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The Dienone–Phenol Rearrangement. A Novel Example of Ring B Cleavage

BY PAUL J. KROPP

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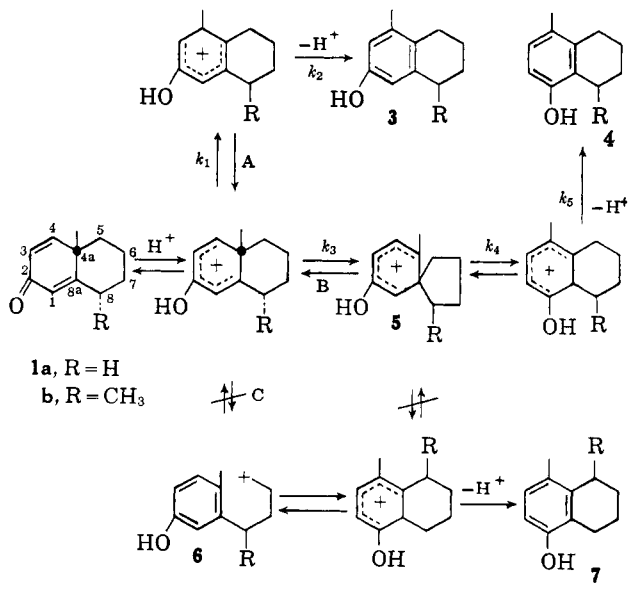
Acid-catalyzed rearrangement of 4aβ,8α-dimethyl-5,6,7,8-tetrahydro-2(4aH)-naphthalenone (**1b**) gave 4,8-dimethyl-5,6,7,8-tetrahydro-1-naphthol (**4b**) and 4,8-dimethyl-5,6,7,8-tetrahydro-2-naphthol (**3b**), with the former product predominating under either aqueous or anhydrous conditions. This is in contrast with the usual predominance of a *m*-cresol-type product (*e.g.*, **3**) under aqueous conditions for such rearrangements. The 8,8a-seco derivatives **12**, **13a**, and **13b** were also formed under various conditions; these represent the first reported examples of ring B cleavage during an acid-catalyzed dienone–phenol rearrangement. The phenol **3b** was identified by an independent synthesis starting with β-(4-methoxy-2-methyl-1-benzoyl)-propionic acid (**14**), obtained by the succinoylation of *m*-methylanisole. Contrary to previous reports, this latter reaction gave, in addition, the 2-methoxy-4-methyl isomer **15**, from which 7,8-dihydro-3,5-dimethyl-1-naphthol (**19b**) was prepared.

Cross-conjugated cyclohexadienones of the type **1** undergo facile isomerization to phenolic products on treatment with aqueous mineral acids or with acetic anhydride containing acidic catalysts. A mixture of two phenols is generally obtained, which result from two separate pathways involving 1,2-methyl migration (path A, Chart I) in one case and rearrangement through an intermediate spiro carbonium ion **5** (path B) in the other.[1-3] The relative yields of *m*-cresol (**3**) and *p*-cresol (**4**) products[4] formed have been found to be highly dependent upon the nature of the media used, with aqueous conditions favoring path A and anhydrous conditions favoring path B.[3] We wish to report that the course of rearrangement of 4a β,8α-dimethyl-5,6,7,8-tetrahydro-2(4aH)-naphthalenone (**1b**)[2,5] is relatively insensitive to the conditions employed, in marked contrast with the behavior of the unsubstituted analog **1a**.[3] Moreover, in certain media the 8,8a-seco derivatives **12**, **13a**, and **13b** are formed in 15–24% yield. These latter products represent a novel course for the dienone–phenol rearrangement.

CHART I



Woodward and Singh[1a] were the first to demonstrate that the major course of the rearrangement in acetic anhydride containing an acid catalyst is conversion to a *p*-cresol structure. Thus rearrangement of **1a** gave the *p*-cresol **4a** in 59% yield.[6] Evidence that the rearrangement proceeds through a spiro carbonium ion[1] (path B) was provided by Bloom,[2] who found that rearrangement of the 8α-methyl derivative **1b** under the same conditions gave the *p*-cresol **4b** in 40% yield.[7] This result precluded a possible alternative mechanism,[1a] path C, which would result in formation of the isomer **7b**.

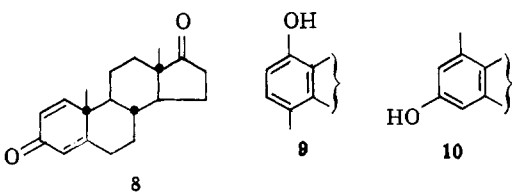
Dreiding, Pummer, and Tomasewski[3] found that when the rearrangement is carried out in aqueous mineral acid, instead of acetic anhydride, the major course becomes simple 1,2-methyl migration (path A), accompanied by a smaller amount of rearrangement by path B. Thus treatment of **1a** with concentrated hydrochloric acid or 50% sulfuric acid gave principally the *m*-cresol **3a**, accompanied by traces of **4a**[3] (see Table I). Similarly, androsta-1,4-dien-3,17-dione (**8**), which

TABLE I

EFFECT OF MEDIA ON THE COURSE OF THE DIENONE–PHENOL REARRANGEMENT

Dienone	Conditions	Yields, % *p*-Cresol (**4a** or **9**)	Yields, % *m*-Cresol (**3a** or **10**)
4a-Methyl-5,6,7,8-tetrahydro-2(4aH)-naphthalenone (**1a**)	Acetic anhyd.[1a]	59	..
	HCl[3]	~10	62
	50% H_2SO_4[3]	Trace	52
Androsta-1,4-dien-3,17-dione (**8**)	Acetic anhyd.[8]	92	..
	HCl[3]	~26	48
	HBr[3]	~10	55

in acetic anhydride gave the normal *p*-cresol product **9** in 92% yield,[8] gave in hydrochloric or hydrobromic acid chiefly the *m*-cresol **10**, along with a smaller amount of **9**.[3]



Of the four B-ring substitution patterns I–IV, involving the two possible migration centers of the spiro intermediate of path B, only compounds of types I (*e.g.*, **1a**) and II (*e.g.*, **8**) have been studied in detail.

(1) (a) R. B. Woodward and T. Singh, *J. Am. Chem. Soc.*, **72**, 494 (1950); (b) R. B. Woodward in A. Todd, "Perspectives in Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1956, p. 178.

(2) S. M. Bloom, *J. Am. Chem. Soc.*, **80**, 6280 (1958).

(3) A. S. Dreiding, W. J. Pummer, and A. J. Tomasewski, *ibid.*, **75**, 3159 (1953).

(4) For convenience and simplicity in the Discussion section, the terms "*m*-cresol" and "*p*-cresol" are used to designate the methyl-substituted tetrahydronaphthol structures **3** and **4**, respectively, and their steroidal analogs **10** and **9**.

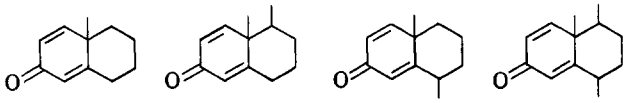
(5) S. M. Bloom, *J. Org. Chem.*, **24**, 278 (1959).

(6) Rearrangements conducted in acid anhydrides give phenol esters, which are usually hydrolyzed to the corresponding phenols without prior isolation. For simplicity only the phenols are represented here.

(7) From an analysis of the infrared spectrum of the crude product, Bloom concluded that the *m*-cresol **3b** had also been formed in 5–10% yield.[2] This material was not isolated or characterized, however.

(8) A. S. Dreiding and A. Voltman, *J. Am. Chem. Soc.*, **76**, 537 (1954).

Both of these types were found to rearrange concurrently *via* paths A and B and to show marked solvent effects on the relative involvement of the two paths. Type III has been investigated in the form of **1b**, but only to the extent to show that path B, rather than C, operates in acetic anhydride.[2] A detailed study of **1b** was undertaken to determine whether similar solvent effects are encountered in the rearrangement of dienones of type III.



I II III IV

The results of this study are summarized in Table II. Under all of the conditions examined, both anhydrous and aqueous, the known *p*-cresol **4b**[2] was the predominant product. Formed in smaller yield in each case was a second phenol which had infrared absorption at 11.56 μ, characteristic of two isolated aromatic hydrogens.[9] From analogy with previous work,[3] the structure **3b** was assigned. Support for this assignment was provided by a comparison of the aromatic region of the n.m.r. spectrum (one two-proton multiplet at 3.42 τ) with that of several model trimethylphenols (see Table III). It was found that the *o*- and *p*-protons of substituted phenols appear at higher frequencies than *m*-protons, presumably because of increased shielding of the *o*- and *p*-protons as a result of higher electron densities at those positions. With 3,4,5-trimethylphenol, in which both of the protons are in *o*-positions, only a single multiplet at 3.49 τ was observed.[10] Final proof for the assignment **3b** was obtained by dehydrogenation studies and an independent synthesis (described below).[12]

TABLE II

REARRANGEMENT OF 4aβ,8α-DIMETHYL-5,6,7,8-TETRAHYDRO 2(4aH)-NAPHTHALENONE (**1b**)

	Yields, %[a]				Path B/
	3b	4b	13	12	path A
$(CH_3CO)_2O$	13	51	15 (X = OH)	..	5.1
$(CF_3CO)_2O$	11[b]	46	17 (X = OH)	7[b]	6.4
HCl[c]	32	46	16 (X = Cl)	..	1.9
50% H_2SO_4	29	63	...	..	2.2

[a] Yields given for a typical run. These results were substantially reproduced in two to four similar determinations. Yields are based on material isolated by column chromatography unless otherwise indicated. [b] Estimated from gas chromatographic analysis. [c] Yields adjusted for 4% recovery of starting material.

TABLE III

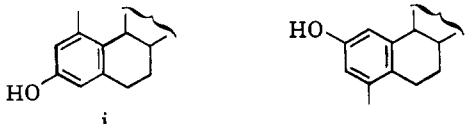
N.M.R. DATA FOR MODEL TRIMETHYLPHENOLS

	Chemical shifts, τ[a]	
Phenol	Aromatic H	$-CH_3$
2,3,5-Trimethyl	3.42,[b] 3.54[b]	7.77, 7.88
2,4,6-Trimethyl	3.23[c]	7.79
3,4,5-Trimethyl	3.49[b]	7.77, 7.91
2,4,5-Trimethyl	3.12,[c] 3.44[b]	7.82

[a] Determined in 10% deuteriochloroform solution; further dilution caused no changes in chemical shifts. [b] *ortho* or *para*. [c] *meta*.

(9) L. J. Bellamy, "Infrared Spectra of Complex Molecules," J. Wiley and Sons, New York, N. Y., 1958, p. 79.

(10) Similarly, 1-methylestradiol 17-acetate (i) gives a single two-proton multiplet at 3.52 τ.[11] However, 2,17β-dihydroxy-4-methyl-1,3,5(10)-estratriene 17-acetate (ii) gives two one-proton multiplets at 3.31 and 3.43 τ.[11] Presumably the 3.31-τ peak is due to the C-1 proton, which is shifted downfield by deshielding from the steroid nucleus.



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(11) P. J. Kropp and W. F. Erman, *J. Am. Chem. Soc.*, **85**, 2456 (1963).

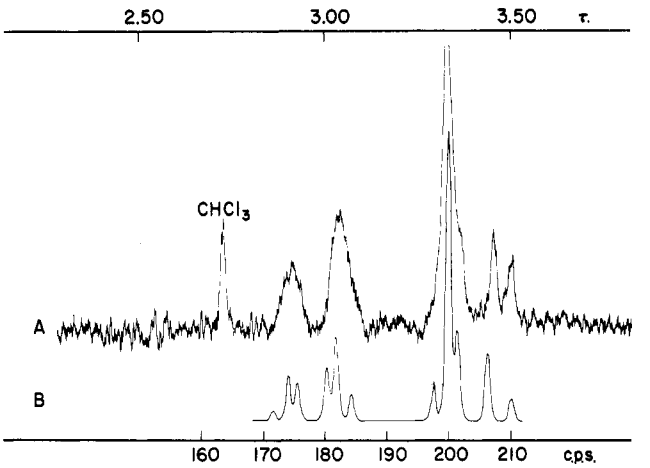


Fig. 1.—Curve A: Aromatic region of the proton spectrum of 5-(5-hydroxy-*o*-tolyl)-2-pentene (**12**). The broadening of the peaks at 172.2 and 182.9 c.p.s. is believed to arise from long range coupling with adjacent alkyl groups. Curve B: Computed spectrum assuming τ_A = 2.908 (144.5 c.p.s.), τ_B = 3.397 (203.8 c.p.s.), τ_C = 3.340 (200.4 c.p.s.), J_{AB} = 7.7 c.p.s., J_{BC} = 4.0 c.p.s., and J_{AC} = 0.

Also obtained in acetic anhydride was a third phenol, which was shown to be 5-(5-hydroxy-*o*-tolyl)-2-pentanol (**13a**). In hydrochloric acid the analogous chloride **13b** was formed instead, and in trifluoroacetic anhydride a mixture of **13a** and the corresponding olefin **12** was obtained. All three of the phenols (**12**, **13a**, **13b**) exhibited the same three-proton pattern in the aromatic region (Fig. 1). This pattern may be analyzed by considering the two peaks at 175.2 and 182.9 c.p.s. to be one half of an AB quartet.[13a] The other proton of this AB pair is spin coupled further to a third proton H_C. This coupling is manifested in the splitting of the high-field member of the AB doublet, which results in peaks at 206.8 and 210.8 c.p.s. The low-field member of the H_B doublet overlaps with the H_C peak at 200.4 c.p.s. From this analysis, which gives J_{AB} = 7.7, J_{BC} = 4.0, and J_{AC} = 0 c.p.s., a computer was used to calculate the spectrum.[14] It is seen that there is reasonable agreement between the experimental and calculated spectra so that the assumed parameters are probably those characteristic of this compound.

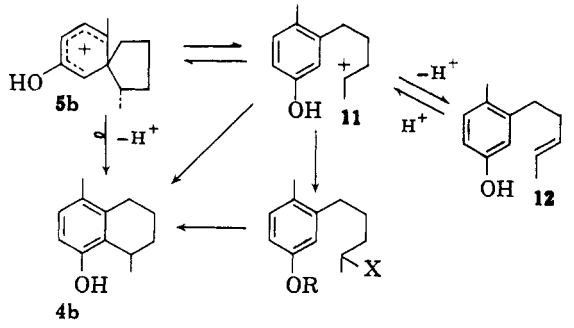
In view of the observations mentioned above, that the protons *ortho* and *para* to the hydroxyl group appear at higher field than protons *meta* to the hydroxyl group in substituted phenols, this pattern is consistent only with the 3,4-disubstituted structure. The low-field proton H_A (2.91 τ) is identified with the C-5 proton (*meta* to the OH). The spin coupling constant J_{AB} (7.7 c.p.s.) is characteristic of coupling with an *o*-proton (C-6). The proton at 3.40 (H_B) arises from the C-6 proton. There are two coupling constants associated with this proton, the 7.7 c.p.s. value (J_{AB}) from coupling with the C-5 proton and a 4.0 c.p.s. value (J_{BC}) from coupling with the *meta* C-2 proton.[13b] The C-2 proton, therefore, has a chemical shift of 3.34 τ. Finally in support of this interpretation, the spectrum of 3,4-dimethylphenol was found to be virtually superimposable in the aromatic region with that of the phenols **12** and **13**.

(12) The *m*-cresol **3b** is also obtained from **1b** in yields up to 43% by photochemical rearrangement in acidic media.[11]

(13) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959: (a) pp. 89–90; (b) p. 85; (c) pp. 53–55.

(14) The calculations were made on an IBM 7090 computer using a program developed by A. A. Bothner-By (FREQINT III).

CHART II



13a, R = H, X = OH
b, R = H, X = Cl
c, R = $COCH_3$, X = $OCOCH_3$

3,4-Dialkyl-substituted phenols could arise from a carbonium ion **11**, formed by opening of the spiro intermediate, **5b**, or from the ion **6b**, involving path C. The latter possibility was ruled out by the presence of a one-proton peak at 6.18 τ in the n.m.r. spectrum of **13a**, which indicates a secondary hydroxyl group.[13c] The methyl group and the methinyl proton of **13a**, the diacetate **13c**, and the chloride **13b** showed the expected chemical shifts[13c] for the part-structure $-CH(X)CH_3$ (see Table IV). Similarly, the spectrum of **12** indicated the presence of two vinylic protons (4.52 τ) and a vinylic methyl group (8.38 τ) in the side chain. The structural assignments **12** and **13a** were confirmed by facile acid-catalyzed cyclization of the compounds to the *p*-cresol **4b**.

Synthesis of *m*-Cresol 3b.—The structural assignment **3b** for the *m*-cresol product was confirmed by an independent synthesis starting with the succinoylation of *m*-methylanisole, as outlined in Chart III. This reaction is reported[15] to give only β-(4-methoxy-2-methyl-1-benzoyl)-propionic acid (**14**) in nitrobenzene. However, in the present work, in which a nitrobenzene–tetrachloroethane solvent mixture[16] was used, an approximately 1:1 mixture of **14** and the 2-methoxy-4-methyl isomer **15**[17] was obtained. The occurrence of a significant amount of attack at C-6 of *m*-methylanisole is not unexpected, since it is both *ortho* to the methoxyl group and *para* to the methyl substituent, but is not as hindered as C-2. Although mixtures of products arising from both *ortho* and *para* attack is common for the succinoylation of phenols, phenol ethers are reported to give only *p*-substituted products.[16]

TABLE IV
N.M.R. EVIDENCE FOR PART STRUCTURE $-CHCH_3$ (X)

Compd.	X =	Chemical shifts, τ —H	Chemical shifts, τ $-CH_3$
13a	OH	6.18[a]	8.82[b]
13b	Cl[c]	5.92[a]	8.48[b]
13c	$OCOCH_3$	5.04[a]	8.80[b]

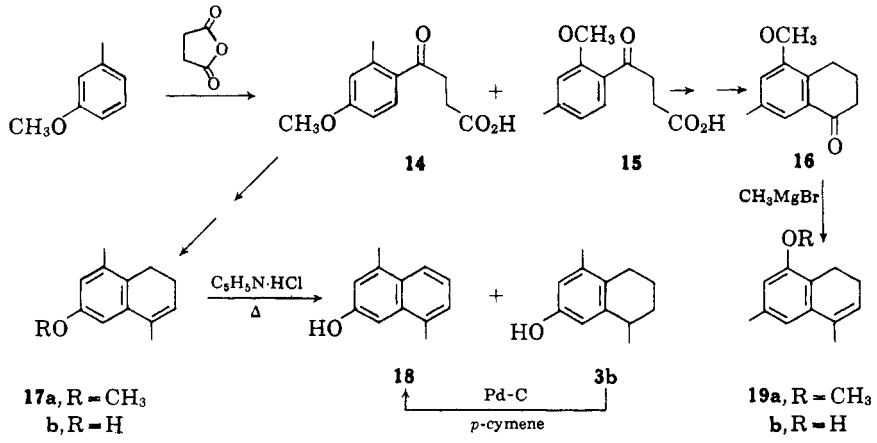
[a] Unresolved multiplet. [b] Doublet. [c] Spectrum determined on the 3,5-dinitrobenzoate derivative.

Clemmensen reduction of **14**,[15b] followed by cyclization and treatment with methyl Grignard reagent gave the known dihydronaphthyl ether **17a**.[18] Similarly the acid **15** was converted to the known tetralone **16**[19] and then to the dihydronaphthyl ether **19a**. Fusion of **19a** with pyridine hydrochloride at 185° gave in 88% yield the dihydronaphthol **19b**. However, when similar treatment of **17a** was attempted, a larger scale was employed and a higher temperature (240°) was required. Instead of the expected dihydronaphthol **17b**, a 1:1 mixture of *m*-cresol **3b** and the naphthol **18**[18] was obtained in 65% yield, which presumably arose from disproportionation of **17b**. The *m*-cresol **3b** obtained by this route was found to be identical with the material formed by the acid-catalyzed rearrangement of the dienone **1b**. The naphthol **18** could also be obtained from **3b** by dehydrogenation over palladium–charcoal in refluxing *p*-cymene.

Discussion

Although ring-B seco derivatives have been obtained previously under reductive,[20] enzymatic,[21] or pyrolytic[22] conditions for dienone–phenol conversions, to our knowledge the formation of **13a**, **13b**, and **12** represents the first reported example of ring B cleavage under the normal conditions of acid-catalyzed rearrangement. It is also the first example of ring-B cleavage under any conditions involving prior rearrangement of ring B. The seco products **13** apparently arise from trapping of the cation **11** by the acid anhydride or by chloride ion. In the less nucleophilic trifluoroacetic anhydride, elimination to the olefin **12** can compete effectively with ester formation.[23] Although the alco-

CHART III



(15) (a) K. W. Rosenmund and D. Shapiro, *Arch. Pharm.*, **272**, 313 (1934) [*Chem. Abstr.*, **28**, 4046 (1934)]; (b) R. D. Desai and M. A. Wali, *Proc. Indian Acad. Sci.*, **6A**, 144 (1937) [*Chem. Abstr.*, **32**, 509 (1938)]; (c) D. Papa, E. Schwenk, and H. Hankin, *J. Am. Chem. Soc.*, **69**, 3018 (1947).

(16) *Cf.* E. Berliner, *Org. Reactions*, **5**, 229 (1949).

(17) J. J. Trivedi and K. S. Nargund, *J. Univ. Bombay*, **10**, Pt. 3, 99 (1941) [*Chem. Abstr.*, **36**, 3801 (1942)].

(18) L. Ruzicka and L. Sternbach, *Helv. Chim. Acta*, **23**, 355 (1940).

(19) R. G. Cooke and H. Dowd, *Australian J. Sci. Res.*, **5A**, 760 (1952) [*Chem. Abstr.*, **48**, 2022 (1954)].

(20) K. Tsuda, E. Ohki, S. Nozoe, and K. Ikekawa, *J. Org. Chem.*, **26**, 2614 (1961).

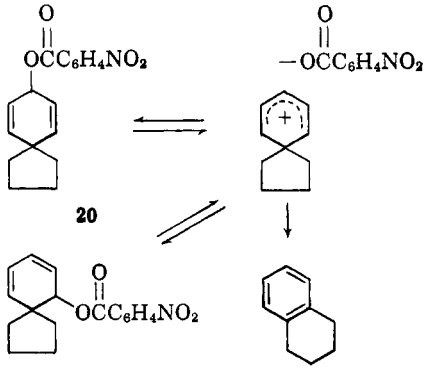
(21) R. M. Dodson and R. D. Muir, *J. Am. Chem. Soc.*, **83**, 4627 (1961).

(22) B. J. Magerlein and J. A. Hogg, *Tetrahedron*, **2**, 80 (1958).

(23) Since sulfuric acid has a very limited solubility in trifluoroacetic

hol **13a** or the olefin **12** may be formed in 50% sulfuric acid as well, they would undergo rapid cyclization to the *p*-cresol **4b** under these conditions and would not be found in the final reaction mixture. Treatment of pure **13a** or **12** with 50% sulfuric acid gave **4b** in quantitative yields.

It is interesting to note that Friedrich and Winstein[24] were able to detect no open-chain products (4-phenyl-1-butanol or 4-phenyl-1-butene) in the acetolysis or formolysis of the *p*-nitrobenzoates **20** and **21**. Apparently ring expansion is considerably faster than ring opening in this system. However, in this case ring opening could give only a primary carbonium ion *vs.* a secondary ion in the case of **11**. In a formal sense the ring opening process is a reversal of the well-known formation of dienones by the solvolysis of substituted 4-arylbutanol esters.[25]



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The striking effect of media on the predominant course of rearrangement of the dienone **1a** is exhibited to a much lesser degree by the 8α-methyl derivative **1b**. Although the ratio path B/path A for **1b** does decrease approximately threefold in going from trifluoroacetic anhydride to aqueous conditions (see Table II), it does not become less than one, and **1b** rearranges predominantly by path B under all of the conditions studied. This marked difference in sensitivity to media exhibited by **1a** and **1b** allows some additional insight into the delicate balance between paths A and B of the dienone–phenol rearrangement and into the nature of media effects upon this balance.[26]

At first glance the occurrence of methyl migration (path A) in dienone–phenol rearrangements of compounds of the type **1** seems surprising. Although little information is available concerning the relative aptitudes of alkyl groups for migration from carbon to an electron-deficient carbon, Stiles and Mayer[27] obtained the order *t*-butyl > ethyl > methyl from a study of the pinacol rearrangement in 50% sulfuric acid.[28] The best example for the present work comes from the dienone–phenol rearrangement itself, in which there is *exclusive* migration by the more highly substituted carbon of spiro intermediates of the type **5**. This is true even under aqueous conditions, in which methyl migration occurs to the greatest extent.

In aqueous media **1a** rearranges predominantly by path A, but **1b** by path B. Of the various factors that might be ascribed to the influence of the additional *equatorial* methyl substituent of **1b**, it does not seem likely that it is a steric effect—either one of increased steric interaction in one of the intermediates or one of steric interference with solvation of any of the intermediates. Indeed, if any added steric interaction exists in the case of **1b**, it would appear to involve path B—which, in fact, is favored by the presence of the methyl substituent.[29] Obviously the course of rearrangement is not determined solely by the rates k_1 and k_3, but also reflects k_4 since the presence of the methyl substituent of **1b** has such a pronounced effect. Apparently in aqueous media methyl migration can compete fairly well with two consecutive migrations involving methylene, but not with migration by methylene followed by methine migration.[30] In nonaqueous media path A cannot compete as effectively with path B in the case of either **1a** or **1b**. The increased aptitude for methyl migration under aqueous conditions could indicate preferential stabilization of that transition state by solvation.

Further studies of the effects of structure and media on the course of the dienone–phenol rearrangement designed to elucidate the mechanistic features are in progress.

Experimental[31]

Rearrangement of 4aβ,8α-Dimethyl-5,6,7,8-tetrahydro-2(4aH)-naphthalenone (1b). A. In Acetic Anhydride.—Following the procedure of Bloom,[2] 462 mg. of the dienone **1b** was treated with a total of 23 ml. of acetic anhydride containing 5 drops of sulfuric acid at room temperature for 6 hr. Isolation as described[2] gave 530 mg. of a colorless oily mixture of phenol acetates, which was found by gas chromatography and infrared analysis to contain no residual dienone. Hydrolysis with ethanolic hydrochloric acid[2] gave 415 mg. of a pale yellow oil, which was chromatographed on 15 g. of silica gel (Davison Chemical Co., 200 mesh). Elution with 900 ml. of 1:3 benzene–hexane gave 235 mg. (51% yield) of **4,8-dimethyl-5,6,7,8-tetrahydro-1-naphthol (4b)**, m.p. 90–91°. Recrystallization from petroleum ether gave colorless plates, m.p. 95–96°, and λ_{max} 12.42 μ; reported[2] m.p. 93–94.5°, 40% yield.

Further elution with 600 ml. of 1:1 benzene–hexane gave 60 mg. (13% yield) of **4,8-dimethyl-5,6,7,8-tetrahydro-2-naphthol (3b)**, m.p. 92–94°. Recrystallization of comparable material

anhydride, rearrangements under these conditions might occur heterogeneously, thus accounting for the appearance of **12**. However, gas chromatographic studies suggest that **12** is also formed in small yield (about 1%) in acetic anhydride.

(24) E. C. Friedrich and S. Winstein, *Tetrahedron Letters*, 475 (1962).

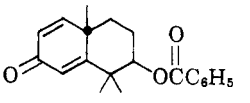
(25) S. Winstein and R. Baird, *J. Am. Chem. Soc.*, **79**, 756 (1957); S. Masamune, *ibid.*, **83**, 1009 (1961); L. Mandell, D. Caine, and G. E. Kilpatrick, *ibid.*, **83**, 4457 (1961).

(26) Although different temperatures are normally employed for the aqueous (100°) and anhydrous (room temperature) conditions, the observed differences in product ratios cannot be attributed to a temperature effect. In the present study substantially the same results were obtained in acetic anhydride at 25 and 100°. Dreiding, Pummer, and Tomasewski[1] report similar results from the treatment of **8** with hydrochloric acid at room temperature or under reflux.

(27) M. Stiles and R. P. Mayer, *J. Am. Chem. Soc.*, **81**, 1497 (1959); see also P. Warrick, Jr., and W. H. Saunders, Jr., *ibid.*, **84**, 4095 (1962).

(28) However, H. O. House, E. J. Grubbs, and W. F. Gannon, *ibid.*, **82**, 4099 (1960), obtained the order methyl ~ propyl > isopropyl ~ *t*-butyl from a study of the reaction of ketones with diazomethane; apparently the same order does not obtain in all types of molecular rearrangements. This may be due in part to the use of different media.

(29) It should be noted that in the case of an axial 8β-methyl substituent considerable steric interaction with the 4a-angular methyl group occurs in the formation of a spiro carbonium ion of the type **5**. This, along with increased eclipsing of the other ring B substituents in spiro carbonium ion formation, is reflected in the exclusive rearrangement of the dienone iii *via* path A; *cf.* B. R. Davis and T. G. Halsall, *J. Chem. Soc.*, 1833 (1962).



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(30) In the case of steroids, in which methyl migration (path A) predominates over methinyl migration (path B or C) in aqueous media, it is not possible to evaluate the effects of the bulky C and D rings on the course of the rearrangement. Furthermore, the available data do not indicate whether path B or path C operates in this case.

(31) Ultraviolet spectra were determined in absolute ethanol using a Cary Model 14 spectrophotometer, and infrared spectra were obtained in 5% methylene chloride solution on a Perkin-Elmer Infracord spectrophotometer. Gas chromatographic separations were effected at 200° using a 5 ft. × 0.25 in. column containing 20% GE-silicone fluid 96 on 60/80 mesh firebrick. Melting points were determined on a micro-hotstage and are calibrated and corrected. N.m.r. spectra were obtained in deuteriochloroform solution with a Varian model A-60 spectrometer, using tetramethylsilane as an internal standard. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

from hexane gave colorless prism clusters, m.p. 95.5–96.0°; λ_{max} 2.75, 6.20, and 11.56 μ, and λ_{max} 283 mμ (ϵ 1,900); n.m.r. spectrum: 3.42 (m, 2, CH-1 and -3),[32a] 7.82 (s, 3, CH_3-4), and 8.76 τ (d, 3, J_{AB} = 7, CH_3-8).[32b]

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.7; H, 9.1.

Elution with benzene and 1:9 ether–benzene gave 7 mg. of oily material which was discarded. Finally, elution with 600 ml. of 1:3 ether–benzene gave 76 mg. (15% yield) of **5-(5-hydroxy-*o*-tolyl)-2-pentanol** (**13a**), m.p. 77–79°. Recrystallization twice from ether–hexane gave colorless needle clusters, m.p. 78–79°; λ_{max} 2.74, 6.20, and 12.24 μ, and λ_{max} 219 (ϵ 4600) and 280 mμ (ϵ 1500); n.m.r. spectrum: 6.18 (m, 1, CH-2), 7.83 (s, 3, aromatic CH_3), and 8.82 τ (d, 3, J_{AB} = 6, CH_3-1).

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.2; H, 9.4.

Treatment with a 2:1 mixture of pyridine–acetic anhydride overnight at room temperature gave an oily **diacetate** (**13c**), λ_{max} 5.68 and 5.78 μ; n.m.r. spectrum: 5.04 (m, 1, CH-2), 7.74 (s, 6, $OCOCH_3$), 8.00 (s, 3, aromatic CH_3), and 8.80 τ (d, 3, J_{AB} = 6, CH_3-1).

B. In 50% Sulfuric Acid.—Following the general procedure of Dreiding, Pummer, and Tomasewski,[3] 1.00 g. of the dienone **1b** was treated with 10 ml. of 50% sulfuric acid at 100° for 30 min. under an atmosphere of nitrogen. The reaction mixture, which became turbid after about 15 min., was cooled to room temperature and extracted with a total of 250 ml. of ether. The combined ether extracts were washed with water, saturated sodium bicarbonate solution, and saturated sodium chloride solution. The combined aqueous portions were neutralized with sodium bicarbonate and extracted with ether. The ether fractions were then dried over anhydrous sodium sulfate. Removal of solvent on a rotary evaporator at 40° and aspirator pressure gave 1.01 g. of a colorless oily mixture of phenols. Chromatographic separation on 30 g. of silica gel as described above gave 630 mg. (63% yield) of 4,8-dimethyl-5,6,7,8-tetrahydro-1-naphthol (**4b**), m.p. 95–96°, which showed no melting point depression on admixture with the material described in part A.

Further elution gave 289 mg. (29% yield) of 4,8-dimethyl-5,6,7,8-tetrahydro-2-naphthol (**3b**), m.p. 92–94°. Recrystallization from hexane provided colorless prism clusters, m.p. 94–95°, m.p. 94–96° when mixed with the material described above.

C. In Hydrochloric Acid.—Following the procedure of Dreiding, Pummer, and Tomasewski,[3] 1.00 g. of the dienone **1b** was treated with 10 ml. of concentrated hydrochloric acid at 100° for 45 min. under an atmosphere of nitrogen. The reaction mixture became turbid after 7 min. Isolation as described in part B gave 1.03 g. of a pale yellow oil, which was chromatographed on 30 g. of silica gel. Elution with 1.5 l. of 1:3 benzene–hexane gave 444 mg. of 4,8-dimethyl-5,6,7,8-tetrahydro-1-naphthol (**4b**), m.p. 96–97° and m.m.p. (with material described in part A) 96–97°.

Further elution with 2.4 l. of 1:3 benzene–hexane gave 306 mg. of 4,8-dimethyl-5,6,7,8-tetrahydro-2-naphthol (**3b**), m.p. 93–94.5° and m.m.p. 93–95°.

Elution with 2.7 l. of 1:1 benzene–hexane provided 180 mg. of **2-chloro-5-(5-hydroxy-*o*-tolyl)-pentane** (**13b**) as a colorless oil, which was characterized as the **3,5-dinitrobenzoate**, fine colorless needles, m.p. 93–94°; λ_{max} 5.70, 6.12, 12.38 μ; n.m.r. spectrum: 5.92 (m, 1, CH-2), 7.67 (s, 3, aromatic CH_3), and 8.48 τ (d, 3, J_{AB} = 6.5, CH_3-1).

Anal. Calcd. for $C_{19}H_{19}O_6N_2Cl$: C, 56.09; H, 4.71; N, 6.89; Cl, 8.72. Found: C, 55.9; H, 4.8; N, 6.8; Cl, 9.1.

Finally, elution with 1:19 ether–benzene gave 39 mg. of crystalline starting dienone. The yields, adjusted for recovered starting material, were 46, 32, and 16%, respectively.

D. In Trifluoroacetic Anhydride.—A solution of 500 mg. of the dienone **1b** in 11 ml. of trifluoroacetic anhydride was stirred with 5 drops of concentrated sulfuric acid at room temperature in the dark for 5 hr. The reaction mixture was then poured into excess saturated sodium carbonate solution. After all of the anhydride was hydrolyzed, the mixture was extracted with four 50-ml. portions of ether. The combined extracts were dried over saturated sodium chloride solution and anhydrous sodium sulfate. Evaporation of the solvent at reduced pressure gave 564 mg. of an amber oil, which was dissolved in 25 ml. of methanol and treated with 25 ml. of 10% potassium carbonate solution for 2 hr. at room temperature. Removal of the methanol at reduced pressure, extraction of the aqueous residue with three 100-ml. portions of ether, drying of the combined extracts over saturated sodium chloride solution and anhydrous sodium sulfate, and evaporation of the solvent at reduced pressure gave 507 mg. of an amber oil. Chromatography on 15 g. of silica gel gave, on elution with 1 l. of 1:3 bezene–hexane, 232 mg. (46% yield) of 4,8-dimethyl-5,6,7,8-tetrahydro-1-naphthol (**4b**), m.p. 95–96°.

Further elution gave 90 mg. of a colorless oil which was separated by gas chromatography into 55 mg. (11% yield) of crystalline 4,8-dimethyl-5,6,7,8-tetrahydro-2-naphthol (**3b**), m.p. 93–95°, and 35 mg. (7% yield) of **5-(5-hydroxy-*o*-tolyl)-2-pentene** (**12**) as a colorless oil, λ_{max} 2.75 and 6.20 μ; n.m.r. spectrum: 4.52 (2, m, CH-2 and -3), 7.80 (m, 3, aromatic CH_3), and 8.38 τ (m, 3, CH_3-1).

Finally, elution with 450 ml. of 1:3 ether–benzene gave 91 mg. (17% yield) of 5-(5-hydroxy-*o*-tolyl)-2-pentanol (**13a**) as colorless needles, m.p. 77–79°.

Cyclization of 5-(5-Hydroxy-*o*-tolyl)-2-pentanol (**13a**).—A solution of 26 mg. of alcohol **13a** in 10 ml. of ethylene dichloride containing 0.2 ml. of boron trifluoride etherate was heated under reflux in an atmosphere of nitrogen. The reaction mixture was diluted with 30 ml. of methylene chloride, washed with 30 ml. of water, dried over saturated sodium chloride solution and anhydrous sodium sulfate, and evaporated to dryness to give 24 mg. of prisms, m.p. 94–97°. Recrystallization from hexane gave 18 mg. of colorless plates, m.p. 96–97°. The melting point was unchanged on admixture with an authentic sample of 4,8-dimethyl-5,6,7,8-tetrahydro-1-naphthol (**4b**). Treatment of a 5-mg. portion of **13a** with 2 ml. of 50% sulfuric acid as described below for **12** gave 4 mg. of a colorless oil which crystallized on seeding with **4b** and which gave only one peak upon gas chromatographic analysis.

Cyclization of 5-(5-Hydroxy-*o*-tolyl)-2-pentene (**12**).—A mixture of 23 mg. of olefin **12** in 2 ml. of 50% sulfuric acid was maintained at 105° under an atmosphere of nitrogen for 30 min. The reaction mixture was cooled, neutralized with excess saturated sodium carbonate solution, and extracted with two 50-ml. portions of ether. The combined ether extracts were dried over saturated sodium chloride solution and anhydrous sodium sulfate and evaporated to dryness to give 24 mg. of an amber oil which crystallized on seeding with a specimen of 4,8-dimethyl-5,6,7,8-tetrahydro-1-naphthol (**4b**) to give colorless plates, m.p. 93–96°; mixture melting point with authentic **4b** 93–97°.

Succinoylation of *m*-Methylanisole.—A modification of the general procedure of Berliner[16] was employed. Treatment of 49 g. (0.40 mole) of *m*-methylanisole with 42 g. (0.42 mole) of succinic anhydride and 112 g. (0.84 mole) of aluminum chloride in 400 ml. of nitrobenzene and 100 ml. of tetrachloroethane at 0° for 3 days gave, after acidification and steam distillation, 50 g. (56% yield) of colorless mixed crystals, m.p. 132–134.5°. Separation by fractional recrystallization from acetone gave in approximately equal amounts colorless needles, m.p. 138–139°, and colorless prisms, m.p. 126–127°. Reported for β-(4-methoxy-2-methyl-1-benzoyl)-propionic acid (**14**)[15] m.p. 138°, and for β-(2-methoxy-4-methyl-1-benzoyl)-propionic acid (**15**),[17] m.p. 126°.

3,5-Dimethyl-7,8-dihydro-1-naphthol (**19b**).—Following the general procedure of Ruzicka and Sternbach,[18] a solution of 5.73 g. (30 mmoles) of 3,4-dihydro-5-methoxy-7-methyl-1(2H)-naphthalenone (**16**)[19] in 25 ml. of anhydrous ether was added dropwise with stirring and ice-bath cooling under an atmosphere of nitrogen to 25 ml. of a solution containing 80 mmoles of methylmagnesium bromide. The resulting mixture was heated under reflux for 30 min., cooled to room temperature, and then added to 50 ml. of iced 10% sulfuric acid. The aqueous mixture was extracted with three 50-ml. portions of ether, and the combined ether extracts were washed with 50-ml. portions of water, saturated sodium carbonate solution, and saturated sodium chloride solution. Drying over anhydrous sodium sulfate and removal of the solvent under reduced pressure gave a brown oil. Distillation through a 6-in. Vigreux column gave 4.04 g. of 4,6-dimethyl-8-methoxy-1,2-dihydronaphthalene (**19a**) as a colorless liquid, b.p. 110–113° at 1.8 mm., λ_{max} 6.20 and 12.00 μ; n.m.r. spectrum: 3.42 (s, 1, CH-5), 3.54 (s, 1, CH-7), 4.26 (m, 1, CH-3), 6.28 (s, 3, CH_3O-), 7.73 (s, 3, CH_3-6), and 8.02 τ (m, 3, CH_3-4).

A mixture of 350 mg. of the ether **19a** and 3.6 g. of freshly prepared anhydrous pyridine hydrochloride was maintained at 185° under an atmosphere of nitrogen for 1.5 hr. The reaction mixture was cooled to room temperature, diluted with 100 ml. of water, and extracted with three 50-ml. portions of ether. The combined ether extracts were washed with water, 10% hydrochloric acid, water, and saturated sodium chloride, and then dried over anhydrous sodium sulfate. Evaporation of the solvent gave 349 mg. of a partially crystalline amber oil, which was chromatographed on 15 g. of silica gel. Elution with 1.2 l. of 1:3 benzene–hexane gave 285 mg. (88% yield) of colorless needles, m.p. 114–117°. Recrystallization from hexane gave long needles, m.p. 117–118.5°; λ_{max} 2.75, 6.20, 6.34, and 11.92 μ; λ_{max} 221 (ϵ 24,800) and 267 mμ (ϵ 10,600); n.m.r spectrum: 3.30 (s, 1, CH-4), 3.50 (s, 1, CH-2), 4.14 (m, 1, CH-6), 7.72 (s, 3, CH_3-3), and 7.98 τ (m, 3, CH_3-5).

Anal. Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 83.0; H, 8.3.

(32) (a) Indicates multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and assignment; (b) coupling constants given in c.p.s.

Cleavage of 4,8-Dimethyl-6-methoxy-1,2-dihydronaphthalene (17a).—A mixture of 1.68 g. of the ether **17a**[18] and 18 g. of freshly prepared anhydrous pyridine hydrochloride was maintained at 240° under an atmosphere of nitrogen for 2 hr. Isolation as described above gave 1.35 g. of an amber oil, which was chromatographed on 50 g. of silica gel. Elution with 2.5 l. of 1:1 benzene–hexane gave 0.99 g. (65% yield) of colorless needles which was shown by gas chromatographic analysis to be a 1:1 mixture of 4,8-dimethyl-5,6,7,8-tetrahydro-2-naphthol (**3b**) and 4,8-dimethyl-2-naphthol (**18**).[18] Recrystallization from ether–hexane gave 304 mg. of naphthol **18** as colorless needles, m.p. 152–154°. The phenol **3b** was separated from a portion of the mother liquors by gas chromatography to give colorless compact needle clusters, m.p. 94–95° after final recrystallization from hexane. The melting point was unchanged on admixture with the material obtained from rearrangement of the dienone **1b** in acetic anhydride as described above.

Dehydrogenation of 4,8-Dimethyl-5,6,7,8-tetrahydro-2-naphthol (3b).—Following the general procedure of Wenkert and Dave,[33] 500 mg. of 4,8-dimethyl-5,6,7,8-tetrahydro-2-naphthol obtained from the acetic anhydride–sulfuric acid rearrangement of the dienone **1b**, as described in part A above, was heated under reflux with 50 ml. of *p*-cymene and 200 mg. of 10% palladium-on-charcoal in a nitrogen atmosphere for 76 hr. The solvent was removed by steam distillation and the resulting aqueous residue in the distilling flask (approximately 250 ml.) was passed through a paper filter while still hot. On cooling, the aqueous solution yielded 86 mg. of **4,8-dimethyl-2-naphthol (18)**[18] as colorless fluffy needles, m.p. 153–154°. Recrystallization from benzene–hexane failed to change the melting point. Admixture with a portion of the material obtained from the dihydronaphthyl ether **17a** as described above gave a melting point of 152–153°; reported[18] for **18**: m.p. 151.5–152.5.

Anal. Calcd. for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.3; H, 7.1.

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The Photochemical Degradation of Riboflavin[1,2]

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Anaerobic photobleaching of riboflavin followed by reoxidation with air is shown by means of microbiological assays and thin layer chromatography to produce a mixture of flavins including unchanged riboflavin, lumiflavin, lumichrome, and two additional compounds. The major new product has been identified as 6,7-dimethyl-9-formylmethylisoalloxazine by means of its chromatographic behavior and chemical reactions.

Introduction

When riboflavin is illuminated anaerobically the yellow color fades and the isoalloxazine ring becomes reduced.[4,5] Since riboflavin is known to induce the photooxidation of a variety of compounds, it is reasonable to assume with the early workers in the field that the anaerobic fading of riboflavin results from photooxidation of its own ribityl side chain. Although a considerable body of evidence, recently reviewed by Oster, *et al.*,[6] supports this idea, some workers have proposed that the hydrogen for the reduction of the isoalloxazine ring comes from the cleavage of water.[7-10] With these two contradictory views in mind, we have performed several experiments which help to clarify the nature of the anaerobic photolysis of riboflavin.

Experimental

Materials.—Riboflavin (6,7-dimethyl-9-(D-1′-ribityl)-isoalloxazine), a gift from Merck & Co., was recrystallized twice from 2 *N* acetic acid and was then extracted with chloroform to remove the lumichrome impurity. Lumiflavin was synthesized by the method of Hemmerich, *et al.*[11] Lumichrome was prepared by the photolysis of riboflavin in 50% methanol–H_2O solution by sunlight.[12] The method of Fall and Petering[13] was used to prepare 6,7-dimethyl-9-formylmethylisoalloxazine and 6,7-dimethyl-9-(2′-hydroxyethyl)-isoalloxazine from riboflavin. Riboflavin assay medium was obtained from Difco Laboratories. Silica gel G and silica gel (less than 0.08 mm.) were obtained from E. Merck AG, Darmstadt, Germany. Freshly boiled glass-redistilled water with a specific conductance of 2.2×10^{-6} ohm^{-1} was used.

Apparatus.—All spectral measurements were made on a Beckman DU spectrophotometer which had a special cell compartment cover to accommodate the cells used for anaerobic measurements. These cells consisted of two pieces connected by a 14/20 standard tapered joint. The base piece was made by sealing a 7-cm. length of Pyrex tubing to a standard 1-cm. Pyrex cuvette and the top section was made by sealing a 3-cm. piece of 12-mm. Pyrex tubing containing a medium sintered-glass filter to a stopcock. The function of the sintered-glass filter was to prevent loss of solution through "bumping" during evacuation. The Desaga thin layer chromatography apparatus was used in the preparation of chromatography plates.

Thin Layer Chromatography.—Silica gel G plates (20 cm. by 20 cm.) of 250 μ thickness were used. Normally about 10^{-3} micromole of flavin (10 μl. of 10^{-4} *M* solution) was applied at spots 1 cm. apart on the plate. Two solvent systems were used: butanol (7):ethanol (2):water (1) and water saturated with isoamyl alcohol.[9] The spots were detected after chromatography by their blue or yellow-green fluorescence under an ultraviolet light.

Microbiological Assay.—The procedure of Snell and Strong[14] based on the titration of acid produced during the growth of *Lactobacillus casei* was employed.

Anaerobic Photolysis.—A 10^{-4} *M* solution of riboflavin was placed in a modified Thunberg tube and evacuated, first with a water aspirator for 15 min. and then with a mechanical pump for the same length of time. During the evacuation the tubes were shaken vigorously several times. The solution was illuminated with a 15-watt Sylvania daylight type fluorescent lamp placed approximately 23 cm. from the sample for 16–24 hr. The photoreduction and subsequent oxidation, when oxygen was admitted, were followed spectrophotometrically at 445 mμ. For larger samples up to 2 l. in volume, a special apparatus was constructed which consisted of two 3-l. round-bottom flasks connected with 300 cm. of 1-cm. Pyrex tubing, coiled in such a way that the light source could be placed directly above it. After a 10^{-4} *M* riboflavin solution was placed in flask A, the whole apparatus was evacuated, by means of a mechanical vacuum pump, for 45 min. The solution then was forced through the coils into flask B by 1 atm. of nitrogen (purified by passing over hot copper and stored in a 12-l. reservoir). The desired amount of photobleaching could be accomplished in 2 ways. First, the flow rate of the solution through the coils could be controlled by introducing several sintered glass filters at the end of the coils and, secondly, by

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