# Synthesis of *trans*-2,6-Dialkylpiperidines by Intramolecular Amidomercuriation and by 1,3-Cycloaddition of Alkenes to 2-Methyl-2,3,4,5-tetrahydropyridine Oxide

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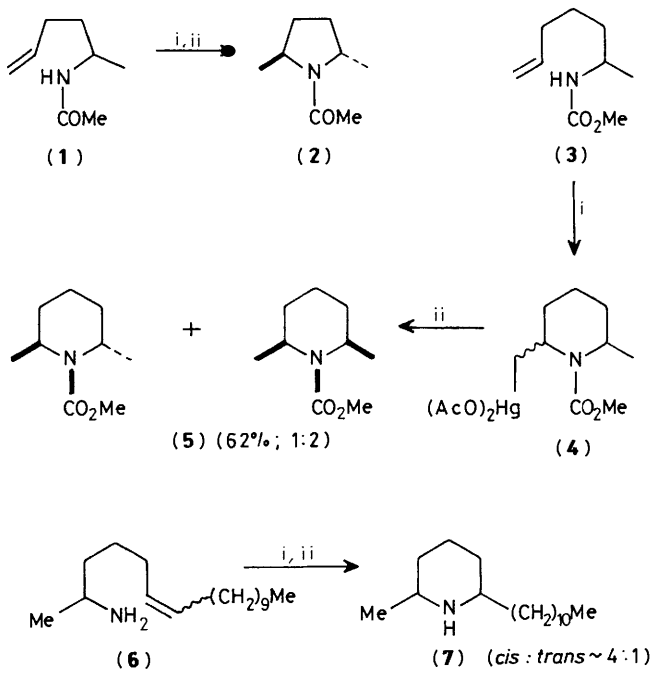
Intramolecular amidomercuriation of methyl *N*-hept-6-en-2-ylcarbamate and reaction of the resulting organomercurial with sodium borohydride in the presence of acrylonitrile or dec-1-en-3-one has been used to prepare *trans*-2,6-dialkylpiperidines. A more stereoselective route lies in the cycloaddition of alkenes to 2-alkyl-2,3,4,5-tetrahydropyridine oxides followed by reductive cleavage of the resulting perhydroisoxazolopyridine. Both procedures are illustrated by synthesis of the fire ant-venom alkaloid, solenopsin A.

Until recently there have been few good general methods for the selective synthesis of *trans*-2,6-dialkylpiperidines, a class of compounds which includes a number of piperidine alkaloids.[1] *cis*-2,6-Dialkylpiperidines can be prepared by several routes,[2] but the *trans* isomers have been comparatively inaccessible. In preliminary communications we have reported the results of experiments aimed at the selective synthesis of *trans*-2,6-dialkylpiperidines by intramolecular amidomercuriation of methyl *N*-hept-6-en-2-ylcarbamates[3] and by 1,3-cycloaddition of alkenes to 2-methyl-2,3,4,5-tetrahydropyridine oxide.[4] We record here full details and further development of these experiments. During the course of our work two other excellent routes to *trans*-2,6-dialkylpiperidines were reported: by selective reduction of 2,3,4,5-tetrahydropyridines[5] and by reductive cleavage of 2,6-dialkyl-2-cyanopiperidines.[6] The latter route has been used in the synthesis of optically active piperidines.[7]

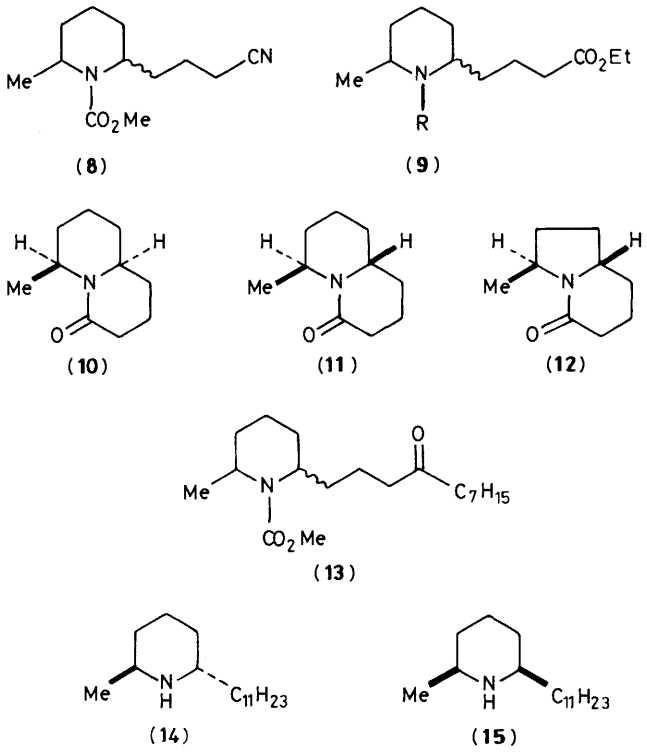
It had been reported that intramolecular amidomercuriation[8] of the 5-acetylaminohex-1-ene (**1**) with mercuric acetate followed by reductive cleavage of the intermediate organomercurial with sodium borohydride led exclusively to the *trans*-2,5-dimethylpyrrolidine (**2**),[9] and it seemed of interest to determine if a similar sequence with appropriate acylaminohept-1-enes might provide a useful general route to *trans*-2,6-dialkylpiperidines. In the event, preliminary experiments with the carbamate (**3**) gave a mixture of the *cis* and *trans* isomers (**5**) (ratio 1:2) in 62% yield. The products were separated by g.l.c. and their structures established by conversion into the corresponding 2,6-dimethylpiperidines. Although the *trans* isomer was the main product of this sequence, the *trans* selectivity was disappointingly lower than that observed in the formation of the pyrrolidine (**2**), but higher than that obtained in the reaction with the free amine (**6**) which gave mainly the *cis*-2,6-dialkylpiperidine (**7**).[10] Recent studies of the intramolecular amidomercuriation of carbamates closely related to (**1**) and (**3**) have shown that the reactions are reversible and that the stereochemistry of the products is dependent on the reaction conditions.[11] In the five-membered ring series, the *trans*-2,5-dimethylpyrrolidine is formed exclusively under kinetic conditions; in the piperidine series, however, the thermodynamically more stable *cis*-2,6-dimethyl derivative is always produced to some extent and conditions for the exclusive formation of the kinetic *trans* isomer have not been established.

It has been shown[12] that reaction of organomercurials with sodium borohydride in the presence of derivatives of acrylic acid affords coupled products through a free-radical chain reaction. We have exploited this to prepare 2-methyl-6-alkylpiperidines




*Reagents:* i, $Hg(OAc)_2$, THF; ii, $NaBH_4$, MeOH

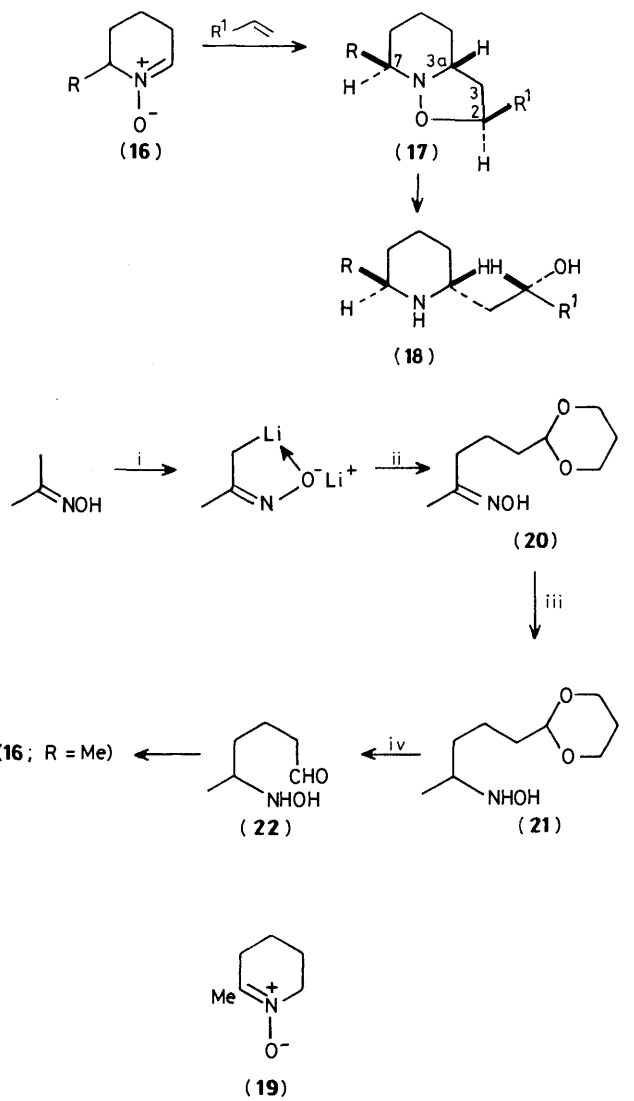
from the mercurial (**4**) obtained from the carbamate (**3**). Thus, reaction of (**4**) with sodium borohydride and acrylonitrile smoothly gave the coupled product (**8**) in 75% yield, as a mixture of *cis* and *trans* isomers (ratio *ca.* 2:3). These were separated by preparative g.l.c. and their stereochemistries established by conversion into the corresponding known[13] 4-methylperhydroquinolizinines. Heating the individual nitriles with ethanolic hydrogen chloride gave the unstable amino esters (**9**; R = H) which were separately cyclised to the perhydroquinolizinones (**10**) and (**11**) in boiling xylene; reduction with lithium aluminium hydride gave the perhydroquinolizinines. A similar sequence of reactions has been used to prepare the *trans*-perhydroindolizinone (**12**).[14] The amino esters (**9**; R = $CO_2Me$) were also obtained directly from (**4**) by reaction with sodium borohydride and ethyl acrylate, but in poorer yield (40%) than by the acrylonitrile route. The superiority of acrylonitrile over ethyl acrylate in radical coupling reactions has been noted before.[15]




It has been reported[16] that the *trans*-6-methylperhydroquinolizinone (**11**) shows a methyl doublet in the $^1$H n.m.r. spectrum at δ 0.67 whose unusually high position was ascribed to a shielding effect of the carbonyl group. In the spectrum of our specimen, however, the doublet appears unexceptionally at δ 1.24; other features of the spectrum are in accordance with the published data.

We have used the radical-coupling reaction in a synthesis of the *trans*-2,6-dialkylpiperidine, solenopsin A (**14**), a constituent of the venom of the fire ant *Solenopsis saevissima*.[17,18] Reductive coupling of the organomercurial (**4**) and dec-1-en-3-one with sodium borohydride gave the *cis* and *trans* isomers (**13**), but in noticeably poorer yield (25%) than in the reactions with acrylonitrile and methyl acrylate. The ratio of isomers formed was *ca.* 4:3 but we cannot say which is which because they could not be separated and the synthesis had to proceed with the mixture. Attempted reduction of the carbonyl group by the Huang–Minlon procedure[19] gave a mixture of products but reduction was smoothly effected by hydrogenolysis of the derived dithioacetals with Raney nickel. Cleavage of the *N*-methoxycarbonyl group with ethanolic hydrogen chloride then gave solenopsin (**14**) and isosolenopsin (**15**) (77% from the ketone, ratio *ca.* 3:4). The isomers were separated by preparative g.l.c. and distinguished through their $^1$H n.m.r. spectra, particularly by the downfield chemical shift of the signal due to 2-H and 6-H in solenopsin (δ 3.08—2.85)[17] compared with that of isosolenopsin (δ 2.72—2.44),[20] and through their crystalline hydrochlorides.

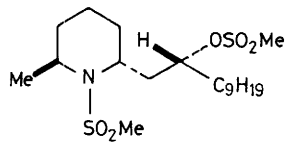
A more selective route to *trans*-2,6-dialkylpiperidines was found in the 1,3-cycloaddition of alkenes to 2-methyl-2,3,4,5-tetrahydropyridine oxide. It has been shown that 1,3-cycloaddition of monosubstituted ethylenes, except those bearing strongly electronegative substituents,[21] to 2,3,4,5-tetrahydropyridine oxide (**16**; R = H), leads predominantly, or exclusively, to 2-substituted perhydroisoxazolinines (**17**; R = H) by way of an *exo* transition state.[22] It seemed to us that cycloaddition to 2-alkyl-2,3,4,5-tetrahydropyridine oxides (**16**; R = alkyl) would take place preferentially by orthogonal approach of the alkene to the nitrone in a conformation in which the alkyl substituent is




**Scheme.** *Reagents:* i, BuLi (2 equiv.); ii, $I(CH_2)_2\overline{CH{\cdot}O{\cdot}(CH_2)_3O}$; iii, $NaBH_3CN$, MeOH; iv, 2M HCl

pseudo-equatorial, to give an adduct (**17**; R = alkyl) which would furnish a *trans*-2,6-dialkylpiperidine (**18**; R = alkyl) by reductive cleavage of the N–O bond. We have shown the validity of this supposition by a short, stereocontrolled synthesis of solenopsin A. Related resulted were reported during the course of our work and employed in a neat synthesis of the alkaloid porantherilidine.[23]

Preparation of the required 2-methyl-2,3,4,5-tetrahydropyridine oxide (**16**; R = Me) was troublesome. Oxidation of 2-methylpiperidine with hydrogen peroxide catalysed by sodium tungstate gave only the alternative 2-methyl-3,4,5,6-tetrahydropyridine oxide (**19**), as reported,[24] and oxidation of 2-methylpiperidin-1-ol with mercuric oxide furnished a mixture of (**16**; R = Me) and (**19**) in which the required aldonitrone was the minor component (ratio 16:19 = 1:3).[25] Although the aldonitrone (**16**; R = Me) in the mixture could be made to react selectively with alkenes in boiling chloroform, the yield of cycloadduct was necessarily limited. The pure nitrone (**16**; R = Me) was eventually cleanly obtained by cyclisation of the hydroxylaminoaldehyde (**22**),[26] itself prepared as shown in the Scheme. The nitrone was an unstable oil and was used immediately without purification. On heating with undec-1-ene it gave the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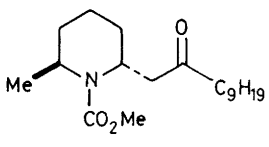
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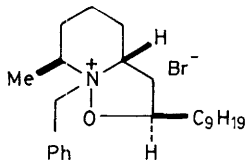
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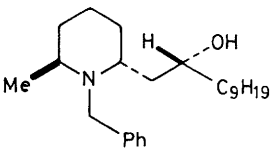
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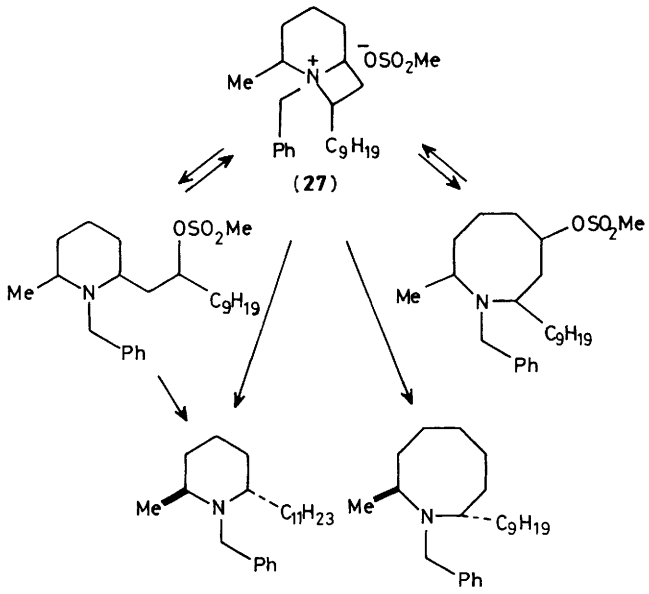
perhydroisoxazolopyridine (**17**; R = Me, $R^1 = C_9H_{19}$) almost exclusively (93% by g.l.c.) in 87% yield. The *trans* stereochemistry at C-3a and C-7 follows from its conversion into solenopsin A; that at C-2 is assigned on analogy.[23]

Reductive cleavage of the perhydroisoxazolopyridine ring of (**17**; R = Me, $R^1 = C_9H_{19}$) with zinc and acetic acid gave the piperidine derivative (**18**; R = Me, $R^1 = C_9H_{19}$) in 92% yield, which was smoothly converted into solenopsin A by successive reduction of the derived mesylate-sulphonamide (**23**) with lithium triethylborohydride and sodium bis(methoxyethoxy)-aluminium hydride.[27] Alternative procedures by reduction of the phenoxy thiocarbonate of the alcohol (**18**; R = Me, $R^1 = C_9H_{19}$) with tributylstannane,[28] or by desulphurisation of the dithioacetal of the ketone (**24**) with Raney nickel followed by acid hydrolysis of the carbamate gave much poorer yields of solenopsin.

Reductive cleavage of the crystalline benzylammonium salt (**25**) with zinc and acetic acid led in high yield to the stereochemically homogeneous *N*-benzylpiperidine derivative (**26**) and in this respect was preferable to direct cleavage of the parent perhydroisoxazolopyridine (**17**; R = Me, $R^1 = C_9H_{19}$). The *N*-benzylpiperidine derivatives [as (**26**)] have the advantage that their $^1$H n.m.r. spectra provide a direct measure of the stereochemistry of the 2- and 6-substituents in the cis-

n.m.r. spectra; in both cases a coupling constant of 14 Hz in the signal due to the benzylic methylene group indicates a *trans* disposition of the α and α′ substituents.[29] The main evidence for structure (**29**) comes from the mass spectrum. Mass spectra of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saturated nitrogen-containing heterocycles show a fragmentation pattern which is dominated by cleavage of the α-C–C bonds[31] and this has been confirmed in the present work in the mass spectra of solenopsin (**14**) and the alcohol (**26**) which both show a base peak due to loss of the long α-substituent, which is by far the predominant signal in the spectrum. The spectra of (**28**) and (**29**) show identical signals at *m/z* 343, 342, 328, and 91, corresponding respectively to the molecular ion ($M^+$), and the $(M - H)^+$, $(M - CH_3)^+$, and $C_6H_5CH_2^+$ fragments. However, the two spectra differ in their important base ion; the base peak of (**28**) occurs at *m/z* 188, corresponding, as expected, to loss of the undecyl side chain, but that of the isomer is at *m/z* 216, corresponding to loss of $C_9H_{19}$. The latter result seems best

chromatography of the crude product on silica (eluant ethyl acetate) followed by distillation gave the title compound (1.36 g, 84%) as an oil at 170 °C/3.5 mmHg; $\delta_H$(100 MHz; $CDCl_3$) 1.06—1.12 (3 H, d, *J* 7.0 Hz, *Me*CH), 1.3—1.6 (4 H, complex, $CH_2CH_2$), 1.7—2.2 (2 H, complex, $CH_2$=CHC$H_2$), 3.4—3.9 (4 H, complex, $CO_2Me$ and C*H*Me), 4.5 (1 H, br s, NH), 4.84—5.10 (2 H, complex, C$H_2$=CH), 5.54—6.0 (1 H, complex, $CH_2$=C*H*) (Found: C, 63.0; H, 10.1; N, 8.35%; $M^+$, 171. $C_9H_{17}NO_2$ requires C, 63.2; H, 9.9; N, 8.19%; *M*, 171).

cis- *and* trans-2,6-*Dimethylpiperidine Hydrochlorides*.— Mercuric acetate (1.28 g, 4.03 mmol) was added to a stirred solution of the above carbamate (0.46 g, 2.69 mmol) in tetrahydrofuran (35 ml) under nitrogen. The flask was shielded from light and the contents stirred for 24 h. After cooling in an ice-bath, the mixture was treated with sodium borohydride (300 mg, 7.9 mmol) in ethanol (3 ml). After 15 min, water (20 ml) was added and the mixture was extracted with ether. Flash chromatography of the crude product gave the methyl piperidine-1-carboxylates (0.28 g, 61%) as an oil, b.p. 70—72 °C at 0.35 mmHg (Found: C, 63.0; H, 10.2; N, 8.2%; $M^+$, 171. $C_9H_{17}NO_2$ requires C, 63.2; H, 9.9; N, 8.2%; *M*, 171). G.l.c. (3% OV 225, 100 °C) showed the presence of two components (ratio 62:38). The low retention isomer (45 mg; 62% of mixture) in boiling ethanolic hydrogen chloride (2 ml) afforded the hydrochloride of *trans*-2,6-dimethylpiperidine (18 mg, 46%) m.p. 240—242 °C (lit.,[38] m.p. 240—242 °C). The high retention isomer similarly yielded the hydrochloride of *cis*-2,6-dimethylpiperidine, m.p. 286—287 °C (lit.,[38] m.p. 289—291 °C). No m.p. depression was observed on admixture of the isolated compounds with authentic specimens.

cis- *and* trans-*Methyl* 2-*Cyanopropyl*-6-*methylpiperidine*-1-*carboxylate* (**8**).—Mercuric acetate (6.97 g, 0.022 mmol) was added to a stirred solution of the carbamate (**3**) (2.50 g, 0.015 mmol) in dichloromethane (60 ml) under nitrogen and the mixture was stirred in the dark for 24 h. Acrylonitrile (25 g, 0.47 mmol) and sodium borohydride (0.083 g, 0.022 mmol) were then added to the mixture and after 3 h water (25 ml) was added dropwise. Mercury was filtered off and the product recovered from the organic layer as an oil (2.70 g). This was purified by flash chromatography (eluant ethyl acetate) and distillation (b.p. 124—126 °C at 0.35 mmHg) to give an oil (2.47 g) shown by g.l.c. to contain two components in the ratio *trans*:*cis* 57:43. These were separated by preparative g.l.c. (10% OV 17, 230 °C). Isomer *trans*-(**8**) was eluted first as an *oil* (39% recovery); $\delta_H$(100 MHz; $CDCl_3$) 1.2 (3 H, d, *J* 6.59 Hz, Me), 1.5—1.9 (10 H, envelope, 5 × C$H_2$), 2.40 (2 H, complex, $CH_2CN$), 3.68 (3 H, s, $CO_2Me$), and 3.8—3.9 (2 H, complex, 2 × C*H*N) (Found: C, 64.2; H, 9.0; N, 12.3. $C_{12}H_{20}N_2O_2$ requires C, 64.3; H, 8.9; N, 12.50%). The corresponding *cis* isomer was eluted later (34% recovery); $\delta_H$(100 MHz; $CDCl_3$) 1.18 (3 H, d, *J* 7.08 Hz, *Me*), 1.6—1.8 (10 H, complex, 5 × C$H_2$), 2.3 (2 H, complex, C$H_2$CN), 3.68 (3 H, s, $CO_2$Me), 4.2—4.3 (2 H, complex, 2 × CHN) (Found: C, 64.1; H, 9.0; N, 12.3%).

cis-2-*Ethoxycarbonylpropyl*-6-*methylpiperidine* (**9**; R = H).—A solution of compound *cis*-(**8**) (186 mg) in anhydrous ethanol saturated with hydrogen chloride was boiled for 3 days. The title ester recovered as its hydrochloride formed colourless crystals (139 mg) from ethanol–ether, m.p. 228—230 °C. The free piperidine (88 mg) had $\delta_H$(100 MHz; $CDCl_3$) 1.07 (3 H, d, *J* 6.10 Hz, Me), 1.25 (3 H, t, *J* 7.08 Hz, $CO_2CH_2CH_3$), 1.3—1.7 (10 H, envelope, 5 × $CH_2$), 2.3 (2 H, q, *J* 7.33 Hz, $CH_2CO_2Et$), 2.6 (3 H, complex, 2 × CHN + NH), 4.12 (2 H, q, *J*, 7.08 Hz, $CO_2CH_2Me$).

cis- *and* trans-4-*Methylperhydroquinolizinine*.—A solution of compound *cis*-(**9**) (88 mg) in xylene (5 ml) was boiled for 90 h under nitrogen. Evaporation of solvent and purification of the product by preparative g.l.c. (3% OV 225, 150 °C) gave isomer *cis*-(**10**) (23 mg); $\delta_H$(100 MHz; $CDCl_3$) 1.25 (3 H, d, *J* 6.59 Hz, Me), 1.2—2.0 (10 H, envelope, 5 × $CH_2$), 2.39 (2 H, complex, $CH_2CO$), 3.4 (1 H, complex, 10-H), and 4.3 (1 H, complex, 6-H). Reduction of this product (22 mg) in ether (10 ml) with lithium aluminium hydride (100 mg) for 2 h gave *cis*-4-methylperhydroquinolizinine (16 mg). The picrate formed yellow needles in ethanol, m.p. 191—192 °C (lit.,[13] 197.5—199 °C), undepressed when mixed with an authentic specimen.

A similar sequence of reactions with *trans*-methyl 2-cyanopropyl-6-methylpiperidine-1-carboxylate gave *trans*-4-methylperhydroquinolizinine, picrate m.p. 191—192 °C (lit.,[13] m.p. 198.5—200 °C).

*Methyl* 2-*Methyl*-6-(4-*oxoundecyl*)*piperidine*-1-*carboxylate* (**13**).—A mixture of the carbamate (**3**) (1.52 g) and mercuric acetate (4.23 g) in dichloromethane (140 ml) shielded from light was stirred under nitrogen for 24 h; dec-1-en-3-one (9.42) and sodium borohydride (0.43 g) were then added. After 2 h at 5 °C, water (10 ml) was added dropwise and the organic phase separated. Flash chromatography of the recovered product gave the ketone as an oil (0.75 g, 26%) which decomposed on attempted distillation [Found: $M^+$, 266.2479. Calc. for $C_{17}H_{32}NO$: ($M^+$ − $CO_2CH_3$) 266.2483]. G.l.c. (3% OV 225, 210 °C) showed the presence of two products (ratio 42:58). These could not be separated by preparative scale h.p.l.c.; preparative scale g.l.c. (3% OV 225, 200 °C) resulted in extensive decomposition, but sufficient material was obtained to determine the $^1H$ n.m.r. spectra. The low-retention isomer (42%) had $\delta_H$(100 MHz; $CDCl_3$) 0.87 (3 H, t, *J* 6.6 Hz, *Me*), 1.1—1.6 (23 H, envelope, 10 × $CH_2$ and Me), 2.4 (4 H, complex, $CH_2COCH_2$), 3.68 (3 H, s, $CO_2$Me), 3.9 (2 H, complex, 2 × CHN); the high-retention isomer (58%) had $\delta_H$(100 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 5.9 Hz, Me), 1.12—1.6 (23 H, envelope, 10 × $CH_2$ and Me), 2.4 (4 H, complex, $CH_2COCH_2$), 3.68 (3 H, s, $CO_2$Me), and 4.1 (2 H, complex, 2 × CHN).

*Methyl* 2-*Methyl*-6-*undecylpiperidine*-1-*carboxylate*.—A solution of the above mixed ketones (0.54 g), ethane-1,2-dithiol (0.31 g), and boron trifluoride–diethyl ether (0.1 ml) in glacial acetic acid (20 ml) was kept at room temperature for 12 h, after which it was poured into water and extracted with ether. The ethereal solution was washed with sodium hydrogen carbonate and the recovered product purified by flash chromatography (eluant: ether–light petroleum 1:2) to afford the dithioketal as a yellow oil (0.43 g, 66%) which could not be distilled. A mixture of this material (0.40 g) and W2 Raney nickel (8 g) in ethanol (200 ml) was boiled for 4 h, and the recovered methyl 2-methyl-6-undecylpiperidine-1-carboxylate was purified by flash chromatography (eluant ether–light petroleum, 1:2) to give an oil (250 mg, 77%) shown by g.l.c. (3% CV 225, 180 °C) to contain two components in the ratio (low retention:high retention 44:56); $\delta_H$(100 MHz; $CDCl_3$) 0.90 (3 H, complex, Me), 1.10—2.0 (29 H, envelope, 13 × $CH_2$ and Me), 3.68 (3 H, s, $CO_2$Me), and 3.9—4.4 (2 H, complex, 2 × CHN); $\nu_{max.}$($CHCl_3$) 2 920, 2 860, and 1 670 $cm^{-1}$ (Found: $M^+$, 311.2797. $C_{19}H_{37}NO_2$ requires *M*, 311.2824).

*Solenopsin* A *and Isosolenopsin* A (**14**) and (**15**).—A solution of the above mixed 1-carboxylates (0.26 g) in ethanol saturated with hydrogen chloride (22 ml) was boiled for 4 days, and evaporated to leave the crude piperidine hydrochlorides (0.26 g). The recovered free amines (160 mg) were separated by preparative g.l.c. (3% OV 225, 140 °C). Isosolenopsin was eluted first (41 mg, 25% recovery); $\delta_H$(100 MHz; $CDCl_3$) 0.83 (3 H, complex, Me), 1.0—1.9 (29 H, complex, 14 × $CH_2$ and

Me), and 2.45—2.60 (2 H, complex, 2CHN) (lit.,[20] δ 2.45—2.87, 2CHN); $\nu_{max.}$(film) 2 960—2 920, 2 860, 2 795, and 2 450 $cm^{-1}$ (Found: $M^+$, 253. Calc. for $C_{17}H_{35}N$: $M$, 253). The hydrochloride had m.p. 154—155 °C (lit.,[17] m.p. 154—155 °C). Solenopsin A was eluted later (29 mg, 18% recovery); $\delta_H$(100 MHz, $CDCl_3$) 0.81 (3 H, complex, Me) 1.0—1.9 (29 H, envelope, 14 × $CH_2$ and Me), and 2.82—3.00 (2 H, complex, 2 × CHN) (lit.,[17] δ 2.7—3.1, 2 × CHN); $\nu_{max.}$(film) 2 960, 2 920, 2 860, 2 800, 2 705, and 1 400 $cm^{-1}$ (Found: $M^+$, 253); hydrochloride m.p. 113—114 °C (lit.,[10] m.p. 114 °C).

5-*Dioxan*-2-*ylpentan*-2-*one Oxime* (**20**).—Butyl-lithium (1.4M in hexane; 78 ml) was slowly added to a stirred solution of acetone oxime (0.387 g) in tetrahydrofuran (20 ml) under nitrogen. After 0.5 h the reaction mixture was cooled to −78 °C and a solution of 2-(2-iodoethyl)-1,3-dioxane (1.17 g) in tetrahydrofuran (30 ml) was added over 15 min, the temperature being kept < −50 °C. The mixture was allowed to warm to room temperature and the reaction was quenched with water (10 ml). The recovered crude product was purified by dry flash chromatography (eluant: chloroform–light petroleum, 1:1) to give the oxime as a viscous oil (0.56 g, 62%); $\delta_H$(250 MHz; $CDCl_3$) 1.25—1.37 (1 H, m), 1.55—1.65 (4 H, m), 1.85 and 1.86 (3 H, 2 s), 1.96—2.16 (1 H, m), 2.16—2.42 (2 H, m), 3.69—4.12 (4 H, m), 4.51—4.56 (1 H, m), and 9.26 (1 H, br s); $\delta_C$(62.9 MHz; $CDCl_3$) 13.27 and 19.66 (2-$CH_3$), 19.94, 20.73 (2-$CH_2$), 25.85 (2-$CH_2$), 28.27, 34.54, 35.05, 35.51 (4-$CH_2$), 66.87 (2-$CH_2$), 101.92 and 101.96 (CH), 158.05 and 158.38 (C) (the spectra were complicated by the presence of two geometrical isomers of the oxime) (Found: C, 57.6; H, 9.1; N, 7.3. $C_9H_{17}NO_3$ requires C, 57.7; H, 9.2; N, 7.5%).

5-*Dioxan*-2-*ylpent*-4-*ylhydroxylamine* (**21**).—Sodium cyanoborohydride (0.92 g) in dry methanol (25 ml) was added under nitrogen to a stirred solution of the above oxime (3.74 g), in methanol (100 ml) containing a trace of Bromocresol Green indicator, at −78 °C. After addition was complete the reaction mixture was allowed to warm to room temperature. Sufficient dry methanolic hydrogen chloride was added dropwise from time to time to maintain the yellow colouration of the indicator. After evaporation of the methanol, aqueous sodium hydroxide (2M; 50 ml) was added and the product extracted with chloroform. Purification by dry flash chromatography (eluant: chloroform + 2% methanol) gave the hydroxylamine as an oil (3.61 g, 95%); $\delta_H$(250 MHz; $CDCl_3$) 1.08 (3 H, d, $J$ 6.3 Hz, Me), 1.18—1.65 (6 H, m, 3 × $CH_2$), 1.96—2.16 (2 H, m, $CH_2$), 2.89—3.02 (1 H, m, $CH$NHOH), 3.68—3.82 and 4.03—4.14 (4 H, multiplets, 2 × $OCH_2$), 4.51 (1 H, t, $J$ 5.0 Hz, 2-H of dioxane), and 6.2 (2 H, br, OH, NH); $\delta_C$(62.9 MHz; $CDCl_3$) 17.67 (Me), 20.38, 25.88, 33.61, 35.31 (4-$CH_2$), 57.17 (CHNHOH), 66.37 (2-$CH_2$), and 102.17 (CH) (Found: $M^+$, 190.1446. $C_9H_{20}NO_3$ requires $M$ + 1, 190.1443).

7-*Methyl*-2-*nonylperhydroisoxazolo*[2,3-a]*pyridine* (**17**; R = Me, $R^1$ = $C_9H_{19}$).—A solution of the hydroxylamine (**21**) (0.59 g) in hydrochloric acid (2M; 5 ml) was stirred at room temperture for 15 min after which it was diluted with water (30 ml), basified with solid sodium carbonate, washed with ether (2 × 50 ml) and extracted with chloroform (5 × 50 ml). 2-Methyl-2,3,4,5-tetrahydropyridine oxide was recovered from the chloroform extract as a pale yellow oil which was used immediately in the next step.

A mixture of the nitrone from the above experiment and undec-1-ene (3 ml) was heated at 150 °C for 25 min. The reaction mixture was cooled and purified by dry flash chromatography (eluant: chloroform) and afforded the perhydroisoxazolopyridine (**17**; R = Me, $R^1$ = $C_9H_{19}$) as a pale yellow oil (0.79 g, 87%), b.p. 120—130 °C at 0.05 mmHg. G.l.c. (3% OVI, 184 °C) showed the presence of *ca.* 7% of a further product which was not investigated; $\delta_H$(250 MHz; $CDCl_3$) 0.85 (3 H, t, $J$ 5 Hz, Me), 1.09 (3 H, d, $J$ 4 Hz, Me), 1.15—1.35 (15 H, m), 1.35—1.50 (3 H, m), 1.50—1.65 (3 H, m), 3.45—3.60 (1 H, m), and 4.15—4.30 (1 H, m); $\delta_C$(62.9 MHz; $CDCl_3$) 13.98 ($CH_3$), 18.81 ($CH_2$), 20.33 (br, $CH_3$), 22.60, 25.53, 25.83, 29.24, 29.49, 29.54, 29.63, 31.83, 32.71, (9-$CH_2$), 35.55 (2-$CH_2$), 53.6 (CH), 59.95 (br, CH), and 76.42 (br, CH) (Found: C, 76.7; H, 12.4; N, 5.3%; $M^+$, 267. $C_{17}N_{33}NO$ requires C, 76.4; H, 12.4; N, 5.2%; $M$, 267).

trans-2-(2-*Hydroxyundecyl*)-6-*methylpiperidine* (**18**; R = Me, $R^1$ = $C_9H_{19}$).—A solution of the above perhydroisoxazolopyridine (0.705 g) in 10M acetic acid (20 ml) was boiled with zinc dust for 2 h. The cooled solution was decanted into water (100 ml) and brought to pH 10 with 2M sodium hydroxide. The product was extracted with ether and obtained as a pale yellow oil (0.66 g, 92%), b.p. 150—154 °C at 0.25 mmHg; $\delta_H$(100 MHz; $CDCl_3$) 0.88 (3 H, t, Me), 1.14 (3 H, d, Me), 1.26—1.96 (24 H, m, 12 × $CH_2$), 2.96—3.40 (4 H, two exchanged by $D_2O$, m, NH, OH, 2 × CHN), and 3.76—3.80 (1 H, m, $CH$OH); $\delta_C$(62.9 MHz; $CDCl_3$) 14.09 ($CH_3$), 18.72 ($CH_3$), 18.76, 22.70, 25.60, 29.36, 29.63, 29.70, 29.80, 29.89, 30.89, 31.93, 37.64, 38.06 (12-$CH_2$), 47.01, 48.13, and 68.03 (3 CH) (Found: $M^+$, 269.2723. $C_{17}H_{35}NO$ requires $M$, 269.2718).

trans-*Methyl* 2-*Methyl*-6-(2-*oxoundecyl*)*piperidine*-1-*carboxylate* (**24**).—A stirred solution of the above amino-alcohol (0.301 g), in sodium hydroxide (2M; 5 ml) was treated with methyl chloroformate (0.50 g) at 5 °C for 6 h. The recovered 1-methoxycarbonyl derivative was chromatographed on silica (eluant; ethyl acetate) and obtained as an oil (0.312 g, 85%) which could not be distilled; $\delta_H$(60 MHz; $CDCl_3$) 0.87 (3 H, t, Me), 0.90—1.3 (27 H, complex, Me, and 12 × $CH_2$), and 3.4—4.5 (7 H, one exchangeable by $D_2O$, complex, CHOH, 2-CHN, $CO_2$Me); $\nu_{max.}$(film), 3 450, 2 950—2 860, and 1 670 $cm^{-1}$ (Found: $M^+$, 327.2769. $C_{19}H_{37}NO_3$ requires $M$, 327.2772).

Oxidation of this product (210 mg) with Jones' reagent[36] gave the ketone as an oil (116 mg, 55%) after preparative t.l.c. (eluant ether); $\delta_H$(60 MHz; $CDCl_3$) 0.87 (3 H, complex, Me), 1.0—2.4 (29 H, envelope), and 3.68 (3 H, s, $CO_2$Me); $\nu_{max.}$(film) 2 950—2 850, 1 720, and 1 680 $cm^{-1}$ [Found: $M^+$, 156.1027. $C_8H_{14}NO_2$ ($C_{19}H_{35}NO_2$-$C_{11}H_{21}O$) requires $M$, 156.1025].

*Solenopsin A from* trans-2-(2-*Hydroxyundecyl*)-6-*methylpiperidine* (**18**; R = Me, $R^1$ = $C_9H_{19}$).—(*a*) The forementioned ketone (**24**) was converted into the corresponding dithioacetal as described above for a related case, and thence into solenopsin A by desulphurisation with Raney Ni and acid hydrolysis of the *N*-methoxycarbonyl group (7.6% for the three steps from the alcohol (**18**). The hydrochloride formed colourless crystals in ethanol, m.p. 109—110 °C, undepressed when mixed with an authentic specimen.

(*b*) A solution of the amino alcohol (**18**; R = Me, $R^1$ = $C_9H_{19}$) (56 mg), *O*-phenyl chlorothiocarbonate (60 μl), and 4-(dimethylamino)pyridine, (5 mg) in acetonitrile (3 ml) was stirred for 3 h under nitrogen. The *O*-thiocarbonate (73 mg) was recovered after preparative t.l.c. A solution of it (55 mg) and freshly distilled tributylstannane (100 mg) and azoisobutyronitrile (1 mg) in toluene (5 ml) was boiled for 10 h, poured into water (10 ml), and extracted with ether. The recovered product (36 mg) after preparative t.l.c. gave pure solenopsin A (22 mg; 16% for the two steps from the amino alcohol), hydrochloride m.p. 107—108 °C.

(*c*) Methanesulphonyl chloride (0.4 ml) and triethylamine (1.4 ml) were added to a solution of the amino alcohol (**18**; R = Me, $R^1$ = $C_9H_{19}$) in dichloromethane (20 ml) at −60 °C, under nitrogen. After 2.5 h at −20 °C the solution was poured into water and the mixture extracted with ether. The ethereal

extract was washed with 2M hydrochloric acid and aqueous sodium hydrogen carbonate and worked up in the customary fashion. The recovered mesylate-sulphonate decomposed on attempted chromatography and was used directly in the next step: $\delta_H$(250 MHz; $CDCl_3$) 0.88 (3 H, t, *J* 6.5 Hz, Me), 1.25—1.45 (14 H, m), 1.50 (3 H, d, *J* 7.0 Hz, Me), 1.55—1.90 (9 H, m), 2.15—2.30 (1 H, m), 3.04 (3 H, s, $SO_2Me$), 3.06 (3 H, s, $SO_2Me$), 3.40—3.60 (1 H, m), 4.20—4.35 (1 H, m), and 4.70—4.85 (1 H, m); $\delta_C$(62.9 MHz; $CDCl_3$) 14.03 (Me), 19.38 ($CH_2$), 19.97 (Me), 22.62, 24.66, 29.22, 29.24, 29.36, 29.41, 29.47, 31.82, 32.01, 35.02, 35.97 (11-$CH_2$), 38.39 (Me), 44.52 (Me), 50.52, 51.72, and 81.27 (3-CH); $\nu_{max.}$(film) 2 927, 2 856, 1 462, and 1 325 $cm^{-1}$; the compound gave no molecular ion in the mass spectrum.

Reduction of this compound (550 mg) in tetrahydrofuran (2 ml) with lithium triethylborohydride in tetrahydrofuran (1M; 6 ml) under nitrogen at room temperature for 12 h gave the corresponding *N*-sulphonamide, obtained after short-column chromatography (eluant: chloroform–light petroleum, 1:9) as an oil (264 mg, 64% from the amino alcohol); $\delta_H$(250 MHz; $CDCl_3$) 0.85 (3 H, t, *J* 6.6 Hz), 1.15—1.35 (18 H, m), 1.43 (3 H, t, *J* 6.9 Hz), 1.45—1.80 (8 H, m), 2.92 (3 H, s), 3.45—3.60 (1 H, m), and 3.90—4.05 (1 H, m); $\delta_C$(62.9 MHz; $CDCl_3$) 14.03 (Me), 19.14 ($CH_2$), 20.27 (Me), 22.62, 26.75, 28.12, 29.28, 29.43 (5-$CH_2$), 29.56 (3-$CH_2$), 29.59, 30.87, 31.86, 32.93 (4-$CH_2$), 44.28 (Me), 50.02, and 55.49 (2-CH); $\nu_{max.}$(film) 2 927, 2 855, 1 463, and 1 325 $cm^{-1}$; the compound showed no molecular ion in the mass spectrum.

Further reduction of this compound (161 mg) in toluene (10 ml) with a solution of sodium bis(2-methoxyethoxy)-aluminium hydride in toluene (3.4M; 1.5 ml) at reflux gave solenopsin A. Chromatography on alumina (eluant: ether–light petroleum, 1:3) gave the pure material as a colourless oil (81 mg) homogeneous by g.l.c. (3% OVI, 215 °C); no isosolenopsin was detected by g.l.c. or in the n.m.r. spectra; $\delta_H$(250 MHz; $CDCl_3$) 0.85 (3 H, t, *J* 6.5 MHz, Me), 1.03 (3 H, d, *J* 6.5 Hz, Me), 1.15—1.65 (27 H, m), 2.78—2.89 (1 H, m), and 2.95—3.03 (1 H, m); $\delta_C$(62.9 MHz; $CDCl_3$) 13.99 (Me), 19.59 ($CH_2$), 21.18 (Me), 22.61, 26.43, 29.28 (3-$CH_2$), 29.58 (2-$CH_2$), 29.61 (2-$CH_2$), 29.75, 30.88, 31.86, 33.04, 34.13 (5-$CH_2$), 45.84, and 50.83 (2-CH) (Found: C, 80.7; H, 13.7; N, 5.5. Calc. for $C_{17}H_{35}N$: C, 80.6; H, 13.9; N, 5.5%).

*1-Benzyl-6-(2-hydroxyundecyl)-2-methylpiperidine* (**26**).—Benzyl bromide (1.0 g) was added to a solution of the perhydroisoxazolopyridine (**17**; R = Me, $R^1 = C_9H_{19}$, 0.71 g) in dichloromethane (3 ml). After 24 h solvent and an excess of benzyl bromide were removed under reduced pressure and the residue was crystallised from ether–chloroform to give the salt as colourless deliquescent crystals (0.98 g), m.p. 131—132 °C.

The salt (1.17 g) was reduced with zinc dust (2.15 g) in acetic acid (10M; 50 ml) at reflux for 3.5 h. The piperidine was recovered as a colourless oil (831 mg; 86%); $\delta_H$(250 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 6.6 Hz), 0.99—1.48 (23 H, envelope), 1.62—1.70 (2 H, m), 1.81—1.86 (1 H, m), 2.19—2.20 (1 H, m), 3.13—3.28 (2 H, m), 3.65—3.80 (3 H, m), 5.18 (1 H, br s), and 7.21—7.32 (5 H, m); $\delta_C$(62.9 MHz; $CDCl_3$) 14.05 (Me), 18.63 (Me), 20.33, 22.67, 23.86, 26.10, 27.14, 29.31, 29.60 (7-$CH_2$), 29.64 (2-$CH_2$), 31.90, 34.62, 36.34 (3-$CH_2$), 48.73 (CH–N), 49.60 ($PhCH_2N$), 50.98 (CH–N), 70.29 (CHO), 127.00, 128.30, 129.34 (5-CH), and 139.71 (1-C) (Found: $M^+$, 359.3183. $C_{24}H_{41}NO$ requires $M^+$, 359.3188).

*1-Benzylsolenopsin* (**28**) *and 1-Benzyl-2-methyl-6-nonylperhydroazocine* (**29**).—Butyl-lithium (1.48M in hexane; 440 μl) was added to a solution of the above 1-benzyl-6-(2-hydroxyundecyl)-2-methylpiperidine (220 mg) in tetrahydrofuran (2 ml) at −58 °C, followed, after 20 min by methanesulphonyl chloride (50 μl) at −20 °C. The reaction mixture was allowed to rise to room temperature and solvent and the excess of methanesulphonyl chloride were removed under reduced pressure. The crude mesylate, which showed two closely contiguous spots on t.l.c. (eluant: chloroform–methanol, 9:1) was reduced directly with a solution of lithium triethylborohydride in tetrahydrofuran (1M; 2 ml) at room temperature for 36 h under nitrogen. The recovered product gave two components as colourless oils on column chromatography over Kieselgel 60H (eluant: chloroform–light petroleum, 1:1). The faster running (57 mg), provisionally regarded as the perhydroazocine (**29**), had $\delta_H$(250 MHz; $CDCl_3$) 0.91 (t, 3 H, *J* 7.0 Hz), 1.00 (d, 3 H, *J* 6.5 Hz), 1.1—1.8 (envelope, 26 H), 2.58—2.72 (1 H, m), 2.80—2.96 (1 H, m), 3.71 and 3.79 (2 H, dd, *J* 14.0 Hz and 14.0 Hz, $PhCH_2$), and 7.2—7.4 (5 H, m); $\delta_C$(62.9 MHz; $CDCl_3$) 14.07 (Me), 18.27 (Me), 22.68, 26.69, 26.92, 27.59, 28.50, 29.34, 29.61, 29.70, 30.06, 31.92, 32.87, 35.17, 35.37 (13-$CH_2$), 49.51 (CH–N), 49.90 ($PhCH_2$), 53.55 (CH–N), 126.31, 127.33, 141.94 (5-CH), and 141.94 (1-C) (Found: $M^+$, 343.3231. $C_{24}H_{41}N$ requires *M*, 343.3239).

The slower running component from the chromatogram (63 mg), could not be obtained completely pure, but is mainly *N*-benzylsolenopsin A as shown by its subsequent conversion into the latter: $\delta_H$(250 MHz; $CDCl_3$) 0.90 (t, 3 H, *J* 7.0 Hz), 1.0—2.0 (envelope, 29 H), 2.8—3.0 (1 H, m), 3.0—3.2 (1 H, m), 3.7 and 4.1 (dd, 2 H, *J* 14 Hz and 14 Hz), and 7.2—7.6 (5 H, m); $\delta_C$(62.9 MHz; $CDCl_2$) 14.03, 17.31 (2-$CH_3$), 18.75, 22.66, 25.62, 26.34 (4-$CH_2$), 29.3—29.6 (8-$CH_2$), 31.91 ($CH_2$), 52.00 ($CH_2$ and CH), 55.76 (CH), 127.65, 128.58, and 129.59 (5-CH) (the aromatic C was not observed) (Found: $M^+$, 343.3246. $C_{24}H_{41}N$ requires *M*, 343.3239).

Debenzylation of this compund (108 mg) was effected with palladium–carbon (10%; 100 mg) and anhydrous ammonium formate[37] (100 mg) in boiling methanol for 6 h. The recovered product had $^1H$ and $^{13}C$ n.m.r. spectra essentially identical with those of solenopsin A; g.l.c. showed the presence of *ca.* 15% of a second component with retention time identical with that of isosolenopsin.

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