

# A NEW SYNTHESIS OF 1-SUBSTITUTED-2,3,5,6-TETRAHYDRO-1-IMIDAZ(1,2-a)IMIDAZOLES<sup>1</sup>

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## ABSTRACT

A number of 1-( $\beta$ -hydroxyethyl)-2-(substituted amino)-2-imidazolines have been prepared by the reaction of amines with 1-( $\beta$ -hydroxyethyl)-2-methylmercapto-2-imidazoline. These intermediates on chlorination and dehydrochlorination give the corresponding 1-substituted-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazoles.

Recently (2) the preparations of 1-benzyl- and 1- $\beta$ -diisopropylaminoethyl-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazoles by the reaction of benzylamine and  $\beta$ -diisopropylaminoethylamine with 1-( $\beta$ -chloroethyl)-2-nitriminoimidazolidine were described. This work presents another new method of preparing 1-substituted-2,3,5,6-tetrahydro-1imidaz(1,2-a)imidazoles (IV) which involves the reaction of an amine with 1-( $\beta$ -hydroxyethyl)-2-methylmercapto-2-imidazoline (I) (1, 3).

1-( $\beta$ -Hydroxyethyl)-2-methylmercapto-2-imidazoline (I) or its hydroiodide salt condenses with amines with the liberation of methyl mercaptan. This reaction proceeds smoothly to give good yields of the 1-( $\beta$ -hydroxyethyl)-2-(substituted amino)-2-imidazolines (II). The properties of some of these intermediates and/or their derivatives are described in Table I. Some of the 1-( $\beta$ -hydroxyethyl)-2-(substituted amino)-2-imidazolines could be distilled *in vacuo* without decomposition to give good yields of purified products whereas others such as 1-( $\beta$ -hydroxyethyl)-2-( $\beta$ -dimethylaminoethylamino)-2imidazoline and 1-( $\beta$ -hydroxyethyl)-2-( $\beta$ -di-*n*-propylaminoethylamino)-2-imidazoline partially cyclized and partially decomposed. The water liberated during the cyclization reaction is thought to be responsible for the observed degradation. The crude or purified 1-( $\beta$ -hydroxyethyl)-2-(substituted-amino)-imidazolines were converted into their cor-



R = alkyl, aralkyl, or dialkylaminoalkyl

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		1-(p-HYDR	JXYETHYL)-2-(SU		11NO)-2-1MID	AZOLINES			
C. L. (it was t	Yield,		Formula	С		Н		N	
Substituent		b.p., °C. (mm.)		Calc.	Found	Calc.	Found	Calc.	Found
n-Butyl	99.7	97-98	$C_{9}H_{19}N_{3}O$	58.34	58.37	10.34	10.29	22.60	22.50
n-OctvI	89.5 54.5	84-80" 118-119 <sup>b</sup>	$C_{15}H_{22}N_6O_8$ $C_{21}H_{41}N_2O_6$	43.47 62 10	43.81	5.30 6.89	$5.41 \\ 6.83$	20.29	20.58
<i>n</i> -Dodecyl	86.5	100-102°	C <sub>24</sub> H <sub>40</sub> N <sub>4</sub> OS	66.61	66.61	9.32	9.38	12.95	13.15
n-Tetradecyl	100.0	$114 - 116^{b}$	C37H53N3O9	65.00	65.01	7.80	7.85	6.14	6.05
n-Hexadecyl	99.9	$110 - 111^{b}$	C39H57N3O9	65.88	66.17	8.07	8.29	5.91	6.01
n-Octadecyl	94.2	62-63	$C_{23}H_{47}N_{3}O$	72.38	72.05	12.42	12.20	11.01	11.04
Benzyl	100.0	$147 - 148^{d}$	C12H18CIN3O	56.35	56.36	7.08	7.28	16.43	16.40
2		124–125ª	$C_{18}H_{20}N_6O_8$	48.22	47.96	4.50	4.62	18.85	19.00
β-Phenylethyl	92.2	118-119 <sup>a</sup>	$C_{19}H_{22}N_6O_8$	49.36	49.46	4.80	4.60	18.18	18.12
β-Dimethylaminoeth	1yl 90.7	$160 - 164(0.05)^{\circ}$							
$\beta$ -Diethylaminoethy	1 69.1	166 - 167(0.20)	$C_{11}H_{24}N_4O$	57.86	58.01	10.59	10.26	<b>24</b> . $54$	24.21
	67.0	$166 - 167^{a}$	C <sub>23</sub> H <sub>30</sub> N <sub>10</sub> O <sub>15</sub>	40.23	40.54	4.40	4.49	20.40	20.33
γ-Dimethylamino-	71.5	183 - 184(3, 0)	$C_{10}H_{22}N_4O$	56.04	55.88	10.35	10.43	26.20	26.10
propyl		$125 - 126^{a}$	$C_{22}H_{28}N_{10}O_{15}$	39.28	39.55	4.20	4.35	20.80	20.40
γ-Diethylaminoprop	yl 65.0	164 - 165(0.20)	$C_{12}H_{24}N_4O$	59.45	59.21	10.82	11.02	23.12	22.85

TABLE I

<sup>a</sup>Picrates. <sup>b</sup>Dibenzoyl-d-tartrates. <sup>c</sup>Phenylisothiocyanate derivative, S calc., 7.41; found, 7.20%. <sup>d</sup>Hydrochloride salt, Cl calc., 13.86; found, 13.90%. <sup>c</sup>Some cyclization occurred during distillation.

McKAY AND GARMAISE: IMIDAZOLES

10

TABLE II 1-Substituted-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazoles

	, 25	5 199	B.p., H ° C. (mm.)	<b>D</b> 1-	С		Н		Ν	
	$n_{\rm D}^{-1}$	$a_{4}^{}$		r orniula	Calc.	Found	Calc.	Found	Calc.	Found
$n$ -Octyl 37. $n$ -Dodecyl 45. $n$ -Tetradecyl 44. $n$ -Tetradecyl 44. $n$ -Hexadecyl <sup>a</sup> 67. $n$ -Octadecyl <sup>b</sup> 60.   Benzyl <sup>c</sup> 70. $\beta$ -Phenylethyl 44. $\beta$ -Dimethylaminoethyl 50. $\beta$ -Diethylaminoethyl 50. $\beta$ -Diethylaminoethyl 52.	$\begin{array}{c ccccc} 0 & 1.4857\\ 2 & 1.4842\\ 7 & 1.4832\\ 7 &\\ 0 &\\ 0 &\\ 0 & 1.5705\\ 0 & 1.5705\\ 0 & 1.5008\\ 1.4984\\ 8 & 1.4938\\ 5 & 1.5033\\ \end{array}$	$\begin{array}{c} 0.959\\ 0.945\\ 0.937\\\\\\ 1.109\\ 1.101\\ 1.018\\ 1.002\\ 0.986\\ 1.013\\ \end{array}$	$\begin{array}{c} 115-117(0.05)\\ 143-145(0.08)\\ 172-173(0.08)\\ 188-190(0.07)\\ 227-228(0.2)\\ 124-126(0.1)\\ 122-214(0.05)\\ \hline \\ 100-102(0.05)\\ 106-108(0.05)\\ 119-121(0.25)\\ \hline \end{array}$	$\begin{array}{c} C_{13}H_{25}N_3\\ C_{17}H_{33}N_3\\ C_{19}H_{37}N_3\\ C_{21}H_{41}N_3\\ C_{23}H_{45}N_3\\ C_{31}H_{45}N_3\\ C_{9}H_{18}N_4\\ C_{11}H_{22}N_4\\ C_{13}H_{26}N_4\\ C_{10}H_{20}N_4\\ \end{array}$	$\begin{array}{c} 69.90\\ 73.05\\ 74.21\\ 75.16\\ 75.97\\ \hline \\ 72.53\\ 59.29\\ 62.81\\ 65.50\\ 61.17\\ \hline \\ \end{array}$	$\begin{array}{c} 70.07\\73.00\\74.43\\75.01\\75.81\\72.14\\59.22\\62.60\\65.43\\61.01\\61.01\end{array}$	$\begin{array}{c} 11.29\\ 11.95\\ 12.13\\ 12.34\\ 12.48\\ \hline 7.96\\ 9.95\\ 10.55\\ 10.99\\ 10.27\\ \hline \end{array}$	$\begin{array}{c} 11.16\\ 11.58\\ 11.88\\ 12.34\\ 12.38\\ 8.29\\ 9.58\\ 10.35\\ 10.81\\ 10.26\\ 10.26\end{array}$	$18.81 \\ 15.04 \\ 13.67 \\ 12.52 \\ 11.56 \\ 19.52 \\ 30.74 \\ 26.64 \\ 23.50 \\ 28.54 \\ 28.5$	$18.52 \\ 14.83 \\ 13.39 \\ 12.35 \\ 11.61 \\ 19.79 \\ 30.50 \\ 26.31 \\ 23.26 \\ 28.32 \\ 28.32 \\ 30.50 \\ 28.32 \\ 30.50 \\ 28.32 \\ 30.50 \\ 30.5$

<sup>a</sup>M.p. 33-34° C. <sup>b</sup>M.p. 36-37° C. <sup>c</sup>M.p. 40.5° C. (3).

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CANADIAN JOURNAL OF CHEMISTRY, VOL. 35, 1957

TABLE III								
Picrates of 1-substituted-2,3,5,6-tetrahydro-1-imidaz $(1,2-a)$ imidazoles								

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Substituent	M.p., ° C.	Formula	С		Н		Ν	
			Calc.	Found	Calc.	Found	Calc.	Found
<i>n</i> -Octyl	75-76	C <sub>19</sub> H <sub>28</sub> N <sub>6</sub> O <sub>7</sub>	50.43	50.48	6.24	6.14	18.57	18.27
<i>n</i> -Dodecyl	65 - 66	$C_{23}H_{36}N_6O_7$	54.30	54.50	7.13	7.35	16.52	16.69
<i>n</i> -Tetradecyl	75 - 76	$C_{25}H_{40}N_6O_7$	55.94	56.16	7.51	7.58	15.66	15.56
<i>n</i> -Hexadecyl	78 - 79	C27H44N6O7	57.42	57.53	7.85	7.87	14.88	14.60
<i>n</i> -Octadecyl	86-87	C29H48N6O7	58.78	58.83	8.16	8.15	14.15	14.01
Benzyl	123 - 124	C18H18N6O7	50.13	49.97	4.21	4.40	19.53	19.70
β-Phénylethyl	145 - 146	$C_{19}H_{20}N_6O_7$	51.35	51.61	4.54	4.76	18.92	19.11
$\beta$ -Dimethylaminoethyl	172 - 173	C21H24N10O14	39.36	39.81	3.78	3.98	21.87	22.30
β-Diethylaminoethyl	172 - 173	C23H28N10O14	41.30	41.33	4.22	4.26	20.95	21.29
$\beta$ -Di- <i>n</i> -propylaminoethyl	169 - 170	C25H32N10O14	43.12	43.31	4.63	4.72	20.11	19.84
y-Dimethylaminopropyl	157 - 158	C22H26N10O14	40.36	40.10	4.00	4.13	21.40	21.20
$\gamma$ -Diethylaminopropyl	139 - 140	C24H30N10O14	41.93	42.22	4.45	4.43	20.40	20.50

### CANADIAN JOURNAL OF CHEMISTRY, VOL. 35, 1957

responding 1-( $\beta$ -chloroethyl)-2-(substituted amino)-2-imidazolinium chlorides by chloroination with thionyl chloride. These chloro derivatives, with the exception of 1-( $\beta$ chloroethyl)-2-benzylamino-2-imidazoline, were used for the next stage of synthesis without further purification. They were dehydrochlorinated to give the 1-substituted-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazoles (IV). Some of the yields reported in Table II are low because of the partial degradation encountered in the distillation of the intermediates. It was observed that the over-all yields of the bicyclic compounds (IV) were much higher when the intermediate 1-( $\beta$ -hydroxyethyl)-2-(substituted amino)-2-imidazolines were used directly without preliminary distillation. The properties of the 1substituted-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazoles and their picrates are given in Tables II and III respectively.

 $1-(\beta-\text{Dimethylaminoethyl})$ - and  $1-(\beta-\text{diethylaminoethyl})-2,3,5,6-\text{tetrahydro-1-imidaz}$ (1,2-a)imidazoles were methylated with methyl iodide. These compounds combined with 2 mole equivalents of methyl iodide to give derivatives whose analytical values are in good agreement with those calculated for structure (V).



 $R' = CH_3 \text{ or } C_2H_5$ 

#### EXPERIMENTAL<sup>2</sup>

### 1-(\beta-Hydroxyethyl)-2-methylmercapto-2-imidazolinium Iodide

 $1-(\beta-Hydroxyethyl)-2-methylmercapto-2-imidazolinium iodide (m.p. 120-121°C.)$  was prepared in 95% yield as previously (3) described.

# 1-Substituted-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazoles

The procedures for the preparations of the 1-substituted-2,3,5,6-tetrahydro-1imidaz(1,2-a)imidazoles are very similar and only three variations in procedure are described below in detail. Tables II and III list the physical properties of the 1-substituted-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazoles and their picrates respectively.

### 1-Benzyl-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole

A solution of 1-( $\beta$ -hydroxyethyl)-2-methylmercapto-2-imidazolinium iodide (144 g., 0.50 mole) and benzylamine (55.0 g., 0.52 mole) in 240 cc. of methanol was refluxed for  $1\frac{1}{2}$  hours. The methanol was removed by evaporation and the residue in water (2% solution) was passed through a column of IRA-400 (1 liter) resin. This column was washed with water and the washings and eluate were combined and acidified with hydrochloric acid solution. On evaporation of the aqueous solution 1-( $\beta$ -hydroxyethyl)-2-benzylamino-2-imidazolinium chloride (m.p. 142–147° C.) was obtained in quantitative yield. A sample was prepared for analysis by crystallization twice from a methanol –

<sup>2</sup>All melting points are uncorrected. Microanalyses were performed by Micro Tech Laboratories, Skokie, Illinois.

12

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#### McKAY AND GARMAISE: IMIDAZOLES

ethyl acetate solution. The final melting point was 147–148° C. Its picrate prepared in the usual manner melted at 124° C. (3).

1-(β-Hydroxyethyl)-2-benzylamino-2-imidazolinium chloride (16.0 g., 0.062 mole) and thionyl chloride (14.0 g., 0.118 mole) in 50 cc. of chloroform were refluxed together for 3 hours. After the excess thionyl chloride and chloroform were removed by distillation, a reddish oil was obtained in quantitative yield. A portion (0.3 g.) of this oil was converted into its picrate melting at 137–138° C. This melting point was not increased on further crystallization. Calc. for  $C_{18}H_{19}Cl N_6O_7$ : C, 46.30; H, 4.11; Cl, 7.59; N, 18.24%. Found: C, 46.35; H, 4.30; Cl, 7.89; N, 18.00%.

The remainder of the reddish oil,  $1-(\beta$ -chloroethyl)-2-benzylamino-2-imidazolinium chloride, was refluxed for 2 hours in a solution of potassium hydroxide (10.0 g., 0.178 mole) in absolute methanol (150 cc.). The precipitated potassium chloride was removed by filtration and the filtrate was evaporated to dryness. The residue was extracted with ether (2 × 50 cc.) and the ethereal solution on evaporation gave 8.8 gm. (70%) of oil. This oil (b.p. 124–126° C. at 0.1 mm.) was distilled *in vacuo* using a Vigreux column. Its picrate melted at 123–124° C. The picrate of 1-benzyl-2,3,5,6-tetrahydro-1-imidaz (1,2-a)imidazole was previously reported (2) to melt at 109–109.5° C. A mixture melting point determination with these two picrates gave a melting point of 123° C. When the low melting picrate was dissolved in water and then seeded with the high melting form, it gave the picrate melting at 123–124° C. It appears that this picrate is dimorphous. Both picrates gave good analytical values for the monopicrate of 1-benzyl-2,3,5,6tetrahydro-1-imidaz(1,2-a)imidazole.

### 1-n-Tetradecyl-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole

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 $1-(\beta$ -Hydroxyethyl)-2-methylmercapto-2-imidazolinium iodide (86.4 g., 0.30 mole) and *n*-tetradecylamine (63.9 g., 0.30 mole) were refluxed for 3 hours in 200 cc. of methanol. This solution was diluted with 600 cc. of methanol and then it was passed through a column of IRA-400 resin (1000 cc., previously washed with 800 cc. of methanol) at a rate of 8 cc. per minute. The column was washed with methanol (1200 cc.) until the eluate gave no further positive test with picric acid solution. The eluate and washing were combined and evaporated to dryness, yield 97.5 g. (100%). Part (65 g., 0.20 mole) of this residue was converted into its hydrochloride. The dry hydrochloride was dissolved in 200 cc. of dry benzene and thionyl chloride (47.6 g., 0.4 mole). After this solution had refluxed for 2 hours, the excess thionyl chloride and solvent were removed by evaporation. This procedure gave a quantitative yield of the intermediate  $1-(\beta$ chloroethyl)-2-*n*-tetradecylamino-2-imidazolinium chloride.

 $1 - (\beta$ -Chloroethyl) - 2-*n*-tetradecylamino - 2-imidazolinium chloride in a solution of potassium hydroxide (24.7 g., 0.442 mole) in 425 cc. of absolute alcohol was refluxed for 3 hours. The resulting mixture was worked up as described in the procedure above for 1-benzyl-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole. A black oily residue was obtained, yield 50.5 g. (82.4%). Fractional distillation using a Vigreux column setup yielded 27.4 g. of colorless oil (b.p. 172–173° C. at 0.08 mm.). Its picrate melted at 75–76° C. after two crystallizations from ether.

## 1 - (Di-n-propylaminoethyl) - 2, 3, 5, 6 - tetrahydro - 1 - imidaz(1, 2-a) imidazole

 $1-(\beta-Hydroxyethyl)-2$ -methylmercapto-2-imidazolinium iodide (40.0 g., 0.115 mole) was condensed with N,N'-di-*n*-propyl ethylenediamine (17.3 g., 0.12 mole) under the conditions described above for the preparation of  $1-(\beta-hydroxyethyl)-2$ -benzylamino-2-imidazoline and the condensation product was dissolved in 100 cc. of water. This aqueous

#### CANADIAN JOURNAL OF CHEMISTRY, VOL. 35, 1957

solution was passed through a column of highly active IRA-400 resin (450 cc.) at a rate of 25 cc. per minute. After the column was washed with water (2000 cc.), the combined washings and eluate were evaporated to dryness, yield 29.0 g. (98%). This oily product on distillation in vacuo underwent extensive decomposition giving 5 g, of di-n-propylaminoethylamine. One fraction (b.p. 114-123° C. at 0.05 mm.) gave a picrate melting at 169-170° C., which was identified as the picrate of the bicyclic product, 1-(di-npropylaminoethyl)-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole, yield 1.2 g.

Another fraction (b.p.  $> 123^{\circ}$  C. at 0.05 mm.) (6 g.), which appeared to be a mixture of  $1-(\beta-hydroxyethyl)-2-(di-n-propylaminoethylamino)-2-imidazoline and the bicyclic$ product, was converted into the bicyclic product by the procedure described in the above examples. The oily product (b.p. 106-108° C. at 0.05 mm.) was obtained in 44.8% yield based on the over-all conversion of  $1-(\beta-hydroxyethyl)-2-methylmercapto-2-imidaz$ olinium iodide into 1-(di-n-propylaminoethyl)-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole. The picrate of the latter compound formed in the usual manner melted at 169-170° C. It was purified by crystallization from ethanol.

# Methylation of $1-(\beta-Dimethylaminoethyl)-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole$

A solution of 4.8 g. (0.0247 mole) of  $1-(\beta-\text{dimethylaminoethyl})-2,3,5,6-\text{tetrahydro-1-}$ imidaz(1,2-a)imidazole and 14.2 g. (0.10 mole) of methyl iodide in 50 cc. of absolute alcohol was refluxed for 1 hour. This solution on evaporation of solvent and excess methyl iodide gave 11.5 g. (93.5%) of a crystalline solid (m.p. 160-170° C.). Several crystallizations from various solvents always gave crystals melting over a range (m.p. 155-170° C.). However, after drying at 64° C. in vacuo, the crystals had a melting point of 234–236° C. Anal. Calc. for C<sub>11</sub>H<sub>24</sub>I<sub>2</sub>N<sub>4</sub>: C, 28.33; H, 5.19; I, 54.45; N, 12.02%. Found: C, 28.36; H, 5.16; I, 54.29; N, 11.99%.

The dipicrate (m.p.  $205-206^{\circ}$  C.) of the dimethiodide of  $1-(\beta-\text{dimethylaminoethyl})$ -2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole was prepared in the usual manner. Anal. Calc. for C23H28N10O14: C, 41.31; H, 4.22; N, 20.95%. Found: C, 41.03; H, 4.01; N, 21.39%.

### Dimethiodide of $1-(\beta$ -Diethylaminoethyl)-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole

The dimethiodide of 1-( $\beta$ -diethylaminoethyl)-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole (m.p. 180-200° C.) was prepared in 97% yield by the procedure described above for preparing the dimethiodide of  $1-(\beta-dimethylaminoethyl)-2,3,5,6-tetrahydro-1$ imidaz(1,2-a)imidazole. Four recrystallizations from methanol-ethyl acetate (1:3) solution raised the melting point to a constant value of  $228-230^{\circ}$  C. Anal. Calc. for C<sub>13</sub> H<sub>28</sub>I<sub>2</sub>N<sub>4</sub>: C, 31.59; H, 5.71; I, 51.37; N, 11.34%. Found: C, 31.71; H, 5.83; I, 51.15; N, 11.31%.

The dipicrate formed in the usual manner melted at 190-191° C. after two crystallizations from alcohol. Anal. Calc. for C<sub>25</sub>H<sub>32</sub>N<sub>10</sub>O<sub>14</sub>: C, 43.09; H, 4.63; N, 20.11%. Found: C, 43.12; H, 4.48; N, 19.83%.

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14

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