precipitate formed on standing overnight was crystallized from 95% ethanol. The hydrochlorides are soluble in ethanol, slightly soluble in water and are insoluble in diethyl ether and dry benzene.

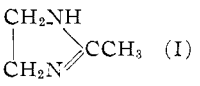
CONTRIBUTION NO. 1180, STERLING CHEMISTRY LAB.
YALE UNIVERSITY
NEW HAVEN, CONNECTICUT

Amidines Derived from Ethylenediamine. II. Imidazolines[1]

BY ARTHUR J. HILL AND JEAN V. JOHNSTON[2]

RECEIVED AUGUST 12, 1953

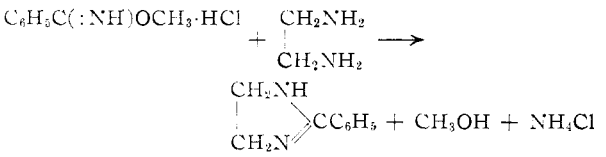
The oldest and most generally used method of entering the imidazoline series is that which involves the dry distillation of a suitable acid derivative of a 1,2-diamine.[3] In general the yields are relatively poor. The authors were unable to duplicate the better yields of 2-methylimidazoline (I) reported by Reid and Chitwood under the



(I)

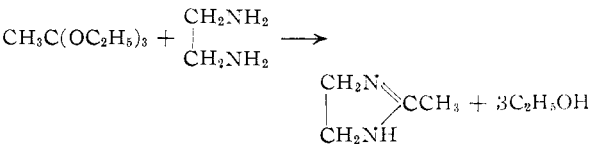
conditions described. They employed magnesium and other acid-binding agents to combine with the acetic acid released in the dry distillation of N,N′-ethylenebisacetamide.

In 1935, Sonn[4] obtained a patent for the preparation of 2-substituted imidazolines by the action of aliphatic 1,2-diamines on imidoesters derived from aryl, aryloxy or carboxyalkyl substituted products of formic, acetic, propionic and butyric acids. Two of the imidazolines prepared in the present investigation from orthoesters were also prepared satisfactorily from the corresponding imidoester hydrochlorides



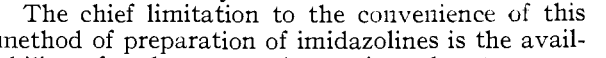
Hill and Aspinall[5] in an investigation parallel to the one presently reported prepared a series of imidazolines by the elimination of water accompanied by ring closure from monoacyl-ethylenediamines. In 1947, Oxley and Short[6] prepared a series of 2-substituted imidazolines by the interaction of a neutral sulfonate of ethylenediamine and the corresponding nitrile.

In 1931, Hill and Rockwell[7] showed that diamines may be condensed with ethyl orthoacetate to give amidines. They prepared 2-methylimidazoline (I) and 2-methylbenzimidazole by this method. Excellent yields of I were obtained. The purpose of the present investigation was to study further



this condensation both from the point of view of preparing imidazolines of possible pharmacological interest and of inquiring into the factors involved in orthoester activity.

The chief limitation to the convenience of this method of preparation of imidazolines is the availability of orthoesters. Aromatic orthoesters may be prepared by the Grignardation of ethyl orthocarbonate. The yields in this reaction are never high and vary with the Grignard reagent used.



Aliphatic orthoesters can not be made in this way. Because the synthesis of aliphatic orthoesters *via* the corresponding imidoesters from nitriles is more time consuming this investigation was confined to the condensation of ethylenediamine with the more accessible orthoesters. Table I summarizes the results of these condensations. Data on imidazolines also prepared from imidoesters are given in the footnotes. Compounds marked with an asterisk are new.

The variation in the time required to effect these condensations is the most significant of the data obtained in regard to the reactivity of the different orthoesters. Unsubstituted 2-phenylimidazoline was the most difficult to prepare. After 84 hours of heating the reaction mixture was still liquid and a third of the orthoester was recovered unchanged. Substitution in the benzene ring appears to exert considerable effect upon the reactivity of the orthoester. In contrast to the sluggish behavior of ethyl orthobenzoate a solid mixture resulted after only 7.5 hours of heating a mixture of ethyl *p*-ethoxyorthobenzoate and ethylenediamine.

Lack of material for an extensive study of purification methods makes some of the data obtained somewhat misleading. Significant loss of product during the purification of some of the more refractory mixtures prevents the great variation in yields obtained from being an accurate criterion of the extent to which the various reactions went to completion. While the analytical data leave no doubt as to the identity of the compounds synthesized, a comparison of the melting points obtained for the four known members of the series with those reported in the literature indicates that they were not isolated in the highest state of purity.

Experimental

(A) **Preparation of Imidazolines from Orthoesters.**—A mixture of anhydrous ethylenediamine and the appropriate orthoester in the proportion of 1 mole of amine/1.2 moles of orthoester was refluxed for varying periods of time over an oil-bath maintained between 110–130°, or was heated in a sealed tube at 130°. The period of reflux was determined

(1) From the dissertation presented by Jean V. Johnston for the degree of Doctor of Philosophy, Yale University.

(2) Connecticut College, New London, Connecticut.

(3) A. Ladenburg, *Ber.*, **8**, 677 (1875); A. W. Hofmann, *ibid.*, **21**, 2332 (1888); A. Ladenburg, *ibid.*, **27**, 2953 (1894); Farbwerke vorm Meister, Lucius and Bruning, German Patent 78,020, April 8, 1884; E. Klingenstein, *Ber.*, **28**, 1173 (1895); G. Baumann, *ibid.*, **28**, 1176 (1895); H. C. Chitwood and E. E. Reid, THIS JOURNAL, **57**, 2424 (1935); E. Waldmann and A. Chwala, French Patent 811,423, April 14, 1937; *C. A.*, **31**, 8550 (1937); C. Forssel, *Ber.*, **25**, 2134 (1892); C. Forssel, *ibid.*, **24**, 1846 (1891).

(4) A. Sonn, German Patent 618,227, October 17, 1935; *C. A.*, **30**, 487, 4313 (1936).

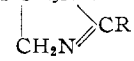
(5) A. J. Hill and S. R. Aspinall, THIS JOURNAL, **61**, 822 (1939).

(6) P. Oxley and W. F. Short, *J. Chem. Soc.*, 497 (1947).

(7) D. M. Rockwell, unpublished dissertation, Yale, 1931.

TABLE I

2-ARYLIMIDAZOLINES PREPARED FROM ORTHOESTERS



R	Total hr. heating	Hr. after which solid appeared	Yield, %	M.p. (cor.), °C.	Formula	Nitrogen, % Calcd.	Found
Phenyl	84	...	17[a]	98[c]	$C_9H_{10}N_2$	19.18	18.99
p-Tolyl	48	48	63.5[b]	175–176[d]	$C_{10}H_{12}N_2$	17.50	17.36
m-Tolyl*	96	...	33	97–98.5	$C_{10}H_{12}N_2$	17.50	16.91
p-Ethoxyphenyl*	12	7.5	92	175.5–177.5	$C_{11}H_{14}N_2O$	14.73	14.49
p-Anisyl	42	18	43	109–110[e]	$C_{10}H_{12}N_2O$	15.91	15.68
p-Diphenyl*	112	112	30	177–179	$C_{15}H_{14}N_2$	12.61	12.96
α-Naphthyl	81	...	30	132–134	$C_{12}H_{12}N_2$	14.28	14.21
4-Ethoxynaphthyl*	116	116	16	167–168	$C_{15}H_{16}N_2O$	11.66	11.38

[a] Yield from imidoester was 34.2%; product melted at 101°. [b] Yield from imidoester was 58%; product melted at 178°. [c] A sample of 2-phenylimidazoline prepared from ethyl orthobenzoate mixed with one made from the corresponding imidoester melted at 97°. A mixture of the former with one furnished by S. R. Aspinall made from benzoylethylenediamine and melting at 100.3° melted at 99°. [d] A sample of 2-*p*-tolylimidazoline prepared from the orthoester mixed with one made from the corresponding imidoester melted at 178°. A mixture of the former with one furnished by S. R. Aspinall made from the monoacylethylenediamine and melted at 183° melted at 177–178°. [e] Oxley and Short[6] report melting point to be 140°.

by the length of time required for solid to appear in the reaction mixture.

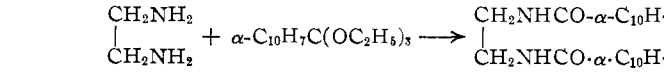
After the removal of the more volatile parts of the reaction mixture by reduced pressure distillation, the product was isolated in most cases by taking up the residue in chloroform or benzene and precipitating the imidazoline with petroleum ether. The solid obtained could then be crystallized from benzene or toluene.

The 2-phenyl- and 2-*p*-tolylimidazolines did not crystallize from a chloroform solution of the reaction mixture upon the addition of petroleum ether but required sublimation at reduced pressure before they could be crystallized. On the other hand, 2-*m*-tolyl-, 2-*p*-anisyl- and 2-α-naphthylimidazolines required no preliminary treatment since the solid reaction mixture was simply recrystallized several times from benzene or toluene.

The products from sealed tube reactions were less discolored, but better yields were obtained from reactions performed under reflux. Among the four unsuccessful attempts to prepare 2-phenylimidazoline was one sealed tube reaction. The fifth and successful attempt was made under reflux.

The imidazolines prepared are soluble in benzene, toluene, chloroform and alcohol, and are insoluble in ether, petroleum ether and water. The hydrochloride of 2-*p*-tolylimidazoline was prepared and found to be soluble in alcohol and water and insoluble in benzene and ether.

A trace of an interesting side product was obtained in the condensation of ethylenediamine with ethyl orthonaphthoate. When the product was recrystallized from benzene some 38 mg. of crystalline benzene-insoluble material melting at 184–185° (cor.) which gave analytical figures[8] for N,N'-ethylenebis-α-naphthamide were removed from the solution. Its presence in the reaction mixture seems to indicate the occurrence to a slight degree of the reaction



(B) Preparation of Imidazolines from Imidoester Hydrochlorides.—Imidoester hydrochloride and anhydrous ethylenediamine in the proportion of one mole of imidoester hydrochloride to 1.3 mole of amine were heated in absolute alcohol solution for 7–8 hours over a water-bath maintained between 60–70°. After the evaporation of the alcohol under diminished pressure the crude imidazoline hydrochloride was dissolved in water and the free base was precipitated by the addition of dilute sodium hydroxide solution. The imidazoline was purified by crystallization from benzene or toluene. The products were identified by means of mixed melting points with analyzed samples prepared from orthoesters.

CONTRIBUTION NO. 1181
STERLING CHEMISTRY LABORATORY
YALE UNIVERSITY
NEW HAVEN, CONN.

(8) *Anal.* Calcd. for $C_{24}H_{20}NO_2$: N, 7.60. Found: N, 8.00.

Mono-alkylation of Sodium 5-Aminotetrazole in Aqueous Medium

BY RONALD A. HENRY AND WILLIAM G. FINNEGAN

RECEIVED OCTOBER 13, 1953

Stolle and co-workers[1] previously prepared 1-methyl-5-aminotetrazole by the alkylation of potassium 5-aminotetrazole with dimethyl sulfate in aqueous solution. They failed, however, to recover the isomeric 2-methyl-5-aminotetrazole which we have now found is formed simultaneously in yields varying from 23 to 32%. Similarly the alkylation of 5-aminotetrazole in basic, aqueous medium with methyl iodide, ethyl iodide, allyl bromide, benzyl chloride, ethylene chlorohydrin or diethyl sulfate always leads to a mixture of isomers substituted in the 1- and 2-positions. Generally the 1-isomers predominate; by way of contrast, the 2-isomers are the principal products when sodium 5-phenyltetrazole[2] and sodium 5-nitrotetrazole are methylated in aqueous acetone.

Alkylation of the 5-amino group apparently occurs only to a very limited extent under the conditions employed in this investigation. For example, 1- and 2-methyl-5-methylaminotetrazole have been isolated in yields amounting to less than one per cent. by careful fractionation of the by-products from experiments with dimethyl sulfate and sodium 5-aminotetrazole; 5-methylamino- or 5-dimethylaminotetrazole have not been identified among the products. This suggests that the dimethylated derivatives result from a further methylation of the 1- and 2-methyl-5-aminotetrazoles. Small quantities of 1,3- and 1,4-dimethyl-5-iminotetrazole[3] also have been isolated as suitable derivatives.

Only one of the ethyl groups in diethyl sulfate appears to be utilized during the alkylation of sodium 5-aminotetrazole in water at 95–100°, whereas both the methyl groups in dimethyl sulfate are effectively used under these conditions. Fur-

(1) R. Stolle, K. Ehrmann, D. Rieder, H. Wille, H. Winter and F. Henke-Stark, *J. prakt. Chem.*, **134**, 282 (1932).

(2) B. Elpern and F. C. Nachod, THIS JOURNAL, **72**, 3379 (1950); R. A. Henry, *ibid.*, **73**, 4470 (1951).

(3) R. A. Henry, W. G. Finnegan and E. Lieber, unpublished results.