Tetrahedron Vol. 48, No. 36, pp. 7479-7488, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

A NEW METHOD FOR BROMINATION OF CARBAZOLES, β-CARBOLINES AND IMINODIBENZYLS BY USE OF *N*-BROMOSUCCINIMIDE AND SILICA GEL†

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(*Received in USA* 31 *March* 1992)

Abstract - Carbazole, *N*-ethylcarbazole, iminodibenzyl (10,11-dihydro-5H-dibenz[b,f]azepine), *N*-ethyliminodibenzyl and imipramine are readily mono-, di- or polybrominated in high yields at ambient temperature in dichloromethane by use of the appropriate quantity of *N*-bromosuccinimide in the presence of silica gel. By contrast, the brominations of the β-carbolines, harmane and norharman, are less selective and give mixtures of products, some of which have unusual substitution patterns.

We recently introduced *N*-bromosuccinimide (NBS) - silica gel as a convenient reagent system for the high yield bromination of indoles and benzimidazoles.[1] Like the indoles and benzimidazoles, other heterocyclic compounds have often presented problems when subjected to bromination reactions, and it was therefore of interest to investigate the wider utility of the new reagent system, for example for the synthesis of biologically active marine natural products such as the eudistomins, which have been isolated from the colonial tunicate *Eudistoma olivaceum*[2]. We now report that carbazoles and iminodibenzyls are readily brominated at ambient temperature. High yields of mono-, di- or poly-bromo products are obtained, depending on the stoichiometry used. In contrast, the brominations of harmane and norharman show low regioselectivity.

Traditional methods of bromination of carbazole generally provide 3-bromocarbazole in poor yield, although one report indicates a high yield.[3] Polybromination is also possible, but more forcing conditions are required in order to obtain good yields. For example, heating carbazole and bromine overnight at 60°C in glacial acetic acid is recommended for the synthesis of 1,3,6,8-tetrabromocarbazole in 66% yield.[4] Bromination of *N*-alkylcarbazoles gives rise to even more problems, usually producing mixtures.[3,5,6] Iminodibenzyl and its *N*-alkyl derivatives have also been brominated, but the yields are generally poor.[7-9]

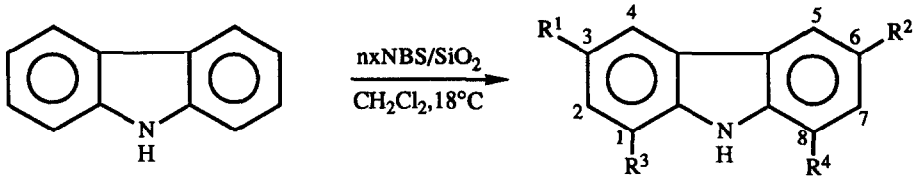
The Caribbean colonial tunicate *Eudistoma olivaceum* produces a series of β-carboline derivatives (eudistomins), some of which exhibit useful antiviral and antimicrobial activity.[2] Although they are by no means the most biologically active of the eudistomins, 6-bromoharmane (eudistomin N) and 7-bromoharmane (eudistomin O) act synergistically to produce moderate *in vitro* antiviral and antimicrobial activity.[2] Both eudistomins N and O have been synthesized,[2] as have several other bromine-containing eudistomins.[10]

With this considerable incentive to find superior procedures for the bromination of heterocycles such as carbazoles, β-carbolines and iminodibenzyls, we decided to apply our newly developed reagent system,[1]

† Dedicated to Professor C W Rees, FRS.

comprising NBS and acidic silica gel (B.D.H. chromatographic grade silica, 100-120 mesh, with pH of a 10% aqueous slurry ≥ 5), to these heterocycles. In order to investigate the bromination reactions, a standard set of conditions was adopted. Although the ratio of substrate to reagent was varied, the reagent always contained 2g of acidic silica gel for each millimole of NBS in 25 ml of dichloromethane.

Carbazole was treated in this way with one to four equivalents of NBS/silica at ambient temperature (equation 1) and the yields of the products were determined by hplc after an appropriate time. The results are presented in Table 1.



(1)

(1)

(2) R^1 = Br; R^2 - R^4 = H
(3) R^1, R^2 = Br; R^3, R^4 = H
(4) R^1 - R^3 = Br; R^4 = H
(5) R^1 - R^4 = Br.

Table 1. Bromination of Carbazole with NBS/silica

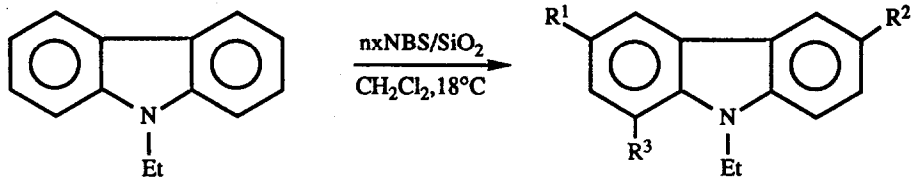
Equivs. NBS used(n)	Reaction Time(h)	Proportions of reaction components(%)[a] (1)	(2)	(3)	(4)	(5)
1	0.33	21	61	18		
2	4.5			100		
3	60			31	69	
4	72			6	87	7

[a] The total recovery of carbazoles was close to 100% in all cases. Proportions were calculated by quantitative hplc.

As can be seen from Table 1, this reaction provides a simple and clean synthesis of 3,6-dibromocarbazole (3) by use of two equivalents of NBS/silica. Production of 1,3,6-tribromocarbazole (4) is also fairly clean but requires a long period for complete reaction even with excess reagent. 1,3,6,8-Tetrabromocarbazole (5) is produced only very slowly, whereas 3-bromocarbazole (2) is produced rapidly, but contains a significant level of dibromocarbazole as impurity.

In a similar manner, *N*-ethylcarbazole (6) could be converted into 3-bromo-*N*-ethylcarbazole (7) rapidly but relatively unselectively or, depending on the stoichiometry, cleanly into either 3,6-dibromo-*N*-ethylcarbazole (8) or 1,3,6-tribromo-*N*-ethylcarbazole (9) (equation 2 and Table 2).

Iminodibenzyls are rather more readily brominated than carbazoles and monobromination of iminodibenzyl itself by NBS occurred without added silica. However, silica was beneficial to the reaction rate and became more necessary for polybromination. Up to four bromine atoms could be introduced (equation 3), and selective production of any desired product could be achieved by use of appropriate stoichiometry (Table 3).



(2)

(6)

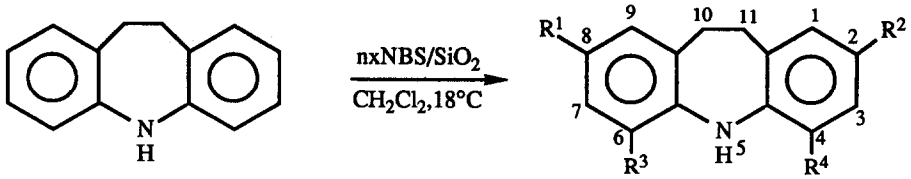
(7) R^1 = Br; R^2, R^3 = H
(8) R^1, R^2 = Br; R^3 = H
(9) R^1 - R^3 = Br

Table 2. Bromination of *N*-ethylcarbazole with NBS/silica

Equivs.NBS used(n)	Reaction Time(h)	Proportions of reaction components(%)[a] (6)	(7)	(8)	(9)
1	4.5	28	48	24	
2	6.0		8	88	4
4	72			17	83[b]

[a] The total recovery of carbazoles was close to 100% in all cases. Proportions were calculated by quantitative hplc.

[b] This yield is increased to 100% by use of an even larger excess of NBS (6 equivalents).



(3)

(10)

(11) R^1 = Br; R^2 - R^4 = H
(12) R^1, R^2 = Br; R^3, R^4 = H
(13) R^1 - R^3 = Br; R^4 = H
(14) R^1 - R^4 = Br.

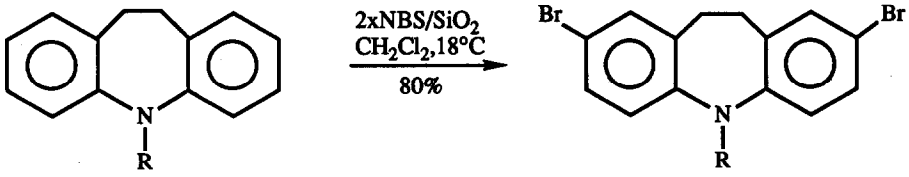
Table 3. Bromination of Iminodibenzyl with NBS/silica

Equivs.NBS used(n)	Reaction Time(h)	Proportions of reaction components(%)[a] (10)	(11)	(12)	(13)	(14)
1	0.15	16	76	8		
2	0.2			100		
3	3.0			7	87	6
4	3.0				10	90[b]

[a] The total recovery of iminodibenzyls was close to 100% in all cases. Proportions were calculated by quantitative hplc.

[b] This yield is increased to 100% by use of a small excess of NBS.

N-Ethyliminodibenzyl (**15**) presented greater difficulty. Mono- and dibromination occurred as with iminodibenzyl itself, but attempts to introduce further bromines resulted in de-ethylation and the eventual production of 2,4,6,8-tetrabromoiminodibenzyl (**14**). Monobromination was not very selective (63% of 2-bromo-*N*-ethyliminodibenzyl, contaminated by equimolar amounts of unbrominated and dibrominated material). Thus, the major benefit of the method arises from the use of two equivalents of NBS/silica as a means of producing 2,8-dibromo-*N*-ethyliminodibenzyl (**16**) in good yield. The method has also been applied to the dibromination of imipramine (**17**) to give 2,8-dibromoimipramine (**18**) (equation 4).

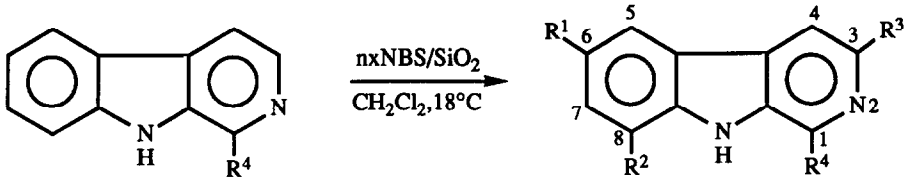


(4)

(**15**) R = CH_2CH_3
(**17**) R = $(CH_2)_3N(CH_3)_2$

(**16**) R = CH_2CH_3
(**18**) R = $(CH_2)_3N(CH_3)_2$

The brominations of harmane (**19**) and norharman (**25**) with NBS/silica were not very selective (equation 5). Monobromination of harmane and norharman produced the expected products, 6-bromoharmane (**20**) and 6-bromonorharman (**26**), respectively. However, both reaction mixtures were contaminated with substantial quantities of the 8-bromo derivatives (**21**) and (**27**), as well as the 3,6- and 6,8-dibrominated products (Table 4). The production of compounds with an 8-bromo substituent in such an easy manner is unprecedented in earlier investigations of brominations of harmane and norharman.



(5)

(**19**) $R^4 = CH_3$
(**25**) $R^4 = H$

(**20**) R^1 = Br; R^2, R^3 = H; $R^4 = CH_3$
(**21**) R^2 = Br; R^1, R^3 = H; $R^4 = CH_3$
(**22**) R^1, R^3 = Br; R^2 = H; $R^4 = CH_3$
(**23**) R^1, R^2 = Br; R^3 = H; $R^4 = CH_3$
(**24**) R^1 - R^3 = Br; $R^4 = CH_3$
(**26**) R^1 = Br; R^2 - R^4 = H
(**27**) R^2 = Br; R^1, R^3, R^4 = H
(**28**) R^1, R^3 = Br; R^4 = H
(**29**) R^1, R^2 = Br; R^3, R^4 = H
(**30**) R^1 - R^3 = Br; R^4 = H

Table 4. Bromination of Harmane and Norharman with NBS/silica

Equivs.NBS used(n)	Starting Material	Reaction Time(h)	Proportions of reaction components(%)[a] 19 or (25)	20 or (26)	21 or (27)	22 or (28)	23 or (29)	24 or (30)
1	**19**	2		29	20	7	5	
2	**19**	48		9	7	16	24	12
1	(25)	24	(20)	(23)	(44)	(1)	(6)	
2	(25)	36		(33)	(10)	(5)	(25)	(10)

[a] Yields of isolated products. Figures in parentheses refer to reactions of norharman.

Dibromination of harmane and norharman gave a similar range of products together with the tribrominated products (**24**) and (**30**), respectively.

As noted above, a mixture of 6-bromonorharman and 7-bromonorharman is reported to possess antiviral and antimicrobial properties, neither compound alone being active.[2] We now report that both 6-bromoharmane (**20**) and 8-bromoharmane (**21**) showed moderate cytotoxicity in the SOS chromotest, but that a 1:1 mixture of the two showed increased toxicity in the test.[11] Corresponding norharman derivatives showed the same trends at a much lower level of activity.

From the above results it is clear that NBS/silica is a particularly useful reagent system for selective di- or tri-bromination of carbazoles, mono- to tetrabromination of iminodibenzyl and dibromination of *N*-alkyliminodibenzyls. It is not highly selective but produces interesting substitution patterns with β-carbolines. We continue to investigate the potential of solid catalysed aromatic substitution reactions.[12]

Experimental Section

General: Nmr spectra were generally recorded using a Bruker Gyrospec WM 250 MHz spectrometer, but where indicated spectra were recorded using a Varian XL-100 spectrometer. The internal standard used in all spectra was tetramethylsilane. Mass spectra were recorded using a VG 12/253J low resolution quadrupole mass spectrometer unless stated otherwise using alternate chemical, electron impact ionization (ACE). The data recorded here are for the molecular ion cluster under electron impact ionization (with relative peak intensities in parentheses). Hplc analyses were carried out on a LDC dual pump system. CHN microanalyses were obtained, using a Carlo Erba 1106 instrument, for new compounds only. Melting points are uncorrected.

Materials: BDH chromatographic grade silica (100-120 mesh) was used in all reactions, and was dried at 120°C before use. All other reagents were used as bought. Solvents were distilled before use.

General Reaction Procedure: To a stirred solution of the heterocycle (1.25 - 5.0 mmol, depending on the stoichiometry used) in dichloromethane (50 mL), containing silica (10 g), a solution of NBS (0.890 g, 5.0 mmol) in dichloromethane (75 mL) was added dropwise. The reaction mixture was stirred for an appropriate time in the absence of light at ambient temperature until hplc indicated that it was complete. The reaction mixture was then filtered and the silica washed with dichloromethane (3 x 15 mL). The combined

extracts were washed with water (100 mL) and the organic layer was dried and evaporated. The product mixture was then dissolved in acetone (30 mL) for hplc analysis.

Hplc Analytical Method. Hplc was carried out using a 25 x 0.42 cm column packed with spherisorb ODS-2. The eluent was a methanol/water gradient (0-20% water) flowing at 1 mL/min. The eluate was monitored by uv absorption at 254 nm 10 μL of the crude reaction mixture (in acetone) was injected and peak areas of products (A_X) and starting heterocycle (A_S) were obtained by integration. A weighed amount of the parent heterocycle (W_S') was then dissolved in the solution of the crude reaction mixture and another sample (10 μl) was injected. New peak areas (A_X' and A_S') were then obtained by integration. A response factor (R_X) was obtained for each product component, in relation to the parent heterocycle, by also injecting a standard mixture of known composition ($W_X^o + W_S^o$) and measuring the areas (A_X^o, A_S^o). Three equations could then be written (equations 6-8).

$$R_X = \frac{A_X^o W_S^o}{A_S^o W_X^o} \tag{6}$$

$$W_S = \frac{R_X A_S W_X}{A_X} \tag{7}$$

$$W_S + W_S' = \frac{R_X A_S' W_X}{A_X'} \tag{8}$$

Equation (6) allowed determination of the response factor, all other variables being known or measured. Subtraction of equation (7) from equation (8) provided a relationship in which everything except W_X was known (equation (9). The weight of component X could therefore be calculated.

$$W_S' = R_X W_X \left[\frac{A_S'}{A_X'} - \frac{A_S}{A_X}\right] \tag{9}$$

Using this method the entire reaction mixture compositions were calculated for the reactions of carbazoles and iminodibenzyls. The total mole balance of reactants and products calculated was generally high (95-100%). In the cases of harmane and norharman the product yields were determined by isolation.

Isolation and Characterization of Products. In most cases the pure products were isolated from the reaction mixtures in which they were most abundant by flash chromatography. In a few cases, when no reaction mixture gave a high enough yield of the particular product, reactions were carried out on a larger scale and/or under more concentrated conditions in order to produce a larger quantity, prior to isolation.

Properties of the products obtained (sometimes after recrystallization) are given below. In the cases of bromination of harmane and norharman, which gave mixtures in which no one product predominated, only small quantities of isolated products were obtained. Recrystallization was not practical and the products were too impure for microanalysis, so were characterized solely by their spectroscopic properties.

3-Bromocarbazole (2). Brown, glass-like crystals (from chloroform/acetone 99:1), mp 189-191°C (lit.[3] 198-199°C). ^{1}H nmr (acetone d_6): δ 7.08 - 7.60 (m, 5H), 8.12 (1H, d, H2), 8.26 (1H, d, H4), 10.45 (1H, s, NH); ^{13}C nmr (acetone-d_6): δ 113.63 (d), 114.80 (d), 121.67 (d), 122.81 (d), 124.21 (s), 125.00 (d), 127.15 (s), 128.81 (d), 130.41 (d), 141.34 (s), 143.00 (s); m/e (M^+) 247 (100), 245 (100).

3,6-Dibromocarbazole (4). White amorphous solid, mp. 206-208°C (lit.[13] mp. 212-213°C). ^{1}H nmr (acetone-d_6): δ 7.5 (2H, d, J = 9.0Hz, H1 and H8), 7.55 (2H, dd, J = 9.0 and 1.8Hz, H2 and H7), 8.30 (2H, d, J = 1.7Hz, H4 and H5), 10.58 (1H, broad s, NH); ^{13}C nmr (acetone-d_6): δ 112.39 (s), 113.69 (d), 123.92 (d), 124.71 (s), 129.68 (d), 139.92 (s); m/e (M^+) 327 (48), 325 (100), 323 (51).

1,3,6-Tribromocarbazole (4). White solid (from chloroform), mp. 172-176°C (lit.[3] mp. 184°C). ^{1}H nmr (acetone-d_6): δ = 7.50 (1H, d, J = 8.0Hz, H8), 7.54 (1H, d, J = 8.0Hz, H7), 7.67 (1H, s, H2); 8.26 (2H, s, H4 and H5); 10.70 (1H, broad s, NH); ^{13}C nmr (acetone-d_6): δ 105.19 (s), 112.12 (s); 113.18 (s), 114.28 (d), 123.30 (d), 124.40 (d); 124.86 (s), 125.51 (s), 130.51 (d), 131.12 (d), 138.54 (s), 139.86 (s); m/e (M^+) 407 (21), 405 (71), 403 (72), 401 (23).

1,3,6,8-Tetrabromocarbazole (5). White solid (from chloroform), mp. 227-229°C (lit.[3] 234-235°C). ^{1}H nmr (DMSO-d_6, 100 MHz): δ 7.70 (2H, d, J = 2Hz, H4 and H5), 8.44 (2H, d, J = 2Hz, H2 and H7); ^{13}C nmr (DMSO-d_6), 25.1MHz) δ 105.1 (s), 111.9 (s), 123.1 (d), 125.1 (s), 131.5 (d), 137.9 (s); m/e (M^+) 487 (12), 485 (64), 483 (100), 481 (66), 479 (15).

3-Bromo-*N*-ethylcarbazole (7). White solid (from pentane), mp. 82-84°C (lit.[14] 82.5 - 84.5°C). ^{1}H nmr ($CDCl_3$): δ 1.28 (3H, t, J = 7.0Hz), 4.15 (2H, q, J = 7.0Hz), 7.1 - 7.4 (5H, m), 7.95 (1H, d, J = 7.0Hz), 8.13 (1H, d, J = 1.8Hz); ^{13}C nmr ($CDCl_3$): δ 13.63 (q), 37.46 (t), 108.62 (d), 109.78 (d), 111.48 (s), 119.13 (d), 120.51 (d), 121.82 (s), 123.01 (d), 124.57 (s), 126.27 (d), 128.13 (d), 138.42 (s), 140.12 (s); m/e (M^+) 275 (67), 273 (68).

3,6-Dibromo-*N*-ethylcarbazole (8). White needles (from chloroform/pentane), mp. 139-141°C (lit.[13] 139-141°C). ^{1}H nmr ($CDCl_3$): δ 1.33 (3H, t, J = 7.1Hz), 4.17 (2H, q, J = 7.1Hz), 7.16 (2H, d, J = 8.5Hz, H1 and H8), 7.48 (dd, J = 8.5Hz and 1.8Hz, H2 and H7), 8.13 (2H, d, J = 1.8Hz, H4 and H5); ^{13}C nmr ($CDCl_3$): δ 13.64 (q), 37.73 (t), 110.05 (d), 111.92 (s), 123.20 (d), 123.48 (s), 128.95 (d), 138.7 (s); m/e (M^+) 355 (49), 353 (100), 351 (49).

1,3,6-Tribromo-*N*-ethylcarbazole (9). White solid (from dichloromethane/pentane, 7:1), mp. 145-148°C. ^{1}H nmr ($CDCl_3$): δ 1.37 (3H, t, J = 7.1Hz), 4.60 (2H, q, J = 7.1Hz), 7.20 (1H, d, J = 8.8Hz, H8),7.51 (1H, dd, J = 8.8Hz and 1.7Hz, H7), 7.64 (1H, d, J = 1.7Hz, H5), 7.90 (1H, d, J = 1.7Hz, H2), 7.96 (1H, d, J = 1.7Hz, H4); ^{13}C nmr ($CDCl_3$): δ 15.44 (q), 39.02 (t), 103.19 (s), 110.01 (s), 110.55 (d), 111.69 (s), 112.77 (s), 122.09 (d), 122.95 (d), 126.09 (s), 129.80 (d), 133.28 (d), 135.44 (s), 139.77 (s); m/e (M^+) 435 (28), 433 (100), 431 (98), 429 (31). Anal.calc. for $C_{14}H_{10}Br_3N$: C 38.90, H 2.31, N 3.24%; found C 38.19, H 2.40, N 3.42%.

2-Bromoiminodibenzyl (11). White solid, mp. 100-101°C. ^{1}H nmr ($CDCl_3$): δ 3.04 (4H, s, H10 and H11), 5.97 (1H, broad s, NH), 6.6 - 7.3 (m, 7H); ^{13}C nmr ($CDCl_3$): δ 34.73 (t), 34.61 (t), 111.30 (s), 118.07 (d), 119.50 (d), 119.95 (d), 127.00 (d), 128.56 (s), 129.53 (d), 130.60 (s), 130.73 (s), 133.09 (s), 141.65 (s), 141.96 (s); m/e (M^+) 275 (97), 273 (100).

2,8-Dibromoiminodibenzyl (12). Pale blue needles (from chloroform), mp. 177-178° (lit.[7] 167°C). ^{1}H nmr ($CDCl_3$): δ 2.99 (4H, s, H10 and H11), 5.95 (1H, broad s, NH), 6.58 (2H, d, J = 9.1 =Hz, H4 and H6), 7.15 (2H, d, J = 2.3Hz, H1 and H9), 7.17 (2H, dd, J = 9.1 and 2.3Hz, H3 and H7); ^{13}C nmr ($CDCl_3$): δ 34.36 (t), 111.75 (s), 119.60 (d), 129.68 (d), 130.42 (s), 133.12 (d), 141.06 (s). m/e (M^+) 355 (48), 353 (100), 351 (52).

2,4,8-Tribromoiminodibenzyl (13). Light brown solid (from acetone), mp. 110-112°C. ^{1}H nmr ($CDCl_3$) δ 3.00 (4H, s, H10 and H11), 6.73 (1H, d, J = 9.0Hz, H6), 7.13 (1H, d, J = 2.3Hz, H1), 7.16 - 7.24 (2H, m, H7 and H9), 7.52 (1H, d, J = 2.3Hz, H3); ^{13}C nmr ($CDCl_3$): δ 34.05 (t), 34.50 (t), 111.25 (s), 112.54 (s), 112.83 (s), 120.48 (d), 129.80 (d), 130.13 (s), 131.86 (s), 132.33 (d), 132.54 (d), 133.12 (d), 138.54 (s), 140.16 (s); m/e (M^+) 435 (30), 433 (95), 431 (100), 429 (31). Anal.calc. for $C_{14}H_9Br_3N$: C 38.96, H 2.37, N 3.43%; found C 38.90, H 2.30, N 3.24%.

2,4,6,8-Tetrabromoiminodibenzyl (14). Amorphous white solid (from acetone, mp. 153-154°C (lit.[7] 153°C). ^{1}H nmr ($CDCl_3$): δ 3.00 (4H, s, H10 and H11), 7.10 (2H, d, J = 2.3Hz, H1 and H9), 7.53 (2H, d, J = 2.3Hz, H3 and H7); ^{13}C nmr ($CDCl_3$): δ 34.62 (d), 111.74 (s), 113.74 (s), 131.52 (d), 132.25 (d), 133.00 (d), 137.83 (s); m/e (M^+) 515 (9), 513 (63), 511 (100), 509 (64), 507 (11).

N-Ethyliminodibenzyl (15). *N*-Butyllithium (18.0 mL, 1.7M) was added dropwise to a stirred solution of iminodibenzyl (5.85 g, 0.030 mol) in dry THF (70 mL) at -78°C. The reaction mixture was then refluxed with bromoethane (6.54g, 0.060 mol) for 2 hours. The cooled mixture was washed with water (150 mL) and the crude product was purified by silica flash chromatography using a gradient from pentane to pentane:CH_2Cl_2 (85:15). White solid, mp. 53-54°C. ^{1}H nmr ($CDCl_3$ 100 MHz): δ 1.10 (3H, t, J = 8.0Hz), 3.10 (4H, s, H10 and H11), 3.71 (2H, t, J = 8.0Hz), 6.7 - 7.1 (m, 8H); ^{13}C nmr ($CDCl_3$ 25.1 MHz): δ 13.90 (q), 32.23 (t), 45.06 (12), 119.95 (d), 122.14 (d), 126.19 (d), 129.58 (d), 134.18 (s), 148.15 (s); m/e (M^+) 223 (46). Anal.calc. for $C_{16}H_{17}N$: C 86.10, H 7.62, N 6.28%; found C 86.16, H 7.92, N 6.12%.

2-Bromo-*N*-ethyliminodibenzyl. White solid, mp 84-85°C. ^{1}H nmr ($CDCl_3$): δ 1.12 (3H, t, J = 7.0Hz), 3.69 (2H, q, J = 7.0Hz), 6.9 - 7.2 (7H, m); ^{13}C nmr ($CDCl_3$): δ 13.82 (q), 31.76 (t), 32.26 (t), 4.5.26 (t), 114.69 (s), 120.27 (d), 121.69 (d), 122.75 (d), 126.51 (d), 129.09 (d), 129.59 (d), 132.45 (d), 134.36 (s), 136.21 (s), 147.24 (s), 147.97 (s); m/e (M^+) 303 (49), 301 (51). Anal. calc. for $C_{16}H_{16}BrN$: C 63.29, H 5.46, N 5.00%; found C 63.53, H 5.29, N 4.63%.

2,8-Dibromo-*N*-ethyliminodibenzyl (16). White solid (from methanol), mp. 94-96°C. ^{1}H nmr ($CDCl_3$): δ 1.10 (3H, t, J = 7.0 Hz), 3.07 (4H, s, H10 and H11), 3.67 (2H, q, J = 7.0 Hz), 6.88 (2H, d, J = 9.3 Hz, H4 and H6), 7.21 (2H, d, J = 2.5 Hz, H1 and H9), 7.22 (2H, dd, J = 9.3 and 2.5 Hz, H3 and H7); ^{13}C nmr ($CDCl_3$): δ 13.70 (q), 31.71 (t), 45.35 (t), 115.19 (s), 121.87 (d), 129.3 (d), 132.33 (d), 136.18 (s), 146.88 (s); m/e (M^+) 383 (35), 381 (74), 379 (33). Anal.calc. for $C_{16}H_{15}Br_2N$: C 50.76, H 3.86, N 3.63%; found C 50.42, H 3.94, N 3.68%.

2,8-Dibromoimipramine (17). Off-white solid, mp. 120-121°. ^{1}H nmr ($CDCl_3$, 100 MHz): δ 1.68 (2H, m), 2.18 (6H, s, N-Me), 2.30 (2H, m), 3.00 (4H, s, H10 and H11), 3.62 (2H, t, J = 7 Hz), 6.85 (2H, d, J = 9 Hz, H4 and H6); 7 - 7.3 (m, 4H); ^{13}C nmr ($CDCl_3$, 25.1 MHz): δ 25.45 (t), 31.58 (t), 45.03 (q), 48.74 (t), 57.00 (t), 115.31 (s), 121.77 (d), 127.27 (d), 132.33 (d), 135.99 (s), 146.76 (s); m/e (M^+) 440 (7), 438 (13), 436 (6). Anal.calc. for $C_{19}H_{22}Br_2N_2$: C 52.05, H 5.02, N 6.39%; found C 52.06, H 4.93, N 6.48%.

6-Bromoharmane (20). ^{1}H nmr ($CDCl_3$): δ 2.78 (3H, s, CH_3), 7.49 (1H, dd, J = 8.3 and 0.5 Hz, H8), 7.63 (1H, dd, J = 8.3 and 2.0 Hz, H7), 7.90 (1H, d, J = 5.5 Hz, H4), 8.16 (1H, d, J = 5.5 Hz, H3), 8.30 (1H, dd, J = 2.0 and 0.4 Hz, H5); m/e (M^+) 262 (97), 260 (100). HRMS calc. for $C_{12}H_{10}N_2{}^{79}Br$ 261.0027 (M+1); found 261.0030.

8-Bromoharmane (21). ^{1}H nmr ($CDCl_3$): δ 2.78 (3H, s, CH_3), 7.16 (1H, dd, J = 7.8 Hz, H6), 7.71 (1H, dd, J = 7.8 Hz, H7), 7.90 (1H, d, J = 5.5 Hz, H4), 8.12 (1H, d, J = 7.8 Hz, H5), 8.19 (1H, d, J = 5.5 Hz, H3); m/e (M^+) 262 (100), 260 (100). HRMS calc. for $C_{12}H_{10}N_2{}^{79}Br$ 261.0027 (M+1); found 261.0030.

3,6-Dibromoharmane (22). ^{1}H nmr ($CDCl_3$): δ 2.78 (3H, s, CH_3), 7.37 (1H, d, J = 8.8 Hz, H8), 7.56 (1H, dd, J = 8.8 and 1.7 Hz, H7), 7.90 (1H, s, H4), 8.12 (1H, d, J = 1.7 Hz, H5); m/e (M^+) 342 (49), 340 (100), 338 (52). HRMS calc. for $C_{12}H_9N_2{}^{79}Br{}^{81}Br$ 340.9112 (M+1); found 340.9110.

6,8-Dibromoharmane (23). ^{1}H nmr ($CDCl_3$): δ 2.78 (3H, s, CH_3), 7.70 (1H, broad d, J = 5.4Hz, H4), 7.75 (1H, d, J = 1.7 Hz, H7), 8.13 (1H, d, J = 1.7 Hz, H5), 8.18 (1H, d, J = 5.4 Hz, H3); m/e (M^+) 342 (50), 340 (100), 338 (50). HRMS calc. for $C_{12}H_8N_2{}^{79}Br{}^{81}Br$ 339.9034; found 339.9034.

3,6,8-Tribromoharmane (24). ^{1}H nmr ($CDCl_3$): δ 2.78 (3H, s, CH_3), 7.84 (1H, d, J = 1.6 Hz, H7), 7.91 (1H, s, H4), 8.12 (1H, d, J = 1.6 Hz, H5); m/e (M^+) 422 (32), 420 (97), 418 (100), 416 (34). HRMS calc. for $C_{12}H_8N_2{}^{79}Br_2{}^{81}Br$ 418.8217 (M+1); found 418.8217.

6-Bromonorharman (26). ^{1}H nmr (acetone-d_6): δ 7.64 (1H, d, J = 8.7 Hz, H8), 7.68 (1H, dd, J = 8.7 and 1.9 Hz, H7), 8.12 (1H, d, J = 5.2 Hz, H4), 8.41 (1H, d, J = 5.2 Hz, H3), 8.44 (1H, d, J = 1.9Hz, H5), 8.96 (1H, s, 1H); m/e (M^+) 248 (100), 246 (100). HRMS calc. for $C_{11}H_7N_2{}^{79}Br$ 245.9793; found 245.9793.

8-Bromonorharman (27). ^{1}H nmr (acetone-d_6): δ 7.24 (1H, dd, J = 7.8 Hz, H6), 7.78 (1H, dd, J = 7.8 and 0.8 Hz, H7), 8.11 (1H, d, J = 5.1 Hz, H4), 8.28 (1H, dd, J = 7.8 and 0.8 Hz, H5), 8.40 (1H, d, J = 5.1 Hz, H3), 9.03 (1H, s, H1). m/e (M^+) 248 (100), 246 (100). HRMS calc. for $C_{11}H_7N_2{}^{79}Br$ 245.9793; found 245.9793.

3,6-Dibromonorharman (28) (as hydrochloride salt). ^{1}H nmr ($CDCl_3$:CD_3OD; 1:1): δ 7.43 (1H, dd, J = 8.7 and 1.9 Hz, H8), 7.63 (1H, dd, J = 8.7 and 1.9 Hz, H7), 8.13 (1H, d, J = 1.9 Hz, H4), 8.23 (1H, d, J = 1.9 Hz, H5), 8.60 (1H, broad s, H1); m/e (M^+) 328 (50), 326 (100), 324 (51). HRMS calc. for $C_{11}H_6N_2{}^{79}Br{}^{81}Br$ 325.8877; found 325.8877.

6,8-Dibromonorharman (29) (as hydrochloride salt). ^{1}H nmr (DMSO-d_6): δ 7.90 (1H, d: J = 1.7 Hz, H7), 8.20 (1H, broad s, H4), 8.40 (1H, broad s, H3), 8.60 (1H, d, J = 1.7 Hz, H5), 9.0 (1H, broad s, H1). HRMS calc. for $C_{11}H_6N_2{}^{79}Br{}^{81}Br$ 325.8877; found 325.8877.

3,6,8-Tribromonorharman (30). ^{1}H nmr ($CDCl_3$:CD_3OD; 1:1): δ 7.81 (1H, d, J = 1.7 Hz, H7), 8.09 (1H, d, J = 0.9 Hz, H4), 8.21 (1H, d, J = 1.7 Hz, H5), 8.63 (1H, d, J = 0.9 Hz, H1); m/e (M^+) 408 (31), 406 (100), 404 (100), 402 (32). HRMS calc. for $C_{11}H_5N_2{}^{79}Br_2{}^{81}Br$ 403.7982; found 403.7980.

Acknowledgements

We thank NATO for a grant, which allowed collaboration between KS and DJF, Amersham International for financial support to DMJ and AGM, and the SERC for a CASE award to AGM. We also thank Mary Kay Harper for performing bioassays and M. Hofnung, Institut Pasteur, Paris, for *E.coli* strain PQ37.

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