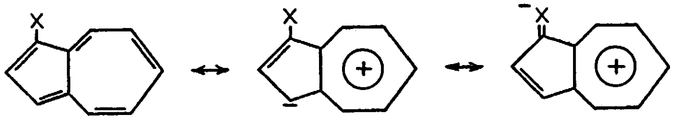
220. *The Azulene Series. Part IV.* The Synthesis and Properties of 3-Acylguaiazulenes.*

By D. H. Reid, W. H. Stafford, and Winifred L. Stafford.

The synthesis and properties of several derivatives of guaiazulene with electron-withdrawing substituents in position 3 are recorded and related to modern concepts of azulene structure.

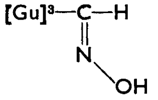
Derivatives of azulene with electron-attracting groups in position 1 should have properties consistent with a hybrid structure derived from the normal azulene forms[1] (Ia and b), together with the fulvenoid forms represented by (Ic). The last should reduce the importance of (Ib) to which typical azulenic properties have been ascribed.[2] The polarisation indicated by (Ic) should affect reciprocally the characteristic properties of both the azulene portion and the group X. In extreme cases the condition should approach that of the 3-benzylideneguaiazulenium salts described in the previous paper. These predictions have been confirmed by examination of a number of 3-acylguaiazulenes (1-acyl-3 : 8-dimethyl-5-*iso*propylazulenes).



(Ia) (Ib) (Ic)

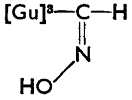
The Gattermann reaction was employed to prepare 3-formylguaiazulene. A red complex was deposited and decomposition of this yielded unchanged guaiazulene and a basic material retained in the red aqueous phase. On basification this became blue but the resulting blue ether extract became brown on concentration, with evident decomposition. However, the blue solution gave derivatives of the correct composition if the carbonyl reagents were added to it and so contained substantial quantities of the aldehyde.

Two aldoximes were isolated by chromatography and, by analogy with the benzaldoximes, were assigned the α- (II) (34% yield) and the β-stereo-form (III) (<3%) yield respectively; they differed in crystal form, m. p., spectra, and *X*-ray powder diagrams. The α- and β-hydrochlorides were distinct, but both afforded the α-oxime when treated with alkali. A third isomer, spectroscopically identical with the α-oxime, is regarded as a crystalline modification of the latter.



$[\mathrm{Gu}]^3{-}\mathrm{CH}{=}\mathrm{N}{-}\mathrm{OH}$

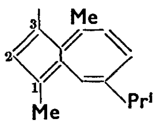
(II) α



$[\mathrm{Gu}]^3{-}\mathrm{CH}{=}\mathrm{N}{-}\mathrm{OH}$

β (III)

[Gu]³≡3′-Guaiazulenyl



It was not possible to confirm the assignment of configuration by the classical means as the expected nitrile was produced from both forms during the attempted formation of the *O*-acetyl compound. The infrared OH stretching frequencies of the oximes (see Table 1) agree qualitatively, but not quantitatively, with Palm and Werbin's generalisation.[3] The C=N vibrational frequency[4] is higher for the β- than for the α-form, which seems to be true also in many other cases though Palm and Werbin were unable to find this consistency.

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* Part III, preceding paper.

[1] Galloway, Reid, and Stafford, *Chem. and Ind.*, 1954, 724.

[2] Stafford and Reid, *Chem. and Ind.*, 1954, 277.

[3] Palm and Werbin, *Canad. J. Chem.*, 1954, **32**, 858; 1953, **31**, 105.

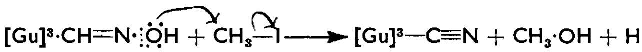
[4] Kahovec and Kohlrausch, *Monatsh.*, 1952, **83**, 614; Duyckaerts, *Bull. Soc. roy. Sci. Liège*, 1952, 196.

TABLE 1. *The infrared absorption frequencies (cm.$^{-1}$) of some 3-substituted guaiazulenes in Nujol.*

Note	CN	NO_2	CMe:N·OH	α, CH:N·OH	β, CH:N·OH	CMe:N·OH,HCl	α-Oxime, HCl	β-Oxime, HCl
1	—	—	3175s	3195s	3155s	2551 } s	2611 } s	2511s
						2469	2488	
2	2183s	—	—	—	—	—	—	—
3	—	1621s	1619m	1605m	1621s	1639m }	1645s }	1642s
		1605w	1608w			1603s	1592s	
	1550m	1582m						
4	1534m	—	1538s	1543s	1534m	1534s	1534s	—
	1520m	1526s	1520m	1520w	1520m		1527s	1522m
							1504m	1506s
*	1412s	1408s	1416s	1408s	1401s	1420m	1431m	1395s
							1389s	
†	1328m	—	1330w	1333w	1319s	1333w	1333s	1342m
*	1299m	1299m	1299w	1290s	1294w	1302w	1304s	1309s
		1230s				1239w	1239w	1232w
			1224s	1217w			1227w	
†	1209m	1212m	—	1205m	1203w	1203w	1205m	—
		1176s	1198s	1176s			1195w	1198m
*	1157s	1153m	1166m	1166s	1167s	1147s	1167s	1171m
*	1122w	1124m	1126w	1121w	1120w	1126w	1135w	1139w
	1099m	1096w	1104m	1103w	1105w	1100w	1106w	—
†	—	1073m	1087w	1087w	1085w	1088m	1092, }	1095m
							1073m	
*	1055s	1054m	1048s	1056s	1049m	1068s	1056w	1058w
						1052m	1042w	1038w
*		1031w }		1027m }				
	1019m	1026m	1020w	1016m	1024m	1025m	1018s	1024w
*	996w	1002s	1006s }	995s	994w	1010m }	998s }	999m }
			984s			996m	988	990s
*	959w	955m	939s	944s	954s	957s	968s	968s
*	917m	941s }	918s	—	934s }	920s	907m	933w }
		936			915			911w
		926						

Notes: 1, OH stretching. 2, C⋮N stretching. 3, C:O and C:N. 4, Skeletal C:C. * Frequencies to be attributed to 3-guaiazulenyl and its component groups. † Possibly to be attributed as *.

The basic character of these oximes suggested that they would readily form nitrones. However, boiling either the α- or the β-oxime in methyl iodide gave a little guaiazulene, the violet 3-cyanoguaiazulene (IV) (in reasonable quantity), and 3-formylguaiazulene (in small quantity), but no nitrone. 3-Formylguaiazulene, thus produced, was a stable



$$[Gu]^3{\cdot}CH{=}N{\cdot}\ddot{O}H + CH_3{-}I \longrightarrow [Gu]^3{-}C{\equiv}N + CH_3{\cdot}OH + HI$$

(IV)

violet compound, which contrasted with the properties of the ether extract obtained in the Gattermann reaction. It was then found that adding light petroleum (b. p. 80—100°) to the ether extract before its evaporation prevented the decomposition, and chromatography separated the formyl compound from a strongly adsorbed material which decomposed on the column. The yield of aldehyde (17%) contrasted with that for the oxime (37%) from the same extract and it was concluded that a blue, unstable, basic precursor must be present; the aldimine (V) was most likely but it could not be isolated.

$$\underset{(V)}{Gu{\cdot}CH{:}NH} \xrightarrow{H} Gu{\cdot}CH{:}NH_2^+ \longleftrightarrow Gu^+{:}CH{\cdot}NH_2$$

(Gu = 3-guaiazulenyl)

The betaine-type contributing forms for azulene (Ib) were suggested by us on analogy with compounds such as the methine enol-betaines.[5] The latter are acylated by acid anhydrides and halides, and guaiazulene was similarly converted by acetyl bromide into the known 3-acetylguaiazulene [6] without the assistance of Friedel–Crafts catalysts.

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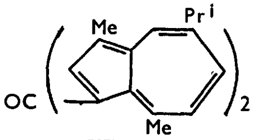
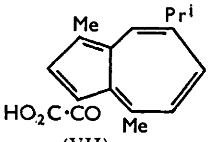
[5] Kröhnke, *Ber.*, 1937, **70**, 1114; 1935, **68**, 1177.

[6] Ukito, Watanabe, and Miyasaki, *J. Amer. Chem. Soc.*, 1954, **76**, 4584.

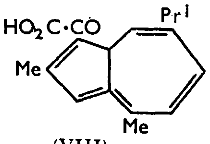
Benzoyl bromide gave a low yield of 3-benzoylguaiazulene, but the yield was also low when a catalyst was used. Oxalyl chloride also reacted swiftly with guaiazulene: if methylene chloride was used as solvent no complex was deposited and di-3-guaiazulenyl ketone (VI) was the only isolable product; in light petroleum the reaction was less complete and a solid complex was precipitated which yielded the ketone (VI) and 3-guaiazulenyl glyoxylic acid (VII). [In one experiment, with a less pure specimen of guaiazulene, an isomeric acid was isolated, which probably has structure (VIII) as the hypsochromic displacement of the visible absorption by 46 mμ relative to (VII) is that expected of a methyl shift from 1 to 2; presence of 2 : 4-dimethyl-7-*iso*propylazulene (*Se*-guaiazulene) in the starting hydrocarbon is not improbable.] Position 1 is preferred to position 3 as the site of reaction because of the probable steric effect of the 4-methyl group. Carbonyl chloride gave the same ketone (VI) and another, red acid. The latter was however not isolated as it was decarboxylated to guaiazulene with great ease. The mechanism of these reactions is interpreted generally as in the annexed scheme. The reactions are regarded as reversible because all the guaiazulene compounds with electron-withdrawing groups in position 3 give guaiazulene on treatment with acid. Diguaiazulenyl ketone when in hydrochloric acid gives guaiazulene quantitatively within a few minutes. The nitrile, the aldoximes, the benzoyl and the acetyl compound all generate guaiazulene in hot acid. The formyl compound is degraded in acid too quickly for spectroscopic measurements in other than the visible region. This method of acylation without catalyst is probably preferable to the use of stannic chloride, for it has been shown that a dimeric hydrocarbon is produced when guaiazulene and stannic chloride are mixed: this dimer has a visible maximum at 630 mμ, indicating that an alkyl group of one guaiazulene group has reacted with position 3 of the other.



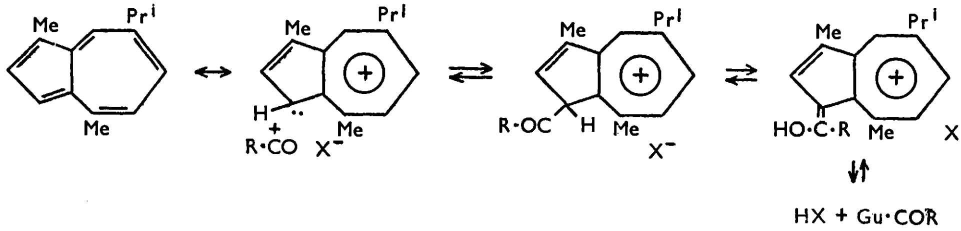
(VI)



(VII)



(VIII)

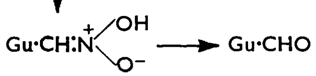


Tetranitromethane with guaiazulene gives 3-nitroguaiazulene and the yield is constant of at least 0·6 mol. of reagent is used. If 0·3 mol. is used guaiazulene remains un-nitrated and is therefore available for a slow reaction with either an impurity in the reagent or with dinitromethane which appears incapable of nitrating guaiazulene; the product isolated, which suggested this secondary process, was 3-formylguaiazulene, possibly formed as in the annexed scheme where the last stage is regarded as analogous to the Nef reaction.

$$CH_2(NO_2)_2 \longrightarrow [CH_2{\cdot}NO_2]^+ + NO_2^-$$

$$GuH + [CH_2{\cdot}NO_2]^+ \longrightarrow Gu{\cdot}CH_2{\cdot}NO_2 + HNO_2$$

$$\downarrow$$



$$Gu{\cdot}CH{:}\overset{+}{N}\begin{matrix}OH\\O^-\end{matrix} \longrightarrow Gu{\cdot}CHO$$

The absorption spectra of the new compounds are recorded in Figs 1—10 and in Table 2, for a non-hydroxylic solvent (hexane when solubility permitted),[7] ethanol and various acidic solvents. Hydrogen-bonding and salt formation caused changes in the absorption spectra interpreted as follows:

	GuX	$\mathrm{GuX\cdots HOR} \longleftrightarrow \mathrm{Gu^{+}{-}XH\cdots{}^{-}OR}$	$\mathrm{Gu^{+}{-}XH} \longleftrightarrow \mathrm{Gu{=}^{+}XH}$
In:	Hexane	Hydroxylic solvents	Acid

In hexane the absorption spectra give a measure of the interaction of the group X with the characteristically absorbing azulene portion, an interaction represented fundamentally by (Ic) but including changes in the contributions of (Ia and b) by processes not involving electron-sharing with X. In Table 2 the results are summarised and four maxima ($A \longrightarrow D$) are considered. It is apparent that *B*, *C*, and *D* suffer bathochromic displacements relative to the parent guaiazulene, but that the shift of *B* is very dependent on X, in the order CN < COMe < CHO < COPh < COGu < NO_2. The visible absorption maximum *A* is displaced hypsochromically but here the effect of NO_2 and CHO is greater than of

FIG. 1. 3-*Formylguaiazulene* (*A*) *in hexane*, (*B*) *in* EtOH.

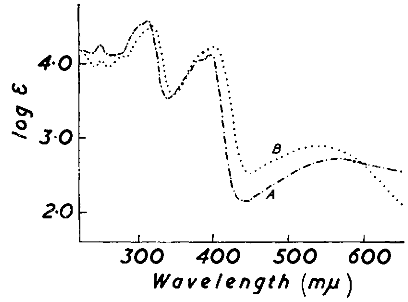


FIG. 2. 3-*Formylguaiazulene* (*A*) *in* EtOH, (*B*) *in* 50%-*aq.* EtOH, (*C*) in N-*aq.* EtOH–HCl, (*D*) in 2N-*aq.* EtOH–HCl, (*E*) *in* 5N-*aq.* EtOH–HCl.

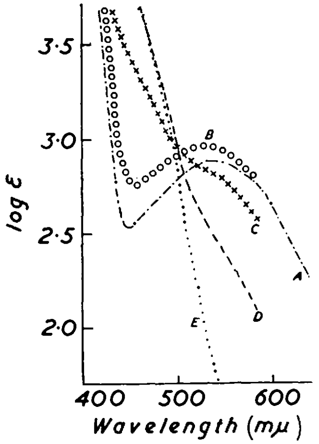


FIG. 3. 3-*Benzoylguaiazulene* (*A*) *in hexane*, (*B*) *in* EtOH, (*C*) *in* 5N-EtOH–HCl, *and* (*D*) 3-*benzylideneguaiazulenium chloride.*

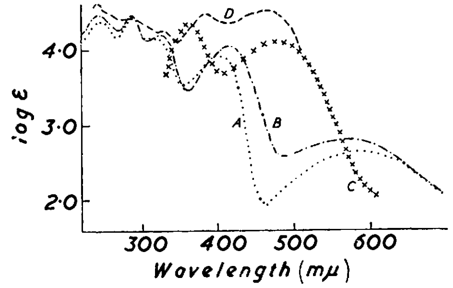
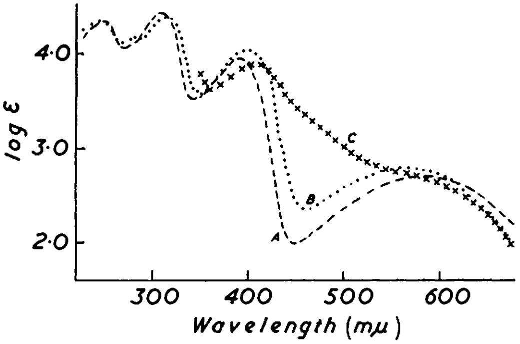


FIG. 4. 3-*Acetylguaiazulene* (*A*) *in hexane*, (*B*) *in* EtOH, (*C*) *in* 5·5N-EtOH–HCl.



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[7] Heilbronner and Schmid, *Helv. Chim. Acta*, 1954, **37**, 2018; Heilbronner and Gerdil, *ibid.*, 1956, **39**, 1996; W. L. Galloway, Ph.D. Thesis, Edinburgh, 1956.

FIG. 5. 3 : 3′-*Diguaiazulenyl ketone* (*A*) *in hexane*, (*B*) *in* EtOH, (*C*) *in* 2·3N-EtOH–AcOH, (*D*) *in* 0·5N-EtOH–HCl, (*E*) *in* 4N-EtOH–HCl.

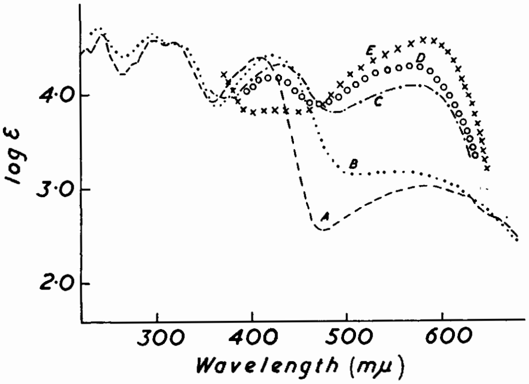


FIG. 6. 3-*Guaiazulenylglyoxylic acid* (*A*) *in* C_6H_6, (*B*) *in* EtOH, (*C*) *in* 2N-EtOH–HCl.

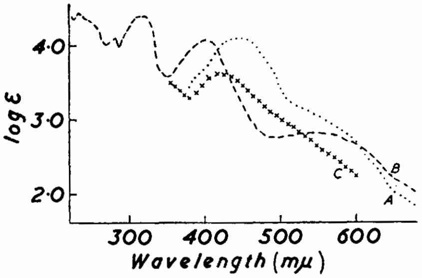


FIG. 7. *Methyl* 3-*guaiazulenylglyoxylic acid* (*A*) *in* EtOH, (*B*) *in* C_6H_6.

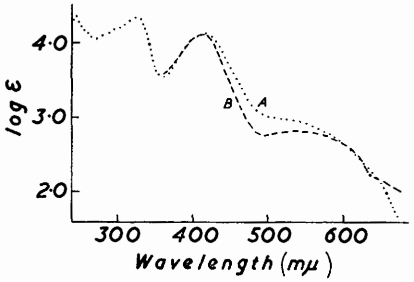


FIG. 8. 3-*Cyanoguaiazulene* (*A*) *in* EtOH, (*B*) *in hexane* (log ε + 0·4), (*C*) *in* 2N-EtOH–HCl (log ε + 0·8).

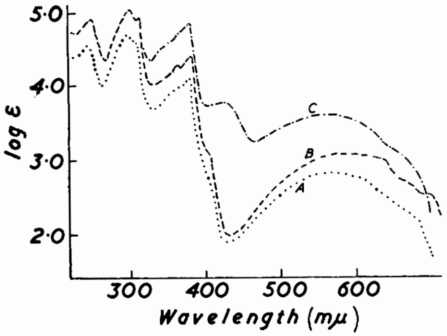


FIG. 9. 3-*Nitroguaiazulene* (*A*) *in hexane*, (*B*) *in* EtOH (log ε + 0·4), (*C*) *in* 2N-EtOH–HCl (log ε + 0·8).

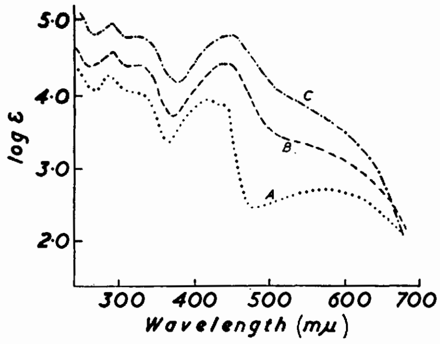
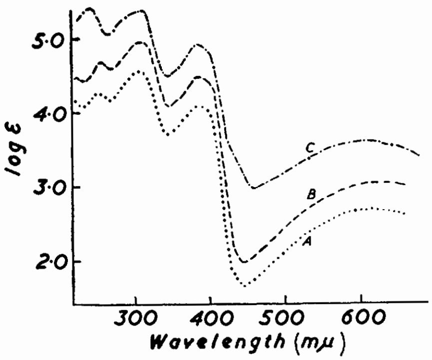


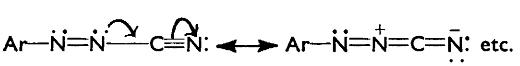
FIG. 10. *The isomeric guaiazulene*-3-*aldoximes*, (*A*) α-*form in* EtOH; (*B*) α-*form in* 9 : 1 *hexane*–EtOH (log ε + 0·4), (*C*) β-*form in* EtOH (log ε + 0·8).

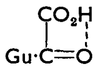


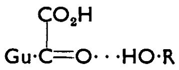
the others. The reciprocal effect of this polarisation change in the light-absorbing azulene portion will be a polarisation of the multiple bond of X demonstrable by the infrared stretching frequencies of there bonds. These are summarised in Table 3. The carbonyl frequencies are comparable and the order of polarisation is COMe $<$ CHO $\leqslant$ COPh $<$ COGu, in reasonable agreement with the relative effects on band *B*. The values indicate a high degree of polarisation, as required by the hybrid structure derived from (Ia, b, and c). The nitro-, cyano-, and hydroxyimino-group are also polarised as expected. The normal absorption frequencies expected for these groups are NO_2 1560—1500 and 1350—1300 cm.$^{-1}$, CN *ca.* 2230 cm.$^{-1}$, and HO·N= *ca.* 1640 cm.$^{-1}$. In the case of the nitrile the closest analogues are the diazocyanides [8] which have a polarised structure (IX).

TABLE 2. *Ultraviolet and visible absorption maxima* (mμ) *of some 3-substituted guaiazulenes in hexane and in ethanol.*

Subst.	*A*	*B*	*C*	*D*	Solvent
CHO	568	397	314, 276	250	Hexane
	538	401	318, 279	251, 238	Ethanol
COMe	580	390	306	249	Hexane
	560	397	311, 277	240	Ethanol
COPh	583	399	314, 289	249	Hexane
	566	413	325, 289	240	Ethanol
COGu	582	407	316, 298	242	Hexane
	550	424	313, 297	240	Ethanol
CN	580	379, 361	312, 298	247	Hexane
	560	378	310, 298	246	Ethanol
α-CH:N·OH	625	385	308	257	Hexane
	620	385	308	254	Ethanol
H	605	367, 350	285	246	Hexane


(IX)


(Xa)


(Xb)

The influence of hydroxylic solvents is marked and demonstrates the polarisability of the system. The general form of the absorption curves do not change but band *A* shifts hypsochromically and band *B* shifts bathochromically. 3-Guaiazulenylglyoxylic acid is exceptional in its behaviour but its methyl ester is normal. This can be explained by postulating the intramolecular hydrogen-bonding as in (Xa) in non-polar solvents and a weaker intermolecular bonding to hydroxylic solvents (cf. Xb). The infrared spectra (Table 3) of the carbonyl compounds in ethanol show the expected displacement.

TABLE 3. *Infrared stretching frequencies* (cm.$^{-1}$) *of the multiple bond in 3-acylguaiazulenes.*

Subst.	CCl_4	EtOH	Nujol	KBr	Subst.	Nujol
Acetyl	1674 1658	1650	—	—	α-Formyl oxime	1605
					β-Formyl oxime	1621
Formyl	1634	1614	—	1618	Acetyl oxime	1629
Benzoyl	—	—	1637	—	Cyano	2183
Guaiazuloyl	1616	1594	—	—	Nitro	1526 1230

In acid solution salt formation generally occurs and the absorption changes radically. In most instances where the formation of a cation is complete, the normal visible absorption *A* disappears, as does band *B*, to be replaced by a single band of high intensity.

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[8] Sheppard and Sutherland, *J.*, 1947, 453.

Investigation of the ultraviolet region was impossible owing to rapid degradation. In two instances the effects of different degrees of acidity on the absorption in the visible region have been studied. In Fig. 2 band *A* for the aldehyde is recorded in ethanol, 50% aqueous ethanol, and 50% aqueous ethanol containing 3 concentrations of hydrochloric acid. Introduction of water causes a normal hydrogen-bonding effect—hypsochromic translation of *A*. As the acidity increases there is evidence of an equilibrium involving the cation and the neutral substance, which progressively favours the former with the disappearance of band *A*. In the second instance, Fig. 5, 3 : 3′-diguaiazulenyl ketone in 5 solvents, high acid concentrations produce a permanganate colour but band *B* decreases in intensity and a new band which coincides with *A* increases rapidly. In these two instances virtually complete production of the cation can be achieved, but in some of the other compounds the change is less complete.

The benzoyl compound (Fig. 3) demonstrates a parallelism between the resulting cation (XIa) and the 3-benzylideneguaiazulenium salts (XIb). There is, in the visible region at least, some similarity in form. When 3-formylguaiazulene reacted with guaiazulene in the presence of hydrogen chloride, the resulting blue compound (XIIa) was unstable but its visible absorption maximum was very similar to that of the cation (XIIb) (formed from diguaiazulenyl ketone in acid) both in intensity and position. This intense absorption was also found in the blue 3-*p*-dimethylaminobenzylideneguaiazulenium chloride which although not obtained pure was shown to have a visible absorption maximum fifty times more intense than that of guaiazulene.

$\mathrm{Gu^{+}{:}CR{\cdot}OH}$ (XIa) $\quad$ $\mathrm{Gu^{+}{:}CHR}$ (XIb) $\quad$ $\mathrm{Gu{\cdot}CH{:}Gu^{+} \longleftrightarrow Gu^{+}{:}CH{\cdot}Gu}$ (XIIa) $\quad$ $\mathrm{GuC(OH){:}Gu}$ etc. (XIIb)

The absorption spectra discussed above agreed well with expectation, but the oximes were divergent (Fig. 10). A bathochromic shift of both bands *A* and *B* occurs and the shift in *A* is slightly less than that due to an alkyl substituent. Any donation of electrons to the azulene moiety, which might explain this shift, would also increase the acidity of the hydroxyimino-group, which is not observed.

Some reactions of these acyl compounds were studied. Attempts to prepare alcohols from 3-formyl- and 3-acetyl-guaiazulene by means of phenylmagnesium bromide or lithium aluminium hydride failed. It appears that nucleophilic reagents attacked the azulene nucleus. However, lithium aluminium hydride reduced the glyoxylic acid to the glycol (XIII); this dissolved in acid to give presumably the yellow salt (XIV), but within a few minutes decomposition occurred and blue material was re-extractable into ether; the blue material had carbonyl reactivity but no pure derivative could be isolated.

The base-catalysed condensation of 3-acetylguaiazulene with benzaldehyde gave no crystalline product, but a material with the characteristic chromatographic behaviour of an acylazulene was separated. An alternative attempt to synthesise 3-cinnamoylguaiazulene from guaiazulene and cinnamoyl bromide gave a similar material. Attempts to prepare 2-3′-guaiazulenylquinoline by the reaction of 3-acetylguaiazulene and *o*-aminobenzaldehyde gave a gummy product in low yield. Salicylaldehyde under acid conditions gave an unstable dark red product which may have been the oxonium salt but neither it nor a derivative could be obtained pure.

$\mathrm{Gu{\cdot}CH(OH){\cdot}CH_2{\cdot}OH}$ (XIII) $\longrightarrow$ $\mathrm{Gu^{+}{:}CH{\cdot}CH_2{\cdot}OH}$ (XIV) $\longrightarrow$ $\mathrm{Gu{\cdot}CH_2{\cdot}CHO}$

3-Cyanoguaiazulene also failed to react with methylmagnesium iodide in very large excess. Methyl iodide and 3-acetylguaiazulene oxime gave at least three products, which were very unstable and were not obtained pure; they appeared to be basic and one on decomposition gave methylamine.

Both 3-formyl- and 3-acetyl-guaiazulene gave normal ketonic derivatives but 3-benzoylguaiazulene and 3 : 3′-diguaiazulenyl ketone did not react with hydroxylamine or dinitrophenylhydrazine. The phenylhydrazone of the acetyl compound was a liquid and was obtained analytically pure; it did not give 2-3′-guaiazulenylindole on treatment with acid.

EXPERIMENTAL

The procedure for chromatography was as in Part III and the guaiazulene used was commerical " Azulen " made by Dragoco Ltd.

3-Formylguaiazulene.—A suspension of zinc cyanide (5·9 g.) in a dry ethereal solution (50 ml.) of guaiazulene (5·0 g.) was saturated with hydrogen chloride. A red complex was deposited, which after 15 hr. was decomposed with dilute hydrochloric acid, repeated warming with methylene chloride and concentrated hydrochloric acid being required to effect dissolution. The red aqueous phase was separated from the blue ether phase, exhaustively extracted with ether to remove guaiazulene, and made alkaline with aqueous sodium hydroxide, and the precipitated blue material was taken into ether. The ether extract was dried (Na_2SO_4), light petroleum (b. p. 80—100°) was added, and the ether distilled off. Dissolved material decomposed at the end of the distillation. The residual solution was chromatographed. Elution with benzene containing a little ether separated a brown band from a strongly adsorbed green band. The purple eluate gave dark red needles (from ethanol), m. p. 84—84·5°. The *formyl compound* (Found: C, 84·7; H, 7·9. $C_{16}H_{18}O$ requires C, 84·9; H, 8·0%), obtained in 17·6% yield, formed a 2 : *4-dinitrophenylhydrazone* as red needles (from glacial acetic acid), m. p. 285° (decomp.) (Found: C, 66·0; H, 5·5; N, 13·3. $C_{22}H_{22}O_4N_4$ requires C, 65·0; H, 5·5; N, 13·8%).

An ethereal solution of the formyl compound gave 3-*hydroxymethyleneguaiazulenium chloride* on saturation with hydrogen chloride. This could not be recrystallised and analysis showed that it was a hydrate (Found: C, 68·5; H, 7·7; Cl, 12·7. $C_{16}H_{21}O_2Cl$ requires C, 68·4; H, 7·5; Cl, 12·7%).

Oximes. (*a*) 3-Formylguaiazulene (50 mg.) was dissolved in ethanol (10 ml.) containing 10% aqueous sodium hydroxide (4 drops). Hydroxylamine hydrochloride (250 mg.) was added and the solution was boiled for 30 min. The blue solution was diluted with water and an ether extract was treated normally. Chromatography yielded a trace of yellow material (ether), and a mixture of the two oximes as a green solution (ether–ethanol, 7 : 1). The solution was taken to dryness and the residue was re-chromatographed, to give two oximes, *form A* as green plates (from light petroleum–ethanol), m. p. 128—130° (Found: C, 79·4; H, 8·0; N, 6·0. $C_{16}H_{19}ON$ requires C, 79·6; H 7·9; N, 5·9%), and *form B* as green needles (from ether–light petroleum), m. p. 162° (Found: C, 79·2; H, 7·9; N, 5·8%). The total yield (40 mg., 80%) of the isomers contained only 5% of form B.

(*b*) To the crude extract from the preparation of the formyl compound, ethanolic hydroxylamine hydrochloride, made just alkaline with 10% aqueous sodium hydroxide, was added and the ether was removed. The above procedure was then followed. No aldehyde remained and a 37% yield of oximes with respect to the guaiazulene was obtained.

(*c*) The *hydrochloride* was prepared by passing hydrogen chloride into an ethereal solution of form A. The red solid initially precipitated became partly purple on the filter. The mixed solid, m. p. 135—145° (decomp.), was analysed in the crude state (Found: C, 68·6; H, 6·2; N, 4·7; Cl, 11·6. Calc. for $C_{16}H_{20}ONCl$: C, 69·1; H, 7·3; N, 5·0; Cl, 12·8%). Freshly prepared hydrochloride of form A was decomposed with 5% sodium hydroxide solution and extracted into ether. The extract was treated normally and chromatography separated a small quantity of form A, m. p. 125°, from a large quantity of form B which crystallised as green needles. m. p. and mixed m. p. 162°.

The *hydrochloride* of form B, similarly prepared, formed purple crystals, m. p. 138—140° (decomp.) (Found: C, 69·4; H, 7·3; N, 5·0; Cl, 12·4%). Decomposition of the hydrochloride of form B with alkali yielded only form B of the oxime.

Hydrolysis of oxime A. The oxime (50 mg.) was heated in ethanol (10 ml.) containing 10% aqueous hydrochloric acid (10 ml.) for 40 min., cooled, and extracted with ether. The extract on normal treatment yielded guaiazulene.

Action of Methyl Iodide on 3-Formylguaiazulene Oximes.—A solution of oxime A (586 mg.)

in methyl iodide (25 ml.) was boiled for 30 min. The residue, after removal of methyl iodide, was chromatographed, yielding (i) a little guaiazulene, (ii) a purple solution (benzene–ether, 7 : 3), and (iii) an orange band eluted as a purple solution (ether). The compound (ii) crystallised from ethanol and was sublimed under reduced pressure. 3-*Cyanoguaiazulene* (75 mg., 13·8%) is very soluble in all organic solvents (Found: C, 85·7; H, 7·8; N, 6·8. $C_{16}H_{17}N$ requires C, 86·1; H, 7·7; N, 6·3%). The eluate (iii) yielded 3-formylguaiazulene (10 mg., 1·8%), m. p. 84–84·5°, confirmed by mixed m. p., analysis, and absorption spectrum. 40% of the α-aldoxime was recovered.

The same products were obtained from form B.

3-*Acetylguaiazulene*.—Acetyl bromide (0·7 ml.) was added to guaiazulene (0·777 g.) in light petroleum (0·8 ml.; b. p. 60—80°) and the solution was left for 24 hr. The brown complex was treated with 1 : 1 aqueous ethanol (20 ml.), and the solution was extracted with ether and treated normally. The first eluate (light petroleum) was green and from it the guaiazulene trinitrobenzene derivative was isolated (m. p. and analysis), leaving bright yellow mother-liquors. The yellow material was unstable to further chromatography. A second product (eluted with benzene) was rechromatographed and crystallised from light petroleum–ethanol as purple plates, m. p. 85·5—86° (349 mg., 37%) (Found: C, 84·6; H, 8·2. $C_{17}H_{20}O$ requires C, 85·0; H, 8·5%). 3-*Acetylguaiazulene* formed a red trinitrobenzene derivative, m. p. 124°, and a red 2 : 4-di-*nitrophenylhydrazone*, m. p. 109—110·5° (Found: C, 65·7; H, 5·7; N, 13·9. $C_{23}H_{24}O_4N_4$ requires C, 65·7; H, 5·7; N, 13·3%).

Use of weaker solutions in light petroleum led to lower yields but when methylene chloride (6 ml.), guaiazulene (0·8 g.), and acetyl bromide (0·75 g.) were employed the yield of ketone was 43%.

Acetylguaiazulene (100 mg.) was heated in trichloroacetic acid (1 g.) at 60° for 1 hr., added to dilute ammonia solution, and extracted with ether. The extract was treated normally, yielding guaiazulene (*ca.* 60 mg.) and brown decomposition products.

Phenylhydrazine (0·5 g.) and 3-acetylguaiazulene (200 mg.) in 10% ethanolic acetic acid (10 ml.) were warmed for a few minutes, then cooled and filtered. The filtrate was poured into water, and an ether extract was prepared. Chromatography yielded a blue-green compound which did not crystallise. The liquid *phenylhydrazone* was analysed (Found : C, 83·7; H, 4·1; N, 8·5. $C_{23}H_{26}N_2$ requires C, 83·7; H, 7·8; N, 8·5%).

A solution of 3-acetylguaiazulene (550 mg.) and hydroxylamine hydrochloride (240 mg.) in pyridine (80 ml.) was boiled for 75 min. More hydroxylamine hydrochloride (330 mg.) was then added and heating continued for 30 min. The solution was poured into water, and an ether extract was made, washed with dilute hydrochloric acid, and prepared for chromatography. Acetylguaiazulene (eluted with benzene) was separated from a blue compound (eluted with ether). The latter crystallised as blue plates (from light petroleum–ethanol), m. p. 140—141·5°, and proved to be a single *oxime* (245 mg., 42%) (Found: C, 79·7; H, 8·3; N, 5·5. $C_{17}H_{21}ON$ requires C, 80·0; H, 8·3; N, 5·5%). This formed a *hydrochloride*, red needles, m. p. 110—120° (decomp.), which were analysed in the crude state (Found: C, 69·7; H, 8·8; N, 4·2; Cl, 11·7. $C_{17}H_{22}ONCl$ requires C, 69·9; H, 7·6; N, 4·8; Cl, 12·2%).

3-*Benzoylguaiazulene*.—Guaiazulene (9·78 g.) was treated in light petroleum (60 ml.; b. p. 60—80°) with benzoyl chloride (10·4 g.) and aluminium chloride (13·5 g.). A red complex was formed with evolution of heat. The mixture was boiled for 15 min. and the complex decomposed by dilute hydrochloric acid. An extract with light petroleum was treated normally. Chromatography gave a brown band, eluted as a blue-green solution by light petroleum which gave a little 3-benzoylguaiazulene and guaiazulene on rechromatography. The major quantity of the ketone came from a benzene–ether (1 : 1) eluate which was green in reflected light and red in transmitted light. 3-*Benzoylguaiazulene* forms violet crystals, m. p. 120—121°, from light petroleum–ethanol (Found: C, 87·0; H, 7·0. $C_{22}H_{22}O$ requires C, 87·5; H, 7·3%) (yield, 1·5 g., 10%). The substance formed no ketonic derivatives and no trinitrobenzene derivative.

The ketone was also made by boiling guaiazulene (0·571 g.) and benzoyl bromide (0·82 ml.) in light petroleum (8 ml.; b. p. 80—100°) for 4·5 hr. The complex was decomposed with 50% aqueous ethanol, and an ether extract was prepared and treated normally. A good return of guaiazulene, together with 3-benzoylguaiazulene (70 mg., 8%), was obtained.

Action of Oxalyl Chloride on Guaiazulene.—(*a*) Oxalyl chloride (0·29 g.) was added dropwise to a solution of guaiazulene (0·46 g.) in methylene chloride (5 ml.). After 2 hr. the reddish-purple solution was diluted with ether and washed free from acid. No azulenic acid was present. The extract was treated normally and chromatography yielded guaiazulene (0·13 g., 28%; eluted with light petroleum) and a brown band (eluted with benzene) from which 3 : 3′-*diguaiazulenyl ketone* was obtained as dark green needles (70 mg., 14·3%), m. p. 189—191° (from ethanol) (Found: C, 87·5; H, 8·1. $C_{31}H_{34}O$ requires C, 88·1; H, 8·1%).

(*b*) Oxalyl chloride (305 mg.) was added to guaiazulene (480 mg.) in light petroleum (5 ml.; b. p. 60—80°). The solvent became red with slow evolution of gas and a brown solid was deposited. The mixture was treated with water after 2¼ hr. at room temperature and an ether extract was made. This was washed with water until extraction of acid was complete and the now orange ethereal extract was treated as above, yielding 3 : 3′-diguaiazulenyl ketone (75 mg., 14·7%). The aqueous extracts were acidified and extracted with ether. The last-mentioned ethereal extract was extracted with successive small portions of 2N-sodium hydroxide. The combined alkaline solutions were washed once with ether and acidified with concentrated hydrochloric acid. The 3-*guaiazulenylglyoxylic acid* was removed by filtration after 2 hr. at 0°. It formed reddish-brown needles, m. p. 115—116° (150 mg., 22·9%), from ether (Found: C, 75·5; H, 6·7. $C_{17}H_{18}O_3$ requires C, 75·5; H, 6·7%), and formed with diazomethane a *methyl ester*, in the normal way. The ester formed red plates, m. p. 97·5—98° (from acetone–light petroleum, 1 : 3) (Found: C, 76·0; H, 7·0. $C_{18}H_{20}O_3$ requires C, 76·1; H, 7·1%).

In an early experiment a red water-soluble acid, isolated in low yield, was perhaps 2 : 4-*dimethyl*-7-iso*propyl*-1-*azulenylglyoxylic acid*, m. p. 125—129°, with an absorption at 500 mμ (Found: C, 75·5; H, 6·8. $C_{17}H_{18}O_3$ requires C, 75·6; H, 6·7%).

3-(1 : 2-*Dihydroxyethyl*)*guaiazulene*.—The 3-glyoxylic acid (270 mg.) in ether (50 ml.) was treated for 1 hr. with lithium aluminium hydride (100 mg.), then with water, and the blue ethereal layer was separated. It gave the *glycol* as cornflower-blue needles, m. p. 116—118° (variable with rate of heating) (Found: C, 78·9; H, 8·8. $C_{17}H_{22}O_2$ requires C, 79·1; H, 8·6%).

3-*Nitroguaiazulene*.—Guaiazulene (200 mg.) in carbon tetrachloride (20 ml.) was treated dropwise with tetranitromethane (200 mg.) in the same solvent at <5°. Immediate colour change to brown occurred. After 30 min. the solvent was removed and the residue chromatographed. The *nitro-compound* (61 mg., 25%) (eluted with benzene–ether, 9 : 1) crystallised in brown plates, m. p. 72°, from light petroleum (Found: C, 74·2; H, 7·3; N, 5·6. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·0; N, 5·8%). The same yield was obtained by using 0·6 mol. of tetranitromethane (120 mg.). When tetranitromethane (60 mg.) was treated as above with guaiazulene (200 mg.) the colour changed only to green and chromatography yielded guaiazulene (37 mg.), 3-nitroguaiazulene (52 mg.), and 3-formylguaiazulene.

Action of Stannic Chloride on Guaiazulene.—Solutions of stannic chloride (3 ml.) and guaiazulene (3·0 g.) in light petroleum (15 ml.; b. p. 40—60°) were mixed. The blue colour disappeared rapidly and a yellow complex was deposited which changed to a blue–grey solid during 24 hr. Decomposition with water was followed by extraction with methylene chloride. The extract was washed, dried, and evaporated, and the residue was taken into hot ethanol and freed from unchanged guaiazulene by treatment with *s*-trinitrobenzene (500 mg., 2 × 200 mg.). Impure guaiazulene–trinitrobenzene complex was deposited. The mother-liquors were taken to dryness and the residue was extracted with boiling light petroleum (b. p. 80—100°) until the solid residue was colourless. The combined extracts deposited a little trinitrobenzene on cooling but were freed completely from it by percolation through a small alumina column. The eluates on concentration and cooling deposited violet-black prisms, m. p. 140·5—142° (1·25 g.), which proved to be a *hydrocarbon* (Found: C, 91·2; H, 7·9. $C_{30}H_{34}$ requires C, 91·4; H, 8·6%).

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