Acetylenic Amines. X. Piperazines from Substituted N-(2-Hydroxyalkyl)propargylamines

ROBERT D. DILLARD AND NELSON R. EASTON

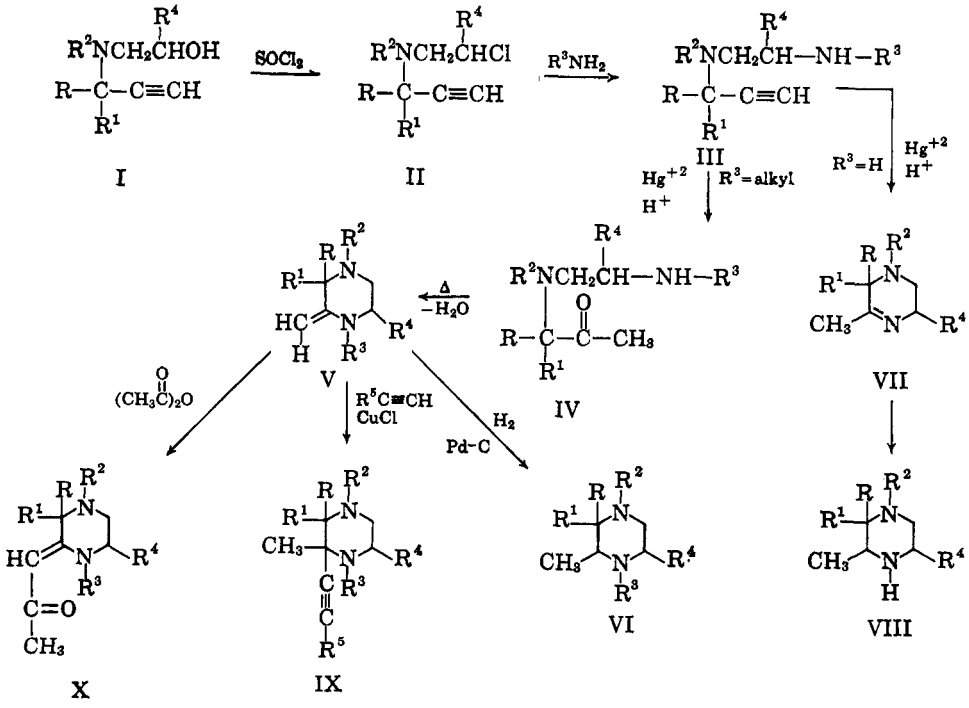
Chemical Research Division, The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis 8, Indiana

Received March 18, 1966

The preparation of 2,2-dimethyl-4-ethyl-3-methylenemorpholine[1] from the acid-catalyzed cyclization of 3-(β-ethylaminoethoxy)-3-methyl-1-butyne suggested the extension of this reaction to the nitrogen analogs, the N-(1,1-dialkylpropargyl)ethylene diamines (III). These compounds should be convertible into methylene piperazines (V) and thence by hydrogenation to substituted piperazines (VI).

The N-(1,1-dialkylpropargyl)ethylene diamines (III) were synthesized from the appropriately substituted β-hydroxyethylamines[1] (I), which have been prepared from readily available 1,1-dialkylpropargylamines.[2,3] Treatment of the amino alcohols (I) with thionyl chloride gave the β-chloroethylamines (II). These were then treated with primary amines to obtain the terminal secondary amines (III, R^3 = alkyl) or with potassium phthalimide followed by replacement with hydrazine[4] to give the primary amino derivatives (III, R^3 = H). (See Scheme I).

SCHEME I



The ethylene diamines, obtained as described above, were treated with mercuric oxide[5] and sulfuric acid in a methanol–water solution. The infrared spectra of the crude reaction products had absorption peaks at 5.8 μ indicating ketone carbonyl functions. Upon distillation, different compounds were produced whose infrared spectra no longer had absorption peaks at 5.8 but new strong peaks at 6.2 μ. These compounds were assigned structure V. The presence of the ketones in the crude reaction products indicates that the cyclization of the ethylene diamines proceeds by hydration of the triple bond. The amino group then adds to the ketone followed by the elimination of water. The cyclization does not proceed by an amine salt addition directly to the triple bond. This mechanism was further evidenced by the unsuccessful cyclization of an ethylenediamine where the R^3 substituent was large (*t*-butyl) and offered steric hinderance to the amine addition to the ketone. Distillation of the reaction products in this case gave only the β-keto alkyl ethylenediamine (IV).

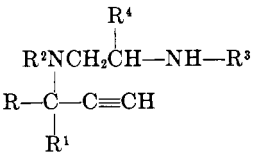
The assignment of structure V was also confirmed by the n.m.r. spectrum[6] of Va (R = R′ = CH_3; R^2 = R^3 = C_2H_5; R^4 = H) which showed unsplit signals at 227 (1H) and 243 c.p.s. (1H) which are ascribed to the vinyl protons; a series of peaks between 140 and 183 c.p.s. (8H) assigned to the protons of the N-methylene groups; an unsplit signal at 76 c.p.s. (6H) assigned to the *gem* dimethyl protons; and triplets centered at 63 (3H) and 66 c.p.s. (3H) assigned to the methyl protons of the ethyl groups.

The hydration and subsequent cyclization was extended to include the aryl and aralkyl groups as the R^3 substituent, giving the substituted methylene piperazines. When N-ethyl-N-[3-(3-methyl-1-butynyl)]-ethylene diamine (IIIa, R = R^1 = CH_3; R^2 = C_2H_5; R^3 = R^4 = H) was hydrated and distilled, two different products were possible, the methylene piperazine where

(1) N. R. Easton, D. R. Cassady, and R. D. Dillard, *J. Org. Chem.*, **28**, 448 (1963).
(2) G. F. Hennion and R. S. Hanzel, *J. Am. Chem. Soc.*, **82**, 4908 (1960).
(3) N. R. Easton, R. D. Dillard, W. J. Doran, M. Livezey, and D. E. Morrison, *J. Org. Chem.*, **26**, 3772 (1961).
(4) H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, 2348 (1926).
(5) G. F. Hennion and P. E. Butler, *J. Org. Chem.*, **26**, 3341 (1961).
(6) The machine used was the Varian Associates Model HR60, 60 Mc. Deuteriochloroform was used as the solvent and tetramethylsilane as the internal reference.

TABLE I

ETHYLENEDIAMINES

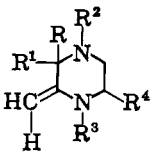


R	R^1	R^2	R^3	R^4	B.p., °C. (mm.)	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
CH_3	CH_3	C_2H_5	H	H	*a*	$C_9H_{20}Cl_2N_2$	47.58	47.62	8.87	9.14
CH_3	CH_3	C_2H_5	C_2H_5	H	70–71 (4)	$C_{11}H_{22}N_2$	72.47	72.28	12.16	12.33
CH_3	CH_3	CH_3	C_2H_5	CH_3	65–67 (4)	$C_{11}H_{22}N_2$	72.47	72.32	12.16	12.39
CH_3	CH_3	CH_3	$CH(3H_3)_2$	H	67 (4)	$C_{11}H_{22}N_2$	72.47	72.85	12.16	12.40
CH_3	CH_3	C_2H_5	$C(CH_3)_3$	H	78–79 (4)	$C_{13}H_{26}N_2$	74.22	73.98	12.45	12.62
CH_3	CH_3	C_2H_5	$-CH_2CH_2C_6H_5$	H	92–95 (0.02)	$C_{17}H_{26}N_2$	79.01	78.87	10.14	10.09
CH_3	CH_3	C_2H_5	C_6H_5	H	105–110 (0.01)	$C_{15}H_{22}N_2$	78.21	78.03	9.62	9.76
$-(CH_2)_5-$		C_2H_5	C_2H_5	H	*b*	$C_{14}H_{28}Cl_2N_2$	56.94	57.16	9.55	9.75

[a] As dihydrochloride, crystallized from ethanol, m.p. 196–198°. [b] As dihydrochloride, crystallized from isopropyl alcohol, m.p. 199–201°.

TABLE II

2-METHYLENEPIPERAZINES



R	R^1	R^2	R^3	R^4	B.p., °C. (mm.)	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
CH_3	CH_3	C_2H_5	C_2H_5	H	71 (4)	$C_{11}H_{22}N_2$	72.47	72.58	12.16	12.33
CH_3	CH_3	CH_3	C_2H_5	CH_3	71–73 (6)	$C_{11}H_{22}N_2$	72.47	72.24	12.16	12.18
CH_3	CH_3	CH_3	$-CH(CH_3)_2$	H	77 (4)	$C_{11}H_{22}N_2$	72.47	72.28	12.16	12.22
CH_3	CH_3	C_2H_5	$-CH_2CH_2C_6H_5$	H	105 (0.05)	$C_{17}H_{26}N_2$	79.02	78.83	10.14	10.05
CH_3	CH_3	C_2H_5	C_6H_5	H	114 (0.01)	$C_{15}H_{22}N_2$	78.21	78.17	9.63	9.78
$-(CH_2)_5-$		C_2H_5	C_2H_5	H	72 (0.3)	$C_{14}H_{26}N_2$	75.61	75.64	11.79	11.92

the double bond was exocyclic or a tetrahydropyrazine where the double bond was in the ring. The infrared and n.m.r. spectra indicated that 4-ethyl-2,3,3-trimethyl-2,3,4,5-tetrahydropyrazine (VII) was obtained. Hydrogenation of the unsaturated piperazines V or VII gave the 2-methylpiperazines (VI or VIII) in 40–80% yields.

The methylene piperazines (V) are readily available stable enamines. Several well-known enamine reactions were performed to obtain piperazines with substituents difficult to obtain by other methods. Phenylacetylene was treated with Va using cuprous chloride as catalyst[7] to obtain 1,4-diethyl-2,3,3-trimethyl-2-phenylethynylpiperazine (IX). The reaction was equally successful using 3-methyl-1-butyn-3-ol and N-3-dimethyl-1-butynyl-3-amine as adducts. Acetylene was reacted with Va in benzene[7] to give a small yield of 1,4-diethyl-2,3,3-trimethyl-2-ethynylpiperazine and some disubstituted acetylenic compound.

When acetic anhydride[8] and Va were refluxed in benzene overnight, 1,4-diethyl-3,3-dimethyl-2-acetonylidenepiperazine was obtained as expected.

(7) K. C. Brannock, R. D. Burpitt, and J. G. Thweatt, *J. Org. Chem.*, **28**, 1462 (1963).

(8) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

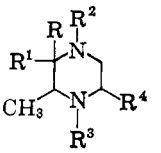
Experimental

Ethylenediamines (III).—The following general procedure was used. The 1,1-dialkyl-N-(β-hydroxyethyl)propargylamine[1] (0.5 mole) was dissolved in methanol and excess anhydrous hydrogen chloride was added. The methanol and excess acid were removed at reduced pressure and the residue was taken up in 500 ml. of chloroform. At reflux temperature, 1 mole of thionyl chloride was added dropwise to the chloroform solution and reflux was maintained for 3 hr. The chloroform and excess thionyl chloride were removed at reduced pressure; the residue was dissolved in water; the solution was made basic with 50% sodium hydroxide solution and extracted with ether. After drying, the ether solution was distilled, giving the crude β-chloroethylamine (II) as the residue. A mixture of unpurified β-chloroethylamine and primary amine was maintained at reflux temperature for 16 hr. using water or acetonitrile as a solvent. The reaction mixture was treated with excess 20% sodium hydroxide solution and extracted with ether. After drying over magnesium sulfate, the ether solution was concentrated and the residue was distilled giving the ethylenediamine in 60–80% yield, based on starting amino alcohol.

To obtain the primary amino derivative (IIIb, R^3 = H), the β-chloroethylamine was refluxed with potassium phthalimide in ethanol followed by treatment with hydrazine.[4] Upon distillation, the ethylenediamine was obtained in 60–65% yield (see Table I).

2-Methylenepiperazines (V).—The ethylenediamine (0.2 mole) was added dropwise to a mixture of 0.6 mole of 98% sulfuric acid, 60 ml. of water, 60 ml. of methanol, and 5 g. of mercuric oxide.[5] After the addition was complete, the mixture was refluxed 4 hr. with air bubbling slowly into the reaction mixture. After cool-

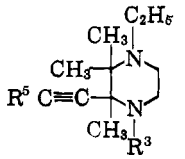
TABLE III
PIPERAZINES



R	R^1	R^2	R^3	R^4	B.p., °C. (mm.)	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
CH_3	CH_3	C_2H_5	H	H	57 (4)	$C_9H_{20}N_2$	69.17	69.42	12.90	13.14
CH_3	CH_3	C_2H_5	C_2H_5	H	64 (4)	$C_{11}H_{24}N_2$	71.68	71.88	13.13	13.38
CH_3	CH_3	CH_3	C_2H_5	CH_3	*a*	$C_{11}H_{26}Cl_2N_2$	51.35	51.27	10.18	10.43
CH_3	CH_3	CH_3	$CH(CH_3)_2$	H	*b*	$C_{11}H_{26}Cl_2N_2$	51.35	51.46	10.18	10.33
CH_3	CH_3	C_2H_5	$CH_2CH_2C_6H_5$	H	99–100 (0.05)	$C_{17}H_{28}N_2$	78.40	78.55	10.84	10.95
CH_3	CH_3	C_2H_5	C_6H_5	H	90 (0.05)	$C_{15}H_{24}N_2$	77.53	77.47	10.41	10.44
$-(CH_2)_5-$		C_2H_5	C_2H_5	H	67 (0.3)	$C_{14}H_{28}N_2$	74.94	75.10	12.58	12.63

[a] As dihydrochloride, crystallized from isopropyl alcohol, m.p. 225–227°. [b] As dihydrochloride, crystallized from isopropyl alcohol, m.p. 223–224°.

TABLE IV
PIPERAZINES



R^3	R	B.p., C. (mm.)	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
C_2H_5	H	*a*	$C_{13}H_{26}Cl_2N_2$	55.51	55.52	9.31	9.50
C_2H_5	C_6H_5	117 (0.008)	$C_{19}H_{28}N_2$	80.23	80.02	9.92	10.03
C_2H_5	$-C(CH_3)_2$ (NHCH$_3$)	80 (0.07)	$C_{17}H_{33}N_3$	73.06	73.32	11.90	12.10
C_2H_5	$-C-(CH_3)_2$ (OH)	73–74 (0.02)	$C_{16}H_{30}N_2O$	72.13	72.32	11.35	11.48
C_6H_5	C_6H_5	145–148 (0.01)	$C_{23}H_{28}N_2$	83.08	82.84	8.49	8.55

[a] As dihydrochloride salt, crystallized from isopropyl alcohol–methyl ethyl ketone, m.p. 190–192°.

ing, the mixture was filtered, and the filtrate was made strongly basic with 50% sodium hydroxide solution and extracted with ether. The ether solution was dried with magnesium sulfate and filtered, and the filtrate was distilled giving the 2-methylenepiperazines in 50–75% yields (see Table II).

4-Ethyl-2,3,3-trimethyl-2,3,4,5-tetrahydropyrazine (VII).—N-Ethyl-N-[3-(3-methyl-1-butynyl)]ethylenediamine was cyclized as described for V and the product was distilled, b.p. 58° (4 mm.).

Anal. Calcd. for $C_9H_{18}N_2$: C, 70.07; H, 11.76. Found: C, 70.03; H, 11.77.

N-[2-(*t*-Butylamino)ethyl]-3-ethylamino-3-methyl-2-butanone (IV).—N-Ethyl-N-[3-(3-methyl-1-butynyl)]-N′-*t*-butylethylene diamine (0.13 mole) was treated with mercuric oxide and sulfuric acid as described for V, and the product was distilled, b.p. 102–104° (7 mm.), giving 15 g. (50%) of colorless oil.

Anal. Calcd. for $C_{13}H_{22}N_2O$: C, 68.37; H, 12.36. Found: C, 68.56; H, 12.61.

2-Methylpiperazines (VI).—The methylenepiperazine (V, 0.1 mole) in 100 ml. of ethanol with 2 g. of 5% palladium on carbon as catalyst was hydrogenated at approximately 40 p.s.i. of hydrogen. The catalyst was filtered and the product was distilled (see Table III). Yields of 60–80% were obtained.

1,4-Diethyl-2,3,3-trimethyl-2-phenylethynylpiperazine (IX).—A mixture of 9.1 g. (0.05 mole) of 1,4-diethyl-3,3-dimethyl-2-methylenepiperazine (Va), 5.1 g. (0.05 mole) of phenylacetylene, and 1 g. of cuprous chloride was stirred in a flask, and the temperature of the reaction mixture rose to 85°. After allowing to cool to 25° (1 hr.), the mixture was filtered and distilled giving 6 g. (42%) of colorless oil boiling at 117° at 0.008 mm. (see Table IV).

1,4-Diethyl-2,3,3-trimethyl-2-ethynylpiperazine and 1,2-Bis[2-(1,4-diethyl-2,3,3-trimethylpiperazino)]ethyne.—A mixture of 0.3 mole of 1,4-diethyl-3,3-dimethyl-2-methylenepiperazine (Va), 4 g. of cuprous chloride, and 300 ml. of benzene was placed in an autoclave and the autoclave was filled with acetylene at 30 p.s.i. The autoclave was warmed at 80° for 2 hr. After cooling, the mixture was filtered and the benzene solution was distilled. A fraction boiling at 89° (4 mm.), 2 g., was collected. The dihydrochloride of the distillate was crystallized from methyl ethyl ketone–isopropyl alcohol (see Table IV). A second fraction boiling at 160–163° (0.3 mm.) was collected, giving 25 g. (43%) of 1,2-bis[(2-(1,4-diethyl-2,3,3-trimethylpiperazino)]ethyne.

Anal. Calcd. for $C_{24}H_{46}N_4$: C, 73.78; H, 11.87; N, 14.34. Found: C, 74.01; H, 12.05; N, 14.23.

1,4-Diethyl-3,3-dimethyl-2-acetonylidenepiperazine (X).—A solution of 0.1 mole of Va and 0.05 mole of acetic anhydride in 100 ml. of benzene was heated overnight at 60°, cooled, washed with cold 10% sodium hydroxide solution, dried over magnesium sulfate, and filtered; the filtrate was distilled. The fraction boiling at 110–112° (0.2 mm.) was collected giving 15 g. (67%) of colorless oil.

Anal. Calcd. for $C_{13}H_{24}N_2O$: C, 69.60; H, 10.78. Found: C, 69.35; H, 11.04.

Acknowledgment.—The microanalyses were performed by Messrs. William Brown, Howard Hunter, George Mackiak, and Alfred Brown. Many of the starting materials were prepared by Mr. Lawrence White. The infrared spectra were obtained by Mrs.

Doris Stephens and Miss Martha Hofmann. The authors wish to thank especially Messrs. Paul Landis and Donald Woolf, Jr., for their invaluable services in interpreting and compiling the infrared and n.m.r. data.

Studies on the Ultraviolet Absorption of Psoralene and Substituted Psoralenes

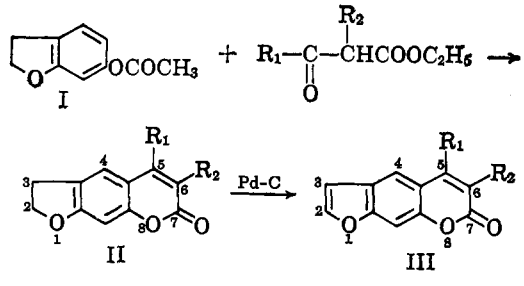
DILIP KUMAR CHATTERJEE, ROBINDRA MOHAN CHATTERJE, AND KALYANMAY SEN

The Research Division, East India Pharmaceutical Works Ltd., Calcutta, India

Received January 9, 1964

Psoralene, the active principle of *Psoralea corylifolia* Linn., has been widely used in the treatment of leucoderma.[1] Many psoralene derivatives obtained both naturally and synthetically have been studied and the photosensitizing activities have been found to vary according to the position as well as to the nature of the substituent.[2] In view of the demonstration of Pathak and Fellman[3] that there is a correlation between light absorption and photosensitizing activity, it was considered to be interesting to study the ultraviolet absorption spectra of psoralenes substituted at various positions. In this note we have dealt with psoralene derivatives substituted at the pyran ring (*viz.*, 5- and 6-positions).

Different methods employed for the syntheses of psoralene and its derivatives have been reviewed by Esse and Christensen[4] and we have employed 6-acetoxycoumaran (I) as a starting material for our syntheses. Compound I has been prepared according to Horning and Reisner's[5] method by condensing resorcinol and



chloroacetonitrile, acetylating the product, and reducing catalytically the 6-acetoxybenzofuranone with palladized charcoal. We have also followed the method employed by Davies,[6] *et al.*, for the synthesis of 6-hydroxybenzofuranone from resorcinol and chloroacetyl chloride. Syntheses of substituted psoralenes (III) were accomplished by condensing 6-acetoxycoumaran (I) with an appropriate β-keto ester followed by dehydrogenation of the resulting dihydropsoralene (II) with palladium–carbon in refluxing diphenyl ether.[7]

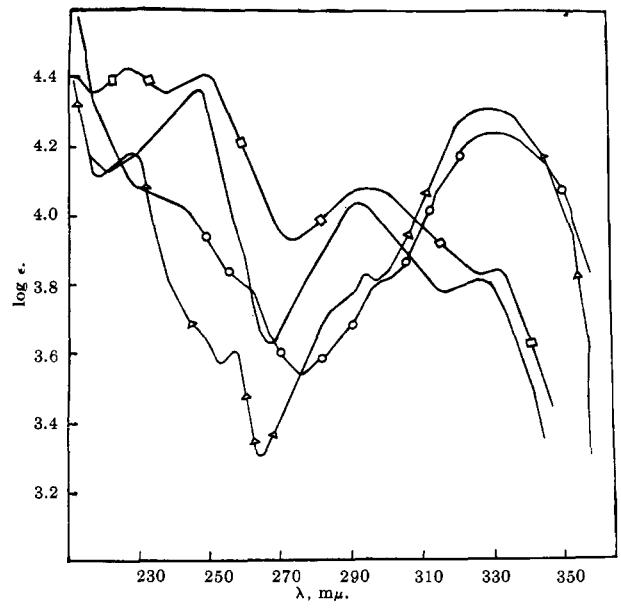


Fig. 1.—Ultraviolet absorption spectra of psoralene, ———; 5-phenylpsoralene (**15**), -□-□-; 5,6-cyclopenteno-2,3-dihydropsoralene (**9**), -△-△-; 5-phenyl-6-methyl-2,3-dihydropsoralene (**7**), -○-○-.

Experimental

Melting points are uncorrected. The compounds were repeatedly crystallized from the solvents until sharp and constant melting points were obtained.

Dihydropsoralenes[6] and psoralenes[7] prepared following the procedure of Horning, *et al.*, are listed in Tables I and II. Natural psoralene as a reference compound was obtained from the seeds of *Psoralea corylifolia* Linn. by the solvent extraction process.[8] The crude product after purification by chromatography and finally by crystallization from benzene, melted at 160–161°.[8]

Absorption was measured with a Uvispek Mark VII photoelectric spectrophotometer, using ethanol as solvent at a concentration of 5–6 mg./l. in the region 200–360 mμ.

Results and Discussion

Important features from the absorption spectra are summarized in Table III. Four types of absorption curves have been observed. One example of each type has been presented in Fig. 1. A study of the data given in Table III will show that substitution of hydrogen at the 5- and 6-positions by the alkyl group in psoralene does not produce any significant change of the absorption pattern; both λ_{max} and log ε remain materially unchanged.

A bathochromic shift as well as increase in log ε value has been observed at a lower wave length when the 5-position of psoralene is substituted by a phenyl group. A new minimum at 221 mμ (log ε 4.26–4.34) and a maximum at 225 mμ (log ε 4.42–4.43) have appeared. The usual minimum at 221 ± 1 has been shifted to 235 ± 1 mμ (log ε 4.24–4.33). The maximum at 245 ± 1 is found at 247–248 mμ (log ε 4.32–4.40), and the characteristic minimum at 265 ± 1 is shifted bathochromically to 270–271 mμ (log ε 3.68–3.91). There is a rather broad band at 297 ± 1 mμ (log ε 3.99–4.06) instead of at

(1) B. Mukherji, *J. Sci. Ind. Res.* (India), **15A**, 256 (1956).
(2) L. Musajoe, G. Rodighiro, and G. Caporale, *Chem. Abstr.*, **48**, 4111 (1954); L. Musajoe, G. Rodighiro, G. Caporale, and C. Antonello, *ibid.*, **53**, 6222[b] (1959).
(3) M. A. Pathak and J. H. Fellman, *Nature*, **185**, 382 (1960).
(4) R. C. Esse and B. E. Christensen, *J. Org. Chem.*, **25**, 1565 (1960).
(5) E. C. Horning and D. B. Reisner, *J. Am. Chem. Soc.*, **70**, 3619 (1948).
(6) J. S. H. Davies, P. A. McCrea, W. L. Norris, and G. R. Ramage, *J. Chem. Soc.*, 3206 (1950).
(7) E. C. Horning and D. B. Reisner, *J. Am. Chem. Soc.*, **72**, 1514 (1950).
(8) H. N. Khastagir, P. C. Duttagupta, and P. Sengupta, *Indian J. Appl. Chem.*, **22**, 82 (1959).