674. *Naphthimidazoles. Part II.*[1] 5,6,7,8-*Tetrahydronaphth*[2,3]-*imidazole and Some Derivatives.*

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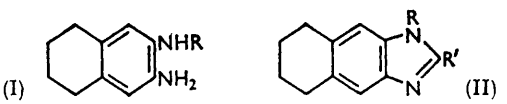
5,6,7,8-Tetrahydronaph[2,3]imidazole and some of its $C_{(2)}$-derivatives have been prepared. In their ionization constants and ultraviolet spectra they resemble the benzimidazoles more than the linear naphthimidazoles.

Following a brief study of 2-substituted linear naphthimidazoles,[1] representative derivatives of the related 5,6,7,8-tetrahydronaphth[2,3]imidazole series have been made. Only one derivative (II; R = H; R′ = Me) has been previously described,[2] and the ultraviolet spectra and pK_a values of the new 2-substituted derivatives form a logical link between those of the benzimidazoles and naphthimidazoles.

6,7-Diaminotetralin (I; R = H) [2,3] was boiled with formic or propionic acid, the parent 5,6,7,8-tetrahydronaphth[2,3]imidazole (II; R = R′ = H) or 2-ethyl derivative being formed, respectively. Fusion of the diamine with urea gave 5,6,7,8-tetrahydro-2-hydroxynaphth[2,3]imidazole which (unlike its fully aromatic analogue [1]) was converted with phosphoryl chloride into the 2-chloro-derivative (II; R = H; R′ = Cl). The chlorine



(I) (II)

was readily replaced by an anilino-group and in poor yield by a dimethylamino-group. From ammonia, methylamine, or methanolic sodium methoxide, the chloro-compound was recovered, or under more severe conditions it was destroyed. However, the 2-amino-derivative was obtained directly from 6,7-diaminotetralin and cyanogen bromide although an attempt to make the 2-ethoxy-derivative with diethyl imidocarbonate (as 2-ethoxybenziminazole [4]) failed. The 2-mercapto-compound was obtained from thiourea and the diaminotetralin; methylation gave the 2-methylthio-derivative, and sodium chloroacetate the 2-carboxymethylthio-derivative, which on treatment with acetic anhydride cyclized by amide linkage on to $N_{(1)}$ giving the naphthothiazoloimidazole (II; RR′ = $CO{\cdot}CH_2{\cdot}S$).

Although the parent compound and its 2-mercapto-derivative could not be *N*-methylated satisfactorily, these compounds were obtained by direct synthesis from 2-amino-5,6,7,8-tetrahydro-3-methylaminonaphthalene [5] (I; R = Me) with, respectively, formic acid and thiourea.

[1] The paper by Brown, *J.*, 1958, 1974, is considered to be Part I of this series.
[2] Schroeter, *Annalen*, 1922, **426**, 17.
[3] Mayer and Schirmacher, D.R.P. 434,403; *Chem. Zentr.*, 1926, II, 2496.
[4] Sandmeyer, *Ber.*, 1884, **19**, 2650.
[5] Kuhn, Vetter, and Rzeppa, *Ber.*, 1937, **70**, 1302.

The transition from benzimidazole to linear naphthimidazole results [1] in a marked weakening of the basic strength, from pK_a 5·53 to pK_a 5·24. When the added ring is paraffinic as in 5,6,7,8-tetrahydronaphthimidazole, no such weakening occurs and the normal increase in basic strength associated with *C*-alkylation is seen in a pK_a of 5·98, comparable for example with that of 5,6-dimethylbenzimidazole (6·11). Further *C*-alkylation at $C_{(2)}$ again increases the basic strength as in 2-ethyl-5,6,7,8-tetrahydronaphthimidazole (pK_a 6·64). 2-Aminotetrahydronaphthimidazole is similarly a stronger base (7·69) than 2-aminonaphthimidazole (7·01). In acidic properties, tetrahydronaphthimidazole (pK_a 13·3) is almost identical with 5,6-dimethylbenzimidazole, and rather weaker than the fully aromatic linear naphthimidazole (12·5); similar relations apply for the 2-hydroxy- and 2-mercapto-derivatives.

The ultraviolet spectra in the Table indicate a closer resemblance of the tetrahydronaphthimidazoles to the benzimidazoles than to the linear naphthimidazoles. There is a slight bathochromic shift of the long wave length bands (cation and neutral molecule) between 5,6-dimethylbenzimidazole and tetrahydronaphthimidazole, but a very marked hypsochromic shift on approaching the latter from linear naphthimidazole. As in the naphthimidazoles, the spectra of the reduced hydroxy-derivative (anion) and the amino-derivative (neutral molecule) are almost identical, as are also those of the carboxymethyl thio-anion and of the corresponding methylthio-derivative. The spectra of the dimethylamino-compound bear the usual close resemblance to those of the parent amino-compound.

5,6,7,8-Tetrahydronaphth[2,3]imidazole derivative	pK_a (20°) [a] and concn. (10^{-5}M) in brackets	Ultraviolet spectra in water		
		pH	$\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$
Unsubst.	—	8·0	291; 282; 252	3·78; 3·78; 3·62
cation	5·98 (±0·02) [b] [100]	3·5	289; 279	3·86; 3·87
anion	13·33 (+0·02) [2·5]			
2-Ethyl-	—	9·5	293; 287; 283; 250	3·82; 3·86; 3·85; 3·65
cation	6·64 (±0·03) [2·5]	3·0	290; 281	3·91; 3·93
2-Hydroxy-	—	7·0	290	3·88
anion	12·21 (±0·03) [2·5]	14·0	298; 245 [f]	3·92; 3·65
di-anion	*ca.* 15·5			
2-Mercapto-	—	6·7	311; 303; 248	4·43; 4·36; 4·15
anion	10·43 (±0·05) [0·65]	12·5	310; 258	4·30; 3·96
2-Methylthio-	—	7·5	302; 294	4·20; 4·20
cation	*ca.* 5·0 [c] [0·625]	0	303; 296	4·30; 4·28
anion	*ca.* 13 [0·625]			
2-Chloro-	—	6·5	293; 283; 251	3·94; 3·94; 3·68
cation	2·68 (±0·05) [1·25]	0	294; 284	4·03; 4·06
2-Dimethylamino-	—	10	301; 248	4·10; 3·82
cation	7·65 (±0·01) [1·25]	4·5	293; 234 [g]	4·08; 3·93
anion	>13 [1·25]			
2-Carboxymethylthio-	—	3·1 [e]	303; 297	4·29; 4·27
anion	*ca.* 5·2 [c]	8·5	303; 295	4·20; 4·20
2-Amino-	—	10	293; 244	3·97; 3·76
cation	7·69 (±0·03) [1·25]	3·5	287	3·99
2-Mercapto-3-methyl-	—	6·5	312; 304 [f]; 244	4·42; 4·39; 4·29
anion	10·78 (±0·07) [0·625]	13·0	313; 263	4·35; 3·99
Other compounds				
Naphth[2,3]imidazole [d]	—		342; 327; 317; 235	3·74; 3·88; 3·83; 4·79
cation	5·24		325; 318; 235	3·90; 3·84; 4·75
anion	12·52			
5,6-Dimethylbenzimidazole [h]	—	8·0	286; 279; 277 [f]; 246	3·67; 3·66; 3·66; 3·59
cation	6·11 (±0·02) [b] [500]	3·5	283; 276 [f]; 274; 246	3·79; 3·77; 3·77; 3·41
anion	12·52			

[a] Most values spectroscopically determined. [b] Potentiometrically determined. [c] The densities of species are too close for an accurate pK_a determination. [d] Figures from ref. 1. [e] Probably contaminated with cation; cationic pK_a unobtainable. [f] Inflexion. [g] Plateau. [h] Prepn.: ref. 7.

[6] Crippa and Maffei, *Gazzetta*, 1941, **71**, 418.
[7] Takatori, Yamada, and Kawashima, *J. Pharm. Soc. Japan*, 1955, **75**, 881.

Experimental

5,6,7,8-*Tetrahydronaphth*[2,3]*imidazole*.—6,7-Diaminotetralin [1,2] (1 g.) was refluxed with 98% formic acid (5 ml.). After 4 hr. the cooled solution was poured on ice and the pH adjusted to 7—8 by addition of sodium carbonate solution. Recrystallisation of the product (1 g.) from benzene (10 ml.) gave an adduct (m. p. 86—88°). The free *tetrahydronaphthimidazole*, m. p. 134—135°, was obtained by sublimation (130°/0·1 mm.) (Found: C, 76·5; H, 7·2; N, 16·2. $C_{11}H_{12}N_2$ requires C, 76·7; H, 7·0; N, 16·3%).

5,6,7,8-*Tetrahydro*-1-*methylnaphth*[2,3]*imidazole*.—6-Amino-7-methylaminotetralin [5] was treated with formic acid as above. The crude oily product was removed with ether and distilled giving the N-*methyl compound* as a pale yellow unstable oil, b. p. 180°/0·2 mm. It solidified at room temperature (Found: N, 15·0. $C_{12}H_{14}N_2$ requires N, 15·0%).

2-*Ethyl*-5,6,7,8-*tetrahydronaphth*[2,3]*imidazole*.—Prepared similarly to the parent compound, the *ethyl* analogue formed needles, m. p. 242—243° (from 50% ethanol, 30 parts) (Found: C, 77·9; H, 8·2; N, 13·95. $C_{13}H_{16}N_2$ requires C, 77·95; H, 8·05; N, 14·0%).

5,6,7,8-*Tetrahydro*-2-*hydroxynaphth*[2,3]*imidazole*.—An intimate mixture of 6,7-diaminotetralin (1 g.) and urea (1 g.) was heated under nitrogen at 160°. After 4 min. the mass solidified and after a further 5 min. it was cooled and water (10 ml.) added. The solid (1·15 g.) was recrystallised from ethanol (100 parts) to give the *hydroxy-derivative* as white laths, m. p. 355° (Found: C, 70·2; H, 6·5; N, 14·8. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·3; N, 14·9%).

5,6,7,8-*Tetrahydro*-2-*mercaptonaphth*[2,3]*imidazole*.—Fusion, as above, of the diaminotetralin and thiourea at 190° and recrystallisation from 70% ethanol (40 parts) gave the *mercapto-derivative* as needles, m. p. 310° (Found: C, 64·7; H, 6·0; N, 13·7. $C_{11}H_{12}N_2S$ requires C, 64·7; H, 5·9; N, 13·7%).

5,6,7,8-*Tetrahydro*-2-*mercapto*-1-*methylnaphth*[2,3]*imidazole*.—6-Amino-7-methylaminotetralin [5] (0·8 g.) and thiourea (0·8 g.) were heated under nitrogen at 200° for 15 min. Water (10 ml.) was added, and the solid (0·5 g.) treated with charcoal and recrystallised from ethanol (50 parts), giving the *mercapto-methylnaphthimidazole* as needles, m. p. 250—252° (Found: C, 66·0; H, 6·6; N, 13·0. $C_{12}H_{14}N_2S$ requires C, 66·0; H, 6·5; N, 12·8%).

5,6,7,8-*Tetrahydro*-2-*methylthionaphth*[2,3]*imidazole*.—The mercapto-derivative (0·8 g.) in 0·1N-sodium hydroxide (45 ml.; 10% excess) was shaken with dimethyl sulphate (0·55 g.) for 1 hr. at 25°. The pH of the solution was adjusted to *ca.* 5 and the solid filtered off. Recrystallisation from 50% aqueous propanol (30 parts) gave the *methylthio-compound* as needles, m. p. 195° (Found: C, 66·0; H, 6·5; N, 12·8. $C_{12}H_{14}N_2S$ requires C, 66·0; H, 6·5; N, 12·8%).

2-*Chloro*-5,6,7,8-*tetrahydronaphth*[2,3]*imidazole*.—2-Hydroxytetrahydronaphthimidazole (0·56 g.) and phosphoryl chloride (6 ml.) were refluxed for 6 hr. Volatile material was partially removed *in vacuo* and the residue poured on ice (20 g.). A little insoluble material was filtered off and the pH of the filtrate adjusted to *ca.* 7 with dilute ammonia solution. The precipitate (0·4 g.) was recrystallised from 50% aqueous ethanol (40 parts) giving the *chloro-compound*, m. p. 211° (Found: C, 64·0; H, 5·4; N, 13·55. $C_{11}H_{11}N_2Cl$ requires C, 63·9; H, 5·4; N, 13·55%)

2-*Anilino*-5,6,7,8-*tetrahydronaphth*[2,3]*imidazole*.—The 2-chloro-derivative (0·5 g.) and aniline (5 ml.) were refluxed under nitrogen for 2·5 hr. Steam-distillation removed excess of aniline, and the crystalline residue (0·5 g.) was washed with dilute ammonia solution, recrystallised from isobutyl methyl ketone (30 parts), and sublimed in a vacuum to give the *anilino-compound*, m. p. 247—249° (Found: C, 77·3; H, 6·4. $C_{17}H_{17}N_3$ requires C, 77·5; H, 6·5%).

2-*Dimethylamino*-5,6,7,8-*tetrahydronaphth*[2,3]*imidazole*.—The 2-chloro-derivative (0·35 g.) and aqueous dimethylamine (30%; 10 ml.) were heated at 150° for 3 hr. The pH was adjusted to *ca.* 1, and the solution treated with charcoal. Adjustment of the pH of the filtrate to 8 gave a crude product (0·2 g.) which was crystallised, sublimed in a vacuum, and recrystallised from benzene (100 parts) to give the *dimethylamino-derivative*, m. p. 210—211° (Found: C, 72·3; H, 7·9. $C_{13}H_{17}N_3$ requires C, 72·5; H, 7·95%).

2-*Carboxymethylthio*-5,6,7,8-*tetrahydronaphth*[2,3]*imidazole*.—Tetrahydro-2-mercaptonaphthimidazole (1·43 g.) in N-sodium hydroxide (7 ml.) was heated at 100° with chloroacetic acid (0·7 g.) in 2·5N-sodium hydroxide (3 ml.) for 2 hr. The solution was cooled and diluted with water (10 ml.), and the pH adjusted to 2—3. Recrystallisation from ethanol (100 parts) gave the *acid* as needles, m. p. 194—195° (1·8 g.) (Found: C, 59·5; H, 5·4; N, 10·5. $C_{13}H_{14}SO_2N_2$ requires C, 59·5; H, 5·4; N, 10·7%).

1,2,6,7,8,9-*Hexahydro*-1-*oxonaphtho*[2,3-*d*]*thiazolo*[3,2-*a*]*imidazole*.—The above acid (0·7 g.) and pyridine (3 ml.) were heated on the steam-bath with acetic anhydride (1 ml.) for 15 min., and the mixture then cooled and diluted with water (25 ml.). The solid was extracted with boiling ethanol (25 ml.), and the extract concentrated to 15 ml., diluted with water (15 ml.), and cooled. The needles of *naphthothiazoloimidazole* had m. p. 161° (Found: C, 63·8; H, 5·0; N, 14·5. $C_{13}H_{12}ON_2S$ requires C, 63·9; H, 4·95; N, 14·5%).

2-*Amino*-5,6,7,8-*tetrahydronaphth*[2,3]*imidazole*.—Cyanogen bromide [6] [from the addition of potassium cyanide (0·63 g.) in water (3 ml.) to bromine (1·45 g.) at 0°] in cold water (15 ml.) was added to a stirred suspension of 6,7-diaminotetralin (1·4 g.). Next morning the oily mixture was diluted with water and made alkaline, and the solid filtered off. After three sublimations *in vacuo*, the *amine* (1·35 g.) had m. p. 220° (Found: C, 70·75; H, 7·15; N, 22·35. $C_{11}H_{13}N_3$ requires C, 70·6; H, 7·0; N, 22·4%).

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