out similarly to expt 2, except 79 g (0.5 mole) of ethyl dimethylacetoacetate was used in place of ethyl acetoacetate. At 160–170°, the reaction was proceeding more vigorously than in the foregoing experiment; it ceased after 12 hr. The condensate (36.1 g) was distilled and the fraction boiling below 105° was collected and analyzed as usual. The remaining portion of the distillate, from which ethyl iodide had been removed by treatment with silver hydroxide, was saponified by refluxing with sodium hydroxide. The aqueous solution was acidified with sulfuric acid and distilled. The liquid collected (bp 154°) was identified as isobutyric acid by conversion to its *p*-toluidide, mp 107°.

(15) **Action of Sodium Iodide on Ethyl Dimethylacetoacetate in the Presence of Phenol.**—The reaction was conducted similarly to expt 3, except that 79 g (0.5 mole) of dimethylacetoacetic ester was used in place of acetoacetic ester. The condensate (3.73 g) was fractionated and analyzed as usual.

(16) **Action of Calcium Iodide on Ethyl Dimethylacetoacetate in the Absence of a Solvent.**—The procedure was the same as that described in expt 4, except that 70 g (0.5 mole) of dimethylacetoacetic ester was used in place of acetoacetic ester. When the reactants were mixed, partial dissolution of calcium iodide occurred with evolution of heat. The reaction took place readily at 130° and was proceeding vigorously at 140–150°. Ethylene was detected in the effluent gas. The condensate (67.5 g) was redistilled and analyzed by usual procedure.

(17) **Action of Calcium Iodide on Ethyl Dimethylacetoacetate in the Presence of Ethylene Glycol.**—The procedure was the same as that in expt 5, except that 79 g (0.5 mole) of ethyl dimethylacetoacetate was used in place of ethyl acetoacetate. When the reactants were mixed, dissolution of calcium iodide occurred with evolution of heat. The reaction temperature was held at 140° most of the time, and finally raised to 150°. Vigorous gas evolution occurred, with formation of finely divided, white precipitates in the reaction mixture. Ethylene was detected from the effluent gas. The condensate (78.2 g) which was found to contain small amounts of diethyl ether and ethylene oxide, was distilled to give a fraction boiling below 105° for analysis and for isolation of methyl isopropyl ketone. The yield of the latter substance attained 28.0 g (0.65 mole/mole of ester), highest among the reactions of this series. To isolate the methyl isopropyl ketone, the distillate was shaken with several portions of saturated sodium chloride solution to remove ethyl alcohol, dried over sodium sulphate, and fractionated. The fraction consisting of a mixture of ethyl iodide and methyl isopropyl ketone, boiling between 65 and 75°, first distilled over. The fraction boiling between 90 and 95° consisted of almost pure methyl isopropyl ketone. About one-half of the ketone produced in the reaction was recovered.

(18) **Action of Calcium Iodide on Ethyl Dimethylacetoacetate in the Presence of Phenol.**—The reaction was conducted in the same manner as expt 6, except that 79 g (0.5 mole) dimethylacetoacetic ester was used in place of acetoacetic ester. The condensate (90.5 g) was redistilled to give the fraction boiling below 105°, which was analyzed by the usual procedure.

(19) **Gas Chromatography of the Distillates.**—The condensates resulting from a part of the reactions described above were gas chromatographed. A Pye argon gas chromatograph was used. The column was packed with kieselguhr containing 30% of polyethylene glycol (mol wt 1000). Operating conditions were fixed as follows: temperature, 50°; flow rate, 30 ml/min; voltage, 1000 v; sensitivity, × 10; chart speed, 10 in/hr.

The condensate, redistilled as indicated in each of the foregoing experiments, was dried over silica gel, and its density was determined. The dried sample was injected into the gas chromatograph in amounts varying from 0.04 to 0.1 ml. The distillates from expt 1 to 6 gave gas chromatograms of identical components. They exhibited five peaks, corresponding to the presence of diethyl ether, acetone, ethyl iodide, ethyl acetate, and ethyl alcohol in the sample. Identity of components was verified by comparing the gas chromatograms of distillates with those of authentic samples. Also from gas chromatograms were estimated amounts in number of moles of those substances in each distillate. Similar operations were performed with distillates resulting from reactions with methylacetoacetic ester and dimethylacetoacetic ester. Each gas chromatogram of distillates from expt 10 and 12 exhibited four peaks corresponding to the presence of diethyl ether, ethyl iodide, methyl ethyl ketone, and ethyl alcohol. Neither ethyl acetate nor ethyl propionate appeared in the gas chromatograms, undoubtedly this was due to proximity of their peaks to those of ethyl iodide and methyl ethyl ketone. The gas chromatograms of distillates from expt 17 and 18 also exhibited four peaks corresponding to the presence of diethyl ester, ethyl iodide, methyl isopropyl ketone, and ethyl alcohol. The peaks of ethyl acetate and ethyl isobutyrate did not appear. Highly volatile distillates obtained by careful fractionation of distillates from expt 5 and 17 were also gas chromatographed. Gas chromatograms showed the presence of ethylene oxide and acetaldehyde. Gas chromatography of the high-boiling fraction (85–120°) of distillate from expt 1 revealed the presence of methyl ethyl ketone.

# Nuclear Magnetic Resonance Spectra of Substituted Naphthoquinones. Influence of Substituents on Tautomerism, Anisotropy, and Stereochemistry in the Naphthazarin System[1]

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Echinoderms elaborate many closely related structural pigments (spinochromes) based on a naphthoquinone skeleton in trace amount. As an aid to structural elucidation of these trace compounds the nmr spectra of a large number of substituted naphthoquinones were examined. The chemical shifts of the substituents and of the nuclear protons were correlated with the quinoid or benzenoid nature of the rings. The chemical shifts of acetyl, ethyl, methoxyl, and acetoxyl substituents and their influence upon each other at various ring positions were examined systematically. The shifts were correlated satisfactorily and could be applied to structural assignments of unknown compounds in the series.

In our continuing investigation of the structural pigments of echinoderms we have been conducting a general survey of this phylum of animals. The echinoids (sea urchins) have received closest attention since they are plentiful, readily accessible, and have a high-pigment content. Recent work has unequivocally established the structures of six echinoid pigments of the naphthoquinone type.[2] Some progress in the examination of the pigments of crinoids (sea lilies) has been made, but the pigments, largely anthraquinones, were isolated from the tissue and the detection of structural pigments was not implied.[3] A naphthoquinone pigment has been identified from a holothuroid (sea

(1) Supported by Public Health Service Grant GM 10413.

(2) I. Singh, R. E. Moore, C. W. J. Chang, and P. J. Scheuer, *J. Am. Chem. Soc.*, **87**, 4023 (1965), and references therein.

(3) M. D. Sutherland and J. W. Wells, *Chem. Ind. (London)*, 291 (1959).

cucumber), but the authors infer that the pigment is present in the animal tissue bound to protein rather than in the minute ossicles just beneath the epidermis.[4] The asteroids (starfish) and ophiuroids (brittlestars) hitherto escaped investigation; undoubtedly collection problems and low concentration of pigment have contributed to this gap in our knowledge.

During the course of this work we have isolated several new spinochromes from echinoderms.[5] Unfortunately, quantities insufficient for structural elucidation by classical methods have generally been obtained and often our total supply amounted to less than 1 mg.

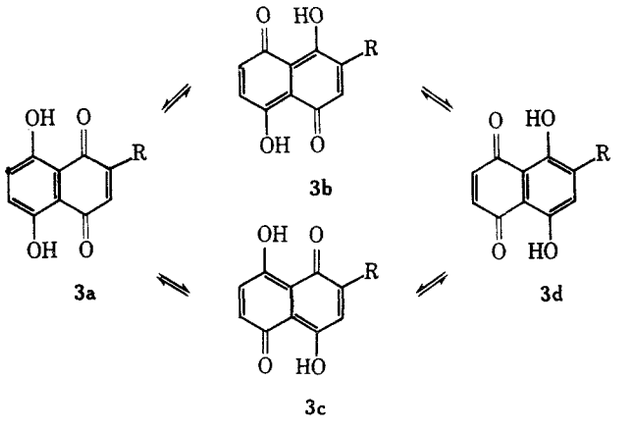
In order to permit structural elucidation of these trace pigments we have undertaken a systematic study of the physical properties of substituted naphthoquinones. In this paper we wish to correlate the nmr spectra of some naphthoquinones which are substituted by functional groups typically found in the more familiar spinochromes and their derivatives, namely, hydroxyl, methoxyl, acetoxyl, acetyl, and ethyl. Thereby we have discovered some interesting and novel effects due to anisotropy, stereochemistry, and tautomerism. Not only can these findings be utilized in the structural elucidation of naphthoquinones, but we believe them applicable to other systems, such as polyhydroxyanthraquinones and certain polyhydroxyflavones.

## Discussion

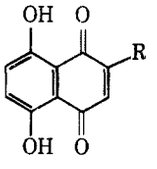
1,4-Naphthoquinone (1) exhibits an $A_2B_2$-type spectrum for its four aromatic protons. The two $\alpha$ protons give the signal at lower field ($\delta$ 8.07) due to a combined effect of the anisotropy and strong electron-withdrawing character of the quinone carbonyls, while the $\beta$ hydrogens show a signal at $\delta$ 7.77, which is a mirror image of the one at 8.07. The quinone hydrogens are found as a singlet at $\delta$ 6.97.

In the spectrum of juglone (2, 5-hydroxy-1,4-naphthoquinone) the two quinone hydrogens still have the same chemical shift as in 1,4-naphthoquinone, but the signal, a slightly broadened singlet, could not be resolved into an AB quartet to show an appreciable difference in the environment of the two protons. The aromatic protons, however, have been influenced as expected by the addition of the strong electron-releasing hydroxyl group onto the aromatic ring. The three aromatic protons now form an ABX spectrum where the C-8 and C-7 protons form the AB portion at *ca.* $\delta$ 7.7 and 7.6, respectively, while the C-6 proton provides the X part at 7.25. The coupling constants are approximately 8, 3, and 10 cps for $J_{7,8}$, $J_{6,8}$, and $J_{6,7}$, respectively.

For naphthazarin, 5,8-dihydroxy-1,4-naphthoquinone, only one signal is observed for both the aromatic and quinoidal hydrogens. The $\delta$ value of 7.13 is intermediate between that of the C-6 hydrogen of juglone ($\delta$ 7.25) and its quinone hydrogens ($\delta$ 6.97), and also lies between the C-6 and C-7 protons of 5,8-dimethoxy-1,4-naphthoquinone ($\delta$ 7.31) and its quinone hydrogens ($\delta$ 6.75). This is readily explained by the rapid tautomerism of the naphthazarin system resulting in the simultaneous existence of benzenoid and quinoid properties in both rings. The tautomers of the parent naphthazarin are depicted by structures **3a**, **3b**, **3c**, and **3d** (R = H) and one would expect that ring substitution would influence the tautomerism and result in a decrease of at least one of these species.




**Tautomerism of the Naphthazarin System. A. Effect of Monosubstitution.**—When naphthazarin is substituted at one of the $\beta$ positions with an ethyl, hydroxyl, methoxyl, or acetoxyl group, the principal tautomer in chloroform solution is **3a**. This conclusion




**3a**, R = OH, $OCH_3$, $OCOCH_3$, $CH_2CH_3$

is based on the following evidence. (1) The chemical shift of the C-3 hydrogen (Table I) is essentially the same as is observed for the corresponding 2-substituted naphthoquinone (Table II) or juglone (Table III) showing that the ring bearing the substituent is quinoidal. (2) The signals for the C-6 and C-7 protons have shifted paramagnetically when compared to naphthazarin itself, thus demonstrating the benzenoid character of the unsubstituted ring. Note that the chemical shifts are near the $\delta$ value observed for the C-6 proton of juglone.[6] (3) Localization of a double bond between C-2 and C-3 is apparent from the sharp triplet for the C-3 hydrogen when R is ethyl, showing coupling ($J$ = 1.5 cps) to the methylene protons. The fine structure of the signal is lost and collapse to a slightly broadened singlet results (showing only a small interaction with the methylene protons) when the double bond is delocalized as in the true aromatic case such as $\beta$-ethylnaphthalene.

When naphthazarin is monosubstituted with an acetyl group, the predominant tautomer in chloroform solution is **3d**. The structure is deduced from the

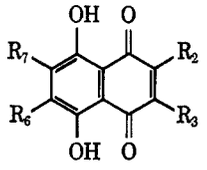
(4) M. Yamaguchi, T. Mukai, and T. Tsumaki, *Mem. Fac. Sci., Kyushu Univ., Ser. C.*, **4**, 193 (1961).

(5) R. E. Moore, H. Singh, and P. J. Scheuer, unpublished work.

(6) The C-5 hydroxyl of juglone has little effect on the *meta*-C-7 hydrogen, for its chemical shift is virtually identical with that observed for the aromatic $\beta$ hydrogens of 1,4-naphthoquinone. Thus the effects of the C-5 and C-8 hydroxyls on the C-7 and C-6 protons, respectively, in the 2-substituted naphthazarins (**3a**) above should be negligible.

TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA OF NAPHTHAZARINS



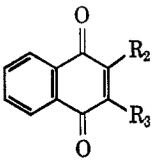

| Substituents | | | | Chemical shift of $R_i$, δ | | | | | | | Chemical shift of *peri*-hydroxyl, δ | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $R_2$ | $R_3$ | $R_6$ | $R_7$ | H | OH | $OCH_3$ | $OCOCH_3$ | $COCH_3$ | $CH_2CH_3$ | $CH_2CH_3$ | C-5 | C-8 |
| H | H | H | H | 7.13 | | | | | | | 12.43 | 12.43 |
| OH | H | H | H | 6.37 (3)[a] | Sno[d] | | | | | | 12.76 | 11.49 |
| | | | | 7.32 (6)[b,c] | | | | | | | | |
| | | | | 7.26 (7)[b,c] | | | | | | | | |
| $OCH_3$ | H | H | H | 6.17 (3) | | 3.92 | | | | | 12.63 | 12.17 |
| | | | | 7.23 (6, 7)[e] | | | | | | | | |
| $OCOCH_3$ | H | H | H | 6.85 (3) | | | 2.39 | | | | 12.33 | 12.07 |
| | | | | 7.25 (6, 7)[e] | | | | | | | | |
| H | H | $COCH_3$ | H | 7.08 (2, 3)[e] | | | | 2.75 | | | 13.08 | 12.15 |
| | | | | 7.56 (7) | | | | | | | | |
| $COCH_3$ | H | $COCH_3$ | H | 7.14 | | | | 2.62 | | | 12.57 | 12.57 |
| $CH_2CH_3$ | H | H | H | 6.84 (3)[f] | | | | | 2.67[g,h] | 1.24[i] | 12.45 | 12.60 |
| | | | | 7.20 (6, 7)[e] | | | | | | | | |
| OH | $CH_2CH_3$ | H | H | 7.30 (6)[b,c] | Sno | | | | 2.61[g] | 1.11[i] | 12.87 | 11.48 |
| | | | | 7.15 (7)[b,c] | | | | | | | | |
| $OCH_3$ | $CH_2CH_3$ | H | H | 7.22 (6, 7)[e] | | 4.14 | | | 2.62[g] | 1.12[i] | 12.78 | 12.33 |
| OH | H | $CH_2CH_3$ | H | 6.34 (3) | Sno | | | | 2.79[g] | 1.27[i] | 13.27 | 11.58 |
| | | | | 7.13 (7)[j] | | | | | | | | |
| OH | H | H | $CH_2CH_3$ | 6.34 (3) | Sno | | | | 2.79[g] | 1.27[i] | 12.77 | 11.98 |
| | | | | 7.17 (6)[j] | | | | | | | | |
| $OCOCH_3$ | H | $CH_2CH_3$ | H | 6.97 (7)[k] | | | 2.37 | | 2.67[g] | 1.23[i] | 12.77 | 12.38 |
| | | | | 6.92 (3) | | | | | | | | |
| $OCOCH_3$ | H | H | $CH_2CH_3$ | 6.97 (6)[k] | | | 2.37 | | 2.67[g] | 1.23[i] | 12.63 | 12.50 |
| | | | | 6.92 (3) | | | | | | | | |
| $OCH_3$ | $OCH_3$ | H | H | 7.18 | | 4.12 | | | | | 12.32 | 12.32 |
| OH | $OCH_3$ | H | H | 7.24 (6)[c,l] | Sno | 4.22 | | | | | 12.40 | 11.55 |
| | | | | 7.20 (7)[c,l] | | | | | | | | |
| OH | H | $OCH_3$ | H | 6.42 (3) | Sno | 3.98 | | | | | 13.29 | 12.33 |
| | | | | 6.48 (7) | | | | | | | | |
| $OCH_3$ | H | $OCH_3$ | H | 6.36 | | 3.93 | | | | | 13.07 | 13.07 |
| OH | H | H | $OCH_3$ | 6.47 (3) | Sno | 3.97 | | | | | 13.13 | 12.07 |
| | | | | 6.53 (6) | | | | | | | | |
| $OCH_3$ | H | H | $OCH_3$ | 6.40 | | 3.94 | | | | | 13.12 | 12.70 |
| $OCOCH_3$ | $OCOCH_3$ | H | H | 7.28 | | | 2.42 | | | | 12.08 | 12.08 |
| $OCOCH_3$ | H | $OCOCH_3$ | H | 6.93 | | | 2.38 | | | | 12.28 | 12.28 |
| $OCOCH_3$ | H | H | $OCOCH_3$ | 6.98 | | | 2.40 | | | | 13.12 | 12.70 |
| $OCH_3$ | H | $OCOCH_3$ | H | 6.17 (3) | | 3.96 | 2.37 | | | | 12.82 | 12.25 |
| | | | | 7.02 (7) | | | | | | | | |
| $OCH_3$ | H | H | $OCOCH_3$ | 6.22 (3) | | 3.94 | 2.37 | | | | 12.65 | 12.23 |
| | | | | 7.09 (6) | | | | | | | | |
| OH | $OCH_3$ | $OCH_3$ | H | 6.50 | Sno | 3.98 (6) | | | | | 13.13 | 12.07 |
| | | | | | | 4.16 (3) | | | | | | |
| $OCH_3$ | $OCH_3$ | $OCH_3$ | H | 6.41 | | 3.93 (6) | | | | | 12.95[m] | 13.00[m] |
| | | | | | | 4.06 (3) | | | | | | |
| | | | | | | 4.14 (2) | | | | | | |
| OH | $OCH_3$ | H | $OCH_3$ | 6.55 | Sno | 3.97 (7) | | | | | 12.93 | 12.12 |
| | | | | | | 4.22 (3) | | | | | | |
| OH | $OCH_3$ | $OCH_3$ | $OCH_3$ | | 6.90[n] | 4.16 (3) | | | | | 13.30 | 12.16 |
| | | | | | | 4.04 (7) | | | | | | |
| | | | | | | 4.08 (6) | | | | | | |
| $OCH_3$ | $OCH_3$ | $OCH_3$ | $OCH_3$ | | | 4.10 | | | | | 12.68 | 12.68 |
| $OCH_3$ | $OCH_3$ | $OCH_3$ | $CH_2CH_3$ | | | 4.05 (3) | | | 2.72[g] | 1.16[i] | 12.85[m] | 13.02[m] |
| | | | | | | 4.07 (6) | | | | | | |
| | | | | | | 4.10 (2) | | | | | | |
| OH | $COCH_3$ | H | OH | 6.68 | Sno | | | 2.85 | | | Nd[o] | Nd[o] |
| OH | $COCH_3$ | H | $OCH_3$ | 6.60 | Sno | 3.96 | | 2.88 | | | Nd | Nd |
| $OCH_3$ | H | $COCH_3$ | $OCH_3$ | 6.20 | | 4.05 (7) | | 2.52 | | | 13.00[m] | 12.61[m] |
| | | | | | | 3.92 (2) | | | | | | |
| $OCH_3$ | $OCH_3$ | $OCH_3$ | $COCH_3$ | | | 4.07 (3) | | 2.51 | | | 12.82[m] | 12.72[m] |
| | | | | | | 4.08 (6) | | | | | | |
| | | | | | | 4.13 (2) | | | | | | |

TABLE I (*Continued*)

[a] Number in parentheses refers to position *i* of substituent $R_i$. [b] Assignments of the C-6 and C-7 protons are based on the significant difference in the chemical shifts of the C-6 proton of 2-hydroxy-7-ethylnaphthazarin and the C-7 proton of 2-hydroxy-6-ethylnaphthazarin. [c] Doublet, $J$ = 10 cps. [d] Signal not observed. [e] Unresolved singlet. [f] Triplet, $J$ = 1.5 cps. [g] Quartet, $J$ = 7.5 cps. [h] The lines of the quartet could not be resolved into doublets, but their broadness depicted coupling to the C-3 proton. [i] Triplet, $J$ = 7.5 cps. [j] Slightly broadened singlet. [k] Triplet, $J$ = 1.2 cps. [l] The C-2 hydroxyl effects a larger paramagnetic shift of the C-6 proton (see naphthopurpurin data). [m] Tentative assignment. [n] Broad band. [o] Not determined.

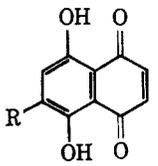
TABLE II

NUCLEAR MAGNETIC RESONANCE SPECTRA OF 1,4-NAPHTHOQUINONES



| Substituents | | Chemical shift of $R_i$, $\delta$ | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| $R_2$ | $R_3$ | H | OH | $OCH_3$ | $OCOCH_3$ | $COCH_3$ | $CH_3$ | $CH_2CH_3$ | $CH_2CH_3$ |
| H | H | 6.97 | | | | | | | |
| OH | H | 6.37 | Sno[a] | | | | | | |
| $OCH_3$ | H | 6.17 | | 3.89 | | | | | |
| $OCOCH_3$ | H | 6.76 | | | 2.38 | | | | |
| $COCH_3$ | H | 7.06 | | | | 2.56 | | | |
| OH | $COCH_3$ | | Sno | | | 2.77 | | | |
| | | | | | | 2.85 | | | |
| $CH_2CH_3$ | H | 6.79[b] | | | | | | 2.63[c,d] | 1.21[e] |
| OH | $CH_2CH_3$ | | 7.32 | | | | | 2.61[c] | 1.11[e] |
| $OCH_3$ | $CH_2CH_3$ | | | 4.12 | | | | 2.61[c] | 1.10[e] |
| $OCOCH_3$ | $CH_2CH_3$ | | | | 2.40 | | | 2.56[c] | 1.11[e] |
| OH | $OCH_3$ | | 6.92 | 4.23 | | | | | |
| $OCOCH_3$ | $OCOCH_3$ | | | | 2.42 | | | | |
| $CH_3$ | H | 6.79[f] | | | | | 2.13[g] | | |
| OH | $CH_3$ | | 7.35 | | | | 2.10 | | |
| $OCOCH_3$ | $CH_3$ | | | | 2.42 | | 2.10 | | |

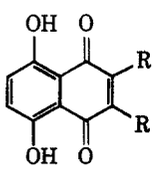
[a] Signal not observed. [b] Triplet, $J$ = 1.7 cps. [c] Quartet, $J$ = 7.5 cps. [d] Each line of the quartet is doubled, $J$ = 1.7 cps. [e] Triplet, $J$ = 7.5 cps. [f] Quartet, $J$ = 1.7 cps. [g] Doublet, $J$ = 1.7 cps.



**3d**, R = $COCH_3$

following facts. (1) The signals for the C-2 and C-3 protons have shifted diamagnetically when compared to naphthazarin showing more quinoid character in the unsubstituted ring. (2) The chemical shift for the C-7 proton ($\delta$ 7.56) is entirely different from that observed for the C-3 proton of a 2-acetyl-1,4-naphthoquinone ($\delta$ 7.06) and can only be rationalized by attachment of the acetyl group to an aromatic ring.[7]

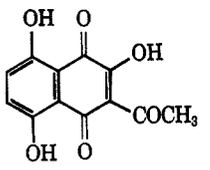
**B. Effect of Disubstitution.**—If naphthazarin is disubstituted on the same ring with substituents such as hydroxyl, methoxyl, acetoxyl, or ethyl, the ring bearing both groups is quinoidal (see structure **4**).



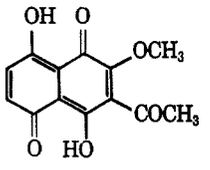
**4**, R = OH, $OCH_3$, $OCOCH_3$, $CH_2CH_3$

(7) Introduction of an acetyl substituent at C-2 of 1-naphthol causes a paramagnetic shift of *ca.* 0.4 ppm for the C-3 proton. Therefore the expected $\delta$ value for the C-7 proton of 6-acetylnaphthazarin should be approximately 7.20 (the chemical shift for the C-6 and C-7 protons of ethylnaphthazarin) + 0.4 ppm = 7.6 ppm. This is indeed the case.

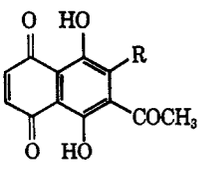
In all the spectra of such 2,3-disubstituted naphthazarins (Table I), the signals for the C-6 and C-7 protons are paramagnetically shifted *ca.* 0.1 ppm compared to naphthazarin showing the unsubstituted ring is benzenoid. If one of the substituents is acetyl, which as a lone substituent prefers to be attached to an aromatic ring, two situations are possible depending on the nature of the second substituent. Based on data obtained from spinochrome A (see part C), the principal tautomer of 2-hydroxy-3-acetylnaphthazarin must be **5**. Insufficient data prevent a rigorous conclusion at this time for the principal tautomer of a disubstituted naphthazarin having an acetyl group and an adjacent substituent such as methoxyl, acetoxyl, or ethyl. We suspect, however, that the methoxyl group attracts the quinoidal properties about as strongly as the acetyl repels them and therefore structure **6** should be con-



**5**



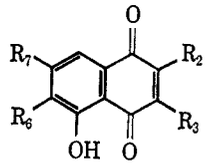
**6**



**7**, R = $OCOCH_3$, $CH_2CH_3$

TABLE III

NUCLEAR MAGNETIC RESONANCE SPECTRA OF JUGLONES

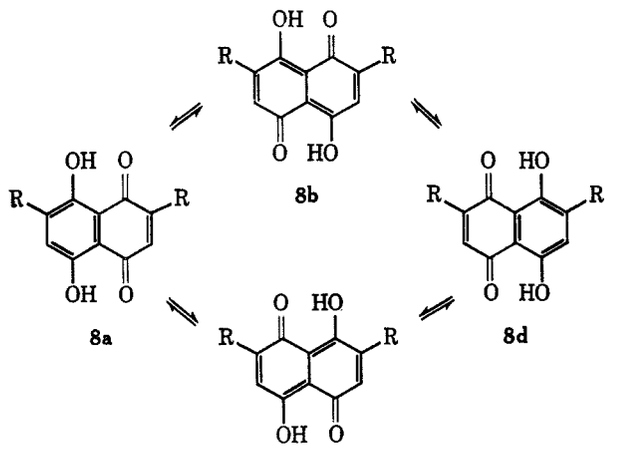


| Substituents | | | | Chemical shift of $R_i$, $\delta$ | | | | | | Chemical shift, $\delta$ | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $R_2$ | $R_3$ | $R_6$ | $R_7$ | H | OH | $OCH_3$ | $OCOCH_3$ | $CH_2CH_3$ | $CH_2CH_3$ | C-5 OH | C-8 H |
| H | H | H | H | 6.97 (2, 3)[a]<br>7.6 (7)<br>7.25 (6) | | | | | | 11.93 | 7.7 |
| OH | H | H | H | 6.28 (3) | Sno[b] | | | | | 12.31 | |
| H | OH | H | H | 6.33 (2) | Sno | | | | | 11.06 | |
| $OCH_3$ | H | H | H | 6.09 (3) | | 3.89 | | | | 12.23 | |
| H | $OCH_3$ | H | H | 6.15 (2) | | 3.90 | | | | 11.70 | |
| H | $OCH_3$ | H | $OCH_3$ | 6.08 (2)<br>6.60 (6)[c] | | 3.91 (3, 7)[d] | | | | 11.97 | 7.08[c] |
| H | $CH_2CH_3$ | H | $OCOCH_3$ | 6.75 (2)[e]<br>6.99 (6)[c] | | | 2.32 | 2.62[f] | 1.20[g] | 12.16 | 7.32[c] |
| $OCH_3$ | $OCH_3$ | H | $OCH_3$ | 6.61[c] | | 3.87 (7)<br>4.07<br>4.11 | | | | 12.09 | 7.17[c] |
| $OCH_3$ | $OCH_3$ | H | OH | 6.63[c] | Sno | 4.07<br>4.11 | | | | 12.04 | 7.16[c] |
| $OCH_3$ | $OCH_3$ | $CH_2CH_3$ | OH | | Sno | 4.03<br>4.08 | | 2.72[f] | 1.11[g] | 12.36 | 7.13 |

[a] Numbers in parentheses refer to position $i$ of substituent $R_i$. [b] Signal not observed. [c] Doublet, $J$ = 2.5 cps. [d] Unresolved, but slightly broadened singlet. [e] Triplet, $J$ = 1.7 cps. [f] Quartet, $J$ = 7.5 cps. [g] Triplet, $J$ = 7.5 cps.

sidered as a predominant tautomer. The preferred location of the quinone carbonyl is next to the substituent of strongest quinoidal attraction (see below). The acetoxyl and ethyl substituents are much weaker quinoidal attractants and the combination of the strong tendency of the acetyl to be located on a benzenoid ring and the higher stability of the 1,4-naphthoquinone system should result in **7** as the preferred tautomer.

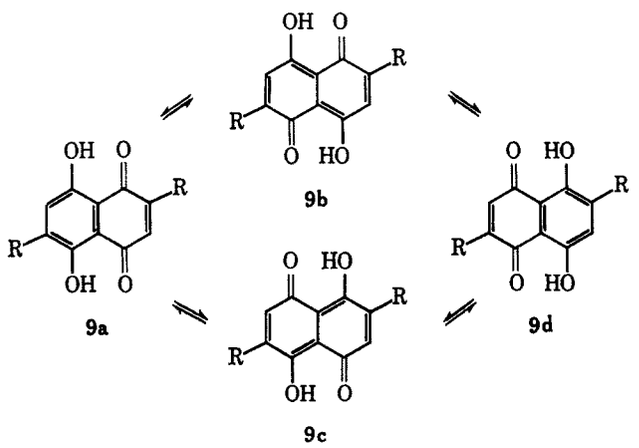
For an identically 2,7-disubstituted naphthazarin, two (**8b** and **8c**) or four (**8a**, **8b**, **8c**, and **8d**) tautomeric species are predominant in solution. The following



**8a** **8b** **8c** **8d**

evidence supports this conclusion. (1) Since the two species **8b** and **8c** (as well as **8a** and **8d**) are structurally *equivalent*, the chemical shift of the C-3 and C-6 protons should be approximately midway between that observed for the C-3 proton of an identically 2-substituted naphthazarin and the C-6 proton of an identically 7-substituted juglone. Note that the ring protons of 2,7-dimethoxynaphthazarin ($\delta$ 6.40) resonate about midway compared to the C-2 hydrogen of 2-methoxynaphthazarin ($\delta$ 6.17) and the C-6 proton of 2,3,7-trimethoxyjuglone ($\delta$ 6.61).[8] (2) An examination of the chemical shifts of the *peri* hydroxyls (see below) show that **8a** and **8d** are not the only species present.

In constrast, a symmetrically 2,6-disubstituted naphthazarin is represented in solution as one (**9b** or **9c**) or three (**9a**, **9b**, and **9d** or **9a**, **9c**, and **9d**) species.



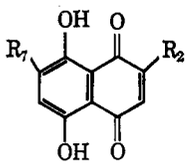
**9a** **9b** **9c** **9d**

The following evidence supports this conclusion. (1) The two species **9b** and **9c** are structurally *non-equivalent* and a chemical shift intermediate but not midway between the pure quinoid and benzenoid states would be generally expected for the ring protons regardless of the presence of one or three principal species in the tautomeric mixture. For example, the C-3 and C-7 protons of 2,6-dimethoxynaphthazarin ($\delta$ 6.36) resonate between the C-3 proton of 2-meth-

(8) Identical substitution of the quinoidal ring of the juglone is not necessary for the comparison. Examination of several spectra reveals that the C-6 proton is fairly insulated from the effects of quinoidal substituents.

oxynaphthazarin ($\delta$ 6.17) and the C-3 and C-6 protons of 2,7-dimethoxynaphthazarin ($\delta$ 6.40). The signal for the ring protons of 2,6-diacetylnaphthazarin ($\delta$ 7.14) is nearer the C-3 proton signal of 2-acetyl-1,4-naphthoquinone ($\delta$ 7.06) than the C-7 proton signal of 6-acetylnaphthazarin ($\delta$ 7.56). These two compounds suggest that the ring protons of the principal 1,5-naphthoquinone species resonate nearer the region of quinoidal protons. (2) A study of the chemical shifts of *peri* hydroxyls of some appropriate model compounds (see below) suggests **9b** (R = $OCH_3$) as the principal 1,5-naphthoquinone tautomer for 2,6-dimethoxynaphthazarin and **9c** (R = $COCH_3$) for 2,6-diacetylnaphthazarin.

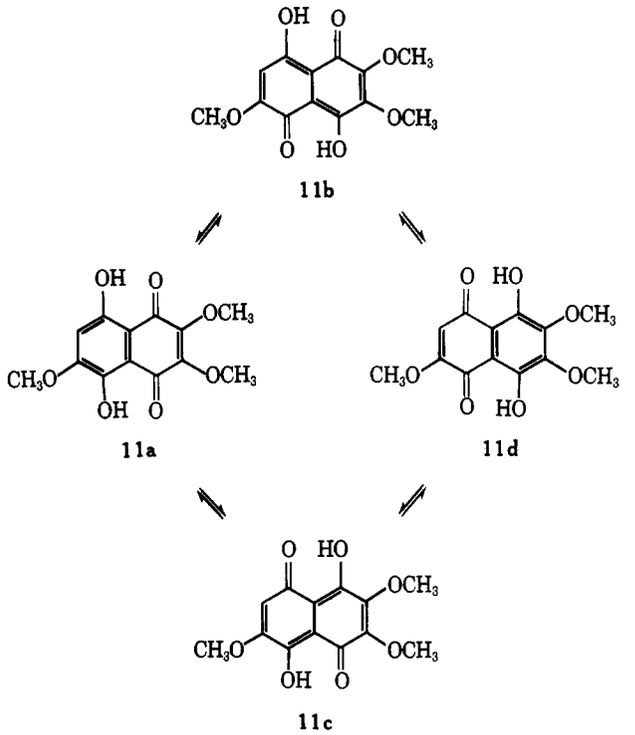
The 2,6- and 2,7-disubstituted naphthazarins possessing different groups generally exhibit only one principal tautomer in solution. From a careful examination of several spectra of these disubstituted naphthazarins, we have concluded the following order for the attraction of quinoidal properties to a ring by a substituent: OH > $OCH_3$ ≫ $OCOCH_3$ > $CH_2CH_3$ ≫ H ≫ $COCH_3$. In other words for a 2,7-disubstituted naphthazarin, the principal tautomer is represented by **10**.



**10**, $R_2$ = OH; $R_7$ = $OCH_3$, $OCOCH_3$, $CH_2CH_3$, $COCH_3$
$R_2$ = $OCH_3$; $R_7$ = $OCOCH_3$, $CH_2CH_3$, $COCH_3$
$R_2$ = $OCOCH_3$; $R_7$ = $CH_2CH_3$, $COCH_3$

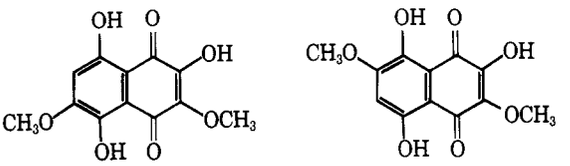
The following evidence supports this conclusion. (1) The chemical shift of the C-3 proton is comparable to that observed for the corresponding 2-substituted 1,4-naphthoquinone or juglone. For example, the C-3 proton of 2-methoxy-7-acetoxynaphthazarin ($\delta$ 6.22) and 2-methoxynaphthazarin ($\delta$ 6.17) have about the same chemical shift. (2) The chemical shift of the C-6 proton is at lower field than that of the C-3 proton of a 2-substituted naphthazarin (group at C-2 same as that at C-7 of the disubstituted naphthazarin). For example, the signal for the C-6 proton of 2-methoxy-7-acetoxynaphthazarin ($\delta$ 7.09) is paramagnetically displaced from the signal for the C-3 proton of 2-acetoxynaphthazarin ($\delta$ 6.85). (3) The chemical shift of the C-6 proton is comparable to that noted for the C-6 proton of the corresponding juglone. (4) In the spectrum of 2-hydroxy-7-ethylnaphthazarin the signal for the C-6 proton is found as a slightly broadened singlet at $\delta$ 7.17. The singlet nature and the small broadened behavior of the signal are characteristic of an aromatic proton adjacent to an ethyl group on an aromatic ring. (5) The chemical shifts for the C-3 proton ($\delta$ 6.47) and the C-6 proton ($\delta$ 6.53) of 2-hydroxy-7-methoxynaphthazarin deviate appreciably from the expected values. If one assumes that the hydroxyl-bearing ring is 75% quinoid, then the estimated chemical shifts for the ring protons ($\delta$ 6.44 and 6.50, respectively) are comparable with the observed values. (6) The chemical shifts for the C-3 proton ($\delta$ 6.92) and the C-6 proton ($\delta$ 6.97) of 2-acetoxy-7-ethylnaphthazarin are quite different from the expected values. The triplet signal at $\delta$ 6.97 is assigned to the proton adjacent to the ethyl substituent and the ring bearing the ethyl group is estimated to be 60% aromatic. The triplet structure of the C-6 proton signal reflects the quinoidal character of the ring (40%) and the smaller coupling constant ($J$ = 1.2 cps) shows that only a portion of the quinoidal properties is present.

**C. Effect of Trisubstitution.**—In the spectrum of 2,3,6-trimethoxynaphthazarin, the C-7 signal is found at $\delta$ 6.41. From its position, which is essentially identical with the chemical shift for the C-6 proton of 2,7-dimethoxynaphthazarin, it is concluded that the following tautomerism is operative.



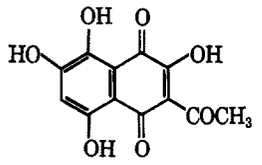
**11b** ⇌ **11a** ⇌ **11d** ⇌ **11c**

For 2-hydroxy-3,6-dimethoxynaphthazarin (**12**) and 2-hydroxy-3,7-dimethoxynaphthazarin (**13**), however, the strong influence of the hydroxyl for augmenting the quinoidal properties of its ring is immediately apparent. The signals for the C-7 proton of **12** and the C-6 proton of **13** are at $\delta$ 6.50 and 6.55, respectively, showing that at least 75% of the quinoidal character is present in the ring bearing the hydroxyl.



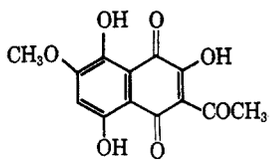
**12** **13**

In the spectrum of 2,7-dihydroxy-3-acetylnaphthazarin (**14**), spinochrome A, the C-6 proton gives rise to a signal at $\delta$ 6.68. The chemical shift is close to that noted for the C-6 proton of 2,3-dimethoxy-7-hydroxyjuglone ($\delta$ 6.63).[8] One must conclude therefore that the ring bearing the acetyl group is predominantly quinoidal.



14

The spectrum of 2-hydroxy-3-acetyl-7-methoxynaphthazarin (**15**) still reflects the aromatic environment of the C-6 proton (δ 6.60). In the spectrum of 2,7-dimethoxy-6-acetylnaphthazarin (**16**), however, the environment of the ring proton is definitely quinoidal. The C-3 proton shows a signal at δ 6.20 which is comparable to that observed for the C-3 proton of 2-methoxynaphthazarin. The principal tautomer is therefore **16**.



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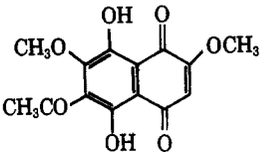
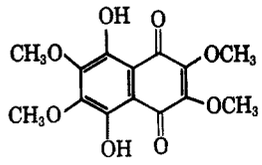


16

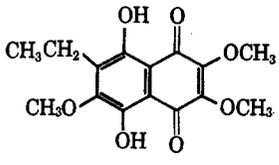
The very strong attraction of quinoidal properties to a ring bearing an acetyl and a hydroxyl is rationalized by the increased stability of this system due to tautomerism (see below for a detailed discussion).

**D. Effect of Tetrasubstitution.**—The quinoidal or aromatic properties cannot obviously be located in a specific ring for 2,3,6,7-tetramethoxynaphthazarin (**17**) and other symmetrically tetrasubstituted naphthazarins.



17

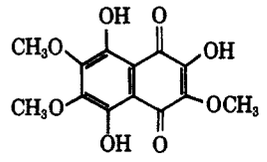
In unsymmetrically tetrasubstituted naphthazarins no ring protons are present which would allow to distinguish the benzenoid and quinoid rings. A decision can be made only after a study of appropriate model compounds. For example the chemical shift for the methylene protons of an ethyl group has been found to be significantly different depending whether it is located on an aromatic or a quinoidal ring (see below for a detailed discussion). The chemical shift for the methylene protons of 2,3,6-trimethoxy-7-ethylnaphthazarin (δ 2.72) favors an aromatic environment and the predominant tautomer is therefore **18**.



18

The following order for the attraction of quinoidal properties by two adjacent substituents is concluded from the preceding discussion: OH, $COCH_3$ > OH, $OCH_3$ > $OCH_3$, $OCH_3$ > $OCH_3$, $CH_2CH_3$ > $OCH_3$, $COCH_3$.

On the basis of these data principal tautomeric structures can be written for 2-hydroxy-3,6,7-trimethoxynaphthazarin (**19**) and 2,3,6-trimethoxy-7-acetylnaphthazarin (**20**).



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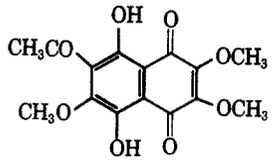
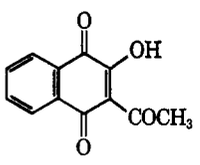


20

**Factors Affecting the Chemical Shifts of Substituents. A. Of Acetyl.**—2-Acetyl-1,4-naphthoquinone shows a signal at δ 2.56 for the acetyl protons whereas 6-acetylnaphthazarin, which has been shown to possess the acetyl on the benzenoid ring, exhibits the acetyl signal at δ 2.75. The preponderance of aromatic or quinoidal character in a specific ring is not possible for 2,6-diacetylnaphthazarin and the acetyl signal is found between these values at δ 2.62.

Introduction of a hydroxyl next to the acetyl on a quinoidal ring results in a pronounced paramagnetic displacement of the acetyl signal to δ 2.81. Actually the signal is doubled (singlet peaks at δ 2.76 and 2.85) due to the presence of two slowly interconverting tautomers **21** and **22** in equal amount. The addition of a trace of dilute acid augments the intermolecular exchange rate of hydroxyl protons and collapse of the doublet structure to a singlet at δ 2.81 results.



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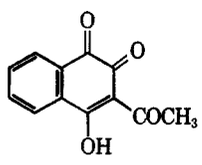


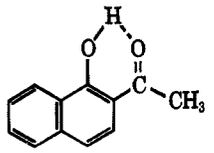
22

To rationalize the rather large paramagnetic shift of the acetyl signal, the spectra of some simple model compounds were examined. Acetophenone shows a signal at δ 2.59 for the acetyl group, which is essentially unchanged in the spectrum of *o*-hydroxyacetophenone (δ 2.57). Similarly 2-acetonaphthalene and 2-aceto-1-naphthol both give the acetyl signal at δ 2.65. The strong intramolecular hydrogen-bonded nature of the carbonyls of *o*-hydroxyacetophenone and 2-aceto-1-naphthol (hydroxyl signal at *ca.* δ 14) apparently is not affecting the chemical shift of the acetyl protons.

In the spectrum of 4-nitro-2-aceto-1-naphthol, however, the acetyl signal is found at δ 2.80. Even the strong electron-withdrawing influence of the nitro group is not sufficient to effect such a large shift. 1-Nitro-3-acetylnaphthalene exhibits the acetyl signal at δ 2.71. The hydrogen-bonded character of the carbonyl is reflected by the hydroxyl signal at δ 14.63.

Our conjecture is that only one structure (**23**) is predominant for 2-aceto-1-naphthol, whereas in the 4-nitro-2-aceto-1-naphthol case two rapidly interconverting tautomers of structure **24** and **25** are possible.

In the case of **23** the phenolic hydroxyl is weakly acidic and cannot readily transfer its proton to the acetyl carbonyl and effect its enolization. As a result



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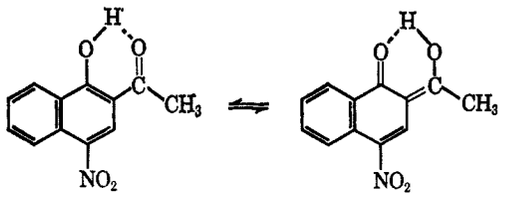
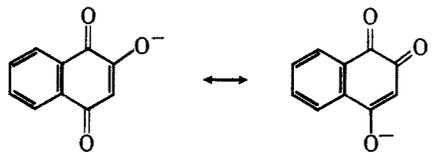


24 25

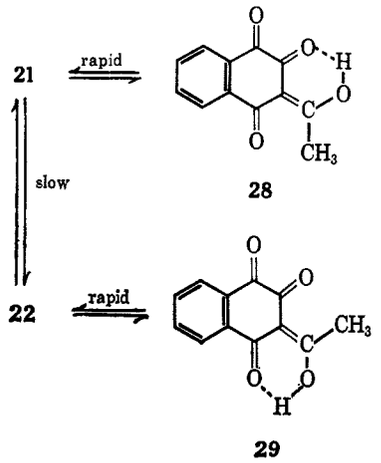
the methyl protons are influenced only by the anisotropy of the carbonyl attached to the aromatic system. The presence of a nitro substituent in the 4 position increases the acidity of the phenolic hydroxyl of **24** markedly and tautomerization to **25** can readily occur. The methyl protons of 4-nitro-2-aceto-1-naphthol are now influenced by two different anisotropies and the over-all effect is a paramagnetic shift of the acetyl signal.

The hydroxy group of 2-hydroxy-1,4-naphthoquinone is also strongly acidic because of its analogy to a carboxylic acid and the increased stability of the anion due to interaction of the *p*- (**26**) and *o*-quinone (**27**) anions.



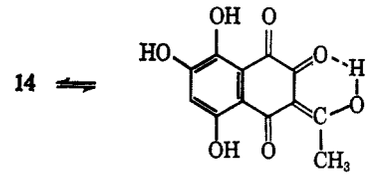
26 27

In 2-hydroxy-3-acetylnaphthoquinone the same situation is present, a strongly acidic hydroxyl hydrogen bonded to the carbonyl of an adjacent acetyl group. Similar tautomeric structures can be written to explain the paramagnetic shift of the acetyl signal.



21 22 28 29

The β-hydroxy groups of substituted naphthazarins are also strongly acidic and in the spectra of spinochrome A (**14**) and its monomethyl ether (**15**) the acetyl signals are found at δ 2.85 and 2.88, respectively, indicating that similar tautomerization is operating. The nonhydrogen-bonded acetyl groups of dimethylspinochrome A (**16**) and trimethylspinochrome C (**20**) are



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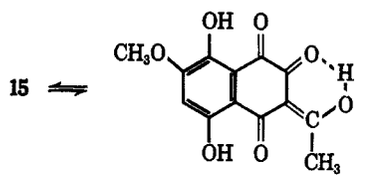
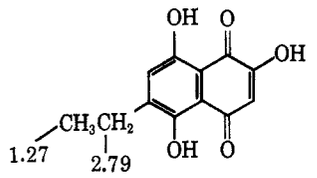


31

no longer stabilized by tautomerization and thus do not remain in the quinoid ring. The chemical shifts of the acetyl signals of **16** (δ 2.52) and **20** (δ 2.51), however, are quite different from that observed for 6-acetylnaphthazarin. To explain the entirely different chemical shift, a steric interaction of the acetyl with the adjacent methoxyl must be operative.

**B. Of Ethyl.**—If one examines the ethyl signals of four appropriate compounds such as 2-hydroxy-6-ethylnaphthazarin (**32**), ethylnaphthazarin (**33**), 2-methoxy-6-ethyl-7-hydroxyjuglone (**34**), and 2-hydroxy-3-ethylnaphthazarin (**35**), the following characteristics for the ethyl group are obtained. (1)



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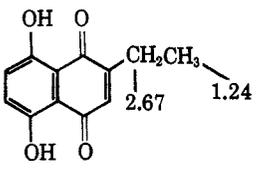

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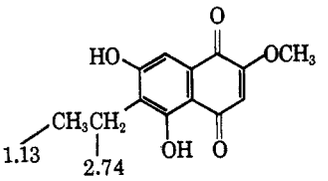

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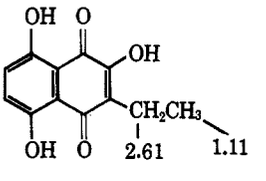


35

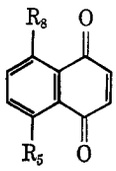
The methylene signal is in the neighborhood of δ 2.79 if the ethyl substituent is unhindered and attached to an aromatic ring. (2) The methylene signal is in the neighborhood of δ 2.67 if the ethyl substituent is unhindered and in a quinoid environment. (3) The methylene signal is shifted diamagnetically 0.02–0.05 ppm if the ethyl substituent is flanked by a hydroxyl. The small diamagnetic displacement is also observed with an adjacent methoxyl.[9] (4) The methyl signal for an unhindered ethyl substituent is found near δ 1.26. (5) The methyl signal is shifted diamagnetically about 0.15 ppm when the ethyl group is flanked by a β substituent such as hydroxyl, methoxyl, or acetoxyl.

In the spectrum of 2,3,6-trimethoxy-7-ethylnaphthazarin (**20**, trimethylechinochrome A), the methylene signal is displayed at δ 2.72 showing that it is attached to a benzenoid ring. The hindered methyl group of the ethyl substituent shows its triplet signal at δ 1.16 as expected.

(9) The conclusion is based on data obtained for the corresponding 1,4-naphthoquinones (see Table I).

TABLE IV

NUCLEAR MAGNETIC RESONANCE SPECTRA OF 1,4-NAPHTHOQUINONES



| Substituent | | Chemical shift of $R_i$, δ | | | Chemical shift of ring proton, δ | | | |
|---|---|---|---|---|---|---|---|---|
| $R_5$ | $R_8$ | H | $OCH_3$ | $OCOCH_3$ | C-2 | C-3 | C-6 | C-7 |
| $OCH_3$ | H | 7.75 | 3.99 | | 6.87 | 6.87 | 7.28 | 7.67 |
| $OCOCH_3$ | H | 8.07 | | 2.46 | 6.85 or 6.93[a] | 6.85 or 6.93[a] | 7.39 | 7.77 |
| $OCH_3$ | $OCH_3$ | | 3.93 | | 6.75 | 6.75 | 7.31 | 7.31 |
| $OCOCH_3$ | $OCOCH_3$ | | | 2.45 | 6.80 | 6.80 | 7.40 | 7.40 |

[a] Doublet, $J$ = 10 cps.

**C. Of Methoxyl.**—Generally the signal for a methoxyl attached to either an aromatic or quinoidal ring is found in the region δ 3.87–3.94 so long as no serious interaction with other functional groups is present. For example, 2-methoxynaphthazarin (δ 3.92), 2,3,7-trimethoxyjuglone (δ 3.87 for the C-7 methoxyl), and 5,8-dimethoxy-1,4-naphthoquinone (δ 3.93, Table IV) all fall into this category.

The chemical shift of a methoxyl on the naphthazarin system is paramagnetically displaced about 0.04 ppm by the presence of a hydroxyl in the opposite ring. Note that the methoxyl signal for 2-hydroxy-6-methoxynaphthazarin is found at δ 3.98.

The chemical shift of a methoxyl which has an adjacent substituent is consistently greater than δ 4. 2-Methoxynaphthoquinones, 2-methoxyjuglones, and 2-methoxynaphthazarins having methoxyl, ethyl, or acetyl substituents at C-3 exhibit the C-2 methoxyl signal in the region δ 4.04–4.14. The effect appears to be independent of the attachment of the methoxyl to the benzenoid or quinoid ring of a naphthazarin as shown by 2,3,6-trimethoxy-7-ethylnaphthazarin (δ 4.05, 4.07, and 4.10) and 2,3,6-trimethoxy-7-acetylnaphthazarin (δ 4.07, 4.08, and 4.13).

When a β hydroxyl is adjacent to the methoxyl, the paramagnetic shift of the methoxy signal is even larger and the signal is now found in the region δ 4.14–4.24. 2-Hydroxy-3-methoxynaphthoquinone (δ 4.23), 2-hydroxy-3-methoxynaphthazarin (δ 4.22), and 2-hydroxy-3,7-dimethoxynaphthazarin (δ 4.22) demonstrate the normal position of the signal. Most importantly, the presence of an unhindered methoxyl at C-6 displaces the signal of a hindered methoxyl at C-3 to the high-field end of the range as shown in the spectrum of 2-hydroxy-3,6-dimethoxynaphthazarin (**14**) (δ 4.16 for the C-3 methoxyl).

Introduction of an *unhindered* methoxyl at C-6 causes the signal of a *hindered* methoxyl at C-3 on a naphthazarin skeleton to be shifted diamagnetically about 0.06 ppm, whereas a C-7 *unhindered* methoxyl produces no appreciable effect on a C-3 *hindered* methoxyl. Taking into consideration the 0.01–0.02-ppm paramagnetic shift of a methoxyl signal by the presence of a methoxyl in the opposite ring,[10] the C-2 methoxyl (δ 4.14) of 2,3,6-trimethoxynaphthazarin (**12**) exhibits about the same chemical shift as the methoxyls of 2,3-dimethoxynaphthazarin (δ 4.12). On the other hand the *hindered* C-3 methoxyl (δ 4.06) of **12** is diamagnetically displaced 0.06 ppm by the presence of the C-6 methoxyl.

Most interesting is the observation that the C-6 methoxyl of **12** (δ 3.93) has essentially the same chemical shift as the methoxyls of 2,7-dimethoxynaphthazarin (3.94). Similarly the C-6 methoxyl of **14** (δ 3.98) resonates at the same field as 2-hydroxy-6-methoxynaphthazarin (δ 3.98). Obviously no appreciable effect is produced on a C-6 *unhindered* methoxyl by a hindered C-3 methoxyl.

From these data the methoxyl signals in the spectrum of **20** can be assigned. (Table V). The effect of an ethyl group at C-7 on a C-2 *hindered* methoxyl is calculated to be a diamagnetic shift of 0.03 ppm.

TABLE V

METHOXYL CHEMICAL SCHIFTS FOR 2,3,6-TRIMETHOXY-7-ETHYLNAPHTHAZARIN

| Methoxyl position | Chemical shift, δ | |
|---|---|---|
| | Calcd | Obsd |
| 3 | $4.12^a - 0.06^b + 0.00^c = 4.06$ | 4.05 |
| 6 | $4.13^d - 0.06^e + 0.00^f = 4.07$ | 4.07 |
| 2 | $4.12^a + 0.01^g + X^h = 4.10$ | 4.10 |
| | $X = -0.03$ ppm | |

[a] Chemical shift for methoxyl protons of 2,3-dimethoxynaphthazarin. [b] Effect of 6-methoxyl. [c] There is no appreciable shift owing to 7-ethyl substituent. The 2-methoxyl of 2,7-dimethoxy-6-ethylnaphthazarin resonates at the same field as the methoxyls of 2,7-dimethoxynaphthazarin (δ 3.94): see R. E. Moore, H. Singh, C. W. J. Chang, and P. J. Scheuer, *J. Org. Chem.*, in press. [d] Chemical shift for methoxyl protons of 2-methoxy-3-ethylnaphthazarin. [e] Effect of 3-methoxyl. [f] There is no appreciable shift due to the 2-methoxyl group. The C-6 methoxyl of **12** has essentially the same chemical shift as the methoxyls of 2,7-dimethoxynaphthazarin. [g] Paramagnetic shift due to 6-methoxyl. See footnote 10. [h] Effect of 7-ethyl.

Compounds **21** and **22** can be treated in a similar manner (see Tables VI and VII). The effect of a hydroxyl group at C-2 on a C-7 *hindered* methoxyl is calculated to be a diamagnetic shift of 0.08 ppm. The C-7 acetyl apparently exhibits no effect on the C-2 *hindered* methoxyl.

**D. Of Acetoxyl.**—β-Acetoxyl substituents with an adjacent β hydrogen exhibit a signal in the region δ 2.36–2.40. 2-Acetoxynaphthazarin (δ 2.39) and 2,5,8-triacetoxy-1,4-naphthoquinone (δ 2.36 for the C-2 acetoxyl, see Table VIII) exhibit normal signals. If a substituent such as methoxyl or ethyl is adjacent to the acetoxyl as in 2-acetoxy-3-ethylnaphthoquinone, the signal may be displaced downfield to *ca.* δ 2.42.

(10) Note that a 0.01–0.02-ppm paramagnetic shift is observed for the methoxyl signal of 2,6- and 2,7-dimethoxynaphthazarin as compared with 2-methoxynaphthazarin.

TABLE VI

METHOXYL CHEMICAL SHIFTS FOR 2-HYDROXY-3,6,7-TRIMETHOXYNAPHTHAZARIN

| Methoxyl position | Chemical shift, δ Calcd | Obsd |
|---|---|---|
| 3 | 4.22[a] − 0.06 + 0.00 = 4.16 | 4.16 |
| 6 | 4.12 − 0.06 + 0.04[b] = 4.10 | 4.08 |
| 7 | 4.12 + 0.00[c] + X[d] = 4.04<br>X = −0.08 ppm | 4.04 |

[a] Chemical shift for methoxyl protons of 2-hydroxy-3-methoxynaphthazarin. [b] Effect of 2-hydroxyl. This correction is the difference between the C-6 methoxyl chemical shift of **12** (δ 3.98) and the methoxyl chemical shift of 2,7-dimethoxynaphthazarin (δ 3.94). [c] There is no appreciable shift due to the C-3 methoxyl. The C-7 methoxyl signal occurs at δ 3.97 for both **13** and 2-hydroxy-7-methoxynaphthazarin. [d] Effect of C-2 hydroxyl.

TABLE VII

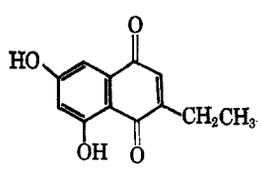
METHOXYL CHEMICAL SHIFTS FOR 2,3,6-TRIMETHOXY-7-ACETYLNAPHTHAZARIN

| Methoxyl position | Chemical shift, δ Calcd | Obsd |
|---|---|---|
| 3 | 4.12 − 0.06 − 0.01[a] = 4.05 | 4.07 |
| 6 | 4.13[b] − 0.06 + 0.00 = 4.07 | 4.08 |
| 2 | 4.12 + 0.01 + X[c] = 4.13<br>X = 0.00 ppm | 4.13 |

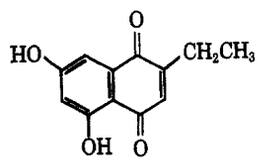
[a] Diamagnetic shift due to 7-acetyl group. Note that the signal for the 2-methoxyl of **16** is at slightly higher field than the methoxyl signal for 2,7-dimethoxynaphthazarin. [b] Chemical shift for methoxyl protons of 2-methoxy-3-acetylnaphthazarin: R. E. Moore, H. Singh, C. W. J. Chang, and P. J. Scheuer, *J. Org. Chem.*, in press. [c] Effect of 7-acetyl.

The protons of strongly hydrogen-bonded hydroxyl groups generally are not affected by traces of impurities and are observed in the region δ 11–17 as sharp singlets. The *peri*-hydroxyl protons of juglone and naphthazarin exhibit signals at δ 11.93 and 12.43, respectively. In Table IX the effect of a substituent attached to the quinoid ring of juglone or naphthazarin on the chemical shift of the *peri*-hydroxyl protons is summarized. The assignments for the naphthazarins are based on the juglones, but for 2-acetoxy- and 2-ethylnaphthazarin it was assumed that the substituent effect would be larger on the nearest *peri* hydroxyl.

Using data from Table IX the structures of two ethyl-7-hydroxyjuglones, obtained by reduction of a mixture of 7-ethyl- and 6-ethyl-2-hydroxynaphthazarin with sodium stannite, are determined. One of the compounds, mp 183.5°, exhibited the C-5 hydroxyl at δ 12.15 whereas the isomer, mp 210° dec, showed this signal at δ 12.30. The difference in chemical shift (0.15 ppm) is the same as the difference for the two *peri* hydroxyls of 2-ethylnaphthazarin (0.15). As the ethyl substituent nearest the *peri* hydroxyl should exhibit the greatest effect, the 210° isomer is assigned **38** and therefore the 183.5° isomer is **39**.



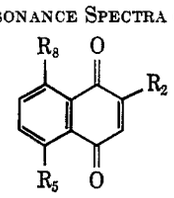

**38**




**39**

TABLE VIII

NUCLEAR MAGNETIC RESONANCE SPECTRA OF 1,4-NAPHTHOQUINONES




| Substituent R2 | Substituent R5 | Substituent R8 | Chemical shift of Ri, δ: OH | OCH3 | OCOCH3 | Chemical shift of ring proton, δ: C-3 | C-6 | C-7 |
|---|---|---|---|---|---|---|---|---|
| OH | $OCH_3$ | $OCH_3$ | Sno[a] | 3.95 (5)[b]<br>4.00 (8) | | 6.23 | 7.40[c] | 7.30[c] |
| $OCOCH_3$ | $OCOCH_3$ | $OCOCH_3$ | | | 2.36 (2)<br>2.45 (5, 8) | 6.62 | 7.38[d] | 7.38[d] |

[a] Signal not observed. [b] Number in parentheses refers to position *i* of substituent $R_i$. [c] Assignments are based on nmr data of naphthopurpurin where the C-2 hydroxyl causes a larger paramagnetic shift of the C-6 proton. [d] Unresolved singlet.

Acetoxyl in the *peri* position as in 5,8-diacetoxy-1,4-naphthoquinone is paramagnetically shifted to *ca.* δ 2.45 (Table IV).

**E. Of *peri* Hydroxyl.**—Phenolic and quinoidal hydroxy protons that are not hydrogen bonded intramolecularly generally exhibit signals in the region δ 6.5–7.5, *i.e.*, if the intermolecular proton exchange rate is relatively slow. In some cases β-hydroxyl signals have been observed as in the spectra of 2-hydroxy-3,6,7-trimethoxynaphthazarin (broad band at δ 6.90) and 2-hydroxy-3-methylnaphthoquinone (δ 7.35). The compounds generally have to be very pure (which as a rule decreases the solubility of the compound in deuteriochloroform and frequently prevents a determination of the spectrum), for slight impurities cause an unfavorable exchange rate so that the signal becomes too broad to be observed at the sample concentration used.

To test whether the groups exert approximately the same effect on the *peri*-hydroxy protons when the quinoid ring is disubstituted, the chemical shifts of the C-5 and C-8 hydroxyls of five 2,3-disubstituted naphthazarins, where the ring bearing the two substituents is known to be predominantly quinoidal, are calculated using the data in Table IX. In Table X the calculated and observed values are compared and the agreement is fairly good. The deviations are attributed to the proximity and out-of-plane deformation of the C-2 and C-3 substituents resulting in changes of anisotropy and ring current.

The effect of substituents attached to a predominantly aromatic ring on the C-5 and C-8 hydroxyls is determined from some 2,6-disubstituted naphthazarins using the data in Table IX. Acetylnaphthazarin is

TABLE IX

EFFECT OF SUBSTITUENT ON QUINOIDAL RING ON CHEMICAL SHIFT OF *peri*-HYDROXY PROTONS

| Compound | Chemical shift, δ C-5 OH | C-8 OH | Displacement (ppm) from chemical shift of parent Juglone C-5 OH | Naphthazarin C-8 OH |
|---|---|---|---|---|
| Juglone | 11.93 | | 0 | |
| Naphthazarin | 12.43 | 12.43 | 0 | 0 |
| 2-Hydroxyjuglone | 12.31 | | +0.38 | |
| 3-Hydroxyjuglone | 11.06 | | −0.87 | |
| Naphthopurpurin[a] | 12.76 | 11.49 | +0.33 | −0.94 |
| 2-Methoxyjuglone | 12.23 | | +0.30 | |
| 3-Methoxyjuglone | 11.70 | | −0.23 | |
| 2-Methoxynaphthazarin[a] | 12.63 | 12.17 | +0.20 | −0.26 |
| 2-Acetoxynaphthazarin[a] | 12.33 | 12.07 | −0.10 | −0.36 |
| 2-Ethylnaphthazarin[a] | 12.45 | 12.60 | +0.02 | +0.17 |

[a] The ring bearing the substituent is predominantly quinoidal.

TABLE X

COMPARISON OF CALCULATED AND OBSERVED CHEMICAL SHIFTS OF *peri*-HYDROXY PROTONS OF SOME 2,3-DISUBSTITUTED NAPHTHAZARINS

| Compound | Chemical shift of C-5 OH, δ Calcd | Obsd | Chemical shift of C-8 OH, δ Calcd | Obsd |
|---|---|---|---|---|
| 2-Hydroxy-3-ethylnaphthazarin | 12.93 | 12.87 | 11.49 | 11.48 |
| 2-Methoxy-3-ethylnaphthazarin | 12.80 | 12.78 | 12.19 | 12.33 |
| 2-Hydroxy-3-methoxynaphthazarin | 12.50 | 12.40 | 11.69 | 11.55 |
| 2,3-Dimethoxynaphthazarin | 12.37 | 12.32 | 12.37 | 12.32 |
| 2,3-Diacetoxynaphthazarin | 11.97 | 12.08 | 11.97 | 12.08 |

treated as a 6-substituted naphthazarin as it has already been shown that the ring bearing the acetyl group is aromatic. The data are summarized in Table XI. Note that the methoxyl of 2-hydroxy-6-methoxynaphthazarin appears to display a greater effect on the more distant *peri* hydroxyl. This apparent greater substituent effect on the more distant *peri* hydroxyl is also obtained from symmetrically disubstituted naphthazarins (data not shown in Table XI).

TABLE XI

EFFECT OF SUBSTITUENT ON AROMATIC RING ON CHEMICAL SHIFT OF *peri*-HYDROXY PROTONS

| Compound | Substituent at C-6 | Chemical shift, δ C-5 OH | C-8 OH | Displacement (ppm) attributed to C-6 substituent C-5 OH | C-8 OH |
|---|---|---|---|---|---|
| 6-Acetylnaphthazarin | $COCH_3$ | 13.08 | 12.15 | +0.65 | −0.28 |
| 2-Hydroxy-6-ethylnaphthazarin | $CH_2CH_3$ | 13.27 | 11.58 | +0.51 | +0.09 |
| 2-Hydroxy-6-methoxynaphthazarin[a] | $OCH_3$ | 13.29 | 12.33 | +0.53 | +0.84 |
| 2-Methoxy-6-acetoxynaphthazarin | $OCOCH_3$ | 12.82 | 12.25 | +0.19 | +0.08 |

[a] The ring bearing the substituent at C-6 is assumed to be entirely aromatic.

Using the data in Table XI the chemical shifts of the C-5 and C-8 hydroxyls of some 2,7-disubstituted naphthazarins are calculated, and in Table XII the calculated and observed values are compared. The agreement for two compounds is good considering the crudeness of the calculation. The calculated value for the C-8 hydroxyl of 2-hydroxy-7-methoxynaphthazarin is in good agreement with the observed; however, the gross difference in the calculated and observed values for the C-5 hydroxyl cannot be rationalized. It has already been shown that the ring bearing the hydroxyl group is not entirely quinoidal. The good agreement of the calculated and observed chemical shifts for the C-8 hydroxyl shows that a quinone carbonyl is predominantly adjacent to the β-hydroxyl.

TABLE XII

COMPARISON OF CALCULATED AND OBSERVED CHEMICAL SHIFTS OF *peri*-HYDROXY PROTONS OF SOME 2,7-DISUBSTITUTED NAPHTHAZARINS

| Compound | Chemical shift of C-5 OH, δ Calcd | Obsd | Chemical shift of C-8 OH, δ Calcd | Obsd |
|---|---|---|---|---|
| 2-Hydroxy-7-ethylnaphthazarin | 12.85 | 12.77 | 12.00 | 11.98 |
| 2-Hydroxy-7-methoxynaphthazarin[a] | 13.60 | 13.13 | 12.02 | 12.07 |
| 2-Methoxy-7-acetoxynaphthazarin | 12.71 | 12.65 | 12.36 | 12.23 |

[a] The ring bearing the methoxy is assumed to be entirely aromatic.

**Solvent Effects.**—Because of the pronounced effect of the solvent on the chemical shift of protons of various functional groups, one solvent, *viz.* deuteriochloroform, was used throughout the investigation. The chemical shift as a function of the solvent merits a detailed study in itself and only a few of these effects will be mentioned at this time.

Aromatic and quinoidal methoxyls of naphthoquinones are generally paramagnetically shifted, some as much as 0.1 ppm, when observed in perdeuterioacetone as compared with deuteriochloroform (see Table XIII). The nature of the shift is not known.

TABLE XIII

EFFECT OF SOLVENT ON CHEMICAL SHIFT OF METHOXYLS OF SOME NAPHTHOQUINONES

| Compound | Chemical shift, δ $CDCl_3$ | $(CD_3)_2CO$ |
|---|---|---|
| 2-Methoxy-1,4-naphthoquinone | 3.89 | 3.97 |
| 2-Methoxynaphthazarin | 3.92 | 4.02 |
| 2,3-Dimethoxy-7-hydroxyjuglone | 4.07 | 4.06 |
| | 4.11 | 4.08 |
| 3-Hydroxy-7-methoxyjuglone | 3.91 | 4.00 |
| 2-Hydroxy-6-methoxynaphthazarin | 3.98 | 3.99 |
| 2-Hydroxy-7-methoxynaphthazarin | 3.97 | 4.03 |
| 2,7-Dimethoxynaphthazarin | 3.94 | 4.00 |

In Table XIV the change in the chemical shift of the C-3 proton of a 1,4-naphthoquinone substituted at C-2 with a hydroxyl and methoxyl in different solvents is shown. Note that the chemical shift of the C-3 proton of 2-hydroxy-1,4-naphthoquinone is shifted to δ 6.18 in dimethyl sulfoxide-$d_6$, a value which is essentially identical with the chemical shift of the C-3 proton of 2-methoxy-1,4-naphthoquinone in deuteriochloroform. The reverse situation is observed for the C-3 proton of 2-methoxy-1,4-naphthoquinone in dimethyl sulfoxide-$d_6$ (δ 6.32), a chemical shift approximately the same as that for the C-3 proton of 2-hydroxy-1,4-naphthoquinone in deuteriochloroform. The same phenomenon is observed for the corresponding

TABLE XIV

EFFECT OF SOLVENT ON CHEMICAL SHIFT OF RING PROTONS OF SOME NAPHTHOQUINONES

| Compound | Position of H | Chemical shift, δ — $CDCl_3$ | $(CD_3)_2CO$ | $(CD_3)_2SO$ |
|---|---|---|---|---|
| 2-Hydroxy-1,4-naphthoquinone | C-3 | 6.37 | 6.27 | 6.18 |
| 2-Methoxy-1,4-naphthoquinone | C-3 | 6.17 | 6.30 | 6.32 |
| Naphthopurpurin | C-3 | 6.37 | 6.29 | 6.17 |
| Methoxynaphthazarin | C-3 | 6.17 | 6.34 | 6.32 |
| 2,7-Dihydroxy-3-acetylnaphthazarin | C-6 | 6.68 | 6.63 | 6.55 |
| 2,7 Dimethoxynaphthazarin | C-3 and C-6 | 6.40 | 6.57 | |
| 2-Hydroxy-6-methoxynaphthazarin | C-3 | 6.42 | 6.41 | |
| | C-7 | 6.48 | 6.58 | |
| 2-Hydroxy-7-methoxynaphthazarin | C-3 | 6.47 | 6.45 | |
| | C-6 | 6.53 | 6.58 | |

naphthazarins. No rational explanation can be offered at this time for these shifts.

The acetyl protons of spinochrome A (2,7-dihydroxy-3-acetylnaphthazarin) resonate at δ 2.85 in deuteriochloroform. In acetone-$d_6$, there is observed only a minor difference in the chemical shift (δ 2.80). However, in dimethyl sulfoxide-$d_6$ there is a pronounced diamagnetic shift of the acetyl signal to δ 2.58, a chemical shift which is reminiscent of an acetyl group in a hindered environment. The same chemical shift is observed for the acetyl signal of spinochrome C (2,3,6-trihydroxy-7-acetylnaphthazarin) in dimethyl sulfoxide-$d_6$. The strong intramolecular hydrogen bond of the acetyl carbonyl and the adjacent β-hydroxyl is apparently broken. Hydrogen bonding of the hydroxyl next to the acetyl with the solvent forces the acetyl to assume a different configuration to relieve steric hindrance, thereby resulting in a diamagnetic shift of its signal.

### Experimental Section

All nmr spectra were determined in deuteriochloroform solution unless designated otherwise on a Varian A-60 instrument. The chloroform peak (δ 7.27) was used as the internal standard and the chemical shifts were checked using tetramethylsilane (δ 0.00) as the reference. The acetone-$d_5$ (δ 2.06) and dimethyl sulfoxide-$d_5$ (δ 2.52) peaks were used as internal standards for acetone-$d_6$ and dimethyl sulfoxide-$d_6$, respectively. Sample concentration was 2–20 mg/0.50 ml. The chemical shifts are reproducible within ±0.01 ppm. For comparison of signals of different compounds which differed closely or within the experimental error, the spectrum of the mixture was also determined as a check. The preparation of all new compounds used in this investigation will be presented elsewhere.

# Photochemical Reactions of Diketones. IV.[1,2] The Photoaddition of *o*- and *p*-Xylene to Camphorquinone

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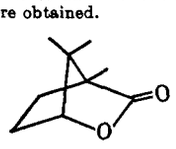
Photoirradiation of DL-camphorquinone (CQ) in *p*-xylene solution in the absence of oxygen at wavelengths above 3000 or 4000 A led to a mixture of DL-3-*endo*-(*p*-methylbenzyl)-3-*exo*-hydroxy-2-bornanone (**6a**, 45%), DL-2-*endo*-(*p*-methylbenzyl)-2-*exo*-hydroxy-3-bornanone (**7a**, 20%), 1,2-di-(*p*-tolyl)ethane (**14a**, 4%), and 3-hydroxy-2-bornanones (**15**) plus 2-hydroxy-3-bornanones (**16**) (total yield of hydroxy bornanones 6%). The same mixture of products was obtained by addition of *p*-methylbenzylmagnesium chloride to CQ. The structures of **6a** and **7a** were established by sodium borohydride reduction of each to a separable mixture of glycols whose stereochemistry was established by infrared and nmr spectroscopy. These were cleaved with sodium periodate to keto aldehydes **12a** or **13a**. The aldehyde proton of **12a** (derived from **6a**) appeared as a sharp singlet in the nmr while that of **13a** (derived from **7a**) appeared as a doublet. Similar results were obtained with *o*-xylene. It is suggested that these reactions proceed *via* hydrogen abstraction by excited CQ leading to a pair of radicals whose principal course of reaction is radical combination in a manner similar to that observed with 9,10-phenanthrenequinone. The photoaddition reaction (quantum yield 0.07) is a less efficient process than the photochemical oxidation (quantum yield 0.16) of CQ which afforded camphoric anhydride and camphoric acid.

An investigation of solution photochemical reactions of the nonenolizable α-diketone, DL-camphorquinone (CQ), has been undertaken. The rigid skeleton and known orientation of the carbonyl groups appeared to make this readily available substance[4a] a particularly suitable choice for an investigation of diketone photochemistry.[4b] The related monoketone, camphor, has been shown to undergo two competing, solvent-dependent ring cleavages upon direct[5] photoirradiation using a variety of light sources. In the presence of oxygen, a variety of products were observed, depending upon the experimental conditions. These included camphoric anhydride and products derived from it as was also observed in the present work. In benzene solution carbon dioxide was evolved and camphono lactone (i) and the isomeric campholyto lactone as well as trace of biphenyl were obtained.



i

(1) (a) For the previous paper in this series, see M. B. Rubin and P. Zwitkowits, *Tetrahedron Letters*, 2453 (1965). (b) Supported in part by a grant (GP-5038) from the National Science Foundation.

(2) Presented in part at the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966.

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(4) (a) W. C. Evans, J. M. Ridgion and J. L. Simonsen, *J. Chem. Soc.*, 137 (1934). (b) After this manuscript was submitted for publication, J. Meinwald and H. O. Klingele [*J. Am. Chem. Soc.*, **88**, 2071 (1966)] reported an investigation of photochemical reactions of CQ. These authors reported that, in the absence of oxygen, CQ failed to react in solvents such as benzene, carbon tetrachloride, *t*-butyl alcohol, methyl alcohol, or aqueous acetone

(5) (a) G. Ciamician and P. Silber, *Ber.*, **43**, 1340 (1910). (b) R. Srinivasan, *J. Am. Chem. Soc.*, **81**, 2604 (1959).