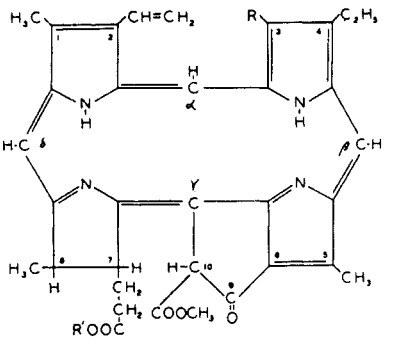
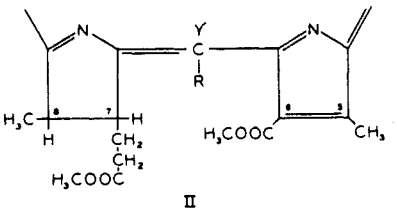


I



II

fraction can be regenerated if desired by making the aqueous extract about 6% with respect to hydrochloric acid and heating at 85° for 15 min. It can then be driven into fresh ether and esterified.

This method has been tried on several different mixtures of *a* and *b* derivatives, *e.g.*, chlorin p_6 trimethyl ester (II, R = $COOCH_3$ in the *a* series) and *b*-chlorin p_6 trimethyl ester (II, R = $COOCH_3$, with a formyl group at position 3); purpurin 7*a* trimethyl ester and purpurin 7*b* trimethyl ester (II, R = C(O)—$COOCH_3$, with a formyl group at position 3), and has been found capable of effecting complete separations. We have been unable to separate pheophytin *a* (I, R = CH_3; R′ = phytyl) from pheophytin *b* (I, R = CHO; R′ = phytyl) however, presumably because the phytol residue renders the *b*-Girard compound somewhat ether soluble. Also, in the case of the pheophorbides (I, R = CH_3 or CHO; R′ = H), we are not certain that they do not suffer some slight degree of oxidation and/or allomerization at the 10- position, when the reaction is carried out as described. Although chromatographic analysis[4] shows only one *a* and one *b* component, and the respective phase tests are still positive, these two criteria alone are not conclusive proof, and examination of the products of a hot quick saponification under nitrogen (modified after Willstätter) should supply definitive evidence. It was noted however, that if the reflux time was extended to 20 min., an additional *a* and *b* component appeared on the chromatogram. The visible spectra of these compounds were similar to the respective pheophorbides, but they both gave a negative phase test.

The chlorophyll derivatives in the foregoing discussion were prepared according to Fischer and his co-workers.[5] They were characterized by means of their hydrochloric acid number, visible and infrared spectra, solubility in buffers of appropriate *p*H, and chromatographic behavior.

Department of Physiology and Pharmacology
University of Nebraska College of Medicine
Omaha, Neb.

(4) M. J. Hendrickson, R. R. Berueffy, and A. R. McIntyre, *Anal. Chem.*, 29, 1810 (1957).

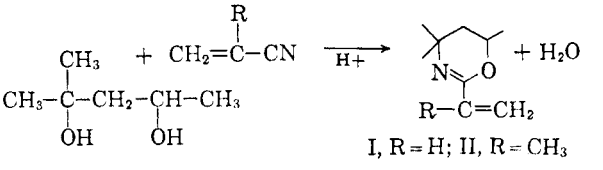
(5) H. Fischer and A. Stern, *Die Chemie des Pyrrols*, Hälfte 2, Bd. II, Akademische Verlagsgesellschaft, Leipzig, 1940.

2-Alkenyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazines

John W. Lynn

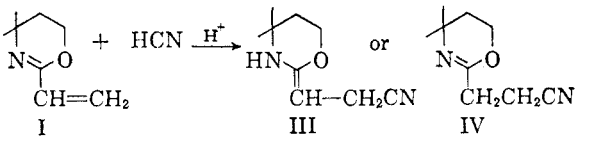
Received November 10, 1958

A novel polymerizable oxazine, 2-vinyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (I), was prepared by the reaction of acrylonitrile with 2-methyl-2,4-pentanediol in sulfuric acid; an extension of the general reaction described by Tillmanns and Ritter.[1] The 2-isopropenyl analog was also prepared by this reaction using methacrylonitrile. Similar 2-alkenyl-5,6-dihydro-1,3-oxazines may be prepared by the aluminum alkoxide catalyzed condensation of 1,3-alkanolamines with α,β-unsaturated esters.[2]



I, R = H; II, R = CH_3

The addition of hydrogen cyanide to I in refluxing acetic acid gave 2-(2′-cyanoethylidene)-4,4,6-trimethyltetrahydro-1,3-oxazine (III). The reaction of HCN could take place by 1,4- addition to give III, or by 3,4-addition to give IV. That III is the product (by direct 1,4- addition or by isomerization of initially formed IV) is clearly shown by the infrared spectrum. A sharp band at 3.00μ as well as absence of typical unconjugated C=N absorption at 6.25μ is in good agreement with structure III, and not at all in accord with IV.



I III IV

(1) E. Tillmanns and J. J. Ritter, *J. Org. Chem.*, 22, 839 (1957).

(2) P. L. de Benneville and L. S. Luskin, U. S. Patent 2,831,858, April 22, 1958

EXPERIMENTAL[3]

2-Vinyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (I). A solution of 500 g. (4.7 moles) of 92% sulfuric acid was stirred at 6–7° during the addition of 56 g. (1.05 moles) of acrylonitrile over a 5-hr. period. The mixture was stirred at 8–10° and 118 g. (1.0 mole) of 2-methyl-2,4-pentanediol was added over a 4-hr. period. The reaction mixture was poured over 1000 g. of ice, treated with 470 g. (4.7 moles) of 40% sodium hydroxide, and washed 3 times with 1/3 volumes of chloroform. The remaining aqueous layer was brought to *p*H 10 with additional 40% sodium hydroxide and extracted with diethyl ether. Distillation of the extract gave 72 g., a 47% yield, of I (b.p. 75°/24 mm.; n_D^{30} 1.4605; n_{20}^{20} 0.9192; infrared maxima: 3.24, 5.37 (=CH_2), 6.05 (C=N—), 6.22 (C=C conugated), 7.22, 7.33 (*gem*-dimethyl), 8.5μ α,β-unsaturated ether).

Anal. Calcd. for $C_9H_{15}NO$: C, 70.7; H, 9.81; N, 9.16. Found: C, 70.4; H, 9.8; N, 9.12.

Copolymer of I with vinylidene chloride. Vinylidene chloride and I in a 7 to 3 mole ratio were agitated in a sealed glass tube at 50° in the presence of 1% azo-bisisobutyronitrile catalyst for 6 hr. A greenish pliable solid polymer was obtained which contained 70.5% of I. The yield was 17%.

2-Isopropenyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (II). The procedure was the same as that used for the preparation of I. II was obtained in 53% yield (b.p. 79°/20 mm.; n_D^{30} 1.4585).

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.9; H, 10.18; N, 8.38. Found: C, 71.54; H, 10.03; N, 8.71.

2-(2'-Cyanoethylidene)-4,6,6-trimethyltetrahydro-1,3-oxazine (III). A solution of 153 g. (1.0 mole) of I, 200 cm.[3] of glacial acetic acid, 34 g. (1.25 moles) of hydrogen cyanide and 1 g. of 2,4-dinitrobenzene was refluxed for 1 hr. during which time the kettle temperature rose from 30° to 115°. Distillation gave a 45% yield of III (b.p. 87°/1.3 mm.; n_D^{30} 1.4542; infrared maxima: 3.00 (—NH—), 4.45 (—C≡N), 6.00 (—C=C—), 8.60 (—C=C—O—).

Anal. Calcd. for $C_{10}H_{16}N_2O$: C, 66.7; H, 8.80; N, 15.55. Found: C, 66.35; H, 8.60; N, 15.9.

Acknowledgment. The author is grateful to Mr. C. M. Lovell for infrared analyses and to Mr. Q. Quick for microanalyses.

RESEARCH DEPARTMENT
UNION CARBIDE CHEMICALS CO.
SOUTH CHARLESTON, W. VA.

(3) All boiling points are uncorrected.

Potential Carcinostatic Agents. Benzimidazole Derivatives

WILLIAM S. GUMP AND EDWARD J. NIKAWITZ

Received November 10, 1958

The need for larger amounts of 2-[bis(2-chloroethyl)aminomethyl]benzimidazole hydrochloride ("benzimidazole mustard")[1] for clinical trials and the intended synthesis of derivatives of this nitrogen mustard made it desirable to look for a more convenient method of preparation than the one previously employed by us[1] and other investigators.[2,3] We wished to eliminate the use of 2-chloromethylbenzimidazole or its hydrochloride as intermediates because these substances are very irritating and sensitizing on the skin and therefore difficult to handle. Substituted 2-chloromethylbenzimidazoles would be expected to have the same disadvantage.

Hughes and Lions[4] had shown that glycine could not be condensed with *o*-phenylenediamine in the presence of 4*N* hydrochloric acid at reflux temperature, according to Phillips' method.[5] Of substituted glycines in which the basicity of the amino group had been depressed by acylation, hippuric acid did not react, and phthalimidoacetic acid only poorly. We found, however, that *N,N*-bis(2-hydroxyethyl)-glycine and *o*-phenylenediamine, refluxed together in 4*N* hydrochloric acid solution, gave a fairly good yield of 2-[bis-(2-hydroxyethyl)aminomethyl]-benzimidazole dihydrochloride, the precursor of the benzimidazole mustard.

Similarly, the reaction of *N,N*-bis(2-hydroxyethyl)glycine with substituted *o*-phenylenediamines, such as 4-chloro-,4,5-dichloro and 4,5-dimethyl-1,2-phenylenediamine led to the desired substituted 2-[bis(2-hydroxyethyl)aminomethyl]benzimidazole dihydrochlorides which were converted into the corresponding bis(2-chloroethyl) compounds by means of thionyl chloride in the usual manner.

One of the benzimidazoles needed for testing, 1-methyl-2-[bis(2-chloroethyl)aminomethyl]benzimidazole hydrochloride, was prepared by the old method, starting from 1-methyl-2-chloromethylbenzimidazole hydrochloride. This substance which is irritating to the skin, but to a lesser degree than the unmethylated compound, was brought to reaction with diethanolamine. The resulting 1-methyl-2-[bis(2-hydroxyethyl)aminomethyl]benzimidazole was purified by means of its picrate and brought to reaction with thionyl chloride, yielding the "1-methylbenzimidazole mustard."

Preliminary studies[6] of the carcinostatic properties of the new compounds indicate that they are less effective against a number of experimental tumors in mice than the unsubstituted "benzimidazole mustard." The final results will be reported elsewhere.

(1) E. Hirschberg, A. Gellhorn, and W. S. Gump, *Cancer Research*, **17**, 904 (1957).

(2) A. R. Day, *Trans. N. Y. Acad. Sci.*, [2] **20**, No. 1, 3 (Nov. 1957).

(3) O. F. Ginzburg, B. A. Porai-Koshits, M. I. Krylova, and S. M. Lotareichik, *Zhur. Obshchet Khim.*, **27**, 411 (1957).

(4) G. K. Hughes and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **71**, 209 (1938).

(5) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).

(6) We are indebted to Drs. A. Gellhorn and E. Hirschberg, Institute of Cancer Research, Columbia University College of Physicians and Surgeons, New York 32, N. Y., for evaluation of the antitumor activity of the compounds.