platelets, m.p. 70–71° both alone and in admixture with authentic[17] β-phenylpropiophenone of m.p. 70–71°.

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.83; H, 6.61.

The crude acids obtained in another run from 11 g. of 3,5-diphenyl-2-isoxazoline treated as above were recovered from the acidified sodium hydrogen carbonate extracts by ether extraction. The crude product (1.1 g.) on crystallizing from petroleum ether yielded a first crop of 0.17 g. of benzoic acid, m.p. 120–121° both alone and when mixed with pure benzoic acid, followed by further crops of less pure benzoic acid (0.339 g. in all). The non-crystalline acids recovered from the mother liquor (0.545 g.) were dissolved in a slight excess of aqueous alkali and refluxed with 0.5 g. of *p*-bromophenacyl bromide in 15 ml. of ethanol for one hour. On cooling 0.402 g. of crystals separated, which from ethanol gave 0.228 g. of platelets, m.p. 103–104°, and no depression of the m.p. when mixed with the authentic *p*-bromophenacyl ester, m.p. 104°, of hydrocinnamic acid.

Anal. Calcd. for $C_{17}H_{15}O_3Br$: C, 58.80; H, 4.35. Found: C, 58.95; H, 4.31.

Aniline was obtained from the original reaction mixture after refluxing 1 g. of 3,5-diphenyl-2-isoxazoline with 15 ml. of constant boiling hydriodic acid for 2.5 hours. The diluted mixture was extracted with ether and then steam distilled after adding 20 g. of sodium hydroxide. The aniline in the condensate was taken up in benzene and converted to the hydrochloride (34 mg.). Benzoylation in pyridine gave benzanilide, m.p. 161–162°, alone and when mixed with authentic benzanilide.

Anal. Calcd. for $C_{13}H_{11}ON$: C, 79.16; H, 5.62. Found: C, 79.13; H, 5.71.

Cyclization of Cinnamanilide.—Cinnamanilide (100 mg., m.p. 151°) was refluxed for 1 hour with 20 ml. of constant boiling hydriodic acid. The neutral product (70 mg., m.p. 178–179°) from ethanol gave 32 mg. of 4-phenyl-3,4-dihydrocarbostyril, compact prisms, m.p. 179.5° and no depression when mixed with the corresponding product above.

Anal. Calcd. for $C_{15}H_{13}ON$: C, 80.69; H, 5.87. Found: C, 80.51; H, 5.86.

The same product was obtained in slightly lower yield when using constant boiling hydrobromic acid as above.

Reduction of 4-Phenyl-3,4-dihydrocarbostyril.—4-Phenyl-3,4-dihydrocarbostyril (156 mg.) in 30 ml. of ethanol was gradually treated under reflux with 4 g. of sodium. After adding water and removing ethanol *in vacuo*, the products were taken up in ether and the base recovered *via* a hydrochloric acid extract as 124 mg. of oil. After two distillations (tube, 110–120° (0.04 mm.)) the product (95 mg.) was filtered in petroleum ether solution through alumina and recovered at 91 mg. of crystals, m.p. 72–74° unchanged on recrystallizing from ethanol of 4-phenyl-1,2,3,4-tetrahydroquinoline.

Anal. Calcd. for $C_{15}H_{15}N$: C, 86.08; H, 7.22. Found: C, 86.03; H, 7.50.

Benzoylation of 65 mg. of base in pyridine gave 105 mg. of neutral product, m.p. 135°, which from ethanol gave the pure benzoyl derivative, m.p. 145°.

Anal. Calcd. for $C_{22}H_{19}ON$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.13; H, 6.37; N, 4.34.

The Reduction of 3,5-Diphenyl-2-isoxazoline with Lithium Aluminum Hydride.—3,5-Diphenyl-2-isoxazoline (1.920 g.) in 50 ml. of anhydrous ether was added to 0.34 g. of lithium aluminum hydride suspended in ether. After stirring under reflux for 5.5 hours, the cooled mixture was decomposed by adding ice-water and hydrochloric acid. After extraction with ether, the acid solution was made alkaline with sodium hydroxide solution and the crystalline precipitate filtered off (1.208 g., m.p. 114–118°). Crystallization from ethanol gave 1,3-diphenyl-3-aminopropanol, prisms, m.p. 121–122°.

Anal. Calcd. for $C_{15}H_{17}ON$: C, 79.25; H, 7.54. Found: C, 79.27; H, 7.59.

The **monobenzoyl derivative** was obtained from 127 mg. of amino-alcohol and 79 mg. (1 mole) of benzoyl chloride in pyridine (1 hour at 96°). The crude product (121 mg., m.p. 120–140°) was recrystallized from benzene and from ethanol to give prisms, m.p. 169–170°.

Anal. Calcd. for $C_{22}H_{21}O_2N$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.92; H, 6.40; N, 4.52.

The **dibenzoyl derivative** was obtained from 235 mg. of amino-alcohol and 491 mg. (3.4 mole) of benzoyl chloride as before as 442 mg. of silky needles, m.p. 175–188°. Crystallization from ethanol raised the m.p. to 190–191°.

Anal. Calcd. for $C_{29}H_{25}O_3N$: C, 79.98; H, 5.79; N, 3.22; mol. wt., 435.5. Found: C, 80.47; H, 5.79; N, 3.25; mol. wt. (ebull. in benzene), 440.

Acknowledgments.—Thanks are recorded to Dr. A. P. Steyn and Miss J. M. Theron of this Department for spectral measurements and microanalyses, respectively. Dr. T. J. W. Jorden, the Manager of this Department, is sincerely thanked for his interest and for permission to publish this paper.

PRETORIA, SOUTH AFRICA

(17) R. Adams, J. W. Kern and R. L. Shriner, *Org. Syntheses*, **8**, 36 (1928).

[CONTRIBUTION FROM CIBA RESEARCH LABORATORIES, BASEL, SWITZERLAND]

The Acylation and Alkylation of Imidazolines and Some New Types of Imidazolines[1]

BY ADRIAN MARXER

RECEIVED AUGUST 13, 1956

The acylation of imidazolines I–III results in the formation of diacylalkylidenimidazolidines IV–VI. Intermediates are pseudobasic esters of type VII, proved by the isolation of diacetylacetoxyphenylimidazolidine (IX) from the acetylation of 2-phenylimidazoline. Alkylation usually yields mixtures of quaternary and non-quaternary imidazolines. One exception is described. Reductive methylation gives N-methylimidazolines. By condensation of nitriles with diethylenetriamine, aminoethylimidazolines (XVIII), with triethylenetetramine, bisimidazolines (XIX) joined through the nitrogen atoms by an ethylene bridge are obtained.

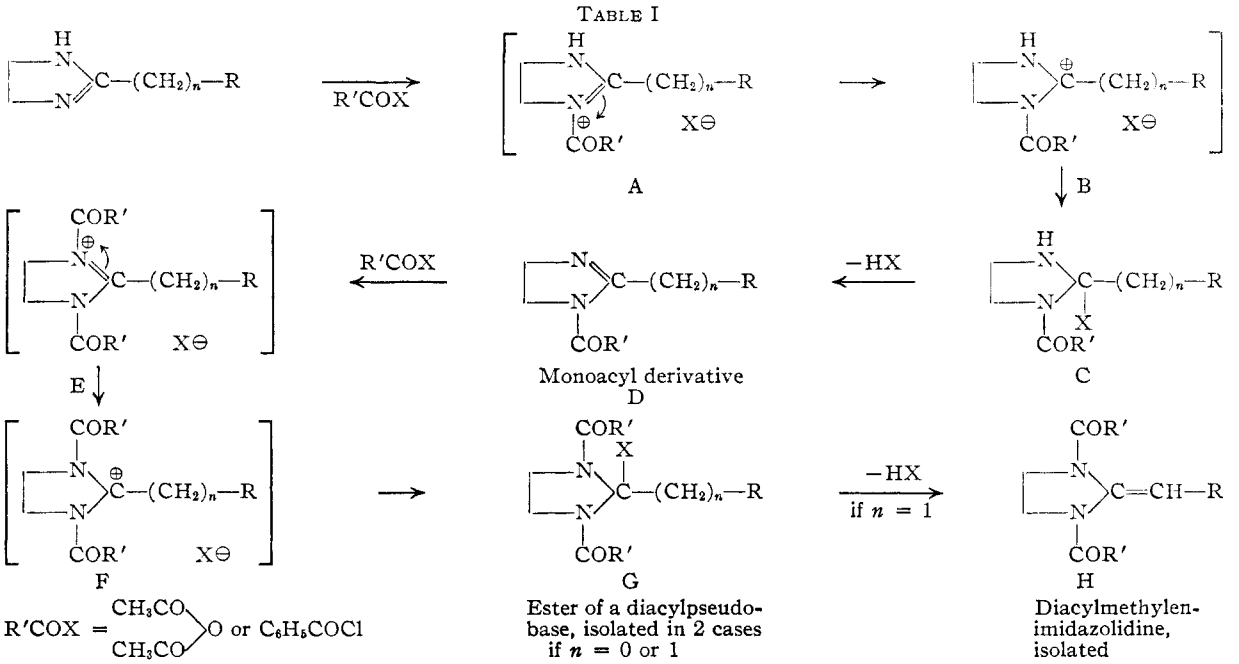
Acylation.—Several imidazolines have proved to be of practical importance in the last ten or fifteen years, and for this reason we published some work on the basic chemistry of the imidazoline ring several years ago.[2]

In particular, the acylation of imidazolines attracted our interest, whereby diacylimidazolidines IV–VI, with the double bond shifted exocyclically, resulted from substituted 2-methylimidazolines I–III. The diacetylalkylidenimidazolidines IVa–VIa have been obtained in good yield, but the dibenzoyl derivatives IVb–VIb were more difficult to prepare. We have succeeded, nevertheless, in making the dibenzoyl compound in good yield

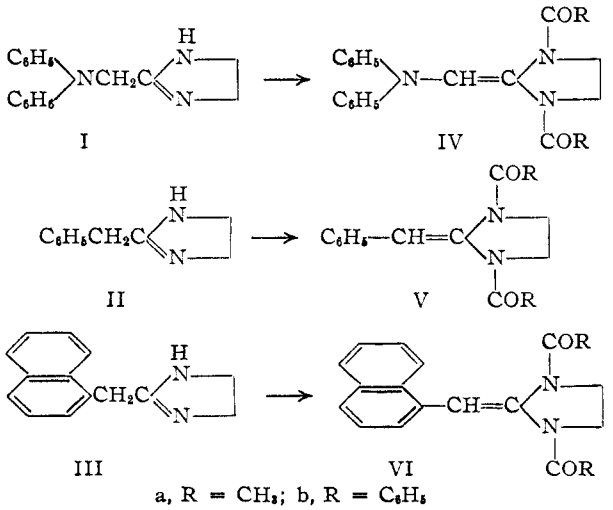
(1) Talk given at Dallas, Texas, 129th National A.C.S. Meeting, April, 1956; *cf.* Abstracts of Papers, 25-M.

(2) K. Miescher, A. Marxer and E. Urech, *Helv. Chim. Acta*, **34**, 1 (1951).

TABLE I

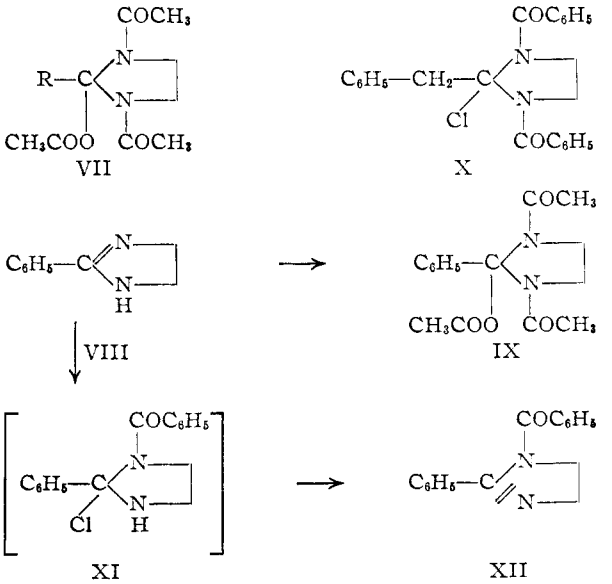


by using triethylamine in place of excess imidazoline as the acid-removing medium.



It is to be supposed that the intermediates for the diacylalkylidenimidazolidines of type IV, V and VI are esters of pseudobases, *e.g.*, in the case of acetylation with acetic anhydride, 1,3-diacetyl-2-acetoxyimidazolidines (VII). As a proof, the pseudobasic intermediate IX should be isolable from the acetylation of 2-phenylimidazoline (VIII), an exocyclic split of acetic acid not being possible as in IV–VI. The expected 1,3-diacetyl-2-acetoxy-2-phenylimidazolidine (IX) was indeed obtained in the form of massive hygroscopic prisms. On standing in air, the crystals first became liquid when the evolution of acetic acid could be clearly discerned. After some time the liquid crystallized again and then consisted of N,N'-diacetyl-N-benzoylethylenediamine. The isolation of IX therefore demonstrates the path of formation of the diacylalkylidenimidazolidines and the validity of the above-mentioned suggestion.

It already has been shown that it is possible to isolate the very unstable 1,3-dibenzoyl-2-chloro-2-benzylimidazolidine (X) on benzoylation of 2-benzylimidazoline.[2] A quaternary form for compounds IX and X is excluded by their solubility in benzene. Attempts to benzoylate 2-phenylimidazoline (VIII) to a stable 2-chloro-1,3-dibenzoyl derivative analogous to X led, however, only to the monobenzoyl compound XII.



The results of the acylations are listed in Table I.

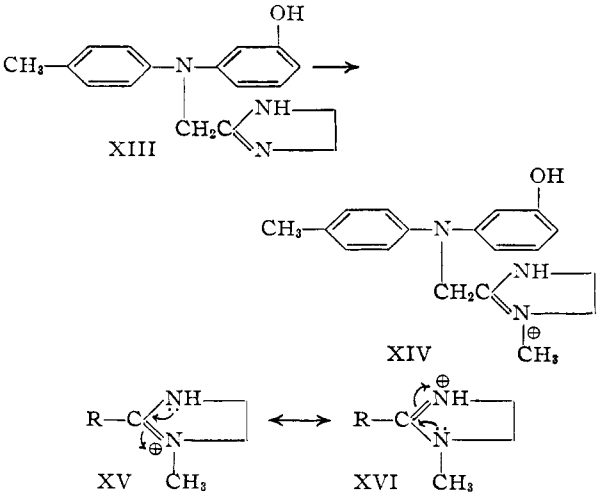
In view of the isolated substances G and H, the acylation must go through the quaternary stages A and E and then through stage B and F by polarization of the double bond to the pseudobase esters, C and G. A monoacylated pseudobase ester like C was never isolated in our experiments, although its existence is very likely in view of the results of the benzoylation of 2-phenylimidazoline (VIII).

With excess benzoyl chloride in benzene, temporary addition to XI probably occurred. Due to the lack of excess base—possibly also to the lower basicity of the starting material—further transformation ceases for the moment. Soon, small quantities of the insoluble monobenzoylphenylimidazoline hydrochloride (XII, or D in Table I) precipitate from the clear benzene solution, each time shortly after the previously formed XII has been removed by filtration. This crystallization could be repeated up to eight times, giving about 10% of the theoretical amount of XII at each separation. As XII in the form of its hydrochloride is insoluble in benzene, the soluble intermediate XI (or C) is very likely to be present in the solution.

The hydrochloride XII is very easily soluble in water, but after a short time the ring-opened dibenzoylethylenediamine crystallizes out of the solution.

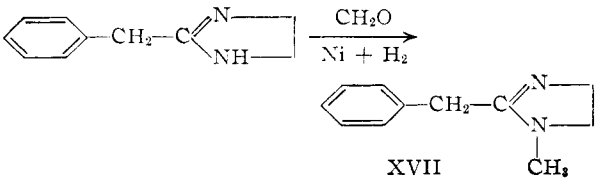
Alkylation.—The alkylation follows the path indicated in Table I. Owing to the lack of the electronegative CO group, however, the quaternary stages A and E, not isolable in the acylation, are stable. Confirming the results of King and McMillan[3] and Kyrides, *et al.*,[4] we isolated a mixture of monoalkylated product, dialkylated monoquaternary salt and starting material hydrohalide. These results should now be amended by some new observations.

While trying to quaternize the methylhydroxydiphenylamine XIII (phentolamine, Regitine®, a sympatholytically active compound) with methyl iodide, we obtained a definitely monomethylated compound XIV. Unlike the starting material it was not possible to precipitate the free base with sodium bicarbonate or ammonia from an aqueous solution of the salt. As a consequence of the mesomerism between quaternary and tertiary salt (XV↔XVI), this was surprising and it was considered that XIV might be of stronger basicity than XIII. This, however, was not the case; both compounds had the same pK_a (about 9.1). Other imidazolines did not give such monomethylated salts without a considerable amount of quaternary dialkyl product, so that it seems possible that this behavior could be a function of the phenolic part of the molecule. With dimethyl sulfate, however, XIII also was converted into the dimethylated quaternary salt.



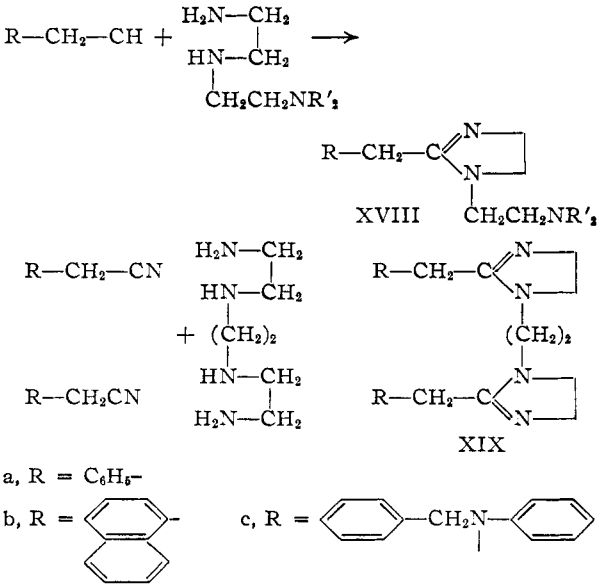
XIII XIV XV XVI

To prepare definitely monomethylated derivatives (*e.g.* XVII), a method was developed which consists in methylating with paraformaldehyde in the presence of nickel and hydrogen, when the monomethylated imidazolines were obtained in fairly good yield. (The well known method of methylating with formaldehyde and formic acid is impracticable, the imidazoline ring being split by concentrated formic acid.)



XVII

New Types of Imidazolines and Bisimidazolines.—One method of building up imidazolines is to condense nitriles with ethylene diamines in the presence of hydrogen sulfide. In the course of other work with polyamines, we tried to replace the ethylene diamine by diethylenetriamine or triethylenetetramine and were able to isolate the corresponding aminoethylimidazolines XVIII, and the bisimidazolines of type XIX in very good yield. During this work we discovered that Blair, Groves and Gross[5] had already obtained imidazolines from the reaction of polyamines with fatty acids. Blair and co-workers do not seem to have extended their work to imidazolines with aromatic substitution. Such compounds are of particular pharmacological interest; the benzyl derivative XIXa, for instance, corresponds to two tolazoline (Priscoline®) molecules joined through the nitrogen atoms by an ethylene bridge, the naphthylmethyl derivative XIXb to two naphthazolines (Privine®)



XVIII XIX

a, R = C_6H_5–

b, R =

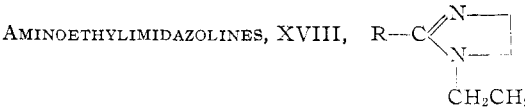
c, R =

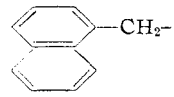
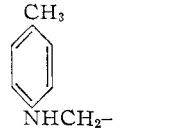
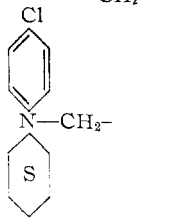
(3) J. A. King and F. H. McMillan, THIS JOURNAL, **68**, 1774 (1946).

(4) L. P. Kyrides, F. P. Zienty, G. W. Steahly and H. L. Morrill, *J. Org. Chem.*, **12**, 577 (1947).

(5) C. M. Blair, W. Groves and W. F. Gross, U. S. Patent 2,468,163 (April 26, 1949).

TABLE II

AMINOETHYLIMIDAZOLINES, XVIII, 

XVIII	R	R′	Base b.p. °C.[a]	Mm.	Hydrochloride, m.p., °C.	Formula	Analyses, % Calculated C	H	N	Cl	Found C	H	N	Cl
1	C_6H_5–	CH_3	135–138	0.05		$C_{13}H_{19}N_3$	71.85	8.81			71.57	8.81		
2	$C_6H_5CH_2$–	H	135	.03		$C_{12}H_{17}N_3$	70.90	8.43	20.67		70.74	8.31	20.61	
2a		H			193–195 d.	$C_{12}H_{19}N_3Cl_2$	52.20	6.92		25.67	52.36	6.77		26.01
3		CH_3	116	.03		$C_{14}H_{21}N_3$	72.68	9.15	18.17		72.49	8.90	17.97	
3a		CH_3			172–173	$C_{14}H_{23}N_3Cl_2$				23.31				23.30
4		H	180–182	.02		$C_{16}H_{19}N_3$	75.85	7.56	16.59		75.86	7.59	16.52	
4a		H			232–233	$C_{16}H_{21}N_3Cl_2$	58.90	6.49	12.88		59.07	6.58	12.81	
5		H	175–177	.03		$C_{13}H_{20}N_4$	67.20	8.68	24.12		67.45	8.98	24.23	
5a		H			165–170	$C_{13}H_{22}N_4Cl_2$				23.23				23.42
6		CH_3	168	.05		$C_{15}H_{24}N_4$	69.19	9.29	21.52		69.08	9.32	21.66	
6a		CH_3			155–157	$C_{15}H_{26}N_4Cl_2$				21.26				21.61
7	$C_6H_5NC_6H_5$ | CH_2–	H	193	.08		$C_{18}H_{22}N_4$			19.03				19.09	
7a		CH_3	185	.15		$C_{20}H_{26}N_4$	74.49	8.13	17.38		74.84	8.06	17.54	
8	$C_6H_5NCH_2C_6H_5$ | CH_2–	H	205–210	.05										
8a		H			229–230	$C_{19}H_{26}N_4Cl_2$	59.84	6.87	14.69		59.87	6.93	14.80	
9		CH_3	188	.06		$C_{21}H_{28}N_4$	74.96	8.39	16.65		74.50	8.33	16.20	
9a		CH_3			210–212	$C_{21}H_{30}N_4Cl_2$				17.32				17.18
10	$C_6H_5CH_2NCH_2C_6H_5$ | CH_2–	H	204	.08		$C_{20}H_{26}N_4$	74.49	8.13			74.41	8.31		
10a		H			178–180	$C_{20}H_{29}N_4Cl_3$	55.62	6.77	12.98		55.67	6.91	12.57	
11		CH_3	200	.04		$C_{20}H_{31}N_4Cl$	66.09	8.57	15.54		66.18	8.61	15.44	
11a		CH_3			214–215	$C_{20}H_{33}N_4Cl_3$				24.40				24.36

[a] The b.p. differed widely, *e.g.*, subst. 2 showed b.p. up to 173°, depending on the width of the neck of the distillation flask

joined in the same way through the nitrogen atoms by an ethylene bridge and the benzylanilino derivative XIXc to two joined antazolines (Antistine®). It is surprising that none of these doubled molecules has shown the same activity as the parent compound.

Several of these bis-imidazolines, especially in the diphenylamine series, have, however, marked bactericidal and fungicidal activity, but all of them produced local irritation. Some of the aminomethylimidazolines and bisimidazolines synthesized are listed in Tables II and III.

Acknowledgments.—I am very much indebted to Prof. R. Meier and his collaborators, Dr. F. Gross, Dr. H. J. Bein, Dr. J. Tripod, Dr. L. Neipp and Dr. F. Kradolfer, for biological testing. The microanalyses were carried out in the microanalytical laboratories of Ciba Limited (Basel) under Dr. H. Gysel, to whom I extend my thanks. Furthermore I should like to thank my assistant, Mr. J. Lampert, for great help with the experimental work. In the translation, help was given by Dr. H. B. McPhillamy and Dr. A. F. Thomas.

Experimental[6]

Acylation.—1,3-Diacetyl-2-alkylidenimidazolidines (IVa–VIa).[2] 1,3-Dibenzoyl-2-benzylidenimidazolidine (Vb).—2-Benzylimidazoline (*16.02 g., 0.1 mole*) was dissolved in 50 ml. of abs. benzene and 20.24 g. (0.2 mole) of triethylamine. With stirring, 28.12 g. (0.2 mole) of benzoyl chloride was added dropwise at 60–70° (cooling), and the mixture was heated for 2 hr. at 100°. After cooling, 100 ml. of water was added and stirring continued to complete solution of the triethylamine hydrochloride. The yellow crystals were isolated, washed with water and benzene, dried and recrystallized from ethyl acetate. The compound Vb obtained in almost quantitative yield had m.p. 137–139° and was identical with the product obtained formerly by other methods.[2]

2-Acetoxy-1,3-diacetyl-2-phenylimidazolidine (IX).—2-Phenylimidazoline (14.62 g., 0.1 mole)[7] was dissolved in 50 ml. of dry pyridine and 75 ml. of acetic anhydride, when the temperature rose to about 40°. The solution was allowed to stand at room temperature until the separation of crystals was complete. *This took several days on the first run but* only a few hours when seeds of IX were already available. The acetylation with 100 ml. of acetic anhydride at 100° gave the same crystals; these were isolated and washed with benzene giving hygroscopic prisms of m.p. 87–89°, yield 8 g.

Anal. Calcd. for $C_{15}H_{18}O_4N_2$: C, 62.05; H, 6.25; N, 9.65. Found: C, 61.87; H, 6.48; N, 9.82.

N,N′-Diacetyl-N-benzoylethylenediamine.—Prolonged standing of IX in the air resulted in an uptake of water, the material becoming liquid, then resolidifying. The crystals were taken up in benzene and precipitated by addition of petroleum ether, m.p. 69–72°.

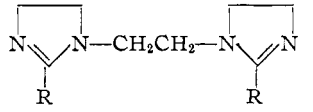
Anal. Calcd. for $C_{13}H_{16}O_3N_2$: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.02; H, 6.74; N, 11.41.

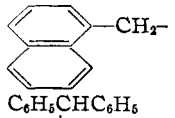
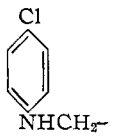
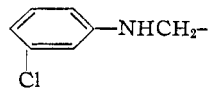
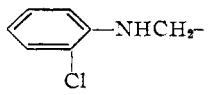
(6) Melting points are uncorrected.

(7) Prepared according to the method given for XVIII and XIX.

TABLE III

BISIMIDAZOLINES (1,1'-BISIMIDAZOLINYLETHANES) (XIX)



XIX	R	Base b.p. (mm.) or m.p., °C.	Hydrochloride m.p., °C.	Formula	Analyses, % Calculated C	H	N	Cl	Found C	H	N	Cl
1	C_6H_5-	202 (0.05)		$C_{20}H_{22}N_4$	75.44	6.96	17.60		75.25	6.90	17.58	
1a			262–263	$C_{20}H_{24}N_4Cl_2$			14.32	18.12			14.43	18.54
2	$C_6H_5CH_2-$	220 (0.15) 121[b]		$C_{22}H_{26}N_47$	6.26	7.56	16.17		76.01	7.80	16.18	
2a			263–266	$C_{22}H_{28}N_4Cl_2$	63.00	6.73	16.91	62.95	6.79			17.04
3			294–295	$C_{36}H_{32}N_4Cl_2$			10.79	13.65			10.44	13.54
4	$C_6H_5CHC_6H_5$ |	198–200		$C_{34}H_{34}N_4$	81.89	6.87	11.24		82.13	6.60	11.26	
5	$C_6H_5NCH_3$ |	88–91[b]		$C_{24}H_{32}N_6$	71.25	7.97	20.78		71.37	7.78	21.09	
5a	CH_2-		155–158	$C_{24}H_{34}N_6Cl_2$	60.37	7.18	17.60		60.57	7.34	17.56	
6	$C_6H_5NC_6H_5$ |	180–182[b]		$C_{34}H_{36}N_6$			15.90				15.47	
6a	CH_2-		250–253	$C_{34}H_{38}N_6Cl_2$	67.87	6.37	13.97	11.79	67.75	6.15	13.98	11.87
7	$C_6H_5NCH_2C_6H_5$ |	168–171		$C_{26}H_{40}N_6$	77.66	7.24	15.10		77.48	7.35	14.85	
7a	CH_2-		180	$C_{36}H_{42}N_6Cl_2$			13.35	11.26			13.14	11.46
8		162[b]		$C_{22}H_{26}N_6Cl_2$	59.32	5.88	18.87		59.05	6.10	18.86	
8a			228–231	$C_{28}H_{34}O_2N_6Cl_4$[c]			14.68	12.39			14.66	12.38
9		139–142		$C_{22}H_{26}N_6Cl_2$	59.32	5.88	18.87		59.17	5.67	18.74	
9a			158–161	$C_{22}H_{28}N_6Cl_4$[d]	50.98	5.45		27.36	50.59	5.43		26.83
10		199–203[b]		$C_{22}H_{26}N_6Cl_2$	59.32	5.88	18.87		59.23	5.98	18.95	
10a			242–244	$C_{22}H_{28}N_6Cl_4$[d]	50.98	5.45	16.22		50.59	5.31	16.01	

[b] M.p. of the substance without recrystallization. [c] The 12 mm. dried material contains 3 moles of water according to mole weight determination, which is given off very slowly in the high vacuum. [d] The anhydrous substance is very hygroscopic and difficult to get absolutely dry. Dried at 12 mm. it contains 1 mole of water.

1-Benzoyl-2-phenylimidazoline (XII).—(a) 2-Phenylimidazoline (14.62 g., 0.1 mole) was dissolved in 50 ml. of benzene. Benzoyl chloride (7.03 g., 0.05 mole), dissolved in 10 ml. of benzene, was added quickly and the mixture was heated at 100° with stirring for 2 hr. More benzene was added and the crystals of 2-phenylimidazoline hydrochloride, m.p. 235°, isolated from the hot solution by suction. The benzene solution was concentrated under reduced pressure and gave XII by careful addition of petroleum ether, m.p. 99–101°, yield 0.05 mole.

Anal. Calcd. for $C_{16}H_{14}ON_2$: C, 76.78; H, 5.84; N, 11.19. Found: C, 77.03; H, 5.93; N, 11.43.

(b) When repeated as above, but using 0.1 or 0.2 mole of benzoyl chloride, only traces of 2-phenylimidazoline hydrochloride (m.p. 235°) were obtained. On standing, the mother liquors yielded a fine crystalline powder, m.p. 169–171°, that was isolated by suction; the mother liquors yielded further crops of material (up to eight), always in about the same amount regardless of the time of standing. This product, m.p. 169–171°, consisted of 1-benzoyl-2-phenylimidazoline hydrochloride (XII·HCl).

Anal. Calcd. for $C_{16}H_{15}ON_2Cl$: C, 67.01; H, 5.27; Cl, 12.37. Found: C, 67.04; H, 5.09; Cl, 12.04.

XII·HCl was soluble in water; after standing, crystals of the ring-opened product, the known[8] dibenzoylethylenediamine of m.p. 246°, separated.

(8) S. R. Aspinall, *J. Org. Chem.*, **6**, 895 (1941).

Alkylation.—1-Methyl-2-[(4'-methyl-3"-hydroxydiphenylamino)-methyl]-imidazolinium Iodide (XIV).–2-[(4'-Methyl-3" - hydroxydiphenylamino) - methyl]-imidazoline (XIII, phentolamine,[9] 42.19 g., 0.15 mole) was dissolved in 200 ml. of chloroform and 150 ml. of abs. alcohol; 22.35 g. (0.1575 mole) of methyl iodide in 50 ml. of abs. alcohol was added dropwise and the mixture heated with stirring for 5 hr. at 90° (bath temperature). The solution was evaporated to one-third of its volume and the crystals isolated, m.p. 213–216°. No precipitation in the aqueous solution with sodium bicarbonate or with ammonia occurred.

Anal. Calcd. for $C_{18}H_{22}ON_3I$: C, 51.07; H, 5.24; I, 29.98. Found: C, 51.09; H, 5.20; I, 29.54. Calcd. for $C_{19}H_{24}ON_3I$ (dimethyl derivative): C, 52.18; H, 5.53; I, 29.02.

1-Methyl-2-benzylimidazoline (XVII) (Reductive Methylation).—2-Benzylimidazoline (16.02 g., 0.1 mole) was dissolved in 175 ml. of abs. alcohol, 3.3 g. (0.11 mole) of paraformaldehyde was added and the mixture hydrogenated in the presence of 10 g. of Rupe or Raney nickel. The hydrogen uptake was sluggish, 24 hr. being required before the theoretical amount was absorbed. The alcohol was evaporated and the base distilled, b.p. 158–161° (12 mm.). The base was hygroscopic. The hydrochloride had m.p. 185–186°.

(9) E. Urech, A. Marxer and K. Miescher, *Helv. Chim. Acta*, **33**, 1386 (1950).

Anal. Calcd. for $C_{11}H_{15}N_2Cl$: C, 62.70; H, 7.18; N, 13.30; Cl, 16.83. Found: C, 62.36; H, 6.97; N, 13.36; Cl, 16.98.

Nitriles used were either commercially available or were prepared according to the method of Marxer.[10]

1-Aminoethylimidazolines (XVIII) (*cf.* Table II). **General Procedure.**—The appropriate nitrile (0.2 mole) was mixed with 0.22 mole of diethylenetriamine or N,N-dimethyldiethylenetriamine, and 200–500 mg. of dry hydrogen sulfide was passed into this mixture. The resulting solution was heated in an oil-bath at 90–120° until evolution of ammonia was complete, this taking sometimes only a few minutes and sometimes 7–8 hr. Usually a temperature of 100–105° was sufficient. The resulting imidazolines were usually distilled twice and the dihydrochlorides prepared.

1,1′-Bisimidazolinylethanes (XIX) (*cf.* Table III) **General Procedure: Bis-[2,*p*-chloroanilinomethylimidazolinyl-(1)]-ethane (XIX/8).**—Dry hydrogen sulfide (400 mg.) was passed into a mixture of 49.98 g. (0.3 mole) of *p*-chloroanilinoacetonitrile and 21.93 g. (0.15 mole) of triethylenetetramine. This was heated in an oil-bath at 110°, when a rapid evolution of ammonia occurred, lasting for 1 hr. and becoming very slow during the next 6 hr. The reaction product crystallized on addition of 200 ml. of ethyl acetate. Crystals of XIX/8 were isolated and washed with ethyl acetate, when they had m.p. 162° (slight sintering at 149°). Since this base conformed to the expected analytical results, the hydrochloride was prepared without further purification, by dissolving in alcohol and adding 2 equivalents of alcoholic hydrochloric acid; hydrochloride m.p. 228–231°.

Generally, the bases of Table III decomposed on distillation, with the exception of XIX/1 and XIX/2. When they did not crystallize upon addition of ethyl acetate, the solution was evaporated, dissolved in dilute hydrochloric acid, the oil reprecipitated by dilute ammonia in the cold and taken up in ethyl acetate or alcohol to prepare the hydrochloride.

Basel, Switzerland

(10) A. Marxer, *Helv. Chim. Acta.*, **37**, 166 (1954).

[Contribution from the Department of Organic Chemistry, Research Laboratories, The William S. Merrell Co.]

Central Stimulants. α,α-Disubstituted 2-Piperidinemethanols and 1,1-Disubstituted Heptahydroöxazolo[3,4-a]pyridines

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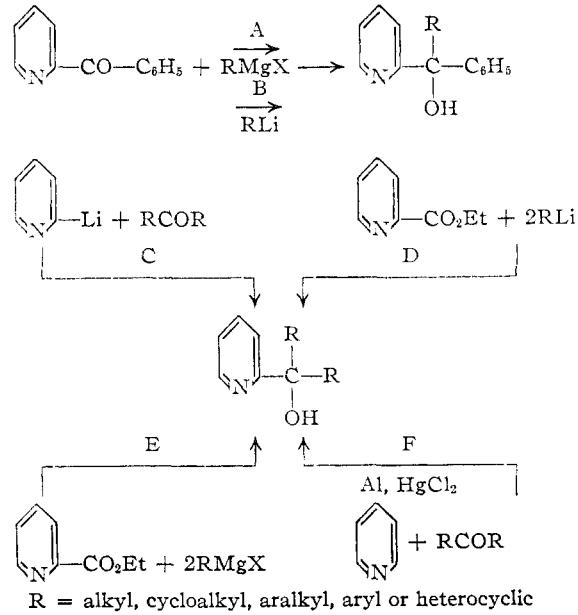
A series of α,α-disubstituted-2-pyridinemethanols was prepared and converted to the corresponding 2-piperidinemethanols by hydrogenation. Heptahydroöxazolo[3,4-a]pyridine derivatives of some of the piperidinemethanols were also prepared. A number of the piperidinemethanols and heptahydroöxazolidines possess central stimulant activity.

This investigation was a continuation of the search for new therapeutic agents in the α,α-disubstituted-2-piperidinealkanol series. A previous paper[1] described the synthesis of a series of α,α-disubstituted-2-piperidine-ethanols and the related octahydropyrid[1,2-c]oxazines. A number of these compounds had diuretic and anti-fungal properties.

The piperidinemethanols of the present investigation are analogs of α,α-diphenyl-2-piperidinemethanol hydrochloride[2,3] which possesses central stimulant activity.[4] Generally, these piperidinemethanols were prepared by hydrogenation of the corresponding pyridinemethanols. Some of them were treated with formaldehyde to yield the oxazolidine derivatives. The synthetic methods used for preparing the intermediate pyridinemethanols are shown.

Previous examples of Grignard reactions in which other pyridyl ketones were substituted for benzoylpyridine have been described in the literature.[5–7] The preparation of α-phenyl-α-(2-thienyl)-2-pyridinemethanol (Table I, 35A) was recently reported.[8]

The synthesis of di- and tripyridinemethanols[9] and other pyridinemethanols by reaction of lithio agents with ketones have been carried out.[10] A ketone synthesis from ethyl picolinate and 2-pyridyllithium has been reported to yield tri-2-pyridinemethanol as a by-product.[9] Preparation



R = alkyl, cycloalkyl, aralkyl, aryl or heterocyclic

of α,α-dimethyl-2-pyridinemethanol from ethyl picolinate and methylmagnesium iodide has been reported.[11] A series of pyridinemethanols, mainly of the type in which one R group is alkyl, has been prepared[2] by condensation of pyridine with the ap-

(1) C. H. Tilford and M. G. Van Campen, Jr., This Journal, **76**, 2431 (1954).

(2) C. H. Tilford, R. S. Shelton and M. G. Van Campen, Jr., *ibid.*, **70**, 4001 (1948).

(3) H. W. Werner and C. H. Tilford, U. S. Patent 2,624,739 (1953).

(4) B. B. Brown and H. W. Werner, *J. Pharmacol. Exptl. Therap.*, **110**, 180 (1954).

(5) K. Schofield, *J. Chem. Soc.*, 2408 (1949).

(6) K. Winterfeld and F. W. Holschneider, *Arch. Pharm.*, **273**, 315 (1935).

(7) N. Sperber, D. Papa, E. Schwenk and M. Sherlock, This Journal, **71**, 887 (1949).

(8) J. Heer, E. Sury and K. Hoffmann, *Helv. Chim. Acta*, **38**, 134 (1955).

(9) J. P. Wibaut, A. P. de Jonge, H. G. P. Van der Voort and P. Ph. H. L. Otto, *Rec. trav. chim.*, **70**, 1054 (1951).

(10) A. J. Nunn and K. Schofield, *J. Chem. Soc.*, 589 (1952).

(11) W. Sobecki, *Ber.*, **41**, 4103 (1908).