gave 168 g. (78% of the total distillate) of product with indices of refraction of $n^{20}D$ 1.4813 ± 0.0002. Ten central fractions, 114 g., comprising 53% of the total distillate had a constant boiling point, 147.5° at 0.08 mm., and a constant index of refraction, $n^{20}D$ 1.4813 ± 0.0001.

Anal. Calcd. for $C_{25}H_{44}$: C, 87.1; H, 12.9. Found: C, 87.1, 87.0, H, 12.6, 12.8.

4-Cyclohexyl-13-*n*-propylhexadecane.—Approximately 213 g. of combined rejected fractions of the foregoing hydrocarbon and material from preliminary experiments was treated with hydrogen and Raney nickel as described before, and 207 g. of the oily product was fractionated through the 20-plate column. Twenty-six fractions (202 g. total), including several obtained when the still pot and column were finally heated to dryness, were collected without any sign of decomposition. Thirteen central fractions (131 g.) comprising 65% of the total distillate had the same boiling point, 148° at 0.02 mm., and identical refractive indices, $n^{20}D$ 1.4654.

Anal. Calcd. for $C_{25}H_{50}$: C, 85.6; H, 14.4. Found: C, 85.8, 85.8; H, 13.8, 14.3

Summary

Five new high molecular weight hydrocarbons, *i.e.*, 1,14-diphenyltetradecane, 1-phenyl-12-*n*-propylpentadecane, 4-phenyl-13-*n*-propylhexadecane, and the cyclohexyl analogs of the latter two, have been prepared in a high state of purity.

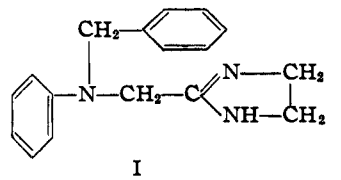
NORTHAMPTON, MASS. RECEIVED DECEMBER 17, 1946

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

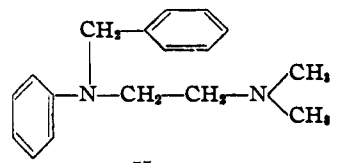
Aryloxyacetamidines and 2-(Aryloxymethyl)-imidazolines[1]

BY CARL DJERASSI AND CAESAR R. SCHOLZ

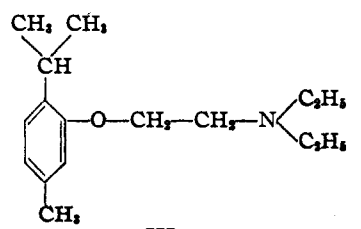
Recent reports have indicated that 2-(N-benzyl-N-phenylaminomethyl)-imidazoline (I), first prepared by Miescher, Urech and Klarer,[2] has strong histaminolytic properties and that this compound, known under the trade name Antistin, has found clinical application[3] against various allergic symptoms. Antistin differs from Antergan (II), a well-known antihistaminic[4] in the nature of the side chain, the 2-methylimidazoline group replacing the dimethylaminoethyl moiety. Since this change seemed to have enhanced the desirable antihistaminic activity, we have extended this observation to other series.



I



II



III

In this paper, we are reporting the results which we obtained in varying the side chain of ring-alkylated aryloxyethyldialkylamines, of which the histaminolytic F 929 (III)[5] is the best known example. Since imidazolines can be considered to be cyclized amidines, we have included aryloxyacetamidines in our investigation, in addition to 2-(aryloxymethyl)-imidazolines.

Of the many amidine syntheses reported in the literature,[6] that of Pinner[7] was most suited to our purpose. Ring-alkylated aryloxyacetonitriles, required as starting materials in our synthesis, have been prepared previously by dehydration of the corresponding amide[8] or aldoxime.[9] The patent literature[10,11,12] contains reports of the alkylation of phenols with chloroacetonitrile, but no details are given. In this work, it was found that the reaction could be carried out in good yields when a modification of the conventional Claisen O-alkylation of phenols[13] was employed.

Conversion of the nitriles into the imidic ester hydrochlorides (Table I) and thence to the amidines (Table II) was carried out by known methods.[6,7] With the exception of thymyloxyacetamidine and its N-dibutyl derivative,[14] all amidines reported in Table II are new compounds as far as we can determine.

The 2-(aryloxymethyl)-imidazolines (VI) (Table III) were synthesized by three different methods.

(1) Presented on the program of the Division of Medicinal Chemistry at the Chicago meeting of the American Chemical Society, September 9–13, 1946.

(2) *Cf.* Meier and Bucher, *Schweiz. med. Wochschr.*, **76**, 294 (1946).

(3) Bourquin, *ibid.*, **76**, 296 (1946); Schindler, *ibid.*, **76**, 300 (1946); Brack, *ibid.*, **76**, 316 (1946).

(4) Halpern, *Arch. Internat. Pharmacodynamie*, **68**, 339 (1942).

(5) Staub, *Ann. Inst. Pasteur*, **63**, 400, 485 (1939).

(6) Shriner and Neumann, *Chem. Rev.*, **35**, 351 (1944).

(7) Pinner, "Die Imidoäther und ihre Derivate," Oppenheim, Berlin, 1892.

(8) *Cf.* (a) Powell and Adams, THIS JOURNAL, **42**, 646 (1920); (b) Higginbotham and Stephen, *J. Chem. Soc.*, 1534 (1920).

(9) Stoermer, *Ber.*, **30**, 1700 (1897).

(10) U. S. Patent 2,149,457; *C. A.*, **33**, 4379 (1939).

(11) U. S. Patent 2,149,473; *C. A.*, **33**, 4380 (1939).

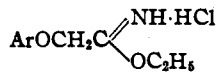
(12) Swiss Patents 204,752–204,766; *C. A.*, **35**, 2280 (1941).

(13) *Cf.* Hurd and Perletz, THIS JOURNAL, **68**, 38 (1946).

(14) German Patent 684,945, *C. A.*, **34**, 2536 (1940).

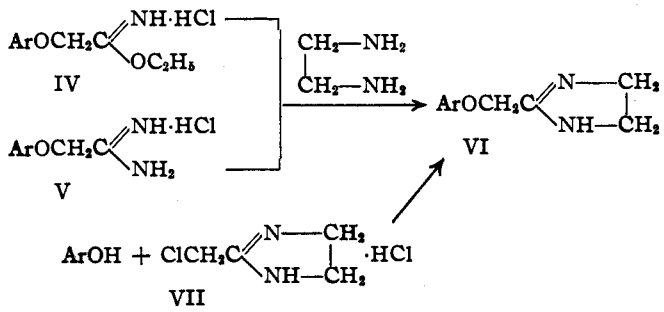
TABLE I

ETHYL ARYLOXYACETIMIDATE HYDROCHLORIDES



ArO	M. p.,[a] °C.	2nd m. p.[b]	M. p. of amide	Yield, %	Formula	Analyses, % HCl Calcd.	HCl Found	N Calcd.	N Found
Phenoxy	111–113	100	101.5[c]	68	$C_{10}H_{14}O_2NCl$	16.91	16.38	6.50	7.07
o-Toloxy	109.5–110.5	127	127[d]	88	$C_{11}H_{16}O_2NCl$	15.88	16.18	6.10	6.36
m-Toloxy	108.5–111	114	118[e]	79	$C_{11}H_{16}O_2NCl$	15.88	16.09	6.10	6.13
p-Toloxy	111–111.5	128	127[f]	92	$C_{11}H_{16}O_2NCl$	15.88	16.29	6.10	6.13
Thymyloxy	109.5–110	93	98[g]	89	$C_{14}H_{22}O_2NCl$	13.42	13.33	5.15	5.10
Carvacryloxy	111–112.5	94	99[h]	66	$C_{14}H_{22}O_2NCl$	13.42	13.33	5.15	5.13
3-Methyl-4-chlorophenoxy	119.5–121	145.5	147[i]	88	$C_{11}H_{15}O_2NCl_2$	13.80	14.26	5.30	5.33
o-i-Propylphenoxy	107.5–109.5	94	100.5[j]	78	$C_{13}H_{20}O_2NCl$	14.15	13.74	5.44	5.67
2,5-Dimethylphenoxy	120.5–121	115.5	120.5[k]	77	$C_{12}H_{18}O_2NCl$	14.96	15.30	5.75	6.02

[a] With gas evolution. [b] Obtained by cooling the once melted material and re-determining the melting point. The second melting point is that of the corresponding amide. [c] Fritzsche, *J. prakt. Chem.*, [2] **20**, 267 (1879). [d] Ref. 8b. [e] Ref. 8b. [f] Forte, *Gazz. chim. ital.*, **22**, II, 525 (1892). [g] Reported by Spica, *Gazz. chim. ital.*, **10**, 340 (1880), for thymyloxyacetamide: m. p. 96–97°. Hydrolysis at 120° under pressure of any of the thymyloxyacetimidines given in Table II yielded thymyloxyacetamide, m. p. 97.5–98° from petroleum ether–acetone. *Anal.* Calcd. for $C_{12}H_{17}O_2N$: N, 6.76. Found: N, 7.20. [h] Spica (ref. *g*) reported m. p. 67–68° for carvacryloxyacetamide, but gave no analysis. Hydrolysis of carvacryloxyacetamidine gave the amide in 86% yield; m. p. 97.5–99° from petroleum ether–acetone. *Anal.* Calcd. for $C_{12}H_{17}O_2N$: N, 6.76. Found: N, 6.83. [i] 3-Methyl-4-chlorophenoxyacetamide, m. p. 146–147° from petroleum ether, was obtained in 53% yield on hydrolysis of N-dimethyl 3-methyl-4-chlorophenoxyactamidine. *Anal.* Calcd. for $C_9H_{10}O_2NCl$: C, 54.14; H, 5.05. Found: C, 53.92; H, 4.83. [j] *o*-Isopropylphenoxyacetamide, m. p. 98–100.5°, was isolated in 67% yield by hydrolysis of the corresponding amidine. *Anal.* Calcd. for $C_{11}H_{15}O_2N$: N, 7.25. Found: N, 7.22. [k] 2,5-Dimethylphenoxyacetamide, m. p. 119.5–120.5° from petroleum ether–acetone; yield, 64% from the corresponding amidine. *Anal.* Calcd. for $C_{10}H_{13}O_2N$: N, 7.82. Found: N, 7.69.



The method of choice was the condensation of the imidic ester hydrochloride (IV) with ethylenediamine.[11] Condensation of the amidine hydrochloride (V) with ethylenediamine[15,16] was also applicable to our series, but since this synthesis involved an additional and unnecessary step, the reaction was not studied in detail. The alkylation of phenols with 2-(chloromethyl)-imidazoline hydrochloride (VII)[15] was also investigated[17] and could be carried out successfully in the presence of alkaline catalysts as described in the experimental section.

Pharmacological Results[18]

The strong vasopressor action of the 2-(aryloxymethyl)-imidazolines claimed previously[11,19] was confirmed in this study. With two exceptions, (the *p*-toloxy and 3-methyl-4-chlorophenoxy derivatives) all of the imidazolines given in Table III were very effective in raising the blood pressure of the dog. The *in vitro* anti-histaminic and antiacetylcholinic activity is given in Table III. 2-(Thymyloxymethyl)-imidazoline hydrochloride was found to be more effective in relaxing histamine-induced spasm than F 929 (III),[5] indicating that in this series the 2-methylimidazoline group was equal or superior to the diethylaminoethyl side chain.

Some of the pharmacological properties of the amidines are given in Table II. Their effects on canine blood pressure were variable and no correlation between chemical constitution and vasomotor effects was observed. The anti-histaminic action of thymyloxyacetamidine was at least as great as that of F 929 and in certain N-substituted thymyloxy- and carvacryloxy-acetamidines, this effect was enhanced manyfold.

The most striking observation was the very strong and persisting anti-cholinergic action shown by some of the amidines, an action approaching that of atropine in the case of the N-dimethyl- and N-diethyl-thymyloxyacetamidines. This anti-cholinergic action was found to be correlated with chemical structure. Substitution on the amidine nitrogen and in the *ortho* position of the aromatic ring was essential. The most effective compounds belonged to the *ortho-meta* disubstituted series, one of the substituents being an isopropyl group; for example, the N-substituted thymyloxy- and carvacryloxyacetamidines. In-

(15) Klarer and Urech, *Helv. Chim. Acta*, **27**, 1762 (1944).

(16) U. S. Patent 2,252,721; *C. A.*, **35**, 7658 (1941).

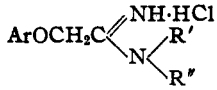
(17) For similar alkylations of amines, *cf.* U. S. Patent 2,252,722; *C. A.*, **35**, 7657 (1941).

(18) The preliminary data given below were furnished to us through the courtesy of Drs. B. N. Craver and F. F. Yonkman of our Pharmacology Department, who will publish the detailed results in another journal.

(19) See Scholz, *Ind. Eng. Chem.*, **37**, 120 (1945), for a review of related imidazolines.

TABLE II

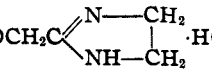
ARYLOXYACETAMIDINE HYDROCHLORIDES



ArO	R	R″	Reaction time (hrs.)	M. p., °C.	Yield, %	Formula	Analyses, % HCl Calcd.	HCl Found	N Calcd.	N Found	Spasmolytic activity Histamine[a]	Spasmolytic activity Acetylcholine[b]	Effect on canine blood pressure[c]
Phenoxy	H	H	72	127.5–128.5	72	$C_9H_{10}ON_2Cl$	19.96	19.54	15.01	14.70	10	[e]	[f]
Phenoxy	CH_3	CH_3	72	187–189	77	$C_{10}H_{12}ON_2Cl$	16.99	17.17	12.46	12.77	[e]	[e]	+++
o-Toloxy	H	H	44	147.5–148.5	86	$C_9H_{12}ON_2Cl$	18.17	18.57	13.96	13.80	[e]	[e]	–
o-Toloxy	CH_3	CH_3	46	177–179	88	$C_{11}H_{17}ON_2Cl$	15.94	16.06	12.25	12.20	[e]	1–10	[f]
m-Toloxy	H	H	42	179–180.5	78	$C_9H_{12}ON_2Cl$	18.17	18.41	13.96	14.05	10	10	+++
m-Toloxy	CH_3	CH_3	42	200–202	65	$C_{11}H_{17}ON_2Cl$	15.94	15.99	12.25	12.06	[e]	[e]	– –
p-Toloxy	H	H	42	169.5–170.5	73	$C_9H_{12}ON_2Cl$	18.17	18.44	13.96	14.03	[e]	[e]	– –
p-Toloxy	CH_3	CH_3	46	173–174.5	75	$C_{11}H_{17}ON_2Cl$	15.94	16.08	12.25	12.29	[e]	[e]	– –
Thymyloxy	H	H	67	185–185.5[d]	85	$C_{12}H_{19}ON_2Cl$	15.02	15.53	11.55	11.87	1–10	[e]	[f]
Thymyloxy	CH_3	CH_3	72	197–198	80	$C_{14}H_{23}ON_2Cl$	13.47	13.93	10.35	10.21	10	0.1	+
Thymyloxy	C_2H_5	C_2H_5	43	212–212.5	57	$C_{16}H_{27}ON_2Cl$	12.20	12.52	9.38	9.18	0.5–1	0.1	–
Thymyloxy	*n*-C_3H_7	*n*-C_3H_7	42	180–182	50	$C_{18}H_{31}ON_2Cl$	11.73	11.91	9.01	8.66	1–10	0.5 –1	– –
Thymyloxy	*n*-C_4H_9	*n*-C_4H_9	72	154–155[g]	61	$C_{20}H_{35}ON_2Cl$	10.28	10.54	7.89	8.19	1	1–10	–
Thymyloxy	$CH_3CH_2C_6H_5$	H	65	145–147	71	$C_{20}H_{27}ON_2Cl$	10.51	10.31	8.08	8.04	1–10	10	– –
Carvacryloxy	H	H	48	183.5–184.5	76	$C_{12}H_{19}ON_2Cl$	15.02	15.20	11.55	11.61	10	[e]	[f]
Carvacryloxy	CH_3	CH_3	46	178–180	67	$C_{14}H_{23}ON_2Cl$	13.47	13.50	10.35	10.04	1–10	0.5 –1	+
Carvacryloxy	$CH_3CH_2C_6H_5$	H	70	158.5–159.5	65	$C_{20}H_{27}ON_2Cl$	10.51	10.79	8.08	8.34	0.1–1	1–10	–
3-Methyl-4-chlorophenoxy	H	H	48	193–194	87	$C_9H_{11}ON_2Cl_2$	15.51	15.82	11.92	12.19	1	10	– –
	CH_3	CH_3	48	183.5–185.5	78	$C_{11}H_{15}ON_2Cl_2$	13.86	14.16	10.65	10.48	10	10	– –
o-Isopropylphenoxy	H	H	48	147.5–149	83	$C_{11}H_{17}ON_2Cl$	15.95	16.12	12.25	12.27	10	10	–
	CH_3	CH_3	48	198–198.5	70	$C_{13}H_{21}ON_2Cl$	14.20	14.38	10.91	10.96	10	1	– –
2,5-Dimethylphenoxy	H	H	68	215–217	88	$C_{10}H_{15}ON_2Cl$	16.98	17.39	13.05	13.10	[e]	[e]	+
	CH_3	CH_3	68	212–214	87	$C_{12}H_{19}ON_2Cl$	15.02	15.11	11.54	11.25	[e]	1–10	–

[a] The approximate activity is expressed in γ of compound per ml. of bath liquid, capable of neutralizing the contraction of an isolated guinea pig gut, caused by 1γ per ml. of histamine diphosphate. [b] As in (a) but using 0.2 γ of acetylcholine bromide. [c] (+) signs refer to a rise, and (−) signs to a fall in blood pressure. Exact dosages will be reported in future pharmacological publications. [d] Reported (ref. 14), m. p. 182–183°. [e] Inactive in doses of 10 γ. [f] No effect with dosage tested. [g] Reported (ref. 14), m. p. 154–156°.

TABLE III

2-(ARYLOXYMETHYL)-IMIDAZOLINE HYDROCHLORIDES $ArOCH_2C$  $\cdot HCl$

ArO	M. p., °C.	Yield, %	Formula	Analyses, % HCl Calcd.	HCl Found	N Calcd.	N Found	Spasmolytic action Histamine[a]	Spasmolytic action Acetylcholine[b]
Phenoxy	168–169.5[c]	82	$C_{10}H_{13}ON_2Cl$	17.15	17.17	13.17	13.10	10	[e]
o-Toloxy	200–202	71	$C_{11}H_{15}ON_2Cl$	16.09	16.32	12.36	12.44	[e]	10
m-Toloxy	225–227	55	$C_{11}H_{15}ON_2Cl$	16.09	16.24	12.36	12.59	[e]	[e]
p-Toloxy	151–153	62	$C_{11}H_{15}ON_2Cl$	16.09	16.27	12.36	12.03	1–10	[e]
Thymyloxy	223.5–225[d]	78	$C_{14}H_{21}ON_2Cl$	13.57	13.64	10.43	10.91	1–10	10
Carvacryloxy	175–176	67	$C_{14}H_{21}ON_2Cl$	13.57	13.35	10.43	10.54	[e]	[e]
3-Methyl-4-chlorophenoxy	221–223	57	$C_{11}H_{14}ON_2Cl_2$	13.96	14.24	10.73	11.12	10	10
o-Isopropylphenoxy	173.5–174.5	58	$C_{13}H_{19}ON_2Cl$	14.90	15.13	11.45	11.42	10	10
2,5-Dimethylphenoxy	223.5–225.5	67	$C_{12}H_{17}ON_2Cl$	15.15	15.50	11.64	11.65	10	[e]

[a] See Table II, footnote *a*. [b] See Table II, footnote *b*. [c] See ref. 26. [d] Reported (ref. 11) m. p. 215–217°. [e] Inactive in 10γ doses.

creasing the chain length between the ether linkage and the amidine moiety was found to decrease the anti-cholinergic activity.[20]

Experimental[21,22]

Aryloxyacetonitriles.—The procedure used for the condensation of chloroacetonitrile with phenols was based on the method of Hurd and Perletz[13] for aryloxyacetones.

To a vigorously stirred and refluxing suspension of 0.2 mole of the phenol and 26 g. (0.19 mole) of anhydrous potassium carbonate in 35 cc. of dry methyl ethyl ketone was added over a period of one and one-half hours a solution of 14 cc. (0.22 mole) of chloroacetonitrile[23] and 0.5 g. of potassium iodide in 15 cc. of methyl ethyl ketone. The chloroacetonitrile solution had been allowed to stand in the dark for eighteen hours prior to addition. After refluxing for an additional one-half to one hour, most of the solvent was distilled off and water was added to the residue. The product was taken up in ether or chloroform, washed several times with 5% sodium hydroxide solution, the solvent was evaporated and the product was fractionated *in vacuo*. The boiling point and refractive index values

(20) Djerassi, Scholz, Craver and Yonkman, unpublished observation.

(21) All melting points are corrected and were determined in sealed capillaries.

(22) The microanalyses were carried out by Mr. Joseph F. Alicino, Metuchen, N. J. We are grateful to Miss Jean Rogers for assistance in the experimental work.

(23) Steinkopf, *Ber.*, **41**, 2540 (1908).

TABLE IV

ARYLOXYACETONITRILES, $ArOCH_2CN$

ArO	B. p. or m. p. °C.	Pressure, mm.	$n^{20}D$	Yield, %	Reported constants b. p. or m. p., °C.	Pressure, mm.	Ref.
Phenoxy	120–123	12	1.5243	75	132	30	8a
o-Toloxy	124–126	12	1.5225	67	133	10	8b
m-Toloxy	126–128	12	1.5211	75	141	10	8b
p-Toloxy	35–36			76	38–39		8b
Thymyloxy	142–147	13	1.5120	81	118	0.8	11
Carvacryloxy	138–143	12	1.5118	75			
3-Methyl-4-chlorophenoxy	43–46			81			
o-Isopropylphenoxy[a]	140–145	12	1.5130	80			
2,5-Dimethylphenoxy	135–138	13	1.5199	71			

[a] *o*-Isopropylphenol was obtained through the courtesy of Sharples Chemicals Inc.

given in Table IV refer to that fraction on which the yield was based and which was used in the next step.

The use of acetone, the omission of potassium iodide or longer refluxing gave inferior results.

Ethyl Aryloxyacetimidate Hydrochlorides (IV).—An ice-cold solution of 0.05 mole of nitrile in 0.053 mole of absolute ethanol was treated with 0.053 mole of dry hydrogen chloride gas. The product was triturated with dry ether, the crystals were collected, washed thoroughly with ether and dried in a vacuum desiccator over potassium hydroxide and phosphorus pentoxide. The hydrochlorides were somewhat hygroscopic, but they could be kept in stoppered bottles in a desiccator for several months without decomposition.

With solid nitriles, the use of a solvent in addition to the ethanol was necessary. Although dry ether was satisfactory, chloroform was more advantageous because the imidic ester hydrochlorides were usually soluble in that solvent and cake formation was thus eliminated as well as clogging up of the gas inlet tube. The product was isolated by concentration of the solution and dilution with ether. When liquid nitriles were used on a larger scale, it was useful to employ chloroform as a solvent.

The imidic ester hydrochlorides reported in Table I were not recrystallized, because warming resulted in evolution of ethyl chloride and formation of the amide.[6,7] This decomposition was noted particularly during melting point determinations, the material melting with gas evolution and the cooled melt possessing a different melting point (see Table I). This ready decomposition into ethyl chloride and the amide had to be taken into account in the Dumas determinations. Mr. Alicino[22] informed us that when the combustion was carried out too quickly, the nitrogen values were often 1–2% too high. No difficulty was encountered on slow combustion.

Aryloxyacetamidines. (a) **Unsubstituted Amidines (V).**—A suspension of 0.01 mole of the imidic ester hydrochloride in 10% ethanolic ammonia solution containing 0.013 mole of ammonia was shaken in a stoppered bottle for the time specified in Table II. The solution was filtered from a small amount of ammonium chloride, the filtrate diluted with ether and the crude amidine hydrochloride was collected. The hydrochlorides were readily recrystallized from a mixture of methyl ethyl ketone and ethanol.

(b) **N-Substituted Amidines.**—When primary or secondary amines were used instead of ammonia, the same molar ratio was employed as in (a). However, in several cases, the separation from unreacted amine hydrochloride was much more difficult than in the case of ammonium chloride because of the almost identical solubility characteristics with the amidine hydrochloride and, therefore, fractional crystallization of the hydrochlorides did not lead to pure products. Nevertheless, it was important to eliminate even small amounts of the amine hydrochloride, *e. g.*, dimethylamine hydrochloride, because its presence would have seriously interfered in the pharmacological tests in view of its high toxicity. The purification was more effectively achieved by evaporating the solution to dryness or precipitating the entire hydrochloride mixture by the addition of ether and to dissolve the residue in potassium carbonate solution. The free amidine was then extracted with chloroform, dried over potassium carbonate, the solvent removed and the residue kept *in vacuo* for a short time to ensure removal of the relatively low boiling amines. The amidine hydrochloride was then obtained in a satisfactory state of purity by adding methanolic hydrogen chloride solution and precipitating with ether.

2-(Aryloxymethyl)-imidazolines (VI). (a) **From the Imidic Ester Hydrochloride.**—A solution of 0.05 mole of the imidic ester hydrochloride and 0.55 mole of anhydrous ethylenediamine in *ca.* 15 cc. of absolute ethanol was refluxed for six hours and then kept in the ice-box overnight. A small amount of ethylenediamine dihydrochloride was filtered, the filtrate evaporated and the residual hydrochloride was recrystallized from a mixture of methyl ethyl ketone and ethanol. All of the yields given in Table III were obtained by this method (*cf.* ref. 11).

(b) **From 2-(Chloromethyl)-imidazoline Hydrochloride (VII).**—Chloroacetonitrile was converted into ethyl chloroacetimidate hydrochloride[24] in 83% yield, m. p. 88–90° (gas).

Ring closure[15,25] with ethylenediamine was effected in 68% yield to give 2-(chloromethyl)-imidazoline hydrochloride (VII), m. p. 193.5–199° (dec.) when immersed at 180°; lit. 202–204°,[15] 185–190°.[25]

To a solution of 0.92 g. (0.04 mole) of sodium in 30 cc. of absolute ethanol was added 1.88 g. (0.02 mole) of phenol followed by 3.08 g. (0.02 mole) of 2-(chloromethyl)-imidazoline hydrochloride (VII). After refluxing for one hour with vigorous stirring, the solution was filtered from sodium chloride (96% of the theoretical) and saturated ethanolic picric acid solution was added until no more precipitate was formed. The bright yellow crystals were collected and washed thoroughly with ethanol to remove traces of phenol; yield, 3 g. (37%), m. p. 190–197°.

The analytical sample of **2-(phenoxymethyl)-imidazoline picrate** crystallized from acetone as bright yellow blades; m. p. 200–202°; sometimes, a mixture of blades and prisms was obtained which melted at 194–199.5°, but melted sharply at 200–202° when the melt was cooled and the m. p. determined again. The picrate seemed to exist in two polymorphic forms.

Anal. Calcd. for $C_{16}H_{15}O_8N_5$: C, 47.41; H, 3.73; N, 17.28. Found: C, 47.16; H, 3.64; N, 16.97.

2-(Phenoxymethyl)-imidazoline, obtained from the picrate, melted at 69–70° after crystallization from petroleum ether–acetone. The base was readily soluble in water and its aqueous solution turned red litmus blue.

Anal. Calcd. for $C_{10}H_{12}ON_2$: N, 15.90. Found: N, 15.74.

2-(Phenoxymethyl)-imidazoline hydrochloride, prepared from the base, was found to be identical by mixed melting point determination with the hydrochloride pre-

(24) McElvain and Nelson, THIS JOURNAL, **64**, 1825 (1942).

(25) U. S. Patent 2,252,723, *C. A.*, **35**, 7658 (1941).

pared by the first method (*via* the imidic ester hydrochloride). The melting point in each case was 168–169.5° and was at variance with the reported value 130–132°.[11,26]

(c) **From the Amidine.**—In analogy to the synthesis of 2-(hydroxymethyl)-imidazoline,[15] 0.607 g. (0.0025 mole) of carvacryloxyacetamidine hydrochloride and 0.165 g. (0.00275 mole) of ethylenediamine were refluxed in ethanol solution for six hours, 0.2 cc. of 4.5 *N* methanolic hydrogen chloride was added and the solution left in the refrigerator overnight. After working up as in (a), there was obtained 0.15 g. (22%) of 2-(carvacryloxymethyl)-imidazoline hydrochloride, m. p. 175–176°, which gave no depression in melting point when mixed with a sample of this substance prepared according to method (a).

Summary

It has been shown that aryloxyacetonitriles can be obtained in good yield by condensation of phenols with chloroacetonitrile.

Treatment of the nitriles with ethanolic hydrogen chloride led to a series of ethyl aryloxyacetimidate hydrochlorides. The imidic esters were converted with ammonia to the amidines and with primary and secondary amines to the corresponding unsymmetrically N-alkylated amidines.

A number of 2-(aryloxymethyl)-imidazolines have been prepared by effecting ring closure of the imidic ester or the amidine hydrochlorides with ethylenediamine. The imidazolines could be obtained also by condensation of the phenol with 2-(chloromethyl)-imidazoline hydrochloride.

Preliminary results on the pharmacological properties of the amidines and imidazolines have been summarized, and have indicated that the usual dialkylaminoalkyl side chain of spasmolytics can be replaced by other radicals.

(26) In a private communication from the author, we have been informed that the compound of m. p. 130–132° contained water and that the anhydrous material melted at 168–170° in agreement with our findings.

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Electronic Interpretation of the Reaction of Olefins with Organic Per-acids

BY DANIEL SWERN

Numerous investigators have shown that, under similar experimental conditions, the rate of reaction of olefins with organic per-acids is dependent on the structure of the unsaturated compounds. This is illustrated in Tables I and II, in which specific reaction rates are given for the reaction of various olefins with peracetic and perbenzoic acids. In the majority of published papers, however, kinetic studies have not been reported, and the oxidation reactions have merely been described as slow or rapid (sometimes violent), or not taking place.

No explanation for this difference in reaction rates has been proposed by earlier workers, although certain empirical rules have been established. Thus, the reaction is either slowed down considerably or does not take place when carboxyl, carboalkoxy, aldehydo or keto groups are either attached to or are in close proximity to the double bond,[2] such as is the case in cinnamic acid and its esters,[2,3] maleic, fumaric and crotonic acids and their esters, and α,β-pentenoic and hexenoic acids.[3,4] Aliphatic mono-olefins with terminal double bonds also react slowly,[5a,6] whereas substitution of the hydrogen atoms attached to the double bond by alkyl groups increases the reaction rate considerably,[5b,7] and phenyl groups usually have only a mildly accelerating effect.[5a,8] Also, in the oxidation of isoprene, the double bond to which the methyl group is attached is attacked first[9,10]; in the oxidation of 2-methyl-2,3-butadiene (a substituted allene), geraniol, linalyl acetate and citral, the double bond to which both methyl groups are attached is attacked first[2b,10]; and in the oxidation of methyl 2,4-hexadienoate the double bond farther from the carbomethoxy group is attacked first.[11]

On the basis of stereochemical considerations alone, it is surprising that olefins with terminal double bonds react much more slowly with per-acids than olefins which contain alkyl groups directly attached to the double bond. In fact, ethylene, which contains no groups which might prevent ready access of the per-acid to the double bond, would be expected to react rapidly with per-acids, yet just the reverse is true. The majority of the specific reaction rates shown in Tables I and II, as well as the empirical rules and preferential reactions discussed above, fit into a logical pattern if one applies to them the electronic interpretations

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

(2) (a) Bodendorf, *Arch. Pharm.*, **268**, 491 (1930); (b) Prileschajew, *J. Russ. Phys.-Chem. Soc.*, **44**, 613 (1912).

(3) Böeseken and de Graaff, *Rec. trav. chim.*, **41**, 199 (1922); Böeseken, *ibid.*, **45**, 838 (1926).

(4) Braun, THIS JOURNAL, **51**, 228 (1929); **52**, 3185, 3188 (1930).

(5) (a) Stuurman, *Proc. Acad. Sci. Amsterdam*, **38**, 450 (1935); (b) Thesis, Delft (1936).

(6) (a) Swern, Billen and Scanlan, THIS JOURNAL, **68**, 1504 (1946); (b) Findley, Swern and Scanlan, *ibid.*, **67**, 412 (1945).

(7) Böeseken and Stuurman, *Proc. Acad. Sci. Amsterdam*, **39**, 2 (1936); *Rec. trav. chim.*, **56**, 1034 (1937); Böeseken and Hanegraaff, *ibid.*, **61**, 69 (1942).

(8) (a) Böeseken and Blumberger, *Rec. trav. chim.*, **44**, 90 (1925); (b) Böeseken and Elsen, *ibid.*, **42**, 363 (1929).

(9) Pummerer and Reindel, *Ber.*, **66**, 335 (1933).

(10) Böeseken, van Asperen, Cauchy, Maters and Ottenhoff, *Rec. trav. chim.*, **54**, 657 (1935).

(11) Heinanen, *Suomen Kemistilehti*, **11B**, 2 (1938); *C. A.*, **32**, 2903.