Rotation changes when I and II were dissolved in 0.526 *M* sodium hydroxide are shown in Fig. 1. The curves are those predicted for enantiomers. The average rate constant ($k_1 + k_2$) for I was 2.50×10^{-3} min.$^{-1}$ and for II 2.53×10^{-3} min.$^{-1}$. The initial three readings gave somewhat high constants, then the individual values were close to the average throughout the run.

To learn whether the mutarotation is a reaction of the anions of I and II and not the lactones aliquots of the solution of I in base were titrated with acid. The volume of acid required to neutralize the solution (phenolphthalein end-point) was the same after 4 minutes as after one hour. The amount of sodium hydroxide consumed in a 10-cc. aliquot at 4 minutes was 0.00098 mole which is close to the calculated 0.00099 mole of oxazoline present. Additional evidence that the lactone ring opened rapidly may be adduced from the rotation. The rotation of I was +254° and of II −251°. The initial readings in Fig. 1 were at 5 and 6 minutes after addition of base.

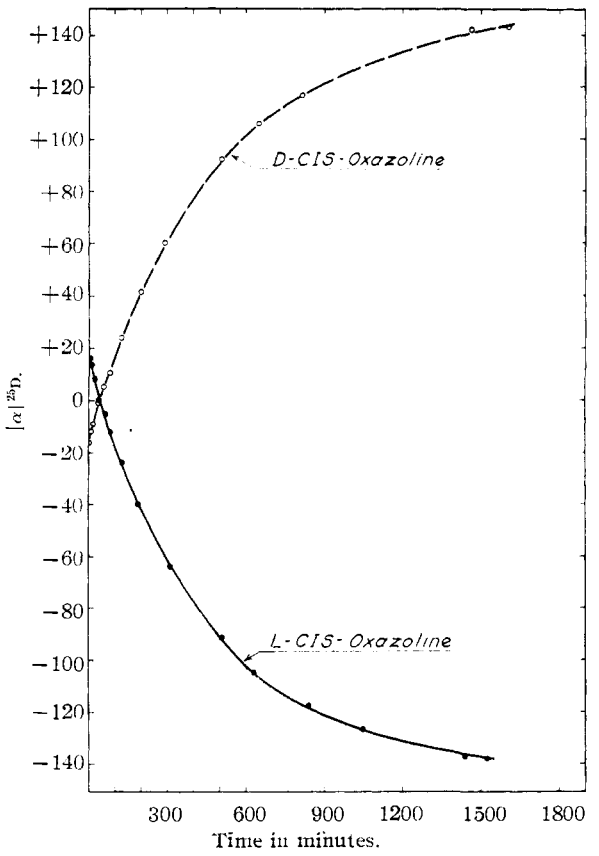
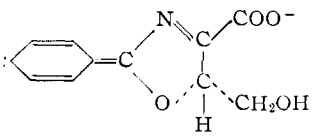


Fig. 1.—Mutarotation of oxazolines in aqueous alcoholic sodium hydroxide solution at 25°.

Whereas peptides and azlactones are racemized by bases, free amino acids and aryl or alkylamido derivatives are relatively stable. Enolization of the anion of I in the manner which appears to satisfactorily explain the racemization of azlactones would lead to a carbanion with both negative charges close together. This does not happen with benzamido derivatives of amino acids. The carbanion in which the charges are widely separated



may be a major contributing species. In view of the similarity of structure of the oxazoline of serine and I and II, it is surprising that Fry[5] reported the methyl ester of the phenyl oxazoline of L-serine did not racemize on alkaline hydrolysis.

The rotations of the anions of I and the corresponding *threo* diastereoisomer are not known so the equilibrium composition cannot be calculated. Only one amino acid (the *threo*) has been obtained from acid hydrolysis of the equilibrium mixture so apparently the equilibrium lies far in favor of the *trans* form.

Experimental

The sodium hydroxide solution contained equal volumes of water and ethanol. Zero time was taken when the solvent was added to the volumetric flask containing the oxazolines, but 2–3 minutes elapsed before the compounds completely dissolved. The solution was transferred to polarimeter tubes and the rotation change followed at 25 ± 0.1°.

(5) E. M. Fry, *J. Org. Chem.*, **15**, 438 (1950).

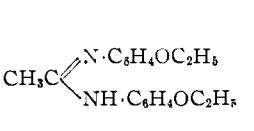
DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALIFORNIA
DAVIS, CALIFORNIA

Amidines Derived from Ethylenediamine. I. Diamidines[1]

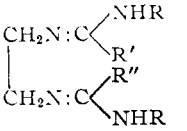
BY ARTHUR J. HILL AND JEAN V. JOHNSTON[2]

RECEIVED AUGUST 12, 1953

The objective of the work described in this paper was to prepare a series of compounds represented by II which might be more useful than phenacaine, the hydrochloride of I as a local anesthetic because, by doubling the number of amidine groups and separating them by a non-toxic bridge, a high activity at a lower and thereby less toxic dosage might result. In choosing the substituent R it seemed desirable to include phenyl and *p*-ethoxy-



I



II

phenyl which are effective in simpler amidines and *p*-carbethoxyphenyl. The effect of aromaticity was studied in regard to R′ and R″ by attaching a phenyl group directly to the amidine carbon and by allowing one and two methylene groups as well as an ether linkage to intervene. The effect of chain branching was studied in the aliphatic series. In only one compound was R′ different from R″. Utilizing the conventional conversion of an amide *via* the chloroimide to an amidine the method of preparation is unique for the synthesis of diamidines from an aliphatic diamine. While this work was in progress, Rao and Wheeler[3] prepared diamidines

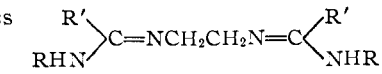
(1) From the dissertation presented by Jean V. Johnston for the degree of Doctor of Philosophy, Yale University.

(2) Connecticut College, New London, Connecticut.

(3) H. K. S. Rao and T. S. Wheeler, *J. Chem. Soc.*, 1743 (1937).

TABLE I

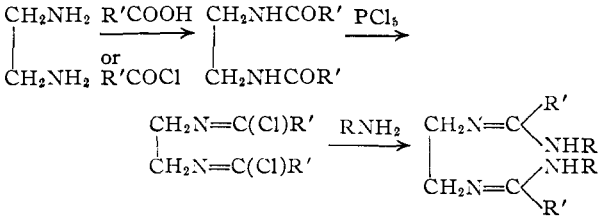
BIS-AMIDINOETHYLENES



	R	R′	Free base: Yield, %	M.p. (cor.), °C.	Formula	Nitrogen, % Calcd.	Found	Hydrochloride: M.p. (cor.), °C.	Formula	Nitrogen, % Calcd.	Found
III	*p*-$C_2H_5OC_6H_4$	CH_3	24	104–106	$C_{22}H_{30}N_4O_2$	14.68	13.92	248–249	$C_{22}H_{32}N_4O_2Cl_2$	12.36	12.42
IV	C_6H_5	CH_3	25	114–116	$C_{18}H_{22}N_4$	19.05	19.09	176–177	$C_{18}H_{24}N_4Cl_2$	15.26	15.38
V	*p*-$C_2H_5CO_2C_6H_4$	CH_3	17	119	$C_{24}H_{30}N_4O_4$	12.78	12.36	216–220	$C_{24}H_{32}N_4O_4Cl_2$	11.00	11.30
VI	C_6H_5	C_6H_5	25	177.5–179	$C_{28}H_{24}N_4$	13.39	12.96	223–225	$C_{28}H_{26}N_4Cl_2$	11.96	11.43
VII	*p*-$C_2H_5OC_6H_4$	C_6H_5	19	129–131	$C_{32}H_{34}N_4O_2$	11.06	10.85	223–225	$C_{32}H_{36}N_4O_2Cl_2$	9.84	9.81
VIII	*p*-$C_2H_5OC_6H_4$	C_6H_5, CH_3[a]	10	.....	.....	...	...	229	$C_{27}H_{34}N_4O_2Cl_2$	10.83	10.64
IX	*p*-$C_2H_5OC_6H_4$	CH_3	16	95	$C_{34}H_{38}N_4O_2$	10.45	9.98	228	$C_{34}H_{40}N_4O_2Cl_2$	9.22	9.02
X	*p*-$C_2H_5OC_6H_4$	$C_6H_5CH_2CH_2$	20	127–129	$C_{36}H_{42}N_2O_2$	9.97	9.91	244	$C_{36}H_{44}N_4O_2Cl_2$	8.82	8.99
XI	*p*-$C_2H_5OC_6H_4$	$C_6H_5OCH_2$	Small	.....	.....	...	...	205	$C_{34}H_{40}N_4O_4Cl_2$	8.83	8.33
XII	*p*-$C_2H_5OC_6H_4$	$CH_3(CH_2)_5CH_2$	Small	.....	.....	...	...	194	$C_{32}H_{50}N_4O_2Cl_2$	9.41	9.54
XIII	*p*-$C_2H_5OC_6H_4$	$(C_2H_5)_2CH$	12	139–141	$C_{30}H_{46}N_4O_2$	11.34	11.32	282 dec.	$C_{32}H_{48}N_4Cl_2$	9.87	9.78
XIV	C_6H_5	$(C_3H_7)_2CH$	Small	144–145	$C_{30}H_{46}N_4$	12.15	12.26	230–232	$C_{30}H_{48}N_4Cl_2$	10.47	10.02
XV	*p*-$C_2H_5OC_6H_4$	$(C_3H_7)_2CH$	12	141–142	$C_{34}H_{54}N_4O_2$	10.33	10.37	264 dec.	$C_{34}H_{56}N_4O_2Cl_2$	8.98	9.21

[a] One R′ is C_6H_5; the other is CH_3.

of the type $NRR'CPhNC_6H_4C_6H_4N{=}CPhNR'R$ by a somewhat analogous method



Data on the amidines prepared are listed in Table I.

Experimental

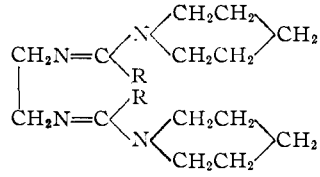
Amides.—Most of the amides used as intermediates were prepared by refluxing anhydrous ethylenediamine with the desired acid. The exceptions are N,N′-ethylenebisbenzamide prepared by the action of benzoyl chloride on ethylenediamine, N-acetyl-N′-benzoylethylenediamine and the amides derived from disubstituted acetic acids. With the last better yields were obtained when the acid was first converted to its acid chloride by the action of thionyl chloride. The unsymmetrical amide was prepared by the benzoylation of N-2-aminoethylacetamide.[4] With the exception of N,N′-ethylenebis-(α,α-diethyl)-acetamide previously prepared and reported as melting at 230–231°[5] by Blicke and Centolella[5] the amides prepared from disubstituted acetic acids are new compounds. Oxley and Short[6] obtained N,N′-ethylenebis-(α-phenyl)-acetamide as a by-product from the synthesis of 2-phenylimidazoline by the interaction of benzyl nitrile, ethylenediammonium bis-(*p*-toluenesulfonate) and ethylenediamine. They reported the melting point to be 204°. Results on these and on all of the new amides prepared are summarized in Table II.

TABLE II

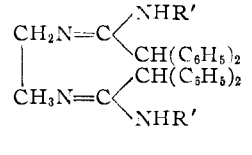
N,N′-ETHYLENEBIS-(ALKYL)-ACETAMIDES, $RCONHCH_2CH_2NHCOR$

R	Yield, %	M.p. (cor.) °C.	Formula	Nitrogen, % Calcd.	Found
$(C_2H_5)_2CH$	42	229–231	$C_{14}H_{28}N_2O_2$	10.93	10.81
$(C_3H_7)_2CH$	50	197–200	$C_{18}H_{36}N_2O_2$	8.97	9.14
$(C_6H_5)_2CH$	13	203.5–205	$C_{30}H_{28}N_2O_2$	6.25	6.21
$C_6H_5CH_2CH_2$	100	204–205	$C_{20}H_{24}N_2O_2$	8.61	8.41
$C_6H_5CH_2$	100	204–205	$C_{18}H_{20}N_2O_2$	9.45	9.57
$C_6H_5OCH_2$	100	144–145	$C_{18}H_{20}N_2O_4$	8.54	8.66

Amidines.—The effect of varying experimental conditions was tested in the preparation of bis-(phenylacetamidino)-ethylene (IV), and of the corresponding phenylbenzamidino compound VI. The observations of Hill and Cox and of Hill and Mandel[7] that phosphorus pentachloride is superior to phosphorus oxychloride for the preparation of imidochlorides were confirmed in as much as the crude amidines were harder to purify when phosphorus oxychloride was used. The amides of the non-branched chain acids dissolved sluggishly in the benzene solution of phosphorus pentachloride. The use of an outside acceptor for the hydrogen chloride formed in the reaction of the imido chloride with the base was studied. The addition of sodium carbonate appeared to be of no help, and a comparison of runs using 2, 3 and 4 moles of the organic base, respectively, indicated that excess base is unnecessary and actually undesirable since the crude amidines produced in the presence of excess amine were gummier and less easily purified. The proportions of reagents found to be optimum were one mole of amide/two moles (plus a slight excess) of phosphorus pentachloride/two moles of amine. Five or ten gram quantities of the amides were used. In the attempted preparation of bis-(piperidylacetamidino)-ethylene (XVI), and of bis-(piperidylbenzamidino)-ethylene (XVII), the addition of base to the reaction mixture was accompanied by the evolution of heat and the formation of a white precipitate, but no amidine was ever isolated. Likewise, attempts to synthesize bis-(phenyldiphenylacetamidino)-ethylene (XVIII), and bis-*p*-ethoxyphenyldiphenylacetamidino)-ethylene (XIX) were also unsuccessful even though the amide appeared to react vigorously with the phosphorus pentachloride solution.



XVI, R = CH_3
XVII, R = C_6H_5



XVIII, R′ = C_6H_5
XIX, R′ = *p*-$C_2H_5OC_6H_4$

Procedure.—The phosphorus pentachloride was refluxed in 50 ml. of dry benzene, the flask cooled, the amide added, and during cooling in an ice–salt-bath freshly distilled amine in an equal volume of dry benzene was added dropwise with stirring. When the mixture reached room temperature it was heated on a water-bath for a period varying in different cases from 2 to 24 hours. The crystalline portion of the reaction mixture was filtered from the accompanying sirup and treated with sodium hydroxide. The resultant oil slowly solidified and the solid was triturated with sodium hydroxide until the solid no longer gave a positive chloride test with alcoholic silver nitrate solution. The amorphous material was crystallized from absolute ethanol. The free bases are insoluble in water, only slightly soluble in diethyl ether and are soluble in benzene and ethanol.

The amidine free bases were converted to the dihydrochlorides by dissolving the crystalline amidine in dry benzene and adding dry hydrogen chloride in the proportion of 4 moles of hydrogen chloride to 1 mole of amidine. The

(4) Furnished by S. R. Aspinall.

(5) F. F. Blicke and A. P. Centolella, THIS JOURNAL, **60**, 2924 (1938).

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

(7) A. J. Hill and M. Cox, THIS JOURNAL, **48**, 3214 (1926); H. G. Mandel, unpublished dissertation, Yale, 1949.

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.

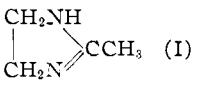
CONTRIBUTION NO. 1180, STERLING CHEMISTRY LAB.
YALE UNIVERSITY
NEW HAVEN, CONNECTICUT

Amidines Derived from Ethylenediamine. II. Imidazolines[1]

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

RECEIVED AUGUST 12, 1953

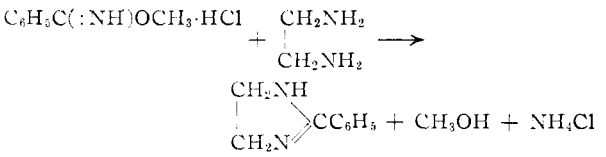
The oldest and most generally used method of entering the imidazoline series is that which involves the dry distillation of a suitable acid derivative of a 1,2-diamine.[3] In general the yields are relatively poor. The authors were unable to duplicate the better yields of 2-methylimidazoline (I) reported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



(I)

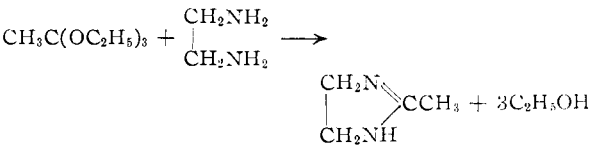
conditions described. They employed magnesium and other acid-binding agents to combine with the acetic acid released in the dry distillation of N,N′-ethylenebisacetamide.

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



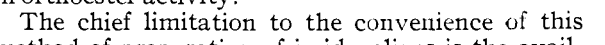
Hill and Aspinall[5] in an investigation parallel to the one presently reported prepared a series of imidazolines by the elimination of water accompanied by ring closure from monoacylethylenediamines. In 1947, Oxley and Short[6] prepared a series of 2-substituted imidazolines by the interaction of a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