

Table IV—Analysis of Methocarbamol–Aspirin and Chlorzoxazone–Acetaminophen in Known Mixtures

Mixture	Components	Amount Added, mg	Amount Found ^a , mg	Accuracy, %
A	Methocarbamol	8.00 ^b	8.19 ± 0.12 ^c	2.38
	Aspirin	6.50	6.67 ± 0.13	2.62
B	Acetaminophen	3.00 ^d	3.08 ± 0.08 ^c	2.67
	Chlorzoxazone	2.51	2.59 ± 0.05	3.19

^a Based on four replicate determinations of the known mixture. ^b Total mg/25 ml of solution. ^c Confidence limits at $p = 0.05$. ^d Total mg/5 ml of solution.

data contained in Table I⁹. Simulated dosage form mixtures containing methocarbamol–aspirin¹⁰ and chlorzoxazone–acetaminophen¹¹ were selected for quantitation to exemplify this situation with Solvents I and B, respectively. Both solvent systems allowed good overall resolution with reasonable retention times.

Typical chromatograms of the drug mixtures are shown in Figs. 2 and 4. Various concentrations of stock solutions of each drug dissolved in the appropriate mobile phase (see *Experimental*) were chromatographed using the octadecylsilane column. Phenacetin was added to each solution as the internal standard. The area under the curve for each peak on the chromatograms was determined with an electronic integrator. The ratio of each drug peak area to the area of the internal standard was calculated for each chromatogram. Regression analysis of these data at the various concentrations of each drug gave the slope, intercept, and correlation coefficient for each calibration curve (Tables II and III).

Solutions containing known quantities of methocarbamol–aspirin and/or chlorzoxazone–acetaminophen in ratios equivalent to those found in the commercial dosage forms were chromatographed, and the ratios

⁹ It is possible to calculate the approximate resolution, R_s , of two components by the equation $R_s = 2(t_2 - t_1)/(w_1 + w_2)$, where t_1 and t_2 are retention times and w_1 and w_2 are base peak widths of Compounds 1 and 2, respectively. In past experience, two components with an R_s value > 1.50 showed satisfactory resolution for quantification by this analytical technique if the peak areas were approximately equal. A significant difference in peak areas for two components may require an R_s value of 2 or greater.

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¹¹ Parafon-Forte, McNeil Laboratories, Fort Washington, Pa.

of drug peak areas to internal standard peak areas (D/IS) were calculated for each drug. The slope and intercept data from the regression analysis for each drug (Tables II and III) were used to solve for drug concentration [$D/IS = (\text{slope} \times \text{concentration}) + \text{intercept}$]¹² in these simulated dosage form mixtures.

The data in Table IV demonstrate the quantitative results obtained for the mixtures. The utility of HPLC in the analysis of methocarbamol–aspirin and chlorzoxazone–acetaminophen mixtures is clearly demonstrated with accuracy in the 2–3% range.

REFERENCES

- (1) I. L. Honigberg, J. T. Stewart, and M. Smith, *J. Pharm. Sci.*, **67**, 675 (1978).
- (2) J. T. Stewart, I. L. Honigberg, J. P. Brant, W. A. Murray, J. L. Webb, and J. B. Smith, *ibid.*, **65**, 1536 (1976).
- (3) S. J. Saxena, J. T. Stewart, I. L. Honigberg, J. G. Washington, and G. R. Keene, *ibid.*, **66**, 813 (1977).
- (4) G. Schill, K. O. Borg, R. Modin, and B. A. Persson, in "Handbook of Derivatives for Chromatography," K. Blau and G. S. King, Eds., Heyden and Sons, London, England, 1977, pp. 500–529.
- (5) K. G. Wahlund, *J. Chromatogr.*, **115**, 411 (1975).
- (6) K. G. Wahlund and U. Lund, *ibid.*, **122**, 269 (1976).
- (7) B. L. Karger and B. A. Persson, *J. Chromatogr. Sci.*, **12**, 521 (1974).
- (8) B. L. Karger, S. C. Su, S. Marchese, and B. A. Persson, *ibid.*, **12**, 678 (1974).
- (9) D. P. Wittmer, N. O. Nuessle, and W. G. Haney, *Anal. Chem.*, **47**, 1422 (1975).
- (10) B. L. Karger, L. R. Snyder, and C. Horvath, "An Introduction to Separation Science," Wiley, New York, N.Y., 1973, pp. 146–150.

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Formation of a Thio Analog of Noracronine

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Abstract □ Acronine was heated with tetraphosphorus decasulfide in benzene to give a mixture of products, the major component (A) being identified tentatively as an unstable product derived from four molecules of noracronine with one molecule of tetraphosphorus decasulfide. Treatment of Compound A with various solvents and heat converted it into a maroon solid (B), which was shown to be 7-thionoracronine.

Keyphrases □ 7-Thionoracronine—synthesized from acronine and tetraphosphorus decasulfide □ Noracronine thio analog—7-thionoracronine synthesized from acronine and tetraphosphorus decasulfide □ Prodrugs, potential—7-thionoracronine synthesized from acronine and tetraphosphorus decasulfide

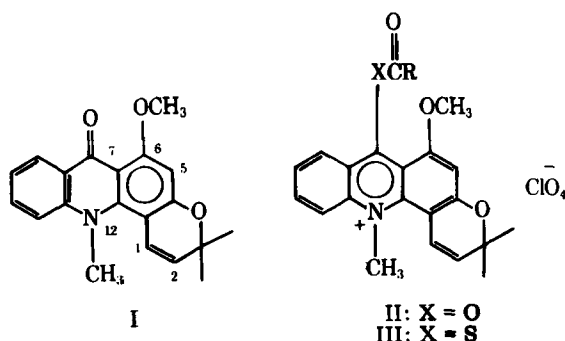
The alkaloid acronine¹ (I) has a wide spectrum of anti-cancer activity (1) but the disadvantage of low aqueous

solubility. Various attempts have been made (2) to improve the formulation of I, including the preparation of molecular complexes of the alkaloid with povidone and gentisic acid. A prodrug (II) that regenerates acronine quantitatively and shows improved water solubility was prepared but suffers from the disadvantage of being hydrolyzed too rapidly under physiological conditions (3). Reaction of II with aniline gave a rapid quantitative yield of anil², and the hydrolysis rates were similar for a series of analogs of II in which the acetyl group was replaced by other acyl functions (2).

Recent studies revealed that hydrolysis in water of II

¹ Previously referred to as acronine (NSC 403169).

² B. Kreilgard, Royal Danish School of Pharmacy, Copenhagen, Denmark, unpublished data.



proceeded by aryl-oxygen cleavage to the extent of about 30% (4). It was considered that molecular modification of II to give the thioesters (III) would enhance the propensity for acyl-sulfur fission since the carbon-sulfur bond would be less susceptible to rupture than the carbon-oxygen bond of II. If this theory is validated in practice, variation in the nature of the thioester function would permit controlled alteration in the hydrolysis rate of III to thioacronine, which could undergo biotransformation to acronine. Such replacement of sulfur by oxygen in drug molecules is well established (5, 6).

DISCUSSION

A synthetic route to produce III (R = CH₃) involved the conversion of acronine to 7-thioacronine (IV), followed by treatment with perchloric acid and acylation with acetic anhydride. Various synthetic procedures are available for converting oxo derivatives to the corresponding thio analogs, including the use of tetraphosphorus decasulfide (P₄S₁₀) in several organic solvents (7, 8). Reaction of acronine with tetraphosphorus decasulfide gave a maroon solid; TLC showed that the principal component (A) was present to an extent of 64%. Preparative TLC led to the isolation of small quantities of Compound A, which was unstable to both heat and solvents, invariably breaking down to Compound B, which appeared to be stable. Mass spectrometry of both A and B showed molecular ions at 323 mass units.

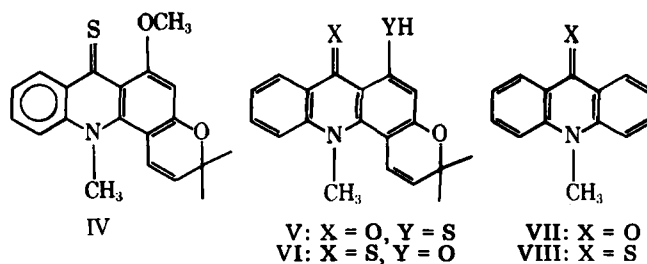
The structure of the stable compound (B), which was formed by heating the crude reaction product between acronine and tetraphosphorus decasulfide in methanol, was investigated since knowledge of its structure might elucidate the nature of Compound A. Elemental analysis of B revealed the presence of carbon, hydrogen, nitrogen, oxygen, and sulfur. Since the molecular weight of 323 was found by mass spectrometry, an elemental formula for B of C₁₉H₁₇NO₂S was suggested; i.e., in comparison to acronine (C₂₀H₁₉NO₃), a methylene group appears to have been lost and one of the oxygen atoms replaced by sulfur.

Two possibilities for the structure of B would be replacement of the 6-methoxy group by sulfur to give V and, alternatively, replacement of the 7-oxo function by sulfur during or subsequent to *O*-demethylation to give VI. It is well established that acronine undergoes *O*-demethylation in the presence of heat and acid (9, 10), and Compound B gave a black color with alcoholic ferric chloride solution.

Electronic absorption spectroscopy was considered a useful tool to differentiate between V and VI since thioketones absorb at much longer wavelengths than the analogous ketones (11) and, with thiophenols and phenols, the long wavelength absorptions differ by less than 15 nm (12). The model Compounds VII and VIII were prepared, and the long wavelength absorptions of the thio VIII were greater than VII by 91 nm (Table I). Thus, if Compound B had Structure V, it would be expected to absorb

Table I—Long Wavelength Electronic Absorptions of VII, VIII, I, IX, and B

Compound	λ_{max} , nm (ϵ)
VII	400 (8555)
VIII	491 (32,750)
I	390 (6820)
IX	410 (5030)
B	490 (5610)

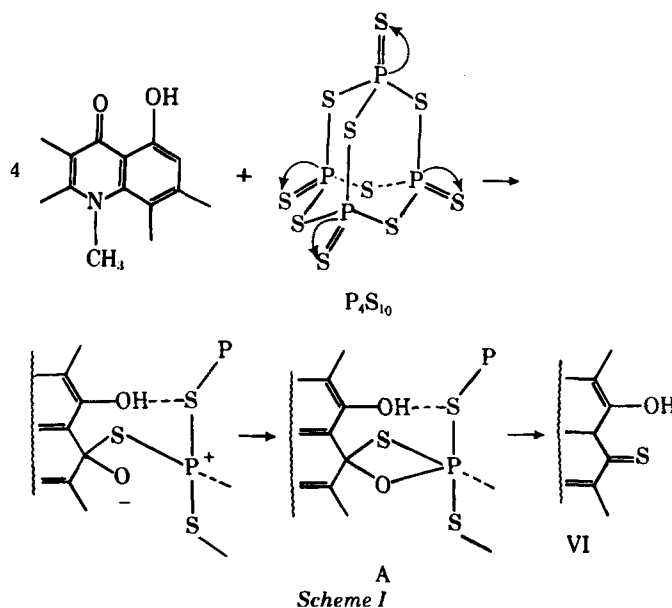


at similar wavelengths to 6-noraacronine (IX), whose preparation was described previously (9, 10); VI would be predicted to exhibit an absorption maximum at approximately 90 nm greater than that of noraacronine.

The visible spectrum of B showed a long wavelength absorption at 80 nm higher than noraacronine and at virtually the same wavelength as 10-methyl-9-thioacridone (VIII). The virtual insolubility of B in organic solvents and water prevented its examination by both PMR spectroscopy and pKa determinations and, although positions for IR C=S absorptions were quoted (13, 14), it also was concluded (15) that meaningful assignments cannot be made. Thus, on the basis of elemental analysis, electronic absorption spectroscopy, and mass spectrometry, it appears that B may be best represented as the thioketone VI.

The question arises as to the nature of the unstable purple component (A) isolated in the initial reaction between acronine and tetraphosphorus decasulfide. Elemental analysis revealed the presence of carbon, hydrogen, oxygen, nitrogen, sulfur, and phosphorus. While the instability of the molecule precludes a dogmatic assertion of its identity, a molecular formula of C₇₆H₆₈N₄O₁₂P₄S₁₀, corresponding to an organophosphorus complex of four molecules of noraacronine with one molecule of tetraphosphorus decasulfide, appears feasible. Such a complex could be formed after initial *O*-demethylation of the 6-methoxy group of acronine to produce noraacronine (IX), which could react with each sulfur atom of the P=S linkage of tetraphosphorus decasulfide, whose molecular architecture is clearly documented (16) (Scheme I).

Although such organophosphorus intermediates are unstable and rarely isolated, hydrogen bonding between the 6-hydroxy group of noraacronine and the nearby sulfur atoms may stabilize the intermediate. Such a structure as A resembles trithianes, which are decomposed by heat to yield the monomeric thiones (17); hence, A could break down to B in the presence of heat or solvent. Finally, reaction of noraacronine with tetraphosphorus decasulfide yielded the purple Compound A, which strengthens further the hypothesis that a 6-hydroxy group is present in A.



³ Reaction of only one molecule of noraacronine with tetraphosphorus decasulfide is shown. It is postulated that one molecule of IX reacts with each of the four P=S bonds of tetraphosphorus decasulfide.

Other attempts were made to produce 7-thioacronine (IV) through reaction of 7-acetylacroninium perchlorate with sodium hydrogen sulfide and the thioacetate ion in aqueous solution. In these cases, it was anticipated that the sulfur nucleophile would displace the acetate group (4) of II. Only B was obtained from these reactions, indicating the lability of the 6-methoxy group of the precursor ester.

Alternative synthetic pathways to the desired thio analog of acronine apparently are required to avoid the demethylation of the 6-methoxy group of acronine and/or the acroninium esters.

EXPERIMENTAL⁴

Melting points are uncorrected. Solvents were dried initially over anhydrous magnesium sulfate and then stored over drying granules⁵. IR spectra⁶ were determined as potassium bromide disks, the instrument being previously calibrated with polystyrene. NMR spectra⁷ were run in deuteriochloroform or trifluoroacetic acid, and tetramethylsilane was used as the internal and external standard. Electronic absorption spectra⁸ were determined by dissolving the compound in dimethylacetamide (1 ml) and diluting the solution to 100 ml with methylene chloride; further dilutions with methylene chloride were undertaken when required.

TLC was conducted on silica gel plastic sheets⁹, 0.25 mm thick; where appropriate, quantitative estimations¹⁰ of the chromatograms were made. Preparative TLC employed 2-mm silica gel plates¹¹. Acronine¹² had λ_{max} 390 nm (ϵ 6820) and R_f 0.28 on silica gel with benzene-acetone (2:1) as the developing solvent.

Reaction of Acronine with Tetraphosphorus Decasulfide—A mixture of acronine (0.5975 g, 0.001861 mole) and tetraphosphorus decasulfide (0.6 g, 0.002703 mole) in dry benzene (18 ml) was heated under reflux with stirring for 2 hr. The mixture was decanted while hot, leaving a maroon solid. This material was removed from the reaction vessel, dried in a vacuum desiccator, and weighed (0.9363 g). TLC on silica gel plastic sheets using benzene-acetone (2:1) revealed the presence of compounds at R_f 0, 0.026, 0.073, 0.28, and 0.59. When viewed under long wavelength UV light, an additional spot, R_f 0.36, became apparent.

Under these conditions, acronine has an R_f value of 0.31 and fluoresces under long wavelength UV light; no acronine was detected in this experiment. Quantitation of the chromatogram indicated that the purple component (A), R_f 0.28, was present to the extent of 64%. When the reaction was carried out in the presence of carbon dioxide, A represented 44% of the mixture.

A small quantity of the crude reaction mixture (0.15 g) was triturated rapidly with chloroform-methanol (9:1), placed on two preparative silica gel plates, and chromatographed with benzene-acetone (2:1). The purple layer was removed and extracted several times with methylene chloride, and the organic extract was dried (anhydrous sodium sulfate). Removal of the solvent *in vacuo* at room temperature yielded A as purple crystals (0.010 g), and TLC showed one component; mass spectrum: parent ion m/e : 323.09658 (calc. for $\text{C}_{19}\text{H}_{17}\text{NO}_2\text{S}$: 323.09790).

Anal.—Calc. for $\text{C}_{19}\text{H}_{17}\text{NO}_2\text{S}$: C, 54.23; H, 4.10; N, 3.35; P, 7.40; S, 19.16. Found: C, 57.73; H, 6.39; N, 2.46; P, 6.64; S, 17.72.

The stability of Compound A was investigated. A small quantity of the crude reaction product was chromatographed on silica gel, and the purple layer containing A was removed. Approximately equal quantities of silica gel containing A were placed in stoppered containers and triturated with the following solvents: benzene, acetone, chloroform, methylene chloride, chloroform-methanol (9:1 v/v), pyridine, and methanol. After 20 min, a small quantity of the slurry was placed on a silica gel plastic sheet and chromatographed with benzene-acetone (2:1). An orange spot, R_f 0.54, was found in the pyridine solution while the methanol extract showed the presence of the major component at the point of application. The

remaining solutions showed the presence of only Compound A.

After 3 days, chromatograms of each solution showed the presence of an orange spot, R_f 0.59; in solutions of benzene and pyridine, no other compounds were seen. In another experiment, small quantities of A were placed in each of six stoppered containers. Three vials were stored at room temperature, 4°, and -17°; one was stored at room temperature under nitrogen; and another vial was stored at room temperature protected from light. In each case, TLC on the following day showed only A; a sixth sample, heated to 70° overnight, gave an orange spot, R_f 0.57, as the major component.

Preparation of 7-Thionoracronine (VI)—The crude mixture (4.9946 g) obtained by reacting acronine with tetraphosphorus decasulfide was heated under reflux with methanol (50 ml) for 37 min, and the hot mixture was filtered. The maroon residue obtained (0.7948 g), mp 193°, was recrystallized repeatedly from ethyl acetate to give VI (0.4046 g), mp 223° dec., as maroon prisms. An alcoholic solution of the compound gave a black color with alcoholic ferric chloride solution. High-resolution mass spectrometry indicated a molecular ion of 323.09572 (calc. for $\text{C}_{19}\text{H}_{17}\text{NO}_2\text{S}$: 323.09790); IR: 2270 w, 1630 s, and 1595 s cm^{-1} ; UV (λ_{max}): 490 (ϵ 5610) and 410 (18,100) nm.

Anal.—Calc. for $\text{C}_{19}\text{H}_{17}\text{NO}_2\text{S}$: C, 70.57; H, 5.29; N, 4.33; O, 9.90; S, 9.90. Found: C, 70.24; H, 5.32; N, 4.03; O, 10.10; S, 9.81.

Preparation of Noracronine—Acronine hydrochloride, prepared from 5.0 g of acronine, was heated at 145–174° for 94 min (9, 10) to give a gold-yellow mass, mp 118.5–194° (4.23 g), shown by quantitative TLC to consist of noracronine (79%) and acronine (21%). Four recrystallizations from ethanol gave pure noracronine (1.42 g, 30%), mp 200° [lit. (10) mp 198–200°], as pale-orange crystals; NMR (deuteriochloroform): δ 1.54 [s, 6H, 3-(CH₃)₂], 3.89 [s, 3H, N(CH₃)₂], 5.51 (d, J = 5 Hz, 1H, 2-H), 6.28 (s, 1H, 5-H), 6.57 (d, J = 5 Hz, 1H, 1-H), 7.12–8.50 (m, 4H, H at C-8, C-9, C-10, and C-11), and 14.78 (s, 1H, 6-OH, exchanged with D₂O) ppm; UV (λ_{max}): 410 (ϵ 5030) nm.

Noracronine (0.15 g, 0.00049 mole) and tetraphosphorus decasulfide (0.15 g, 0.00068 mole) were heated together in dry benzene (55 ml) for 2 hr, and the hot mother liquid was decanted. The residue (0.2110 g) was dried in a desiccator. TLC showed a purple spot, R_f 0.44, as the major component and minor products at R_f 0.65 and 0.097, as well as some material at the point of application. Compounds VI and VIII, when chromatographed simultaneously, had R_f values of 0.61 and 0.59, respectively.

Preparation of 10-Methyl-9(10H)-acridone (VII)—Acridine (1.4677 g, 0.00820 mole) and dimethyl sulfate (4.00 g, 0.0317 mole) were heated together in dry benzene (15 ml) for 70 min, and the deposited yellow crystals were removed by filtration to give 10-methylacridinium methylsulfate (2.1 g), mp 214–215° dec. The methylsulfate was oxidized with potassium ferricyanide in potassium hydroxide solution, using the reported method for the preparation of 1,3-dimethoxy-10-methylacridone from the corresponding methylsulfate (18), to give a light-brown crystalline mass, which was shaken with chloroform and water. The chloroform extract was separated, washed with water, and dried (anhydrous magnesium sulfate). Evaporation of the solvent gave yellow crystals, which were recrystallized from methanol to yield VII (50%), mp 202–202.5° [lit. (19) mp 202°]; UV (λ_{max}): 400 (ϵ 11,750) and 380 (8555) nm.

Preparation of 10-Methyl-9(10H)-thioacridone (VIII)—10-Methyl-9-chloroacridinium dichlorophosphate, prepared from VII (11.00 g) by a reported method (20), was added to a stirred solution of sodium hydrogen sulfide dihydrate (4.27 g) in ethanol (119 ml). After stirring at room temperature for 1 hr, the precipitate was collected by filtration, washed repeatedly with water to remove unreacted sodium hydrogen sulfide dihydrate, and dried to give deep-red needles (11.64 g). Eight recrystallizations from dry xylene gave VIII (2.68 g, 23%), mp 265.5–267° [lit. (21) mp 263°]; UV (λ_{max}): 491 (ϵ 32,750) and 461 (17,960) nm.

Reaction of Acetylacroninium Perchlorate with Sodium Hydrogen Sulfide and Thioacetic Acid—A solution of sodium hydrogen sulfide dihydrate (0.04 g, 0.00043 mole) in water (10 ml) was added to a stirring solution of acetylacroninium perchlorate (0.0261 g, 0.000056 mole) in water (100 ml). After the mixture had stirred at room temperature for 1 hr, the precipitate was collected and dried at room temperature in a desiccator. TLC indicated the presence of four compounds with R_f values of 0.014, 0.070, and 0.34 and an orange spot with a value of 0.65. Another spot, R_f 0.52, was visible under short wavelength UV light. TLC of the acetylacroninium perchlorate sample indicated components with similar R_f values and color corresponding to the spots with the three lowest R_f values of the compound isolated in the reaction.

Increasing the molar ratio of sodium hydrogen sulfide dihydrate and acetylacroninium perchlorate to 11:1 gave a product with similar TLC

⁴ Elemental analyses were carried out by Mr. T. N. Nguyen, Department of Medicinal Chemistry, College of Pharmacy, University of Kansas, Lawrence, KS 66044, Schwarzkopf Microanalytical Laboratories, Woodside, NY 11377, and Mr. R. G. Teed, Department of Chemistry and Chemical Engineering, University of Saskatchewan, Saskatoon, Saskatchewan, Canada. Mass spectra were determined by Mr. R. Drake, Department of Chemistry, University of Kansas, Lawrence, KS 66044, on a CH-5 instrument (Varian Associates, Chicago, IL 60670).

⁵ Linde molecular sieve, type 4A, Union Carbide Corp., Chicago, IL 60638.

⁶ Beckman AccuLab 4, Irvine, CA 92664.

⁷ T-60 spectrometer, Varian Associates, Chicago, IL 60670.

⁸ Cary 15 spectrophotometer, Varian Associates, Chicago, IL 60670.

⁹ Polygram, Brinkmann Instruments, Westbury, NY 11590.

¹⁰ TLC densitometer (Kontes, Vineland, NJ 08360) attached to a potentiometric amplifier, dc offset module, and strip-chart recorder (Heath Co., Benton Harbor, MI 49022).

¹¹ Silica gel 60, F-254 TLC plates, Brinkmann Instruments, Des Plaines, IL 60016.

¹² Obtained from the National Cancer Institute, Bethesda, MD 20014.

characteristics as in the previous experiment, although the intensity of the orange compound was increased.

A solution of sodium hydrogen sulfide dihydrate (0.3146 g, 0.0034 mole) in propylene glycol (3.7 ml) and a solution of acetylacroninium perchlorate (0.0110 g, 0.000034 mole) in propylene glycol (4.7 ml) were stirred at room temperature for 1 hr. The resultant viscous, orange solution was poured into water (20 ml), and the yellow precipitate was collected and dried. TLC showed a yellow component (with similar R_f value and fluorescence properties as acronine) and an orange component, R_f 0.70, as the major product.

In a further experiment, acetylacroninium perchlorate (0.0245 g, 0.0000528 mole) was added to a stirred solution of thioacetic acid (0.4296 g, 0.00565 mole) and sodium hydroxide (0.20 g, 0.005 mole) in water (100 ml). After stirring at room temperature for 1 hr, the precipitate was collected and dried. TLC showed a yellow spot, R_f 0.39, fluorescing under UV light and an orange component, R_f 0.68, in major amount.

REFERENCES

- (1) G. H. Svoboda, G. A. Poore, P. J. Simpson, and G. B. Bodor, *J. Pharm. Sci.*, **55**, 758 (1966).
- (2) A. J. Repta, in "Prodrugs as Novel Drug Delivery Systems," T. Higuchi and V. Stella, Eds., American Chemical Society, Washington, D.C., 1975, p. 196.
- (3) D. W. A. Bourne, T. Higuchi, and A. J. Repta, *J. Pharm. Sci.*, **66**, 628 (1977).
- (4) A. J. Repta, J. R. Dimmock, B. Kreilgard, and J. J. Kaminski, *ibid.*, **66**, 1501 (1977).
- (5) "The Pharmacological Basis of Therapeutics," 3rd ed., L. S. Goodman and A. Gilman, Eds., Macmillan, New York, N.Y., 1965, p. 120.
- (6) A. Albert, "Selective Toxicity," 3rd ed., Wiley, New York, N.Y., 1965, p. 281.
- (7) H. de Diesbach and H. Kramer, *Helv. Chim. Acta*, **28**, 1399 (1945).
- (8) W. Baker, J. B. Harborne, and W. D. Ollis, *J. Chem. Soc.*, **1952**, 1303.

- (9) R. D. Brown, L. J. Drummond, F. N. Lahey, and W. C. Thomas, *Aust. J. Sci. Res.*, **A2**, 622 (1949).
- (10) T. R. Govindachari, B. R. Pai, and P. S. Subramanian, *Tetrahedron*, **22**, 3245 (1966).
- (11) H. H. Jaffe and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, N.Y., 1962, p. 182.
- (12) *Ibid.*, p. 477.
- (13) K. Nakanishi, "Infrared Absorption Spectroscopy—Practical," Holden-Day, San Francisco, Calif., 1962, p. 54.
- (14) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed., Wiley, New York, N.Y., 1967, p. 76.
- (15) L. J. Bellamy, "The Infra-Red Spectra of Complex Molecules," Wiley, New York, N.Y., 1954, p. 293, and references cited therein.
- (16) R. B. Heslop and K. Jones, "Inorganic Chemistry and a Guide to Advanced Study," Elsevier, Amsterdam, The Netherlands, 1976, p. 444.
- (17) E. Campaigne, in "The Chemistry of Carbonyl Compounds," S. Patai, Ed., Interscience, London, England, 1966, p. 931, and references cited therein.
- (18) G. K. Hughes and E. Ritchie, *Aust. J. Sci. Res.*, **A2**, 423 (1949).
- (19) K. D. Legg and D. M. Hercules, *J. Am. Chem. Soc.*, **91**, 1902 (1969).
- (20) A. Albert, "The Acridines," Edward Arnold, London, England, 1951, p. 228.
- (21) K. Gleu and S. Nitzsche, *J. Prakt. Chem.*, **153**, 225 (1939).

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Molecular Connectivity Study of Halocarbon Anesthetics

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Abstract □ The structure-activity relationships of 45 halogenated hydrocarbons using molecular connectivity were studied. A very good correlation was obtained between the anesthetic activity and the molecular connectivity term $^0\chi^v$ in addition to the polar hydrogen factor, Q_H . The equation reported accounts for and quantifies the known structure-activity observations on general anesthetics. The results are discussed briefly with reference to the mechanisms of action of general anesthetics.

Keyphrases □ Molecular connectivity indexes—related to anesthetic activity of various halogenated hydrocarbons □ Halogenated hydrocarbons, various—molecular connectivity indexes related to anesthetic activity □ Anesthetic activity—various halogenated hydrocarbons, related to molecular connectivity indexes □ Structure-activity relationships—molecular connectivity indexes related to anesthetic activity of various halogenated hydrocarbons □ Topological indexes—molecular connectivity, related to anesthetic activity of various halogenated hydrocarbons

To derive information about the mechanism of action of anesthetic gases, some investigators attempted to relate potency to physicochemical properties, including boiling points, solubilities, partition coefficients, molar volumes, molar refractions, and van der Waals equation constants. The finding of a significant correlation indicated that mechanisms of action parallel the physicochemical property.

These property studies (1) did not give any direct insight into the structural features influencing potency. The first real effort to gain such insight used a calculation of molecular structure known as molecular connectivity (2). That study, on a diverse group of anesthetic gases, resulted in a good correlation between potency and a combination of a molecular connectivity index and an electronic charge description. The correlation ($r = 0.982$) was good enough