tions will be those derived from V which we have found to brominate at a rate comparable with that of I.

The kinetic results support the failure of Swain and Dunlap[1] to detect appreciable deuterium incorporation in unreacted III under conditions where it had undergone 57% conversion to V in alkaline D_2O.

Experimental Section

Materials.—3-Bromo-2-butanone [n^{20}D 1.4575, bp 85° (118 mm)] and 1-bromo-2-butanone [n^{20}D 1.4676, bp 104° (118 mm)] were prepared by the procedure of Catch, *et al.*[8] Upon hydrolysis of the corresponding bromobutanones (5 g, 0.033 mol) in aqueous sodium hydroxide (100 ml, 2 *M*) at room temperature there was obtained 1-hydroxy-2-butanone (n^{20}D 1.4271, bp 158°) and 3-hydroxy-2-butanone (n^{20}D 1.4168, bp 144°), respectively, in high yield.

Kinetics.—Reactions of the bromobutanones with sodium hydroxide were initiated using a Durrum Gibson stop-flow apparatus fitted with a T-jump cell. The syringes contained bromo ketone (0.005 *M*) and sodium hydroxide (0.001 *M*), respectively. Reactions were followed by monitoring change in conductivity between the plates of the T-jump compartment.[9] A Radiometer automatic titration assembly was also used for an alternative pH-Stat procedure.

Reactions of 1- and 3-bromo- and of 1- and 3-hydroxy-2-butanone (0.005 *M*) with bromine (0.024 *M*) in aqueous hydroxide (0.1 *M*) were initiated by stop-flow techniques and followed by colorimetric observation of the change in absorbance at 398 nm. Stop-flow results were consistent with those obtained using a Gilford 2400 spectrometer to monitor (at 350 nm) consumption of BrO^- in a solution which initially contained hydroxide (0.01 *M*), bromine (0.003 *M*), and bromo ketone (<0.001 *M*).

Registry No.—I, 78-93-3; II, 816-40-0; III, 814-75-5; IV, 5077-67-8; V, 513-86-0.

(8) J. R. Catch, D. F. Elliott, D. H. Hey, and E. R. H. Jones, *J. Chem. Soc.*, 272 (1948).

(9) Unpublished procedure: A. C. Knipe and R. L. Tranter.

Pyrolytic Cleavage of Antibiotic X-537A and Related Reactions

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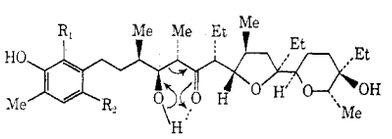
Received April 23, 1973

Investigations into the structure,[1] biosynthesis,[2] nitration,[3] and antibacterial activity[4] of antibiotic X-537A (**1a**) have resulted in the transformation of the



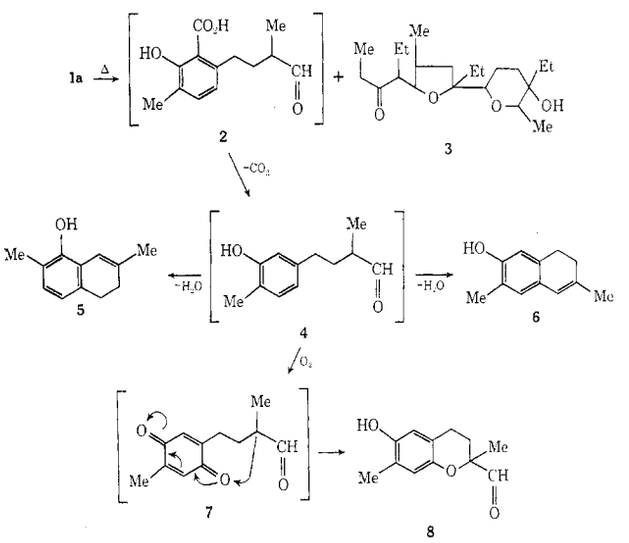
1a, $R_1 = CO_2H$; $R_2 = H$
b, $R_1 = CO_2H$; $R_2 = Br$
c, $R_1 = R_2 = NO_2$

antibiotic into a number of novel compounds. The isolation and characterization of several additional degradation products from **1a** is the subject of this report.

The most useful degradation reaction in the structural and biosynthetic studies on **1a** was the base-catalyzed retroaldol cleavage[1,2] reaction. A competing dehydration reaction[3,4] restricted the yield of the retroaldol ketone **3** to approximately 70%. However, pyrolysis of **1a** has now been shown to give a quantitative yield of **3**, indicating that under pyrolytic conditions, **1a** is degraded *solely via* the retroaldol cleavage route. This reaction is presently under investigation as the basis of a possible pyrolysis–glc method for the assay of **1a**.

The other cleavage product **2** from the pyrolysis of **1a** (Scheme I) spontaneously decarboxylates to the

SCHEME I



phenol **4**, which in turn cyclizes with dehydration to a mixture of 5,6-dihydro-2,7-dimethyl-1-naphthol (**5**) and a 7,8-dihydro-3,6-dimethyl-2-naphthol (**6**). When the antibiotic was heated at 220° for 1 hr in an open tube, 3,4-dihydro-2,7-dimethyl-6-hydroxy-2*H*-1-benzopyran-2-carboxaldehyde (**8**) was isolated in addition to **3**, **5**, and **6**. Production of **8** suggests that, in the presence of air, partial oxidation of the intermediate phenol **4** to a quinone **7** occurred prior to cyclization.

Conversion of **1a** to the 5-bromo derivative **1b** was described in an earlier report.[4] Pyrolysis of **1b** also gave a quantitative yield of the retroaldol ketone **3** together with 3,6-dimethyl-2-naphthol (**9**)[5] and 4-bromo-5,6-dihydro-2,7-dimethyl-1-naphthol (**10**) (Scheme II). The conversion of **1b** into the naphthol **9** in contrast to the 7,8-dihydronaphthol **6** produced on pyrolysis of **1a** was the result of an additional elimination step (loss of HBr) in the case of the bromo derivative. In an analogous reaction, base-catalyzed retroaldol cleavage of **1b** gave 3,6-dimethyl-2-hydroxy-1-naphthoic acid (**11**) whereas base cleavage of **1a** is known[1] to produce the 7,8-dihydro derivative of **11**. Another interesting example of this base cleavage–cyclization reaction was the facile conversion of the dinitrodecarboxy derivative of antibiotic X-537A (**1c**) to 6-hydroxy-2,7-dimethyl-5-nitroquinoline.[3]

(1) J. W. Westley, R. H. Evans, Jr., T. Williams, and A. Stempel, *Chem. Commun.*, 71 (1970).

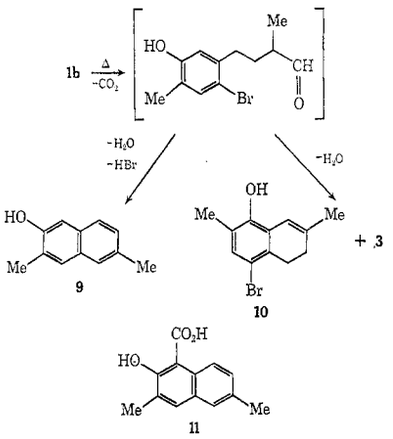
(2) J. W. Westley, R. H. Evans, Jr., D. L. Pruess, and A. Stempel, *Chem. Commun.*, 1467 (1970).

(3) J. W. Westley, J. Schneider, R. H. Evans, Jr., T. Williams, A. D. Batcho, and A. Stempel, *J. Org. Chem.*, **36**, 3621 (1971).

(4) J. W. Westley, E. P. Oliveto, J. Berger, R. H. Evans, Jr., R. Glass, A. Stempel, V. Toome, and T. Williams, *J. Med. Chem.*, **16**, 397 (1973).

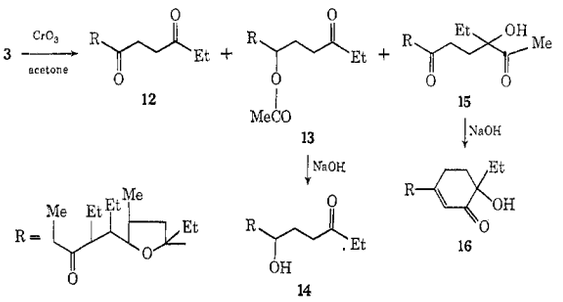
(5) R. Weisgeiner and O. Kruber, *Chem. Ber.*, **52**, 367 (1919).

SCHEME II



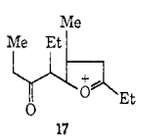
The retroaldol ketone **3** has been further degraded (Scheme III) in connection with our biosynthetic

SCHEME III



studies.[2] In an attempt to isolate the *C*-methyl group in the terminal tetrahydropyranyl ring, **3** was subjected to Jones oxidation.[6] In addition to the desired acetoxy ketone **13**, a triketone **12** was also isolated and characterized. Hydrolysis of **13** in base gave hydroxy ketone **14** and acetic acid. It was from this set of reactions using ^{14}C-labeled substrates that we were able to establish[2] that the terminal C–Me group is biosynthetically derived from acetate in contrast to the other four *C*-methyls in **1a**, which are all propionate derived. When the base hydrolysis reaction was carried out on the crude oxidation product from **3**, the hydroxycyclohexenone **16** was also isolated. The structure of **16** implies the presence of hydroxy triketone **15** in the oxidation mixture from **3**.

Mass spectrometry was essential in determining the structures of compounds **12**, **13**, **14**, and **16**. These compounds, like ketone **3**, all had their base peak at *m/e* 211 which is due to the fragment **17**. This result



indicated that Jones oxidation of **3** caused decomposition only in the tetrahydropyranyl ring.

(6) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N. Y., 1967, p 142.

Experimental Section[7]

Pyrolytic Cleavage of Antibiotic X-537A (1a) under Reduced Pressure to 4-[5-Ethyl-3-methyl-5-(5-ethyl-5-hydroxy-6-methyl-2-tetrahydropyranyl)-2-tetrahydrofuryl]-3-hexanone (3), 5,6-Dihydro-2,7-dimethyl-1-naphthol (5), and 7,8-Dihydro-3,6-dimethyl-2-naphthol (6).—Heating 2.0 g (3.39 mmol) of **1a** under reduced pressure (0.05 mm) at 200° gave 1.69 g of an oily distillate. The oil was chromatographed on 100 g of silica gel using a linear gradient from 1 l. of 1:4 methylene chloride–hexane to 1 l. of methylene chloride. The first fraction was concentrated and crystallized to give 81 mg (14%) of **5**: mp 45–47°; nmr ($CDCl_3$) δ 1.94 (s, 3, CH_3C=), 2.20 (s, 3, aromatic CH_3), 2.20, 2.84 (m, 4, J_{vic} = 8 Hz, CH_2CH_2), 6.47 (s, 1, CH=C), 6.59, 6.82 (AB, 2, J_{ortho} = 9 Hz, aromatic); mass spectrum *m/e* 174 (M^+). *Anal.* Calcd for $C_{12}H_{14}O$ (174.23): C, 82.71; H, 8.09. Found: C, 82.53; H, 7.85.

The second fraction gave, on concentration and crystallization, 307 mg (52%) of **6**: mp 140°; nmr ($CDCl_3$) δ 1.85 (s, 3, CH_3C=), 2.16 (s, 3, aromatic CH_3), 2.20, 2.70 (m, 4, J_{vic} = 8 Hz, CH_2CH_2), 6.11 (s, 1, CH=C), 5.71, 6.51 (AX, 2, J_{para} = 1 Hz, aromatic); mass spectrum *m/e* 174 (M^+). *Anal.* Calcd for $C_{12}H_{14}O$ (174.23): C, 82.71; H, 8.09. Found: C, 82.51; H, 8.31.

The third fraction was concentrated to give 1.2 g (100%) of the ketone **3**.[1]

Pyrolysis of Antibiotic X-537A (1a) at Atmospheric Pressure to Give 3,4-Dihydro-2,7-dimethyl-6-hydroxy-2*H*-1-benzopyran-2-carboxaldehyde (8).—Heating 2.0 g (3.39 mmol) of **1a** in an open tube at 220° for 1 hr yielded a heavy black oil. The oil was chromatographed on 250 g of silica gel using a gradient between 2 l. methylene chloride to 2 l. of 1:1 methylene chloride–ether. The first three fractions contained, respectively, **5**, **6**, and **3** and were followed by a fourth fraction which on evaporation gave 400 mg of an oily solid. This material was rechromatographed on 50 g of silica gel using 95:5 benzene–methanol to give a major fraction which was evaporated and crystallized from methylene chloride–hexane to give 171 mg (25%) of **8**: mp 109–111°; nmr ($CDCl_3$) δ 2.13 (s, 3, CH_3CO), 2.23 (s, 3, aromatic CH_3), 2.78, 3.20 (m, 4, J = 7 Hz, CH_2CH_2), 6.81, 7.54 (AX, 2, J_{para} = 1 Hz, aromatic), 9.93 (s, 1, CHO); mass spectrum *m/e* 206 (M^+), 163 (M − 43). *Anal.* Calcd for $C_{12}H_{14}O_3$ (206.23): C, 69.88; H, 6.84. Found: C, 69.61; H, 6.89.

Base Transformation of 5-Bromo Antibiotic X-537A (1b)[4] into 3,6-Dimethyl-2-hydroxy-1-naphthoic Acid (11).—To a solution of 1 g (1.5 mmol) of **1b** in 10 ml of dioxane was added 4 ml of 10% aqueous NaOH. The mixture was stirred for 20 hr at room temperature and then diluted with 20 ml of water and extracted with three 20-ml portions of ethyl acetate. Evaporation of the combined extracts to dryness gave a 75% yield of ketone **3**[1]. The aqueous phase was acidified with 1 *N* HCl and extracted with three 20-ml portions of ether. The combined extracts were evaporated to dryness and the resulting solid was chromatographed on 5 g of silica gel using a linear gradient between methylene chloride and 1:1 methylene chloride–ether. The first fraction eluted from the column was concentrated and crystallized from acetone–hexane to give 37 mg (11%) of **11**: mp 185°; nmr ($CDCl_3$) δ 2.35 (s, 3, aromatic CH_3), 2.41 (s, 3, aromatic CH_3), 7.28 (d of d, 1, J_{meta} = 2, J_{ortho} = 9 Hz, aromatic), 7.40 (d, 1, J_{meta} = 2 Hz, aromatic), 7.61 (s, 1, aromatic), 8.77 (d, 1, J_{ortho} = 9 Hz, aromatic); mass spectrum *m/e* 216 (M^+), 172 (M − CO_2). *Anal.* Calcd for $C_{13}H_{12}O_3$ (216.22): C, 72.20; H, 5.59. Found: C, 71.87; H, 5.41.

Pyrolytic Cleavage of 5-Bromo Antibiotic X-537A (1b)[4] under Reduced Pressure to 3,6-Dimethyl-2-naphthol[5] (9) and 4-Bromo-5,6-dihydro-2,7-dimethyl-1-naphthol (10).—Heating 2.0 g (3 mmol) of **1b** at 174° under reduced pressure (0.05 mm) gave an oily distillate which was dissolved in hexane and chromatographed on 130 g of silica gel using a gradient from 2 l. of hexane to 2 l. of methylene chloride. The first fraction was concentrated to dryness and vacuum distilled at 170° (0.05 mm) to give 75 mg (10%) of **10**: mp 91–92°; nmr ($CDCl_3$) δ 1.93

(7) The ultraviolet spectra were obtained with a Cary Model 14M recording spectrometer. Nuclear magnetic resonance spectra were obtained with a Varian Associates Model A-60 or HA-100 spectrophotometer. Chemical shifts are reported in δ units with the following abbreviations: s, singlet; d, doublet; m, multiplet. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter at 25°. The mass spectra were taken with a CEC-21-110 mass spectrometer at 70 eV.

(s, 3, CH_3C=), 2.14 (s, 3, aromatic CH_3), 2.1, 2.8 (m, 4, J = 7 Hz, CH_2CH_2), 6.39 (s, 1, CH=C), 7.07 (s, 1, aromatic); mass spectrum m/e 252 (M^+). *Anal.* Calcd for $C_{12}H_{13}BrO$ (253.14): C, 56.93; H, 5.18; Br, 31.57. Found: C, 57.19; H, 5.28; Br, 31.68.

The second fraction gave on concentration to dryness and vacuum distillation at 120° (0.05 mm) 36 mg (7%) of **9**: mp 159–162°; nmr ($CDCl_3$) δ 2.37 (s, 3, aromatic CH_3), 2.42 (s, 3, aromatic CH_3), 7.00 (s, 1, aromatic), 7.17 (d of d, J_{meta} = 2, J_{ortho} = 8 Hz, aromatic), 7.45 (d, 1, J_{meta} = 2 Hz, aromatic), 7.51 (d, 1, J_{ortho} = 8 Hz, aromatic); mass spectrum m/e 172 (M^+). *Anal.* Calcd for $C_{12}H_{12}O$ (172.22): C, 83.69; H, 7.02. Found: C, 83.37; H, 6.95.

The third fraction gave on evaporation a 100% yield of ketone **3**.[1]

Oxidation of Ketone 3 to 2-Ethyl-4-methyl-2-(1,4-dioxo-1-hexyl)-5-(4-oxo-3-hexyl)tetrahydrofuran (12) and 2-Ethyl-4-methyl-2-(1-acetoxy-4-oxohexyl)-5-(4-oxo-3-hexyl)tetrahydrofuran (13).—To a solution of 9.16 g (27 mmol) of ketone **3** in 150 ml of acetone was added 25 ml of Jones reagent[6] over 1 hr at room temperature. After a further 16 hr, the reaction solution was diluted with 500 ml of water and extracted with three 500-ml portions of methylene chloride. The pooled extract was washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated under reduced pressure to 8.6 g of an oil. The oil was chromatographed on 400 g of silica gel using a gradient from 1 l. of 1:1 methylene chloride–hexane to 1 l. of methylene chloride followed by a second gradient from 4 l. of methylene chloride to 4 l. of 2:3 methylene chloride–ether. A fraction eluted after 4 l. of solvent had passed through the column gave on evaporation 1.38 g (16%) of **12**: $[\alpha]_D$ −12.6° (c 1, CH_3OH); ir ($CHCl_3$) 1720 cm^{-1} (CO); uv max (2-propanol) 285 nm (ε 127); mass spectrum m/e 323 (M − 1), 309 (M − CH_3), 295 (M − C_2H_5), 211 (M − 113); nmr ($CDCl_3$) δ 2.50 (m, 8, 4 CH_2CO), 3.60 (m, 1, CHOC). *Anal.* Calcd for $C_{19}H_{32}O_4$ (324.45): C, 70.33; H, 9.94. Found: C, 70.11; H, 9.65.

Immediately following **12**, a second fraction was eluted which on evaporation gave 3.83 g (37%) of **13**: $[\alpha]_D$ +20° (c 1, CH_3OH); ir ($CHCl_3$) 1715 (ketone), 1730 cm^{-1} (ester); uv max (2-propanol) 281 nm (ε 80); mass spectrum m/e 368 (M^+), 339 (M − C_2H_5), 308 (M − $C_2H_4O_2$), 211 (M − 157); nmr ($CDCl_3$) δ 2.05 (s, 3, CH_3CO), 3.49 (m, 1, CHOC), 4.97 (d of d, 1, $CH_2CHOCOCH_3$, J = 4, 9.5 Hz). *Anal.* Calcd for $C_{21}H_{36}O_5$ (368.50): C, 68.44; H, 9.85. Found: C, 68.73; H, 9.65.

Preparation of 2-Ethyl-4-methyl-2-(1-hydroxy-4-oxo-1-hexyl)-5-(4-oxo-3-hexyl)tetrahydrofuran (14).—To a solution of 1.41 g (3.8 mmol) of acetoxy acetone **13** in 25 ml of methanol was added 19 ml of 10% aqueous NaOH. The reaction mixture was stirred for 18 hr at room temperature and then diluted with 50 ml of water and extracted with three 50-ml portions of ethyl acetate. The extracts were combined, dried (Na_2SO_4), and evaporated to an oil. Distillation of the oil gave 1.2 g (96%) of **14**: bp 170° (0.05 mm); $[\alpha]_D$ +18° (c 1, CH_3OH); ir ($CHCl_3$) 1715 (ketone), 3630 cm^{-1} (OH); uv max (2-propanol) 278 nm (ε 102); mass spectrum m/e 326 (M^+), 308 (M − H_2O), 211 (M − 115); nmr ($CDCl_3$) δ 3.55 (m, 1, CHOC), *no* $CHOCOCH_3$. *Anal.* Calcd for $C_{19}H_{34}O_4$ (326.46): C, 69.90; H, 10.50. Found: C, 69.64; H, 10.52.

Preparation of 2-Ethyl-4-methyl-2-(2-ethyl-2-hydroxycyclohex-5-enon-5-yl)-5-(4-oxo-3-hexyl)tetrahydrofuran (16).—To a solution of 484 mg (1.37 mmol) of ketone **3** in 25 ml of acetone was added 1.8 ml of Jones reagent[6] over 1 hr at room temperature. After a further 16 hr, the reaction was diluted with 100 ml of water and extracted with three 100-ml portions of methylene chloride. The extracts were pooled, washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated under reduced pressure to 450 mg of an oil. Without further purification the oil was dissolved in 10 ml of methanol and hydrolyzed using 5 ml of 10% aqueous NaOH. After 18 hr at room temperature the reaction was acidified with 1 N HCl and extracted with methylene chloride to give 378 mg of oily product. This product was then chromatographed on 150 g of silica gel using a gradient from 2 l. of methylene chloride to 2 l. of 9:1 methylene chloride–ether. After 2.7 l. of solvent had passed through the column, a uv-absorbing fraction was collected. Evaporation under reduced pressure gave 112 mg (23%) of **16** as a colorless oil: ir ($CHCl_3$) 1670 (C=CCO), 1710 cm^{-1} (CO); uv max (CH_3OH) 238 nm (ε 10,950); nmr ($CDCl_3$) δ 3.58 (m, 1, CHOC), 3.63 (s, 1, OH), 6.14 (s, 1, C=CHCO); mass spectrum m/e 350 (M^+), 335 (M − CH_3), 332 (M − H_2O), 321 (M − C_2H_5), 211 (M − 139). *Anal.* Calcd for $C_{21}H_{34}O_4$ (350.48): C, 71.96; H, 9.78. Found: C, 72.22; H, 9.84.

Acknowledgment.—We are indebted to the Physical Chemistry Department, Hoffmann-La Roche Inc., Nutley, N. J., under the supervision of Dr. R. P. W. Scott, for the analytical and spectral data.

Registry No.—**1a**, 25999-31-9; **1b**, 38784-08-6; **3**, 31478-26-9; **5**, 40919-48-0; **6**, 40919-49-1; **8**, 40919-50-4; **9**, 40919-51-5; **10**, 40919-52-6; **11**, 40919-53-7; **12**, 40919-54-8; **13**, 40919-55-9; **13**, 40919-55-9; **14**, 40919-56-0; **16**, 40919-57-1.

Synthesis of 2,4,6-Triphenyl-1,4-oxazine

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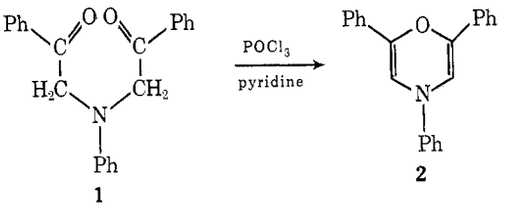
Received January 16, 1973

Although monocyclic 1,4-oxazines are known, only those with an oxygen or nitrogen substituent on the oxazine ring have been prepared.[1] In pursuing studies on the reactions of diphenacylaniline (**1**), the synthesis of a relatively stable, simply substituted oxazine was visualized. Thus, reaction of diphenacylaniline with an excess of $POCl_3$ in pyridine resulted in the formation of a red, crystalline compound with the proposed structure, 2,4,6-triphenyl-1,4-oxazine (**2**).



1 **2**

The oxazine formation can be explained easily by postulating a hemiketal intermediate which undergoes dehydration.

The structure of **2** is based on its analysis, spectral data, and chemical properties. The ir and nmr spectra are particularly informative. In addition to the usual aromatic absorption in the infrared, compound **2** has an intense peak at 1640 cm^{-1}, consistent with the vinyl ether–enamine structure.[2] The nmr spectrum provides additional evidence: a two-proton singlet at δ 6.44 (olefinic hydrogens); a one-proton multiplet centered at δ 6.83 (para hydrogen on aniline moiety); a two-proton multiplet centered at δ 6.95 (ortho hydrogens on aniline moiety); and a 12-proton multiplet centered at δ 7.30 (aromatic hydrogens). The uv spectrum, with absorption at 238 and 348 nm and a weak band at 440 nm, indicates some interaction of the oxazine double bonds with the attached aromatic rings.

The synthesis of **2** proceeded in good yield to give a moderately pure compound, but removal of a remaining impurity, which may be a decomposition prod-

(1) *Cf.*, *e.g.*, G. T. Newbold, F. S. Spring, and W. Sweeny, *J. Chem. Soc.*, 909 (1950); W. Paterson and G. R. Proctor, *Chem. Ind. (London)*, 254 (1961).

(2) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 41.