Syntheses of Carpyrinic Acid and of Related Pyridines with Long Aliphatik Chains

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Four different syntheses of carpyrinic acid, i.e. 8-(5-hydroxy-6-methyl-2-pyridyl)octanoic acid, are reviewed in this paper and the synthetic value of individual steps is compared and discussed.

The synthesis of another type of a long-chain pyridine derivative is presented, namely that of dehydroprosopine [5-hydroxy-2-(11-hydroxydodecyl)-6-hydroxymethylpyridine] which is a key intermediate in the total synthesis of the alkaloids prosopine and prosopinine.

Finally, the syntheses of the ant venoms of related structures via the corresponding pyridines are reviewed. The long-chain pyridines are potential intermediates for a large group of piperidine derivatives of considerable and manyfold biological interest.

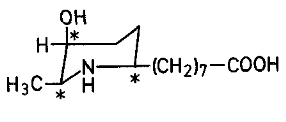
Es werden vier verschiedene Synthesen von Carpyrinsäure 8-(5-Hydroxy-6-methyl-2-pyridyl)octansäure beschrieben und der synthetische Wert einzelner Schritte innerhalb dieser Synthesen miteinander verglichen und erörtert.

Ferner wird die Synthese eines langkettigen Pyridinderivates einer anderen Substanzklasse, und zwar von Dehydroprosopin [5-hydroxy-2-(11-hydroxydodecyl)-6-hydroxymethylpyridine], aufgezeigt. Diese Verbindung ist ein wichtiges Zwischenprodukt bei der Totalsynthese der Alkaloide Prosopin und Prosopinin.

Es werden schließlich die Synthesen der Ameisengifte (letztere besitzen eine verwandte Struktur), die über die entsprechenden Pyridine ablaufen, beschrieben. Die langkettigen Pyridine stellen mögliche Zwischenprodukte für eine sehr große Zahl von Piperidinderivaten dar, die in vieler Hinsicht beträchtliches biologisches Interesse besitzen.

Nature produces a number of piperidines having a long side chain. Among these compounds, the structure of carpaine being a dimeric[1] lactone[21] of carpamic acid (**1**) was completely elucidated as late as 1964. Since then, a number of related polyfunctional piperidine alkaloids such as cassine[2], carnavaline[3], prosopine and prosopinine[4] containing a C_{12}-side chain as contrasted with the C_8-side chain of carpaine have been isolated from Cassia and Prosopis plant families. Lately, five new alkaloids of fire ant[5,6] venom have proved to be 6-substituted 2-methylpiperidines[7,8] possessing a saturated C_{11}, C_{13} or C_{15} or an unsaturated C_{13} or C_{15} side chain. Carpaine shows antituberculotic[9], digitalis-like[10] and hypotensive[10] effects. Prosopine and prosopinine display local anesthetic[11,12], analgesic[13], and antibiotic[14] activity. The ant venoms are, depending on the concentration, hemolytic[6], antibiotic[5], or insecticidal agents.

Among all these alkaloids of considerable biological interest, only those of *Solenopsis saevissima* which do not have auxiliary functional groups have been synthesized[8] to date, while the others have escaped synthesis, probably owing to their more complex stereochemistry. Carpaine has been correlated[15] at C-5 with R(−)tetradecanol. Also, it has been established that carpaine is an *all-cis* derivative[16,17], like cassine (**2**) (carnavaline is most probably the alcohol corresponding to **2** or to its antipode) the antipode of which has been synthesized[18] from carpaine. By analogy, but without rigorous proof, it is assumed[4] that members of the prosopine group (**3**, **4**) *have the same structural feature.*



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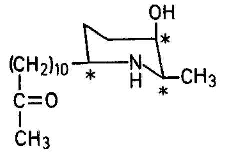

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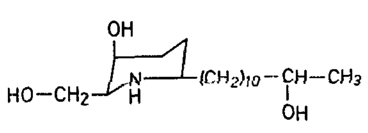

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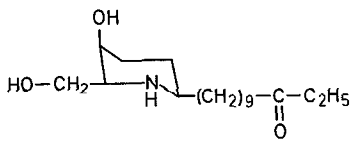

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Therefore, we have decided to synthesize the whole group of piperidines via the corresponding pyridines through sterically controlled hydrogenation, i.e., by blocking one side of the pyridine system to free access by hydrogen from the catalyst.

Although the hydrogenation route seems logical, there is but one attempt[19] to obtain carpamic acid in this manner from carpyrinic acid (5). Failure of that approach was probably due to the lack of control in stereoselectivity of hydrogenation (carpamic acid has three asymmetric centers); hence, any of the four possible racements can be formed.

The low yields involved in the synthesis of carpyrinic acid may well have added to the problem of obtaining reproducible amounts of this key intermediate. Therefore, practical synthetic routes had to be elaborated first for the long-chain pyridines.

In this review, we compare the results of these routes with those of previous syntheses of dehydrocarpamic acid, i.e. carpyrinic acid having a C_8-side chain. Also, the first, moreover practical synthesis of dehydroprosopine (6, Scheme E) is described. The latter compound contains a C_{12} chain which is functionalized such that it can be used as an intermediate for a general synthesis of the C_{12} piperidines.

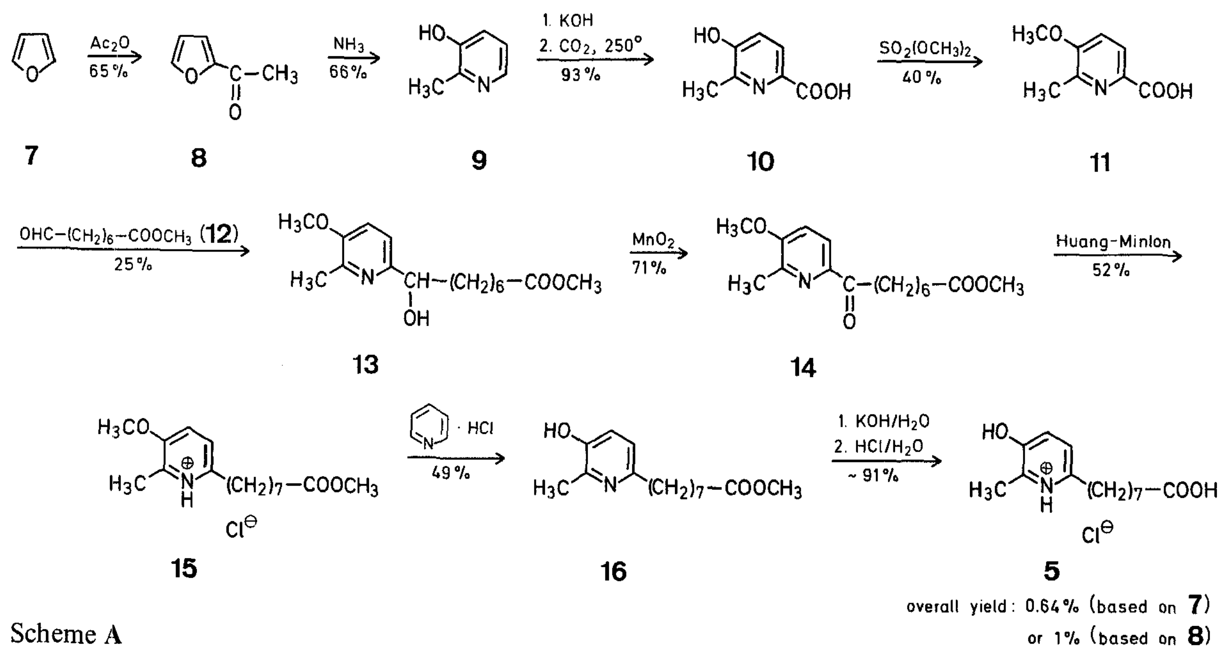
1. Syntheses of Carpyrinic Acid

Without going into details of elucidating the structure of carpaine, which involved G. Barger, R. Robinson[20], and lately of H. Rapoport's[21,22] and T. R. Govindachari's groups[17,19], it should be mentioned that carpyrinic acid ester was first obtained by Pd/charcoal dehydrogenation of ethyl carpamate and that it proved to be ethyl 8-(5-hydroxy-6-methyl-2-pyridyl)-octanoate (**24c**).

1.1. Rapoport's Synthesis

The first synthesis of **5** as a structural proof was realized by Rapoport's[22] group, started from furan (**7**) and is described in Scheme **A**.

Rearrangement by ammonolysis of 2-acetylfuran (**8**) to 3-hydroxy-2-methylpyridine (**9**) is followed by a Kolbe synthesis and protective methylation of the hydroxy group to give 5-methoxy-6-methyl-2-pyridine carboxylic acid (**11**). The subsequent Hammick condensation[23] of **11** with methyl suberic ester aldehyde (**12**, prepared by partial reduction of the methyl ester chloride) to methyl 8-hydroxy-8-(5-methoxy-6-methyl-2-pyridyl)octanoate (**13**) represents an elegant step in the total synthesis of **5**.



Scheme A

Unfortunately, the yield is rather low at this stage. The next step involves oxidation of the hydroxy group to give compound **14** the Huang-Minlon reduction of which affords the pyridine hydrochloride ester **15**. Demethylation of **15** to **16** followed by hydrolysis of the methoxycarbonyl group gives carpyrinic acid hydrochloride **5** in approximately 0.6% (based on furan) or 1% (based on acetylfuran) overall yield.

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[1] M. Spitteler-Friedmann, G. Spitteler, Monatsh. Chem. **95**, 1234 (1964).

[2] R. J. Highet, J. Org. Chem. **29**, 471 (1964); R. J. Highet, P. F. Highet, J. Org. Chem. **31**, 1275 (1966).

[3] D. Lythgoe, M. J. Vernengo, Tetrahedron Lett. **1967**, 1133.

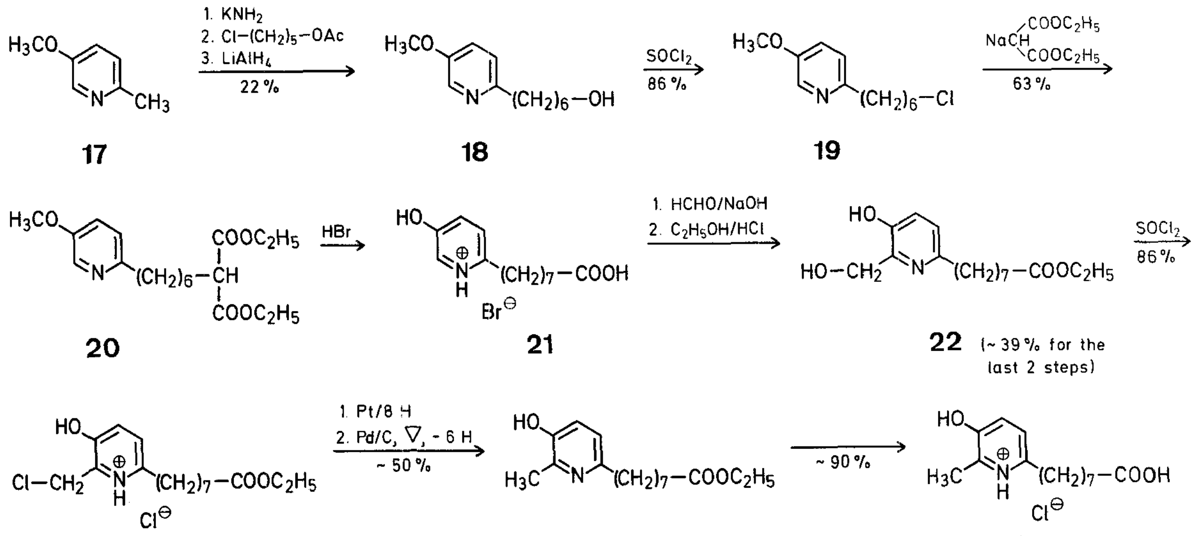
[4] G. Ratle, X. Montseur, B. C. Das, J. Yassi, Q. Khuong-Huu, R. Goutarel, Bull Soc. Chim. France **1966**, 2945.

[5] M. S. Blum, J. R. Walker, P. S. Callahan, A. F. Novak, Science **128**, 306 (1958).

[6] G. A. Adrouny, V. J. Derbes, R. C. Jung, Science **130**, 449 (1959).

1.2. Govindachari's Synthesis

The second synthesis achieved by Govindachari's group[19] was closer to a practical preparation (Scheme **B**).



overall yield: 1.76 % (based on **17**)

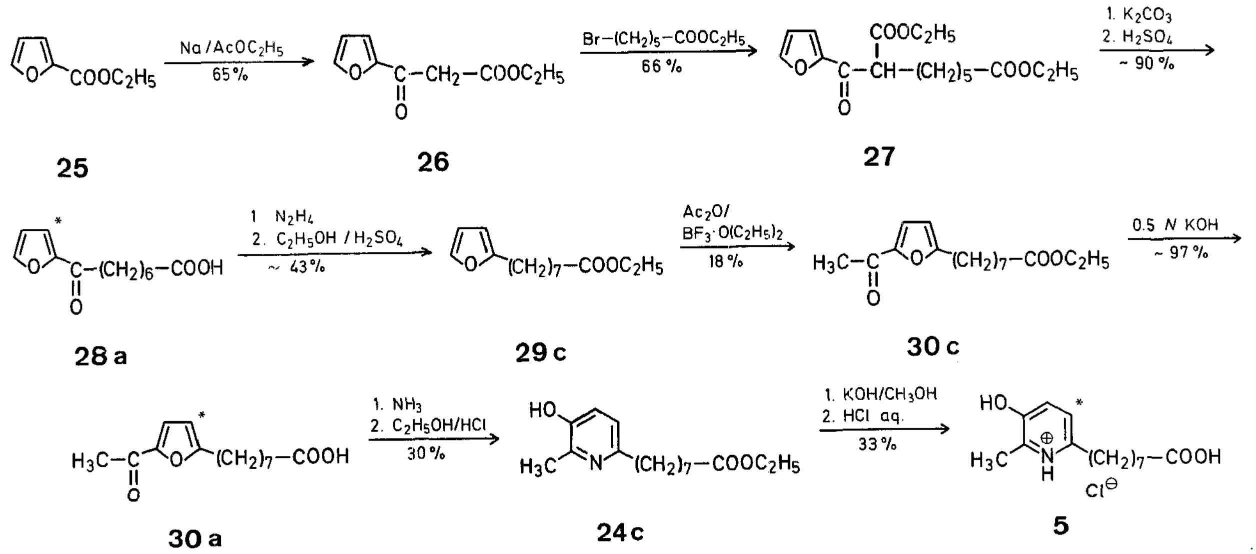
Scheme **B**

Starting from 5-methoxy-2-methylpyridine (**17**), a C_5-chain is introduced to afford compound **19**. The alkyl side chain is then extended by two carbon atoms using sodium diethyl malonate. Hydrolysis and decarboxylation of the resultant compound **20** yields **21** which is hydroxymethylated on the ring at C-6 on treatment with alkaline formaldehyde solution. The hydroxymethyl group is converted into a chloromethyl group (**22** to **23**). Hydrogenolysis of the C—Cl bond (**23** to **24c**) by means of platinum involving complete hydrogenation of the pyridine ring followed by palladium-dehydrogenation affords the pyridine **24c**. Unfortunately, no yields are reported for either steps **21** to **22**, or for **23** to **5**. We have assumed by analogy that the reaction **22** to **23** gives about 86% yield and that hydrogenolysis and subsequent dehydrogenation of the piperidine ring gives about 50% yield, and finally that hydrolysis (**24c** to **5**) proceeds nearly quantitatively (90% yield).

The estimated overall yield of carpyrinic acid is 1,76%.

1.3. Gruber's Synthesis[24]

Gruber's approach which is illustrated by Scheme **C** starts from ethyl furoate (**25**) and presents a novel combination of steps. Carpyrinic acid itself has been synthesized by that route. At some stages, our estimate in yield is chiefly based on the assumption that a change in chain length does not significantly affect the yields of the individual steps. An asterisk designates compounds which are lower or higher homologs of the intermediate that would be required for an analogous synthesis of carpyrinic acid.



overall yield: 34% (based on 2-furoic acid)

Scheme **C**

Starting from compound **25**, the reaction sequence of scheme **3** involves formation of 8-(2-furyl)-8-oxo-octanoic acid (**28a**) proceeding via **26** and **27**; **28a** is then reduced by the Huang-Minlon method to 8-(2-furyl)octanoic acid (**29a**) which is converted into its ethyl ester (**29c**). This ester is acetylated on the furan ring at C-5 to afford ethyl 8-(5-acetyl-2-furyl)octanoate (**30c**). Assuming that hydrolysis of the latter is nearly quantitative and that rearrangement of **30a** to 8-(5-hydroxy-6-methyl-2-pyridyl)octanoic acid **5** occurs with a yield comparable to that of the C_6-acid, a total yield of 0.34% (based on furoic acid) for **5** can be calculated. The yield is somewhat improved by proceeding through carpyrinic acid amide, but its hydrolysis involves an additional step.

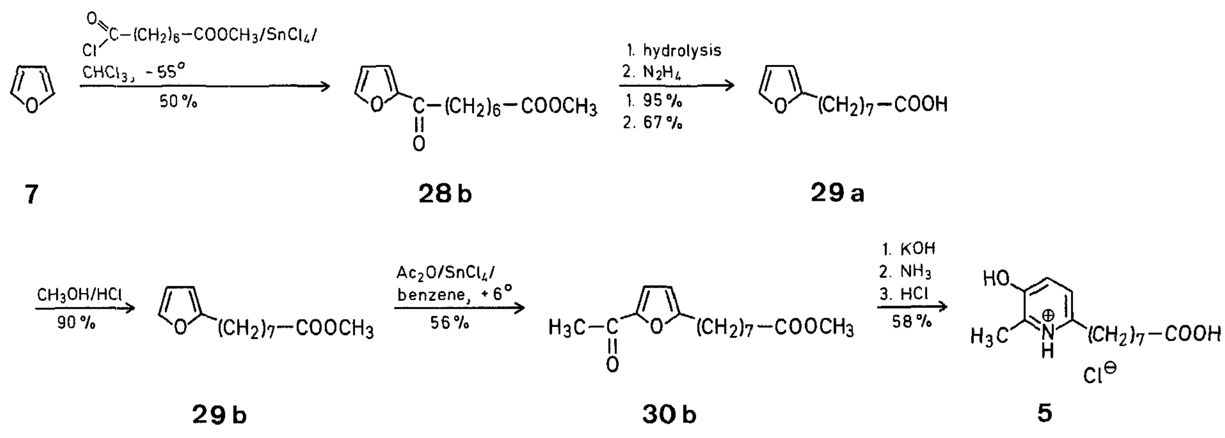
Although this scheme does not promise good yields, one step deserves special mention, namely the conversion of the acylfuran (**30a**) to the corresponding 3-hydroxypyridine which is carried out at the last stage when all substituents (or their precursors) of carpyrinic acid are already attached to the furan skeleton. A critical survey of Schemes **2** and **3** further reveals:

- the method for preparing **5** can only be considerably improved if the number of steps is drastically reduced;
- the more reactive furan seems to be a more suitable starting material since it can attach desirable groups more selectively than the pyridine nucleus.

Therefore, we tried to undertake a more direct synthesis of 8-(2-furyl)octanoic acid (**29a**) and of its methyl ester (**29b**) and to improve the yields of several steps, in particular that of the acetylation of the 8-(2-furyl)octanoic ester (**29b**, **c** to **30b**, **c**).

1.4. A Novel Synthesis

In order to achieve these two goals we have attempted to attach the C_8-chain directly to the furan ring. Since, however, Friedel-Crafts alkylation of furan is rarely successful[26], we decided to introduce the C-8 moiety by reaction of furan with suberic ester chloride[27] (**7** to **28b,c**) instead of attempting alkylation with an 8-chloro (or bromo) octanoic ester to **29b,c** (Scheme **D**).



overall yield: 9%
(based on methyl
7-chlorocarbonylheptanoate)

Scheme **D**

No such case is known for furan and its alkyl homolog except for C-acylations with monocarboxylic acid chlorides; yields of ketones ranging from 21 to 52% are reported when anhydrous aluminum chloride is employed. Reaction of benzofuran affords somewhat better yields[28]. On the other hand, thiophene, which is much more stable than furan, reacts with methyl 7-chlorocarbonylheptanoate and tin(IV) chloride in benzene to give 67–69% yield of methyl 8-oxo-8-(2-thienyl)-octanoate[29,30,31].

We have made a systematic study of catalysts, solvents, temperature and sequence of addition for the formation of **28b** from **7** (Scheme **D**).

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[7] J. G. McConnell, M. S. Blum, H. M. Fales, Science **168**, 840 (1970).

[8] J. G. McConnell, M. S. Blum, H. M. Fales, Tetrahedron **27**, 1129 (1971).

[9] A. S. Ramaswany, M. Sirsi, Ind. J. Pharm. **22**, 34 (1960).

[10] I. G. Noble, Anales acad. cienc. med., fis. y nat. Habana **85**, 198 (1946–47).

[11] P. Bourinet, A. Quevauviller, C. R. Soc. Biol. France, **162**, 1138 (1968).

[12] P. Bourinet, A. Quevauviller, Ann. Pharm. France **26**, 787 (1968).

[13] C. R. Craig, Department of Pharmacology, West Virginia University, private communication.

[14] J. M. Slack, Department of Microbiology, West Virginia University, private communication.

[15] J. L. Coke, W. Y. Rice, J. Org. Chem. **30**, 3420 (1965).

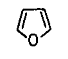
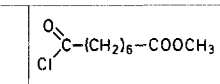
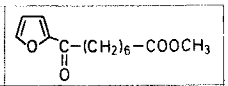
[16] M. Tichy, J. Sicher, Tetrahedron Lett. **1962**, 511.

[17] J. R. Govindachari, N. S. Narasimham, J. Chem. Soc. **1955**, 1563.

[18] W. Y. Rice, J. L. Coke, J. Org. Chem. **31**, 1210 (1966).

[19] T. R. Govindachari, N. S. Narasimham, S. Rajadurai, J. Chem. Soc. **1957**, 560.

Table 1. Reaction of Furan with Methyl 7-Chlorocarbonylheptanoate

		 $ClC(=O)-(CH_2)_6-COOCH_3$		$SnCl_4$		Solvent	Temperature	 $C_4H_3O-C(=O)-(CH_2)_6-COOCH_3$	
g	mol	g	mol	g	mol		°C	g	yield %
24.5	0.36	25.3	0.123	32.0	0.123	$CHCl_3$	−30	14.3	49.0
24.5	0.36	24.1	0.116	30.2	0.116	$CHCl_3$	−50	14.5[a]	52.1
110.0	1.615	103.2	0.500	130.0	0.500	$CHCl_3$	−50	55.3	46.5
24.6	0.362	25.0	0.121	31.5	0.121	CCl_4	−40	9.0	35.9
25.0	0.367	25.3	0.123	32.0	0.123	C_6H_6	+2	4.5	15.3

[a] Purified by chromatography on neutral alumina.

The data in Table 1 show that the use of tin(IV) chloride in chloroform at −50° gives rise to optimum yields of about 50% after purification on alumina. Considering the fact that utilizing Gruber's[24] route, compound **28c** has been prepared in four steps with an estimated yield of 31%, this improvement is appreciable. Further, this route requires fewer manipulations.

Conversion of the keto ester **28b** into **29a** by the Huang-Minlon reduction has been extensively studied. The use of better techniques allows to increase the yield of 8-(2-furyl)octanoic acid from 43 to 70%.

The crucial step is the introduction of the acetyl group into the 4-position of **29a, b, c**. Again, optimum conditions have been selected. Acetic anhydride in benzene in the presence of tin(IV) chloride as the catalyst affords a 56% yield of **30a** instead of 18% as reported by Gruber who used boron trifluoride for the preparation of 8-(5-acetyl-2-furyl)octanoic acid[24].

Finally, ammonolysis and rearrangement of **30b** to carpyrinic acid has been achieved in 58% yield. Gruber[24] has reported a yield of 30% for a similar interconversion.

Hence, the overall yield of **5** is 9% (based on methyl 7-chlorocarbonylheptanoate, see Scheme **D**). It follows a systematic study of the hydrogenation leading to piperidines.

All compounds described in the experimental procedures were duly characterized both by elemental analyses and spectral data although not all are being reported.

Methyl 8-(2-Furyl)-8-oxooctanoate (28b):

Freshly distilled furan (24.48 g, 0.36 mol) is dissolved in dry chloroform (200 ml) and cooled to −50°. Methyl 7-chlorocarbonylheptanoate (24.12 g, 0.12 mol) in dry chloroform (60 ml) is added under nitrogen during 25 min with vigorous stirring. The colorless solution is stirred for additional 30 min. Then, anhydrous tin(IV) chloride (15 ml, 0.12 mol) dissolved in chloroform (25 ml) is added dropwise over 45 min. The resultant yellow suspension is stirred for 6 hr at −50° and kept overnight below −60°. Finally, 6 *N* sulfuric acid (60 ml) is added over 45 min to give a deep-blue colored complex salt. The solid is filtered and triturated 3 times with 15 ml 6 *N* sulfuric acid and chloroform. The combined chloroform extracts are washed with a 2 *N* potassium bicarbonate solution, then with water, and dried ($MgSO_4$). Evaporation of the solvent gives 20.4 g of a thick yellow oil, which is chromatographed over a 60 cm column (3 cm diameter) filled with 200 g of neutral alumina, using benzene as the eluent. The second fraction affords product **28b**; yield: 14.5 g (50%).

I. R. (film): 1740 (CO-ester); 1680 (ketone); 1570 and 885 cm^{-1} (furan).

N.M.R. (CCl_4): 7.52 (d, 1 H, H-5); 7.10 (d, 1 H, H-3); 6.50 (q, 1 H, H-4) (furan); 3.59 (s, 3 H, OCH_3); 2.90–1.10 ppm (m, 12 H, methylene).

Using 110 g furan and 103 g methyl 7-chlorocarbonylheptanoate under the conditions described above, 55.3 g (48.8%) **28b** is obtained after purification by distillation, instead of column chromatography. Further data are listed in Table 1.

8-(Furyl)-8-oxooctanoic Acid (28a):

Ester **28b** (64.0 g, 0.269 mol) is refluxed with 1 *N* potassium hydroxide (700 ml) in methanol for 2.5 hr and then evaporated to dryness. The residue is dissolved in water (20 ml) and carefully acidified with 2 *N* hydrochloric acid while cooling with ice. The precipitated solid is extracted with ether, washed with water, and dried ($MgSO_4$). Evaporation of the solvent gives the acid **28a**; yield: 57.3 g (96%); m.p. 58–62°. Gruber[24] has recorded m.p. 63–65°.

I.R. (KBr): 1700, 1680 and 1770 (COOH and CO); 1585, 1520 and 895 cm^{-1} (furan).

N.M.R. (CCl_4): 11.73 (1 H, COOH); 7.45 (d, 1 H, H-5); 7.02 (d, 1 H, H-3); 6.41 (q, 1 H, H-4, furan); 2.85–1.0 ppm (m, 12 H, CH_2).

8-(2-Furyl)octanoic Acid (29a):

A mixture of acid **28a** (57.0 g, 0.254 mol), 70% hydrazine hydrate (57 g, 1.22 mol) and sodium hydroxide (57 g, 1.4 mol) in ethylene glycol (1.5 l) is heated for 18 hr to 170–180°. Work-up of the reaction mixture is performed in the usual manner for Huang-Minlon reductions[22,24]. Further purification is achieved by distillation under 0.1 mm pressure from an oil bath at 150° to give a colorless liquid which solidified at room temperature; yield: 66.5%; m.p. 30°; Gruber[24] has described "Furylcaprylsäure" as an oil, and has prepared its crystalline S-benzylisothiuronium salt; m.p. 130°.

$C_{12}H_{18}O_3$	calc.	C 68.55	H 8.63	O 22.83%
(210.27)	found	68.72	8.70	22.77%

I.R. (KBr), 1720 (COOH); 1580 and 885 cm^{-1} (furan).

N.M.R. (CCl_4); 12.08 (1 H, COOH); 7.10 (d, 1 H, H-5); 6.10 (d, 1 H, H-3); and 5.80 (q, 1 H, H-4, furan); 1.10 ppm (m, 14 H, CH_2).

Methyl 8-(2-Furyl)octanoate (29b)

The acid **29a** (49.1 g) is dissolved in a mixture of methanol (400 ml), benzene (1000 ml) and 10 drops of conc. sulfuric acid and refluxed for 12 hr on a rotary evaporator. The solvent is thus removed and the residue dissolved in ether (500 ml), and washed twice with 2 *N* potassium bicarbonate solution (500 ml), then three times with a saturated sodium chloride solution (100 ml), and finally dried ($MgSO_4$).

Distillation gives **29b**; yield: 51.1 g (90%); b.p. 72–75°/0.005 mm.

I.R. (film): 1740 (CO ester); 1595, 1508 and 882 cm^{-1} (furan).

N.M.R. (CCl_4): 7.25 (d, 1 H, H-5); 6.15 (d, 1 H, H-3); 5.80 (q, 1 H, H-4, furan); 3.60 (s, 3 H, OCH_3); 2.75–1.10 ppm (s, 14 H, CH_2).

Methyl 8-(5-Acetyl-2-furyl)octanoate (30b):

A solution of the ester **29b** (30.5 g, 0.117 mol) in dry benzene

(1200 ml) is cooled with ice to 6–7°. A solution of acetic anhydride (13.8 g, 0.117 mol) in dry benzene (150 ml) cooled with ice is added dropwise with vigorous stirring under nitrogen and the mixture is stirred for 15 min. Thereafter, a solution of anhydrous tin(IV) chloride (18.83 ml, 0.117 mol) in dry benzene (150 ml) is added during 1 hr and the mixture is kept at 7° for 1 hr, then ice (600 g) is added to decompose the complex. The aqueous solution is decanted and extracted two times with benzene (100 ml). The benzene layers are combined, washed three times with a total of 1500 ml of 2*N* potassium bicarbonate solution, then with water (1,5 l) and dried (Na_2SO_4). Distillation gives **30b**; yield: 17.5 g (57%); b.p. 132°/0.005 mm which rapidly solidifies; m.p. 38–40°. Gruber[24] describes the ethyl ester **30c** as an oil.

I.R. (KBr): 1735 (CO ester); 1658 (CO ketone); 1582, 1512 and 885 cm^{-1} (furan).

N.M.R. ($CDCl_3$): 7.0 (d, 1H, H-4); 6.15 (d, 1H, H-3) (furan); 3.62 (s, 3H, OCH_3); 2.92–1.0 ppm (m, 17H, CH_2 and $COCH_3$).

8-(5-Acetyl-2-furyl)octanoic Acid (30a):

The ester **30b** (17.2 g, 0.064 mol) is added to 1*N* potassium hydroxide (100 ml) in methanol and kept at 25° for 1 hr. After evaporation to dryness, the residue is dissolved in water (500 ml), cooled with ice and carefully acidified with 2*N* hydrochloric acid. The yellowish precipitate is extracted three times with a total of 750 ml of ether, washed twice with water (200 ml) and dried (Na_2SO_4). Evaporation of the solvent affords pale yellow needles; yield: 16.3 g (100%); m.p. 73–76°. Recrystallization from aqueous ethanol gives colorless needles; m.p. 78–80°. Gruber[24] describes this compound as an oil.

$C_{14}H_{20}O_4$	calc.	C 66.65	H 7.99%
(252.32):	found	66.52	7.92%

I.R. (KBr): 1700, 1680 and 1670 (CO, acid and ketone); 1588, 1522 and 895 cm^{-1} (furan).

N.M.R.: 10.6 (1H, COOH; exchanged by D_2O); 7.12 (d, 1H, H-4); 6.11 (d, 1H, H-3, furan); 3.00–1.05 ppm (m, 17H, $COCH_3$ and CH_2).

8-(5-Hydroxy-6-methyl-2-pyridyl)octanoic Acid Hydrochloride (5) (Carpyrinic Acid)

Acid **30a** (9.0 g, 0.036 mol), ammonium chloride (1.2 g), and aqueous 27% ammonium hydroxide (35 ml) are heated in a sealed glass tube to 170° for 20 hr. The resulting brown-colored solution is evaporated to dryness and the residue shaken with 3*N* NaOH (150 ml) for 7 hr. After extraction with chloroform (2 × 50 ml), the solution is cooled with ice and carefully acidified with 1*N* hydrogen chloride to pH 1; then extracted three times with ether (100 ml each time). The aqueous solution is evaporated to dryness and the residue extracted with dry acetone. The solvent is removed in a rotary evaporator and the brownish residue recrystallized from dry acetone using charcoal to give carpyrinic acid hydrochloride monohydrate; yield: 5.8 g (57.5%); m.p. 86–88°. Govindachari[19] reports m.p. 88–89° for a product obtained on dehydrogenation of carpamic acid, Gruber reports[24] m.p. 85–86.5° for his synthetic product and Govindachari m.p. 110–111° after drying for 15 hr at 50°/0.005 mm.

I.R.: (KBr): 3460 (OH); 3370 (COOH); 2700 ($NH^{\oplus}$); 1720 and 1740 cm^{-1} (dimer COOH).

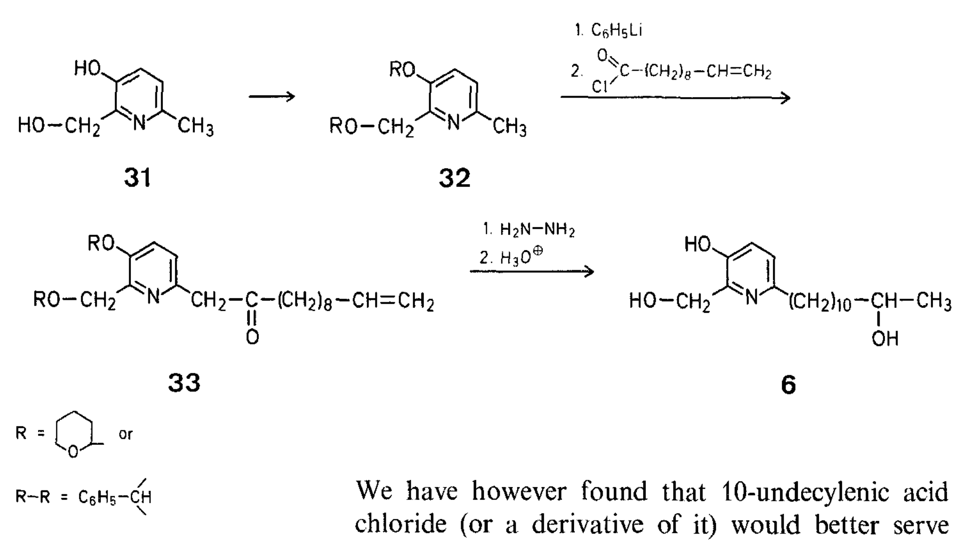
N.M.R. (DMSO-d_6): 8.10 and 7.67 (d, 2H, *J*=8 cps); pyridine; 3.2–1.15 ppm (m, 17H, CH_2 and CH_3).

2. Synthesis of Dehydroprosopine

Except for some model experiments[32] for building up stepwisely the cassine and prosopine skeletons, no synthesis of the dehydro compounds has hitherto been reported.

We now wish to report the successful preparation of hexadehydroprosopine (**6**). The furan route could be used for this synthesis, too, provided:

- an adequately functionalized C_{12}-carboxylic acid chloride is available, and
- introduction of a methoxyacetyl group instead of an acetyl group is performed during the step analogous to **29b** to **30b**, before rearrangement to the 3-hydroxypyridine derivative.



Scheme E

We have however found that 10-undecylenic acid chloride (or a derivative of it) would better serve the purpose of providing an easily accessible industrial product for the starting material. It appears reasonable to expect that the use of an already functionalized pyridine, such as 2-methyl-5-hydroxy-6-hydroxymethylpyridine (**31**), with both hydroxy groups blocked prior to conversion into the organolithium compound, allows to realize the synthesis outlined in Scheme E.

Tetrahydropyranyl or benzylidene groups may be used as protecting groups in **32**. Inadequate selectivity in the formation of the benzylic carbanion analog (produced from **32** and phenyllithium) leads to mixture of the ketone **33** and other ketones (e.g. C-2, C-6 diundecenoyl derivatives) both on reaction with methyl 10-undecenoate and its acid chloride.

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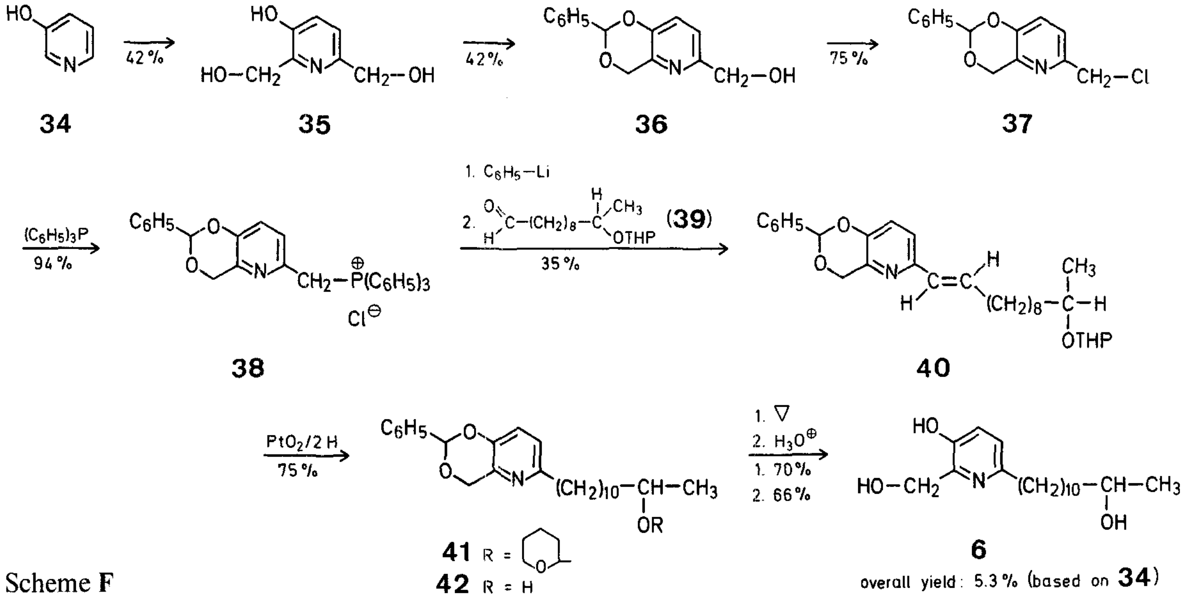
[20] G. Barger, R. Robinson, T. S. Work, J. Chem. Soc. **1937**, 711.



Scheme F

Complete selectivity has finally been achieved by preparing the benzylidene acetal **36** from 2,6-bis-hydroxymethyl-3-hydroxypyridine (**35**), benzaldehyde and boron trifluoride. Compound **35** is easily prepared on a large scale using the inexpensive 3-hydroxypyridine (**34**) and formaldehyde.

Scheme F describes this route. An exchange of hydroxyl by chloride gives the chloromethyl derivative **37**. Further reaction with triphenylphosphine gives the phosphonium salt **38**, the ylide of which is subjected to the Wittig reaction first with the unsaturated 10-undecenal and later with aldehyde **39**. In the latter reaction, the blocked olefin **40** is obtained in high yield. **39** has been prepared from commercial 10-undecenal via acetoxymercuration of its ethylene cycloacetal followed by sodium borohydride reduction, acetal hydrolysis and reaction of 10-hydroxyundecanal with dihydropyran (DHP) in 80% overall yield. Catalytic hydrogenation at low pressure leads to the double acetal of **6**, i.e. **41** (R = THP). Cleavage of the tetrahydropyranyl moiety in **41** by heating affords **42** while cleavage of the benzylidene group requires more energetic i.e., hydrolytic treatment. The overall yield of chromatographically pure dehydroprosopine (dehydro-**4**) is 17%, based on the phosphonium salt **38** (or on the aldehyde **39**).

6-Hydroxymethyl-2-phenyl-4*H*-pyrido[3,2-*d*]-1,3-dioxin (36):
Boron trifluoride etherate (170 g, 1.2 mol) is added dropwise during one hr to a stirred solution of freshly distilled benzaldehyde (300 ml) containing 2,6-bis-(hydroxymethyl)-3-hydroxypyridine (**35**; 39 g, 0.6 mol). The mixture is stirred for two additional hr, then most of the benzaldehyde is distilled off at 0.1 mm pressure and the residue is poured with stirring into a 10 *M* sodium hydroxide solution (200 ml) at 0 °C. The alkaline solution is extracted three times with ether (a total of 2 *l*), then washed with water and dried (Na_2SO_4). Evaporation of the solvent gives 100.2 g of a brown liquid still containing benzaldehyde. The brown oil is triturated with petroleum ether (b.p. 30–60°; 2 × *l* l) to remove the last traces of benzaldehyde. On recrystallization from benzene, the crude solid (77.0 g) gives **36**; yield: 61.2 g (42%); m.p. 119–121°.

I.R. (KBr): 1170–1000 cm^{-1}.
N.M.R. ($CDCl_3$): 4.55 (s, 2H, 2-CH_2); 4.9 (s, 2H, 6-CH_2); 5.85 ppm (s, 1H, CH, benzylidene).

6-Chloromethyl-2-phenyl-4*H*-pyrido[3,2-*d*]-1,3-dioxin (37):
From **36** (24.3 g, 0.1 mol) and thionyl chloride (13 g, 0.11 mol) in benzene (50 ml), the chloromethyl derivative **37** is obtained; yield: 19.28 g (74.5%); m.p. 108–111°.
I.R. (KBr): 1170–1000 cm^{-1}.
N.M.R. ($CDCl_3$): 4.5 (s, 2H, 2-CH_2); 5.0 (d, 2H, $J = 2$ cps, 6-CH_2); 5.9 ppm (s, CH, benzylidene).

2-Phenyl-6-triphenylphosphoniomethyl-4-*H*-pyrido[3,2-*d*-]-1,3-dioxin Chloride (38):
The mixture of **37** (26.2 g, 0.1 mol) and triphenylphosphine (26.2 g, 0.1 mol) is kept at 95–100° for 4 hr. The cooled melt is triturated with ether to remove all unreacted triphenylphosphine, leaving **38**; yield: 49.3 g (94%); m.p. 234–247°, which is recrystallized from a 6:4 chloroform/ether mixture to give **38**; m.p. 238–240°.
I.R. (KBr): 2840, 1170–1015, 710 cm^{-1}.
N.M.R. ($CDCl_3$): 4.7 (d, $J = 8$ cps, 2-CH_2); 5.7 ppm (q, $J = 6$ cps, 6-CH_2). The phosphorane is prepared in the usual way using phenyllithium in anhydrous tetrahydrofuran.

Ethylene Cycloacetal of 10-Undecenal:
The mixture of 10-undecenal (50.4 g, 0.3 mol), ethylene glycol (37.2 g, 0.6 mol) and *p*-toluenesulfonic acid (0.6 g, 0.03 mol) in benzene (300 ml) is refluxed for 24 hr and then distilled to give the ethylene cycloacetal; yield: 55.2 g (86.8%); b.p. 75°/0.05 mm.
I.R. (film): 2860, 1640, 1140–1120 cm^{-1}.
N.M.R. (CCl_4): 3.8 ppm m, $(O{-}CH_2)_2$.

Ethylene Cycloacetal of 10-Hydroxyundecenal
Undecenal-1-acetal (106 g, 0.5 mol) is added with stirring to a mixture of mercury(II) acetate (159.3 g, 0.5 mol), tetrahydrofuran (500 ml) and water (500 ml). The mixture is stirred for further 10 min. To complete the acetoxymercuration, 3 *N* sodium hydroxide (500 ml) is added, followed by 0.5 *M* sodium borohydride (500 ml) in 3 *N* sodium hydroxide solution. Tetrahydrofuran is separated after saturation of the aqueous layer with sodium chloride (40 g). Evaporation yields a mixture of a white solid and an organic portion which is extracted with petroleum ether (500 ml). After evaporation, a colorless liquid (94 g) is obtained. Distillation at 110–112°/0.05 mm gives the corresponding cycloacetal; yield: 84 g (73%).
I.R. (film): 3600–3300, 1140 cm^{-1}.
N.M.R. (CCl_4): 3.2 ppm (s, OH).

10-Hydroxyundecanal (39a):
A mixture consisting of the cycloacetal of 10-hydroxyundecanal (76.6 g, 0.33 mol) and an acetone/water mixture (2:1, 600 ml) containing 37% hydrochloric acid (30 ml) is refluxed for 6 hr to give **39a**; yield: 32 g (62.1%).
I.R. (film): 3600–3300, 1720 cm^{-1}.
N.M.R. (CCl_4): 9.8 ppm (t, $J=2$ cps, CHO).

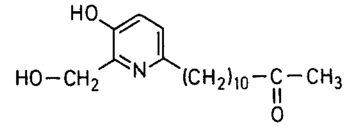
10-Tetrahydropyranyloxyundecanal (39b):
Pure dihydropyran (16.8 g, 0.2 mol) is stirred with 10-hydroxyundecanal (28 g, 0.15 mol) and two drops of conc. hydrochloric acid for 6 hr to give crude **39b**; yield: 38 g (93.8%).
I.R. (film): 2720, 1725 cm^{-1}.
N.M.R. (CCl_4): 3.2–4.0 ppm (m, tetrahydropyran).

Preparation of Blocked Olefin 40:
Phenyllithium (18.2 ml, 0.04 mol) in dry THF (100 ml) is added dropwise over a 30-minute period with stirring to a suspension of pyridylmethylphosphonium salt **38** (20.9 g, 0.04 mol) in dry THF (200 ml) under nitrogen. An intense yellow coloration develops immediately. The ylide is stirred for two additional hr. **39b** (10.8 g, 0.04 mol) in dry THF (100 ml) is then added dropwise during 30 min. After 2 hr, the intense yellow color has disappeared. The solution is then stirred for 24 hr. The residue obtained after evaporation of the solvent is triturated with dry ether causing most of the triphenylphosphine oxide/lithium chloride complex to separate. Evaporation of the ether gives a thick yellow oil (19.5 g) which is treated with petroleum ether (200 ml) to give a solid (1.4 g). The remaining yellow oil (18.1 g) is chromatographed over a neutral alumina columm using benzene as the eluent. Compound **40** is obtained as a light yellow oil; yield: 6.6 g (34.5%).
I.R. (film): 1660–1640 cm^{-1}.
N.M.R. (CCl_4): 6.4–6.7 ppm (m, —CH=CH).

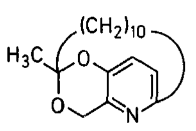
6-(11-Hydroxydodecyl)-2-phenyl-4*H*-pyrido[3,2-*d*]-1,3-dioxin (42):
The double acetal **40** (2.4 g, 0.05 mol) in glacial acetic acid (20 ml) is hydrogenated at 2 atm with platinum(IV) oxide catalyst (0.05 g) for 22 hr. Platinum is filtered off and the glacial acetic acid is neutralized with 10% sodium carbonate solution. The organic material is extracted with chloroform, washed with water, and dried (Na_2SO_4). Evaporation of the solvent and recrystallization of the crude compound from benzene gives the saturated acetal **41**; yield: 1.8 g (75%); m.p. 92–94°.
I.R. (KBr): 2920–2860, 1580, 1120–1020 cm^{-1}.
N.M.R. ($CDCl_3$): 2.7 ppm (t, $J=6$ cps, 6-CH_2).
Heating of **41** (1.4 g) at 100°/0.5 mm for 6 hr gives **42**; yield: 0.8 g (66%); m.p. 99–102°.
I.R. (KBr): 3500–3250 cm^{-1}.
N.M.R. ($CDCl_3$): 3.5–4.0 ppm (m, —CH—OH).

5-Hydroxy-2-(11-hydroxydodecyl)-6-hydroxymethyl)pyridine (Dehydroprosopine) (6):
Boiling of **42** (500 mg, 0.0013 mol) in acetone/water (1:1) (50 ml) containing conc. hydrochloric acid (2.5 ml) for 5 hr gives the title compound; yield: 300 mg (80%); m.p. 70–72°.
I.R. (KBr): 3500–3200 cm^{-1}.
N.M.R. ($CDCl_3$): 4.8 ppm (broad singlet, 3H, (OH).)

By partial oxidation of the benzylidene acetal **42** of **6** with either the chromic acid-pyridine complex or with ruthenium oxide, the most appropriate precursor of prosopine, **44**, is obtained by cyclization to the "blocked" pyridine **43**. This compound, in turn, shall be subjected to hydrogenation (hopefully an *all-cis* steric course) to yield (racemic) prosopinone. Dehydroprosopinine (**6**) is also accessible through this route. Allylic oxidation of 10-undecenal ethylene acetal followed by hydrogenation should give 9-hydroxyundecanal. The tetrahydropyranyl ether of the latter should undergo a Wittig reaction in the same way as 10-hydroxyundecenal.



43
hexadehydroprosopinone



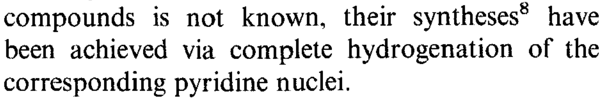
44

Further versatility of this route is indicated by the approach it provides for the synthesis of cassine (**2**). Dehydrocassine is now accessible by using 3-hydroxy-6-hydroxymethyl-2-methylpyridine rather than the 2,6-bis-hydroxymethyl derivatives **35** and **36** in a sequence of reactions analogous to **37** to **38**, plus **39**, leading via **40** to **42**.

The two alternative pathways leading to long-chain pyridines which we have elaborated offer wide possibilities for syntheses of long-chain pyridine (and possibly piperidine) derivatives. A preliminary paper on this subject has been presented[33].

3. Synthesis of Ant Venoms (2-Methyl-6-alkyl- and -6-alkenylpyridines, their Derivatives and Homologs)

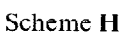
The only known non-proteinaceous venom[5,6], solenopsin A′, delivered by bite or sting of the fire ant (red form) has recently proved[8] to be *trans*-2-methyl-6-*n*-undecylpiperidine. In fact, four more components have been detected[8] and all five venoms are characterized by the two general formulae **45** and **46** (Scheme G).



45 **46**
n = 10, 12, 14 n = 3, 5

Scheme G

Although the absolute stereochemistry of these compounds is not known, their syntheses[8] have been achieved via complete hydrogenation of the corresponding pyridine nuclei.

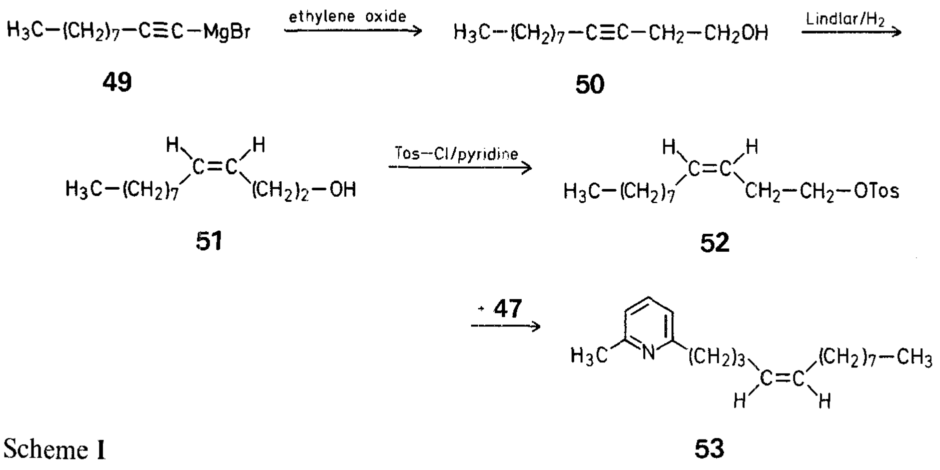


47 **48**

Scheme H

Scheme **H** describes the synthesis of the pyridine precursor of **46**. Compounds of the type **49** have been obtained by the reaction of the lithio derivative with alkyl bromides.

All these facts indicate the biological importance of long-chain piperidines, and consequently particular emphasis is on the syntheses of the corresponding pyridines being the most appropriate intermediates for both types of piperidines derivatives.



Scheme I

Catalytic hydrogenation of **48** and **53** leads to *cis*-2,6-dialkylpyridine while reduction by lithium in ethanol affords 85% *cis* and 15% *trans* isomers.

The striking difference between the plant alkaloids and the ant venoms is that the former exhibit *cis*-configuration and the latter *trans*-configuration. Another interesting fact is that the plant products have an even-numbered carbon chain at C-2 while all the venoms possess odd-numbered carbon chains.

This review article is dedicated by G. Fodor to Professor Victor Bruckner in honour of his 70th birthday.

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[21] H. Rapoport, H. D. Baldridge, J. Am. Chem. Soc. **74**, 5365 (**1952**).

[22] H. Rapoport, E. J. Volcheck, J. Am. Chem. Soc. **78**, 2451 (1956).

[23] D. L. Hammick, B. R. Brown, J. Chem. Soc. **1949**, 659; B. R. Brown, Quart. Rev. Chem. Soc. **5**, 131 (1951).

[24] W. Gruber, Chem. Ber. **88**, 178, (1955).

[25] P. H. Gore, *Aromatic Ketone Synthesis*, in *Friedel-Crafts and Related Reactions*, edited by G. A. Olah, Vol. 2, p. 1, Wiley-Interscience, New York, 1964.

[26] F. A. Drahowzal, *Alkylation of Aromatics with Haloalkanes* in *Friedel-Crafts* and *Related Reactions*, edited by G. A. Olah, Vol. 2, p. 433, Wiley-Interscience, New York, 1964.

[27] G. T. Morgan, E. Walton, J. Chem. Soc. **1935**, 290.

[28] A. G. Peto, *Aliphatic Acylation with Ester Acid Chlorides* in *Friedel-Crafts and Related Reactions*, edited by G. A. Olah, p. 602, Wiley-Interscience, New York, 1964.

[29] P. Cagniant, D. Cagniant, A. Deluzarche, Bull. Soc. Chim. France **1948**, 1083.

[30] Y. L. Goldfarb, B. F. Fabrichnyi, I. F. Shalavina, Dok. Akad. Nauk. SSSR. **109**, 305 (1956); C.A. **51**, 1839 (1957).

[31] T. F. Grey, J. F. McChie, W. A. Ross, J. Chem. Soc. **1960**, 1502.

[32] E. Brown, R. Dhal, J. Lavoue, Tetrahedron Lett. **1971**, 1055.

[33] G. Fodor, J.-P. Fumeaux, V. Sankaran, Abstracts of Papers, 161st National Meeting American Chemical Society, Los Angeles, California, 1971, p. ORGN 118.

[34] A. Stempel, E. C. Buzzi, J. Amer. Chem. Soc. **71**, 2972 (1949).