Preparation of the Hydroxy Acetate 29a.—A solution of 1.98 g (5.8 mmol) of the ketone **28** and 500 mg (13.2 mmol) of $NaBH_4$ in 75 ml of tetrahydrofuran and 110 ml of MeOH was stirred at 0° for 2.5 hr and at 25° for 1 hr. After 2 ml of HOAc had been added to consume the excess hydride, the solution was concentrated under reduced pressure and the residue was partitioned between $CHCl_3$ and aqueous $NaHCO_3$. The organic phase was washed with H_2O, dried, and concentrated to leave 2.20 g of residual liquid. Crystallization from Et_2O–hexane afforded 1.883 g (95%) of the alcohol **29a** as white prisms: mp 169–171°; ir ($CHCl_3$) 3480 (associated OH) and 1725 cm^{-1} (ester C=O); uv max (95% EtOH) 264 mμ (ε 315) and 272 (258); nmr ($CDCl_3$) δ 6.9–7.4 (3 H, m, aryl CH) 4.53 (1 H, d of d, J = 6 and 10 Hz, >CHO), 3.6–4.0 (5 H, m, including a singlet at 3.71, benzylic CH and CH_3O), and 1.5–3.5 [15 H, m including singlets at 2.28 and 1.94 (aryl CH_3 and CH_3CO)]; mass spectrum m/e (rel intensity) 344 (13, M^+), 267 (21), 266 (100), 224 (17), 207 (44), and 43 (19).

Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.73; H, 6.93.

Preparation of the Olefin 30.—To a cold (0°) solution of 1.87 g (5.43 mmol) of the alcohol **29a** in 40 ml of pyridine was added, dropwise and with stirring, 4.2 ml of CH_3SO_2Cl. The resulting solution was allowed to stand at 5° for 26 hr and then partitioned between $CHCl_3$ and aqueous 1 M HCl. After the organic solution had been washed successively with aqueous HCl, aqueous $NaHCO_3$, and H_2O, it was dried and concentrated to leave 2.33 g of white solid. Recrystallization from Et_2O separated 2.204 g (97%) of the methanesulfonate **29b** as white prisms: mp 148.5–150°; ir ($CHCl_3$) 1730 (ester C=O), 1340, and 1365 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 6.9–7.4 (3 H, m, aryl CH), 5.33 (1 H, d of d, J = 6 and 9 Hz, >CHO), 3.6–4.1 (5 H, m including a singlet at 3.69, CH_3O and benzylic CH), 3.03 (3 H, s, CH_3SO_2), and 1.6–2.9 [14 H, m, including singlets at 2.18 and 1.97 (aryl CH_3 and CH_3CO)].

A solution of 309 mg (0.733 mmol) of the methanesulfonate **29b** in 9.0 ml of γ-collidine was refluxed for 30 hr and then cooled and partitioned between $CHCl_3$ and dilute aqueous HCl. The organic layer was washed successively with aqueous $NaHCO_3$ and aqueous NaCl and then dried and concentrated. The residual semisolid (249 mg) was chromatographed on 11 g of silica gel and the fractions eluted with 16% Et_2O in hexane were recrystallized from hexane to separate 166 mg (70%) of the acetoxy olefin **30** as white needles: mp 100–101°; ir ($CHCl_3$) 1730 cm^{-1} (ester C=O); uv max (95% EtOH) 265 mμ (ε 334) with intense end absorption (ε 19,800 at 206 mμ); nmr ($CDCl_3$) δ 6.8–7.3 (3 H, m, aryl CH), 6.38 (1 H, d, J = 6 Hz, vinyl CH), 6.08 (1 H, d, J = 6 Hz, vinyl CH), 3.83 (1 H, s, benzylic CH), 3.68 (3 H, s, OCH_3), 3.1–3.5 (1 H, m, benzylic CH), and 1.5–2.6 [12 H, m including singlets at 2.25 and 1.97 (aryl CH_3 and CH_3CO)]; mass spectrum m/e (rel intensity) 326 (4, M^+), 267 (26), 266 (100), 255 (21), 227 (61), 225 (85), 207 (45), 196 (32), 195 (45), and 155 (20).

Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.87; H, 6.66.

Registry No.—**5**, 15448-20-1; **6**, 15448-23-4; **7a**, 37741-20-1; **7b**, 37741-21-2; **8a**, 37741-22-3; **8b**, 37741-23-4; **9**, 37741-24-5; **10a**, 37741-25-6; **10b**, 37741-26-7; **11**, 37741-27-8; **12**, 37741-28-9; **13a**, 37741-29-0; **13b**, 37741-30-3; **14a**, 37741-31-4; **14b**, 37741-32-5; **15a**, 37741-33-6; **15b**, 37741-34-7; **15c**, 37741-35-8; **16**, 37741-36-9; **19**, 37741-37-0; **21a**, 37741-38-1; **21b**, 37741-39-2; **22**, 37741-40-5; **23**, 37741-41-6; **24**, 37741-42-7; **28**, 37741-43-8; **29a**, 37805-64-4; **29b**, 37741-44-9; **30**, 37741-45-0; **31**, 15448-25-6; **32**, 37741-47-2; **33**, 37805-65-5; **33** copper complex, 37818-71-6; **34**, 37741-48-3; **35**, 37741-49-4; **36a**, 37741-50-7; **36b**, 37741-51-8; **42**, 37741-52-9; β-(*o*-tolyl)propionic acid, 22084-89-5; methyl β-(*o*-tolyl)propionate, 37741-54-1; *o*-tolylsuccinic acid dimethyl ester, 37741-55-2; epiallogibberic acid, 13613-87-1.

A Study of Mechanism for the Formolysis of a 20α-Tosyloxy Steroid[1]

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The mechanism of the formolysis of 3β-acetoxy-5α-pregnan-20α-yl *p*-toluenesulfonate (**1b**) was studied with preparations containing deuterium or tritium in the 17α position. The isotopic atom was retained in the formation of 17β-methyl-18-nor-5α,17α-pregn-13-en-3β-yl acetate (**2b**). Neither of the two geometric isomers of the 5α-pregn-17-en-3β-yl acetate (**7b**, **8b**), therefore, is an intermediate in this reaction, although both are readily converted to this product (**2b**). The rate ratios, k_H/k_T, for the disappearance of the tosylate ester **1b** and for the formation of its major formolysis products were determined. The isotope effect on the rate of formolysis was higher than expected for the formation of a C-20 cation. This could be due to an accompanying 17-hydrogen-assisted formolysis yielding at least some of **2b** or due to a high rate of return from the ion pair. The latter explanation seems less likely. The unexpected formation of a uranediol derivative (**4b**) in this and a similar reaction which tentatively had been attributed by us and others to a two-step mechanism that included a methyl shift does not take this course because the deuterium that was located at C-17 in the starting compound was found at C-17a in the product **4b**. A different mechanism, analogous to a postulate made by Eschenmoser, *et al.*, for the biosynthesis of various steroids, is considered.

In a recent investigation[2] of the formolysis of 3β-acetoxy-5α-pregnan-20α-yl tosylate (**1b**) five compounds (**2**–**6**) were identified, which are listed in Table I. Questions arose about the mode of formation of the two rearrangement products, compounds **2b** and **4b**. Of these, the Δ^{13} olefin **2b** could arise by dehydration to a Δ^{17} olefin (**7**, **8**) which after protonation at C-20 would rearrange to the isolated product. Such a mechanism was first proposed by Leboeuf, *et al.*,[3] to explain the formation of a Δ^{13} olefin (**2c**) from a 20β-tosylate on prolonged boiling in benzene and was adopted by Aoyama, *et al.*,[4] to account for the formation of **2b** from a 20α-acetate on exposure to boron trifluoride etherate for several days. The following observations are consistent with such a scheme. Treatment of a 20α-tosylate (*e.g.*, **1b**, **1c**) with basic solvents

(1) Supported by U. S. Public Health Service Grants AM-9105 and K6-AM-14367.

(2) F. B. Hirschmann, D. M. Kautz, S. S. Deshmane, and H. Hirschmann, *Tetrahedron*, **27**, 2041 (1971).

(3) M. Leboeuf, A. Cavé, and R. Goutarel, *Bull. Soc. Chim. Fr.*, 1624, 1628 (1969).

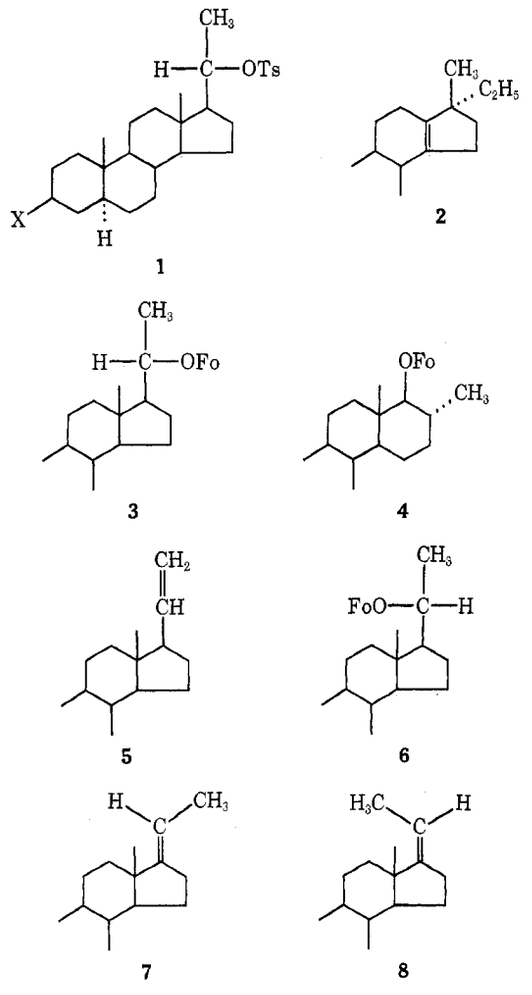
(4) S. Aoyama, K. Kamata, and T. Komeno, *Chem. Pharm. Bull.*, **19**, 1329 (1971).

TABLE I

YIELDS AND 17α-TRITIUM ISOTOPE EFFECTS FOR PRODUCTS OF FORMOLYSIS OF 3β-ACETOXY-5α-PREGNAN-20α-YL TOSYLATE

Compd	Yield from 17α-H (1b), %	$(R^i/R^0)^a$	Δ,[b] %	Yield from 17α-T, %	$(k_H^i/k_T^i)^c$
17β-Methyl-18-nor-5α,17α-pregn-13-en-3β-yl acetate (2b)	68.7	0.675[d]	0.1	46.4	2.55
3β-Acetoxy-5α-pregnan-20α-yl formate (3b)	14.9	1.67[e]	0.3	24.9	1.03
3β-Acetoxy-17α-methyl-*D*-homo-5α-androstan-17aβ-yl formate (4b)	8.4	1.77[e]	0.4	14.9	0.97
5α-Pregn-20-en-3β-yl acetate (5b)	6.5	1.75[d]	0.4	11.4	0.99
3β-Acetoxy-5α-pregnan-20β-yl formate (6b)	1.2				
Unidentified	0.2				

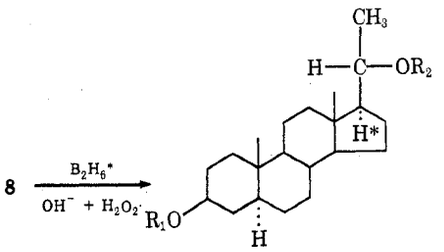
[a] R indicates the ratio $^3H_1/^{14}C_2$, *i.e.*, the tritium counts in channel 1 divided by the ^{14}C counts in channel 2 of the scintillation counter This ratio is calculated from the net registered counts in the two channels (N_1, N_2 respectively) by the equation $R = {}^3H_1/{}^{14}C_2 = [1 - (N_2/N_1)(1/b)]/[(N_2/N_1) - a]$, where a and b refer to N_2/N_1 for 5α-pregnane-3β,20α-diol 3-acetate containing only ^3H (9d) or ^{14}C (9e), respectively (values about 0.05 and 10). The term R^0 indicates the isotope counts ratio R for the starting compound (9g), and R^i for product i isolated at the end of the reaction. [b] Δ gives in per cent the (absolute value of the) difference in N_2/N_1 between the final crystals and their last mother liquor, divided by N_2/N_1 of the crystals. [c] Isotope effect for the formation of product i calculated by means of eq 9:[12] $k_H^i/k_T^i = (R^0/R^i)(k_H/k_T)$, where k_H/k_T refers to the isotope effect on the disappearance of the tosylate ester (see Table II). [d] Measured on the corresponding 3β-ol. [e] Measured on the corresponding diacetate.



Fo = HCO, Ts = p-$CH_3C_6H_4SO_2$

a, X = OH;
b, X = OAc;
c, X = H

(pyridine,[3,5] hexamethylphosphotriamide[3]) yielded either predominantly or exclusively the *E* isomer (**7b**, **7c**) of the Δ^{17} olefin but no Δ^{13} compound, whereas only the latter was obtained in formic acid[2] or in benzene containing boron trifluoride.[3] In methanol a mixture of **7c**, **8c**, and **2c** was obtained.[3] Finally, in formic acid[2,3,6] or in benzene containing toluenesulfonic acid,[3] either isomer of the Δ^{17} olefin was converted to **2**. These observations, however, do not preclude that at least some of the Δ^{13} olefin is formed from the 20α-substituted steroid by a hydride shift from C-17 to C-20, which would either accompany or follow the ionization step. To distinguish the Δ^{17} route from the direct mechanism we prepared 17α-deuterated 3β-acetoxy-5α-pregnan-20α-yl tosylate (**9c**) and subjected it to formolysis. If the free Δ^{17} olefin is an intermediate, the deuteron is lost into the medium, whereas a shift of deuteride would yield labeled Δ^{13} olefin.



	R_1	R_2	H*	C-4
9a	H	H	D	
b	Ac	H	D	
c	Ac	Ts	D	
d	Ac	H	T	
e	Ac	H	H	^{14}C
f	Ac	H	T	^{14}C
g	Ac	Ts	T	^{14}C

The Wittig reaction of a 17-keto steroid[7] yields predominantly[8] the *Z* isomer of the 17-ethylidene com-

(5) (a) H. Hirschmann, *J. Biol. Chem.*, **140**, 797 (1941); (b) D. M. Glick and H. Hirschmann, *J. Org. Chem.*, **27**, 3212 (1962).

(6) C. Ouannes, M. Dvolaitzky, and J. Jacques, *Bull. Soc. Chim. Fr.*, 776 (1964).

(7) G. Drefahl, K. Ponsold, and H. Schick, *Chem. Ber.*, **98**, 604 (1965).

(8) A. M. Krubiner and E. P. Oliveto, *J. Org. Chem.*, **31**, 24 (1966).

pound, which has been used for the synthesis of 5α-pregnane-3β-20α-diol by hydroboration.[8] By substituting $B_2{}^2H_6$ for diborane we obtained the 17α-deuterated analog **9a** of the diol which was preferentially acetylated to the 3-acetate **9b** by heating with acetic acid (*cf.* ref 5a). As the selectivity of the acetylation is only moderate, repeated recycling of the hydrolyzed diacetate and 20-monoacetate was required to provide a sufficient amount of **9b**. Its nmr spectrum verified the presence of deuterium at C-17.

As expected for either of the two mechanisms discussed above, the formolysis of the deuterated analog **9c** of the 3-acetate 20-tosylate of the 5α-pregnanediol gave the Δ^{13} olefin in diminished yield (54%). The mass spectrum of its parent alcohol, when compared with that of its unlabeled analog **2a**, showed shifts in peaks for M^+ and for M^+ − methyl by one mass unit but no change for M^+ − ethyl. The presence of deuterium in the ethyl side chain of the olefin was confirmed by the nmr spectrum of the 3 ketone, which showed at 0.775 ppm a doublet instead of the pair of doublets reported for the unlabeled 3 ketone.[2] Therefore, the deuterium atom was not eliminated but had migrated to C-20. As our starting material was only about 94% deuterated and as the formation of the deuterated olefin was slower than that of the formates, some diminution of the D/H ratio was to be anticipated for the olefin even if the formolysis of the unlabeled tosylate proceeds entirely by hydride shift. We did not consider our analysis of peak heights in the mass spectra precise enough to decide whether *any* loss of label had occurred into the medium and attempted to settle the question by conducting a formolysis of unlabeled tosylate in a medium containing HCOOT. Tritium uptake during the formation of the Δ^{13} olefin **2b** was observed but signified no Δ^{17} pathway because an unlabeled sample of **2b** showed an even larger uptake of tritium when exposed to the tritiated reaction medium.[9] Our most reliable demonstration that the formolysis does not cause any significant loss of hydrogen from C-17 came from a study of doubly labeled (4-^{14}C–17α-^{3}H) tosylate (**9g**) to be described below. The isotope ratio of the total reaction product agreed with that of the solvolyzed tosylate (Table II). Therefore, at least in the formolysis of the 20α-tosylate, only a negligibly small fraction of the reaction can proceed *via* a Δ^{17} olefin.

TABLE II
KINETIC MEASUREMENTS

Time, min	Tosylate fraction remaining (y)	Rate k_H, min^{-1}	R^t[a]	k_H/k_T[b]
0	1		1.47	
10	0.537	0.0622	1.90	1.70
20	0.313	0.0580	2.41	1.74
212			1.47[c]	
Mean		0.0601[d]		1.72

[a] R^t signifies the isotope counts ratio R as defined in Table I for the tosylate ester (**9g**) after t minutes of formolysis. [b] Calculated by means of eq 1:[12] $k_H/k_T = \log(1/y)/[\log(1/y) - \log(R^t/R^0)]$, where k_H/k_T and R^0 are used as defined in Table I. [c] This R value refers to the total reaction product. [d] The previously determined mean was 0.061 min^{-1} and was measured at half the concentration of the tosylate ester.[2]

(9) The uptake of tritium in the two experiments agreed if the shorter exposure of the Δ^{13} olefin formed *in situ* is taken into account.

This finding raised the further question as to whether the hydride shift accompanies or follows the ionization of the tosyloxy group. We have studied this problem by measuring the effects of isotopic substitution of the 17α hydrogen on the rates of disappearance of the tosylate ester and of the formation of its main products. This approach seemed promising, as it had been used with apparent success in studies of the mechanism of solvolysis of 3-methyl-2-butyl tosylate,[10,11] which resembles the steroid in having a methyl group and a methine carbon adjacent to the reacting center.

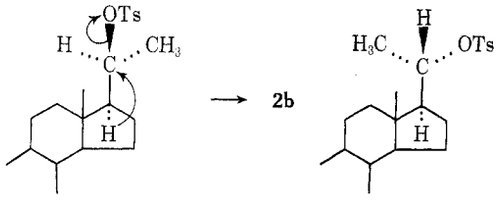
As in an earlier study,[12] we conducted the formolysis of the normal and of the isotopically substituted tosylate concomitantly. This is conveniently done if the 17α hydrogen is labeled with tritium and the reaction of its normal analog is observed by following that of tosylate labeled in the steroid nucleus with ^{14}C. The required 3-acetates of 5α-pregnanediol (**9d** and **9e**) were prepared, respectively, from **8b** by hydroboration with tritiated diborane and from 3β-hydroxy-5-pregnen-20-one-4-^{14}C by known procedures.[2,5b] The two preparations were mixed (**9f**), diluted with unlabeled carrier, and converted to the tosylate **9g**. In order to determine the effect of 17α-T on the rate of disappearance of the tosylate it is necessary to isolate this compound after a partial solvolysis. As has been observed repeatedly,[3,13] 20α-tosylates are destroyed by adsorption chromatography under usual conditions. They remain unaltered during partition chromatography in neutral solvents, but we were unable to take advantage of this fact because we obtained no adequate separation of the tosylate and its formolysis products with various solvent systems, including one used previously in a similar case.[12] Chromatography with acetone or methanol on Sephadex (LH-20) likewise failed to give us satisfactory separations. Eventually we obtained a useful fractionation without any sign of decomposition by chromatography on silica gel deactivated with large amounts of water. The bands of products and of tosylate still showed some overlap, but the tosylate that had separated and the fraction contaminated with products gave the same isotope ratio after recrystallization. This showed that recrystallization after the addition of carrier tosylate sufficed for the purification of the labeled tosylates and this procedure was used for the analysis of a second sample. The results of both runs (Table II) were in satisfactory agreement and indicated a rate ratio k_H/k_T of 1.7 for disappearance of the tosylate.

From this value and from the isotope ratios observed for the major reaction products isolated after a complete formolysis, the rate ratios, k_H/k_T, for the formation of these products can be calculated (Table I). They were near unity for the formates **3b** and **4b** and the Δ^{20} olefin **5b**, but high for the product (**2b**), that undergoes a shift of the isotopic hydrogen during its formation. The interpretation that can be placed

(10) S. Winstein and J. Takahashi, *Tetrahedron*, **2**, 316 (1958).
(11) V. J. Shiner, Jr., in "Isotope Effects in Chemical Reactions," C. J. Collins and N. S. Bowman, Ed., Van Nostrand-Reinhold, Princeton, N. J., 1970, pp 129–133.
(12) J. Ramseyer and H. Hirschmann, *J. Org. Chem.*, **32**, 1850 (1967).
(13) H. Lee and M. E. Wolff, *ibid.*, **32**, 192 (1967).

on these results depends on one's estimate of the isotope effect on the formation of the open C-20 cation. If this effect is comparable to the isotope effect on the formation of the products that are derived from this ion, the formation of the Δ^{13} olefin does not compete in the partitioning of the C-20 cation and, therefore, involves a different process of ionization. This could be envisaged as the migration of the 17α hydrogen in concert with the ionization of the tosyloxy group. Such a process would have a low activation energy only if the participating bonds are antiparallel, as in **10**. If **2b** forms in this manner, no loss of the labeled atom into the medium can occur.

Sunko and Borčić[14a] in a recent summary of the literature stated that deuterium substitution adjacent to the reaction center will cause in solvolytic reactions at room temperature a rate decrease of about 10–20% per atom D. Shiner, *et al.*,[15] reported a strong conformational dependence of this β-isotope effect. Thus they deduced from the noncummulative effect of successive substitution with D in a single methyl group of *tert*-butyl chloride that k_H/k_D was 1.30 for the deuterium that was anti to the chlorine, but only 1.01 if the disposition of these atoms was gauche.[16] In the case of 5α-pregnane-3β,20α-diol and presumably its esters the gauche conformation shown in **11** is more stable than the anti conformation (**10**),[17] and, if the latter



10 **11**

reacts only with participation of the 17α hydrogen, it would be appropriate to use conformation **11** as the model for estimating the isotope effect on the unassisted solvolysis (k_s). A value consistent with Shiner's deduction (k_H/k_D = 1.01 corresponds[18] to 1.02 for k_H/k_T) would be no larger than the isotope effect on the formation of **3b** and, therefore, would be consistent with a mechanism of solvolysis that yields all of **2b** by a hydrogen-assisted formolysis.

If, however, the above estimate of the gauche effect should be too low or if this low value[19] should be inapplicable to our case, some of **2b** would be derived from the C-20 cation. The relative contributions of the hydrogen-assisted (k_Δ) and unassisted solvolysis can be calculated (eq 18)[12] if one knows the magnitude of the individual isotope effects. If for the sake of illustration, $(k_H/k_T)_s$ is now assumed to be 1.2 and $(k_H/k_T)_\Delta$ is taken to be 2.55 (as was observed for the formation of **2b**), 84% of **2b** would still be formed by the hydrogen-assisted ionization. The remaining fraction of **2b** (16%) derived from the C-20 cation would be substantially reduced if the ion is tritiated, because this reaction breaks a bond with the isotopic atom. Consequently, an increased fraction of a more slowly forming ion will go to other products. An estimate showed that these effects are apt to cancel each other and that rate ratios k_H/k_T near unity could be expected as were observed. In this interpretation of our findings we have assumed that there is no significant return from the ion pair to the tosylate ester. If it should occur, this step too would be in competition with the hydride shift and, therefore, be accelerated with the tritiated ester. Consequently, the *net* formation of the cation would be more retarded than its forward component.[20] We have calculated (eq 18)[12] the fraction of return that would have to occur with the unlabeled tosylate to result in the observed k_H/k_T (1.7) for the net solvolysis if (a) there is no hydrogen-assisted formolysis; (b) the isotope effect on the forward component of the formolysis is 1.2 as before; and (c) the isotope effect on the reversal which yields the 20α-tosylate is the same as on the formation of the 20α-formate **3b**. The fraction of return thus estimated is 0.65, which implies that the intrinsic rate of the ionization of **1b** is about three times the measured rate.

It seems pertinent to compare our results with observations on the solvolysis of 3-methyl-2-butyl tosylate, as it has been concluded that its solvolysis is predominantly hydrogen assisted.[10,11] Using the data and assumptions of Winstein and Takahashi,[10] we have calculated, as above, the fraction of return needed to explain their results without invoking a hydrogen-assisted process. Although the effect of replacing the 3 H by deuterium in the methylbutyl tosylate was much higher ($k_H/k_D \sim 2.2$ for formolysis and other solvolyses) than the isotope effect in our case, the estimated fraction of return would be about the same (0.63). Shiner[11] discussed the possibility that there might be a rapid and reversible ionization followed by a rate-determining hydride shift, but considered it improbable because the rate seemed too fast to accommodate this mechanism. The rate of formolysis of the steroid was about four times faster than that of the simpler model.[21] If it is considered probable then that both compounds react in part by a hydrogen-assisted mechanism, it becomes necessary to account for the much smaller isotope effect on the disappearance of the steroid tosylate (k_H/k_T 1.72 corresponds[18] to k_H/k_D 1.46). Two factors may play a role. As C-13 of the steroid is fully substituted, the conformation favorable to participation is relatively less stable than in the model. As one would expect from this, the fraction of products formed with hydride shift is smaller for the steroid than for the model (>90%)[11] and the contribution of any k_Δ to the overall rate must be less important. Furthermore, the faster rate of the steroid might signify that its transition state of formolysis occurs earlier on the reaction coordinate and that the magnitude of the isotope effect is accordingly reduced.

(14) D. E. Sunko and S. Borčić in "Isotope Effects in Chemical Reactions," C. J. Collins and N. S. Bowman, Ed., Van Nostrand-Reinhold, Princeton, N. J., 1970: (a) pp 165, 171; (b) p 204.

(15) V. J. Shiner, Jr., B. L. Murr, and G. Heinemann, *J. Amer. Chem. Soc.*, **85**, 2413 (1963).

(16) These different contributions would result in a mean value of 1.09 for monodeuteration, which is consistent with observation and with the generalization of Sunko and Borčić.

(17) C. Altona and H. Hirschmann, *Tetrahedron*, **26**, 2173 (1970).

(18) For calculation see C. G. Swain, E. C. Stivers, J. F. Reuwer, Jr., and L. J. Schaad, *J. Amer. Chem. Soc.*, **80**, 5885 (1958).

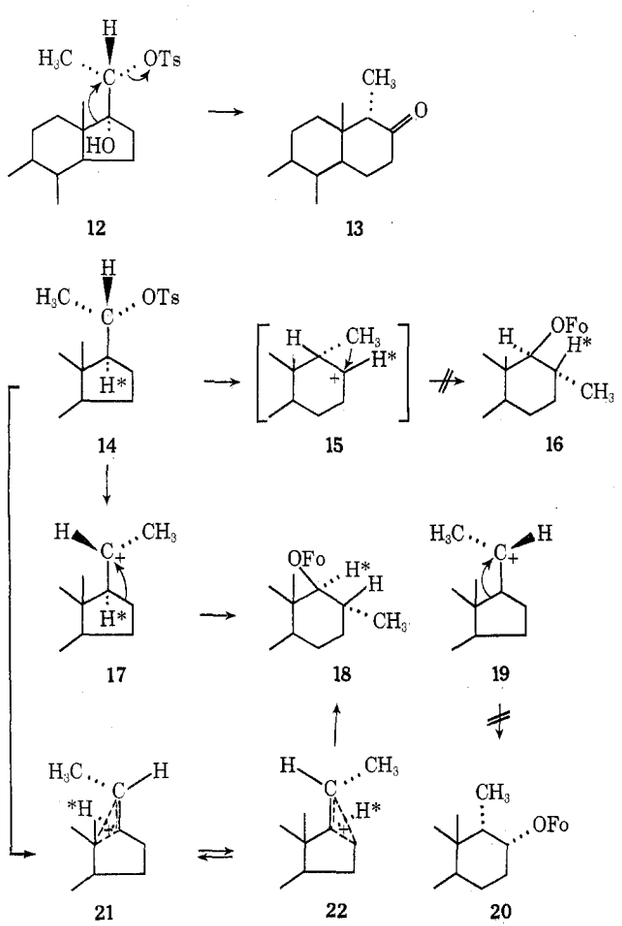
(19) A much higher isotope effect (k_H/k_T 1.37) was reported for the formolysis of 2α-tritiated androsterone tosylate.[12] However, as will be discussed below, this determination is a measurement of a gauche effect only if there was no significant return of tosylate ion, because the elimination of the 2α hydrogen is a major pathway from the cation.[12] Moreover, this solvolysis does not appear to be a simple ionization.

(20) S. G. Smith and D. J. W. Goon, *J. Org. Chem.*, **34**, 3127 (1969).

(21) S. Winstein and H. Marshall, *J. Amer. Chem. Soc.*, **74**, 1120 (1952).

Although these various considerations do not prove hydrogen participation in our case, this hypothesis seems probable enough to justify further efforts at its verification.

Another question which we investigated concerned the mode of formation of the D-homo steroid **4b**. Its presence among the reaction products was unexpected, as the solvolysis of a 17α-hydroxy-20α-tosyloxypregnane (**12**) had yielded a 17aα-methyl-17 ketone (**13**)[22] in a reaction which could be pictured as an ionization facilitated by the simultaneous attack of an antiparallel bond. In contrast, the formation of a uranediol 17aβ-formate (**4b**) from **1b** in a single step would require the far less favorable transition state of a substitution with retention of configuration.[23] We, therefore, considered two successive rearrangements.[2] The first would consist in the simultaneous ionization of the tosyloxy group and the migration of the 13–17 bond to C-20 (**14** → **15**) and therefore be analogous to the ring enlargement observed for the reaction of **12**;



the second rearrangement would consist in the migration of the axial 17aα-methyl of **15** to the equatorial α facet at C-17 and conversion to **16**. This mechanism[24] can be distinguished from a single-step ring enlargement (**17** → **18**) by the location of a deuterium atom originally located at C-17. If the reaction is two-step as shown, the deuterium would end up at C-17 of **16**. When the nmr spectrum of uranediol 3-acetate derived from 17-deuterated tosylate (**9c**) was examined it showed no change in the doublet of the 17-methyl group compared to its normal analog. A difference was seen, however, at 2.7 ppm where the doublet of the 17a hydrogen had almost disappeared. Therefore, the deuterium is at C-17a (as in **18**) and not at C-17 and the two-step pathway involving a methyl migration is disproved.

This finding calls anew for an explanation of the remarkable preference for the migration of the 16–17 bond. Electronic factors seem to favor an attack by the cation on the bond linking C-17 with the more substituted atom, C-13.[25] However, as the migration of the 13–17 bond to a C-20 cation would yield a D-homo steroid with an axial methyl (**20**) and that of the 16–17 bond one with an equatorial methyl group (**18**) in the D ring, the observed preference might be explained if the transition state of the ring enlargement resembled the product. According to Hammond's postulate[26] this is unlikely because the conversion of a pregnan-20-yl to a D-homoandrostan-17a-yl cation should release the strain energy of the trans hydrindan system and require less activation energy than the reverse process.[27] An early transition state which would resemble the initial ion seems to involve different considerations. If the plane of the C-20 cation is perpendicular to the incoming bond, some interaction between the hydrogen at C-20 and the 18-methyl results if the reacting bond is the 16–17 linkage (**17**), whereas there is no such strain in the alternative conformation (**19**).[28] We would expect, therefore, that steric and electronic factors would reinforce each other in an early transition state and lead to the preferred migration of the 13–17 bond toward a C-20 cation (**19** → **20**).[29] As this is not observed, an open C-20 carbocation may not be the intermediate. We therefore are considering also a pathway *via* two bridged ions. The first of these (**21**) would arise by partial bonding between C-13 and C-20 simultaneous with the rupture of the antiparallel carbon–oxygen bond, while the second (**22**) would involve bridging between C-16 and C-20. On reaction with solvent the latter (**22**) would yield the more stable of the D-homo steroids (**18**) whereas **21** might be attacked at C-20 to give the 20α-formate **3b**. This would account for the formation of **3b** by two successive inversions and thus provide a reasonable alternative to the explanation given before[2] for the predominant retention of configuration. The main point of interest is the transformation **21** → **22** because it would be in close analogy to a key step in the biogenesis of various steroids and triterpenoids (tirucallol, lanosterol, etc.) as postulated by Eschenmoser, *et al.*[30]

(22) K. I. H. Williams, M. Smulowitz, and D. K. Fukushima, *J. Org. Chem.*, **30**, 1447 (1965).

(23) N. L. Allinger, J. C. Tai, and F. T. Wu, *J. Amer. Chem. Soc.*, **92**, 579 (1970).

(24) An analogous proposal was made independently by Aoyama, *et al.*,[4] to explain the formation of uranediol diacetate from 5α-pregnane-3β,20α-diol diacetate in BF_3–Et_2O.

(25) H. Minato, J. C. Ware, and T. G. Traylor, *J. Amer. Chem. Soc.*, **85**, 3024 (1963).

(26) G. S. Hammond, *ibid.*, **77**, 334 (1955).

(27) In equilibration studies of *D*-homo ketols, which implicate 17-hydroxypregnan-20-ones as intermediates, the concentrations of the latter were evidently too small to be detected: N. L. Wendler, D. Taub, and R. W. Walker, *Tetrahedron*, **11**, 163 (1960).

(28) The dihedral angle of C-16–C-17 with C-20–C-21 of **19** is close to the one for the preferred conformation of pregnan-20-one, as determined by N. L. Allinger, P. Crabbé, and G. Pérez, *Tetrahedron*, **22**, 1615 (1966).

(29) See also M. Stiles and R. P. Mayer, *J. Amer. Chem. Soc.*, **81**, 1497 (1959), for examples which seem explicable on an analogous basis.

(30) A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955).

The β-isotope effect can be expected to be markedly reduced[14b] if the solvolysis yields a bridged (**21**) rather than a classical (**17**) ion. In a search for such distinct intermediates we compared the effects of 17 tritium on the rates of formation of **3b–5b** (Table I). Compounds **4b** and **5b**, the ones most apt to be derived from diverse primary ionization products, gave no indication of this, because their k_H/k_T ratios showed no significant difference. In contrast, the difference between the tritium effects on the rates of formation of **3b** and **4b** appears to be real,[31] but its sign is puzzling if both compounds are derived from the same primary ionic precursor. It seems that a different approach will be needed to ascertain whether **21** could be an intermediate in the formation of the uranediol ester **4b** from the tosylate **1b**.

Experimental Section

Ir spectra were recorded on solutions in CS_2 on a Perkin-Elmer grating photometer (Model 421). Nmr spectra were measured on solutions in $CDCl_3$ containing TMS, on a Varian HA-100 spectrometer. Results are given in parts per million downfield from TMS. Mass spectra were scanned with a Varian double-focusing M-66 spectrometer on samples introduced directly with a probe heated to 100°. Source temperature was 250°, and the ionization voltage was 70 eV for 5α-pregnanediol 3-acetate, 40 eV for the formates, and 30 eV for the Δ^{13} compound. Isotope analysis was done by the method of Biemann.[32] Radioactivity was determined on a Packard two-channel spectrometer (Model 314 EX). Conditions of measurement were as specified before.[12] Equations used for calculating the results are derived in the earlier paper.[12] Most of the symbols used are also defined in the legends to the Tables.

The melting points reported are corrected. Steroids were generally isolated by extraction with ether or with benzene (as in all formolyses) after adding water to the reaction medium. The organic phase was usually washed with dilute hydrochloric acid, sodium carbonate, and water and taken to dryness *in vacuo*. Unless otherwise specified, chromatography was done on silica gel (100–200 mesh) activated at 120°. Ir and tlc were used extensively to monitor the fractionations. For the latter, plates were made from Adsorbosil 1 (Applied Science Laboratories) which were dried at room temperature (4 hr). Steroids were detected by exposure to iodine vapors.

3β-Acetoxy-5α-pregnan-20α-ol-17α-^2H (9b).—$B_2{}^2H_6$ generated from 240 mg of sodium borodeuteride in 10 ml of dry diglyme and 3 ml of boron trifluoride etherate in 3 ml of diglyme was passed into a solution of (*Z*)-5α-pregn-17-en-3β-ol (**8a**)[7,8] (482 mg) in 8 ml of tetrahydrofuran. After standing at room temperature for 4 hr the excess of diborane-$^2H_6$ was hydrolyzed. To this mixture were added 13 ml of tetrahydrofuran and dropwise 12 ml of 10% NaOH and 8 ml of 30% H_2O_2. After being stirred at 0–10° for 1 hr the product was isolated by ether extraction and refluxed with 60 ml of glacial acetic acid for 190 min. The cooled solution was poured on crushed ice and the steroids isolated by ether extraction were adsorbed on a column of silica gel (50 g). (When the starting material of the acetylation was pure 5α-pregnane-3β,20α-diol, the respective yields of the diacetate, the 3-monoacetate, the 20-monoacetate, and the diol were 25, 33, 17, and 25%.) The diacetate and the 20-acetate were hydrolyzed with methanolic KOH, and the product was combined with diol and again acetylated. Several such fractions of 3-acetate were combined and recrystallized and had mp 132–134° (387 mg). Mass peaks shifted by +1 from those of normal 3-monoacetate were at *m/e* 363 (M^+, weak), 345, 330, 303, 288. Prominent unchanged peaks were at *m/e* 276 (base peak), 275, 216, 215, 201; ^2H, 94% of 1 atom measured for ($M^+ - 60$); nmr 0.64 (18-H), 0.82 (19-H), 1.21 (d, $J = 6$, 21-H), 2.01 (Ac), 3.70 (quartet, $J = 6$, 20-H), ~4.69 ppm (m, 3-H). These signals agreed with those of the undeuterated analog, which, however, had eight lines for the signal at 3.70 ppm.

3β-Acetoxy-5α-pregnan-20α-yl-17α-^2H Tosylate (9c) and Its Formolysis.—Compound **9c**, which was prepared from **9b** and purified as described for its unlabeled analog,[5b] had mp 142–143°. Its solution (434 mg in 9 ml of benzene) was diluted with 868 ml of formic acid and kept at 25.2° for 2 hr. Chromatography[2] of the product gave 182 mg in the olefin and 116 mg in the formate fractions. **17β-Methyl-18-nor-5α,17α-pregn-13-en-3β-ol**, isolated as described,[2] had mp 130–132° and base peak in the mass spectrum at *m/e* 273 as for its normal analog. The M^+ peak (*m/e* 303) was weak but was used for ^2H analysis after some widening of the slits; found, 90% of 1 atom. An aliquot was oxidized to the 3 ketone[2] which had nmr signals at 0.755 (d, $J = 7.35$ cps), 0.95, and 0.99 ppm.

The formates were effectively separated and with less loss than before[2] on long columns (425 × 13 mm) of silica gel (30 g deactivated with 1 ml of water) by elution with benzene containing 0.5% ethyl acetate. **3β-Acetoxy-5α-pregnan-20α-yl-^2H formate** (mp 153.5–155.5°) had mass peaks containing ^2H at *m/e* 391 (M^+, weak), 345, 331, 316. The peak at *m/e* 230 was not shifted from its position in the reference curve; ^2H measured for ($M^+ - 75$), 92% of 1 atom. **3β-Acetoxy-17α-methyl-*D*-homo-5α-androstan-17aβ-yl-17aα-^2H formate** had mp 217–219°, ^2H-containing peaks at *m/e* 345, 331, 316, 285, 277, 270, 231. The peak at *m/e* 215 was not shifted from reference curve of the unlabeled analog: ^2H measured for ($M^+ - 60$) or ($M^+ - 75$), 94% of 1 atom. A sample was partially hydrolyzed to the 3-acetate[33] which had mp 167–169.5° and δ 0.80, 0.955 (d, $J = 6$ cps), 2.02, and ~4.7 ppm (m). The residues of the peaks of the unlabeled compound at 2.66 and 2.75 ppm were too weak to be reliably distinguished from the noise. There was no other signal near 2.7 ppm.

3β-Acetoxy-5α-pregnan-20α-yl-4-^{14}C,17α-^3H Tosylate (9g).—3β-Acetoxy-5α-pregnan-20α-ol-17α-^3H (**9d**) was prepared as described for **9b** from 4.5 mg of $NaBH_4$-^3H (42 mCi) diluted with 60 mg of $NaBH_4$, 1.5 ml of BF_3–Et_2O, and 110 mg of (*Z*)-5α-pregn-17-en-3β-yl acetate. In this run, in contrast to earlier trial experiments with the same starting material, enough of the 3-acetate (63 mg of **9d**) survived the alkali treatment to make the acetylation step unnecessary. Compound **9d** was isolated by chromatography and recrystallized, mp 132–134°.

3β-Acetoxy-5α-pregnan-20α-ol-4-^{14}C (**9e**) was obtained from 6 μCi of 3β-hydroxy-5-pregnen-20-one (53 mCi/mmol) and 104 mg of unlabeled carrier by acetylation and successive hydrogenations with Pd/$CaCO_3$ and Raney nickel, and chromatography essentially as described.[5b] The final sample had mp 133–135°.

A mixture of 0.91 mg of **9d**, 25 mg of **9e**, and 475 mg of nonradioactive carrier was recrystallized until the count ratios N_2/N_1 became constant (0.726 final crystals and 0.732 and 0.728 for the last two mother liquors). This product (**9f**) was converted to the tosylate **9g** and again recrystallized to constant count ratio.[34]

To test the stability of the tosylate under the conditions of chromatography described below, another preparation of **9g** (7.2 mg) which had N_2/N_1 0.629 was mixed with 3.5 mg of unlabeled Δ^{13} olefin **2b** and 1.7 mg of an unlabeled mixture of the two principal formates **3b**, and **4b** and chromatographed. The early eluates contained mostly **2–4** (1.4 mg), the next fraction was a mixture having N_2/N_1 0.632, and the late fractions were mostly tosylate (4.7 mg) which after recrystallization had N_2/N_1 0.626.

Formolysis of 3β-Acetoxy-5α-pregnan-20α-yl-4-^{14}C,17-^3H Tosylate (9g).—Three experiments were conducted at the same time at 25.0°. These differ only in reaction times and size of samples (25.0 mg for the 10- and 20-min runs, and 159 mg for 212 min) whereas the solvents and concentrations were the same (1.2 ml of dry benzene/25 mg of tosylate, diluted at zero time with 50.0 ml of dried[2] formic acid). The reaction products were iso-

(31) This is indicated by the constancy of the ratio $R^{20\alpha}/R^{17a\beta}$, which was determined once for the final preparations of the formates **3b** and **4b** and after several further purification steps twice on the final crystals of the diacetates with these results: 0.951, 0.947, and 0.937. (The error of the *absolute* values of k_H/k_T for these products is larger, as it depends not only on such measurements of radioactivity but also on tosylate determinations by ir spectroscopy.)

(32) K. Biemann, "Mass Spectroscopy: Organic Chemical Applications," McGraw-Hill, New York, N. Y., 1962, pp 223–226.

(33) H. Hirschmann, F. B. Hirschmann, and A. P. Zala, *J. Org. Chem.*, **31**, 375 (1966).

(34) The ratio of **9g** (N_2/N_1 0.694) was lower than that of **9f**. This probably can be attributed to the decomposition that accompanies the tosylation of the 20α-hydroxy group because any elimination reaction would be expected to be slower for the ^3H-labeled component.

lated as described for the earlier kinetic runs.[2] From each experiment an aliquot derived from 5.0 mg of tosylate was removed, freed of solvent as before,[2] and analyzed in the ir by measuring its absorbances at 813, 781, and 687 cm^{-1}. Mean tosylate fractions remaining after 10 and 20 min were calculated and are given in Table II. The remainders of each sample were processed as follows.

A. 10-Min Run.—A solution in 0.5 ml of acetone was applied to a column (110 × 10 mm) of silica gel which was packed as a suspension in the upper phase of ligroin (bp 88–90°), methanol, and water (10:9:1). The silica gel used had been thoroughly washed with water, dried to constant weight by exposure to air, and then hydrated (silica–water, 3:1).[35] Elution with the same upper phase was completed within 30 min. Fraction 4 (1 ml) was 6.0 mg. Fractions 5 (1 ml, 4.7 mg) and 6 (5 ml, 4.4 mg), which were essentially tosylate, were combined and recrystallized until N_2/N_1 of crystals (0.559) and last mother liquor agreed (Δ 1%). Fraction 4 was diluted with 8.2 mg of unlabeled tosylate and recrystallized to give N_2/N_1 0.553 (Δ 0.5%).

B. 20-Min Run.—As the data presented under A showed that even samples high in product could be recrystallized to give pure tosylate, the material remaining from B (15.6 mg) was mixed with 25 mg of unlabeled tosylate and recrystallized until $\Delta N_2/N_1$ was 0.7%.

C. 212-Min Run.—No tosylate remained as even the tritiated component had formolyzed for >10 half lives. This sample (N_2/N_1 0.693 as compared to 0.694 for the starting material) was, therefore, fractionated as described for the products of **9c**. To avoid any possible fractionation of the two radioactive components of any compound by chromatography, incompletely separated fractions were mixed with cold carriers and again subjected to the separation procedure. The 5α-pregn-20-en-3β-ol needed for this purpose was prepared by the method of Barton.[36] The chromatographically separated olefins were recrystallized as the 3β-ols, and the formates were recrystallized as such, hydrolyzed, recrystallized, acetylated, and recrystallized. The percentage differences in N_2/N_1 between final crystals and their mother liquors are given in Table I.

Dynamic State of 17β-Methyl-18-nor-5α,17α-pregn-13-en-3β-yl Acetate (2b) in Formolysis Medium.—A mixture of 0.66 ml of tritiated water (66 mCi) with 110 ml of dry formic acid was used to prepare solutions as follows: (a) 3β-acetoxy-5α-pregnan-20α-yl tosylate (**1b**), 25 mg in 0.6 ml of benzene and 50 ml of formic acid-^3H; (b) (*Z*)-5α-pregn-17-en-3β-yl acetate (**8b**), 12 mg in 0.3 ml of benzene, 6.0 mg of *p*-toluenesulfonic acid monohydrate, and 36 ml of formic acid-^3H; (c) 17β-methyl-18-nor-5α,17α-pregn-13-en-3β-yl acetate (**2b**) in the same medium and in the same concentration as b. All stood for 150 min at 25.0°. The 3β-hydroxy-Δ^{13} olefin was isolated from all runs by the usual procedures (except that chromatography was omitted from run b). The recrystallized products (mp 130–132°) had in channel 1 the following cpm/mg; (a) 2520, (b) 4210, and (c) 2870. In run a the fraction of **2b** available for exchange during the whole reaction period/total **2b** formed was 0.89 (= $1 - 1/kt$, eq 14[12]), while (cpm/mg from a)/(cpm/mg from c) was 0.88.

Registry No.—**2a**, 33299-99-9; **2b**, 33300-00-4; **3b**, 37705-53-6; **4b**, 37759-63-0; **5b**, 22831-64-7; **8a**, 1159-24-6; **8b**, 1167-32-4; **9b**, 37759-67-4; **9c**, 37759-68-5; **9d**, 37759-69-6; **9e**, 33299-98-8; **9g**, 37759-71-0; 3β-hydroxy-5-pregnen-20-one 145-13-1.

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(35) The ratio of water to silica had to be within narrow limits to prevent destruction and still allow separation. The optimal amount of water may not be the same for all batches of silica.

(36) D. H. R. Barton, R. E. O'Brien, and S. Sternhell, *J. Chem. Soc.*, 470 (1962); A. M. Krubiner, N. Gottfried, and E. P. Oliveto, *J. Org. Chem.*, **34**, 3502 (1969).

Lactonization of Methyl *o*-Formylbenzoate by Secondary Amines

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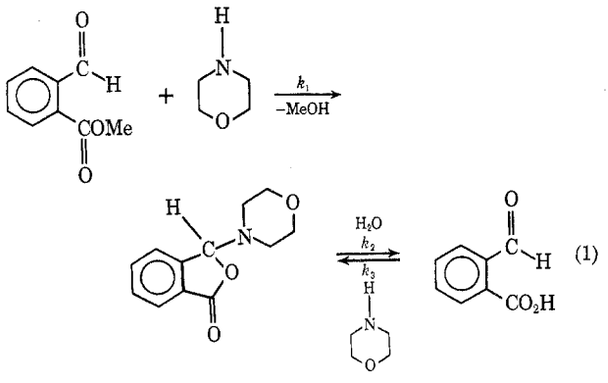
The unusual stability in dioxane of lactones formed by the reactions of MOFB with amines permitted a kinetic study of the effect of amine structure on the course of the reaction. While many classes of amines effected the reaction, the reactions of cyclic secondary amines were especially fast. The second-order rate constants for these fast reactions at 21° were dependent on ring size (pyrrolidine, 34.0 m^{-1} sec^{-1}; piperidine, 27.5; 1*H*-hexahydroazepine, <1), on ring substituents (4-pipecoline, 30.0; 3-pipecoline, 22.5; 2-pipecoline, <1; 2,6-dimethylpiperidine, 2-ethylpiperidine, and 2,6-dimethylpyrrolidine did not react), and on ring heteroatoms (piperazine, 468; 1 methylpiperazine, 7.4; morpholine, 3.7; 1,4-dimethylpiperazine did not react). With the exception of piperazine, the second-order rate constants at 25° paralleled the pK_B values according to the Brønsted relation $\log k_2 = 0.33 \log K_B + 2.39$. Thermodynamic activation parameters at 25° are given for some of the compounds.

The mechanism of ortho carbonyl group participation in the hydrolysis of methyl benzoates has in recent years received a great deal of attention.[1,2] The most extensively studied system involves the amine-assisted hydrolysis of methyl *o*-formylbenzoate.[3,4] The proposed mechanism (eq 1) for the hydrolysis of the ortho-substituted esters accounts for the enormous rate enhancement over the meta and para ester analogs.



(1)

The purpose of this investigation was to attempt to determine some of the structural requirements of the amine nucleophile which promote the rapid formation of the intermediate complex as shown in eq 1. Preliminary work with nonaqueous solvents showed that the intermediate, which quickly hydrolyzed in water, remained quite stable for periods of 24 hr or longer in dioxane solvent. Therefore, the work described below

(1) M. L. Bender and M. S. Silver, *J. Amer. Chem. Soc.*, **84**, 4589 (1962).
(2) M. S. Newman and A. L. Leegwater, *ibid.*, **90**, 4410 (1968).
(3) M. L. Bender, J. A. Reinstein, M. S. Silver, and R. Mikulak, *ibid.*, **87**, 4545 (1965).
(4) G. Dahlgren and D. M. Schell, *J. Org. Chem.*, **32**, 3200 (1967).