401. *Some 2-Substituted Linear Naphthiminazoles.*

By D. J. Brown.

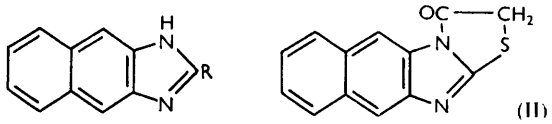
Several 2-substituted linear naphthiminazoles have been prepared; in their ionization and ultraviolet spectra the linear and the angular naphthiminazoles are shown to form a graded series with glyoxaline and benziminazole.

The scanty literature [1] of the angular (or αβ-) and the linear (or ββ-)naphthiminazoles (I; R = H) reveals that only two monosubstituted derivatives [2,3] are known in the linear series, and no spectra are recorded. To remedy this, some 2-substituted members have been prepared and their pK_a values and ultraviolet spectra determined.

When 2 : 3-diaminonaphthalene was fused with urea, 2-hydroxynaphth[2,3]iminazole (I; R = OH) resulted, but phosphoryl chloride did not yield the 2-chloro-derivative from it. A similar fusion with thiourea produced 2-mercaptonaphth[2,3]iminazole which on methylation gave the methylthio-derivative. This reacted with benzylamine,

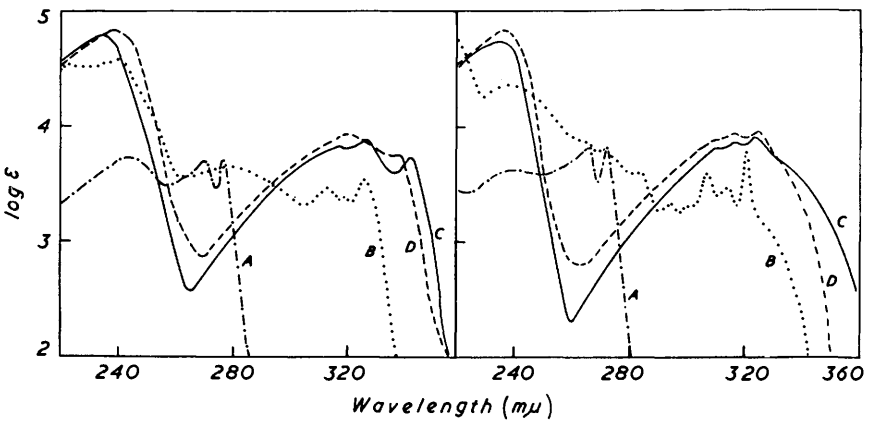
[1] Cf. Brown in the Symposium Report, " Current Trends in Heterocyclic Chemistry," Butterworths, London, 1958, p. 75.
[2] Fries, Walter, and Schilling, *Annalen*, 1935, **516**, 248.
[3] Goldstein and Streuli, *Helv. Chim. Acta*, 1937, **20**, 520.

aniline, and, more slowly, benzylmethylamine, to give respectively 2-benzylamino-, anilino-, and benzylmethylamino-derivatives. It did not react however in the same way with ammonia, methylamine, or ethylamine at the same temperature (sealed tubes), and above 180° it was destroyed by these reagents. It has been suggested [4] that this lack



of reactivity might be due to deprotonation at $N_{(1)}$ by these stronger bases, but a solution of methylamine buffered at pH 9 also did not react. The 2-amino-derivative was finally prepared by the action of cyanogen bromide on 2 : 3-diaminonaphthalene, by analogy with an example in the angular series.[5] Although 2-methylthiobenziminazole has been oxidised to the sulphone [6] 2-methylthionaphth[2,3]iminazole under similar conditions gave no isolable product. The 2-mercapto-compound with chloroacetic acid gave a

FIG. 1. FIG. 2.



Absorption: FIG. 1, *as neutral molecules*; FIG. 2, *as cations*.
A, Benziminazole; *B, naphth*[1,2]*iminazole*; *C, naphth*[2,3]*iminazole*; *D, 2-ethylnaphth*[2,3]*iminazole*.

carboxymethylthio-derivative (I; R = $S{\cdot}CH_2{\cdot}CO_2H$), which with acetic anhydride produced the cyclic amide (II) analogous to that described in the benziminazole series.[7]

Progressive annelation of glyoxaline weakens the basic properties, as would be expected. The basic pK_a of glyoxaline [8] (7·03) is decreased by addition of a benzene ring [9] to 5·53 in benziminazole, and again for linear (5·24) and angular naphthiminazole (5·28). Similarly, that of 2-aminobenziminazole [9] is 7·54, and of the corresponding linear naphthiminazole is 7·01. The feeble acidity (pK_a 14·5) of glyoxaline [10] is increased as expected by annelation (benziminazole: 13·2 *), and the naphthiminazoles are stronger acids (12·52; 12·54). With the 2-hydroxy- and the mercapto-derivative, the change from one to two benzene rings is also acid-strengthening. Alkyl groups have the usual base-strengthening and acid-weakening effects on linear naphthiminazole (cf. Table).

The ultraviolet spectra recorded in the Table form an extension to those of glyoxaline

* The earlier potentiometric figure [9] is considered to be less accurate than this spectroscopic value (see Table).

[4] *Op. cit.*, p. 79.
[5] Crippa and Maffei, *Gazzetta*, 1941, **71**, 418.
[6] Hoggarth, *J.*, 1949, 3311.
[7] Duffin and Kendall, *J.*, 1956, 361.
[8] Kirby and Neuberger, *Biochem. J.*, 1938, **32**, 1146.
[9] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[10] Walba and Isensee, *J. Org. Chem.*, 1956, **21**, 702.

Naphth[2,3]-iminazole derivative	pK_a (20°) and concn. (10^{-5}M) in brackets	Solubility in water at 20°; 1 in	Ultraviolet spectra in water		
			pH	$\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$
Unsubst.[a]	—	5500	7·35	342; 327; 317; 235	3·74; 3·88; 3·83; 4·79
cation	5·24 (±0·01) [d] [100]	—	2·0	325; 318; 235	3·90; 3·84; 4·75
anion	12·52 (±0·02) [e] [5]	—	—	—	—
2-Mercapto	—	—	6·0	343; 328 [b]; 272	4·57; 4·25; 4·81
anion	9·84 (±0·04) [e]; [1·25]	—	12·0	346; 272	4·34; 4·76
2-Hydroxy [c]	—	3·4 × 10^5	6·04	330; 315; 301; 295; 240	3·93; 3·74; 3·75; 3·76; 4·82
anion	11·62 (±0·01) [e] [1·25]	—	13·0	337; 329; 326; 314 [b]; 249	3·93; 3·87; 3·86; 3·79; 4·79
2-Amino	—	8500	9·2	334; 320; 310; 247	3·94; 3·89; 3·86; 4·80
cation [h]	7·01 (±0·02) [d] (100)	—	4·9	328; 320; 313; 306; 300; 287 [b]; 241	3·98; 3·74; 3·85; 3·78; 3·84; 3·67; 4·82
anion	12·8 [e] (10)	—	—	—	—
2-Methyl [a]	—	51,000	9·0	337 [b]; 320; 237	3·76; 3·91; 4·81
cation	6·11 (±0·02) [d] [25]	—	2·0	326; 318; 236	3·93; 3·91; 4·79
anion	12·9 [e] [5]	—	—	—	—
2-Ethyl	—	62,000	9·0	338; 321; 239	3·76; 3·92; 4·84
cation	6·14 (±0·03) [d] [25]	—	2·0	326; 318; 237	3·95; 3·92; 4·82
anion	12·9 [e] [20]	—	—	—	—
2-Carboxymethyl-thio	—	44,000	3·14 [f]	335; 326; 263	4·28; 4·19; 4·73
cation	1·9 [e] [1·25]	—	—	334; 326; 261	4·26; 4·16; 4·73
anion	4·68 (±0·07) [e] [1·25]	—	7·36	338; 327; 263; 223	4·19; 4·16; 4·72; 4·54
2-Methylthio	—	—	8·0	338; 326; 262; 223	4·09; 4·04; 4·67; 4·42
Other compounds					
Cyclic amide (II)	—	—	8·0	337; 332; 328; 320; 315; 263; 225	4·19; 4·11; 4·16; 4·09; 4·03; 4·74; 4·55
Naphth[1,2]imin-azole [g]	—	—	9·2	326; 319; 313; 279; 273; 240; 222	3·54; 3·38; 3·46; 3·65; 3·63; 4·57, 4·54
cation	5·28 (±0·02) [d] (100)	—	2·0	322; 315; 308; 295; 284 [b]; 273; 240	3·76; 3·46; 3·58; 3·32; 3·57; 3·78; 4·37
anion	12·54 (±0·04) [e] [5]	—	—	—	—
2-Hydroxybenz-iminazole	—	—	—	—	—
cation	−1·7 [e] [10]	—	—	—	—
anion	11·95 (±0·02) [e] [10]	—	—	—	—
2-Mercaptobenz-iminazole (anion)	10·24 (±0·02) [e] [1·25]	—	—	—	—
Benziminazole (anion)	13·2 [e] [10]	—	—	see Figures [j]	—

[a] Prep.: see ref. 2. [b] Shoulder. [c] Cationic pK_a is <0. [d] Potentiometric titration. [e] Spectroscopic determination. [f] Mainly neutral molecule. [g] Prep.: Fischer, *J. prakt. Chem.*, 1922, **104**, 118. [h] Dicationic pK_a is <1. [j] Curves constructed from Mason, *J.*, 1954, 2071, and personal communication.

and benziminazole. Thus there is a considerable bathochromic shift of the long-wavelength band (neutral molecule and cation) on passing from benziminazole to angular naphthiminazole and still more to the linear isomer and its alkyl derivatives (cf. Figures). Fine structure also increases with complexity of the ring system and naturally in this respect the unsymmetrical angular shows more than does the linear isomer. The same shift and increase in fine structure are true of the amide (II) in comparison with its benzo-analogue.[7] In the linear series the rule [11] holds good: the spectrum of the hydroxy-anion is almost identical with that of the neutral molecule of the corresponding amino-derivative (cf. Table). Likewise the anion of the carboxymethylthio- closely resembles its parent methylthio-derivative.

When viewed on a paper chromatogram in ultraviolet light, 2-mercaptonaphth[2,3]-iminazole shows a brilliant yellow phosphorescence for several seconds after withdrawal of the light source. 2-Mercaptobenziminazole does not do this.

2-Aminonaphth[2,3]iminazole showed slight antibacterial activity against *Strep. pyogenes*, *Staph. aureus*, *E. coli*, and *Pr. vulgaris* (kindly tested by Professor S. D. Rubbo, University of Melbourne).

[11] Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127.

Experimental

2-Hydroxynaphth[2,3]*iminazole.*—2 : 3-Diaminonaphthalene (10 g.) and urea (10 g.) were heated at 180°. After 5 min. the mass solidified and after a further 5 min. it was cooled, triturated with water (25 ml.), and adjusted to pH *ca.* 5, and the solid was filtered off (11·2 g.). Recrystallization from pentyl alcohol (1500 ml.) gave colourless plates of the *hydroxy-compound* (8·5 g.), m. p. ‹320° (Found, in sample dried at 140°: C, 72·2; H, 4·4; N, 15·05. $C_{11}H_8ON_2$ requires C, 71·7; H, 4·35; N, 15·2%).

2-Mercaptonaphth[2,3]*iminazole.*—The crude solid from fusion as above of diaminonaphthalene and thiourea at 195° was extracted with 0·5N-sodium hydroxide (1500 ml.) at 50°. Treatment with carbon and adjustment of the warm solution to pH 4 with acetic acid gave a solid *thiol* (10 g.). It was recrystallised from ethyl acetate (50 parts) giving, after concentration, colourless crystals (6·8 g.), m. p. 305° (Found, in sample dried at 160°: C, 66·15; H, 3·8; N, 13·9. $C_{11}H_8N_2S$ requires C, 66·0; H, 4·0; N, 14·0%).

2-Methylthionaphth[2,3]*iminazole.*—The thiol (4·6 g.) was dissolved in 0·25N-potassium hydroxide (200 ml.) at 50°, and the solution filtered and cooled to 30°. Methyl iodide (4 ml.) was added and the mixture was vigorously shaken for 20 min. The suspension was adjusted to pH *ca.* 4, then chilled, and the solid filtered off (3·9 g.). Recrystallization twice from ethanol (80 ml.), with concentration, gave the *methylthio-derivative*, m. p. 241° (Found: C, 67·45; H, 4·45; S, 14·9. $C_{12}H_{10}N_2S$ requires C, 67·3; H, 4·7; S, 14·95%).

2-Benzylaminonaphth[2,3]*iminazole.*—The methylthio-derivative (0·5 g.) was heated with benzylamine (5 ml.) at 180° for 2 hr. After 24 hr. the solid was filtered off, washed with water, and dried (0·5 g.). Recrystallization from ethyl acetate (320 parts) gave the *benzylamino-compound* as needles, m. p. 246° (Found: C, 79·05; H, 5·6; N, 15·4. $C_{18}H_{15}N_3$ requires C, 79·1; H, 5·5; N, 15·4%).

2-Benzylmethylaminonaphth[2,3]*iminazole.*—The methylthio-derivative was heated with benzylmethylamine as above for 12 hr. Excess of amine was removed *in vacuo* at 100° and the solid after refrigeration was recrystallised from ethyl acetate. The *base* (0·1 g.) had m. p. 235° (Found: C, 78·7; H, 5·95. $C_{19}H_{17}N_3$ requires C, 79·4; H, 5·95%).

2-Anilinonaphth[2,3]*iminazole.*—Prepared as was the benzylamino-derivative, the crude *anilino-compound* (0·25 g.) was recrystallized from butyl acetate (140 parts), then having m. p. 284—285° (Found: C, 78·85; H, 5·15. $C_{17}H_{13}N_3$ requires C, 78·75; H, 5·05%).

2-Carboxymethylthionaphth[2,3]*iminazole.*—2-Mercaptonaphthiminazole (2·0 g.) and N-sodium hydroxide (10 ml.) were heated with chloroacetic acid (1·0 g.) in 2·5N-sodium hydroxide (4·0 ml.) for 2 hr., then cooled, diluted with water (10 ml.), and adjusted to pH 3 with hydrochloric acid. Recrystallization from pentyl alcohol (65 parts) gave the *acid* (1·1 g.), m. p. 208° (decomp.) (Found: N, 10·9. $C_{13}H_{10}O_2N_2S$ requires N, 10·85%).

1 : 2-*Dihydro*-1-*oxothiazolo*[2,3-a]*naphthiminazole.*—Acetic anhydride (1 ml.) was added to the above acid (1 g.). in pyridine (3 ml.). After 5 min. on the water-bath and cooling, the solid was removed, washed with ether, and recrystallized from ethanol (110 ml.), to give the colourless *amide* (0·4 g.), m. p. 236° (Found: C, 65·0; H, 3·45; N, 11·6. $C_{13}H_8ON_2S$ requires C, 65·0; H, 3·35; N, 11·65%).

2-Aminonaphth[2,3]*iminazole.*—Cyanogen bromide [from potassium cyanide [5] (3·3 g.)] in cold water (25 ml.) was added during 2 hr. to a stirred suspension of 2 : 3-diaminonaphthalene (7 g.) in water (130 ml.). After a further 4 hours' stirring at 20°, the mixture was set aside for 4 days. The solid was then filtered off and gave, after recrystallization from ethanol, the unchanged diamine (3·6 g.). The filtrate was made alkaline and chilled; the solid was filtered off and recrystallized from ethanol (25 parts), giving the *2-amino-derivative* (2·1 g.), m. p. 301° (decomp.) (Found: C, 72·4; H, 4·85. $C_{11}H_9N_3$ requires C, 72·1; H, 4·95%).

2-Ethylnaphth[2,3]*iminazole.*—Prepared similarly to the parent compound,[2,3] the *ethyl analogue* [from ethyl acetate (140 parts)] had m. p. 250° (Found: C, 79·3; H, 6·25. $C_{13}H_{12}N_2$ requires C, 79·55; H, 6·15%).

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