$C=CH_{a+b}$); 5.83 (1H/broad *d*, J = 16 Hz, $C=CH_c$); 7.0 (1H/broad *d*, J = 16 Hz, $C=CH_d$) ppm. – IR. spectrum (neat): 1727 (C=O conj.); 1660 (C=C conj.); 970 (C=C *trans*, conj.); 720 (C=C *cis*) cm^{-1}. – MS.: *m/e*: 210 (<1), 179 (2), 100 (100), 81 (8), 69 (69), 55 (52), 41 (57).

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12. Quinacridones: Structure and Mechanism of Formation

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(16. VIII. 71)

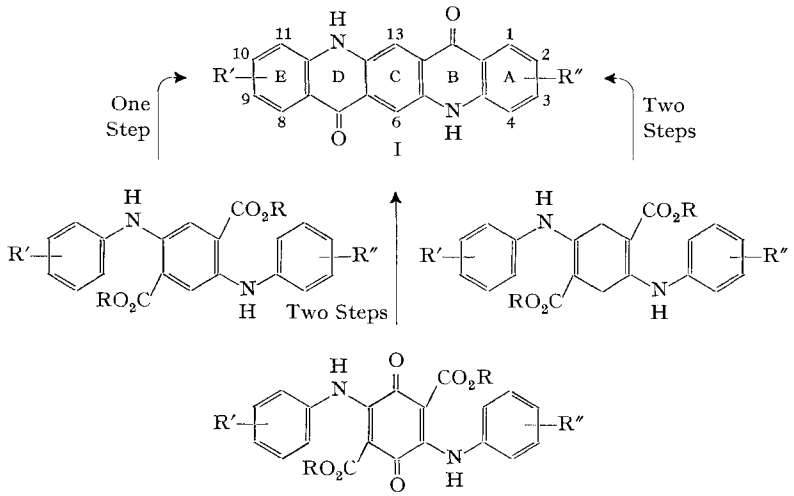
Summary. The NMR. spectra of two acridones and twenty-two quinacridones in $(CD_3)_2SO$—NaOD are reported. A NMR. technique is described for determining the composition of mixtures of various substituted quinacridones. A general mechanism is proposed for quinacridone formation *via* cyclodehydration of 2,5-diarylamino-terephthalic and 2,5-diarylamino-1,4-benzoquinone-3,6-dicarboxylic acids/esters.

Introduction. – After the initial controversy over the structure of 5,7,12,14-tetrahydro-quino[2,3-*b*]acridine-7,14-diones[1]) (I) (linear *trans*-quinacridones) had been resolved in 1935 by *Liebermann* [1], research in the chemistry of these heterocycles remained quiescent for the next two decades. The utility of quinacridones as synthetic organic pigments was first recognized by *DuPont* chemists, and interest in their chemistry subsequently revived.

The most commonly used methods for the synthesis of quinacridones (I) are shown in Chart 1 [2]:

[1]) Chemical Alstracts name: quino[2,3-*b*]acridine-5, 12-dihydro-7, 14-diones (Editor).

Chart 1



R′ and R″ = H, halogen, alkyl, alkoxy, etc.
R = H, alkyl

Although the *trans*-linearity of the resulting quinacridones is unequivocal, the formation of various isomers can be envisaged when one or both of the arylamine moieties are *meta*-substituted. Both classical and spectral methods of isomer characterization are limited by the extreme insolubility of quinacridones in most organic solvents. Although the more modern spectral analysis would be simpler and more convenient, UV.-visible spectral studies indicate that the specific positioning of the substituents in quinacridone rings A and E have little effect on the spectra [3], while infrared studies have shed no light on isomer characterization [4]. To our knowledge, the NMR. spectra of quinacridones have not been reported in the literature.

We now have recorded the NMR. spectra of two acridones and twenty-two quinacridones, exploiting their solubility in $(CD_3)_2SO$–NaOD solutions. The results permit:

i) The structural elucidation of a number of isomeric quinacridones;

ii) The determination of isomer ratios in quinacridone mixtures; and

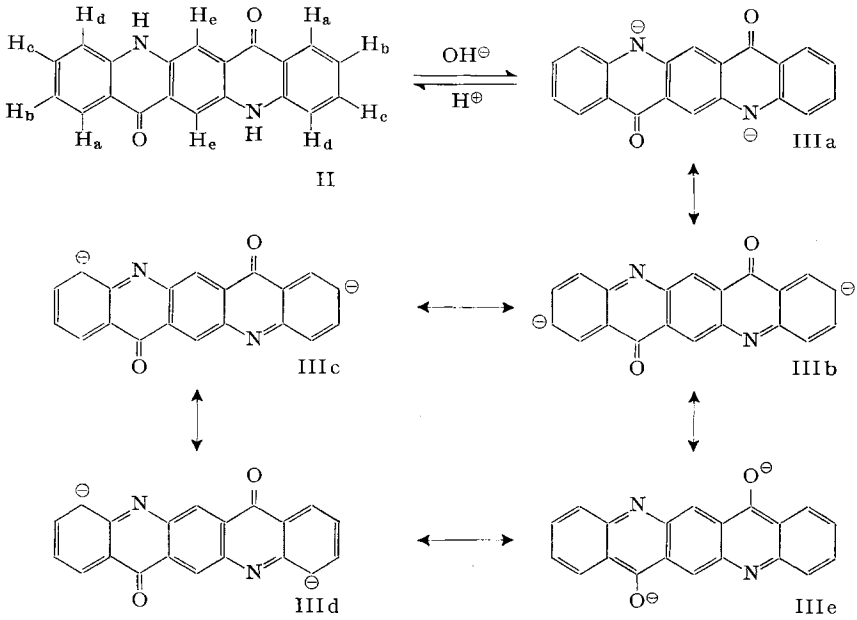
iii) Proposal of a mechanism for quinacridone formation *via* cyclodehydration reactions.

It may be expected that treatment of parent quinacridone II with NaOD in $(CD_3)_2SO$ converts it to a dianion[2]), depicted in Chart 2 as a hybrid of such contributing structures as IIIa–IIIe, etc.

Although IIIa and IIIe are undoubtedly the major contributors, one consequence of contributions by IIIb–IIIe would be enhanced electron densities at C-2, C-4, C-9 and C-11 (*ortho* and *para* to the N-atoms), and C-1, C-3, C-8 and C-10 (*ortho* and *para*

[2]) Since the NMR. spectra were essentially independent of NaOD concentration, we assume the presence of dianions. However, even if monoanions were involved, averaging of the spectra would permit the same analysis of quinacridone spectra.

Chart 2



to the C–O$^{\ominus}$ groups). The extent of these electron density increases would be reflected in corresponding diamagnetic shifts of the protons attached to these C-atoms. However, protons H_d[3]) might resonate at lower field since they are *peri* to the negatively charged N (III a) and the N-lone pair of electrons (III b–III e). Protons H_a would also be expected to resonate at lower field since both are in the deshielding cone of the *peri* C=O groups (III a–III d); this effect may be exaggerated by the high electron density at the O-atoms (III e). Protons H_c should also be deshielded since they are *para* to the electronegative C=O groups (III a–III d); this effect may also be balanced by the extent of contribution of structure III e. Finally, protons H_e should be most deshielded since they are sandwiched between two anisotropic moieties. The NMR. results on quinacridones summarized in Table B and a comparison of their spectra with those of structurally similar acridones (Table A) fully support these predicted paramagnetic and diamagnetic effects.

NMR. Spectra of Acridones (Fig. 1a and 1b, Chart 3, and Table A). – In the spectrum of 2,7-dibromoacridone (IV) in $(CD_3)_2SO$, protons designated as H_d (Fig. 1a) absorb at highest field (7.41)[4]), followed closely by the quartet absorptions of H_c at 7.72. In $(CD_3)_2SO$–NaOD solutions, marked shielding of protons H_c and deshielding of protons H_d are clearly discernible. Further, protons H_a, which absorb at 8.21 in $(CD_3)_2SO$, are shifted downfield to 8.34 in $(CD_3)_2SO$–NaOD, a consequence of contributing structure IV a. The effect of contributing structure b can be discerned

[3]) For convenience in presenting the NMR. data, the protons of quinacridone and symmetrically disubstituted quinacridones are designated as in II. In the monosubstituted and unsymmetrically disubstituted quinacridones, assignments are made as in I.

[4]) Chemical shifts in δ ppm.

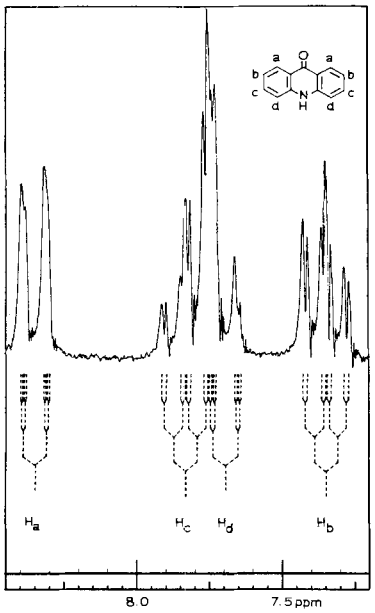


Fig. 1a. *NMR. spectrum of acridone(V) in* $(CD_3)_2SO$

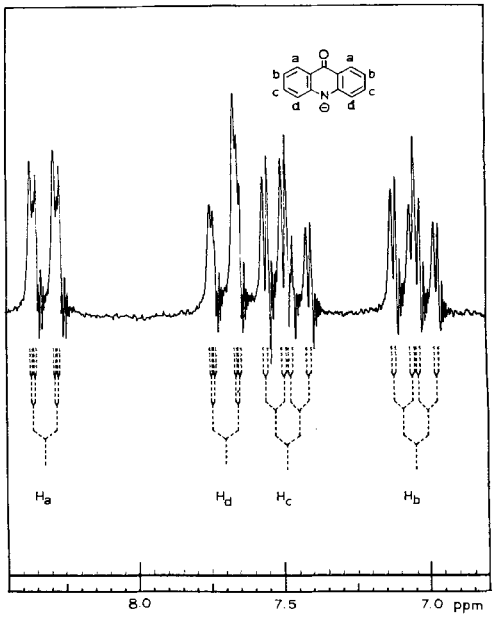
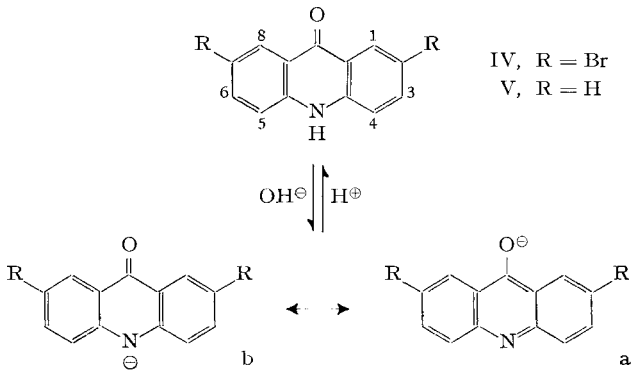


Fig. 1b. *NMR. spectrum of acridone(V) in* $(CD_3)_2SO$*—NaOD*

Chart 3



from the spectra of acridone (V) itself. Thus the octet at highest field (7.35) in $(CD_3)_2SO$, assigned to protons H_b, is shifted further upfield to 7.05 in $(CD_3)_2SO$–NaOD. Since the spectra of acridones are quite similar to those of the corresponding quinacridone analogues in $(CD_3)_2SO$–NaOD (*cf.* Fig. 1b and 2), it is reasonable to assume that the rationale for diamagnetic and paramagnetic shifts observed for acridone protons in basic solution is also valid for ring-A and -E protons in quinacridones.

NMR. Spectra of Quinacridones of Known Structures. – In the spectrum of quinacridone II in $(CD_3)_2SO$–NaOD (Fig. 2) protons H_b and H_c each appear as doubly *ortho*-coupled and singly *meta*-coupled octets at 6.91 and 7.42, respectively. The octet absorptions due to protons H_a and H_d are seen at 8.30 and 7.645, respectively.

The middle ring proton absorptions appear as a singlet at 8.79. The spectra of the corresponding 2,9-dichloro- (VI) and 2,9-dimethyl-quinacridone (VII) are transparent above 7.30 in the aromatic region, since the protons which normally absorb at highest field are no longer present. The absorptions due to protons H_a, H_c and H_d appear as an *ABC* spectrum with stronger coupling (*ortho*) between H_c and H_d, and weaker coupling

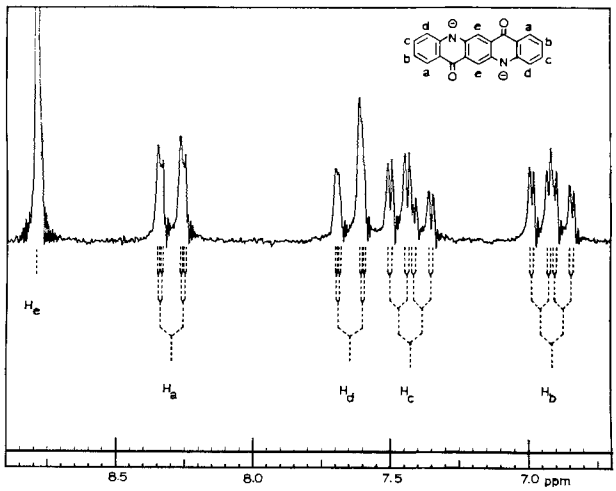


Fig. 2. *NMR. spectrum of quinacridone(II) in* $(CD_3)_2SO$*—NaOD*

(*meta*) between H_a and H_c. The spectra of 2-chloro- (VIII) and 2-methyl-quinacridone (IX) appear almost as a superimposition of that of unsubstituted II and the corresponding 2,9-disubstituted quinacridones, VI and VII. Not only are the proton absorptions of rings A and E non-equivalent, but also the C-ring protons in 2-chloro-quinacridone (VIII) appear as two distinct signals. In 2-methyl derivative IX, however, no such non-equivalence of C-ring protons is discernible.

In 4,11-dichloro- (X) and 4,11-dimethyl-quinacridone (XI), protons H_b appear as the highest field quartets at 6.79 and 6.75, protons H_c as quartets at 7.57 and 7.27, and protons H_a as quartets at 8.26 and 8.20. Quartet absorptions due to protons H_b indicate non-equivalent coupling between H_a and H_b, and H_b and H_c. Similar non-equivalent coupling between these protons has been reported in the spectrum of V in $(CD_3)_2SO$ [5].

The spectra of 4-chloro- (XII) and 4-methyl-quinacridone (XIII) are related to those of their 4,11-disubstituted derivatives in the same way as the spectra of VIII and IX are related to those of VI and VII, respectively. Unlike IX, however, the C-ring protons of XIII are magnetically non-equivalent.

NMR. Determination of Quinacridone Isomer Ratios (Chart 4 and Table C). – In the cyclization of 2,5-di-(*m*-chloroanilino)-terephthalic acid (XIV), three isomeric quinacridone products may be formed, 3,10-dichloro- (XVI), 1,8-dichloro- (XVII) and 1,10-dichloro-quinacridone (XVIII).

Table A. *NMR. Data for Acridones*

No.	Acridone	Solvent	Chemical Shifts (δ ppm)								Coupling Constants (Hz)
			$H_{(1)}$	$H_{(2)}$	$H_{(3)}$	$H_{(4)}$	$H_{(5)}$	$H_{(6)}$	$H_{(7)}$	$H_{(8)}$	
IV	2,7-Dibromo	$(CD_3)_2SO$	8.21	–	7.72	7.41	7.41	7.72	–	8.21	$J_{1,3} = J_{6,8} = 2.0$; $J_{3,4} = J_{5,6} = 9.0$; $J_{1,4} = J_{5,8} \simeq 0.4$
		$(CD_3)_2SO$—NaOD	8.34	–	7.47	7.61	7.61	7.47	–	8.34	$J_{1,3} = J_{6,8} = 2.0$; $J_{3,4} = J_{5,6} = 9.0$; $J_{1,4} = J_{5,8} = 0.4$
V	Unsubstituted	$(CD_3)_2SO$	8.35	7.35	7.83	7.69	7.69	7.83	7.35	8.35	$J_{1,2} = J_{7,8} = 8.3$; $J_{1,3} = J_{6,8} = 1.6$; $J_{1,4} = J_{5,8} \simeq 0.5$; $J_{2,3} = J_{6,7} = 7.0$; $J_{2,4} = J_{5,7} = 1.4$; $J_{3,4} = J_{5,6} = 8.6$
		$(CD_3)_2SO$—NaOD	8.32	7.05	7.49	7.77	7.77	7.49	7.05	8.32	$J_{1,2} = J_{7,8} = 8.4$; $J_{1,3} = J_{6,8} = 1.6$; $J_{1,4} = J_{5,8} \simeq 0.5$; $J_{2,3} = J_{6,7} = 7.0$; $J_{2,4} = J_{5,7} = 1.4$; $J_{3,4} = J_{5,6} = 8.6$

Table B. *NMR. Data for Quinacridones in* $(CD_3)_2SO$—*NaOD* [a])

No.	Quinacridone	Chemical Shifts (δ ppm)										Coupling Constants (Hz)
		$H_{(1)}$	$H_{(2)}$	$H_{(3)}$	$H_{(4)}$	$H_{(6)}$	$H_{(8)}$	$H_{(9)}$	$H_{(10)}$	$H_{(11)}$	$H_{(13)}$	
II	Unsubstituted	8.3	6.91	7.42	7.645	8.79	8.3	6.91	7.42	7.645	8.79	$J_{1,2} = J_{8,9} = 8.4$; $J_{1,3} = J_{8,10} = 1.6$; $J_{1,4} = J_{8,11} \simeq 0.5$; $J_{2,3} = J_{9,10} = 6.3$; $J_{2,4} = J_{9,11} = 1.4$; $J_{3,4} = J_{10,11} = 8.8$
VI	2,9-Dichloro	8.22	–	7.35	7.64	8.75	8.22	–	7.35	7.64	8.75	$J_{1,3} = J_{8,10} = 2.2$; $J_{1,4} = J_{8,11} \simeq 0$; $J_{3,4} = J_{10,11} = 9.2$
VII	2,9-Dimethyl	8.07	2.44 [b])	7.36	7.62	8.772	8.07	2.44 [b])	7.36	7.62	8.772	$J_{1,3} = J_{8,10} = 1.8$; $J_{1,4} = J_{8,11} \simeq 0$; $J_{3,4} = J_{10,11} = 8.7$
VIII	2-Chloro	8.21	–	7.28	7.61	8.75	8.25	6.86	7.37	7.59	8.72	$J_{1,3} = 2.2$; $J_{8,10} = 1.5$; $J_{1,4} = J_{8,11} \simeq 0$; $J_{3,4} = 9.2$; $J_{9,10} = 6.3$; $J_{9,11} = 1.4$; $J_{10,11} = 8.8$; $J_{8,9} = 8.4$
IX	2-Methyl	8.05	2.41 [b])	7.23	7.55	8.73	8.26	6.84	7.35	7.59	8.73	$J_{1,3} = 1.8$; $J_{1,4} = J_{8,11} \simeq 0$; $J_{8,10} = 1.6$; $J_{9,10} = 6.3$; $J_{9,11} = 1.4$; $J_{3,4} = J_{10,11} = 8.7$; $J_{8,9} = 8.4$
X	4,11-Dichloro	8.26	6.79	7.57	–	8.837	8.26	6.79	7.57	–	8.837	$J_{1,2} = J_{8,9} = 8.4$; $J_{1,3} = J_{8,10} = 1.6$; $J_{2,3} = J_{9,10} = 6.6$
XI	4,11-Dimethyl	8.20	6.75	7.27	2.68 [b])	8.85	8.20	6.75	7.27	2.68 [b])	8.85	$J_{1,2} = J_{8,9} = 8.4$; $J_{1,3} = J_{8,10} = 1.4$; $J_{2,3} = J_{9,10} = 6.6$
XII	4-Chloro	8.27	6.82	7.587	–	8.88	8.25	6.92	7.445	7.635	8.75	$J_{1,2} = J_{8,9} = 8.4$; $J_{1,3} = J_{8,10} = 1.6$; $J_{8,11} \simeq 0$; $J_{2,3} = 6.6$; $J_{9,10} = 6.3$; $J_{9,11} = 1.4$; $J_{10,11} = 8.7$
XIII	4-Methyl	8.20	6.77	7.27	2.68 [b])	8.88	8.29	6.84	7.37	7.62	8.76	$J_{1,2} = J_{8,9} = 8.4$; $J_{1,3} = 1.4$; $J_{2,3} = 6.6$; $J_{1,4} = J_{8,11} \simeq 0$; $J_{9,11} = 1.4$; $J_{10,11} = 8.7$; $J_{8,10} = 1.6$; $J_{9,10} = 6.3$

Table B. (Cont.)

No.	Quinacridone	Chemical Shifts (δ ppm)										Coupling Constants (Hz)
		$H_{(1)}$	$H_{(2)}$	$H_{(3)}$	$H_{(4)}$	$H_{(6)}$	$H_{(8)}$	$H_{(9)}$	$H_{(10)}$	$H_{(11)}$	$H_{(13)}$	
XVI	3,10-Dichloro [c])	8.251	6.8	–	7.585	8.705	8.251	6.8	–	7.585	8.705	$J_{1,2} = J_{8,9} = 8.9$; $J_{1,4} = J_{8,11} \simeq 0$; $J_{2,4} = J_{9,11} = 2.2$
XVII	1,8-Dichloro [e])	–	6.745	7.2	7.495	8.605	–	6.745	7.2	7.495	8.605	$J_{2,3} = J_{9,10} = 7$; $J_{2,4} = J_{9,11} = 2.25$; $J_{3,4} = J_{10,11} = 8.8$
XVIII	1,10-Dichloro [c])	–	6.745	7.21	7.495	8.67	8.251	6.8	–	7.585	8.635	$J_{2,3} = 7$; $J_{2,4} = 2.25$; $J_{8,9} = 8.9$; $J_{8,11} \simeq 0$; $J_{9,11} = 2.2$; $J_{6,13} = 1.1$; $J_{3,4} = 8.8$
XXI	3-Chloro [d])	8.22	6.72	–	7.535	8.685	8.22	6.83	7.345	7.585	8.685	$J_{1,2} = 8.9$; $J_{1,4} = J_{8,11} = 0$; $J_{2,4} = 2.2$; $J_{8,9} = 8.5$; $J_{8,10} = 1.5$; $J_{9,10} = 6.6$; $J_{9,11} = 1.4$; $J_{10,11} = 8.7$
XXII	1-Chloro [d])	–	6.665	7.135	7.44	8.66	8.22	6.83	7.345	7.585	8.615	$J_{2,3} = 7$; $J_{2,4} = 2.25$; $J_{3,4} = 8.8$; $J_{8,9} = 8.5$; $J_{8,10} = 1.5$; $J_{8,11} \simeq 0$; $J_{9,10} = 6.6$; $J_{9,11} = 1.4$; $J_{10,11} = 8.7$; $J_{6,13} = 0.9$
XXIII	3-Methyl [e])	8.16	6.725	2.45 [b])	7.38	8.73	8.255	6.875	7.385	7.61	8.715	$J_{1,2} = 9$; $J_{1,4} = J_{8,11} \simeq 0$; $J_{2,4} = 2.4$; $J_{8,9} = 8.4$; $J_{8,10} = 1.6$; $J_{9,10} = 6.3$; $J_{9,11} = 1.4$; $J_{10,11} = 8.7$; $J_{6,13} = 0,9$
XXIV	1-Methyl [e])	2.99 [b])	6.53	7.185	7.42	8.705	8.255	6.875	7.385	7.61	8.63	$J_{2,3} = 6.6$; $J_{2,4} = 2.2$; $J_{3,4} = 8.6$; $J_{8,9} = 8.4$; $J_{8,10} = 1.6$; $J_{8,11} \simeq 0$; $J_{9,11} = 1.4$; $J_{10,11} = 8.7$; $J_{6,13} = 0.9$; $J_{9,10} = 6.3$
XXVIII	3,10-Dimethyl [f])	8.13	6.655	2.43 [b])	7.33	8.65	8.13	6.655	2.43 [b])	7.33	8.65	$J_{1,2} = J_{8,9} = 9$; $J_{1,4} = J_{8,11} \simeq 0$; $J_{9,11} = J_{2,4} = 2.4$
XXIX	1,10-Dimethyl [f])	2.98 [b])	6.445	7.215	7.37	8.62	8.13	6.655	2.43 [b])	7.33	8.575	$J_{2,3} = 6.6$; $J_{2,4} = 2.2$; $J_{3,4} = 8.6$; $J_{8,9} = 9$; $J_{8,11} \simeq 0$; $J_{6,13} = 1$; $J_{9,11} = 2.4$

Table B. (Cont.)

No.	Quinacridone	Chemical Shifts (δ ppm)										Coupling Constants (Hz)
		$H_{(1)}$	$H_{(2)}$	$H_{(3)}$	$H_{(4)}$	$H_{(6)}$	$H_{(8)}$	$H_{(9)}$	$H_{(10)}$	$H_{(11)}$	$H_{(13)}$	
XXX	1,8-Dimethyl[f]	2.98[b]	6.445	7.215	7.37	8.546	2.98[b]	6.445	7.215	7.37	8.546	$J_{2,3} = J_{9,10} = 6.6$; $J_{2,4} = J_{9,11} = 2.2$; $J_{3,4} = J_{10,11} = 8.6$
XXVII	Unsubstituted	8.18	6.76	7.34	7.48	7.65	8.18	7.76	7.34	7.48	9.37	$J_{1,2} = J_{8,9} = 8.0$; $J_{1,3} = J_{8,10} = 2$; $J_{1,4} = J_{8,11} \simeq 0$; $J_{2,3} = J_{9,10} = 6.6$; $J_{2,4} = J_{9,11} = 1.5$; $J_{3,4} = J_{10,11} = 8.0$; $J_{6,13} = 0.9$
XXXVI	1,10-Dimethoxy[g]	4.33[h]	6.23	7.16	7.115	8.625	8.17	6.55	3.92[h]	6.92	8.575	$J_{2,3} = 6.4$; $J_{2,4} = 1.8$; $J_{3,4} \simeq 8.5$; $J_{8,9} = 9.2$; $J_{9,11} = 2.3$; $J_{6,13} = 1.1$; $J_{1,4} = J_{8,11} \simeq 0$
XXXVII	3,10-Dimethoxy[g]	8.17	6.55	3.92[h]	6.92	8.625	8.17	6.55	3.92[h]	6.92	8.625	$J_{1,2} = J_{8,9} = 9.2$; $J_{1,4} = J_{8,11} \simeq 0$; $J_{2,4} = J_{9,11} = 2.3$

[a] Since the spectra were not calculated by computer analysis, the accuracy of the quoted chemical shifts is restricted to the nearest 0.1 with respect to the internal lock. However, to stress small chemical shift differences between the closely resonating protons (which were discernible in 250 Hz sweep width spectra), these shifts have been quoted up to the nearest 0.001 and are meaningful only for internal comparison. For similar considerations the accuracy of coupling constants is also restricted to ± 0.2 Hz. *Para* couplings have been quoted only when they were discernible.

[b] Methyl absorptions.

[c] As a mixture in the cyclization (followed by reduction or oxidation wherever necessary) of XIV, XV, XXV and XXVIa and XLIII.

[d] As a mixture in the cyclization of XIX.

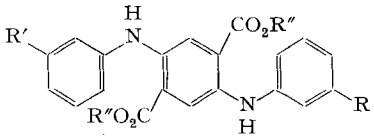
[e] As a mixture in the cyclization of XX.

[f] As a mixture in the cyclization (followed by reduction wherever necessary) of XXXVIII and XL.

[g] As a mixture in the cyclization of XXXIV.

[h] Methoxide absorptions.

Chart 4



XIV, $R'' = H$; R, $R' = Cl$
XV, $R'' = CH_3$; R, $R' = Cl$
XIX, $R'' = H$; $R' = H$; $R = Cl$
XX, $R'' = H$; $R' = H$; $R = CH_3$
XXXIV, $R'' = H$; R, $R' = OCH_3$
XL, $R'' = H$; R, $R' = CH_3$

We had earlier assumed the predominance of XVI and also suggested the formation of XVII and XVIII [6]. Our present investigations, however, clearly and unequivocally demonstrate the formation of all three isomers. Thus in the region where the C-ring protons of quinacridones absorb, the spectrum of the XIV cyclization product shows three sets of signals (Fig. 3), singlets at 8.605 and 8.705, and a pair of doublets at 8.635 and 8.67. The singlet absorptions are obviously due to the two symmetrical isomers XVI and XVII; the low field absorption was assigned to the 3,10-isomer XVI by comparison with the spectrum of authentic XVI obtained by rather an unambiguous synthesis [7][5]). The pair of doublets are assigned to protons $H_{(13)}$ and $H_{(6)}$ of XVIII; the splitting is due to their mutual coupling. In the proton absorption region of rings A and E, signals due to both XVI and XVII are individually conspicuous; the absorption due to ring-A protons of XVIII are masked, however, by those of isomer XVII,

Table C. *Quinacridone Isomer Ratios* (%) *Formed in Cyclodehydration Reactions*[a])

Acid or the Ester	Substituted Quinacridones				
	1	3	1,8	1,10	3,10
XIV	–	–	14.5[c])	53.5	32
	–	–	17[b])	48	35
	–	–	20.5[d])	47	32.5
XV	–	–	9[b])	33	58
XX	46[b])	54	–	–	–
XIX	38[b])	62	–	–	–
XXV	–	–	70[e])	30	0
XXVIa	–	–	6[f])	30	64
XXXIV	–	–	0[b])	35	65
XXXVIII	–	–	45[e])	40	15
XL	–	–	15[b])	39	46
XLIII	–	–	21[g])	46	33

[a]) The isomer ratios were invariably determined by the integrations of the C-ring protons; the ratios thus obtained are within the accuracy of NMR. integrals (within $\pm 2\%$ error).
[b]) Cyclodehydration conducted with polyphosphoric acid at 150–155° [2].
[c]) Cyclodehydration conducted with sulfuric acid at 120°.
[d]) Cyclodehydration carried out with phosphorus oxychloride at 200° (in trichlorobenzene) [2].
[e]) Cyclodehydration and subsequent reduction carried out as stated in [7] (conc. sulfuric acid at 80°).
[f]) Cyclodehydration and reduction carried out as stated for XXVI in [7] (Dowtherm at 220°).
[g]) Cyclodehydration and oxidation carried out as stated in [17] (Dowtherm at 250°).

[5]) Formation of the theoretically possible *cis*-isomer was ruled out on the basis of NMR. evidence from 5, 7, 12, 14-tetrahydro-quino[3, 2-*b*]acridine-12, 14-dione (quino[3, 2-*b*]acridine-5, 7-dihydro-12, 14-dione) (XXVII) cited later in this publication.

and those due to ring E by those of isomer XVI (for assignments of individual signals see Fig. 3 and Table B). The ratio of isomers, as determined by the integration of the C-ring protons, are summarized in Table C. Cyclization of the dimethyl ester XV of XIV afforded predominantly XVI and XVIII, with lesser amounts of XVII.

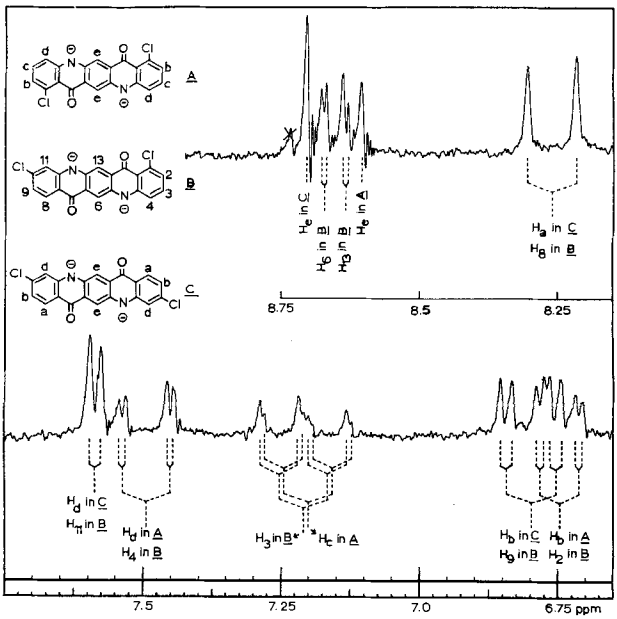


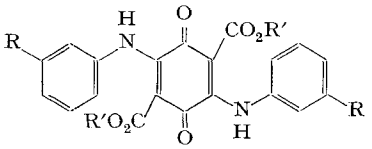
Fig. 3. *NMR. spectrum of the cyclization product of XIV* (a mixture of XVI, XVII and XVIII) *in* $(CD_3)_2SO$–*NaOD*

Similarly, in the cyclization of 2-(*m*-chloroanilino)-5-anilino- (XIX) and 2-(*m*-toluidino)-5-anilino-terephthalic acid (XX), both 1-substituted (XXII and XXIV, respectively), and 3-substituted (XXI and XXIII, respectively) quinacridone products are possible. The presence of 1-chloroquinacridone (XXII) in the cyclization product of XIX is apparent from the appearance of the C-ring protons as two distinct mutually coupled doublets at 8.615 and 8.66 assigned respectively to $H_{(13)}$ and $H_{(6)}$. Similarly, the presence of the isomeric 3-chloroquinacridone (XXI) is established by an unresolved pair of doublets centred at 8.685 due to the same protons. The appearance of two pairs of doublets in this region of the spectrum of the cyclization product of XX indicate the presence of both the 3-methyl- (XXIII) and 1-methyl-quinacridone (XXIV); each pair of doublets representing one isomer (for the assignments see Table B). These assignments are supported by the appearance of two distinct methyl signals in the aliphatic region; the low-field methyl is assigned to the isomer XXIV.

In the cyclization of dimethyl 2,5-di-(*m*-chloranilino)-1,4-benzoquinone-3,6-dicarboxylate (XXVI), and subsequent reduction, exclusive formation of XVI has recently been reported [7], while the corresponding acid XXV has been reported to yield XVII predominantly.

We have repeated these reactions and applied our NMR. technique to the determination of quinacridone isomer ratios. Examination of the NMR. spectra of the resulting quinacridones originating from both XXV and XXVIa, confirms the predominant but not exclusive formation of the reported isomers. Thus in the former reaction, the unsymmetrical isomer XVIII is found to the extent of 30%, while cyclization and subsequent reduction of the latter afforded all three isomers XVI, XVII and XVIII in the ratio 64:6:30.

Chart 5

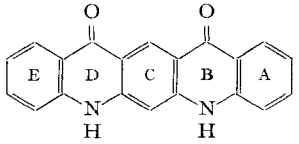


XXV, R = Cl; R′ = H
XXVI, R = Cl; R′ = CH_3
XXVIa, R = Cl; R′ = C_2H_5
XXXVIII, R = CH_3; R′ = H

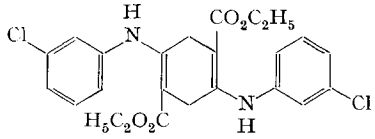
We have also examined the quinacridone isomer ratio resulting from the cyclodehydration of 2,5-di-(*m*-anisidino)- (XXXIV) and 2,5-di-(*m*-toluidino)-terephthalic acid (XL), 2,5-di-(*m*-toluidino)-1,4-benzoquinone-3,6-dicarboxylic acid (XXXVIII) and diethyl 2,5-di-(*m*-chloroanilino)-3,6-dihydroterephthalate (XLIII). The results are summarized in Table C.

NMR. Spectrum of 5,7,12,14-Tetrahydro-quino[3,2-b]acridine-12,14-dione[6] (XXVII). – We have also recorded the spectrum of the linear-*cis*-quinacridone XXVII (Chart 6) for possible delineation of *cis* and the *trans* isomers (*cf.*[5]). The A- and E-ring

Chart 6



XXVII



XLIII

proton absorptions of XXVII are similar to those of the *trans* isomer II. The C-ring proton absorptions appear as two distinct doublets 1.72 ppm apart. The low field absorption at 9.37 is assigned to $H_{(13)}$ sandwiched between the two carbonyls, and the absorption at 7.65 to the $H_{(6)}$ proton.

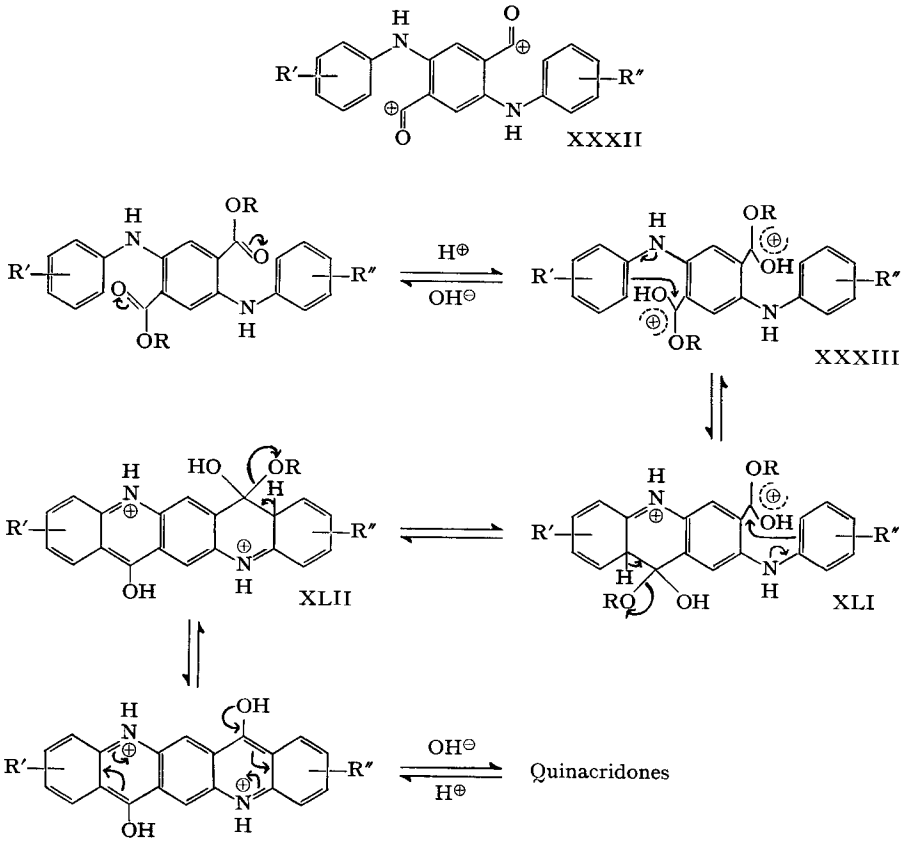
NMR. Absorptions of the C-ring Protons. – As has been noted, the C-ring absorptions in both monosubstituted and unsymmetrically disubstituted quinacridones generally give rise to two sets of signals. While it is difficult to make unequivocal assignments of these resonances to protons $H_{(6)}$ and $H_{(13)}$, it is our view that substituents *ortho* and/or *para* to carbonyl should mainly influence the chemical shift of the $H_{(13)}$ proton while that of $H_{(6)}$ should likewise be influenced by substituents *ortho* and/or *para* to N. *Ortho* substituents are also assumed to have a more pronounced effect than *para* substituents. These views are supported by our observation that in monosubstituted quinacridones one of the C-ring proton signals appears almost exactly where it does in unsubstituted quinacridone II. The splitting (in the line positions) is larger when the substituents are positioned *ortho* either to C=O or to N. The most important observation, however, is that the substituents *ortho* to N cause

[6]) Chemical Abstracts name: quino[3, 2-*b*]acridine-5, 7-dihydro-12, 14-dione.

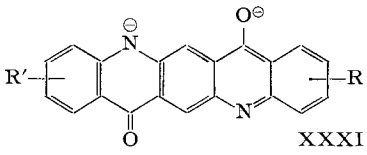
distinct deshielding of the C-ring proton *peri* to this N, while the substituents *ortho* to C=O have a converse effect upon its *peri* proton[7]).

Mechanism of the Cyclodehydration Reaction (Chart 7). – It is worthy of note that the quinacridone isomer ratios in the cyclization of XIV do not change significantly when the cyclodehydration conditions and/or reagents are altered. Thus the isomer ratios remain practically the same when the cyclodehydration is carried out with polyphosphoric acid at 150–155°, with sulfuric acid at 120°, and with phosphorus oxychloride at 200°. The alteration in the isomer ratios when acid XIV and its ester

Chart 7



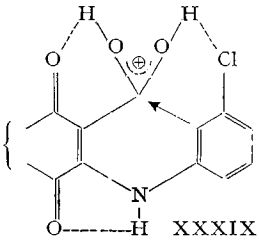
[7]) The non-equivalence of C-ring protons in unsymmetrically substituted quinacridones may also be due to the contribution of species XXXI in $(CD_3)_2SO$—NaOD.



XV are cyclized, immediately rules out the major intermediacy of the aroyl dication XXXII, which has been postulated in the cyclodehydration under acidic conditions of diphenylamine-2-carboxylic acid (to acridone) [8]. Instead, the major involvement of the conjugate acid species XXXIII is suggested[8]). Under non-acidic conditions, however, the direct nucleophilic addition at the electron-deficient carbon of the acid or the ester function may also lead to the transition state. Stepwise electrophilic substitution and elimination *via* such intermediate stages as XLI and XLII would ultimately lead to quinacridones. In species XXXIII one of the conjugate acid cations is activated by the other (*cf.* the reactivity of tetrazotized *p*-phenylenediamine, etc. [9]), resulting in preferential monocyclization. These highly reactive electrophiles are less selective [10] and consequently, indiscriminate attack at either *ortho* position of the arylamine moiety would be expected. The remaining, less reactive conjugate acid cation probably would then be more selective in its electrophilic attack on the second arylamine moiety. The mechanism is depicted in Chart 7.

The proposed mechanism could explain the isomeric quinacridones formed in rather statistically irrational proportions in most of the cyclodehydration reactions studied by us[9]). Further support, however, is provided by the absence of 1,8-dimethoxy-quinacridone (XXXV) in the cyclization of XXXIV. Only 1,10-dimethoxy- (XXXVI) (35%) and 3,10-dimethoxy-quinacridone (XXXVII) (65%) were obtained. While the initial cyclization may occur at both *ortho* positions to the amino group, the second cyclization would occur at the less sterically hindered *ortho* position (*para* to the OCH_3 group). All the *ortho* (to OCH_3) cyclized product in the first cyclization is consumed in the formation of unsymmetrical isomer XXXVI during the second.

The predominant formation of the most disfavored XVII and particularly the absence of any XVI in the cyclization (followed by reduction) of XXV suggests, besides the stepwise mechanism, involvement of some additional factors in this cyclization. We believe that the intramolecular hydrogen bonding of one of the hydroxyls of the intermediate conjugate acid cations with the Cl aligns the *ortho* position (with respect to Cl) of the arylamine moiety with the electrophilic carbon atom and thereby facilitates their interaction and formation of the transition state. This situation may, however, be aided by the additional interactions of the second hydroxyl (of the conjugate acid cation) and NH with the quinone carbonyls, depicted as followes:



XXXIX

[8]) The strong acidic reaction conditions militate against protonation of only one COOR group at a time.

[9]) If the cyclizations on either side occured without the mutual influence and/or simultaneously, *ortho*/*para* ratio (with respect to the *meta* substituent) would be almost identical in both the cyclizations, leading to statistical isomer ratios as have been observed in the cyclodehydration (followed by oxidation) of XLIII (compared with those of XV and XXVIa).

Alignment of the reactive sites to facilitate similar reactions and enhance catalysis is a well established phenomenon both within and outside enzyme systems, and is apparently operating in the present cyclization as well [11][10][11]. Our speculation is supported by the fact that the cyclodehydration of 2,5-di-(*m*-toluidino)-1,4-benzoquinone-3,6-dicarboxylic acid (XXXVIII) (followed by reduction) under identical conditions does not result in the formation of 1,8-dimethylquinacridone (XXX) to such an appreciable extent[12], nor does the ester XXVIa lead to a predominance of XVII (under neutral conditions). Further, XIV and its methyl ester XV are also incapable of giving XVII predominantly. Finally, in the cyclodehydration (followed by oxidation) of diethyl 2,5-di-(*m*-chloroanilino)-3,6-dihydroterephthalate (XLIII), where neither the activation of one of the COOR groups by the other nor the 'three point' intramolecular hydrogen bonding is possible, the isomeric quinacridones are produced in quite different proportions (Table C). From the reported electrophilic substitution reactions of toluene and chlorobenzene it appears that the *ortho* substitution can exceed *para* substitution in the reactions of toluene [13], but none of the well-known electrophiles ever predominantly attack the *ortho*-position of chlorobenzene [14].

Conclusions. – From UV.-visible spectral studies [2], quinacridone has been reported to exist exclusively in form IIIe in basic solutions. Our NMR. results suggest, however, that it is a hybrid of a number of contributing structures (IIIa–IIIe). Such contributing structures can account for:

1. The chemical shifts of the A- and E-ring protons and particularly, the marked shielding experienced both by protons H_b and H_c in $(CD_3)_2SO$–NaOD;

2. The greater resemblence of the quinacridone spectrum to that of acridone rather than that of acridine [5].

Our NMR. technique provides a simple and precise method of determining the composition of a mixture containing various quinacridones in general and isomeric quinacridones in particular. The results thus obtained may be employed for correlating the composition of these mixtures with their physical characteristics (*e.g.* colour, *X*-ray diffraction patterns, fastness properties, etc.).

Contact shifts induced by certain salts [15] and the selective shifts produced by some solvents [16] have been used for the resolution of the otherwise difficultly resolved spectra. The use of $(CD_3)_2SO$–NaOD served a quite similar purpose in our present studies and perhaps might find further application in recording and interpreting the spectra of related systems.

Experimental. – The quinacridones described were made by known procedures [2] (*cf.* also text). Among the numerous methods reported for the synthesis, those specifically described in Table C were chosen wherever the possibility of the formation of isomers existed. Acridones were made as described in [8].

[10] If one considers the sites of intramolecular hydrogen bonding in species XXXIX as the binding pockets of an enzyme system at its active site, one can immediately notice that the present system is a self-consistent enzyme-substrate system.

[11] This concept of alignment has been redefined as 'orbital steering' by *Koshland* [12]. Studies with 2,5-di-(*m*-fluoro-anilino)- and 2,5-di-(*m*-bromoanilino)-1,4-benzoquinone-3,6-dicarboxylic acid could shed further light upon this point.

[12] Contribution of the hyperconjugated structure $\overset{\oplus}{C}$ might make the interaction between the methyl carbon and —OH possible to a slight extent.

The NMR. spectra were recorded on a *Varian* HA-100 spectrometer using sodium 3-trimethylsilyl-propanesulfonate as an internal lock. The solutions of quinacridones in $(CD_3)_2SO$—NaOD were effected by warming a suspension of the quinacridone (ca. 15 mg) in $(CD_3)_2SO$ (250–300 μl) to 50–60° and adding the NaOD solution till complete disolution (50–100 μl of 2 N NaOD, obtained by dissolving NaOH in D_2O). The reference compound (for the internal lock) was then added (ca. 15 mg) and the filtered solutions were transferred into a NMR. tube. The ultimate volume of the solutions was usually about 350 μl. Reproducibility of the spectra, with varying amounts of $(CD_3)_2SO$ and the NaOD solutions (within the described limits), was within 0.01 ppm.

In order to observe smaller splittings due to chemical shift differences or coupling, some of the spectra were additionally run on 250 Hz sweep width, with 600 or 650 Hz sweep offset.

We are greatly indebted to the management of the *Dyestuff and Chemicals Division* for granting us the permission to publish these results. Our thanks are also due to the physical chemistry laboratory of the *Pharmaceuticals Research* for recording the spectra, and to some of our colleagues, particularly *E. J. Moriconi*, for stimulating discussions.

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