[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MONSANTO CHEMICAL CO.]

SUBSTITUTED IMIDAZOLES AND 2-IMIDAZOLINES

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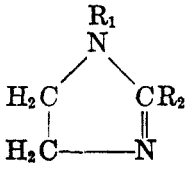
In the investigation of products for possible use against malaria, a number of 2-alkyl-substituted imidazoles (1) were found to have marked antimalarial activity[1] when tested against *Plasmodium lophurae* in ducklings. A number of 1,2-disubstituted 2-imidazolines (2) were found to have high *in vitro* activity against several bacteria, including *Streptococcus hemolyticus*, *Staphylococcus*



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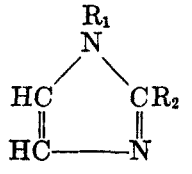

II

aureus, *Pneumococcus* Type I, and *S. dysenteriae*. Related 2-alkyl-2-imidazolines of Formula Type I, where R_1 is hydrogen, were prepared and tested for comparison with the imidazoles which had antimalarial activity, and 1,2-disubstituted imidazoles of Formula Type II were made for comparison with the corresponding 2-imidazolines. The compounds were evaluated for chemotherapeutic and pharmacologic activity in The Lilly Research Laboratories.

In the series of 2-alkylimidazoles prepared to investigate the effect of chain length on antimalarial activity, the most effective compound was found to be 2-tridecylimidazole, while 2-tetradecylimidazole was only slightly less active. The activity dropped markedly when the length of the alkyl chain was increased or decreased, 2-pentadecylimidazole being almost inactive, while 2-dodecylimidazole was fairly active and 2-hendecylimidazole (3) was slightly active. Although the most active compound sharply reduced the number of infecting organisms in the blood stream, it did not completely eliminate them. The corresponding 2-imidazolines, as well as the 1,2-dialkylimidazoles and the 1,2-dialkyl-2-imidazolines were devoid of any significant antimalarial activity.

Seven products, all 2-imidazolines, were found to be active *in vitro* against the *Streptococcus*, *Staphylococcus*, and *Pneumococcus*. When the 2-substituent was methyl, active compounds were obtained when decyl, dodecyl, or tetradecyl was introduced into the 1-position. 2-Imidazolines having a 2-hendecyl group were active when the 1-substituent was hydrogen, methyl, ethyl, or amyl. The entire series of compounds required to exhaust all the possible derivatives in the molecular weight range giving active products was not completed, but the

[1] Antimalarial activities of some of these compounds are tabulated in the monograph, "A Survey of Antimalarial Drugs, 1941–1945," F. Y. Wiselogle, Editor; Edwards, Ann Arbor, 1946.

data indicate that if one substituent is a short alkyl chain, the other must be in the range of C_{10} to C_{14}.

Four products had appreciable *in vitro* activity against *S. dysenteriae.* They were 1-decyl-2-methyl-2-imidazoline, 1-dodecyl-2-methylimidazole (4), 2-hendecyl-2-imidazoline, and 1-methyl-2-hendecyl-2-imidazoline.

Several compounds showed some activity against only one of the test organisms.

Ten compounds were found to possess mild to prolonged local anesthetic activity when applied to the cornea of a rabbit's eye. Three were imidazoles: 1-decyl-2-methyl-, 2-hendecyl-, and 1-methyl-2-hendecyl- (5), while the following 2-imidazolines were active:
1-decyl-2-methyl-, 1-dodecyl-2-methyl-, 1-methyl-2-nonyl-, 2-hendecyl-, 1-methyl-2-hendecyl-, 1-amyl-2-hendecyl-, and 2-(3-cyclohexylpropyl)-.

The introduction of benzyl, 3-phenylpropyl, and 3-cyclohexylpropyl groups into the 2-position of the imidazoles and 2-imidazolines produced compounds with no antimalarial or bactericidal activity.

Several of the 2-alkyl-2-imidazolines were found to be active insecticides. For example, 2-tridecyl-2-imidazoline is highly toxic to the red spider, *Tetranychus telarius* Linné. The activity of 2-alkyl-2-imidazolines as foliage fungicides has been reported recently by several workers (6, 7).

Numerous references have appeared in the literature showing many imidazolines and imidazoles to have marked pharmacological activity. Hartmann and Isler (8) tested a large number of 2-imidazolines and found that some were vasoconstrictors while others were vasodilators. An extensive report on derivatives with sympathomimetic activity was made by Scholz (9).

2-Alkyl-2-imidazolines were prepared by the reaction of esters with ethylenediamine to produce N-acylethylenediamines (10, 11, 12) which were not isolated but were cyclized directly by heating alone or with calcium oxide (11). In each of the acylation reactions there were obtained small to appreciable quantities of N,N′-diacylethylenediamines which could be converted into the corresponding 2-alkyl-2-imidazolines by treatment with magnesium as described by Chitwood and Reid (13). The yields of 2-imidazolines reported were those obtained directly, without consideration of recovery from the N,N′-diacylethylenediamines, although in several cases this was successfully accomplished. The preparation of N-monoacylethylenediamines was not investigated, but the application of an efficient method, such as that described by Weiner (12), who obtained excellent yields of monoacyl derivatives by reaction of 70% ethylenediamine with methyl esters of carboxylic acids at 100°, would undoubtedly result in improved over-all yields of 2-imidazolines using the simplified process described below.

Certain monoacylethylenediamines tend to lose water readily on heating, as shown by Hill and Aspinall (11), who observed that many aromatic monoacylethylenediamines undergo dehydration and cyclization to the 2-imidazolines merely on distillation. In his extended studies Aspinall (14) found that N-caproylethylenediamine is converted slowly into 2-amyl-2-imidazoline on dis-

tillation at temperatures in the range of 110–135°, but he was able to prepare N-caproylethylenediamine in 80% yield by reaction of ethyl caproate with ethylenediamine at 100°. In our experience, it was found possible to obtain a 65% yield of 2-amyl-2-imidazoline by the simple expedient of refluxing a mixture of one mole of methyl caproate with 3 moles of 90–100% ethylenediamine for about six hours, followed by removal of the excess ethylenediamine and distillation of the residue at a temperature above 125°. Other, higher, 2-alkyl- and 2-substituted alkyl-2-imidazolines were prepared with equal facility. For example, reaction of ethyl dodecanoate with ethylenediamine at reflux for 6 hours produced 70% of distilled 2-hendecyl-2-imidazoline. The time required for the acylation of ethylenediamine with the ester could be estimated conveniently by performing the reaction in a flask fitted with a fractionating column and carefully distilling off the methanol or ethanol until no further alcohol was liberated.

There are several alternative methods for preparing 2-imidazolines, one of the better being the reaction of ethylenediamine, ethylenediamine hydrochloride, and a carboxylic acid at about 300°, as described by Waldmann and Chwala (15).

The 2-alkylimidazoles were produced by dehydrogenation of the corresponding 2-imidazolines (3) by heating with a nickel hydrogenation catalyst (16) in the liquid phase.

In our experiments on the alkylation of 2-imidazolines with alkyl halides (2, 17), the formation of considerable quantities of by-products was observed. The results generally checked those recorded very recently by King and McMillan (18), who, working with 2-methyl-2-imidazoline, showed that in addition to the expected alkylation product, the alkyl halide quaternary salt of the alkylated 2-methyl-2-imidazoline was produced. The quaternary salt was found by them to hydrolyze readily to the acetylethylenediamine. When one mole of dodecyl bromide reacted with two moles of 2-methyl-2-imidazoline in refluxing anhydrous benzene, followed by treatment with cold aqueous alkali, about 40% of 1-dodecyl-2-methyl-2-imidazoline was formed, and there was obtained as a by-product a substantial amount of N-acetyl-N,N′-didodecylethylenediamine (III), resulting from hydrolysis of the intermediate quaternary compound.

$$C_{12}H_{25}NCH_2CH_2NHC_{12}H_{25}$$
$$|$$
$$COCH_3$$

III

When the same reaction was performed using no precautions to exclude traces of water, the reaction of dodecyl bromide or dodecyl chloride with 2-methyl-2-imidazoline produced, in addition to the other two products, a quantity of N,N′-didodecylethylenediamine, isolated directly from the reaction mixture as the hydrate upon quenching with water. This observation suggests that some of the 2-methyl-2-imidazoline was hydrolyzed to N-acetylethylenediamine early in the reaction or that some of the 1-dodecyl-2-methyl-2-imidazoline was hydrolyzed to N-acetyl-N′-dodecylethylenediamine, probably followed by further hydrolysis of the respective acetyl derivatives to the corresponding

ethylenediamines prior to dialkylation. The ready hydrolysis of 2-imidazolines would be expected since they are cyclic amidines and it is well known that amidines are susceptible to hydrolysis with water (19). The easy hydrolysis of 2-imidazolines has been demonstrated by experiment (20), and the catalyzing effect of acids in the hydrolysis of certain 2-imidazolines (21) and acid amides (22) is recorded. The conditions during the alkylation with an alkyl halide in the presence of water would provide hydrogen ions which could catalyze the several hydrolytic reactions. This interpretation of the occurrence of the N,N'-dialkylethylenediamine is preferred over another possible mechanism, namely, the hydrolysis of the quaternary compound to III and further hydrolysis of the latter to N,N'-didodecylethylenediamine, because it was found that III is extremely difficult to hydrolyze either by acid or by alkali. This checks the conclusion of King and McMillan who stated that the acetyl derivatives in which the acyl group is attached to a secondary nitrogen atom of an ethylenediamine are resistant to hydrolysis.

The formation of by-products was observed in the alkylation of all 2-imidazolines used, but only the by-products obtained in a few cases were purified and identified.

1,2-Dialkylimidazoles were obtained either by nickel dehydrogenation of the 1,2-dialkyl-2-imidazolines or by alkylation of the 2-alkylimidazoles with alkyl halides (23). In the case of 1-methylation and 1-ethylation, dimethyl sulfate and diethyl sulfate were used, respectively. By-products formed in the alkylation of the imidazoles or in the lower alkylations were not investigated.

EXPERIMENTAL

All melting points are corrected. The analyses were performed by Mrs. J. D. Nevins, Mrs. R. C. Schropp, and Miss G. Pranger of the Monsanto Analytical Laboratory.

General methods of preparation. The procedures used for the preparation of the 2-imidazoline derivatives described in Table I and the imidazole derivatives described in Table II were as follows:

Procedure A. An ester of the appropriate acid reacted with ethylenediamine followed by thermal cyclization of the N-acylethylenediamine.

Procedure B. Similar to procedure A, but cyclization was effected with calcium oxide.

Procedure C. The corresponding 2-substituted or 1,2-disubstituted 2-imidazoline was dehydrogenated by heating with a nickel catalyst in the liquid phase.

Procedure D. The appropriate 2-substituted 2-imidazoline (2 moles) was alkylated with one mole of an alkyl halide in the presence or absence of an organic solvent like toluene or butanol or with an alkyl sulfate in the presence of aqueous alkali.

Procedure E. The appropriate 2-substituted imidazole was alkylated with one mole of an alkyl halide or with an alkyl sulfate, without the use of a solvent in either case.

2-Amyl-2-imidazoline. (*Procedure A*). A mixture of 78.1 g. (0.6 mole) of methyl caproate and 55.9 g. (0.9 mole) of 96.8% ethylenediamine was stirred and heated at reflux for 8 hours. The excess ethylenediamine was recovered by distillation, a small head fraction

TABLE I

SUBSTITUTED 2-IMIDAZOLINES

R_1[a]	R_2[a]	PROCEDURE	YIELD	B.P., °C.	MM. Hg	M.P., °C.	EMPIRICAL FORMULA	ANALYSIS[b]	
								Calc'd	Found
			%					N	N
C_7H_{15}	CH_3[c]	D	69	107–109	2.5	Oil	$C_{11}H_{22}N_2$	15.4	15.8
$C_{10}H_{21}$	CH_3[d]	D	59	135–136	3	Oil	$C_{14}H_{28}N_2$	12.5	12.4
$C_{12}H_{25}$	CH_3[d]	D	38	161–162	2	Oil	$C_{16}H_{32}N_2$	11.1	11.1
$C_{14}H_{29}$	CH_3[d]	D	50	191–193	6	Oil	$C_{18}H_{36}N_2$	10.0	9.8
$C_6H_5CH_2$	CH_3	D	39	162–163	16	Oil	$C_{11}H_{14}N_2$	16.1	15.9
$C_{10}H_{21}$	C_5H_{11}[e, f]	D	43	164–166	1.5	Oil	$C_{18}H_{36}N_2$	10.0	10.0
$C_{12}H_{25}$	C_5H_{11}[d]	D	46	196–197	3	Oil	$C_{20}H_{40}N_2$	9.1	8.9
CH_3	C_7H_{15}[e]	D	33	93–96	2	Oil	$C_{11}H_{22}N_2$	15.4	14.9
CH_3	C_9H_{19}[e]	D	60	142–143	5	Oil	$C_{13}H_{26}N_2$	13.3	13.1
CH_3	$C_{11}H_{23}$[e, g]	D	41	167–172	6	Oil	$C_{15}H_{30}N_2$	11.8	11.9
C_2H_5	$C_{11}H_{23}$[g]	D	42	170–178	2.5	[h]	$C_{16}H_{32}N_2$	11.1	10.9
C_5H_{11}	$C_{11}H_{23}$[g]	D	61	172–173	2	Oil	$C_{19}H_{38}N_2$	9.5	9.2
H	$C_{12}H_{25}$[i]	A	57	163–165	3	87–88[j]	$C_{15}H_{30}N_2$	11.8	11.7
H	$C_{13}H_{27}$[k]	A	65	179–180	2	88–89[j]	$C_{16}H_{32}N_2$	11.1	11.0
H	$C_{13}H_{25}$[l]	B	66	207–218	13	[h]	$C_{16}H_{30}N_2$	11.2	10.9
H	$C_{14}H_{29}$	A	72	191–195	4	92–93[j]	$C_{17}H_{34}N_2$	10.5	10.4
H	$C_6H_5(CH_2)_3$	A	71	202–203	20	Oil	$C_{12}H_{16}N_2$	14.9	14.6
H	$C_6H_{11}(CH_2)_3$	A	73	159–160	5	[m]	$C_{12}H_{22}N_2$	14.4	14.5

[a] All alkyl radicals are normal.

[b] Determined by the Dumas combustion method.

[c] 2-Methyl-2-imidazoline used as an intermediate was described by Hill and Aspinall (11), and others. It was prepared by procedure B.

[d] Described in ref. (2).

[e] 2-Amyl-, 2-heptyl-, 2-nonyl-, and 2-hendecyl-2-imidazoline, used as intermediates, were described by Chitwood and Reid (13). They were prepared by procedure A.

[f] Described in ref. (4).

[g] Described in ref. (5).

[h] Waxy solid.

[i] 2-Dodecyl-2-imidazoline also was made from dodecyl cyanide by converting it to the imino ether which was reacted with ethylenediamine; yield, 70%.

[j] Recrystallized from methanol.

[k] 2-Tridecyl-2-imidazoline was mentioned by Waldmann and Chwala, U. S. Patent 2,215,862 (9-24-40), and described in ref. (1).

[l] 1-Tridecenyl.

[m] Solid. Can be recrystallized from ligroin.

was taken to 148° (33 mm.), and the main fraction was distilled slowly at 150—157° (35 mm.); yield 57–65%. On redistillation the 2-amyl-2-imidazoline boiled at 139–141° (17 mm.).

Treatment of the still residue with magnesium (13) at 300° under 35 mm. absolute pressure produced additional product, raising the yield to well over 90%.

1-Amyl-2-hendecylimidazole. (*Procedure C*). A mixture of 37.1 g. of 1-amyl-2-hendecyl-2-imidazoline and 4.2 g. of 50% nickel-petroleum paste, in a flask equipped with a stirrer,

thermometer, and reflux condenser connected to a bubble-counter, was stirred and heated. The evolution of hydrogen began at 210°. The batch temperature was raised gradually

TABLE II

SUBSTITUTED IMIDAZOLES

R_1[a]	R_2[a]	PROCEDURE	YIELD	B.P., °C.	MM. Hg	M.P., °C.	EMPIRICAL FORMULA	ANALYSIS[b]	
								Calc'd	Found
			%					N	N
C_7H_{15}	CH_3	C	89	118–122	2.5	Oil	$C_{11}H_{20}N_2$	15.5	15.6
$C_{10}H_{21}$	CH_3[c]	C	96	157–158	3	Oil	$C_{14}H_{26}N_2$	12.6	12.7
$C_{12}H_{25}$	CH_3[c]	C	93	164–166	3	Oil	$C_{16}H_{30}N_2$	11.2	11.4
$C_{14}H_{29}$	CH_3[c]	C	90	185–186	2	Oil	$C_{18}H_{34}N_2$	10.1	10.4
$C_{10}H_{21}$	C_5H_{11}[c]	C	94	175–176	2	Oil	$C_{18}H_{34}N_2$	10.1	9.8
$C_{12}H_{25}$	C_5H_{11}[c]	C	95	184–185	1	Oil	$C_{20}H_{38}N_2$	9.1	8.8
CH_3	C_7H_{15}	C	86	166–169	25	Oil	$C_{11}H_{20}N_2$	15.5	15.1
CH_3	C_9H_{19}	C	81	149–154	3.5	Oil	$C_{13}H_{24}N_2$	13.5	13.3
CH_3	$C_{11}H_{23}$[d]	E	39	134–167	3.5	Oil	$C_{15}H_{28}N_2$	11.9	11.6
		C	67	158–172	2.5	Oil		—	—
C_5H_{11}	$C_{11}H_{23}$[d]	E	55	218–219	10	Oil	$C_{19}H_{36}N_2$	9.6	9.8
		C	88	—	—	Oil		—	—
H	$C_{12}H_{25}$[e]	C	85	194–196	3	77–78[f]	$C_{15}H_{28}N_2$	11.9	12.3
H	$C_{13}H_{27}$[g]	C	89	208–210	1.5	81–82[f]	$C_{16}H_{30}N_2$	11.2	11.5
H	$C_{13}H_{25}$[h]	C	81	230–241	13	Paste	$C_{16}H_{28}N_2$	11.3	11.4
H	$C_{14}H_{29}$	C	81	219–221	3	83–84[f]	$C_{17}H_{32}N_2$	10.6	10.5
H	$C_{15}H_{31}$[i, j]	C	84	220–223	3.5	87–88[f]	$C_{18}H_{34}N_2$	10.1	10.0
H	$C_6H_5CH_2$[k]	C	92	201–202	12	125–126[l]	$C_{10}H_{10}N_2$	17.7	17.7
H	$C_6H_5(CH_2)_3$	C	77	194–195	2	90–91[f]	$C_{12}H_{14}N_2$	15.0	15.0
H	$C_6H_{11}(CH_2)_3$	C	85	190–195	7	78–79[m]	$C_{12}H_{20}N_2$	14.6	14.6

[a] All alkyl radicals are normal.

[b] Determined by the Dumas combustion method.

[c] Described in ref. (4).

[d] Described in ref. (5).

[e] 2-Dodecylimidazole was mentioned by name, but not further described, by Graenacher and Meyer (3).

[f] Recrystallized from methanol.

[g] Described in ref. (1).

[h] 1-Tridecenyl.

[i] 2-Pentadecyl-2-imidazoline, the intermediate, was described in French Patent 835,426 (12-21-38); *Chem. Zentr.*, **1939**, I, 3824. It was prepared by procedure B.

[j] 2-Pentadecylimidazole was mentioned by Waldmann and Chwala, French Patent 49,039 (10-14-38); *Chem. Zentr.*, **1939**, I, 286.

[k] 2-Benzyl-2-imidazoline, the intermediate, was described by Sonn (26), and by Aspinall (14). It was prepared by procedure A.

[l] Recrystallized from aqueous methanol. Sonn and Greif, *Ber.*, **66**, 1900 (1933), prepared 2-benzylimidazole by decarboxylation of 2-benzylimidazole-4,5-dicarboxylic acid, and reported m.p. 125–126°.

[m] Recrystallized from acetone.

to 245°, at which temperature dehydrogenation was essentially complete; the total reaction time was 20 minutes. Distillation directly from the catalyst yielded 3.5 g. of head fraction, b.p. 100–179° (5 mm.), and 25.6 g. (76.6%) of 1-amyl-2-hendecylimidazole, b.p. 170–180° (1.5 mm.).

Alkylation of 2-methyl-2-imidazoline with dodecyl bromide. (*Procedure D*). A mixture of 50.4 g. (0.6 mole) of 2-methyl-2-imidazoline, 74.7 g. (0.3 mole) of dodecyl bromide, and 100 cc. of benzene was refluxed for 7 hours and cooled to 25°. Water, 150 cc., and 24 g. of 50% sodium hydroxide solution were added, the mixture was stirred for one hour, and a colorless, waxy solid, dry weight, 15 g., was filtered from the mixture. This proved to be N,N′-didodecylethylenediamine hydrate, m.p. 71–72° (melt not entirely clear), after recrystallization from 95% ethanol.

Anal. Calc'd for $C_{26}H_{56}N_2 \cdot H_2O$: C, 75.3; H, 14.1; N, 6.8; H_2O, 4.3.
Found: C, 75.1; H, 14.0; N, 7.1; H_2O, 4.4.

The anhydrous base was obtained by distillation, b.p. 225–230° (1.5 mm.); f.p. 39.8°, with no further purification. Recently the m.p. 15–17° was reported in the literature (24) for N,N′-didodecylethylenediamine.

The dihydrochloride was prepared by treating an alcoholic solution of N,N′-didodecylethylenediamine hydrate with aqueous hydrochloric acid. After recrystallization from 95% ethanol, it sintered at about 272°.

Anal. Calc'd for $C_{26}H_{56}N_2 \cdot 2HCl$: Cl, 15.1. Found: Cl, 15.1.

The above salt apparently was identical with N,N′-didodecylethylenediamine dihydrochloride prepared from the pure base made by alkylation of ethylenediamine with dodecyl bromide, since a mixture with the authentic sample sintered at about 272°.

The benzene layer was separated from the filtrate obtained after removal of the waxy solid, and the products were distilled. Three fractions were collected. (a) 1-Dodecyl-2-methyl-2-imidazoline was obtained at 204–209° (13 mm.); yield, 30 g. (38%). Upon redistillation the product boiled at 158-159° (4 mm.). (b) An intermediate fraction, 8 g., was collected at 190–240° (4 mm.). (c) N-acetyl-N,N′-didodecylethylenediamine (III), 20 g., was collected at 243–250° (4 mm.).

Anal. Calc'd for $C_{28}H_{58}N_2O$ (III): C, 76.6; H, 13.3; N, 6.4.
Found: C, 76.6; H, 13.6; N, 6.3.

III was found to be highly resistant to hydrolysis with alkali or acid, but upon refluxing with aqueous-alcoholic hydrochloric acid for 15–20 hours, followed by cooling, crystals of N,N′-didodecylethylenediamine dihydrochloride, sintering point about 268°, were obtained. A mixture of this salt with the authentic sample did not show a depressed sintering point.

Anal. Calc'd for $C_{26}H_{56}N_2 \cdot 2HCl$: Cl, 15.1. Found: Cl, 15.1.

Virtually the same yield of 1-dodecyl-2-methyl-2-imidazoline was obtained when the alkylation was performed with dodecyl chloride. When strictly anhydrous reagents were used, no N,N′-didodecylethylenediamine was formed, but N-acetyl-N,N′-didodecylethylenediamine was isolated as before; the yield of alkylated 2-imidazoline, however, was not improved by using anhydrous conditions.

1-Ethyl-2-hendecyl-2-imidazoline. (*Procedure D*). Fifty grams of 2-hendecyl-2-imidazoline (13) (0.223 mole) was melted and the temperature maintained at 70–80° while 34.4 g. of diethyl sulfate (0.224 mole) and 8.9 g. of sodium hydroxide in 15 cc. of water were added slowly and simultaneously from separate burettes, keeping the reaction mixture just alkaline to phenolphthalein. After all the alkali and diethyl sulfate had been added, the mixture was heated for 2 hours at 80°, cooled to 25°, treated with 100 cc. of butanol and 40 g. of 50% aqueous sodium hydroxide solution, and stirred for one hour. The butanol layer was separated, washed twice with 50-cc. portions of water, the solvent was removed and the product distilled. A 19.7 g. forerun, taken at 142–172° (2.5 mm.), contained 13 g. of 2-hendecyl-2-imidazoline, isolated by redistillation. The 1-ethyl-2-hendecyl-2-imidazoline boiled at 170–178° (2.5 mm.); yield, 23.5 g. (42%).

1-Amyl-2-hendecyl-2-imidazoline. (*Procedure D*). A charge of 90 g. (0.4 mole) of 2-hendecyl-2-imidazoline (13), in a flask equipped with an agitator, thermometer and reflux condenser, was stirred and heated at 140–150°. Amyl chloride, 21.3 g. (0.2 mole), was added during about 30 minutes. The reaction mixture was held at about 150° for 16 hours and then cooled to 60°. Water, butanol, and 17 g. of 50% aqueous sodium hydroxide solution were added, the mixture was stirred for one hour at 30°, and the butanol layer was

separated and fractionated. The head fraction, 7.2 g., boiled at 60–125° (5 mm.). The recovered 2-hendecyl-2-imidazoline was collected in the range 145–180° (5 mm.); weight, 43 g. Yield of 1-amyl-2-hendecyl-2-imidazoline, b.p. 180–200° (5.5 mm.), 41.5 g. (70%).

1-Amyl-2-hendecylimidazole. (Procedure E). A mixture of 20 g. (0.09 mole) of 2-hendecylimidazole (3) and 9.4 g. (0.09 mole) of amyl chloride in a flask equipped with an agitator, thermometer, and reflux condenser was stirred and heated at 125–150° for 3 hours, cooled to 30°, dissolved in 25 cc. of water, and treated with 10 g. of 50% aqueous sodium hydroxide solution. The solid that precipitated was filtered from the reaction mixture and washed with water; dry weight, 4 g. The oily product in the filtrate was taken up with benzene, the non-aqueous (upper) layer was separated and distilled. A small forerun boiling at 145–205° (10 mm.) was obtained; weight, 1.7 g. The 1-amyl-2-hendecylimidazole boiled at 218–219° (10 mm.); yield, 14.4 g. (55%).

Sebacic acid diimino ether. A mixture of 8.2 g. (0.05 mole) of sebaconitrile (25) and 4.6 g. (0.10 mole) of absolute alcohol was stirred and cooled in an ice-bath and dry hydrogen chloride was passed in until no more was absorbed. The mixture became thick, and in about an hour following the start of hydrogen chloride addition, it solidified. The crude diimino ether, 19.4 g., was a hygroscopic solid soluble in hot chloroform; m.p. 85–86° with evolution of gas. No loss in weight occurred when the product was placed under reduced pressure.

The reagents and apparatus used in this experiment must be strictly dry, or a large amount of sebacic acid diamide will be formed.

2,2'-Octamethylenedi-2-imidazoline. This compound was prepared by the general method described by Sonn (26). Crude sebacic acid diimino ether (19.4 g.) was dissolved in 50 cc. of chloroform by refluxing, the excess hydrogen chloride being driven off by this procedure. The solution was cooled to 30° and 6.0 g. (0.1 mole) of anhydrous ethylenediamine was added; a precipitate formed immediately, and some heat was evolved. The mixture was refluxed until no more ammonia gas was liberated, cooled to 25°, and the solid remaining was filtered off and washed with chloroform. The filtrate was evaporated to dryness under reduced pressure, the residue was dissolved in 50 cc. of water, and the solution was treated with 4.0 g. of aqueous 50% sodium hydroxide solution added dropwise. The colorless solid that precipitated was filtered off, washed with water, and dried at 70°; yield 8.8 g. (70%); m.p. 179–181°. On recrystallization from ethanol it was obtained as long prismatic needles, m.p. 185–187°.

This product was described in a French Patent (27), where it was made by heating a mixture of sebacic acid, ethylenediamine, and ethylenediamine hydrochloride, and in a U. S. Patent (28), where it was made by heating ethyleneurea with sebacic acid. The latter reference gives the m.p. as 185–187°.

1-Dodecyl-2-methylbenzimidazole. This product was made in 58% yield by reaction of two moles of 2-methylbenzimidazole (29) and one mole of dodecyl chloride in boiling xylene. A similar procedure was used in a patent (30), but the product was not described. It is a yellow liquid, b.p. 225–227° (5 mm.).

Anal. Calc'd for $C_{20}H_{32}N_2$: N, 9.3. Found: N, 9.3.

A number of 1,2-dialkylbenzimidazoles were made recently by Weidenhagen and coworkers (31).

Ethyl pentadecanoate. A mixture of 150 g. of 95% ethanol, 150 g. of concentrated sulfuric acid, and 68 g. of tetradecyl cyanide (0.305 mole) was agitated at reflux temperature for four hours. The reaction product was poured into 400 cc. of ice and water, and extracted with 100 cc. of ether and then with 100 cc. of benzene. The combined ether and benzene extracts were washed with water and dried. The solvent was removed, and the product distilled; b.p. 156–158° (5 mm.); yield, 69.3 g. (87%). A test of the method of Christmann (32), using hydrogen chloride, gave a 77% yield. The ester was used in the preparation of 2-tetradecyl-2-imidazoline.

Ethyl tridecanoate. This ester was obtained in 91% yield using dodecyl cyanide, ethanol and sulfuric acid in the process described above for ethyl pentadecanoate; b.p. 133–134°

(4 mm.). The process given in *Organic Syntheses* (33), is considerably more complicated, requiring hydrolysis of the nitrile, followed by forty-eight hours' esterification of the crude acid. The ester was used in the preparation of 2-dodecyl-2-imidazoline.

Ethyl 2-tetradecenoate. 2-Tetradecenoic acid was made by bromination of myristic acid (1, 34) followed by dehydrohalogenation with quinoline at 200°. The acid was esterified with absolute ethanol and sulfuric acid, yielding 62% of ester, b.p. 165–167° (11 mm.), which was used in the preparation of 2-(1′-tridecenyl)-2-imidazoline.

Methyl 4-cyclohexylbutyrate. This ester, required for the preparation of 2-(3′-cyclohexylpropyl)-2-imidazoline, was made in 75% yield by Dr. F. C. Meyer by hydrogenation of methyl 4-phenylbutyrate (35) without a solvent, using a nickel catalyst; b.p. 124° (24 mm.). Ethyl 5-cyclohexylvalerate was prepared in a similar manner by Baker and Dodson (36), who hydrogenated ethyl 5-phenylvalerate in alcohol solution using Raney nickel.

N,N′-Ditetradecylethylenediamine hydrate. This material was isolated as a by-product in the reaction of 2-methyl-2-imidazoline with tetradecyl chloride. Upon recrystallization from 95% ethanol, it was obtained in the form of white, waxy crystals, m.p. 72–73° (the melt was cloudy); Linsker and Evans (24) reported m.p. 24–26° for N,N′-ditetradecylethylenediamine.

Anal. Calc'd for $C_{30}H_{64}N_2 \cdot H_2O$: N, 6.0; H_2O, 3.8.
Found: N, 5.9; H_2O, 3.8.

SUMMARY

The preparation and properties of a number of substituted 2-imidazolines and imidazoles have been reported.

A simplified method of preparing 2-alkyl-2-imidazolines has been described.

The reaction of 2-alkyl-2-imidazolines with alkyl halides has been investigated and the products formed have been identified in several instances.

Many of the compounds described have activity in the biological field.

St. Louis 4, Mo.

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