Run 8.—Thionyl chloride (reagent, 400 ml) and **1d** (13 g) were heated under reflux for 15 min. Work-up according to run 3, except that column chromatography was not employed, afforded 5.93 g of crude **2d**, mp 222–232°. Recrystallization from chloroform–ethanol afforded 4.8 g (34%) of pure **2d**: mp 245–248°; ir (KBr) 5.85, 6.04, and 6.37 μ; uv max (CH_3OH) 248 (ε 18,200), 270 (ε 13,900), and 342 mμ (ε 15,200); nmr ($CDCl_3$) δ 3.48 (s, 3), 3.80 (s, 3), 7.55 (m, 3), and 8.05 ppm (m, 2).

Conversion of 1e to 4,6-Dimethyl-2-trifluoromethyl-4,5,6,7-tetrahydro-5,7-dioxothiazolo[4,5-*d*]pyrimidine (2e). Run 9.—Thionyl chloride (reagent, 200 ml) and **1e** (800 mg) were heated under reflux for 6 hr. Work-up according to run 3 afforded 490 mg (55%) of **2e**, mp 74–76°. Recrystallization from chloroform–hexane afforded pure **2e**: mp 77.5–78.5°; ir (KBr) 5.80, 6.02, and 6.33 μ; uv max (CH_3OH) 317 mμ (ε 4800); nmr ($CDCl_3$) δ 3.48 (s, 3) and 3.77 ppm (s, 3); mass spectrum (70 eV) *m/e* (rel intensity and pertinent metastables) 265 (93), 246 (8), 208 (12), 180 (37), 153 (3), 113 (42), 85 (100), 70 (50); 163.2 (265 → 208), 155.7 (208 → 180), 130.0 (180 → 153), 122.1 (265 → 180), 63.9 (113 → 85), and 57.6 (85 → 70).

Run 9. Isolation of 8e.—Thionyl chloride (practical, 10 ml) was added to **1e** (500 mg). A clear yellow solution resulted immediately, and the thionyl chloride was removed *in vacuo*. The residue was recrystallized from methylene chloride–hexane to give 300 mg of crude **8e**, mp 250–253°. Sublimation afforded pure **8e** as colorless crystals: mp 251–253.5°; ir (KBr) 3.1, 5.86, 6.09, and 8.67 μ; uv max (CH_3OH) 280 mμ (ε 20,800); nmr ($CDCl_3$) δ 3.37 (s, 3), 3.49 (s, 3), 3.80 (m, 2, J = 8 Hz), and 8.33 ppm (t, 1, J = 8 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 504 (34), 269 (29), 268 (41), 238 (64), 237 (100), 224 (14), 209 (23), 198 (19), 180 (14), 152 (17), 150 (14), 139 (100), and 119 (25).

Anal. Calcd for $C_{16}H_{18}N_6O_4F_6S$: C, 38.10; H, 3.60; N, 16.66. Found: C, 38.16; H, 3.45; N, 16.57.

Run 10.—Thionyl chloride (reagent, 10 ml) and pyridine (1 ml) were added to **1e** (121 mg) and the mixture was heated under reflux for 45 min. Tlc analysis showed only trace amounts of **2e** along with a large amount of polar material. Work-up in the usual way followed by column chromatography did not lead to the isolation of any **2e**.

Registry No.—**1b**, 21544-64-9; **1e**, 21544-65-0; **2a**, 1781-18-6; **2c**, 3764-04-3; **2d**, 21544-68-3; **2e**, 21544-69-4; **8a**, 21544-70-7; **8e**, 21544-71-8; **9a**, 21544-72-9; **10**, 21544-73-0.

Observation of a Large Isotope Effect in the Manganese Dioxide Oxidation of Benzyl Alcohol

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An intramolecular isotope effect for the manganese dioxide oxidation of α-deuteriobenzyl alcohol in benzene solution is determined to be 14.2 ± 0.9, indicating that the rate-determining step for this heterogeneous reaction involves C–H bond cleavage. When equal amounts of benzyl alcohol and α,α-dideuteriobenzyl alcohol are allowed to compete for a limited amount of activated manganese dioxide, an isotope effect of 18.2 is observed, presumably resulting from the combined primary and secondary kinetic isotope effects, and indicating that the assumed adsorption step is reversible. A primary adsorptive isotope effect is postulated as a possible explanation for the magnitude of the isotope effect observed in this work. These findings are considered in terms of current concepts about the mechanism of oxidations with activated manganese dioxide.

Attempts to elucidate the mechanism of manganese dioxide oxidations underscore the difficulties encountered in the study of heterogeneous reactions.[1] The undetermined nature of the adsorptive process and the chemistry of the surface add to the challenges posed by the usual steric and electronic effects in organic reactions. Previous studies suggest the presence of an adsorptive process[2] and formation of a complex,[3] assert the intermediacy of free radicals,[4] and document the significance of solvent, type and quantity of manganese dioxide, temperature, and time[5] in a variety of oxidations with manganese dioxide.[6] We have attempted to provide further insight into the mechanism by an examination of the oxidation of α-deuteriobenzyl and α,α-dideuteriobenzyl alcohols. Isotope effect data is presented which suggests that the rate-determining step in the manganese dioxide oxidation of benzyl alcohols involves C–H bond cleavage, and that the assumed adsorption step is reversible.

In a previous publication, we reported[7] that activation of precipitated manganese dioxide can be achieved by simple dehydrative techniques, including azeotropic removal of water with benzene. It was also observed that some degree of activation can be achieved simply by extractive removal of water from the wet filter cake, using solvents having an avidity for water. Acetonitrile was found to be especially effective for this purpose. These observations lend credulence to the assumption of Ball, Goodwin, and Morton[2a] that there is an adsorption step in manganese dioxide oxidations of allylic alcohols, in that the thermal, azeotropic, and solvent extraction activation procedures probably serve to liberate active sites on the reagent surface by desorption of adsorbed water. The oxidative process on such a surface would reasonably involve a prior adsorption step which is facilitated by polar functionalities.

Accepting the presence of an adsorptive process, two sets of experiments were planned with a typical substrate, benzyl alcohol, to see if α-C–H bond cleav-

(1) For a pertinent review on heterogeneous reactions, see W. F. Pickering, *Rev. Pure Appl. Chem.*, **16**, 185 (1966).

(2) (a) S. Ball, T. W. Goodwin, and R. A. Morton, *Biochem. J.*, **42**, 516 (1948); (b) M. Harfenist, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954); (c) O. H. Wheeler and D. Gonzalez, *Tetrahedron*, **20**, 189 (1964).

(3) R. J. Gritter, G. D. Dupre, and T. J. Wallace, *Nature*, **202**, 179 (1964);

(4) (a) E. F. Pratt and J. F. Van de Castle, *J. Org. Chem.*, **26**, 2973 (1961); (b) E. F. Pratt and S. P. Suskind, *ibid.*, **28**, 638 (1963); (c) E. F. Pratt and T. P. McGovern, *ibid.*, **29**, 1540 (1964); (d) H. B. Henbest and M. J. W. Stratford, *Chem. Ind.* (London), 1170 (1961); (e) ref 3.

(5) (a) R. J. Gritter and T. J. Wallace, *J. Org. Chem.*, **24**, 1051 (1959); (b) ref 2b, 3, 4b; (c) R. J. Highet and W. C. Wildman, *J. Amer. Chem. Soc.*, **77**, 4399 (1955); (d) J. Attenburrow, *et al.*, *J. Chem. Soc.*, 1094 (1952); (e) I. T. Harrison, *Proc. Chem. Soc.* (London), 110 (1964).

(6) For comprehensive reviews on diverse aspects of manganese dioxide oxidations, see (a) S. P. Korshunov and L. I. Vereshchagin, *Russ. Chem. Rev.*, **35**, 942 (1966); (b) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," 1st ed, John Wiley & Sons, Inc., New York, N. Y., 1967, p 637; (c) R. M. Evans, *Quart. Rev.* (London), **13**, 61 (1959).

(7) I. M. Goldman, *J. Org. Chem.*, **34**, 1979 (1969).

TABLE I

MANGANESE DIOXIDE OXIDATION OF DEUTERATED BENZYL AND 2,6-DICHLOROBENZYL ALCOHOLS[a]

Run no.	Substrate	% Monodeuteriocaldehyde *via* Combustion[b,f]	Nmr[c]	Mass spectrometry[b]	k_H/k_D[d]
1	C_6H_5CHDOH[e]	91.7 ± 2		91.2[g]	13.6, 12.6
2	C_6H_5CHDOH[e]	93.0 ± 2		91.2[g]	17.2, 12.6
3	C_6H_5CHDOH[e]		92[h,k]		14.3
4	C_6H_5CHDOH[i]		92.8 ± 0.5[h,k]		14.2
5, 6, 7	C_6H_5CHDOH[i]		92.9 ± 1.0[h,i]		14.4
8	C_6H_5CHDOH[i]		93.1,[h,k] 93.4[l,k]	93.4	14.9, 15.8, 15.8
9	$C_6H_5CH_2OH$ and $C_6H_5CD_2OH$ (1:1)[m]			5.9	18.2
10	$C_6H_5CD_2OH$[n]	98.5 ± 2		99.5	
11	2,6-Dichloro-$C_6H_3CH_2OH$ and 2,6-Dichloro-$C_6H_3CD_2OH$ (1:1)[m]			5.4	19.5
12	2,6-Dichloro-$C_6H_3CD_2OH$[o]			99.5	

[a] Products analyzed as the aldehyde and/or the 2,4-dinitrophenylhydrazone, as designated. See Experimental Section for details. [b] Analysis on the 2,4-dinitrophenylhydrazone. [c] Analysis on the aldehyde. [d] Corrected for undeuterated or monodeuterated substrate. [e] 98 ± 1.6% d_1 by combustion analysis; 1.6% d_0 and 0.4% d_2 by mass spectrometry. [f] Analysis by the falling drop method, J. Nemeth, University of Illinois. [g] Raw data kindly provided by Professor Biemann and Dr. Falshaw, Massachusetts Institute of Technology. [h] Determined from ratio of aldehydic to aromatic proton integrals. [i] 0.7% d_0 and 0.4% d_2 by mass spectrometry. [j] Product isolated by glpc. [k] Product isolated by distillation. [l] Determined using trifluoroacetic acid as internal standard. [m] Competition experiment using limited amount of manganese dioxide. [n] 2.0% d_1 by nmr using 2,6-dichlorobenzyl alcohol as internal standard. [o] 1.6% d_1 by nmr using benzyl alcohol-O-*d* as internal standard.

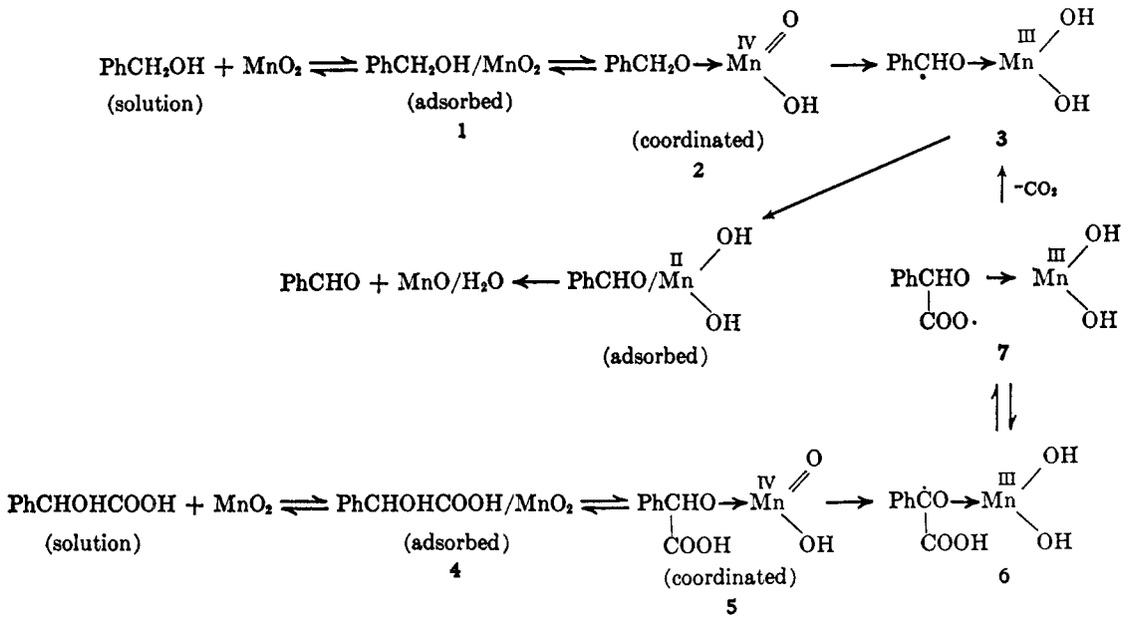
age were involved in the rate-determining step leading to formation of product benzaldehyde, and to see if the assumed adsorption process was reversible. In the first case, α-deuteriobenzyl alcohol would, after adsorption and oxidation, lead to a mixture of deuterated and undeuterated benzaldehydes. The product ratio would also be the intramolecular isotope effect, k_H/k_D.[8] Preferential cleavage of the α-C–H bond would lead to a *preponderance of the deuterated product*, indicating that the rate-determining step for this oxidation involves α-C–H bond cleavage. In the second case, in which an excess of a 1:1 mixture of undeuterated and dideuterated benzyl alcohols would compete for a limited amount of reagent, a product ratio of one would result if the adsorption process were simply statistical and irreversible, or if there were no isotope effect for this reaction. A product ratio greater than one, on the other hand, would result if there were a kinetic isotope effect for this reaction, provided that the assumed adsorption process were reversible. In this case there would be a *preponderance of the undeuterated aldehyde.* Furthermore, the product ratio would be expected to be at least as large as the intramolecular isotope effect, for reasons which are discussed below.

α-Deuteriobenzyl, α,α-dideuteriobenzyl, and α,α-dideuterio-2,6-dichlorobenzyl alcohols were prepared by reduction of the corresponding aldehyde, ester, and acid, respectively, with lithium aluminum deuteride. The alcohols were oxidized with activated manganese dioxide, the mixtures of aldehydes were analyzed for deuterium, and the isotope effects were calculated. The results of several runs and methods of analysis are summarized in Table I and in the Experimental Section. The manganese dioxide used in this work was prepared by activation of precipitated manganese dioxide by azeotropic removal of water.[7] Inspection of the data for runs 1–8, Table I, shows that the manganese dioxide oxidation of benzyl alcohol-α-d_1 proceeds with an intramolecular isotope effect of 14.2 ±0.9 (excluding the high value in run 2). The lack of precision in these runs is attributed to the fact that the isotope effect is calculated by dividing a large number by a small number, the latter having a relatively large experimental error. Although we have no independent measure of the absolute accuracy of these determinations, it is encouraging to note that similar values were obtained using a variety of analytical techniques. The possibility that the isotope effect determined in the present work was erroneously high, owing to an indeterminate amount of oxidation of the product aldehyde mixture *via* an unidentified process with a sizable isotope effect, is ruled out by the results of runs 9 and 11, Table I. In these runs, equal amounts of undeuterated and α,α-dideuterated substrates were allowed to compete for a limited amount of activated manganese dioxide, and the reaction products were analyzed in the usual way. Whereas preferential destruction of benzaldehyde-α-d_0 in runs 1–8 would have given unrealistically high values for the isotope effect, preferential destruction of product aldehyde-α-d_0 in runs 9 and 11 would have given low values for the intermolecular isotope effects. The high values found in these competition experiments preclude the intervention of an isotopically selective destructive step in the intramolecular case.

It can be concluded from the present experiments that the rate-determining step in the oxidation of benzyl alcohols with activated manganese dioxide involves cleavage of the α-C–H bond, and that the assumed adsorption step is reversible. Whereas the theoretical limit for an H/D isotope effect is 48,[8c] resulting from loss of the symmetrical stretching and bending vibrations in the transition state, primary kinetic H/D isotope effects usually fall between 5 and 8. The large isotope effects observed in this work may be due to the presence of consecutive, dependent steps, each with a smaller isotope effect; to tunneling

(8) For reviews on isotope effects see (a) K. B. Wiberg, *Chem. Rev.*, **55**, 713 (1955); (b) F. H. Westheimer, *ibid.*, **61**, 265 (1961); (c) K. B. Wiberg, "Physical Organic Chemistry," 1st ed, John Wiley & Sons, Inc., New York, N. Y., 1964, p 351; (d) L. Melander, "Isotope Effects on Reaction Rates," Ronald Press, New York, N. Y., 1960.

CHART I



of protium through the energy barrier;[9] or to loss of the symmetrical stretching vibration, and some of the four bending vibrations as well, in the activated complex. A recent pertinent example of a large kinetic isotope effect is found in the study of Stewart and Van der Linden in which it is shown that the aqueous alkaline permanganate oxidation of phenyl trifluoromethyl carbinols has a deuterium isotope effect of 16.[10]

The observation that the values determined for the intermolecular isotope effects are substantially higher than those determined for the intramolecular case deserves comment. The highly preferential oxidation of the undeuterated alcohols in the competition experiments, runs 9 and 11, is attributed to the combined contributions of primary and secondary isotope effects for this reaction. While the magnitude of the intramolecular kinetic isotope effect for a given reaction will be approximately the same as that for the corresponding intermolecular kinetic isotope effect, removal of a hydrogen atom from a carbon bearing another hydrogen atom is up to two times faster than if a deuterium were the other atom, this being a secondary kinetic isotope effect. For the case of the undeuterated *vs.* the dideuterated benzyl alcohols, the cleavage of a C–D bond, showing a primary isotope effect, will be further slowed owing to the presence of another deuterium on the same carbon. If the value of 18.2 for run 9 is reliable,[11] the secondary isotope effect for this oxidation is calculated to be 1.3, well within the range of 1–2 usually found for secondary kinetic isotope effects.

While the present studies do not permit a distinction to be made between hydride, proton, or hydrogen-atom abstraction in the rate-determining step,[8a] free-radical intermediates have been proposed[4] for a variety of oxidations with manganese dioxide. An energy diagram for the manganese dioxide oxidation of benzyl alcohol can be constructed as shown in Figure 1. The present

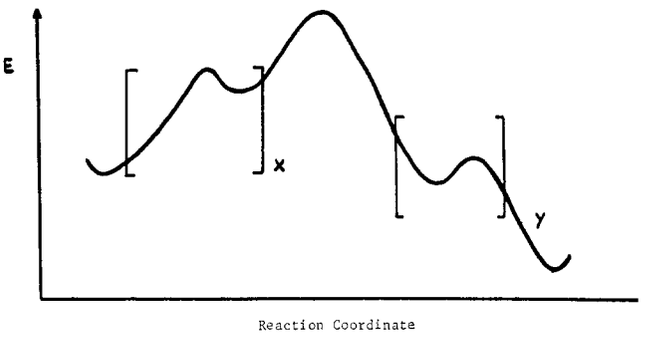


Figure 1.—Energy diagram for manganese dioxide oxidations.

results would be consistent with the presence of a variety of reversible processes, denoted by x, prior to the slow step. The prior processes might include an adsorption step, formation of a coordinated complex with the reagent, or electron removal from the π system in analogy to the recent work of Dewar[12] on the mechanism of manganic acetate oxidations. If two dependent processes each involved preferential interactions with α-C–H *vs.* α-C–D, as postulated below, a large intramolecular isotope effect might result. The process denoted by y might include a fast bond cleavage and a desorption step. The rate of oxidation, then, for a heterogeneous reaction such as manganese dioxide oxidation of benzyl alcohols and related substrates, is a function of the concentrations of adsorbed and coordinated species, as well as the ease of formation of the assumed radical intermediates.

In view of the seeming diversity of oxidations which can be carried out using manganese dioxide under a wide range of conditions, it is of interest to speculate about the present results as they might relate to the broader mechanism picture for manganese dioxide oxidations. Most of the conventional substrates for activated manganese dioxide oxidation contain at least one polar, coordinating functionality, *e.g.*, benzyl alcohol, ethyl mandelate, N-benzylaniline, geraniol, benzoin;

(9) See, for an example of proton tunneling, V. J. Shiner, Jr., and M. L. Smith, *J. Amer. Chem. Soc.*, **83**, 593 (1961).

(10) R. Stewart and R. Van der Linden, *Tetrahedron Lett.*, No. 2, 28 (1960).

(11) This value is based on one run only. It is estimated that the determined value is reliable to about ±1, based on the results of runs 1–8 and the analogous competition experiment, run 11.

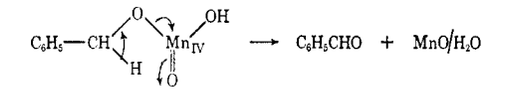
(12) P. J. Andrulis, Jr., and M. J. S. Dewar, *J. Amer. Chem. Soc.*, **88**, 5483 (1966).

and *meso*-dihydrobenzoin, 2-phenylethanolamine, and mandelic acid. All of these substrates are readily attacked by activated manganese dioxide in nonpolar solvents, the first five compounds undergoing C–H bond cleavage, and the last three undergoing C–C bond cleavage. A common mechanistic pathway, based in part on the proposals of Pratt and Van de Castle[4a] and of Gritter, Dupre, and Wallace,[3] can be devised to accommodate these C–H and C–C bond cleavages, as depicted in Chart I for benzyl alcohol and mandelic acid.[13]

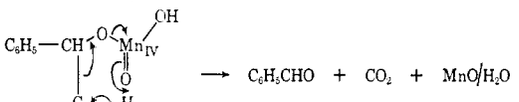
In the sequences in Chart I, the polar functionalities facilitate adsorption on the oxidizing surface. The adsorbed compounds **1** and **4** then form the coordinated compounds **2** and **5**,[14] which undergo oxidation *via* hydrogen-atom transfer in the rate-determining step to form the most stable radicals **3** and **6**, respectively. The hydrogen-atom transfer from **2** and **6** could be a two-step process in which an electron is transferred from the π system followed by α-proton transfer[12] to form diradical intermediates **3** and **6**. Intermediate **6** is envisioned as being in equilibrium with intermediate **7**, which can decarboxylate to form the common benzylic intermediate **3**, which then goes on to form product benzaldehyde. The intermediates **3**, **6**, and **7** are manganic esters and are actually diradicals, which can break down to form products by an intramolecular electron-transfer reaction. An analogous sequence can be devised to rationalize the oxidative course observed for the other substrates listed above, although there is no apparent reason why C–C bond cleavage occurs preferentially in the cases of mandelic acid and *meso*-dihydrobenzoin.

The reaction pathways for the manganese dioxide oxidations of benzopinacol, benzilic acid, and hydroquinone, representative substrates lacking a benzylic hydrogen, can be envisioned as following an analogous course, as depicted in Chart II. Following the adsorption and coordination processes, and formation of manganic esters (and oxy radicals), intermediates **8** and **9** break down in the (presumed) slow step to form the more stable benzylic radicals **10** and **11**, which then go on to form products. The hydroquinone process is envisioned as proceeding *via* slow abstraction of a hy-

(13) Alternate pathways involving concerted bond cleavages *via* the seemingly reasonable cyclic transition states i and ii are excluded on the basis of the proposed intermediacy of free radicals in manganese dioxide oxidations.[4]



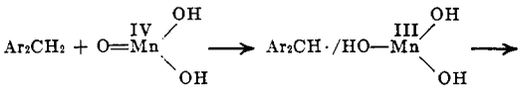
i



ii

The stepwise reaction sequences depicted in Charts I and II are probably oversimplified in the sense that the reagent surface is represented as a single molecule of MnO_2, and the same molecule is pictured as participating in the several stages of electron transfer (*e.g.*, **1** → **2** → **3** → products, Chart I). That this may not be correct, and that other molecules on the reagent surface may be involved in the stepwise transformations leading to rate-determining C–H bond cleavage, can be deduced from the argument by Wiberg[8c] that small isotope effects are predicted to result from reactions in which the activated complex is nonlinear, such as that for hydrogen migration in a pinacol rearrangement. (It is assumed here that the activated complex expected for the sequence **2** → **3**, Chart I, if but a single molecule of MnO_2 were involved, would meet the criterion of nonlinearity and would lead to a smaller isotope effect than that observed.)

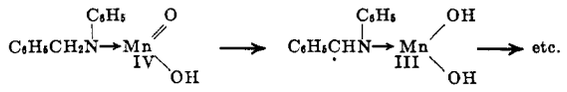
(14) The Mn(IV) coordination compounds **2** and **5** are postulated as obligatory intermediates to explain the fact that benzylic and allylic ethers and esters are inert to activated manganese dioxide under the usual mild reaction conditions; *i.e.*, they do not show the lability of the α proton which would be expected if a simple adsorptive process were the only prerequisite to C–H bond cleavage. Oxidation does occur, of course, in other cases in which analogous coordination compounds cannot be invoked, *e.g.*, β-ionylidene compounds[15] and diarylmethanes.[4b] These latter reactions probably follow a different course from the proposed one above, involving diradical manganic ester intermediates. Cationic impurities, postulated by Gritter, Dupre, and Wallace[3] to play a role in determining the activity of various preparations of manganese dioxide, may reasonably be involved in the present scheme in facilitating the formation of coordinated intermediates **2** and **5**. It is to be noted that Pratt and Suskind[4b] have proposed a pathway for the oxidation of diarylmethanes to benzophenones which, in a formal sense, may involve a coordinated species ("hydrated" manganese dioxide), a manganic (III) hydroxide–diarylmethyl intermediate (diradical), and an electron-transfer process (if the proposed[4b] concerted process is viewed as proceeding in a stepwise manner).



II

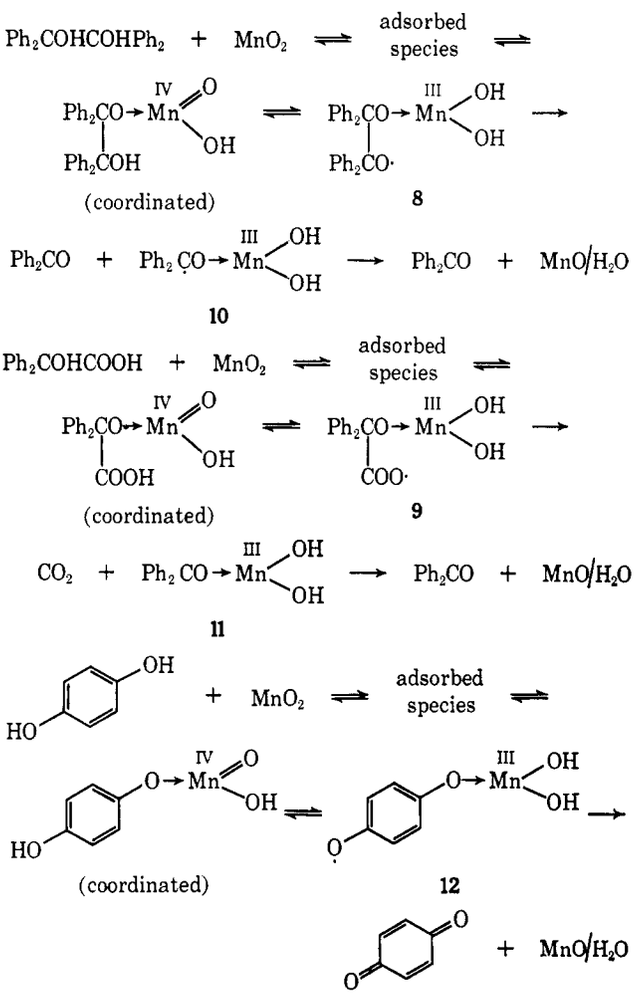
$Ar_2CHOH + Mn(OH)_2$, etc.

Pratt and McGovern[4c] have reported a free-radical reaction sequence for the conversion of N-benzylaniline to benzalaniline, in which homolytic N–H bond cleavage is postulated as the first step. We would propose an intermediate coordination compound, in analogy to the scheme proposed in the present work. The rate-determining step would then be C–H bond cleavage.



(15) H. B. Henbest, E. R. H. Jones, and T. C. Owens, *J. Chem. Soc.*, 4909 (1957).

CHART II



drogen to form the oxy radical **12** (presumably *via* participation of distal portions of the reagent surface), which then goes on to form products. The present results are consistent with the observation by Nickon[16] that the manganese dioxide oxidation of cholest-4-en-3α- and -3β-ols proceeds with conformationally selective rate-controlling cleavage of the allylic C–H bond, axial C–H bond cleavage being preferred.

Melander has alluded to the question of solvation and activity coefficients in a theoretical treatment of kinetic isotope effects,[17] stating that, while it is generally assumed that external influences have little isotopic specificity, ideal conditions are likely to prevail only in the gas phase. In the present work, we are dealing with a heterogeneous reaction in which adsorptive interactions of substrate α-deuteriobenzyl alcohol with the surface may have significant isotopic specificity. This latter possibility finds support from the following considerations. It is known that a C–D bond is shorter than the corresponding C–H bond, and deuterium has smaller amplitudes of bending and stretching, resulting in a smaller van der Waals radius for deuterium.[18,19] The existence of secondary steric isotope effects has been postulated,[20] and examples of rate differences have been attributed to this size differential.[21] A difference in the adsorption characteristics of C–H *vs.* C–D, deriving from the reduced polarizability of C–D *vs.* C–H, and leading to a smaller interaction of the deuterium than of the hydrogen with the surface, has been offered as the basis for the observed differences in adsorption of deuterated *vs.* nondeuterated methanes.[18] It is therefore seen that C–H and C–D bonds differ in a way which could be significant in a heterogeneous reaction, in which an adsorption process is a prerequisite to a chemical transformation.

On the basis of the foregoing results and discussion, we postulate a *primary adsorptive isotope effect* as a possible explanation for the magnitude of the effects observed in this work. In general terms, the primary adsorptive isotope effect is defined as the quotient of the rates for the slow step in a process showing a primary kinetic isotope effect, for which a reversible preferential adsorption step involves the same isotopic species as are involved in the ensuing rate-determining step. A primary adsorptive isotope effect in the manganese dioxide oxidation of α-deuteriobenzyl alcohol would arise as follows. If, after formation of the coordinated complex corresponding to **2**, Chart I, there were preferential reversible adsorption of α-C–H *vs.* α-C–D, followed by preferential cleavage of α-C–H *vs.* α-C–D, the observed isotope effect would be the product of the two ratios: adsorbed α-C–H over adsorbed α-C–D, and rate of α-C–H cleavage over rate of α-C–D cleavage. Heterogeneous reactions at a rigid surface, where steric requirements are maximum, might be expected to magnify subtle differences based on size.[22]

(16) A. Nickon, N. Schwartz, J. B. DiGiorgio, and D. A. Widdowson, *J. Org. Chem.*, **30**, 1711 (1965).

(17) Reference 8d, p 41.

(18) R. Yaris and J. R. Sams, Jr., *J. Chem. Phys.*, **37**, 571 (1962); P. L. Gant and K. Yang, *J. Amer. Chem. Soc.*, **86**, 5063 (1964).

(19) W. F. Libby, *J. Chem. Phys.*, **35**, 1527 (1961).

(20) L. S. Bartell, *J. Amer. Chem. Soc.*, **83**, 3567 (1961).

(21) K. Mislow, R. Graeve, A. J. Gordon, and G. H. Wahl, Jr., *ibid.*, **85**, 1199 (1963), and references cited therein; L. Melander and R. E. Carter, *ibid.*, **86**, 295 (1964).

(22) There is precedent for the intervention of gross steric factors in manganese dioxide oxidations. See ref 5a and 2b; also H. Rapoport and S. Masamune, *ibid.*, **77**, 4330 (1955). Pratt and van de Castle, ref 4a, have shown that the rate of manganese dioxide oxidation of PhCHOHR alcohols increases with R in the order: $CHCH_3Ph$, $CH(CH_3)_2$, CH_2Ph, CH_3, H.

(23) S. Meyerson, P. N. Rylander, E. L. Eliel, and J. D. McCollum, *J. Amer. Chem. Soc.*, **81**, 2606 (1959).

(24) Combustion deuterium analyses by the falling drop method were performed by Mr. J. Nemeth, University of Illinois.

Experimental Section

Preparation of Deuterated Substrates.—Benzyl alcohol-α-d_1 employed in runs 1–3 was prepared by treating freshly distilled benzaldehyde [bp 53° (10 mm), 0.216 mol] with lithium aluminum deuteride (Metal Hydrides, 0.062 mol) in 250 ml of ether under reflux for 3 hr. Following work-up in the usual way, the product was distilled, giving the pure benzyl alcohol-α-d_1 (87%): bp 83–85° (10.5 mm); n^{25}D 1.5375 [lit.[23] bp 97–99° (16 mm); n^{20}D 1.5392]. Homogeneity and absence of aldehyde were established by infrared, nmr, and glpc analyses. The isotopic composition was determined by mass spectrometry at low voltage: 1.6% d_0, 98% d_1, 0.4% d_2 (*cf.* values of 3.8% d_0, 93.9% d_1, and 2.3% d_2 reported for the same procedure[23]), as described below.

Anal. Calcd for C_7H_7DO: C, 77.03; H, 8.30. Found: C, 77.25; H, 8.25. Deuterium analysis:[24] Calcd for C_7H_7DO: 12.50 atom % D. Found: 12.5 ± 0.20 atom % D.

The nmr doublet at δ 4.38 (2, J = 5.5 Hz) due to the methylene protons in benzyl alcohol was replaced by a poorly resolved doublet at δ 4.33 (1, J = 5.5 Hz, CHDOH).

A second batch of benzyl alcohol-α-d_1, employed in runs 4–8, was prepared using lithium aluminum deuteride as above (81%): n^{25}D 1.5377. Homogeneity and absence of aldehyde were established by glpc. The isotopic composition was determined by mass spectrometry: 0.7% d_0, 98.9%, d_1, and 0.4% d_2. Benzyl alcohol-α-d_2 was prepared by reduction of methyl benzoate with lithium aluminum deuteride in the usual way: n^{25}D 1.5370 (lit.[23] n^{20}D 1.5389). Homogeneity was established by glpc. The nmr spectrum showed a peak at δ 5.33 (s, 1, OH); the methylene peak at δ 4.37 was barely detectable. The isotopic composition was determined by nmr using an internal standard as described below: 2.0% d_1, 98% d_2 (*cf.* lit.[23] values: 5.3% d_1, 94.7% d_2).

Anal. Calcd for $C_7H_6D_2O$: C, 76.32; H, 9.15. Found: C, 76.62; H, 8.93.

2,6-Dichlorobenzyl alcohol-α-d_2 was prepared by treating 2,6-dichlorobenzoic acid (4.6 g, 0.024 mol) with lithium aluminum deuteride (1.0 g, 0.024 mol) in ether at reflux for 16 hr. Work-up in the usual way afforded 1.14 g (27%) of the pure alcohol after sublimation: mp 96.5–97.5°; the nmr spectrum ($CDCl_3$) showed a peak at δ 2.68 (s, 1, OH); the methylene peak at δ 4.90 was barely detectable, and integrated for 1.6% d_1 using an internal standard as described below.

Anal. Calcd for $C_7H_4D_2OCl_2$: C, 46.96; H, 4.50; Cl, 39.60. Found: C, 47.04; H, 4.47; Cl, 39.31.

Mass Spectra.—Mass spectra were recorded on a Consolidated Model 21-103C at 9.5 eV and/or a Hitachi Perkin-Elmer Model RMU-6D at nominal values of 7–10 eV. The RMU-6D direct sample inlet system was used for the 2,4-dinitrophenylhydrazones (2,4-DNP's) run on this instrument. Ionizing voltages were selected so as to minimize the contribution of the M − 1 peaks while retaining M peaks of sufficient size to permit accurate and reproducible measurements. An average of three to nine scans was used for each run. A slow scan rate was employed to eliminate errors in pen response and to give nearly theoretically correct values for (M + 1)/M ratios for reference compounds. Peak height ratios were corrected for increasing or decreasing sample pressures (assumed to be linear over short time intervals) for samples introduced *via* the direct and indirect inlet systems, respectively. Instrument background was either negligible or corrected for.

Owing to the fact that the M − 1 peak for benzyl alcohol could not be eliminated at ionizing voltages producing a measurable M peak, corrections were made for the presence of M − 1 peaks as follows. At a nominal setting of about 8 eV, a sample of pure benzyl alcohol gave M + 1 = 7.7%, M = 100%, and M − 1 = 1.3 ±0.4%. The two samples of benzyl alcohol-α-d_1 were then run at the same voltage setting, showing M + 1 = 8.1 and 8.1%, M = 100 and 100%, and M − 1 = 2.7 and 1.8%, respectively. The isotopic compositions for these deuterated samples were determined from ratios of M, M + 1, and M − 1, correcting for ^{13}C, and assuming that the M to M − 1 transition for benzyl alcohol-α-d_1 is 87%[23] as efficient as the corresponding transition for

benzyl alcohol-d_0. The isotopic compositions for the two samples are calculated to be 1.6% d_0, 0.4% d_2; and 0.7% d_0, 0.4% d_2.

A sample of pure benzaldehyde-2,4-DNP shows M = 100 and 100%, M − 1 = 0.0 and < 0.5%, and M + 1 = 16.5 and 15.9% (theory for M + 1 = 15.7%) at nominal values of 9.5 and 7 eV, respectively. The isotopic compositions of deuterated benzaldehyde-2,4-DNP's were therefore determined from ratios of M and M + 1, correcting for ^{13}C and ^{15}N, and assuming negligible M − 1 peaks at the voltage (7 eV) employed.

Nuclear Magnetic Resonance Spectra.—Nmr spectra were observed in carbon tetrachloride or chloroform-*d* on a Varian Model A-60 or a Hitachi Perkin-Elmer Model R-20 spectrometer. Peaks are reported as parts per million downfield from internal tetramethylsilane. Aldehydes were diluted with 2–4 volumes of solvent and then sealed in nmr tubes under nitrogen. Integrals were taken as averages of 4 to 12 scans. A sample of pure benzaldehyde, collected from gas–liquid chromatography, was used as a reference standard: aromatic protons, 5.00 H ±0.06; aldehydic proton, 0.98 H ±0.03.

The use of trifluoroacetic acid as an internal standard for the determination in run 8 was based on a trial run, as follows. A sample of freshly distilled benzaldehyde (20 μl, 0.0202 g, 0.191 mmol) and a sample of distilled trifluoroacetic acid (20 μl, 0.0289 g, 0.254 mmol) were added under nitrogen to chloroform-*d* in an nmr sample tube. On the basis of 10 integrations, the aldehyde content was calculated to be 97% of the amount added. In a similar manner, the isotopic compositions of benzyl alcohol-α-d_2 and 2,6-dichlorobenzyl alcohol-α-d_2 were determined using 2,6-dichlorobenzyl alcohol and benzyl alcohol-O-*d*, respectively, as internal standards.

Oxidations and Determinations of Isotope Effects.—Active manganese dioxide was prepared by azeotropic removal of water as described earlier.[7] Except for the competition experiments, runs 9 and 11, 1 g of substrate was reacted, under nitrogen, with a stirred mixture of 10.5 g (from 25 g wet) of activated manganese dioxide in 125 ml of benzene for 1 hr. The reaction mixtures were filtered through Celite and the benzene was removed carefully under reduced pressure. Products of oxidation were analyzed directly, following purification by glpc or distillation, or as the 2,4-DNP's, as designated. Additional details are provided in pertinent sections below, and in Table I.

Run 1.—After removal of solvent, the 2,4-DNP was formed directly, giving 1.6 g (60%) of crude material, recrystallized from ethyl acetate for analysis: mp 242–244°.

Anal. Calcd for $C_{13}H_9DO_4N_4$: C, 54.36; H, 3.86. Found: C, 54.36; H, 3.75.

The isotopic composition, determined by combustion analysis and mass spectrometry, is 91.7 ±2 and 91.2% monodeuteriobenzaldehyde 2,4-DNP, respectively. Under conditions in which there was no M − 1 peak for benzaldehyde 2,4-DNP, the mass spectrometry values obtained for this run were M_{286} = 9.5% and M_{287} = 100%, corresponding to 91.2% monodeuterioaldehyde. The isotope effect, correcting for the isotopic composition of the starting benzyl alcohol-α-d_1 is calculated as follows.

$$\frac{k_H}{k_D} = \frac{91.2 - 0.4\%}{8.8 - 1.6\%} = 12.6$$

Run 2.—The 2,4-DNP was formed directly (65%): mp 241–245°. The isotopic composition and isotope effects were determined as in run 1.

Anal. Calcd for $C_{13}H_9DO_4N_4$: C, 54.36; H, 3.86. Found: C, 54.44; H, 3.98.

Run 3.—The aldehyde was purified by distillation in a small Hickman still and analyzed by nmr for ratio of aldehydic to aromatic protons. Integral values, average of four scans: aldehydic proton, 3.5 mm; aromatic protons, 219 mm; corresponding to 7.8% of undeuterated benzaldehyde.

Run 4.—The aldehyde was purified by distillation and analyzed by nmr. Integral values, average of six scans: aldehydic proton, 3.3 ±0.1 mm; aromatic protons, 230 ±10 mm; corresponding to 7.2% of undeuterated benzaldehyde.

Runs 5, 6, 7.—Three separate runs, as in runs 3 and 4 above, except that products were purified by glpc.

Run 8.—The distilled benzaldehyde product mixture, $n^{25}D$ 1.5417, was homogeneous by glpc except for a trace of benzene, with no detectable benzyl alcohol or benzoic acid. A portion of the product was converted to the 2,4-DNP for low voltage mass spectral analysis. Mass spectrometry values, average of six scans, at a nominal value of 8 eV were M_{286} = 7.0 ±0.4%; M_{287} = 100%; corresponding to 6.6% benzaldehyde. A portion of the product aldehyde was analyzed directly by nmr in carbon tetrachloride solution. The aldehydic proton at 9.95 ppm was very small. Integral values, average of eight scans, were aldehydic proton, 2.4 ±0.2 mm; aromatic protons, 175 ± 2 mm; corresponding to 6.9% of undeuterated aldehyde. Another portion of the pure product mixture was analyzed by nmr *vs.* a weighed internal trifluoroacetic acid standard in chloroform-*d* solution. The aldehyde (1.67 μmol) was found to contain 0.11 μmol (6.6%) of benzaldehyde by comparison with 0.254 μmol of trifluoroacetic acid. The integral here, average of seven scans, was more respectable, measuring 30 ±0.5 mm and 69.4 ±0.9 mm for the aldehydic and acid protons, respectively.

Run 9.—A mixture of benzyl alcohol (1.000 g) and benzyl alcohol-α-d_2 (1.000 g) in 25 ml of benzene was added all at once to a stirred mixture of 0.25 g of activated manganese dioxide in 25 ml of benzene under nitrogen. After stirring for 0.5 hr, the reaction was worked up in the usual way and the aldehyde mixture was converted to the 2,4-DNP, 327 mg (6%). The competition experiment, therefore, had proceeded without appreciable loss of the starting alcohols. Mass spectrometric analysis of this 2,4-DNP mixture was carried out as follows. A sample of authentic benzaldehyde 2,4-DNP was introduced into the mass spectrometer *via* the direct inlet system at an ionizing voltage, nominally 10 eV, at which there was no measurable M − 1 peak. The M + 1 peak, average of 10 scans, was determined to be 16.25 ±0.25% of the M peak at *m/e* 286. The theoretical value for this M + 1 peak is calculated to be 15.7%. The 2,4-DNP mixture from the competition experiment was then run under identical conditions, after the 286–287 background was negligible. The M + 1 peak here (*m/e* 287), corresponding to aldehyde formed from the slower oxidation of benzyl alcohol-α-d_2 and the isotopic contribution from the *m/e* 286 peak, was determined to be 22.5 ± 0.3% of the peak at *m/e* 286, based on an average of seven scans.

The isotopic composition, correcting for the $^{13}C^{15}N$ (16.25%) contribution of *m/e* 286 to *m/e* 287, is determined to be benzaldehyde 2,4-DNP, 94.1%; benzaldehyde-*d* 2,4-DNP, 5.9%. The isotope effect for this reaction, correcting for both the isotopic composition determined for the benzyl alcohol-α-d_2 and the statistical effect of the presence of 2% benzyl alcohol-α-d_1, is calculated to be 18.2. Since this calculation is based on the results of only one oxidation, the average deviation is estimated to be about +1%.

$$\frac{k_H}{k_D} = \frac{94.1}{5.9 - \left[\frac{(7.1)(0.02)}{(7.1)(0.02) + (1)(0.98)}\right] 5.9} = 18.2$$

Run 10.—At a nominal value of 7-eV ionizing voltage, the isotopic composition determined for a sample of benzaldehyde-α-d_1 2,4-DNP, prepared in the usual way from benzyl alcohol-α-d_2, was >99.5% d_1.

Anal. Calcd for $C_{13}H_9DO_4N_4$: C, 54.36; H, 3.86. Found: C, 54.28; H, 3.70.

The isotopic composition of the benzyl alcohol-α-d_2 was determined by nmr *vs.* a weighed internal 2,6-dichlorobenzyl alcohol standard in chloroform-*d* solution. The deuterated alcohol (8.9 mmol) was found to contain 0.178 mmol (2.0%) of benzyl alcohol-α-d_1 by comparison with 0.142 mmol of 2,6-dichlorobenzyl alcohol. The integrals, average of six scans, measured 26 ±0.8 mm and 16.3 ±1.3 mm for the benzylic hydrogens of the standard (doublet at δ 4.71 ppm) and unknown (broad multiplet at δ 4.40 ppm), respectively.

Run 11.—As in run 9, a mixture of 2,6-dichlorobenzyl alcohol (0.700 g) and 2,6-dichlorobenzyl alcohol-α-d_2 (0.700 g) in benzene was added to a stirred mixture of activated manganese dioxide. After stirring for 1 hr, the reaction was worked up in the usual way and converted to the 2,4-DNP derivative (1%), mp 257–258°. Mass spectrometric analysis of this 2,4-DNP mixture was carried out as follows. A sample of authentic 2,6-dichlorobenzaldehyde 2,4-DNP was introduced into the mass spectrometer as in run 9. The M + 1 peak, average of eight scans, was determined to be 16.1 ±0.1% of the M peak at *m/e* 354. The theoretical value for this M + 1 peak is calculated to be 15.7%. The 2,4-DNP mixture from the competition experiment was then run under identical conditions. The M + 1 peak here (*m/e* 355), average of 15 scans, was determined to be 21.8 ± 0.6% of the peak at *m/e* 354. The isotopic composition is

determined to be 2,6-dichlorobenzaldehyde 2,4-DNP, 94.6%; 2,6-dichlorobenzaldehyde-*d* 2,4-DNP, 5.4%. The isotope effect for this reaction, with corrections as in run 9, is calculated to be 19.5.

The isotopic composition, determined *via* mass spectrometry, for 2,6-dichlorobenzaldehyde-*d* 2,4-DNP, prepared in the usual way from 2,6-dichlorobenzyl alcohol-α-d_2, was >99.5% d_1.

The isotopic composition of the 2,6-dichlorobenzyl alcohol-α-d_2 was determined by nmr *vs.* a weighed internal benzyl alcohol-O-*d* standard in chloroform-*d* solution. The dideuterated alcohol (1.02 mmol) was found to contain 0.016 mmol (1.6%) of monodeuterio alcohol (broad multiplet at δ 4.70 ppm) by comparison with 0.019 mmol of the standard (sharp singlet at δ 4.40 ppm), average of nine scans.

Registry No.—Manganese dioxide, 1313-13-9; benzyl alcohol, 100-51-6; 2,6-dichlorobenzyl alcohol-α-d_2, 21369-49-3; benzaldehyde-α-d_1 (2,4-dinitrophenylhydrazone), 21273-19-8.

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9-Aza Steroids. III.[1] The Synthesis of Some 2-Cyclopentylquinolines as Models for Rings A, B, and D

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A number of 2-(2-quinolyl)cyclopentanones, **2**, **19**–**22**, and **24**, potential intermediates in a 9-aza steroid synthesis, have been prepared by two routes from quinoline N-oxide. The first involves reaction with the enamine of cyclopentanone; the second, condensation with a suitably activated cyclopentanone in the presence of acetic anhydride. Attempts to add a two-carbon unit bridging ring C either by condensation at the cyclopentanone carbonyl or by alkylation at the nitrogen atom have failed. The 2-(2-quinolyl)-2-carbethoxycyclopentylidenecyanoacetate (**40**) could not be reduced or cyclized to a tetracyclic derivative. Quinoline reacted with acetyl chloride and 2-substituted cyclopentanones to give either an N-acetyl-1,4-dihydroquinoline (**47**) or an N-acetyl-1,2-dihydroquinoline (**48**). The reaction failed with other acyl chlorides, giving instead the enol acetates derived from the cyclopentanones.

We have reported[1,2] approaches to a 9-aza steroid synthesis in which rings A, B, and C were prepared bearing substituents suitable for the elaboration of ring D (**1**). However we have had difficulty in obtaining a quantity of intermediate **1**, and lack of success in alkylation experiments on this intermediate[3] and on N-phenyl-4-piperidone, combined with variable success in the cyclization of 3-acetonyl-4-piperidones,[4] have led us to abandon this approach. We discuss here investigation of an alternative route to 9-aza steroids involving the preparation of 2-cyclopentylquinolines (representing rings A, B, and D in the final steroid).

The simplest model for our purpose was 2-(2-quinolyl)cyclopentanone (**2**); Hamana and Noda[5] have prepared 2-(2-quinolyl)cyclohexanone (**3**) from quinoline N-oxide and the morpholine enamine of cyclohexanone, in the presence of benzoyl chloride. By using the enamine of cyclopentanone under their conditions, a good yield of a compound having the correct molecular formula was obtained. However, its orange color, the absence of any absorption in the normal saturated carbonyl region of the infrared, and its nmr spectrum could be interpreted in terms of the 1,2-dihydroquinolylidenecyclopentanone (**2a**); Hamana and Noda's compound might be similarly **3a**.[6] Compound **2** failed to react with methylmagnesium iodide, as did also its hydrochloride, which is certainly in the quinoline form. Not unexpectedly, the compound **2** also failed to react under Knoevenagel conditions with malononitrile, cyanoacetic esters, or cyanoacetamide, nor could an ethylene ketal be obtained. Reduction of the compound **2a** with sodium borohydride gave 2-(2-quinolyl)cyclopentanol (**4**), which was dehydrated by distillation from potassium hydroxide to give 2-(2-quinolyl)cyclopentene (**5**). We were unable to obtain Michael addition products from the cyclopentene **5** under a variety of conditions (listed in the Experimental Section) with malonic ester, cyanoacetic esters, or *t*-butyl acetoacetate, and hence were forced to abandon this attempt to introduce the required two-carbon bridge for ring C.

As the major obstacle to further elaboration of the cyclopentanone in compound **2a** seems to involve the potential conjugation between ketone and quinoline, we have investigated the properties of 2-(2-quinolyl)-cyclopentanones in which a second 2 substituent prevents the formation of dihydroquinolylidene tautomer. An excellent route to 2-substituted quinolines is offered by the reaction between quinoline N-oxide and active methylene derivatives in acetic anhydride, reported by Hamana and Yamazaki;[7] a discussion of the structure of two such compounds (prepared by an alternative route from 2-chloroquinoline and the appropriate sodium salt) has been given by Borror and Haeberer.[8]

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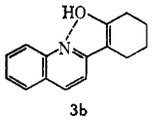
(6) Hamana and Noda interpret their results in terms of the enol structure **3b**; however, 2-cyclopentenylquinoline is not colored. Note also the similarity with compound **25** described subsequently.



3b

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