in a glass column measuring 0.125 in. in diameter and 52 in. in length at 275 °C with a nitrogen flow of 2.0 cm s^{-1}. A flame-ionization detector was used. The injections of each isolated product and of each mixture were performed in triplicate. The identity of the peaks was established by the comparison of the retention times of the pure isolated product and of the various products contained in the mixtures. Quantitative analyses were performed by the comparison of the surfaces of the peaks of the mixtures, compared with those of known quantities of pure products. The surfaces were determined by weight and by triangulation.

Infrared spectra were recorded on Beckman IR 4 and IR 12 spectrophotometers and ultraviolet spectra on a Beckman DK-1A spectrophotometer. The NMR spectra were recorded at 60 MHz on a Varian A-60 spectrometer and at 90 MHz on a Bruker HX-90 spectrometer, tetramethylsilane serving as internal reference at 0 Hz.

The microanalyses were performed by the late Dr. F. Pascher, Bonn, Germany, and by Dr. G. Schilling, Ayerst Laboratories, Montreal. We pay tribute to Dr. Pascher and express sincere thanks to Dr. Schilling and his staff for their excellent cooperation.

Rearrangement of 21-Bromopregnenolone Acetate (10a). To a suspension of freshly prepared sodium methoxide, prepared from 1.48 g of sodium and absolute methanol, in 75 mL of absolute 1,2-dimethoxyethane there was added, with stirring, a solution of 6.75 g of analytically pure 21-bromo-3β-acetoxy-5-pregnen-20-one (**10a**,[1] mp 144.5–145 °C). The mixture was refluxed with stirring for 2 h and was subsequently precipitated in ice–water. The precipitate was extracted first with ether and then three times with a 7:3 ether–chloroform mixture, each extraction being repeated three times. The extracts were washed with 2 N sulfuric acid, with saturated sodium bicarbonate, and with distilled water, were dried with sodium sulfate, and were taken to dryness. All the fractions collected showed similar infrared spectra [ν_{max} (KBr) 3440, 1740–1735 (large), 1065–1060 cm^{-1}]. These fractions (totalling 4.72 g) represented the crude "neutral fraction". The remaining aqueous alkaline solution was acidified with 200 mL of 2 N sulfuric acid and extracted with chloroform. The organic solution was washed with water until neutral, was dried over sodium sulfate, and was taken to dryness, affording 380 mg of a semicrystalline product, representing the crude "acid fraction": IR (KBr) ν_{max} 3400, 3200 (very large), 1715 (large), 1055 cm^{-1}.

The four components of the neutral fraction (2.072 g, 1.514 g, 683 mg, and 450 mg) were acetylated separately with acetic anhydride (2, 2, 1.5, and 1 mL, respectively) in pyridine (6, 6, 4.5, and 3 mL, respectively) at room temperature for 15 h. Excess acetic anhydride was destroyed with methanol and each fraction was extracted with ether, the ethereal layer being washed with water, an iced hydrochloric acid solution, an iced sodium bicarbonate solution, and again with water. Evaporation of the solvents (after drying over Na_2SO_4) gave 2.267 g, 1.55 g, 693 mg, and 461 mg of amorphous "acetylated neutral fractions", with similar infrared spectra [ν_{max} (KBr) 1740, 1250 cm^{-1}]. The acid fraction was dissolved in 30 mL of absolute methanol and 30 mL of absolute ether and treated, with stirring at 0 °C, with 52 mL of a 3.2% ethereal diazomethane solution. The product was allowed to reach room temperature where it was maintained for 2 h, the solvents were removed, and the residue was taken up in benzene and filtered. The filtrate was taken to dryness and the residue [452 mg; IR (KBr) ν_{max} 3400, 1740, 1060 cm^{-1}] was treated

with 2 mL of acetic anhydride in 6 mL of pyridine for 16 h. The usual workup gave 413 mg of a yellow oil [IR (KBr) ν_{max} 1740, 1250 cm^{-1}], representing the "methylated acetylated acid fraction".

Isolation of Methyl 3β-Acetoxy-17α-methyl-5-etienate (12b) and of Methyl 3β-Acetoxy-5-etienate (16b) from the Acetylated and Methylated Acid Fraction. The methylated and acetylated acid fraction was subjected to thin-layer chromatography on silica gel (thickness 0.75 mm) by using the continuous elution technique[21] with 1% ethyl acetate in benzene for 10 h. Thus, 22 mg of **methyl 3β-acetoxy-17α-methyl-5-etienate (12b,** mp 162–164 °C) was isolated (cf. below). There was also obtained 104 mg of **methyl 3β-acetoxy-5-etienate (16b,** mp 146–151 °C). This product was recrystallized for analysis from dichloromethane–methanol: mp 155.5–156 °C (lit.[43,44] 153–154, 155–157 °C); $[\alpha]^{23}_D$ –20.6° (*c* 1.000, $CHCl_3$) (lit.[43] –24°); IR (KBr) ν_{max} 1740 (acetate), 1735 (methyl ester), 1242 (acetate), 1043 (ester); ^1H NMR (CCl_4) δ 0.65 (s, 19-CH_3), 1.02 (s, 18-CH_3), 1.92 (s, CH_3COO), 3.63 (s, $COOCH_3$), 4.5 (m, 3α-H), 5.39 (m, 6-H).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.77; H, 9.24.

Isolation of Methyl 3β-Acetoxy-17α-methyl-5-etienate (12b), Methyl 3β-Acetoxy-17β-methyl-17α-eti-5-enate (13b), 3β,21-Diacetoxy-5-pregnen-20-one (14a), 3β-Acetoxy-21-methoxy-5-pregnen-20-one (15a), and Methyl 3β-Acetoxy-7-oxo-5-etienate (17b) from the Acetylated Neutral Fraction. (a) Exploratory Experiments. Separations by thin-layer chromatography of the product (461 mg) obtained upon acetylation of the third dichloromethane–ether extract of the neutral constituent of the original reaction mixture did not afford a satisfactory separation. An attempt to purify the acetylated material (693 mg) obtained from the second chloroform–ether extract of the neutral constituent by chromatography on 34 g of silica gel, by elutions with ethyl acetate–benzene (3:97), gave no reasonable separation. An attempt to purify the acetylated product (1.55 g) obtained upon acetylation of the first chloroform–ether extract by chromatography on 70 g of aluminum oxide, by elutions with various mixtures of petroleum ether and benzene, resulted only in very incomplete separations.

(b) Effective Separations. A portion of 2.2 g of the acetylated neutral fraction (obtained by acetylation of the ether extract of the neutral constituent) was subjected to preparative thin-layer chromatography on silica gel (thickness of silica gel 0.75 mm, elutions with 1% of ethyl acetate in benzene for 8 h according to the continuous-elution technique[21]). Four main fractions were obtained: fraction 1 (201 mg), a yellow oil; fraction 2 (772 mg), representing crystalline **3β,21-diacetoxy-5-pregnen-20-one (14a),** mp 158–162 °C (cf. below); fraction 3 (329 mg), representing crystalline **3β-acetoxy-21-methoxy-5-pregnen-20-one (15a)** (cf. below); fraction 4 (722 mg), a yellow oil: IR (KBr) ν_{max} 3440 (OH), 1740 (acetate), 1682 and 1635 (α,β-unsaturated ketone), 1250 (acetate), 1040 cm^{-1} (ester); UV (EtOH) λ_{max} 235 nm (ε 2640).

Fraction 1 was again subjected to thin-layer chromatography as above for 10 h, two main bands being obtained. From band 1, 16 mg of crystalline **methyl 3β-acetoxy-17α-methyl-5-etienate (12b,** mp 165–166 °C) was isolated. The product, identified by spectral comparisons and a mixture melting point determination with an authentic sample, was combined with the equivalent product isolated from the acetylated and methylated acid fraction (cf. above) and was recrystallized three times from methanol for analysis: mp 166.5–167 °C (lit.[29,45,46] mp 163, 162–163 °C); $[\alpha]^{23}_D$ –54.8° (*c* 1.000, $CHCl_3$) (lit.[29,45,46] –57.4°, –60.4°); IR (KBr) ν_{max} 1742 (acetate), 1738 (methyl ester), 1242 (acetate), 1042 cm^{-1} (ester).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.51; H, 9.59.

From band 2, 42 mg of crystalline **methyl 3β-acetoxy-17β-methyl-17α-eti-5-enate (13b,** mp 132–136 °C) was obtained. It was recrystallized three times from methanol for analysis: mp 149.5–150 °C (lit.[29] mp 152 °C); $[\alpha]^{23}_D$ –74.3° (*c* 1.000, $CHCl_3$) (lit.[29] $[\alpha]^{23}_D$ –76.1°); IR (KBr) ν_{max} 1735 (acetate), 1720 (methyl ester), 1250 (acetate), 1040 cm^{-1} (ester); the identity of the product was confirmed by the comparison of its infrared spectrum with that of an authentic sample and by the determination of a mixture melting point.

The main fraction 2 of the original thin-layer chromatogram (cf. above; 722 mg), representing **3β,21-diacetoxy-5-pregnen-20-one (14a),** was recrystallized three times from dichloromethane–methanol for analysis: mp 162.5–163 °C (lit.[47,48] mp 167, 166–167.5 °C); $[\alpha]^{23}_D$ +27.1° (*c* 1.000, $CHCl_3$) (lit.[48] +29°); IR (KBr) ν_{max} 1754 (20-keto 21-acetate), 1738 (21-acetoxy 20-ketone), 1728 (acetate), 1252 and 1241 (acetates), 1042 cm^{-1} (ester); ^1H NMR (CCl_4) δ 0.65 (s, 19-CH_3), 1.03 (s, 18-CH_3), 1.96 (s, 3β-CH_3COO), 2.22 (s, 21-CH_3COO), 4.41–4.48 (q, *J* = 17 Hz, 21-CH_2), 5.4 (m, 6-H). The identity of the product was confirmed by comparison of its spectra with those of an authentic sample and by the determination of a mixture melting point.

Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.09; H, 8.71. Found: C, 72.27; H, 8.93.

Fraction 3 of the main chromatogram (329 mg), representing **3β-acetoxy-21-methoxy-5-pregnen-20-one (15a),** was recrystallized three times from methanol for analysis and sublimed under high vacuum: mp 117–117.5 °C (lit.[49] mp 110–111 °C); $[\alpha]^{23}_D$ +11.4° (*c* 1.000, $CHCl_3$) (lit.[49] +14.3°); IR (KBr) ν_{max} 1740 (21-methoxy 20-ketone), 1715 (acetate), 1255 (acetate), 1045 cm^{-1} (ether); ^1H NMR δ (CCl_4) 0.61 (s, 19-CH_3), 1.03 (s, 18-CH_3), 1.96 (s, CH_3COO), 3.34 (s, OCH_3), 3.82 (s, 21-CH_2), 4.46 (m, 3α-H), 5.4 (m, 6-H).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 73.97; H, 9.40.

Fraction 4 (722 mg) of the main thin-layer chromatogram, presenting itself as an oil, was reacetylated in 3.7 mL of pyridine with 2 mL of acetic anhydride at room temperature for 16 h. The usual workup gave 886 mg of a brown oil which was chromatographed on 20 g of aluminum oxide. Elutions with ether afforded 121 mg of **methyl 3β-acetoxy-7-oxo-5-etienate (17b),** which was recrystallized from ether–hexane for analysis: colorless, long needles; mp 190–190.5 °C (lit.[50] mp 182–186 °C); $[\alpha]^{23}_D$ –59.2° (*c* 1.000, $CHCl_3$) [lit.[50] –74.8° (acetone)]; IR (KBr) ν_{max} 1754 (acetate), 1737 (methyl ester), 1672 and 1635 (α,β-unsaturated ketone), 1240 (acetate), 1040 (ester); UV (EtOH) λ_{max} 235 nm (ε 14 950); ^1H NMR (CCl_4) δ 0.66 (s, 19-CH_3), 1.01 (s, 18-CH_3), 2.0 (s, CH_3COO), 3.36 (s, $COOCH_3$), 3.87 (m, 8β-H), 4.65 (m, 3α-H), 5.73 (m, 6-H).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 71.11; H, 8.30. Found: C, 71.38; H, 8.02.

Quantitative Analyses by Gas Chromatography. According to the procedure outlined above in the General Methods, both the acetylated neutral fraction and the methylated and acetylated acid fraction were analyzed gas chromatographically with the following results: the acetylated neutral fraction contained 3.6% of methyl 3β-acetoxy-17α-methyl-5-etienate (**12b**), 2.4% of methyl 3β-acetoxy-17β-methyl-17α-eti-5-enate (**13b**), 11.6% of 3β,21-diacetoxy-5-pregnen-20-one (**14a**), 4.3% of 3β-acetoxy-21-methoxy-5-pregnen-20-one (**15a**), 7.6% of methyl 3β-acetoxy-5-etienate (**16b**), and small amounts of methyl 3β-acetoxy-7-oxo-5-etienate (**17b**). The methylated and acetylated acid fraction contained 6.0% of methyl 3β-acetoxy-17α-methyl-5-etienate (**12b**), 2.6% of methyl 3β-acetoxy-17β-methyl-17α-eti-5-enate (**13b**), and 55.8% of methyl 3β-acetoxy-5-etienate (**16b**).

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Registry No. 10a, 20576-31-2; **11a**, 7391-03-9; **12**, 25352-86-7; **12a**, 25352-87-8; **12b**, 5230-57-9; **13**, 82979-86-0; **13a**, 10292-12-3; **13b**, 5230-58-0; **14**, 1164-98-3; **14a**, 1693-63-6; **15**, 82995-02-6; **15a**, 82979-89-3; **16**, 10325-79-8; **16a**, 7254-03-7; **16b**, 4139-90-6; **17**, 82979-85-9; **17a**, 82979-87-1; **17b**, 82979-88-2; cyclopropanone, 5009-27-8; sodium methoxide, 124-41-4.

Thermal Isomerization of Isodicyclopentadiene and Its Cycloaddition Reactions

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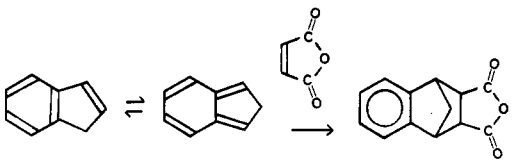
Isodicyclopentadiene (**4**) undergoes a [1,5] sigmatropic hydrogen shift at elevated temperatures (170–180 °C) to form an isomeric, highly reactive diene intermediate **5** which readily undergoes [4 + 2] cycloaddition reactions with dienophiles like dichlorovinylene carbonate (DCVC, **8**), vinylene carbonate (VC, **7**), and maleic anhydride (**9**). In all cases addition to **5** occurs exclusively from the exo face. While **7** and **8** under these high-temperature conditions give one major addition product each (**12** and **13**, respectively), in accord with Alder's rule, **9** at high temperature yields the two isomeric products **15** and **16** initially in the ratio 1:3 of which the isomer **16** (Alder's rule product) on prolonged heating is converted into the stable isomer **15** (anti Alder's rule product). The cycloaddition reactions of 4-cyclopentene-1,3-dione (**10**), 2,2-dimethyl-4-cyclopentene-1,3-dione (**11**), and dimethyl acetylenedicarboxylate (**28**) with **4** and **5** are also discussed. In situ formation of **5** at 0 °C by photolytic cleavage of diketone **14** is proved by trapping **5** with maleic anhydride. X-ray crystallographic data are provided for the adducts **12**, **13**, **15**, **16**, and **21**.

Cyclopentadiene is such an active diene that its presence as a unit in an organic structure generally determines the course of a Diels–Alder reaction in such a compound. However, cases are known in which, depending on the dienophile, the Diels–Alder reaction occurs only after an isomerization of the diene system.

Indene provides a special example of this behavior. It was observed years ago[2] that maleic anhydride at 250 °C adds to indene (**1**) to yield the symmetrical adduct **3**. The

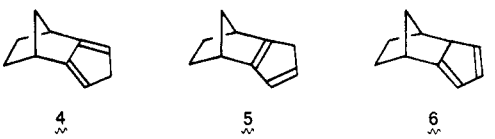


1 **2** **3**

intermediacy of the isoindene **2** has been established by deuterium tracer studies.[3] Although the rearrangement of **1** into **2** might be accelerated by bases, the isomerization during a Diels–Alder reaction is not base catalyzed and has been shown[5] to belong to the class of concerted [1,5] sigmatropic rearrangements,[4] since bases preferentially redistribute hydrogen between positions 1 and 3 in indene, while the concerted rearrangement equilibrates these with position 2.

Although isoindene **2** is highly reactive, there are dienophiles which will attack the original indene structure at the expense of the aromatic ring system; dimethyl acetylenedicarboxylate is one of these and yields successive reaction products which depend upon temperature and substitution in the indene.[6]

Another hydrocarbon of great interest in connection with [1,5] sigmatropic shifts is isodicyclopentadiene **4**. Unlike



4 **5** **6**

2, which has an interrupted aromatic π system, **4** is favored at equilibrium over its isomers **5** and **6**, which have not been isolated. Isomer **4** reacts at moderate temperatures with acrylic and propiolic esters[7] and with phenylvinyl sulfone[8] to yield derivatives of *syn*-sesquinorbornene, while with maleic anhydride it yields mixtures of *syn*-sesquinorbornene *exo*-anhydride **29** and *anti*-sesquinorbornene *endo*-anhydride **30**.[9]

Because there is an obvious balance of forces determining the products of these reactions, we have investi-

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