Synthesis of Nitidine (8,9-Dimethoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridinium); a Comparison of Electrochemical and Photochemical Methods

By **William J. Begley** and **James Grimshaw,*** Department of Chemistry, Queen's University, Belfast BT9 5AG

Electrochemical reduction of the 2-bromo-*N*-methyl-*N*-naphthylbenzamide (5) gave a 1-phenylnaphthalene derivative and no benzophenanthridone. The latter was the sole product from photocyclisation of the amide (5). The electrochemical reaction generates an aryl radical which attacks the adjacent naphthalene ring to give the product isolated, whereas the photoreaction probably proceeds by cyclisation of the excited state of (5) to form a new six-membered ring and then loss of hydrogen bromide. The benzophenanthridone was converted into nitidine tetrafluoroborate.

STUDIES [1] on the radical cyclisation of 2-halogeno-*N*-methylbenzanilides by an electrochemical method led us to examine the possibility of using this reaction in the synthesis of benzo[*c*]phenanthridine alkaloids. A number of syntheses of alkaloids in this class have recently been published [2-5] and some of these alkaloids have been shown to exhibit cytotoxic and antileukemic effects.[2] We applied our route to the synthesis of nitidine (10),[6] which has been isolated from plants of the genera *Fagara* and *Zanthoxylum*, placed by botanists in the Zanthoxyleae tribe of the family Rutaceae. The structure of nitidine has been confirmed by synthesis,[7] and more recently [4] it has been obtained from a sequence of reactions where the essential step was photocyclisation of the amide (1) to give a benzophenanthridone. This encouraged our investigation since we thought that the photoreaction, like the electrochemical reaction, could be expected to generate an aryl radical, after which the two reactions would proceed by essentially similar

[1] J. Grimshaw, R. J. Haslett, and J. Trocha-Grimsh *J.C.S. Perkin I*, in the press.

[2] K. Y. Zee-Chang and C. C. Cheng, *J. Heterocyclic Chem.*, 1973, **10**, 85; *J. Medicin. Chem.*, 1975, **18**, 66; J. P. Gillespie, L. G. Amoros, and F. R. Stermitz, *J. Org. Chem.*, 1974, **39**, 3239; F. R. Stermitz, J. P. Gillespie, L. G. Amoros, R. Romero, T. A. Stermitz, K. A. Larson, S. Earl, and J. E. Ogg, *J. Medicin. Chem.*, 1975, **18**, 708.

[3] S. F. Dyke, M. Sainsbury, and B. J. Morn, *Tetrahedron*, 1968, **24**, 1467; H. Iida, K. Takahashi, and T. Kikuchi, *Heterocycles*, 1976, **4**, 1497.

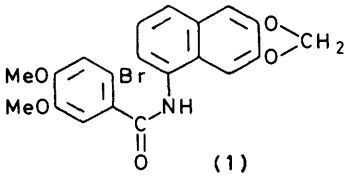
[4] S. V. Kessar, G. Singh, and P. Balakrishnan, *Tetrahedron Letters*, 1974, 2269.

[5] S. V. Kessar, M. Singh, and P. Balakrishnan, *Indian J. Chem.*, 1974, **12**, 323.

[6] H. R. Arthur, W. H. Hui, and Y. L. Ng, *J. Chem. Soc.*, 1959, 1840.

[7] K. W. Gopinath, T. R. Govindachari, P. C. Parthasarathy, and N. Viswanathan, *J. Chem. Soc.*, 1959, 4012.

pathways. We prepared the amide (5) and examined its conversion into a benzophenanthridone by both photochemical and electrochemical methods.



(1)

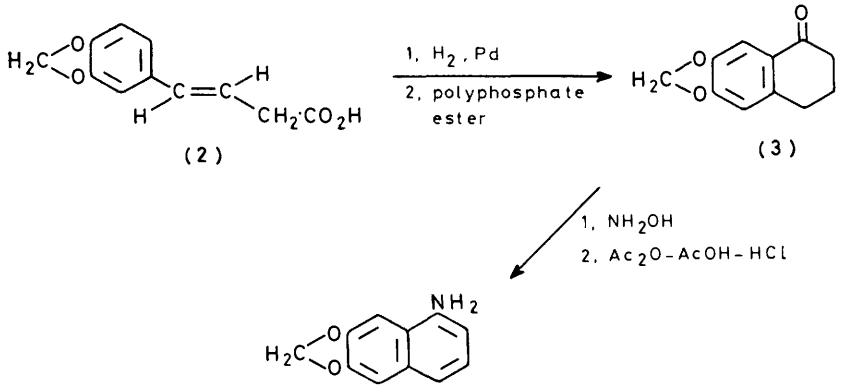
The required 5-amino-2,3-methylenedioxynaphthalene was prepared from safrole. Another route to this amine has been described briefly.[5] Ozonolysis of safrole in acetic acid then reduction [8] of the intermediate hydroperoxide with dimethyl sulphide gave 3,4-methylenedioxyphenylacetaldehyde, which was condensed with malonic acid in acetic acid to afford the olefinic acid (2). The olefinic acid was identified as the $\beta\gamma$-isomer since on ozonolysis it afforded a good yield of piperonal. The olefinic protons show a large n.m.r. coupling constant (J 16 Hz) so this olefin must be the *trans*-isomer. This olefinic acid has previously been obtained [9] from piperonal in low yields by the Stobbé reaction.

Hydrogenation of the olefinic acid gave the saturated acid, which was best converted into the tetralone (3) (80% yield) by use of polyphosphate ester, prepared [10] from diethyl ether and phosphorus(v) oxide in chloroform.

The corresponding α-tetralone oxime was converted directly into the aminonaphthalene (4) by forming the oxime acetate with acetic anhydride and acetic acid and treating this *in situ* with hydrogen chloride. This aromatisation process (the Semmler–Wolff rearrangement [11]) is known to occur with α-tetralone oxime and also with some cyclohexenone oximes. A mechanism has been proposed.[12]

The N-methylbenzamide (5) was prepared *via* (1) by standard procedures. It showed two sets of NMe and OMe signals in the ^{1}H n.m.r. spectrum due to isomers with either *syn*- or *anti*-arrangement of the aryl groups about the amide bond. Previously we have found that in related compounds the low field NMe signal is due to the rotamer with *syn*-aryl groups. In the spectrum of this *syn*-rotamer the OMe signals are at higher fields than for the other rotamer, owing to the influence of the neighbouring naphthyl ring, and one signal almost coincides with the *anti*-rotamer NMe signal. The n.m.r. spectrum of (5) showed the presence of 90% *syn*-rotamer, illustrated in the diagram, at equilibrium.

Electroreduction of this N-methylbenzamide (5) gave none of the benzophenanthridone (9). The only product isolated was the phenylnaphthalene derivative (7), which arises by cyclisation of the first-formed aryl radical (6) as shown and then further reduction and protonation. Photoreaction of (5) did however yield the desired benzophenanthridone (9), and in this case none of the phenylnaphthalene was formed.



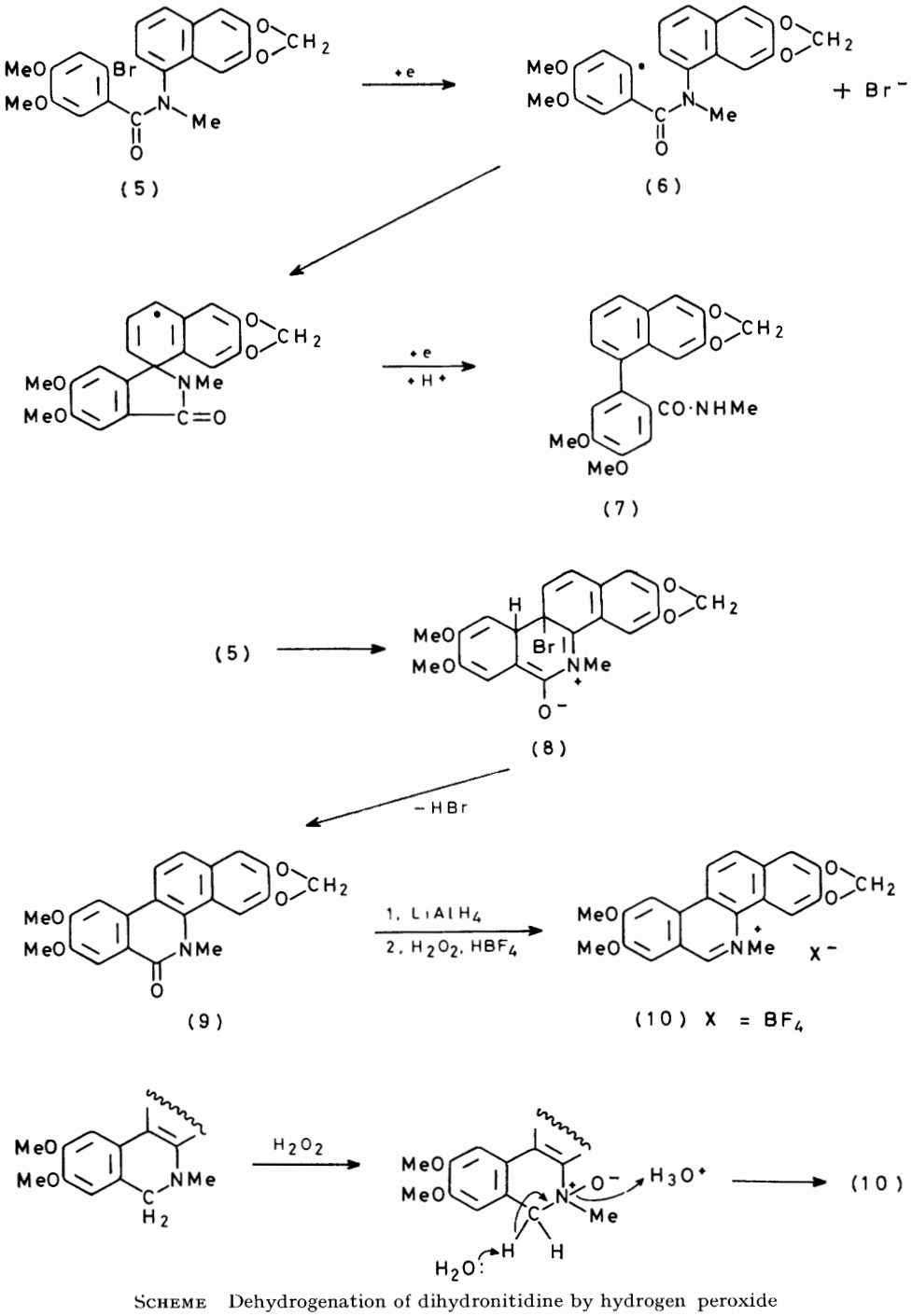
(2) (3) (4)

The results from electrochemical reduction of (5) and 2-halogeno-N,2′-dimethylbenzanilides, which we have studied previously,[1] parallel each other in that both reactions give a biaryl as the principal product. Both amides can be regarded as derivatives of an *ortho*-substituted aniline. These electrochemical reactions follow similar pathways and the initial step in each case is the generation of an aryl radical by cleavage of the carbon–halogen bond. Since the photoreaction of (5) yields a different product, it cannot involve initial homolytic cleavage of the carbon–bromine bond. This photoreaction must be related to the photocyclisation of stilbenes [13] and proceed from the excited stage of (5) to an intermediate of type (8) which loses hydrogen bromide.

Photoreaction [4] of (1) has also been shown to give a

[8] J. J. Pappas, *Tetrahedron Letters*, 1966, 4273.
[9] W. Borsche and W. Eberlein, *Ber.*, 1914, **47**, 1460; J. Bougault, *Compt. rend.*, 1908, **146**, 411; J. W. Cornforth, G. K. Hughes, and F. Lions, *J. Proc. Roy. Soc. N.S.W.*, 1939, **72**, 228.
[10] W. Pollmann and G. Schramm, *Biochim. Biophys. Acta*, 1964, **80**, 1.
[11] W. Semmler, *Ber.*, 1892, **25**, 3352; L. Wolff, M. Gabler, and F. Heyl, *Annalen*, 1902, **322**, 351.
[12] M. V. Bhatt, *Experientia*, 1957, **13**, 70; L. Bauer and R. E. Hewitson, *J. Org. Chem.*, 1962, **27**, 3982.
[13] E. V. Blackburn and C. J. Timmons, *Quart. Rev.*, 1969, **23**, 482.

good yield of a benzophenanthridone. Benzanilides with no *N*-substituent exist in solution predominantly in the *anti*-rotamer form [the *syn*-rotamer is illustrated in diagram (1)]. The photocyclisation of (1) must also precluded the use of selective reducing agents which might have yielded the pseudobase of (10) directly. The benzophenanthridone was reduced with lithium aluminium hydride to dihydronitidine, which was readily



SCHEME Dehydrogenation of dihydronitidine by hydrogen peroxide

be related to the photocyclisation of stilbenes and involve *anti–syn* equilibration followed by cyclisation of the *syn*-rotamer and loss of hydrogen bromide.

The insolubility of the benzophenanthridone (9) oxidised to nitidine by hydrogen peroxide in acidic solution. The oxidation probably proceeds by elimination from the first-formed amine oxide as indicated in the Scheme.

EXPERIMENTAL

N.m.r. spectra were recorded for solutions in $CDCl_3$. Dimethylformamide was dried over $CuSO_4$ and distilled at 10 mmHg under nitrogen.

3,4-*Methylenedioxyphenylacetaldehyde*.—A solution of safrole (4-allyl-1,2-methylenedioxybenzene) (60 g) in anhydrous acetic acid (400 ml) was cooled to 10 °C and treated with a stream of ozonised oxygen (65.2 mg l^{-1} ozone) for 7 h, the temperature being slowly lowered to 0 °C. The excess of ozone was removed in a stream of oxygen, after which dimethyl sulphide was added slowly with the temperature kept below 20 °C. The resulting solution was kept overnight at 0 °C and the acetic acid removed under vacuum. The residue was diluted with water and neutralised with sodium carbonate, and the product isolated with ether, dried ($MgSO_4$), and distilled to afford 3,4-dimethoxyphenylacetaldehyde (32 g, 52%), b.p. 104—106° at 1.5 mmHg (lit.,[14] 131—133° at 8 mmHg). When methanol was used as the solvent for this ozonolysis, the yield of aldehyde was greatly reduced.

trans-4-(3,4-*Methylenedioxyphenyl*)*but*-3-*enoic Acid* (2).—The above aldehyde (20 g) and malonic acid (14 g) were refluxed for 3 h with acetic acid (60 ml). The solution was then poured into water (800 ml) and the precipitated 4-(3,4-methylenedioxyphenyl)but-3-enoic acid (22.0 g, 87%) collected and dried. A sample crystallised from benzene–light petroleum (b.p. 80—100 °C) had m.p. 116—117° (lit.,[9] 117—118°), τ 0.82 (1 H, s, CO_2H), 2.7—3.0 (3 H, m, aromatic), 3.52 (1 H, d, J 16 Hz, olefinic), 3.94 (1 H, m, olefinic), 4.06 (2 H, s, OCH_2O), and 6.76 (2 H, d, C=CH–CH_2). This condensation failed when pyridine was used as solvent with piperidine as catalyst. The corresponding methyl ester, prepared with diazomethane, was ozonised in acetic acid as for safrole to yield piperonal, characterised as the 2,4-dinitrophenylhydrazone, m.p. 270—271°.

4-(3,4-*Methylenedioxyphenyl*)*butanoic Acid*.—The above olefinic acid (10 g) in ethyl acetate (150 ml) was hydrogenated at room temperature and pressure over 5% palladium–charcoal. The butanoic acid isolated by removal of the solvent was sufficiently pure for the next stage. A sample crystallised from light petroleum (b.p. 80—100 °C) had m.p. 79—80° (lit.,[15] 75—76°) (Found: C, 63.5; H, 5.9. Calc. for $C_{11}H_{12}O_4$: C, 63.5; H, 5.8%).

6,7-*Methylenedioxy*-1-*tetralone* (3).—Phosphorus(v) oxide (1 050 g), anhydrous ether (1 050 ml), and ethanol-free chloroform (2 100 ml) were stirred under reflux for 48 h with exclusion of moisture. The solution was filtered through glass wool and the solvents were removed under vacuum at 30—40 °C to leave polyphosphate ester as a viscous oil (1 100 ml).

Finely powdered 4-(3,4-methylenedioxyphenyl)butanoic acid (10 g) was stirred with polyphosphate ester (300 ml) for 2 h at room temperature. The mixture was then poured into water (1 500 ml) and stirred for 10 h to destroy the reagent.

6,7-Methylenedioxy-1-tetralone was collected in ether; the solution was washed with sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated. The product crystallised from 50% ethanol as needles (7.2 g, 80%), m.p. 75—76° (lit.,[15] 71—72°), ν_{CO} 1 670 cm^{-1}, M^+ 190 (Found: C, 69.3; H, 5.3. Calc. for $C_{11}H_{10}O_3$: C, 69.4; H, 5.3%). Attempts to use polyphosphoric acid or hydrofluoric acid as dehydrating agent gave only polymeric material.

The ketone (10 g) in ethanol (100 ml) was refluxed for 30 min with hydroxylamine hydrochloride (25 g) in 5% sodium hydroxide (200 ml). The *oxime* (10 g, 98%) crystallised on cooling; a sample crystallised from 30% ethanol as needles, m.p. 145—147° (Found: C, 64.4; H, 5.4; N, 6.7. $C_{11}H_{11}NO_3$ requires C, 64.4; H, 5.4; N, 6.8%), M^+ 205.

6,7-*Methylenedioxy*-1-*naphthylamine* (4).—The above oxime (5.0 g) was treated with acetic anhydride (3 ml) in acetic acid (50 ml) for 15 min, after which a slow stream of hydrogen chloride was passed through the solution for 3 h. The precipitated amine hydrochloride was collected and stirred with 5% sodium hydroxide (40 ml) to liberate the aminonaphthalene (1.7 g, 40%), which sublimed at 120° and 0.01 mmHg; m.p. 154—155° (Found: C, 70.5; H, 4.7; N, 7.5. Calc. for $C_{11}H_9NO_2$: C, 70.6; H, 4.8; N, 7.5%), τ 2.5—3.3 (5 H, m, aromatic), 3.89 (2 H, s, OCH_2O), and 6.13 (2 H, s, NH_2).

2-*Bromo*-4,5-*dimethoxybenzoic Acid*.—2-Bromo-4,5-dimethoxybenzaldehyde (10 g) in 50% aqueous pyridine (250 ml) was stirred with potassium permanganate (12.4 g) at room temperature for 3 h. Acidification and treatment with sulphur dioxide gave 2-bromo-4,5-dimethoxybenzoic acid (7.0 g, 66%), m.p. 182—185° (lit.,[16] 183—184°). The acid chloride was prepared using thionyl chloride.

2-*Bromo*-4,5-*dimethoxy*-N-*methyl*-N-(6,7-*methylenedioxy*-1-*naphthyl*)*benzamide* (5).—Reaction between the above acid chloride and 6,7-methylenedioxy-1-naphthylamine in pyridine afforded 2-bromo-4,5-dimethoxy-*N*-(2,3-methylenedioxy-1-naphthyl)benzamide, (1), m.p. 250—252° (from ethanol) (Found: C, 56.0; H, 3.7; Br, 18.4; N, 3.1. Calc. for $C_{20}H_{16}BrNO_5$: C, 55.8; H, 3.7; Br, 18.6; N, 3.2%) (lit.,[4] m.p. 246—247°). This amide (2.5 g) was dissolved in acetone (30 ml) and sodium hydroxide (10%; 30 ml) and the mixture refluxed during the addition of dimethyl sulphate (2 ml). After a further 30 min, the mixture was poured into water and the product collected. The *benzamide* (5) crystallised from ethanol as pale yellow prisms (2.5 g, 81%), m.p. 186—187° (Found: C, 57.0; H, 4.1; Br, 18.0; N, 3.1; $C_{21}H_{18}BrNO_5$ requires C, 56.8; H, 4.1; Br, 18.0; N, 3.1%), ν_{CO} 1 650 cm^{-1}, M^+ 445 and 443, τ (*syn*-rotamer) 6.29 and 6.67 (two OMe) and 6.47 (NMe) *, τ (*anti*-rotamer) 6.05, 6.07 (two OCH_3), 6.71 ($N-CH_3$) * polarographic $E_{\frac{1}{2}}$ −2.23 and −2.49 V *vs.* s.c.e.

Electrochemical Reduction of the Benzamide (5).—The supporting electrolyte was 0.1M-tetra-n-propylammonium perchlorate in dimethylformamide.[17] A H-type electrochemical cell was used with a mercury cathode, a platinum anode, and s.c.e. reference. The electrolyte was introduced into the anode compartment and a solution of the amide (5) (0.5 g) in electrolyte (20 ml) into the cathode compartment. Electrolysis was continued at a cathode potential of −2.2 V *vs.* s.c.e. until the current fell to a negligible value; the catholyte was then added to a small amount of alumina and the solvent removed under reduced pressure. The residue was added to a short column of alumina and eluted

* For comparison 2-bromo-*N*-methyl-*N*-naphthylbenzamide shows for NMe, τ(*syn*-rotamer) 6.41 and (*anti*-rotamer) 6.77.

[14] S. Nagai, *J. Faculty Engineering, Tokyo Imperial Univ.*, 1923, **13**, 185.

[15] T. Kametani, K. Kigasawa, M. Hiiragi, and O. Kusama, *J. Heterocyclic Chem.*, 1973, **10**, 31.

[16] Th. Zincke and Br. Franche, *Annalen*, 1896, **293**, 186.

[17] For general directions see J. Grimshaw and H. R. Juneja, *J.C.S. Perkin I*, 1972, 2529; also 'Organic Electrochemistry,' ed. M. M. Baizer, Dekker, New York, 1973.

with ether. Evaporation of the eluate left a residue of *4,5-dimethoxy-N-methyl-2-(6,7-methylenedioxy-1-naphthyl)-benzamide* (7), prisms (0.18 g, 44%), m.p. 205—208° (from ethanol) (Found: C, 69.1; H, 5.3; N, 3.8. $C_{21}H_{19}NO_5$ requires C, 69.0; H, 5.2; N, 3.8%), ν_{CO} 1 660 cm^{-1}, *m/e* 365 (M^+, 100%), 335 (65, $M^+ - NHMe$), and 165 (20), τ 2.18—2.88 (5 H, m, naphthalene), 3.08 (1 H, s, benzenoid), 3.22 (1 H, s, benzenoid), 3.98 (2 H, s, OCH_2O), 4.74br (1 H, s, N*H*Me), 5.98 (3 H, s, OMe), 6.12 (3 H, s, OMe), and 7.60 (3 H, d, *J* 6 Hz, NHC*H*$_3$).

Photochemical Cyclisation of the Benzamide (5).—The amide (5) (0.6 g) was dissolved in acetonitrile (100 ml) and the solution irradiated with a low-pressure mercury resonance lamp, in quartz apparatus, for 24 h. Oxynitidine (9) precipitated and crystallised from bis-(2-methoxyethyl) ether as needles (0.17 g, 35%), m.p. 284—285° (lit.,[6] 284—285°) (Found: C, 69.0; H, 4.8; N, 3.6. Calc. for $C_{21}H_{17}NO_5$: C, 69.4; H, 4.6; N, 3.9%), *m/e* 363 (M^+, 100%), 362 (47), and 348 (31, $M^+ - CH_3$), τ 1.9—2.9 (6 H, m, aromatic), 3.87 (2 H, s, OCH_2O), 5.86 (3 H, s, OMe), 5.90 (3 H, s, OMe), and 5.99 (3 H, s, NMe).

Dihydronitidine.—Oxynitidine (0.21 g) was reduced in tetrahydrofuran (15 ml) with lithium aluminium hydride (0.11 g). After 3 h, the excess of reagent was destroyed with a little 2M-hydrochloric acid, the inorganic salts were filtered off, and the filtrate was diluted with water (15 ml). Dihydronitidine then separated (0.13 g, 65%), giving needles (from ethanol), m.p. 216—217° (lit.,[7] 217—218°) (Found: C, 72.2; H, 5.5; N, 3.9. Calc. for $C_{21}H_{19}NO_4$: C, 72.2; H, 5.5; N, 4.0%), *m/e* 349 (M^+, 87%) and 348 (100).

Nitidine Tetrafluoroborate (10).—Dihydronitidine (20 mg) in ethanol (10 ml) was treated with hydrogen peroxide (30%; 5 drops) and fluoroboric acid (40%; 5 drops) and heated on a steam-bath for 30 min. The solution became yellow and *nitidine tetrafluoroborate* separated as yellow needles (17 mg, 68%), m.p. 300° (decomp.) (Found: C, 54.8; H, 4.4; N, 3.0. $C_{21}H_{18}BF_4NO_4,1\frac{1}{2}H_2O$ requires C, 54.6; H, 4.6; N, 3.0%). The anhydrous salt was obtained after drying for 24 h at 90 °C and 0.01 mmHg (Found: C, 57.8; H, 4.3; N, 3.1. $C_{21}H_{18}BF_4NO_4$ requires C, 58.0, H, 4.2; N, 3.2%).

We thank the Department of Education, Northern Ireland, for a studentship (to W. J. B.).

[7/774 *Received*, 6*th May*, 1977]