Tetrahedron Vol. 37, No. 18, pp. 3171 to 3174, 1981
Printed in Great Britain.

0040-4020/81/183171-04$02.00/0
Pergamon Press Ltd.

THE BIOSYNTHESIS OF LAURIFININE†

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(*Received in UK 6 January* 1981)

Abstract—The incorporation of (±)-nor-laudanosoline, (±)-N-nor-protosinomenine, (±)-N-nor-orientaline, (±)-N-nor-reticuline, and N-[2-(3-hydroxy-4-methoxyphenyl) ethyl]-2-(4'-hydroxyphenyl) ethylamine into laurifinine has been studied and the specific utilisation of the (±)-N-norprotosinomenine demonstrated. Double labelling experiments with (±)-[1-^{3}H, 4'-methoxy-^{14}C]-, and (±)-[1-^{3}H, 7-methoxy-^{14}C]-N-norprotosinomenines showed that 4' and 7, OMe groups and the H atom at the asymmetric centre of the precursor are retained in the bioconversion into laurifinine. Parallel experiments with (+)- and (−)-N-norprotosinomenine demonstrated specific utilisation of (+)-isomer into laurifinine.

Laurifinine, a representative of trisubstituted dibenz [d,f] azonine alkaloids isolated from the leaves of *Cocculus laurifolius*[1] D. C. (Menispermaceae) has been assigned the structure **6** which has been confirmed by its two syntheses.[2,3]

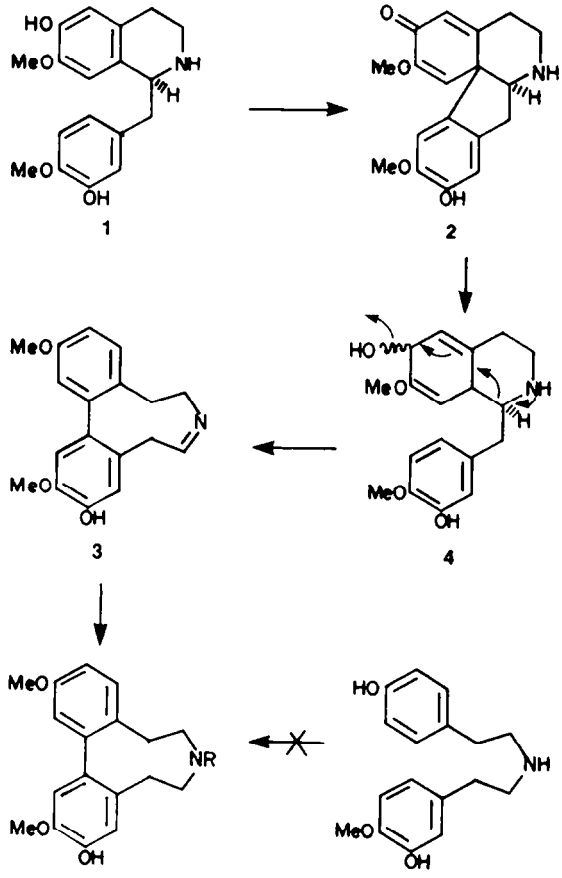
According to the most accepted biogenetic theory[4] laurifinine **6** can biosynthesise in nature from N-norprotosinomenine (**1**), an established precursor of *Erythrina* alkaloids[5] as follows. *Para–Para* oxidative coupling of norprotosinomenine (**1**) can give neoproaporphine (**2**). Reduction of **2** to the dienol (**4**) followed by elimination and rearrangement[6] as shown in **4** can give **3** which can then reduce to **5**. N-Methylation of the secondary amine function in **5** can finally yield laurifinine (**6**).

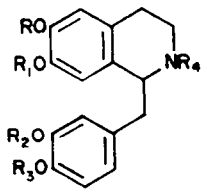
Laurifinine (**6**) can also form in nature from other 1-benzyltetrahydroisoquinolines such as nor-orientaline (**11**), and nor-reticuline (**10**) and from N-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-2-(4'-hydroxyphenyl)ethylamine (**7**) by alternate biogenetic pathways.

(L)-[U-^{14}C] Tyrosine (expt 1), was initially fed to young cut branches of *C. laurifolius* (Menispermaceae) and it was found that the plants were actively biosynthesising laurifinine (**6**). In subsequent experiments when tyrosine was fed in parallel with (±)-nor-reticuline (**10**, expt 4), (±)-nor-orientaline (**11**, expt 5) and N-[2-(3-hydroxy-4-methoxyphenyl) ethyl]-2-(4'-hydroxyphenyl) ethylamine (**7**) to young cut branches of *C. laurifolius* it was found that **7**, **10** and **11** were very poorly metabolised by the plants to form **6**. The very low incorporation (Table 1) of **7**, **10** and **11** ruled out any significant involvement of these precursors in the biosynthesis of laurifinine (**6**) in *C. laurifolius*. Feeding of (±)-nor-laudanosoline (**8**, expt 2) and (±)-N-norprotosinomenine (**9**, expt 3) showed that both **8** and **9** are efficient precursors of **6**. Feeding of (±)-protosinomenine (**12**, expt 6) revealed that the plants do not have the ability to utilise **12** to form **6**.

Feeding of (±)-[1-^{3}H, 7-methoxy-^{14}C] N-norprotosinomenine (expt 8) gave **6** labelled with both ^{14}C and ^{3}H. The ^{14}C: ^{3}H ratio in the precursor was 27:1 and in biosynthetic **6**, 29:1. Cleavage of the OMe groups of **6** by Ziezel method afforded radio active methyl iodide, trapped as triethylmethyl ammonium iodide which had, as expected, essentially half the molar activity of the biosynthetic laurifinine.

Feeding of (±)-[1-^{3}H, 4'-methoxy-^{14}C] N-nor-protosinomenine (expt 9) gave **6** labelled with ^{14}C and ^{3}H.





8: R = R$_1$ = R$_2$ = R$_3$ = R$_4$ = H
9: R$_1$ = R$_3$ = Me; R = R$_2$ = R$_4$ = H
10: R = R$_3$ = Me; R$_1$ = R$_2$ = R$_4$ = H
11: R = R$_2$ = Me; R$_1$ = R$_3$ = R$_4$ = H
12: R$_1$ = R$_3$ = R$_4$ = Me; R = R$_2$ = H

†C.D.R.I. Communication No. 2875.

Table 1. Tracer experiments on *C. laurifolius*

Expt.	Precursor fed	% Incorporation into laurifinine
1.	(L)-[U-^{14}C] Tyrosine	0.13
2.	(±)-[1-^{3}H]Norlaudanosoline(8)	0.32
3.	(±)-[1-^{3}H]N-Norprotosinomenine(9)	0.42
4.	(±)-[2',6',8-$^{3}H_3$] N-Nor-reticuline(10)	0.006
5.	(±)-[2',8-$^{3}H_2$] N-Nor-orientaline(11)	0.003
6.	(±)-[Aryl-^{3}H] Protosinomenine(12)	0.002
7.	[Aryl-^{3}H] N-[2-(3-Hydroxy-4-methoxyphenyl) ethyl]-2-(4'-hydroxyphenyl)ethylamine(7)	0.001
8.	(±)-[1-^{3}H, 7-methoxy-^{14}C] N-Norprotosinomenine(9) (^{14}C:^{3}H, 27:1)	0.52 (^{14}C:^{3}H, 29:1)
9.	(±)-[1-^{3}H, 4'-methoxy-^{14}C] N-Norprotosinomenine (^{14}C:^{3}H, 32:1)	0.39 (^{14}C:^{3}H, 30:1)
10.	(-)-(R)-[Aryl-^{3}H] N-Norprotosinomenine	0.01
11.	(+)-(S)-[Aryl-^{3}H] N-Norprotosinomenine(1)	0.84

The ^{14}C:^{3}H ratio in the precursor was 32:1 and in the biosynthetic **6**, 30:1. Cleavage of the OMe groups of the biosynthetic **6** by Ziezel method as above afforded radioactive methyl iodide which had, as expected, essentially half the molar activity of the parent base.

The foregoing experiments with doubly labelled (±)-N-nor-protosinomenines (**9**) established intact incorporation of **9** into **6**. The result also demonstrated that the H atom at the asymmetric centre C_1 and the OMe groups at C_7 and C_4' of nor-protosinomenine (**9**) are retained in the bioconversion of **9** into **6**. The results although established specific incorporation of nor-protosinomenine (**9**) into **6**, the precursors used, however, were racemic. Parallel feedings with (+)-N-nor-protosinomenine (**1**, expt 11) and (-)-N-norprotosinomenine (expt 10) demonstrated that the stereospecificity is maintained in the bioconversion of 1-benzylisoquinoline precursor into laurifinine. The former was incorporated about 84 times more efficiently than the latter.

Nor-protosinomenine (**9**) is stereospecifically incorporated into **6** and the presence of **9** in *C. laurifolius* is shown by trapping experiment by feeding labelled tyrosine. Thus **9** is a true precursor of **6**. The foregoing experiments thus strongly support the following sequence for the biosynthesis of laurifinine (**6**) in *C. laurifolius*.

Tyrosine⟶norlaudansoline (**8**)⟶(*S*)-N-norprotosinomenine (**1**)⟶laurifinine (**6**).

EXPERIMENTAL

For general directions (spectroscopy details and counting method) see Ref. 7.

Synthesis of precursors. The racemates of **9**,[7] **11**,[8] **10**,[9] **8**,[10] **12** and **7**[11] were prepared by the known procedures.

Resolution (±)-0,0-Dibenzyl-N-nor-protosinomenine was resolved by (+)- and (-)-dibenzoyltartaric acids according to the publication[13] to give (+)-, and (-)-0,0-dibenzyl-norprotosinomenines respectively.

(-)-N-*Norprotosinomenine.* (+)-0,0-Dibenzyl-N-norprotosinomenine (200 mg) in MeOH (5 ml) was heated at 100° for 1 hr with 12 N HCl (3 ml) to give (-)-N-nor-protosinomenine hydrochloride (115 mg), $[\alpha]_D$-18.8° (*c*, 1.8 in EtOH) (lit.[13]-18°, c, 1.7 in EtOH).

(+)-N-*Norprotosinomenine* (**1**). (-)-0,0-Dibenzyl-N-norprotosinomenine (150 mg) in MeOH (5 ml) was hydrogenalised with 12 N HCl (3 ml) to give (+)-N-norprotosinomenine hydrochloride (85 mg), $[\alpha]_D$+17° (*c*, 1.5 in EtOH) (lit.[13] 16°, *c* 1.7 in EtOH).

Labelling of precursors

Tritiation. (±) **10** (130 mg) in tritiated water 0.5 ml; activity 65 mCi) containing t-BuOK (200 mg) was heated under N_2 (sealed tube) for 110 hr at 100°. The resulting mixture was diluted with water, ammonium chloride was added (pH7) and the liberated base was extracted with $CHCl_3$ (4 × 10 ml). The $CHCl_3$ extract was washed with water, dried (Na_2SO_4) and the solvent removed. The crude product was chromatogrpahed on a column of neutral alumina. Elution with $CHCl_3$:MeOH (92:8) afforded the material which was further purified through its hydrochloride to give (±)-[2',6',8-$^{3}H_3$] nor-reticuline (**10**) [2',6',8-^{3}H] Nor-orientaline (**11**) was similarly prepared.

(±)-[*Aryl-^{3}H*] N-*norprotosinomenine* (**9**). $SOCl_2$ (0.1 ml) was added to tritiated water (0.5 ml, activity 80 mCi). To it was added (±)-**9** (100 mg) and the resulting mixture was heated under N_2 (sealed tube) at 100° for 95 hr. Water was added to the resulting mixture and basified with $NaHCO_3$ aq. The liberated base was extracted with $CHCl_3$, washed with water, dried (Na_2SO_4) and the solvent removed. The residue was dissolved in EtOH and treated with ethereal HCl to give (±)-**9** hydrochloride (65 mg), crystallised from EtOH–ether to constant activity.

[Aryl-^{3}H] N-[2-(3-Hydroxy-4-methoxyphenyl)ethyl]-2-(4'-hydroxyphenyl) ethylamine (**7**), (+)-, and (-)-[aryl-^{3}H] N-nor-protosinomenine and (±)-[aryl-^{3}H] protosinomenine were prepared in the similar manner as above.

(±)-[1-^{3}H] Norlaudanosoline (**8**), and (±)-[1-^{3}H] N-nor-protosinomenine (**9**) were prepared by reduction of the corresponding dihydroisoquinoline derivatives in dry dimethyl formamide with sodium-[^{3}H] borohydride.

(±)-[4'-methoxy-^{14}C]-, and [7-methoxy-^{14}C]-N-norprotosinomenines were prepared by complete syntheses. (±)-[1-^{3}H, 4'-methoxy-^{14}C] N-Norprotosinomenine was prepared by mixing (±)-[4'-methoxy-^{14}C] N-norprotosinomenine and (±)-[1-^{3}H] N-norprotosinomenine. (±)-[1-^{3}H, 7-methoxy-^{14}C] N-Norprotosinomenine was prepared by mixing (±)-[7-methoxy-^{14}C] N-norprotosinomenine and (±)-N-[1-^{3}H] norprotosinomenine.

Feeding of tyrosine. Young cut branches of *C. laurifolius* were dipped into an aqueous soln (1 ml) of (L)-[U-^{14}C] tyrosine (activity 0.1 mCi) (expt 1). When uptake was complete, water was added for washing. The twigs were kept alive for 8 days and then harvested. The plant material (139 g wet wt) was macerated in MeOH (300 ml) with radioinactive laurifinine (85 mg) and left for 18 hr. The MeOH was then decanted and the plant material was percolated with fresh MeOH (4 × 200 ml). The solvent from the methanolic extract was removed *in vacuo* to give greenish viscous residue which was extracted with 5% HCl (5 × 10 ml). The acidic extract was defatted with petroleum ether (5 × 10 ml) and then basified with Na_2CO_3. The liberated bases were extracted with $CHCl_3$ (5 × 15 ml), washed with water, dried (Na_2SO_4) and the solvent removed to yield crude base (80 mg). The crude base was subjected to preparative silica gel chromatography (solvent: $CHCl_3$:MeOH, 90:10) to give **6** (50 mg) (specific activity 3.40 × 10^3 disint. min^{-1} mg.$^{-1}$); base perchlorate m.p. 244–245°(lit.[1] 243–245°). The radio chemical purity of the radioactive biosynthetic laurifinine was checked by the dilution method.

Feeding of (±)-[1-^{3}H] *Norlaudanosoline* (**8**) Young cut branches of *C. laurifolius* were dipped into a soln of (±)-[1-^{3}H] norlaudanosoline (**8**) hydrochloride (13.2 mg, activity 0.05 mCi, expt 2) in water (1 ml) containing dimethyl sulphoxide (0.2 ml). When uptake was complete, the twigs were dipped into water, left for 8 days and harvested. The plant material (147 g wet wt) was macerated in MeOH (300 ml) with radioinactive laurifinine (81 mg) and then extracted with MeOH (4 × 200 ml). The methanolic extract was worked up as above to give radioactive **6** (47 mg, specific activity, 4.37 × 10^3 disint. min.$^{-1}$ mg^{-1}).

Feeding of (±)-[1-^{3}H] N-*norprotosinomenine* (**9**). Young cut branches of *C. laurifolius* were dipped into a soln of (±)-[1-^{3}H] N-norprotosinomenine (**9**) hydrochloride (3.8 mg, activity 0.11 mCi, experiment 3) in water (1 ml) containing tartaric acid (10 mg). When uptake was complete the twigs were dipped into water, left for 8 days and harvested. The plant material (129 g wet wt) was macerated in MeOH (300 ml) with radioinactive laurifinine (75.5 mg) and then extracted with MeOH (4 × 200 ml). The methanolic extract was worked up as above to give radioactive **6** (45 mg, specific activity 1.36 × 10^4 disint. min.$^{-1}$ mg^{-1}).

Feeding of (±)-[2′,6′,8-$^3H_3$] N-*norreticuline* (**10**). Young cut branches of *C. laurifolius* were dipped into a soln of (±)-[2′,6′,8-$^3H_3$] N-norreticuline (**10**) (8.6 mg, activity 0.3 mCi, experiment 4) in water (1 ml) containing tartaric acid (12 mg). When uptake was complete, the twigs were dipped into water, left for 8 days and harvested. The plant material (143 g wet wt) was macerated in MeOH (300 ml) with radioinactive laurifinine (80 mg) and extracted with MeOH (4 × 200 ml). The methanolic extract was worked up in the usual manner to give **6** (46 mg, specific activity 4.98 × 10^2 disint. min.$^{-1}$ mg^{-1}).

Feeding of (±)-[3′,8-$^3H_2$] N-*nororientaline* (**11**). Young cut branches of *C. laurifolius* were dipped into a soln of (±)-[3′,8-$^3H_2$] N-nororientaline (**11**) (7.4 mg, activity 0.35 mCi expt 5) in water (1 ml) containing dimethyl sulphoxide (0.2 ml). When uptake was complete, the twigs were dipped into water, left for 8 days and harvested. The plant material (139 g wet wt) was macerated in MeOH (300 ml) with radioinactive **6** (79 mg) and extracted with MeOH (4 × 200 ml). The methanolic extract was worked up in the usual manner to give **6** (47 mg, specific activity 2.96 × 10^2 disint. min.$^{-1}$ mg^{-1}).

Feeding of (±)-[*aryl*-^{3}H] *protosinomenine* (**12**). Young cut branches of *C. laurifolius* were dipped into a soln of (±)-[aryl-^{3}H] protosinomenine (**12**) (10.8 mg, activity 0.45 mCi, expt 6) in water (1 ml) containing tartaric acid (12 mg). When uptake was complete, the twigs were dipped into water, left for 8 days and harvested. The plant material (123 g wet wt) was macerated in MeOH (300 ml) with radioinactive **6** (74.4 mg) and extracted with MeOH (4 × 200 ml). The methanolic extract was worked up in the usual manner to give **6** (44.3 mg, specific activity 2.69 × 10^2 disint. min.$^{-1}$ mg^{-1}).

Feeding of [*aryl*-^{3}H] N-[2-(3-hydroxy-4-methoxyphenyl) ethyl]-2-(4′-hydroxyphenyl)ethylamine (**7**). Young cut branches of *C. laurifolius* were dipped into a soln of [aryl-^{3}H] N-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-2-(4′-hydroxyphenyl) ethylamine (**7**) (12.1 mg, activity 0.3 mCi, expt 7) in water (1 ml) containing dimethyl sulphoxide (0.2 ml). When uptake was complete the twigs were dipped into water, left for 8 days and harvested. The plant material (145 g wet wt) was macerated in MeOH (300 ml) with radioinactive **6** (76.2 mg) and extracted with MeOH (4 × 200 ml). The methanolic extract was worked up in the usual manner to give **6** (44.2 mg, specific activity 87 disint. min.$^{-1}$ mg^{-1}).

Feeding of (±)-[1-^{3}H, 7-*methoxy*-^{14}C] N-*norprotosinomenine* (**9**). Young cut branches of *C. laurifolius* were dipped into a soln of (±)-[1-^{3}H, 7-methoxy-^{14}C] N-norprotosinomenine (**9**) hydrochloride (15 mg, ^{3}H activity 0.06 mCi; ^{14}C activity 0.00223 mCi; ^{3}H: ^{14}C, 27:1; expt 8) in water (1 ml) containing dimethyl sulphoxide (0.2 ml). When uptake was complete, the twigs were dipped into water, left for 8 days and harvested. The plant material (149 g wet wt) was macerated in MeOH (300 ml) with radioinactive laurifinine (78.2 mg) and extracted with MeOH (4 × 200 ml). The methanolic extract was worked up in the usual manner to give radioactive **6** (46.3 mg, ^{3}H activity 8.85 × 10^3 disint. min.$^{-1}$ mg^{-1}; ^{14}C specific activity 3.05 × 10^2 disint. min.$^{-1}$ mg^{-1}; ^{3}H: ^{14}C 29:1).

Feeding of (±)-[1-^{3}H, 4′-*methoxy*-^{14}C] N-*norprotosinomenine* (**9**). Young cut branches of *C. laurifolius* were dipped into a soln of (±)-[1-^{3}H, 4′-methoxy-^{14}C] N-norprotosinomenine (**9**) hydrochloride (19 mg, ^{3}H activity 0.068 mCi; ^{14}C activity 0.00213 mCi, ^{3}H: ^{14}C, 32:1, expt 9) in water (1 ml) containing tartaric acid (12 mg). When uptake was complete, the twigs were dipped into water, left for 8 days and harvested. The plant material (140 g wet wt) was macerated in MeOH (300 ml) with radioinactive **6** (72.2 mg) and extracted with MeOH (4 × 200 ml). The methanolic extract was worked up in the usual manner to give radioactive **6** (45.5 mg, ^{3}H, activity 8.15 × 10^3 disint. min.$^{-1}$ mg.$^{-1}$; ^{14}C specific activity 2.72 × 10^2 disint. min.$^{-1}$ mg.$^{-1}$, ^{3}H: ^{14}C, 30:1).

Feeding of (−)-(R)-[*aryl*-^{3}H] N-*norprotosinomenine.* Young cut branches of *C. laurifolius* were dipped into a soln of (−)-(*R*)-[aryl-^{3}H] N-norprotosinomenine hydrochloride (12 mg, activity 0.121 mCi, expt 10) in water (1 ml) containing tartaric acid (12 mg). When uptake was complete, the twigs were dipped into water, left for 8 days and harvested. The plant material (149 g wet wt) was macerated in MeOH (300 ml) with radioinactive laurifinine (80 mg) and extracted with MeOH (4 × 200 ml). The methanolic extract was worked up in the usual manner to give **6** (47.2 mg, specific activity 3.35 × 10^2 disint. min.$^{-1}$ mg.$^{-1}$).

Feeding of (+)-(S)-[*aryl*-^{3}H] N-*norprotosinomenine* (**1**). Young cut branches of *C. laurifolius* were dipped into a soln of (+)-(*S*)-[aryl-^{3}H] N-norprotosinomenine (**1**) hydrochloride (10 mg, activity 0.1 mCi, expt 11) in water (1 ml) containing tartaric acid (12 mg). When uptake was complete, the twigs were dipped into water, left for 8 days and harvested. The plant material (157 g wet wt) was macerated in MeOH (300 ml) with radioinactive **6** (82.2 mg) and extracted with MeOH (4 × 200 ml). The methanolic extract was worked up in the usual manner to give radioactive **6** (48.6 mg, specific activity 2.27 × 10^4 disint. min.$^{-1}$ mg.$^{-1}$).

Degradation of labelled laurifinine derived from the feeding of (±)-[1-^{3}H, 7-*methoxy*-^{14}C] N-*norprotosinomenine.* A mixture of labelled **6** (22 mg; ^{14}C molar activity 1.03 × 10^5 disint. min.$^{-1}$ m mol^{-1}, expt 8), phenol (70 mg), propionic anhydride (270 mg) and freshly distilled HI (55%, 2.8 ml) in an atmosphere of N_2 was gently refluxed for 45 min. The radioactive MeI, so formed, was collected in a soln of Et_3N in EtOH (1:9, 10 ml). Worked up in the usual way gave radioactive *triethylmethylammonium iodide* (12 mg, ^{14}C molar activity 0.5 × 10^5 disint. min.$^{-1}$ mmol.$^{-1}$).

Degradation of labelled laurifinine derived from the feeding of (±)-[1-^{3}H, 4′-*methoxy*-^{14}C]N-*norprotosinomenine.* A mixture of labelled **6** (28 mg, ^{14}C molar activity 7.975 × 10^4 disint. min^{-1} mmol^{-1}, expt 9) phenol (61 mg), propionic anhydride (262 mg) and freshly distilled HI (55%, 2.5 ml) in an atmosphere of N_2 was gently refluxed for 45 min to give radioactive MeI trapped as radioactive *triethylmethylammonium iodide* (15 mg, ^{14}C molar activity 3.86 × 10^4 disint. min^{-1} mmol.$^{-1}$).

Trapping experiment. Young cut branches of *C. laurifolius* plant were dipped into an aqueous soln (1 ml) of (L)-[U-^{14}C] tyrosine (0.1 mCi). When uptake was complete, water was added for washing. The twigs were then dipped into water, left for 8

days and harvested. The plant material (125 g wet wt) was macerated in MeOH (300 ml) with radioinactive (±)-N-norprotosinomenine (110 mg) (dissolved in 2% HCl in MeOH) and left for 5 hr. The MeOH was decanted and the plant material was percolated with fresh MeOH (4 × 200 ml) containing conc HCl (1 ml). The combined percolate was concentrated *in vacuo*, diluted with water (30 ml) and extracted with ether (4 × 30 ml). The defatted acidic soln was basified with $NaHCO_3$ aq. The liberated bases were extracted with $CHCl_3$:MeOH (90:10; 4 × 25 *ml*). The combined extract was washed with water, dried and evaporated to give the crude base, which was treated with ethereal HCl to give *N-norprotosinomenine* hydrochloride (55 mg), m.p. 239–240° (lit,[14] 241°), which was crystallized from MeOH ether to constant activity; specific activity 9.21×10^3 disint. min^{-1} mg^{-1}; incorporation 0.47%).

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