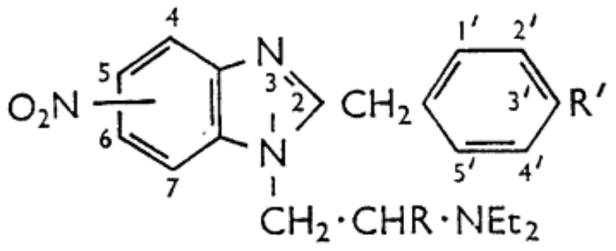
Some 2-Benzyl-5-nitrobenzimidazoles

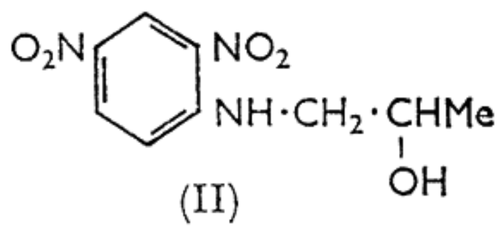
By A. F. Casy and J. Wright

The synthesis of 2-benzyl-1-(2-hydroxypropyl)-5-nitrobenzimidazole, 2-benzyl[and 2-(4-ethoxybenzyl)]-1-(2-diethylamino-propyl)-5-nitrobenzimidazole and related compounds is reported. The nitration of 2-benzylbenzimidazole gives 5(6)-nitro-2-(4-nitrobenzyl)-benzimidazole (structure established by p.m.r. spectroscopy).

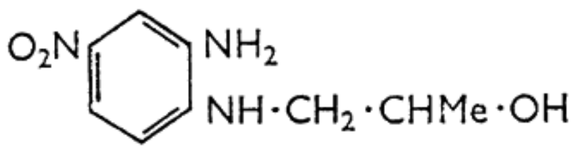
THE benzimidazole derivatives (I) described in this Paper were required for the study of structure–activity relationships in analgesics based upon 2-benzylbenzimidazole.[1] A specific route to the 5-nitro-derivative (I; R = Me, R′ = H) was first attempted. 2,4-Dinitro-*N*-(2-hydroxypropyl)aniline (II), obtained from 1-chloro-2,4-dinitrobenzene and 1-aminopropan-2-ol, was selectively reduced to the corresponding nitro-diamine derivative (III). Sodium hydrosulphide in methanol [2] proved the best reagent for this partial reduction, giving a 91% yield. Thioacetamide in ammonia–methanol was also satisfactory (58% yield) but was ineffective in ammonia–ethanol; hydrogen sulphide in ammonia–ethanol and stannous chloride in ethanolic hydrochloric acid gave the desired product, but in low yield. The 5-nitro-diamine derivative (III) with ethyl phenylacetimidate hydrochloride gave 2-benzyl-1-(2-hydroxypropyl)-5-nitrobenzimidazole (IV), the success of this cyclisation establishing that the 2-nitro- rather than 4-nitro-group of the dinitro-derivative (II) is the group affected in the partial reduction of this compound. The 1-(2-hydroxyethyl)benzimidazole (IV) with thionyl chloride gave the 2-chloroethyl analogue but attempts to replace the chlorine atom of the latter derivative with diethylamino and other basic groups failed. The dinitro-alcohol (II) was unaffected by thionyl chloride or by phosphorus chlorides, a result in contrast with the reported [3] (and here confirmed) smooth conversion of the unbranched analogue 2,4-dinitro-*N*-(2-hydroxyethyl)-aniline, into a chloro-derivative by thionyl chloride.



(I: R = H or Me, R′ = H or OEt)



(II)



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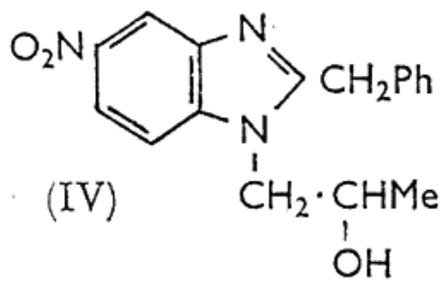

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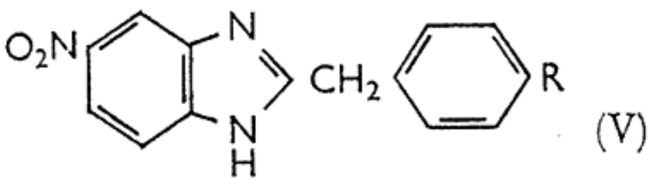


(V)

R = (a) H, (b) OEt, (c) NO_2

The branched chain derivative (III) reacted with thionyl chloride but the resultant chloro-compound did not react readily with secondary amines.

Since specific routes to the 5-nitrobenzimidazoles (I) could not be developed, a method involving the alkylation of 5(6)-nitrobenzimidazoles (V) with 1-amino-2-chloropropane (or 2-amino-1-chloro-isomer) was investigated. This route was not considered at first because it could lead to four isomeric products in consequence of the tautomeric nature of the N(1) hydrogen atom and the ethyleneimonium ion character of the alkylating reagent.[4] In respect of the latter factor, however, subsequent study of the alkylation of 2-benzylbenzimidazole with 1-amino-2-chloropropanes [5] showed that, although two isomers resulted, the 1-n-propyl derivative greatly preponderated over the 1-isopropyl isomer and could be isolated in good yield; hence only nitro-isomers needed to be differentiated in the present reactions. Alkylation of 2-benzyl-5(6)nitrobenzimidazole (Va) and of 2-(4-ethoxybenzyl)-5(6)-nitrobenzimidazole (Vb) with 1-chloro-2-diethylaminopropane gave the corresponding 5-nitro-1-aminoalkyl derivatives, provisionally assigned the 1-propyl structures (I; R = Me, R′ = H or OEt) in moderate yields; no 6-nitro-isomer was isolated. The position of the nitro-group in these products was established by comparing their ultraviolet absorption spectra with those of 5- and 6-nitrobenzimidazoles of established structure [1] (Table 1). Both 5- and 6-nitro-derivatives have absorption peaks near 240 and 300 mμ but the intensity of the former band is markedly greater in the case of the 5-nitro-derivatives.

TABLE 1

Ultraviolet absorption spectra of some 1-diethylaminoalkyl-2-benzylnitrobenzimidazole (I) hydrochlorides in ethanol

NO_2 position	R	R′	$\lambda_{max.}$ (mμ) (ε)
5	H	H	241 (29,000), 302 (10,400)
5	H	OEt	240 (32,700), 302 (11,700)
5	Me	H	240 (29,000), 301 (11,000)
5	Me	OEt	240 (28,000), 301·5 (11,800)
6	H	H	236 (18,030), 307 (11,310)

During this work, the nitration of 2-benzylbenzimidazole was investigated as a possible alternative route to 2-benzyl-5(6)-nitrobenzimidazole (Va) (the reported method [1] requires 4-nitro-1,2-phenylenediamine and

[1] A. Hunger, J. Kebrle, A. Rossi, and K. Hoffmann, *Helv. Chim. Acta*, 1960, **43**, 1032.
[2] H. H. Hodgson and E. R. Ward, *J. Chem. Soc.*, 1948, 242.
[3] H. Hippchen, *Chem. Ber.*, 1947, **80**, 263.
[4] E. M. Schultz and J. M. Sprague, *J. Amer. Chem. Soc.*, 1948, **70**, 48.
[5] A. F. Casy and J. Wright, *J. Chem. Soc.*(*C*), 1966, 1167.

benzyl cyanide). Low-temperature nitration, however, gave 5(6)-nitro-2-(4-nitrobenzyl)benzimidazole (Vc), the positions of the nitro-groups being established by comparing the p.m.r. spectrum of the nitration product with those of benzimidazole, 4(7)- and 5(6)-nitro-2-benzylbenzimidazole, and 2-(*p*-nitrobenzyl)benzimidazole (Table 2).

EXPERIMENTAL

N-(2-*Hydroxypropyl*)-2,4-*dinitroaniline* (II).—1-Chloro-2,4-dinitrobenzene (25 g.) in ethanol (100 ml.) was added to 1-aminopropan-2-ol (15·5 g.) in ethanol (100 ml.), and the product heated under reflux for 1 hr. The solution, while hot, was made alkaline with aqueous ammonia, whereupon orange-yellow crystals of N-(2-*hydroxypropyl*)-2,4-*dinitroaniline* (9·6 g.), m. p. 97—97·5° from ethanol, separated (Found: C, 45·4; H, 4·7; N, 17·5. $C_9H_{11}N_3O_5$ requires C, 44·8; H, 4·6; N, 17·4%). The dinitroaniline (II) was recovered after treatment with thionyl chloride or phosphorus trichloride (chloroform as solvent) and with phosphorus pentachloride (no solvent).

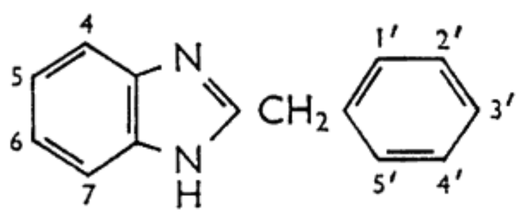
2-*Amino*-N-(2-*Hydroxypropyl*)-4-*nitroaniline* (III).—*Method* 1. Hydrogen sulphide was passed through a mixture of the dinitroaniline (II) (10 g.), concentrated aqueous ammonia (100 ml.), and ethanol (100 ml.) for 4 hr. The product was heated under reflux for 1 hr., left overnight, and filtered. The filtrate, on evaporation under reduced pressure, gave a brown oil which was boiled with ethanol, and the solution was filtered to remove sulphur. Repeated crystallisation of the product from ethanol gave orange-red needles of the *nitro-diamine* (III) (0·5 g.), m. p. 165—166° (Found: C, 51·45; H, 6·2; N, 19·9. $C_9H_{13}N_3O_3$ requires C, 51·2; H, 6·2; N, 19·9%) in 5% yield.

Method 2. Thioacetamide (1·5 g.) and concentrated aqueous ammonia (30 ml.) was added to the dinitroaniline (II) (5 g.) in methanol (50 ml.). The mixture was stirred overnight at room temperature and then heated under reflux for 4 hr. On cooling, the 5-nitroaniline (III) (2·5 g.), m. p. and mixed m. p. 165—166°, separated in 57% yield.

Method 3. Sodium sulphide (180 g.; $Na_2S,9H_2O$) and sodium hydrogen carbonate (63 g.) in water (300 ml.) was added to the dinitroaniline (II) (50 g.) in methanol (500 ml.). The mixture was heated under reflux for 2 hr. and the hot solution filtered. The solid which separated was washed with hot water and crystallised from methanol to give the 5-nitroaniline (III) (40 g.), m. p. and mixed m. p. 165—166°, in 91% yield.

TABLE 2

P.m.r. characteristics of some nitro-2-benzylbenzimidazoles in dimethyl sulphoxide



Compound	Substituent(s)	Aryl proton resonance signals [a]: Benzimidazole	Benzyl	8-CH_2 (singlet)
1	3′-NO_2	H (4/7) [b]: 463, 459,[c] 457, 454, 450 H (5/6): 442·5, 439, 435·5, 433, 429·5	H (2′/4′) [d]: 503, 494 H (1′/5′): 467·5, 459 [c]	267
2	5-NO_2	H (4): 511 [e] *J meta* 2 H (6): 490·5 [f] *J meta* 2, *J ortho* 9 H (7): 464·5 [e] *J ortho* 9	H (1′—5′): 445 [g]	262
3	4-NO_2	H (5): 488 [f] *J meta* 1, *J ortho* 8 H (6): 443 [h] *J ortho* 8 H (7): 485 [f] *J meta* 1, *J ortho* 8	H (1′—5′): 443 [g]	263
4	5,3′-diNO_2	H (4): 512 [e] *J meta* 2 H (6) [i]: 492 [f] *J meta* 2, *J ortho* 9 H (7) [j]: 465·5 [e] *J ortho* 9	H (2′/4′) [d]: 503·5, 494·5 H (1′/5′): 470, 461·5	275
Benzimidazole		H (4/7) [b]: 466·5, 463, 460·5, 457, 454 H (5/6): 443, 440, 437, 434, 430·5	—	[H(2), 498·5]

[a] In c./sec. from tetramethylsilane, spectra recorded at 60 Mc./sec. [b] Signals due to 4/7 and 5/6 protons form an A_2B_2 pattern (two symmetrical quintets). [c] Signal due to both the 4/7 and 1′/5′ protons. [d] Signals due to 2′/4′ and 1′/5′ protons form an A_2X_2 pattern (two symmetrical doublets). [e] Doublet. [f] Centre of two doublets. [g] Near-singlet. [h] Triplet, centre coincides with 1′—5′ proton signal. [i] Higher-field component of the lower field H (6) doublet overlaps the higher field component of the H (2′/4′) doublet. [j] Overlaps the H (1′/5′) doublet.

Method 4. Stannous chloride (68 g.) in ethanolic hydrochloric acid (100 ml.) was added to a solution of the dinitroaniline (II) (24 g.) in warm ethanol. The mixture was cooled, diluted to 800 ml. with ethanol, and then 50% sodium hydroxide in water added until the initial precipitate redissolved. The solid which separated from the solution on storage was collected and recrystallised from ethanol to give the nitro-diamine (III) (5 g.), m. p. and mixed m. p. 165°.

Thionyl chloride (3 ml.) was added to an ice-cooled solution of the nitro-diamine (III) (2·1 g.) in chloroform (10 ml.), the mixture heated under reflux for 1 hr., and then evaporated under reduced pressure. The basic product, recovered as usual, was crystallised from ethanol to give 2-*amino*-N-(2-*chloropropyl*)-4-*nitroaniline* (1·5 g.), m. p. 100—101° (Found: C, 46·1; H, 5·2; N, 18·2; Cl, 15·3. $C_9H_{12}ClN_3O_2$ requires C, 47·1; H, 5·2; N, 18·3; Cl, 15·5%). When the chloro-derivative (0·5 g.) was heated under reflux with piperidine (3 ml.) for 12 hr., a small yield of 2-*amino*-4-*nitro*-2-(2-*piperidinopropylaniline* (0·1 g.), m. p. 130°

from ethanol, was obtained (Found: C, 59·6; H, 8·0. $C_{14}H_{22}N_4O_2$ requires C, 60·4; H, 7·9%).

2-Benzyl-1-(2-hydroxypropyl)-5-nitrobenzimidazole (IV) *and Related Compounds.*—An ice-cooled mixture of benzyl cyanide (11·7 g.), ethanol (4·6 g.), and chloroform (50 ml.) was saturated with hydrogen chloride and left at room temperature for 24 hr. The product was evaporated under reduced pressure and the residue dissolved in a solution of the 5-nitroaniline (III) (10 g.) in glacial acetic acid (100 ml.). The mixture was kept at 45° for 16 hr., then treated with hydrochloric acid (10 ml.; 2N) and concentrated. The residue was dissolved in dilute hydrochloric acid, extracted twice with chloroform, and the free base liberated from the aqueous phase with aqueous ammonia and extracted with chloroform. The dried extract was evaporated to give *2-benzyl-1-(2-hydroxypropyl)-5-nitrobenzimidazole* (10 g.), m. p. 100—102° from ethanol (Found: N, 13·25. $C_{17}H_{17}N_3O_3$ requires N, 13·5%). *2-Benzyl-1-(2-hydroxyethyl)-5-nitrobenzimidazole,* m. p. 121—122° from ethanol (Found: C, 64·5; H, 5·0; N, 14·0. $C_{16}H_{15}N_3O_3$ requires C, 64·65; H, 5·05; N, 14·1%) was obtained in a similar manner from 2-amino-*N*-(2-hydroxyethyl)-4-nitroaniline.[3] A mixture of the hydroxybenzimidazole (IV) (3·1 g.), thionyl chloride (2·3 g.), and chloroform (20 ml.) was heated under reflux for 2 hr., cooled, and poured on ice. The product was made basic with aqueous ammonia and extracted with chloroform, and the dried ($MgSO_4$) extract evaporated to give impure 2-benzyl-1(2-chloropropyl)-5-nitrobenzimidazole (3 g.). It gave a *picrate,* m. p. 160° from ethanol (Found: C, 49·3; H, 3·5. $C_{23}H_{19}ClN_6O_9$ requires C, 49·4; H, 3·4%). The chlorobenzimidazole (2 g.) was recovered after being heated under reflux with diethylamine (10 ml.) for 7 days. No product could be isolated when the same reaction was carried out under pressure (140° for 6 hr.).

2-Benzyl-1-(2-diethylaminopropyl)-5-nitrobenzimidazole (I; R = Me, R′ = H) *and Related Compounds.*—A mixture of 2-benzyl-5(6)-nitrobenzimidazole [1] (3 g.), sodamide (0·5 g.), and dioxan were heated at 60° for 24 hr., and then treated with 1-chloro-2-diethylaminopropane (2 g.). The mixture was stirred for a further hr. and filtered and the filtrate evaporated under reduced pressure. The residue from the filtrate was acidified with ethanolic hydrogen chloride and diluted with ether whereupon the *dihydrochloride* of the 5-nitrobenzimidazole (I; R = Me, R′ = H) (1 g.) separated as a monohydrate, m. p. 180—183°, from ethanol–ether (Found: C, 54·35; H, 6·9%; Equiv., 222.) $C_{21}H_{28}Cl_2N_4O_2,H_2O$ requires C, 55·1; H, 6·6%; Equiv., 229); $\nu_{max.}$ 3400 cm.$^{-1}$ (H_2O). 1-(2-Diethylaminopropyl)-2-(4-ethoxybenzyl)-5-nitrobenzimidazole (I; R = Me, R′ = OEt) was prepared similarly from 2-(4-ethoxybenzyl)-5(6)-nitrobenzimidazole.[1] It formed a *dihydrochloride monohydrate,* m. p. 210°, from ethanol–ether (Found: C, 54·3; H, 7·0%; Equiv., 260. $C_{23}H_{32}Cl_2N_4O_3,H_2O$ requires C, 55·1; H, 6·8%; Equiv., 260); $\nu_{max.}$ 3400 cm.$^{-1}$ (H_2O).

5(6)-Nitro-2-(4-nitrobenzyl)benzimidazole and Related Compounds.—2-Benzylbenzimidazole (2 g.) was added to an ice-cooled, stirred, mixture of concentrated nitric and sulphuric acids (50 ml.; equal volumes) during 30 min. 15 min. after addition was complete, the mixture was poured on ice, and the resultant precipitate collected and ground in a mortar with concentrated ammonia solution to liberate the free base. This was crystallised from dioxan to give the *dinitro-derivative* (Vc) (2 g.), m. p. 210° (Found: C, 56·4; H, 3·6; N, 18·9. $C_{14}H_{10}N_4O_4$ requires C, 56·4; H, 3·4; N, 18·8%). An ice-cooled, stirred, mixture of 4-nitrobenzyl cyanide (10 g.), ethanol (5 ml.), and chloroform (50 ml.) was saturated with hydrogen chloride, left overnight, and then evaporated under reduced pressure. The residue was heated under reflux with *o*-phenylenediamine (7 g.) in chloroform (100 ml.) for 5 hr. The product was made alkaline with aqueous ammonia and the organic phase separated, dried (Na_2SO_4), and evaporated. The residue was crystallised from ethanol (after decolourisation with charcoal) to give *2-(4-nitrobenzyl)benzimidazole* (7 g.), m. p. 210—212° (Found: C, 67·1; H, 4·7; N, 16·45. $C_{14}H_{11}N_3O_2$ requires C, 66·4; H, 4·35; N, 16·6%). 2-Benzyl-5(6)-nitrobenzimidazole, m. p. 188·5° (lit.,[1] m. p. 189°), and *2-benzyl-4(7)-nitrobenzimidazole,* m. p. 125° (Found: C, 66·3; H, 4·5. $C_{14}H_{11}N_3O_2$ requires C, 66·4; H, 4·3%) were obtained in a similar manner from 4-nitro- and 3-nitro-1,2-phenylenediamine,[6] respectively.

The p.m.r. spectra were recorded on a Perkin-Elmer R-10 instrument (operating at 60 Mc./sec.) with tetramethylsilane as internal standard, and the ultraviolet spectra on a Unicam S.P. 800 spectrophotometer.

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[6] G. M. Van der Want, *Rec. Trav. chim.*, 1948, **67**, 45.