500-ml flask. The solution was heated to 50° and stirred during the slow addition of 3 g of sodium azide. After the addition was complete, the reaction mixture was maintained at 50° for 30 min, cooled, and diluted with 400 g of ice. The solution was basified by the addition of 30% sodium hydroxide solution and extracted five times with ether. The ethereal solution was extracted five times with 5% hydrochloric acid and the aqueous acid extract was made basic with 15% sodium hydroxide solution. This latter solution was extracted five times with ether and the ethereal solution was separated and dried over potassium hydroxide pellets. Removal of the ether yielded 0.9 g of an oil which was distilled, bp 93–97° (1 mm). The oil was converted into its dihydrochloride, using alcoholic hydrogen chloride and ethanol. Boiling methanol was added until the precipitate redissolved and the product was allowed to cool. The dihydrochloride (0.7 g) did not melt at 370° and when mixed with a sample prepared from the dioxime (as in Scheme I) the mixture did not melt at 370°. The infrared spectra (KBr disk) were identical for samples prepared by Scheme I or II.

The picrate of the compound prepared in Scheme I was the same as that derivative prepared in Scheme II, mp 250–252° dec. A mixture melting point of the picrates showed no depression.

*Anal.* Calcd for $C_{23}H_{28}N_8O_{14}$: N, 17.50. Found: N, 17.69.

The di(phenylurea) derivative, prepared from either of the diamines X, obtained from the method of Scheme I or II, melted at 251–253° when the compound was immersed in the bath at 245°. A mixture melting point showed no depression.

*Anal.* Calcd for $C_{26}H_{32}N_4O_2$: C, 71.40; H, 7.67; N, 13.32. Found: C, 71.19; H, 7.61; N, 13.07.

**Registry No.**—I (R = Et), 10428-65-6; II, 10428-66-7; III, 180-47-2; IV, 5794-98-9; V, 10428-68-9; VI (R = H), 10428-69-0; VI (R = $C_2H_5$), 10428-70-3; VII, 10428-71-4; VIII, 5607-35-2; IX, 10428-73-6; X, 1042-74-7; dihydrochloride of X, 10428-75-8; picrate of X, 10428-76-9; di(phenylurea) derivative of X, 10428-77-0; XII (R = H), 10428-78-1; XII (R = $C_2H_5$), 10428-79-2; XIII (R = H), 10428-80-5; XIII (R = $C_2H_5$), 10428-81-6; XIV, 10428-82-7; XV, 10428-83-8; XVI, 10428-84-9; XVII, 10428-85-0; XVIII (R = H), 10428-86-1; XVIII (R = $C_2H_5$), 10428-87-2; XIX (R = $C_2H_5$), 10428-88-3; XIX (R = H), 10428-89-4; XX, 10428-90-7.

# Nuclear Magnetic Resonance Investigation of Acyl Azulenes

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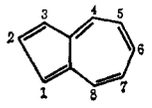
Nuclear magnetic resonance (nmr) spectra of 1-acetylazulene, 1,3-diacetylazulene, 1,3-diacetyl-4,6,8-trimethylazulene, diguaiazulyl ketone, and 1-formylguaiazulene have been measured at 60 Mc. Ring-proton resonance assignments have been made, and the influence of acyl substituents on ring-proton positions has been determined.

Azulene (1) and its derivatives constitute an exceedingly interesting class of compounds due to the fused five–seven bicyclic aromatic ring system. The two rings are physically and chemically quite different (as predicted from molecular orbital calculations), and thus the system should be especially vulnerable to a systematic investigation of substituent effects as a function of ring position. Both chemical and physical methods are available for such a study.

Anderson and co-workers[1] several years ago verified theoretical predictions[2] that the 1 and 3 positions of the azulene nucleus should be most easily attacked by electrophilic reagents.




**1**

This is consistent with the fact that the molecule possesses a permanent dipole with the small ring slightly electron rich, the large ring corresponding electron poor. We have previously studied the azulene system by preparing the variously substituted azulenecarboxylic acids and ethyl esters thereof and measuring $pK_a$'s and saponification rates, respectively.[3] Both relatively good and weak correlations were found between ring position of the reactive functional group and its relative reactivity (using the unperturbed azulene nucleus charge densities as a model).

Heilbronner has extensively reviewed the literature[4] dealing with preparation and physical properties of the very large number of substituted azulenes known through 1959. In sum, the review reveals a relatively widespread interest in the system from a purely synthetic standpoint, and also demonstrates conclusively from the results of several studies that the chemistry of the azulenes is in accord with theoretical predictions.

Attempts to investigate the azulenes by nuclear magnetic resonance (nmr) techniques have been somewhat limited in scope.[5,6] The complex spectrum of azulene itself has yielded to analysis.[6]

The purpose of the present investigation was to use three model compounds, azulene, 4,6,8-trimethylazulene and guaiazulene, the nmr spectra of which have previously been assigned,[5,6] in order to study the effects of acyl substitution on the ring protons in the known compounds 1-acetylazulene (2), 1,3-diacetylazulene (3), 1,1′-diguaiazulyl ketone (4), 1-formyl guaiazulene (5), and a new compound, 1,3-diacetyl-4,6,8-trimethylazulene (6).

## Results and Discussion

Table I presents the ring proton assignments made in the present investigation, along with the accepted as-

(1) A. G. Anderson and R. G. Anderson, *J. Org. Chem.*, **27**, 3578 (1962); A. G. Anderson and J. J. Tazuma, *J. Am. Chem. Soc.*, **75**, 4979 (1953), and other papers.

(2) A. Julg, *Compt. Rend.*, **239**, 1498 (1954).

(3) P. A. Leermakers and W. A. Bowman, *J. Org. Chem.*, **29**, 3708 (1964).

(4) E. Heilbronner in "Non-benzenoid Aromatic Compounds," D. Ginsburg, Ed., Interscience, New York, N. Y., 1959, pp 171–276; see also W. Keller-Schierlein and E. Heilbronner, pp 277–338.

(5) S. S. Danyluk and W. G. Schneider, *Can. J. Chem.*, **40**, 1777 (1962).

(6) W. G. Schneider, H. J. Bernstein, and J. A. Pople, *J. Am. Chem. Soc.*, **80**, 3497 (1958).

TABLE I

CHEMICAL SHIFTS[a] OF RING PROTONS ($\tau$)

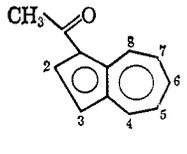
| Compound | H-1 | H-2 | H-3 | H-4 | H-5 | H-6[b] | H-7 | H-8 |
|---|---|---|---|---|---|---|---|---|
| Azulene (1)[c] | 2.79 d | 2.25 t | 2.79 d | 1.88 dd | 3.08 dd | 2.8 c | 3.08 dd | 1.88 dd |
| 1-Acetylazulene (2) | | 1.88 d | C | 1.68 d | C | C | C | 0.19 d |
| 1,3-Diacetylazulene (3) | | 1.47 s | | 0.08 d | C | C | C | 0.08 d |
| 1,1′-Diguaiazulyl ketone (4) | | 2.47 s | | 1.90 d | | 2.68 dd | 2.95 d | |
| 1-Formylguaiazulene (5) | | 1.78 s | | 1.73 d | | 2.45 dd | 2.64 d | |
| 1,3-Diacetyl-4,6,8-trimethylazulene (6) | | 1.78 s | | | 2.60 s | | 2.60 s | |
| 4,6,8-Trimethylazulene (7)[d] | 2.86 d | 2.52 t | 2.86 d | | 3.17 s | | 3.17 s | |
| Guaiazulene (8)[d] | 3.05 d | 2.63 d | | 1.95 d | | 2.76 dd | 3.29 d | |

[a] s, singlet; d, doublet; t, triplet; dd, doublet of doublets; C, complex, overlapping or incompletely resolved multiplets. [b] H-6 is split by long-range coupling to H-8. [c] Reference 6; this complex spectrum was fully analyzed. [d] Reference 5.

signments for azulene (**1**), 4,6,8-trimethylazulene (**7**), and guaiazulene (**8**). Quite large upfield effects of alkyl substitution upon the chemical shift of azulene ring protons have previously been noted.[5,6] (Effects of simple alkyl substituents, incidentally, are also manifested in relatively large shifts in the electronic spectrum of the azulene nucleus.)[4] For example, Danyluk and Schneider noted that the proton in the 2 position of azulene at $\tau$ 2.25 is shifted to $\tau$ 2.52 in 4,6,8-trimethylazulene—clearly a potent long-range effect. As may be seen from Table I, we have also observed large and highly interesting spectral shifts upon introduction of carbonyl substituents at the 1 (and/or 3) positions of azulenes. Protons, even those quite removed from the acyl groups, are moved uniformly downfield from their positions in the model compounds. These downfield shifts might, *a priori*, be due to either (or both) *electronic or anisotropic effects*. We have attempted to sort out the contributions from each of these effects.

1-Acetylazulene (**2**), as may be seen from Table I, possesses a rather highly complex spectrum which, however, may be rationalized in part when viewed both with respect to the simpler spectra of the other acyl azulenes in this study, and with respect to previously established values for coupling constants in the azulenes.[7] The spectrum of **2** shows A half of an AX quartet at $\tau$ 0.19 ($J$ = 9.5 cps), and the A halves of two AB quartets at $\tau$ 1.68 ($J$ = 10.5 cps) and 1.88 ($J$ = 4.2 cps),[7] relative areas 1:1:1, respectively, a multiplet from $\tau$ 2 to 2.9, relative area 4, and a sharp singlet at $\tau$ 7.43 for the acetyl methyl. From the magnitude of the coupling constants the low-field doublets at $\tau$ 0.19 and 1.68 are assigned as due to the 8 and 4 protons, respectively, and the doublet at $\tau$ 1.88 as the 2 proton.

It is interesting to note the magnitude of the respective shifts relative to azulene itself. The 8 proton is moved downfield the greatest extent, 1.69 ppm, the 2 proton (closest to the carbonyl group) is shifted 0.37 ppm, and the 4 proton is shifted 0.20 ppm. It is thus proposed that steric considerations fix 1-acetylazulene in conformation **9** with the carbonyl group closer to H-8 than to H-2,[8] and hence better able to exert its anisotropic effect on H-8. All of the protons in **2** are shifted downfield due to the dipolar contribution by **11** to the structure of **2**. (It may be noted that in the case of 1-formylguaiazulene, *vide infra*, models predict no particular preference in the orientation of the carbonyl group. This is manifested by the slightly lower field position relative to 1-acetylazulene of the 2 proton in 1-formylguaiazulene—lower even in spite of the general upfield influence of the alkyl substituents in the guaiazulene system.)



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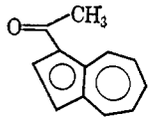

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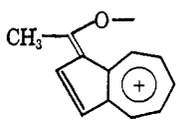

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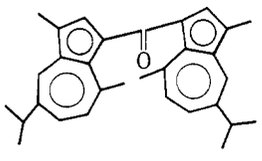
In 1,3-diacetylazulene (**3**) the combination of anisotropic and electronic effects serves to position the 4 and 8 protons at $\tau$ 0.08, a shift of 1.80 ppm from their position in the spectrum of azulene itself. Proton 2 appears 0.78 ppm downfield from its corresponding position in azulene. It is also observed from an examination of the spectra of **2**, **3**, **6**, and **7** that the upfield shifts due to alkyl substitution and the downfield shifts due to the acetyl groups are roughly additive. For instance, the 2 proton in **3** is moved downfield 0.78 ppm from azulene, and upfield 0.27 ppm in 4,6,8-trimethylazulene (**7**). This leads to a predicted position for H-2 of $\tau$ 1.74 in 1,3-diacetyl-4,6,8-trimethylazulene (**6**); it occurs at $\tau$ 1.78 which is in remarkably good agreement with prediction. The additivity is not so good for the 5 and 7 protons; they are expected at $\tau$ 2.32 in **6** and are found at $\tau$ 2.60. The spectrum of **6** is extremely simple as expected, with all protons—both ring and methyl—appearing as singlets.

The nmr spectra of the acylated quaiazulenes **4** and **5** are relatively easily interpretable from the parent compound guaiazulene **8**. The spectra and corresponding interpretations are roughly comparable with the acylated azulenes already discussed, except for the 2 proton which occurs at much lower field in 1-formylguaiazulene (**5**) than in diguaiazulyl ketone (**4**). Although not obvious from the structural formulas



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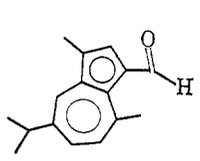

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drawn, it is absolutely clear from models that **4** will exist either in the planar conformation as drawn or in a form with one of the azulene nuclei twisted out of the

(7) $J_{45}$ = $J_{56}$ = 9.5–10.0 cps, $J_{12} \cong$ 4 cps, and $J_{62}$ = 1.5–2.0 cps. See ref 5.

(8) Cenco–Petersen models clearly show steric preference for conformation **9** over **10**.

plane. It *cannot* exist with the carbonyl oxygen aligned toward the 2 proton in *either ring*. Thus one would not expect, and does not find, anisotropic deshielding of H-2 in **4**. This is analogous to the case of the acetylazulenes. (We cannot exclude a possible upfield anisotropic effect of one ring on the other in the ketone **4**, however.)

As mentioned earlier in our discussion of 1-acetylazulene, the conformation of 1-formylguaiazulene cannot be predicted from examination of models. It probably does exist to some extent in the conformation drawn (with the carbonyl inducing an anisotropic downfield effect on H-2), as well as other conformations including the one analogous to **9** as drawn, *vide supra* (with the carbonyl having little or no influence on the 2 proton other than a simple inductive effect).

Assignments for the methyl protons in **2**–**8** are presented in Table II. Some of these assignments deserve comment. The spectrum of 1,3-diacetyl-4,6,8-trimethylazulene (**6**) shows three singlets at $\tau$ 7.17, 7.29, and 7.39, relative areas 2:2:1, which we have, respectively, assigned to the 4 and 8 methyls, acetyl methyls, and 6-methyl. The resonance at $\tau$ 7.17 is attributed to the 4 and 8 methyls because it is slightly broadened by long-range coupling to protons 5 and 7.[9] Ground-state electron densities calculated by LCAO–MO techniques[2] suggest that the 6-methyl should appear at slightly higher field than the 4- and 8-methyls. Apparently the acetyls exert no downfield anisotropic effect on the 4- and 8-methyls since the spacing between the 4- and 8-methyls and the 6-methyl is about the same in **6** (0.22 ppm) as in 4,6,8-trimethylazulene (**7**) (0.25 ppm).

TABLE II

CHEMICAL SHIFTS OF METHYL PROTONS ($\tau$)

| Compd | 3-Me | 4-Me | 6-Me | 8-Me | 7-*i*-Pr[a] | 1-Ac | 3-Ac |
|---|---|---|---|---|---|---|---|
| **2** | | | | | | 7.43 | |
| **3** | | | | | | 7.32 | 7.32 |
| **4** | 7.42 | | | 7.18 | 8.67 | | |
| **5** | 7.43 | | | 6.92 | 8.62 | | |
| **6** | | 7.17 | 7.39 | 7.17 | | 7.29 | 7.29 |
| **7**[b] | | 7.30 | 7.55 | 7.30 | | | |
| **8**[b] | 7.20 | | | 7.14 | 8.55 | | |

[a] Doublet, $J$ = 6.5–7.0 cps. [b] See ref 5. Solvent was $CH_2Cl_2$.

A final interesting observation is the fact that the aldehydic proton in 1-formylguaiazulene, at $\tau$ −0.58, occurs at the lowest field of any aldehyde of which we are aware.[10]

## Experimental Section

**Spectra.**—All nmr spectra were obtained on a Varian A-60A spectrometer, using tetramethylsilane as an external standard. Infrared and ultraviolet–visible spectra were recorded on a Perkin-Elmer Infracord and a Perkin-Elmer Model 202 ultraviolet–visible recording spectrophotometer, respectively.

**Materials.**—Azulene, 4,6,8-trimethylazulene, and guaiazulene were obtained from Aldrich Chemical Co. and were used without further purification. 1-Acetyl- and 1,3-diacetylazulene were prepared and purified by the method of Anderson and co-workers[11] involving the acylation of azulene with acetic anhydride in the presence of stannic chloride catalyst. 1,3-Diacetyl-4,6,8-trimethylazulene was prepared from compound **7** exactly analogously to the preparation of 1,3-diacetylazulene from azulene. The compound crystallizes as dark violet needles, mp 172°. It was characterized by its very simple and unambiguous nmr spectrum; the infrared spectrum was entirely consistent. Diguaiazulyl ketone was prepared by the method of Reid, Stafford, and Stafford[12] in whiich guaiazulene was treated with oxalyl chloride in methylene chloride with the reaction mixture chromatographed. The compound was recrystallized from ethanol as dark green needles, mp 190°, lit.[11] 189–191°.

1-Formylguaiazulene was prepared by the method of Hafner and Bernhard.[13]

**Registry No.**—**1**, 275-51-4; **2**, 7206-57-7; **3**, 10487-55-5; **4**, 10487-58-8; **5**, 3331-47-3; **6**, 841-71-4.

**Acknowledgments.**—We are indebted to the A.C.S. Petroleum Research Fund, Grants 1467-A and 2572-B, and to the National Science Foundation, Grant GP2848, for financial assistance. We also thank Mr. Wayne A. Bowman for preparing some of the azulenes used in this study.

(9) These protons similarly occur as a slightly broadened singlet.

(10) For example, N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "High Resolution NMR Spectra Catalog," Vol. 1, Varian Associates, Palo Alto, Calif., 1962.

(11) A. G. Anderson and J. A. Nelson, *J. Am. Chem. Soc.*, **72**, 3824 (1950); A. G. Anderson, J. A. Nelson, and J. J. Tazuma, *ibid.*, **75**, 4980 (1953).

(12) D. H. Reid, W. H. Stafford, and W. L. Stafford, *J. Chem. Soc.*, 1118 (1958).

(13) K. Hafner and C. Bernhard, *Angew. Chem.*, **69**, 533 (1957).