J. Org. Chem., Vol. 42, No. 6, 1977 **1041**

Acetylenic Analogues of the Cyanine Dyes. 3. Visible Absorption Properties and Relative Thermodynamic Stabilities of Isomeric Dyes

John D. Mee* and David M. Sturmer

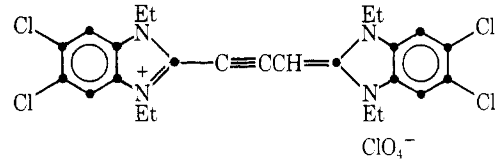
Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

Received August 4, 1976

It has been found that acid-catalyzed interconversion of isomeric acetylenic dyes can occur. A discussion of the factors which influence the visible absorption properties and relative thermodynamic stabilities of pairs of isomeric dyes is presented.

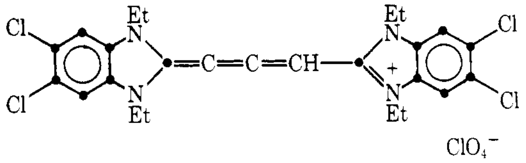
Syntheses of acetylenic analogues of the cyanines have been described in earlier papers of this series.[1,2] In contrast to the cyanines, these compounds are intrinsically unsymmetrical. We report here a study of some of the effects of this asymmetry upon the visible absorption spectra and thermodynamic properties of the dyes.

Spectral Properties. Acetylenic dyes possessing two identical heterocyclic nuclei, for example 1, have visible absorption maxima hypsochromically displaced from those of the corresponding carbocyanines by 30–40 nm. This was interpreted[1] as resulting from energetic nonequivalence of the extreme structures 1a and 1b.



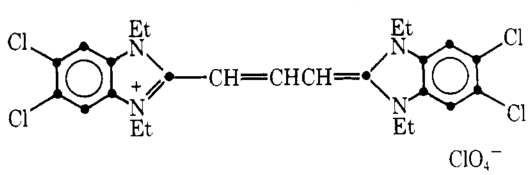
1a

↕



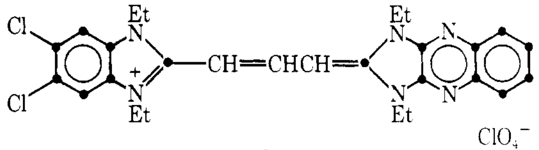
1b

Further, comparison of the structures of 1 and its carbocyanine analogue 2 by x-ray crystallography[3] supports the view that 1a is of lower energy than 1b and reflects the differences in geometry between these two dye classes. For convenience, extreme structures such as 1a and 1b are referred to as "acetylene" and "cumulene".



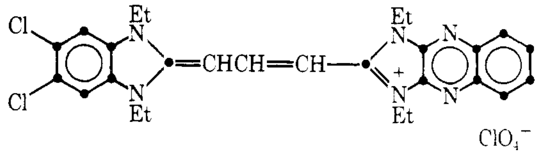
2

Acetylenic dyes containing nonidentical heterocyclic nuclei can exist in two isomeric forms, differentiated as in 19 and 20 by the position of the single hydrogen substituent on the chromophoric chain, relative to the heterocyclic nuclei. For each of the isomeric pairs shown in Table I, both dyes absorb at shorter wavelength than the unsymmetrical carbocyanine analogue (e.g., dye 3). However, a more interesting feature of these dyes is the difference between absorption maxima of isomeric dyes. The structural factors which influence this difference may be explained as resulting from the interplay of two factors: the lower energy, other things being equal, of the acetylene rather than the cumulene extreme structure and the relative basicities of the two heterocyclic nuclei in question. Brooker[4] has established a scale of relative basicity, or ability to stabilize a positive charge, for a large number of heterocyclic nuclei. Thus in an unsymmetrical carbocyanine 3, the extreme structure 3a, in which the positive charge is located on the more basic benzimidazole nucleus, is of lower energy than 3b.



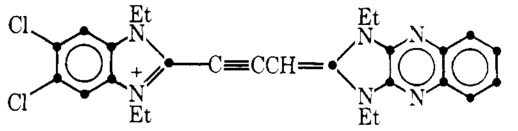
3a

↕



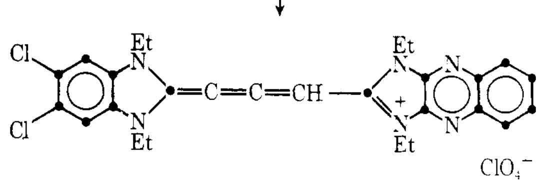
3b

In the acetylenic analogue 19, the tendency for the acetylenic extreme structure to be of lower energy is further reinforced by the location of the positive charge on the more basic benzimidazole nucleus. Conversely, in the isomeric dye 20, the

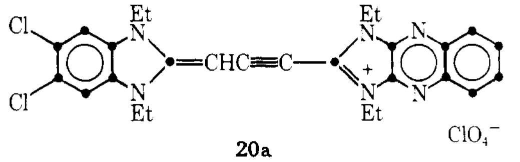


19a

↕

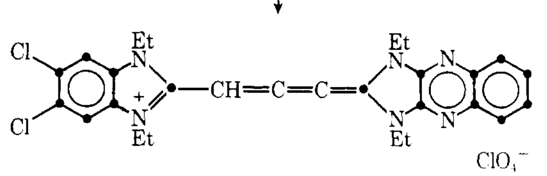


19b



20a

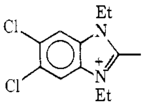
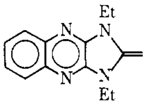
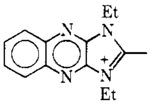
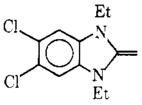
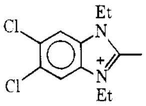
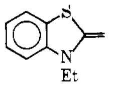
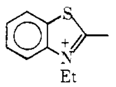
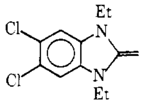
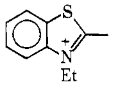
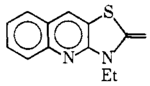
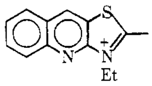
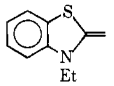
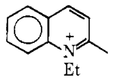
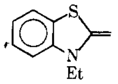
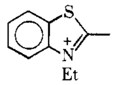
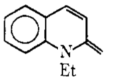
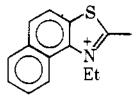
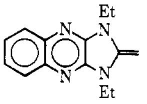
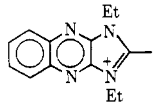
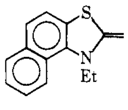
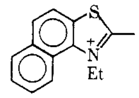
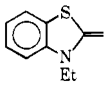
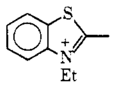
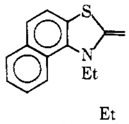
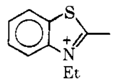
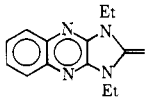
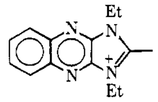
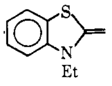
↕



20b

Table I. Isomeric Acetylenic Dyes

$\overset{+}{R}_1C{\equiv}CCH{=}R_2\ ClO_4^-$

Registry no.	Dye[a]	R_1	R_2	Rel basicity[b] R_1	Rel basicity[b] R_2	Δ basicity	λ_{max} (CH_3CN), nm	$\Delta\lambda_{max}$, nm	% of equilibrium mixture
61268-47-1	19			120	50	70	488	44	>99
61268-49-3	20			50	120		532		<1
56387-15-6	21			120	58	62	468	42	>98
61268-50-6	22[c]			58	120		510		<2
61268-52-8	23			58	24	34	508	38	>95
61268-54-0	24			24	58		546		<5
56387-17-8	25			80	58	22	543	0	>90
56387-19-0	26			58	80		543		<10
61268-56-2	27			70	50	20	537	19	75 ± 5
61268-58-4	28			50	70		556		25 ± 5
61268-60-8	4			70	58	12	526	9	75 ± 5
61268-62-0	5			58	70		535		25 ± 5
61268-64-2	29			58	50	8	523	8	23 ± 5
61268-66-4	30			50	58		531		77 ± 5

[a] For convenience, the dyes of this table are identified by the same numbers used in the preceding paper. [b] See ref 4. [c] Iodide salt.

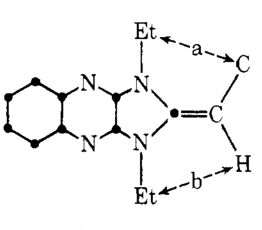
acetylenic extreme structure has the positive charge located on the less basic imidazo[4,5-*b*]quinoxaline nucleus, and the two factors oppose one another. Thus the energy difference between the extreme structures is greater for **19** than for **20**, and the consequently greater degree of electron delocalization in **20** is responsible for the bathochromic displacement of its absorption maximum relative to that of **19**. In Table I, isomeric pairs of dyes are listed in order of decreasing difference in basicity between the two terminal nuclei. It is apparent that, in general, the dye in which the single hydrogen atom on the conjugated chain is adjacent to the more basic nucleus has an absorption maximum at longer wavelengths than that of its isomer. In addition, the greater the difference in basicity between the two nuclei, the greater is the difference between the absorption maxima of the corresponding pair of isomeric dyes. The dye pair **25** and **26** constitute an exception, for the absorption maxima of these dyes are identical, although **25** has a much broader absorption envelope. The origin of this anomalous behavior is, at present, unexplained.

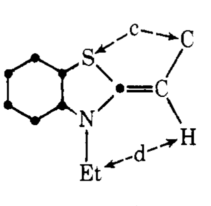
Relative Thermodynamic Stability of Isomeric Dyes. Although the addition of acids such as hydrogen chloride across the triple bond of acetylenic dyes occurs readily,[1] under suitable conditions acid-catalyzed interconversion of isomeric dyes can occur. Thus treatment of an acetonitrile solution of either isomer of a pair of acetylenic dyes with a trace of acetic acid leads to an equilibrium mixture of the two dyes. It is presumed that the equilibrium is established via a common dication formed by protonation of either isomeric dye.

$$R^{+}{}_{1}C{\equiv}CCH{=}R_2 \overset{H^+}{\rightleftharpoons} R^{+}{}_{1}CH{=}C{=}CHR^{+}{}_{2} \overset{H^+}{\rightleftharpoons} R_1{=}CHC{\equiv}CR^{+}{}_{2}$$

The relative proportion of each isomer at equilibrium is shown in Table I. For each pair, the isomer having an absorption maximum at shorter wavelength is the thermodynamically more stable. Paralleling the arguments presented to account for the spectral absorption characteristics of the dyes, this behavior is attributed to the increased stabilization of the acetylenic extreme structure in the hypsochromic isomer. The greater the difference in basicity between the two nuclei, the more strongly is the equilibrium displaced in favor of the hypsochromic isomer.

An exception to the above is found in the dye pair **29** and **30**, in which case the equilibrium is unexpectedly displaced in favor of the bathochromic isomer **30**. A possible explanation for this behavior is as follows: planar projections[5] of isomers





29 and **30** indicate that although the four steric interactions a–d are possible, only a is significant, and this interaction occurs only in **29**. No steric interactions are indicated involving *N*-ethyl groups of either nucleus attached to the terminal sp carbon atom at the opposite end of the dye chain. It is suggested that in **29** and **30**, where the basicity difference between the two heterocyclic nuclei is small, the steric hindrance to planarity, caused by interaction a, destabilizes **29** sufficiently for **30** to predominate in the equilibrium mixture. It should be pointed out that the equilibrium ratio of **29** to **30** (23:77) corresponds to a very small energy difference (~0.9 kcal/mol) between the two isomers.

Molecular Orbital Calculations. The experimental results for acetylenic dyes correspond closely to absorption shifts and tautomer stabilities expected from Brooker's concepts about unsymmetrical dyes, the electronic properties of heterocycles, and deviations.[4] Since these concepts were based primarily on the π-electronic character of dyes without acetylenic bonds, it was of interest to use molecular orbital theory to examine the conjugated π-electron system of the present acetylenic dyes, treating them as geometrical isomers of their symmetrical carbocyanine analogues. The geometry for the acetylenic extreme structure of dye **1** is shown in Figure 1 along with that of the carbocyanine analogue **2**. The molecular orbital calculations for most of the dyes used Pariser–Parr–Pople methods,[6] modified to include σ-inductive effects.[6b,7] In addition, valence electron calculations using the CNDO/S formalism of Jaffé and co-workers[8] were carried out for model dyes. The results of these calculations and related experimental data are summarized in Table II for three classes of dyes: (A) dyes containing identical heterocycles, (B) model acetylenic and carbocyanine chromophores, and (C) isomeric dyes containing nonidentical heterocycles. The dyes containing identical heterocycles were examined with two Pariser–Parr–Pople parameter sets.[6b,7] Both provide reasonable estimates of the relative transition energies for acetylenic and carbocyanine dyes (Table IIA). Results based on the first set are in better agreement with experimental values, and these are used for the discussion below.

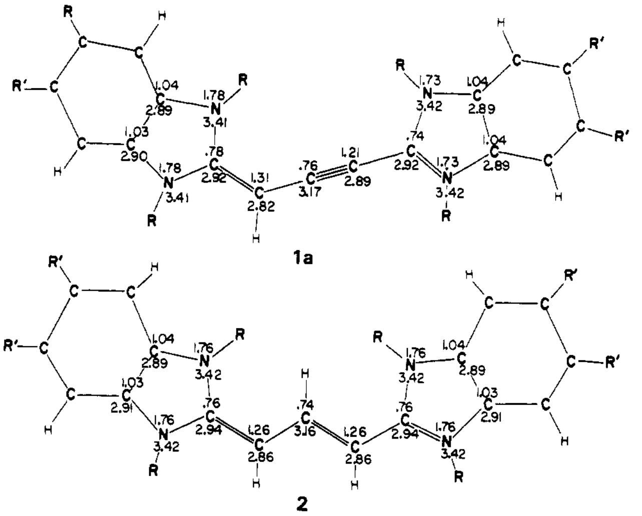


Figure 1. Acetylenic dyes and carbocyanine analogues (R = R′ = H). Charge densities [$\pi(\sigma)$] as calculated by the CNDO/S method of Jaffé and co-workers.[8] The carbocyanine analogue is predicted to absorb at significantly longer wavelength (430 nm) than the corresponding acetylenic dye (415 nm, Table IIB). Pariser–Parr–Pople calculations are summarized in Table IIA,C.

The allowed visible transition of acetylenic dyes occurs at shorter wavelength than for the corresponding carbocyanines, indicating chromophoric asymmetry as discussed in the previous sections. In the molecular orbital calculations for π electrons, introduction of this asymmetry as simple geometrical changes (bond lengths and bond angles) was sufficient to shift the predicted absorptions to shorter wavelength and localize more of the π-electron density on the heterocycle nearest the C–H carbon of the chromophore (Figure 1).

Dye **1** with the acetylenic geometry, **1a**, showed a predicted transition at 489 nm (2.53 eV), whereas the observed value is 473 nm. A "cumulene" geometry for the dye, obtained by adjusting only the sp-carbon positions to equalize all the bond lengths, gave a similar transition (488 nm).[9] The carbocyanine analogue **2** has a calculated transition at 524 nm (2.37 eV), corresponding to an observed value of 513 nm. The dyes **1**, **2**, and **6–9**, each containing identical heterocycles, exhibit a close

Table II. Spectroscopic Properties and Relative Stabilities of Acetylenic Dyes and Carbocyanine Analogues

A. Dyes with Identical Heterocyclic Nuclei

			Calcd by Pariser–Parr–Pople methods		
			Parameter set 1		Set 2,
Registry no.	Dye[a]	E_T (10^{-4} ϵ)[b] obsd	$E_T(f)$[c]	π energy[d]	$E_T(f)$[e]
52846-51-2	**1a**	2.62 (14)	2.53 (1.81)	495.86	2.30 (1.87)
61268-71-1	**1b**		2.54 (1.98)	495.62	
61268-72-2	**2**	2.42 (21)	2.37 (1.79)	494.34	2.21 (1.78)
		ΔE = 0.20 eV	ΔE = 0.16 eV		ΔE = 0.09 eV
56387-12-3	**6**	2.30 (21)	2.27 (1.96)	475.29	2.28 (2.10)
50818-84-3	**7**	2.13 (32)	2.15 (1.95)	473.79	2.20 (2.00)
		ΔE = 0.17 eV	ΔE = 0.138 eV		ΔE = 0.08 eV
61268-68-6	**8**	2.42 (9.9)	2.36 (1.72)	347.12	2.24 (1.73)
61268-69-7	**9**	2.24 (16)	2.22 (1.64)	345.71	2.14 (1.62)
		ΔE = 0.17 eV	ΔE = 0.165 eV		ΔE = 0.10 eV

B. Model Acetylenic and Carbocyanine Chromophores

		Calcd values	
Structure	Calcd quantity	PPP method[c]	CNDO/S method[f]
Acetylenic dye (Figure 1, R = R′ = H)	ϵ_{HF}	−9.40	−10.933 (π)
	E_T (*f*)	2.57 (1.70)	2.99 (1.37)
		3.68 (0.10)	3.51 (0.00001)
		3.99 (0.03)	4.15 (0.09)
Carbocyanine (Figure 1, R = R′ = H)	ϵ_{HF}	−9.37	−10.971 (π)
	E_T (*f*)	2.41 (1.68)	2.88 (1.29)
		3.64 (0.13)	4.09 (0.10)

C. Isomeric Dyes with Different Heterocyclic Nuclei

	Obsd in CH_3CN		Calcd by Pariser–Parr–Pople methods	
Dye[a]	E_T (10^{-4} ϵ),[b]	% isomer	E_T (*f*)[c]	π energy[d]
19	2.54 (13)	>99	2.42 (1.86)	485.71
20	2.33 (>13)	<1	2.31 (1.85)	485.57
	ΔE = 0.21 eV		ΔE = 0.11 eV	
21	2.65 (9)	>98	2.47 (1.74)	421.57
22	2.43 (12)	<2	2.42 (1.81)	421.41
	ΔE = 0.22 eV		ΔE = 0.05 eV	
29	2.37 (16)	23	2.33 (1.85)	411.22
30	2.33 (13)	77	2.26 (1.80)	411.23
	ΔE = 0.04 eV		ΔE = 0.07 eV	

[a] Dye structures: acetylenic dye **1a**/**1b** from 1,3-diethyl-5,6-dichlorobenzimidazole and carbocyanine analogue **2**; acetylenic dye **6** from 1,3-diethylimidazo[4,5-*b*]quinoxaline and carbocyanine analogue **7**; acetylenic dye **8** from 3-ethylbenzothiazole and carbocyanine analogue **9**; tautomeric dyes (**19–22, 29, 30**) from Table I. [b] Observed transition energies (E_T, eV) and extinction coefficients (10^{-4} ϵ, l. mol^{-1} cm^{-1}) in acetonitrile (Table I and ref 1). [c] Calculated transition energies (E_T, eV) and oscillator strengths (*f*) for the π-electron system excluding the acetylenic bond in the plane of the molecule. The basic program (QCPE, No. 71),[6a] modified to include heteroatom inductive effects, was used with standard parameters[6c] and additional inductive effects within the chromophore.[7] [d] Total π energy in eV, as calculated by equation 2.20 in ref 12. H. A. Hammond, private communication. [e] Results using the original parameter set devised by Hammond.[6b] [f] CNDO/S method of Jaffé and co-workers.[8]

correspondence between the predicted and observed transition energies (Table IIA). In addition, transition energy *differences* between acetylenic/carbocyanine pairs of dyes are close.

Model acetylenic and carbocyanine chromophores with terminal benzimidazoles were examined by PPP and CNDO/S calculations (Table IIB and Figure 1, R = R′ = H). Calculations on acetylenic hydrocarbons have suggested weak UV transitions at longer wavelength than the allowed $\pi \rightarrow \pi^*$ transitions.[11] In dyes **1** and **2**, the CNDO/S calculations predict the lowest energy transition to be in the visible region of the spectrum with high oscillator strength, and weak transitions involving the acetylenic bond in the UV. In agreement with the π-electron calculations comparing acetylenic and carbocyanine dyes, shorter wavelength absorption for the acetylenic dye is also predicted, along with similar highest filled orbital energies and higher π-electron density on the heterocycle nearest the methine carbon in the acetylenic dye.

The isomeric acetylenic dyes (**19/20, 21/22,** and **29/30**) were examined using a fixed acetylenic geometry for all isomers (see dye **1a,** Figure 1). The results of these π-electron calculations generally exhibited better agreement with spectral data than isomer stabilities (Table IIC). Calculated and observed transition energies were within 3% for dyes **20, 22, 29,** and **30** and within 6% for **19** and **21.** The dominant isomers in two dye sets (**19/20, 21/22**) were observed to be **19** and **21.** These also exhibited slightly higher total π energies,[12] but the high stability observed for these isomers is not adequately reflected in the total π energies. Dyes **29/30** are much closer in stability as shown by equivalent total π energies and a 23%/77% tautomeric mixture at equilibrium. Although it is reasonable to suggest that the small differences in total π energy may be an artifact of the calculations, it is nevertheless interesting that the π energies qualitatively parallel the observed isomer stabilities.

The Pariser–Parr–Pople calculations used here (cyanine dye parameters, fixed acetylenic bond lengths, nonconjugated bond omitted) reproduce most of the characteristics in the visible spectra of acetylenic dyes and their carbocyanine analogues. Some π-charge localization was observed in dye **1a** similar to previous suggestions made on the basis of experimental bond lengths from an x-ray crystal structure.[3a] In addition, total π energies excluding components of the triple bond in the molecular plane provide qualitative estimates of the relative stabilities of isomeric acetylenic dyes. Thus, in both a qualitative and quantitative sense, the primary differences between acetylenic dyes and their symmetrical carbocyanine analogues can be understood as a consequence of asymmetry in the conjugated π-electron chromophore.

Experimental Section

Electronic spectra were recorded using a Perkin-Elmer Model 450 spectrophotometer.

Equilibration Experiments. Solutions of the acetylenic dyes in acetonitrile, in the concentration range of $1–2 \times 10^{-5}$ M, were used. To 3 ml of dye solution was added 1–2 drops of acetic acid. Visible absorption spectra were then recorded periodically until equilibrium was attained, giving a family of absorption curves passing through an isosbestic point (the time required to reach equilibrium varied from a few minutes to several hours). The equilibrium proportion of each acetylenic dye of a pair was readily computed using the absorption curves of the two pure isomers and that of the equilibrium mixture.

Acknowledgments. The authors would like to thank Mrs. T. M. Berke and Dr. J. M. McKelvey for valuable discussions and assistance with the molecular orbital calculations, and Mr. J. T. Gefell for assistance with the equilibration experiments.

References and Notes

(1) J. D. Mee, *J. Am. Chem. Soc.*, **96,** 4712 (1974).

(2) J. D. Mee, *J. Org. Chem.*, preceding paper in this issue.

(3) (a) D. L. Smith and H. R. Luss, *Acta Crystallogr., Sect. B,* **31,** 402 (1975); (b) D. L. Smith and H. R. Luss, *ibid.*, **28,** 2793 (1972).

(4) L. G. S. Brooker, A. L. Sklar, H. W. J. Cressman, G. H. Keyes, L. A. Smith, R. H. Sprague, E. Van Lare, G. Van Zandt, F. L. White, and W. W. Williams, *J. Am. Chem. Soc.,* **67,** 1875 (1945), and references cited therein.

(5) Similar to those used previously to explain steric effects in cyanines, e.g., see L. G. S. Brooker, F. L. White, D. W. Heseltine, G. H. Keyes, S. G. Dent, and E. J. Van Lare, *J. Photogr. Sci.,* **1,** 173 (1953).

(6) (a) Quantum-Chemistry Program Exchange (Program No. 71), Chemistry Department, Indiana University, Bloomington, Ind. 47401. (b) H. A. Hammond, *Theor. Chim. Acta,* **18,** 239 (1970). (c) Parameters and calculational methods were the same as in ref 6b except for σ-inductive effects[7] and the use of modified parameters for oxygen, nitrogen, and sulfur atoms: D. L. Beveridge and J. Hinze, *J. Am. Chem. Soc.,* **93,** 3107 (1971); J. Hinze and H. H. Jaffé, *J. Phys. Chem.,* **67,** 1501 (1963).

(7) (a) σ-inductive effects between neutral atoms was originally based on Pauling σ-electronegativity values (χ_p).[6b] Additional inductive effects between directly bonded atoms of the same type (e.g., C–C) significantly improve calculations of spectral transitions for these and other dyes. For the chromophoric carbon atoms $C_\alpha–C_\beta–C_\alpha'$, the following χ_p values (dependent on net π charge) were used to estimate additional inductive effects between carbon atoms: C(aromatic), 2.75; C_α, 2.2–2.4; C_β, 2.7–2.8; C_α', 2.3–2.5 where $C_\beta–C_\alpha'$ were the acetylenic carbon atoms.

(8) (a) Quantum Chemistry Program Exchange (Program No. 174, CNDO/M with CNDO/2 and CNDO/S options), Chemistry Department, Indiana University, Bloomington, Ind. 47401. (b) The present calculations utilized the CNDO/S options in a more recent version of CNDO/M, kindly provided by Professor H. H. Jaffé, Chemistry Department, University of Cincinnati, Cincinnati, Ohio (see ref 8c–e) and adapted for calculations on larger molecules by J. M. McKelvey and R. A. Phillips, Eastman Kodak Co., Rochester, N.Y. 14650. (c) J. DelBene and H. H. Jaffé, *J. Chem. Phys.*, **48,** 1807, 4050 (1968); **49,** 1221 (1968); **50,** 1126 (1969). (d) R. L. Ellis, G. Kuehnlenz, and H. H. Jaffé, *Theor. Chim. Acta,* **26,** 131 (1972). (e) H. M. Chang, H. H. Jaffé, and C. A. Masmandis, *J. Phys. Chem.*, **79,** 1108, 1109 (1975).

(9) The relative orientations of the heterocycles in conformations **1a** and **1b** were identical, and only the positions of the sp carbons were modified. Carbon–carbon bond distances of the chromophore (heterocycle–CH–C–C–heterocycle) were 1.38, 1.37, 1.20, and 1.40 Å in the acetylenic dye and 1.38, 1.32, 1.32, and 1.33 Å in the cumulene dye. The absorption of a "cumulene" conformation **1b** of dye **1** was calculated as 488 nm (2.540 eV), which is close to both the observed value for dye **1** and the calculated value for the acetylenic conformation **1a.** The close correspondence between predicted absorption energies for **1a** and **1b** indicates that the calculated results are not critically dependent on the exact specification of geometry within the chromophore.

(10) S. S. Malhotra and M. C. Whiting, *J. Chem. Soc.*, 3812 (1960).

(11) H. H. Jensen, *Acta Chem. Scand.*, **25,** 235 (1971).

(12) J. A. Pople, *Trans. Faraday Soc.,* **49,** 1375 (1953), equation 2 20

Synthesis of 6,9-Bisnormethyl-8-methoxy-12,13-epoxy-6,8,10-trichothecatriene

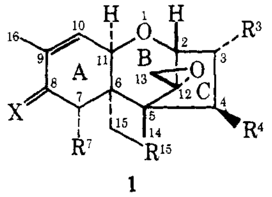
Wayne K. Anderson,* Edmond J. LaVoie, and George E. Lee

Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14214

Received August 23, 1976

An efficient synthesis of an A-ring aromatic trichothecane analogue, 6,9-bisnormethyl-8-methoxy-12,13-epoxy-6,8,10-trichothecatriene (**11**), has been developed. The aryl allyl ether, **2**, was converted in a series of six steps to **7b** in ca. 74% overall yield. Bromination of the enolate anion of **7b**, removal of the benzyl protecting group, and cyclization (sodium hydride in ether) gave the tricyclic ketone, **9**, in very high yield. Alternatively, hydrogenolysis of **7b** followed by acetylation and bromination gave **13c**. Treatment of **13c** with DBN gave **9**. The spiro epoxide, **11**, was prepared from **9** by treatment with dimethylsulfonium methylide.

The trichothecanes are a group of sesquiterpene mycotoxins which possess the general structure **1**. Interest in this group emanates from the discovery that a number of the trichothecanes display potent activity against fungi, protozoa, viruses, and/or neoplasms. The significant mammalian toxicity which most of the trichothecanes exhibit has also been implicated as a cause of massive livestock poisoning, a result of ingestion of certain moldy foods.[1]



1

Structurally, the trichothecanes range in complexity from 12,13β-epoxytrichothec-9-ene (**1**, $R^3 = R^4 = R^7 = R^{15} = H$; $X = H_2$) to highly oxidized compounds such as nivalenol (**1**, $R^3 = R^4 = R^6 = R^{15} = OH$; $X = O$).[1] Macrocyclic lactone derivatives, bridging C-4 to C-15, are also quite common.[1] Three