[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF G. D. SEARLE & CO.]

3-Imidomethyloxazolidines

MAX J. KALM

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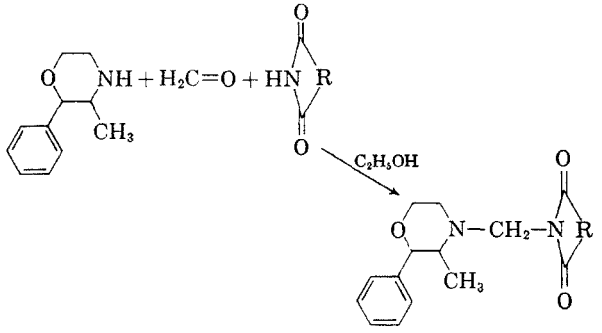
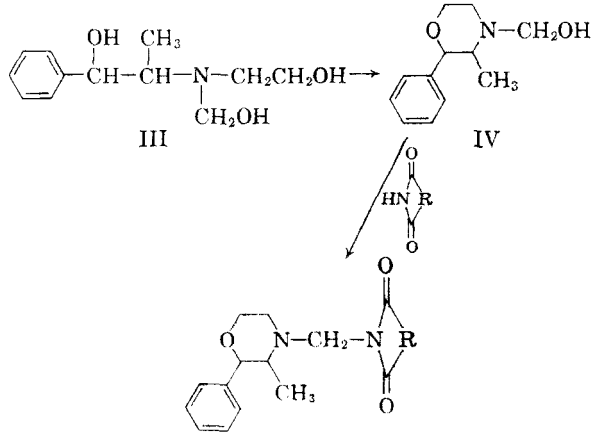
Several 4,5-disubstituted oxazolidines have been prepared and these have been converted to a variety of 4,5-disubstituted 3-imidomethyloxazolidines. In the case of the 4-methyl-5-phenyloxazolidines, both racemic diastereoisomers were prepared and converted to the imidomethyloxazolidines. The reactions leading to these compounds are stereospecific and a number of the optically active isomers were prepared by the use of resolved starting materials. These compounds exhibit a variety of interesting biological activities.

It had been shown in these laboratories that two imidomethyl derivatives of 2-phenyl-3-methylmorpholine (Preludin) had potent appetite inhibitory activity.[1,2] These compounds were prepared by reaction of 2-phenyl-3-methylmorpholine with formaldehyde and an imide, according to the procedure of Moore and Rapala.[3]



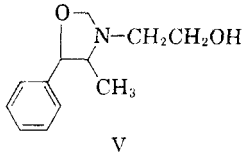
I. R = $-CH_2CH_2-$ II. R = 

It became desirable to find an alternate route of preparation for these compounds; one which would bypass 2-phenyl-3-methylmorpholine as an intermediate. It had previously been shown that hydroxymethylamines react with imides to give imidomethylamines.[4] An attempt was therefore made to prepare 2-phenyl-3-methyl-4-hydroxymethylmorpholine (IV) by ring closure of *N*-β-hydroxyethyl-*N*-hydroxymethylnorephedrine (III).

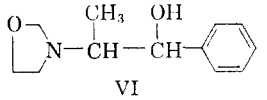


III IV

Reaction of *N*-β-hydroxyethylnorephedrine with aqueous formaldehyde followed by ring closure with concentrated sulfuric acid gave a yellow oil which on reaction with succinimide gave I identical with the material prepared by reaction of 2-phenyl-3-methylmorpholine with formaldehyde and succinimide. Although it was first thought that the reaction between *N*-β-hydroxyethylnorephedrine and formaldehyde had led to the formation of *N*-β-hydroxyethyl-*N*-hydroxymethylnorephedrine (III), there was doubt about the structure of this intermediate because the literature states that reaction of β-hydroxyethylamines with carbonyl compounds leads to the formation of either the Schiff base or an oxazolidine.[5] The original assignment of the triol (III) for this intermediate was made because reaction was achieved by simply shaking the amine with aqueous formaldehyde, conditions felt to be too mild for anything but the addition of an amine across the double bond of formaldehyde. Analysis, however, showed the hydrochloride of this compound to have the empirical formula which corresponds to either the Schiff base or the oxazolidine, while infrared spectral analysis showed no band in the 1670 cm.$^{-1}$ region characteristic of the —CH=N— absorption of aliphatic Schiff bases.[6] It was now necessary to find additional methods for identifying this intermediate, as it was necessary to prove with certainty that the compound was the oxazolidine and because two isomeric oxazolidines (V) and (VI) can be postulated as the product of the reaction between formaldehyde and *N*-β-hy-



V



VI

(1) Belgian Patent No. **567,664**, Nov. 14, 1958.
(2) South African Patent No. **1627/58**, Sept. 23, 1959.
(3) M. B. Moore and R. T. Rapala, *J. Am. Chem. Soc.*, **68**, 1657 (1946).
(4) W. I. Weaver, J. K. Simons, and W. E. Baldwin, *J. Am. Chem. Soc.*, **66**, 222 (1944).
(5) E. D. Bergmann, *Chem. Revs.*, **53**, 309 (1953).
(6) L. Kahovec, *Acta Phys. Austriaca*, **1**, 307 (1948); *Chem. Abstr.*, **42**, 6665 (1948).

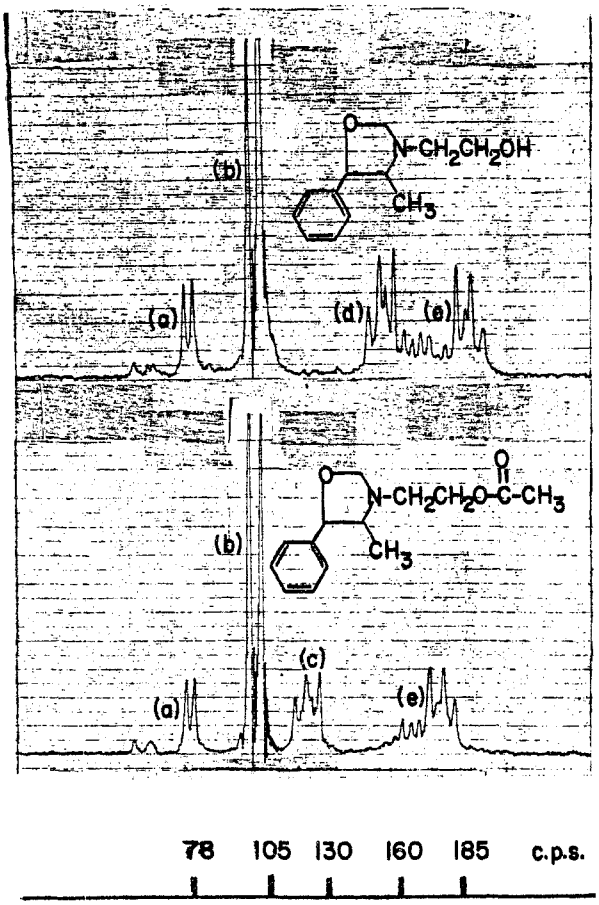


Fig. 1. N.M.R. spectra of 3-β-hydroxyethyl-4-methyl-5-phenyloxazolidine and 3-β-acetoxyethyl-4-methyl-5-phenyloxazolidine in D_2O.

(a) C_6H_5—*CH*, (b) —O*CH*$_2$—N,

(c) —*CH*$_2$—O—C(=O)—CH_3 (d) —*CH*$_2$OH,

(e) —CH_2—N—

droxyethylnorephedrine, depending on which hydroxyl group participates in the reaction.

Nuclear magnetic resonance spectroscopy served as an excellent tool both for confirming the oxazolidine structure of the product and for establishing which isomer had been formed. The oxazolidine was converted to the acetate and the NMR spectra of both the carbinol and its acetate in the form of their hydrochlorides were compared. The oxazolidine structure was confirmed by the presence of a —O—CH_2—N— band at 100 c.p.s. and the compounds were shown to possess structure V by a shift of the —CH_2OH bands at 160 c.p.s. to 130 c.p.s. for the —CH_2OAc bands. On the other hand the C_6H_5—CH band at 77 c.p.s. was not displaced in going from the free alcohol to the acetate as would be the case if structure VI were correct. Portions of these NMR spectra are reproduced in Fig. 1.

It now became of interest to see if the reaction with aqueous formaldehyde were a general one for β-hydroxyethylamines. To test this the reaction was run with *d,l*-norephedrine to prepare the 3-unsubstituted oxazolidine. This compound had been prepared previously[7] but the reaction conditions had been much more vigorous. The reaction between *d,l*-norephedrine and aqueous formaldehyde yielded an oil which had no absorption at 1670 cm.$^{-1}$ attributable to the Schiff base structure[6] but had a very weak absorption band at 1610 cm.$^{-1}$. There were in addition bands at 1092 cm.$^{-1}$, 1130 cm.$^{-1}$, and 1177 cm.$^{-1}$, a region which is supposed to contain a triplet of bands due to the —O—C—N— structure. It is therefore believed that this reaction also led to the formation of an oxazolidine as the major product. A crystalline hydrochloride was obtained and this also lacked absorption in the 1670 cm.$^{-1}$ region.

No additional structure work was done on the *N*-unsubstituted oxazolidines, as the major interest lay in the preparation of 3-imidomethyloxazolidines, oxazolidine analogs of I and II. Such compounds, if formed, must possess the oxazolidine structure even if the precursors are in equilibrium between the oxazolidine and Schiff base structure.

Using a variety of imides a number of 3-imidomethyloxazolidines were prepared by the method of Moore and Rapala.[3] These compounds are stable crystalline solids with analyses and infrared spectra consistent with the proposed structures. The compounds prepared are given in Table I.

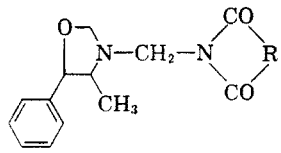
The next step was to investigate the preparation of the diastereoisomeric compounds from norpseudoephedrine. Pfanz and Kirchner[7] had shown that the oxazolidines from norpseudoephedrine had the *threo* configuration and that this isomer was more stable as a ring than the *erythro* isomer from norephedrine. It was therefore not surprising that the product from reaction of norpseudoephedrine with formaldehyde readily formed a variety of 3-imidomethyloxazolidines which differed in their physical properties from the corresponding derivatives prepared from norephedrine. These compounds are described in Table II.

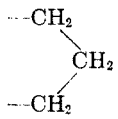
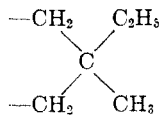
In an attempt to prepare some 2-substituted oxazolidines, norephedrine was allowed to react with acetaldehyde and with *n*-heptaldehyde. In both instances, the intermediate 3-unsubstituted oxazolidine was not purified or characterized, but was carried directly to the 3-imidomethyloxazolidine. The products thus obtained were not the 2-substituted oxazolidines but were identical with the imidomethyloxazolidines prepared from norephedrine and formaldehyde. Two possible explanations for the formation of these compounds are that either the reaction between norephedrine and alkyl aldehydes gives predominantly the Schiff base and that further reaction with the imide and formaldehyde causes first aldehyde interchange followed by ring closure, or that the greater stability of the 2-unsubstituted ring leads to ring opening followed by

(7) H. Pfanz and G. Kirchner, *Ann.*, 614, 149 (1958)

TABLE I

IMIDOMETHYLOXAZOLIDINES DERIVED FROM *d,l*-NOREPHEDRINE

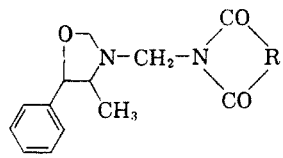


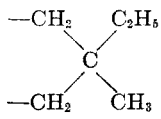
No.	R	Formula	M.P.	Carbon, %		Hydrogen, %		Nitrogen, %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
VII		$C_{15}H_{18}N_2O_3$	132.0–134.0[a]					10.22	10.01
VIII		$C_{15}H_{16}N_2O_3$	99.0–102.0[a]					10.29	10.13
IX		$C_{16}H_{20}N_2O_3$	92.0–94.0[b]	66.64	66.70	6.99	7.06	9.72	9.58
X		$C_{19}H_{26}N_2O_3$	76.0–78.0[b]					8.48	8.35
XI		$C_{19}H_{24}N_2O_3$	82.0–84.0[b]	69.49	69.51	7.37	7.43	8.53	8.25
XII		$C_{19}H_{22}N_2O_3$	98.5–100.5[a]	69.91	69.83	6.80	7.02		
XIII		$C_{19}H_{18}N_2O_3$	111.0–113.0[a]	70.79	70.98	5.63	5.79	8.69	8.52

[a] Crystallized from absolute ethanol. [b] Crystallized from ethanol and water.

TABLE II

IMIDOMETHYLOXAZOLIDINES DERIVED FROM *d,l*-NORPSEUDOEPHEDRINE

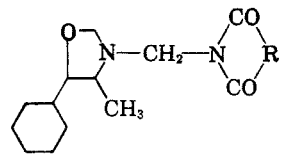


No.	R	Formula	M.P.	Nitrogen, %	
				Calcd.	Found
XIV		$C_{15}H_{18}N_2O_3$	70.5–73.0[a]	10.22	10.22
XV		$C_{15}H_{16}N_2O_3$	92.0–96.0[a]	10.29	10.21
XVI		$C_{19}H_{26}N_2O_3$	86.0–88.0[b]	8.48	8.55
XVII		$C_{19}H_{22}N_2O_3$	92.5–95.0[b]	8.59	8.53
XVIII		$C_{19}H_{18}N_2O_3$	91.5–94.5[a]	8.69	8.73

[a] Crystallized from absolute ethanol. [b] Crystallized from ethanol and water.

TABLE III

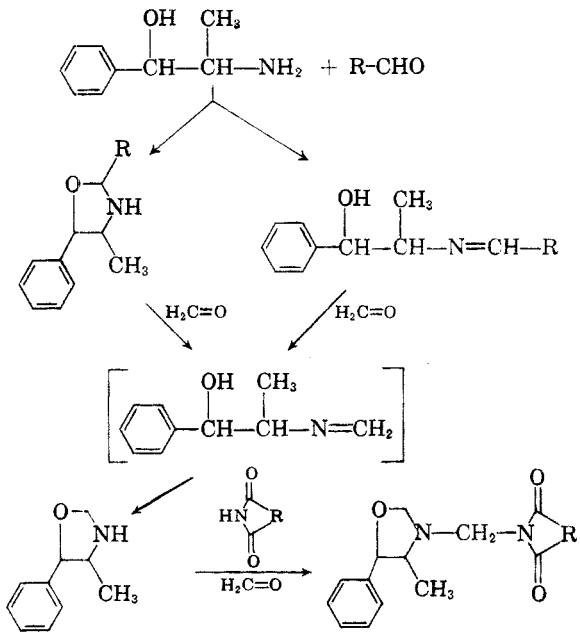
3-IMIDOMETHYL-4-METHYL-5-CYCLOHEXYLOXAZOLIDINES



No.	R	Formula	M.P.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
XIX		$C_{15}H_{24}N_2O_3$	73.0–75.0[b]	64.26	64.66	8.63	8.63		
XX		$C_{15}H_{22}N_2O_3$	82.5–88.0[a]					10.07	9.92
XXI		$C_{19}H_{24}N_2O_3$	90.5–93.0[a]	69.49	69.19	7.37	7.30	8.53	8.34

[a] Crystallized from absolute ethanol. [b] Crystallized from ethanol and water.

aldehyde interchange and reclosing of the ring. Since excess formaldehyde is used in the imidomethylation step the aldehyde interchange is possible. The two possible reaction mechanisms are shown below.



Although 2-substituted 3-imidomethyloxazolidines could not be formed by this method, various modifications in the substituent at C_5 did not affect or alter the course of the reaction. Hexahydronorephedrine, which had previously been prepared by reduction of 1-cyclohexyl-2-nitro-1-propanol,[8] was prepared by reduction of norephedrine with ruthenium oxide. This was readily converted to 4-methyl-5-cyclohexyloxazolidine, which could be transformed into a variety of 3-imidomethyloxazolidines. The *p*-chloro-[9] and *p*-methoxynorephedrines[10] were also prepared. These were converted to their respective oxazolidines by reaction with aqueous formaldehyde and a variety of 3-imidomethyloxazolidines were prepared from them. The compounds are shown in Tables III, IV, and V.

All the substances so far discussed possessed a wide spectrum of biological activities. The compounds prepared from norpseudoephedrine showed a separation of biological properties from those prepared from norephedrine. It therefore was of interest to determine if such a separation of activities also occurred in the case of the individual enantiomorphs. At the same time the preparation of the enantiomorphs would provide information about the stereospecificity of the reactions involved.

As the imidomethyloxazolidines from norephedrine showed the greatest biological activity, it was decided to prepare the enantiomorphs of several of these compounds. Resolution of *d,l*-norephedrine with *d*-tartaric acid yielded after hydrolysis the *d*-isomer of norephedrine. Hydrolysis of the mother liquors from this resolution gave the *l*-isomer in impure form which could be completely resolved by the use of *l*-tartaric acid. The conditions used for these resolutions were a modification[11] of the method of Kanao and Nagai.[12] The *d*- and *l*-norephedrines thus obtained served as starting materials for the stereospecific syntheses of some of the compounds shown in Table I.

The enantiomorphic norephedrines were each

(8) R. R. Burtner and W. M. Selby, U. S. Patent No. 2,586,512, Feb. 19, 1952.

(9) B. L. Zenitz and W. H. Hartung, *J. Org. Chem.*, **11**, 444 (1946).

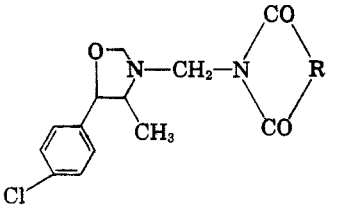
(10) W. H. Hartung, J. C. Munch, E. Miller, and F. Crossley, *J. Am. Chem. Soc.*, **53**, 4149 (1931).

(11) The conditions used for resolving *d,l*-norephedrine constitute unpublished results communicated to me by Dr. Gordon A. Alles of Pasadena, California. I am greatly indebted to Dr. Alles for this information as well as for conditions for isomerizing *d,l*-norephedrine to *d,l*-norpseudoephedrine and the resolution of the latter compound.

(12) S. Kanao and W. N. Nagai, *Ann.*, **470**, 157 (1929).

TABLE IV

3-IMIDOMETHYL-4-METHYL-5-*p*-CHLOROPHENYLOXAZOLIDINES

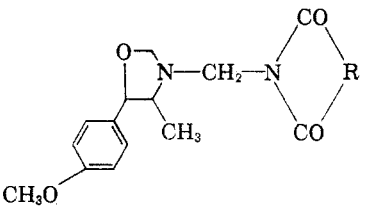


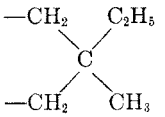
No.	R	Formula	M.P.	Nitrogen, % Calcd.	Nitrogen, % Found
XXII	—CH₂ —CH₂	$C_{15}H_{17}ClN_2O_3$	113.0–115.5[a]	9.08	9.24
XXIII	—CH ‖ —CH	$C_{15}H_{15}ClN_2O_3$	97.0–99.5[a]	9.14	9.35
XXIV		$C_{19}H_{17}ClN_2O_3$	115.0–118.0[a]	7.85	7.98

[a] Crystallized from absolute ethanol.

TABLE V

3-IMIDOMETHYL-4-METHYL-5-*p*-METHOXYPHENYLOXAZOLIDINES



No.	R	Formula	M.P.	Nitrogen, % Calcd.	Nitrogen, % Found	Nitrogen,[a] % Calcd.	Nitrogen,[a] % Found	Methoxyl, % Calcd.	Methoxyl, % Found
XXV	—CH₂ —CH₂	$C_{16}H_{20}N_2O_4$	103.0–105.0[b]	9.21	9.06	4.60	4.66	10.20	10.23
XXVI	—CH ‖ —CH	$C_{16}H_{18}N_2O_4$	116.0–119.0[b]	9.27	9.28	4.63	4.70	10.26	10.01
XXVII		$C_{20}H_{28}N_2O_4$	61.5–63.0[c]	7.77	7.90	3.89	4.02		
XXVIII		$C_{20}H_{20}N_2O_4$	127.0–129.0[b]	7.95	7.92	3.97	4.04		

[a] Nonaqueous titration of amino nitrogen. [b] Crystallized from absolute ethanol. [c] Crystallized from ethanol and water.

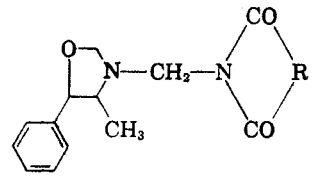
ring closed to the corresponding oxazolidines by treatment with aqueous formaldehyde and the oxazolidines were in turn converted to imidomethyloxazolidines shown in Tables VI and VII. In the case of the compounds where both isomers were prepared the rotations indicated that absolute optical purity was not achieved in some instances and this may well have been the result of slight racemization during ring closure or during the formation of the imidomethyl derivatives.

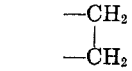
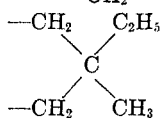
The *d,l*-norpseudoephedrine was also resolved[11] but only one imidomethyl derivative was prepared. This compound was the 3-succinimidomethyl derivative of the oxazolidine obtained from *l*-norpseudoephedrine.

The compounds described have shown activity as appetite inhibitors, diuretics, anti-inflammatory agents, antibacterial agents, and antifungal agents. A brief summary of some of these biological activities is shown in Table VIII.

TABLE VI

IMIDOMETHYLOXAZOLIDINES DERIVED FROM *d*-NOREPHEDRINE

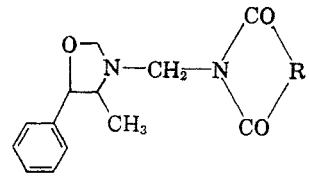


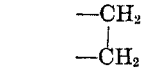
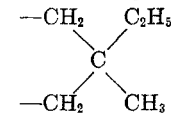
No.	R	Formula	M.P.	α_D	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
XXIX		$C_{15}H_{18}N_2O_3$	99.0–101.0[a]	+8.7°	65.67	65.77	6.61	6.78	10.22	10.33
XXX		$C_{19}H_{26}N_2O_3$	93.0–95.0[b]	+28.3°					8.48	8.31
XXXI		$C_{19}H_{18}N_2O_3$	108.0–110.0[a]	−7.5°					8.69	8.57

[a] Crystallized from absolute ethanol. [b] Crystallized from ethanol and water.

TABLE VII

IMIDOMETHYLOXAZOLIDINES DERIVED FROM *l*-NOREPHEDRINE



No.	R	Formula	M.P.	α_D	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
XXXII		$C_{15}H_{18}N_2O_3$	101.0–103.0[a]	−7.1°	65.67	65.78	6.61	6.89	10.22	10.50
XXXIII		$C_{19}H_{26}N_2O_3$	91.0–94.0[b]	−23.2°	69.06	68.83	7.93	8.15	8.48	8.49
XXXIV		$C_{19}H_{24}N_2O_3$	55.0–62.0[a]	−2.1°					8.53	8.30
XXXV		$C_{19}H_{18}N_2O_3$	106.5–108.5[a]	+6.2°	70.79	70.45	5.63	5.80	8.69	8.60

[a] Crystallized from absolute ethanol. [b] Crystallized from ethanol and water.

EXPERIMENTAL[13]

N-β-Hydroxyethylnorephedrine. Two methods which differ from the procedures in the literature[14,15] were used for the preparation of this compound.

A. A solution of 151 g. (1.0 mole) of *d,l*-norephedrine and 44.0 g. (1.0 mole) of ethylene oxide in 1000 ml. of absolute ethanol was placed in a 2-l. Parr hydrogenation bomb and was heated at 60° with stirring for 18 hr. The solvent was stripped at reduced pressure and the residue was triturated with anhydrous ether to yield 104 g. (53.3%) of the product as a white crystalline solid, m.p. 110–111.5°; lit.,[15] m.p. 109°.

B. A solution of 113.5 g. (0.75 mole) of *d,l*-norephedrine in 100 ml. of absolute ethanol was treated with 79.6 g. (0.75 mole) of benzaldehyde and the mixture was stirred until Schiff base formation was completed. The material was transferred to a 2-l. Parr hydrogenation bomb with 525 ml. of absolute ethanol and approximately 2.7 g. of commercial Raney Nickel catalyst was added. The material was hydrogenated at 70° using a pressure of 700 p.s.i., uptake being 93% of theory.

After removal of catalyst and addition of 36.2 g. (0.825 mole) of ethylene oxide the solution was heated at 60° for 18 hr. in a hydrogenation bomb. After the solution had cooled to room temperature, 20 g. of 5% palladium on charcoal catalyst was added. The debenzylation was carried out at 50° at a pressure of 800 p.s.i., hydrogen uptake being

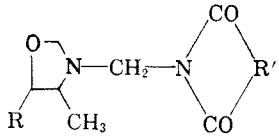
(13) All melting points are uncorrected. Rotations were determined at 26 ± 1° at a concentration of 1.2% in methanol unless otherwise specified.

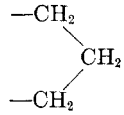
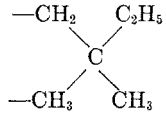
(14) R. H. F.Manske and T. B. Johnson, *J. Am. Chem. Soc.*, **51**, 1906 (1929).

(15) A. Skita and F. Keil, *Ber.*, **63B**, 34 (1930).

TABLE VIII

BIOLOGICAL ACTIVITIES OF 3-IMIDOMETHYLOXAZOLIDINES



No.	R	R′	Appetite Inhibition: % of Std.[f]	Appetite Inhibition: Dose, mpK in Rats	Appetite Inhibition: Route	Diuresis,[h] Rat: M.E.D., mpK I.G.	Anti-inflammatory Ankle Edema: M.E.D. Mg./rat	Anti-inflammatory Ankle Edema: Route
VII[a]	C_6H_5		50	150	I.G.	6	40	I.G.[g]
XIV[b]	C_6H_5		54	150	I.G.	24[i]	5	I.G.
XXIX[c]	C_6H_5		225	20	I.G.	12	Inactive[g]	
XXXII[d]	C_6H_5	$-CH_2$	50	150	I.G.	3	<10	S.C.[g]
XXXVI[e]	C_6H_5	$-CH_2$	53	150	I.G.	Inactive	<10	S.C.
XIX	C_6H_{11}	$-CH_2$	50	150	I.G.	Inactive	Inactive	
XXII	p-ClC_6H_4		30	150	I.G.	Inactive	5	I.G.
XXV	p-$CH_3OC_6H_4$		40	20	S.C.	12	<10	S.C.
VIII[a]	C_6H_5		40	150	I.G.[g]	12	<10	S.C.
XV[b]	C_6H_5	$-CH$	30	20	S.C.	Inactive	<10	S.C.
XX	C_6H_{11}	$\|$	Inactive			Inactive	7.5	I.G.
XXIII	p-ClC_6H_4	$-CH$	20	20	S.C.	Inactive	11	I.G.
XXVI	p-$CH_3OC_6H_4$		50	20	S.C.	Inactive	<10	S.C.
IX[a]	C_6H_5		100	150	I.G.	6	5	I.G.[g]
X[a]	C_6H_5		85	20	S.C.[g]	6	Inactive	
XVI[b]	C_6H_5		325	20	I.G.	24[i]	2	I.G.
XXX[c]	C_6H_5		180	50	I.G.[g]	24	Inactive	
XXXIII[d]	C_6H_5		75	20	S.C.[g]	6	<40	I.G.
XXVII	p-$CH_3OC_6H_4$		51	20	S.C.	—	<10	I.G.
XI[a]	C_6H_5		45	20	S.C.	6	<20	I.G.
XXXIV[d]	C_6H_5		34	150	I.G.	6	Inactive[g]	
XII[a]	C_6H_5		Inactive			12	Inactive	
XVII[b]	C_6H_5		20	20	S.C.	Inactive	11	I.G.
XIII[a]	C_6H_5		40	150	I.G.	6	1	I.G.
XVIII[b]	C_6H_5		82	150	I.G.	Inactive	2	I.G.
XXXV[d]	C_6H_5		50	150	I.G.	6	Inactive	
XXXI[c]	C_6H_5		25	20	S.C.	Inactive	1	I.G.
XXI	C_6H_{11}		Inactive			Inactive	Inactive	
XXIV	p-ClC_6H_4		56	150	I.G.	Inactive	Inactive	
XXVIII	p-$CH_3OC_6H_4$		38	20	I.G.	24	<10	S.C.

[a] From *d,l*-norephedrine. [b] From *d,l*-norpseudoephedrine. [c] From *d*-norephedrine. [d] From *l*-norephedrine. [e] From *l*-norpseudoephedrine. [f] Preludin was used as the standard. [g] Compounds showed some lethality in this test. [h] C. G. Van Armen, *Gen. Pharm. and Exptl. Therap.*, **111**, 285 (1954). [i] Active as sodium excretor only.

95% of theory. After removal of catalyst the solvent was stripped at reduced pressure and the residue was recrystallized from 300 ml. of benzene. The white crystalline product melted at 105–107°. The yield varied between 67 and 85% based on *d,l*-norephedrine.

3-β-Hydroxyethyl-4-methyl-5-phenyloxazolidine (V). To a suspension of 19.5 g. (0.1 mole) of *N*-β-hydroxyethylnorephedrine in 50 ml. of water in a separatory funnel was added 8.75 g. (0.105 mole) of 36% aqueous formaldehyde. The mixture was shaken vigorously for 5 min. followed by extraction of the product with two 100-ml. portions of chloroform. The extracts were dried over anhydrous sodium sulfate and evaporation of solvent gave 19.1 g. (84.9%) of a yellow oil. The crude base was then converted to the *hydrochloride:* Solution of 19.0 g. of the base in 25 ml. of absolute ethanol followed by treatment with 1 equivalent of hydrogen chloride in 2-propanol (0.25 g./ml.) gave the salt which was crystallized by addition of anhydrous ether to turbidity. Recrystallization from ethanol and ether gave the product as a white crystalline solid, m.p. 107–110°.

Anal. Calcd. for $C_{12}H_{18}ClNO_2$: C, 59.12; H, 7.44; N, 5.75; Cl, 14.55. Found: C, 59.03; H, 7.44; N, 5.72; Cl, 14.40.

3-β-Acetoxyethyl-4-methyl-5-phenyloxazolidine. To a stirred solution of 40.7 g. (0.197 mole) of 3-β-hydroxyethyl-4-methyl-5-phenyloxazolidine in 100 ml. of pyridine was added, dropwise, 21.6 g. (0.21 mole) of acetic anhydride. The solution was allowed to stir overnight. The solvent was removed by distillation at reduced pressure giving as the product an orange oil. The crude base was then converted to the *hydrochloride:* A solution of 10 g. of base in 20 ml. of absolute ethanol was treated with 1 equivalent of hydrogen chloride in 2-propanol (0.25 g./ml.) and the salt was crystallized by addition of anhydrous ether. Recrystallization from ethanol and ether gave 7.75 g. (67.7%) of the product in the form of white needles, m.p. 134–138° with decomposition.

Anal. Calcd. for $C_{14}H_{20}ClNO_3$: C, 58.84; H, 7.06; N, 4.90; Cl, 12.41. Found: C, 58.77; H, 7.44; N, 4.93; Cl, 12.23.

d,l-Norpseudoephedrine.[11] *d,l*-Norephedrine hydrochloride (94 g., 0.5 mole) was added in portions to 146 ml. (2.0 moles) of thionyl chloride with stirring. The mixture was then warmed to 45°, at which point the reaction began, as evidenced by gas evolution. When gas evolution had ceased the mixture was heated at 50–60° for 20 min., stirring being discontinued. While an internal temperature of 50–60° was maintained, 200 ml. of water was slowly added, stirring being resumed after the addition of about 100 ml. This was followed by rapid addition of 800 ml. of water and the resulting solution was heated under reflux for 2 hr. There was added 10 g. of Darco G-60 and the mixture was allowed to cool to room temperature. The Darco was removed by filtration and the filtrate was neutralized with 160 ml. of 18*N* sodium hydroxide. The product crystallized on cooling in an ice bath, and filtration followed by washing with ice water gave 37.6 g. (49.8%) of a white crystalline solid with m.p. 73–78°; lit.,[12] m.p. 71°.

Resolution of d,l-norephedrine.[11] A solution of 302.4 g. (2.0 moles) of *d,l*-norephedrine in 600 ml. of hot methanol was added to a solution of 300 g. (2.0 moles) of *d*-tartaric acid in 1000 ml. of hot methanol. The product crystallized overnight and was twice recrystallized from 1600 ml. of methanol to yield 139.9 g. of *d*-norephedrine-*d*-bitartrate, m.p. 153–163°, α_D +31.8° (2% in water).

The above bitartrate was dissolved in 280 ml. of warm water and was made basic with 113 ml. of 18*N* sodium hydroxide. Extraction with three 200-ml. portions of benzene followed by removal of solvent gave 61.7 g. of *d-norephedrine*, α_D +14.0°; lit.,[12] is α_D +14.8°.

The combined filtrates from the crystallization of the *d*-bitartrate were stripped of solvent at reduced pressure and the residue extracted with 4000 ml. of boiling ethanol. On cooling, the ethanol solution gave a gel-like precipitate which was filtered, washed, and dried to give 374.8 g. of solid with α_D +8.2° (2% in water). This material was dissolved in 750 ml. of water and was made basic by addition of 300 ml. of 18*N* sodium hydroxide. The base was extracted with benzene and solvent removed at reduced pressure.

The residual base was dissolved in 400 ml. of hot methanol and was treated with a solution of 168 g. of *l*-tartaric acid in 400 ml. of hot methanol. This gave 191.2 g. of *l*-norephedrine-*l*-bitartrate, m.p. 149–156° which on recrystallization from 1500 ml. of methanol yielded 118.6 g. of the bitartrate, m.p. 156–160° and α_D −34.6° (2% in water).

Liberation of the free base as described for the *d*-isomer using 95 ml. of 18*N* sodium hydroxide gave 49.2 g. of *l-norephedrine*, α_D −14.5°; lit.,[12] is α_D −14.6°.

l-Norpseudoephedrine. To a solution of 118.2 g. (0.784 mole) of *d*-tartaric acid in 275 ml. of hot water was added 118.7 g. (0.784 mole) of *d,l*-norpseudoephrine. This yielded 78.3 g. of crude bitartrate which on recrystallization from 250 ml. of water gave 65.5 g. of pure product, m.p. 201–202° and α_D −12.0° (2% in water). The salt was dissolved in 250 ml. of hot water and made basic with 18*N* sodium hydroxide, and the product was extracted with benzene to yield 29.2 g. of *l-norpseudoephedrine*, m.p. 75–78° and α_D −30.9°; lit.,[12] m.p. 77.5–78°, α_D −32.6°.

Hexahydronorephedrine. A solution of 250 g. (1.65 moles) of *d,l*-norephedrine in 750 ml. of 95% ethanol was reduced at 83° using 2.5 g. of ruthenium oxide catalyst. Uptake of the theoretical amount of hydrogen required 6.5 hr. After filtration of the catalyst the solvent was stripped at reduced pressure and the residue was suspended in 250 ml. of water. Sufficient concentrated hydrochloric acid was added to make the solution acid and this was filtered to remove some colloidal catalyst. The filtrate was made basic with 6*N* sodium hydroxide and the product was extracted with chloroform to yield 185.5 g. (71.6%) of a crystalline solid. The crude base was converted to the *hydrochloride:* A 5.0-g. sample of the base in 20 ml. of absolute ethanol was treated with 1 equivalent of hydrogen chloride in 2-propanol (0.25 g./ml.) and the salt was crystallized by addition of anhydrous ether. Recrystallization from ethanol and ether gave the product as a white crystalline solid, m.p. 218–219°.

Anal. Calcd. for $C_9H_{20}ClNO$: N, 7.23; Cl, 18.31. Found: N, 7.20; Cl, 18.14.

General procedure for the preparation of 4-methyl-5-substituted oxazolidines. To a suspension of 0.1 mole of the appropriate norephedrine in 50 ml. of water in a separatory funnel is added 0.105 mole of 36% aqueous formaldehyde and the mixture is shaken vigorously for 5–10 min. The product is extracted with several portions of chloroform and the extracts are dried over anhydrous sodium sulfate. Evaporation of solvent gives as a residue the crude oxazolidine. The *hydrochloride* can be prepared by solution of the base in absolute ethanol and conversion to the salt by addition of one equivalent of hydrogen chloride in 2-propanol. The product is crystallized by addition of anhydrous ether and is recrystallized from ethanol and ether. In some cases the products were not fully characterized but were used as intermediates in the crude form.

A. 4-Methyl-5-phenyloxazolidine. The various isomers were prepared by the above procedure in yields varying between 89 and 99%.

(*1*) *From d,l-norephedrine.* The product was a colorless oil.

Anal. Calcd. for $C_{10}H_{13}NO$: N, 8.58. Found: N, 8.41. Hydrochloride salt, m.p. 143–148°.

Anal. Calcd. for $C_{10}H_{14}ClNO$: N, 7.02; Cl, 17.76. Found: N, 7.04; Cl, 17.80.

(*2*) *From d,l-norpseudoephedrine.* The product was a pale green oil.

(*3*) *From d-norephedrine.* The product was a colorless oil, α_D +17.9°; hydrochloride salt, m.p. 170–172° and α_D +47.5°.

Anal. Calcd. for $C_{10}H_{14}ClNO$: N, 7.02. Found: N, 7.33.

(*4*) *From l-norephedrine.* The product was a colorless oil, α_D −16.9°.

(*5*) *From l-norpseudoephedrine.* The product was a colorless oil, α_D −59.7°.

B. 4-Methyl-5-cyclohexyloxazolidine was prepared by the general procedure above giving a near quantitative yield of the product; hydrochloride salt, m.p. 137.5–140°.

Anal. Calcd. for $C_{10}H_{20}ClNO$: C, 58.38; H, 9.80; N, 6.81; Cl, 17.24. Found: C, 58.28; H, 9.58; N, 6.43; Cl, 16.86.

C. 4-Methyl-5-p-chlorophenyloxazolidine was prepared from *p*-chloronorephedrine[9,16] by the above general procedure, giving a near quantitative yield of the oxazolidine.

D. 4-Methyl-5-p-methoxyphenyloxazolidine was prepared from *p*-methoxynorephedrine[10] by the above general procedure in 97% yield. The product, a yellow oil, was crystallized from ethanol to yield a white solid, m.p. 106–110°.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.83; N, 7.25. Found: C, 68.65; H, 7.87; N, 7.71.

General procedure for the preparation of 3-imidomethyl-4-methyl-5-substituted oxazolidines. To a solution of 0.03 mole of the appropriate 3-unsubstituted oxazolidine in 25–50 ml. of absolute ethanol is added 0.0306 mole of the desired imide and the mixture is warmed to give a clear solution. To this is added 0.06 mole of 36% aqueous formaldehyde and the resulting solution is heated for 15 min. at the boiling point of ethanol. The hot solution is filtered and the product crystallizes on cooling in an ice bath, in some cases addition of water to turbidity being necessary. Recrystallization from ethanol or ethanol and water affords the pure products. Compounds VII to XXXV were prepared in this manner and the physical properties and analyses are given in Tables I to VII.

A. 3-Succinimidomethyl-4-methyl-5-phenyloxazolidine from l-norpseudoephedrine (XXXVI). This imidomethyloxazolidine was prepared by the above procedure using 4.89 g.

(16) W. H. Hartung, J. C. Munch, and F. S. Crossley, *J. Am. Chem. Soc.*, **57**, 1091 (1935).

(0.03 mole) of 4-methyl-5-phenyloxazolidine (from *l*-norpseudoephedrine), 3.02 g. (0.0306 mole) of succinimide, 5.0 g. (0.06 mole) of 36% aqueous formaldehyde, and 35 ml. of absolute ethanol. Crystallization from absolute ethanol gave the product as a white crystalline solid, m.p. 74–77.5° and α_D −57.6°.

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.22. Found: C, 65.99; H, 6.56; N, 10.18.

Acknowledgment. The help of the following persons who contributed materially to this research is acknowledged: Dr. Robert T. Dillon and his associates for analyses and determination of physical properties; Mr. William Selby and his associates for the running of all catalytic reductions and pressure reactions; Drs. C. G. Van Armen and C. Kagawa and their associates for diuretic assays; Dr. R. E. Ranney and his associates for the appetite inhibition assays; Drs. F. Saunders and L. Herschberger and their associates for the anti-inflammatory assays. I would also like to acknowledge the assistance of Varian Associates, Palo Alto, California, for the NMR spectra and analysis of the data.

CHICAGO 80, ILL.

[CONTRIBUTION FROM THE RADIUM INSTITUTE, UNIVERSITY OF PARIS]

Some Reactions of 5H-Benzo[b]carbazole

PHILIPPE MABILLE* AND N. P. BUU-HOÏ

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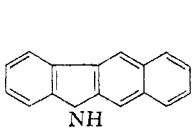
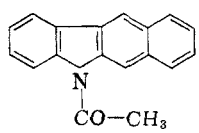
Chrysene obtained from commercial sources, even purified by recrystallization, has been found to contain from 10 to 12% 5H-benzo[b]carbazole. This heterocycle, especially in dilution with chrysene, readily undergoes Friedel-Crafts diacylations with aliphatic and aromatic acid chlorides.

In the course of an investigation on potential antileukemic agents derived from chrysene,[1] large quantities of chrysene were submitted to various chemical reactions, especially Friedel-Crafts acylations. The product used was commercial chrysene purified by recrystallization from toluene and treated with maleic anhydride to remove naphthacene, and was thus obtained as a colorless material having the melting point indicated in the literature. Friedel-Crafts acetylation of this substance yielded, as reported earlier,[1a] 6-acetylchrysene. It is now shown that it is possible to isolate in sizable amounts, from the mother liquors of this ketone, a new compound containing nitrogen, whose composition corresponds to the formula $C_{20}H_{15}NO_2$; it was therefore suspected to arise from a nitrogen-containing impurity that must have been present in appreciable quantities in the starting chrysene. Such an impurity could be one of the benzocarbazoles known to exist in coal tar,[2] for instance, 5H-benzo[b]carbazole (I). Should this be so, the compound $C_{20}H_{15}NO_2$ would be a product of Friedel-Crafts diacetylation of I. Indeed, the same compound was obtained, although in very low yield, along with the known 5-acetyl-5H-benzo[b]carbazole (II), when 5H-benzo[b]carbazole was submitted to acylation under similar conditions. That the compound $C_{20}H_{15}NO_2$ was a diketone, *i.e.*, that the —NH— group was not acetylated, was proven by its ready conversion into a diethyl-5H-benzo[b]-carbazole by means of a Wolff-Kishner reaction. The ultraviolet spectrum of this reduction product closely resembles that of 5H-benzo[b]carbazole itself (see Fig. 1).



I



II

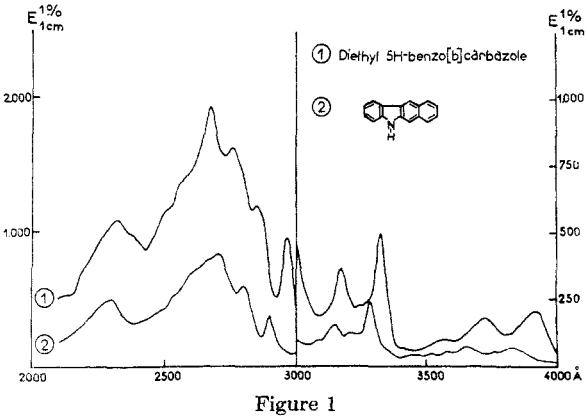


Figure 1

As so little is known of the chemistry of 5H-benzo[b]carbazole, the sites occupied by the substituents in the molecule of its diacetyl compound could not be established, but in view of the rules governing substitution in carbazole itself,[3] one of

(*) Present address: Institut National d'Hygiène, 21 rue de l'Ecole de Medecine, Paris, France.

(1) (a) P. Mabille and N. P. Buu-Hoï, *J. Org. Chem.*, **25**, 216 (1960). (b) P. Mabille and N. P. Buu-Hoï, *J. Org. Chem.*, **25**, 1092 (1960). (c) P. Mabille and N. P. Buu-Hoï, *J. Org. Chem.*, **25**, 1094 (1960).

(2) S. Kikkawa, *J. Chem. Soc. Japan (Ind. Chem. Section)*, **54**, 631 (1951).

(3) For a review of this subject, see N. P. Buu-Hoï and R. Royer, *Rec. trav. chim.*, **66**, 533 (1947).