Synthesis of Morphine Analogues. Part 2.[1] Substituted Pyrrolo[3,4-*h*]-isoquinolines

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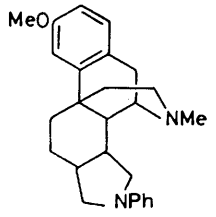
9-*p*-Anisyl-8-methyl-2-phenyl-2,3,3a,4,6,7,8,9,9a,9b-decahydro-1*H*-pyrrolo[3,4-*h*]isoquinoline has been synthesised from 1-methyl-4-vinylpyridinium iodide in five steps.

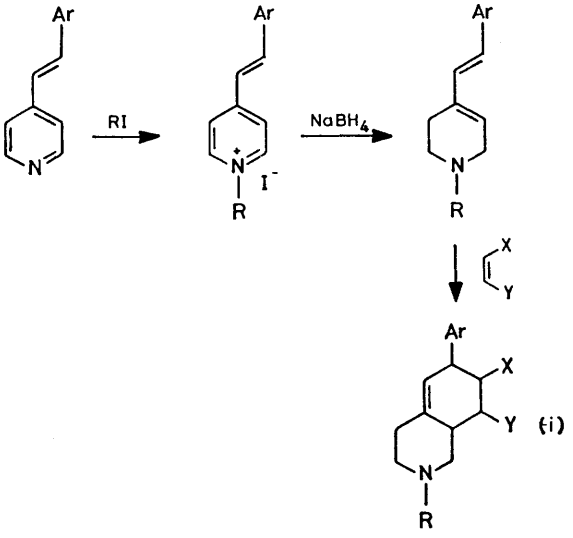
As part of a study of the effect of extending the morphinan ring skeleton on analgesic activity, compound (1) was required. We describe here the synthesis of the



(1)

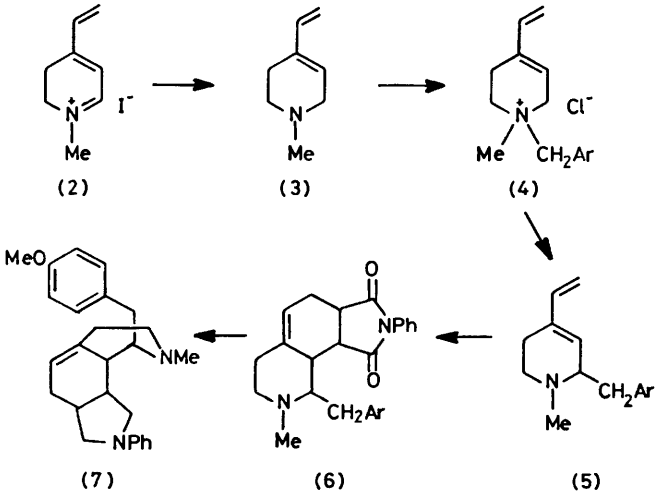
appropriately substituted isoquinoline intermediate (7) (Scheme), based on the general route to isoquinolines shown in reaction (i).[2,3] The aryl group from this reaction was not required since the morphinan derived from this isoquinoline would be correspondingly substituted at C-6. In its absence, however, the 4-vinylpyridine and its derivatives polymerise readily and difficulties were to be expected in the early stages of the synthesis.

The quaternary salt (2) has been obtained previously, in 25% yield, from 4-vinylpyridine with iodomethane in 1,2-dimethoxyethane, the remainder of the olefin apparently undergoing polymerisation,[4] but with minor modifications we obtained a quantitative conversion. An attempt to dissolve the salt in aqueous alkali, preparatory to reduction by $NaBH_4$, caused almost immediate polymerisation, but reduction was successful when small portions of $NaBH_4$ were added to a suspension of the salt in methanol. However, the monoene (8) was formed in addition to the required diene (3); as reaction proceeded, the proportion of the former was found (g.l.c.) to increase until it was the dominant product. We found that compound (3) is not itself reduced to (8) under these conditions, suggesting that whereas the formation of (3) is initiated by hydride-uptake at the pyridine C-2, as in reaction (ii), the formation of (8) is initiated by attack at olefinic carbon [reaction (iii)].



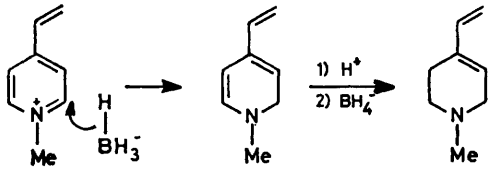
The increase in the proportion of the latter with time suggested, then, that the products complex with boron through their basic nitrogen atoms to give species, $\geq\overset{+}{N}-\overset{-}{B}H_3$, which are more hindered than BH_4^- and are more selective in favour of the olefinic carbon. If this is so, then addition of the salt (2) to a large excess of $NaBH_4$ would be expected to increase the relative yield of the required (3). This proved to be the case: reaction at −50 °C gave an approximately quantitative yield of the two reduction products, of which the major product was the required (3). Chromatography gave up to 60% of the diene; a trace of monoene contaminant could be disregarded since it would not take part in the subsequent Diels–Alder reaction.

We studied the Diels–Alder reactions of the diene (3)



SCHEME

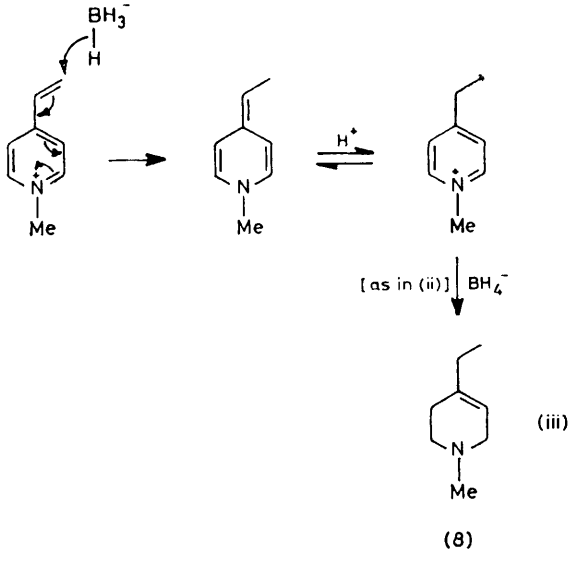
before attempting to introduce the 4-methoxybenzyl substituent. With maleic anhydride, only a black, intractable tar could be obtained, but reaction with *N*-phenylmaleimide gave the adduct (9) in 63% yield.



(ii)

(3)

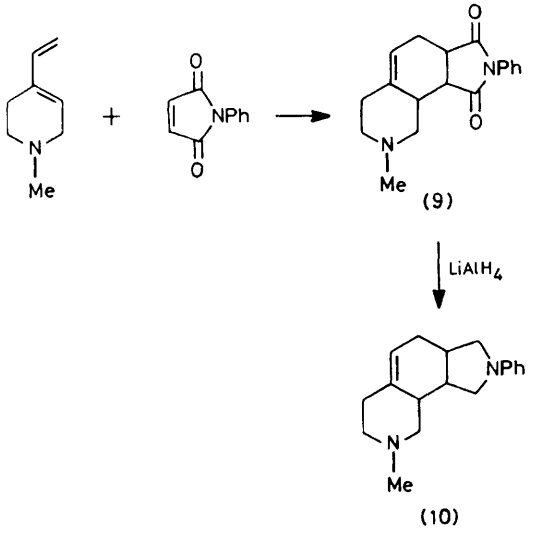
Similar dienes have been found to behave likewise towards these dienophiles.[3] Reduction of the adduct with lithium aluminium hydride did not occur in CH_2Cl_2–Et_2O, but gave (10) in THF.[5]



(iii)

(8)

We returned to the problem of introducing the required substituent into the 2-position of the diene (3). Our first approach was to attempt to form the triene (11) and reduce it to the diene (5), but reaction of the salt



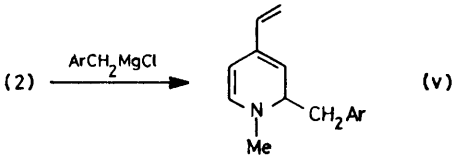
(iv)

(10)

(2) with 4-methoxybenzylmagnesium chloride gave only a low yield of basic products, not including (11). The failure probably stems from the insolubility of the salt in solvents suitable for Grignard reagents.

The alternative route, (3) ⟶ (4) ⟶ (5), was at first less attractive because of the low yields reported for Stevens rearrangements in comparable cases;[6] yields of the required amine are usually <20% in the benzomorphan series.[7]

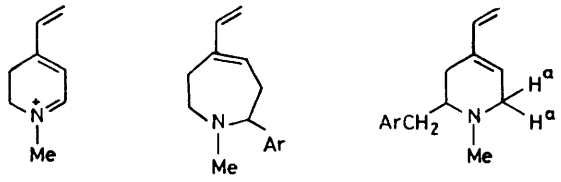
Most of the amine (3) was recovered after stirring with 4-methoxybenzyl chloride in ether or acetone–ether,



(v)

(11)

even after 20 days; the little that had reacted had mostly polymerised. Reaction in the absence of a solvent gave a glass which, when dissolved in methanol, was found to contain a large amount of the starting materials. However, quaternisation was successful when it was carried out in refluxing ether which was removed over 24 h in a stream of nitrogen; after five such treatments the reactants had been consumed and the salt (4) was obtained as a hygroscopic white cake. Treatment with phenyllithium gave the required rearrangement product (5) in up to 47% yield from (3). [The structure of (5) followed from its ^1H n.m.r. spectrum, which showed four vinylic protons, and from its mass spectrum, the base peak in which accorded with the stable ion (12), expected by loss of the 4-methoxybenzyl radical from the molecular ion. The latter is not consistent with the structure (13) produced by carbanion formation at the benzylic carbon followed by ring-enlargement, and the absence of n.m.r. signals for the protons H^a rules out the third possible Stevens product (14) (which is in any case less probable than (5) since the intermediate carbanion lacks the stabilising influence of conjugation with the olefinic bonds).]

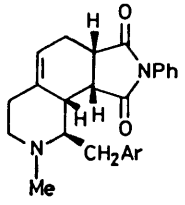


(12) (13) (14)

The Diels–Alder conversion of (5) into (6) was accomplished in 64% yield, and the reduction of (6) to give (7) was effected with $LiAlH_4$ in tetrahydrofuran in up to 65% yield. It is presumed that in the former reaction the dienophile approaches from the side opposite the benzylic substituent, to give (15) and its enantiomer, and that this stereochemistry is preserved in the reduction.

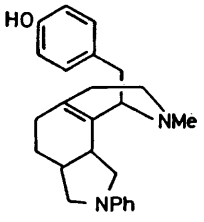
Attempts to induce cyclisation of (7) to form (1),

especially by acid-catalysed reactions (Grewe procedure [8]), were unsuccessful. Treatment with 88% phosphoric acid at 140—150 °C for 2 days gave a mixture of which the chief component, although not fully



(15)

characterised, had spectra (mass and ^1H and ^{13}C n.m.r.) consistent with structure (16); there was also evidence for the presence of a diastereoisomer of (16) and for (17). 48% Hydrobromic acid at 145 °C for 24 h also gave (16) and probably a diastereoisomer; fluoroboric acid at 100—110 °C behaved similarly. More extensive isomerisation occurred when the boron trifluoride–ether complex was used in refluxing trifluoroacetic acid; (18) was formed. Demethylation could be avoided by the use of fluorosulphonic acid at room temperature, but although the starting material disappeared rapidly, only the isomer believed to be (19) was formed; nor did



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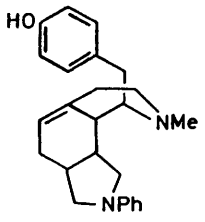

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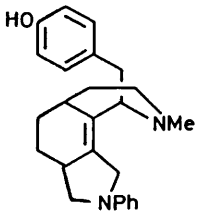

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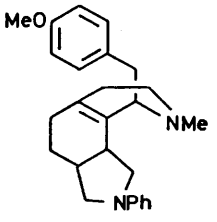

(19)

cyclisation occur when the temperature was raised to 90 °C. Finally, we hoped to effect cyclisation by addition of an iodine atom to the less substituted carbon of the olefinic double bond in (7), followed by ring-closure, but no reaction occurred when a mixture of (7) and iodine was irradiated under conditions which yield iodine atoms.[9]

The octahydroisoquinolines (10) and (16) were completely devoid of analgesic action in the standard phenylquinone writhing [10] and rat tail pressure [11] tests.

EXPERIMENTAL

General methods and the sources of materials have been described.[1]

1-Methyl-4-vinylpyridinium Iodide (2).—Freshly distilled 4-vinylpyridine (1 equiv.) was added to a solution of iodomethane (5 equiv.) in 1,2-dimethoxyethane (12.5 cm³ per 1 cm³ CH_3I) at 0—5 °C. After 3—4 days 1-methyl-4-vinylpyridinium iodide was isolated by filtration as bright yellow needles (93—100%), m.p. 270.5—272 °C (lit.,[12] 270—271.5 °C) or, with rapid heating, 137—140 °C (decomp.) (lit.,[4] 137 °C); τ (D_2O) 1.2—2.2 (4 H, m, ArH), 2.7—4.3 (3 H, m, $CH{=}CH_2$), and 5.68 (3 H, s, NMe).

1-Methyl-4-vinyl-1,2,5,6-tetrahydropyridine (3).—A suspension of the salt (2) (15 g) in methanol (300 cm³) at −50 °C was added rapidly to sodium borohydride (9.2 g) in methanol (300 cm³) at −50 °C in a large (2 l) flask. The initial reaction was vigorous, with frothing, and subsequently the temperature was allowed to rise slowly, with stirring, to room temperature. After a further 30 min, 2M-HCl was added to pH <1. The methanol was removed under reduced pressure and, after basification (NH_3), the mixture was extracted with ether. The ethereal extract was dried ($MgSO_4$) and the solvent was removed by distillation. Chromatography on alumina with methanol as eluant gave the diene (3), increasingly contaminated with the monoene (8) (identified by g.l.c.-mass spectrometry). When the ratio of (3) to (8) in the eluant had decreased to *ca.* 10 : 1, the eluate was acidified to *ca.* pH 1 (2M-HCl) and then worked up as above to give the diene (3) (4.16 g); τ 3.4—5.3 (4 H, m), 7.0 (2 H, br, d), and 7.3—8.0 (*ca.* 7 H, m). Further elution, until the ratio of (3) to (8) was *ca.* 1 : 1, gave a further batch for addition to the next reaction mixture. Both this and the diene (in Et_2O) were stored at low temperature with the addition of a small quantity of hydroquinone. When a mixture of (3) and (8) (74 mg) was stirred in ethanol (1 cm³) with an excess of sodium borohydride for 3 h, g.l.c. showed that the relative amounts of the two (1.6 : 1) were unchanged.

1-(4-Methoxybenzyl)-1-methyl-4-vinyl-1,2,5,6-tetrahydropyridinium Chloride (4).—4-Methoxybenzyl chloride (10.1 g) in dry ether (55 cm³) was added with stirring to the diene (3) (7.5 g, containing *ca.* 10% of the monoene) in dry ether (80 cm³). A slow stream of nitrogen was passed over the solution under reflux until all the solvent had been removed (*ca.* 24 h). Ether (50 cm³) was added to the resulting white cake, and g.l.c. showed the presence of a large amount of unchanged amine. The mixture was again heated in a stream of nitrogen, and after five such treatments essentially no amine remained. The white solid (4) had τ(D_2O) 2.4—3.0 (4 H, m, ArH), 3.2—3.8 (*ca.* 4 H, m, olefinic H), 5.48 (2 H, s, NCH_2Ar), 5.9—6.5 (*ca.* 7 H, m, including s at 6.1, OMe and $CH_2{-}N{-}CH_2$), 6.95 (3 H, s, NMe), and 7.25 (*ca.* 2 H, br, $=C{-}CH_2$).

2-(4-Methoxybenzyl)-1-methyl-4-vinyl-1,2,5,6-tetrahydropyridine (5).—A suspension of the white solid (4) [originally from the diene (3); 7.5 g] in ether (270 cm³) under dry N_2 was treated with phenyl-lithium (61 cm³ of a 2M-solution in $PhH{-}Et_2O$). After the vigorous reaction had subsided, the solution was heated under reflux for 1.5 h, poured onto ice, and extracted with ether. The extract (4 × 100 cm³) was dried ($MgSO_4$) and evaporated; chromatography of the residue on silica gel with methanol gave the product (5) (6.86 g); τ 2.7—3.4 (4 H, m, ArH), 3.5—5.3 (4 H, m, olefinic H), 6.25 (3 H, s, OMe), and 6.4—8.0 (*ca.* 10 H, m). Further elution gave a compound believed to be the corresponding derivative from the monoene (8); τ 2.8—3.4 (4 H, m, ArH), 4.9 (1 H, br, olefinic H), 6.3 (3 H, s, OMe), 6.7—8.5 (*ca.* 12 H, m), and 9.1 (*ca.* 3 H, t, CH_2CH_3).

Diels–Alder Reactions.—When a mixture of the diene (3) (62 mg) and maleic anhydride (49 mg) in toluene (1 cm^3) or ether (1 cm^3), or without solvent, was heated under reflux in nitrogen, it became cloudy and deposited a red oil which darkened to give a black tar.

N-Phenylmaleimide (6.4 g) was added to the amine (3) [2.2 g, contaminated with *ca.* 15% of (8) and a trace of hydroquinone] in dry toluene (40 cm^3). After 16 h at 60 °C under nitrogen, the toluene was removed under reduced pressure, and benzene (40 cm^3) was added and evaporated off to leave the adduct (9); τ 2.5—3.1 (5 H, m, ArH), 4.47 (*ca.* 1 H, br, =CH), and 6.4—8.3 (*ca.* 15 H, m); *m/e* 296 ($M^{+\cdot}$). Its solution in isopropyl alcohol was treated with HCl in ether to precipitate the hydrochloride. This was converted into the *picrate*, m.p. 118—124 °C [from ethanol–light petroleum (b.p. 60—80°)], and was probably a mixture of diastereoisomers (4 spots on t.l.c.) (Found: C, 54.9; H, 4.6; N, 13.4. $C_{24}H_{23}N_5O_9$ requires C, 54.9; H, 4.4; N, 13.3%). The adduct (9) (1.4 g) in THF (20 cm^3) was treated with lithium aluminium hydride (0.77 g) in THF (20 cm^3), with stirring. After 20 h under reflux, saturated sodium carbonate solution was added and the mixture was extracted with dichloromethane. The extract was dried (Na_2SO_4) and evaporated to give a yellow oil (1 g) which rapidly darkened in air. Chromatography on silica gel with chloroform–methanol (4 : 1 v/v) gave the product (10) (two diastereoisomers by t.l.c.); τ 2.6—3.7 (5 H, m, ArH), 4.6 (1 H, br, =CH), and 6.3—8.5 (*ca.* 18 H, m).

N-Phenylmaleimide (3.16 g) and hydroquinone (20 mg) were added to the amine (5) (2.22 g) in dry toluene (65 cm^3). After 18 h at 80 °C under N_2, the solvent was removed under reduced pressure and benzene was added and likewise removed. Chromatography on silica gel gave, with ethyl acetate, unchanged dienophile and, with methanol, the *adduct* (6) (2.42 g; 64%; single spot on t.l.c.); τ 2.5—3.4 (9 H, m, ArH), 4.3 (1 H, br, =CH), 6.3 (3 H, s, OMe), and 6.8—8.0 (15 H, m); *m/e* 416 ($M^{+\cdot}$) (very weak), 415 ($M - 1$) (very weak), 295 (100%, $M - ArCH_2$), 122 (83.5), 121 (50, $ArCH_2^+$), 91 (39, $C_7H_7^+$), 77 (41, $C_6H_5^+$), and 42 (56, $CH_2{=}N{=}CH_2^+$). The *picrate* had m.p. 108—114 °C (from H_2O–MeOH–EtOH) (Found: C, 59.7; H, 4.9; N, 10.8. $C_{32}H_{31}N_5O_{10}$ requires C, 59.5; H, 4.8; N, 10.8%).

The adduct (6) (2.42 g) in dry THF (27 cm^3) was added dropwise to lithium aluminium hydride (0.89 g) in dry THF (27 cm^3). Reaction and work-up as for reduction of the adduct (8), followed by chromatography on silica gel with $CHCl_3$–MeOH (4 : 1 v/v), trituration with ether–light petroleum (b.p. 40—60°) (1 : 2 v/v), and evaporation of the filtrate gave the *pyrrolidinoisoquinoline* (7) as a colourless oil (1.43 g, 63%) which was pure by t.l.c.; τ 2.5—3.6 (9 H, m, ArH), 4.6 (1 H, br, =CH), 6.3 (3 H, s, OMe), 6.5—8.2 (19 H, m); *m/e* 388 (1.5%, $M^{+\cdot}$), 267 (65, $M - ArCH_2$), 141 (40), 121 (40, $ArCH_2^+$), 106 (30), 91 (100, $C_7H_7^+$), and 77 (25, $C_6H_5^+$).

Attempted Cyclisation of (7).—A solution of (7) (0.16 g) and 88% H_3PO_4 (3 cm^3) was stirred under N_2 for 2 days at 140—150 °C and then dripped into water. Non-basic materials were extracted into ether, and the aqueous solution was basified (NH_3) and extracted with dichloromethane. This extract (50 cm^3) was dried ($MgSO_4$) and evaporated. Preparative t.l.c. (MeOH) gave the compound thought to have structure (16) (11 mg), m.p. 166—169 °C (decomp.) [from benzene–light petroleum (b.p. 60—80°)]; *m/e* 374 (0.5%, $M^{+\cdot}$), 267 (100, M — 4-HO·C_6H_4·CH_2), 107 (35, 4-HO·C_6H_4·CH_2^+), 106 (33), 91 (45), and 77 (47); τ 2.5—3.6 (9 H, m, ArH) and 6.3—8.5 (19 H, m, and 1 H, t centred at 6.4, =C–C*H*–N); and compound (17) (2 mg), m.p. *ca.* 160 °C (decomp.) (see below). Reaction on a larger scale, work-up as before, and recrystallisation from toluene–light petroleum gave 18% of a compound showing properties consistent with structure (16); δ_C 154.9—111.4 (9 lines, 14 C, aromatic and olefinic) and 64.2—25.0 (10 lines, 11 C, aliphatic) (all split as required in the off-resonance spectrum). Preparative t.l.c. (MeOH) of the residue from the mother liquor gave compound (17) (12 mg) [weak ^1H n.m.r. spectrum with olefinic absorption at τ 4.4 but none at τ 6.4 from =C–CH–N, and, apart from no OMe absorption, otherwise similar to that of (7)], *m/e* 374.235 8 (4%, $M^{+\cdot}$) ($C_{25}H_{30}N_2O$ requires 374.235 8), 267 (100, M — 4-HO·C_6H_4·CH_2), 107 (50, 4-HO·C_6H_4·CH_2^+), 91 (58), and 77 (53); and a product (21 mg) believed to be a diastereoisomer of (16) (mass spectra indistinguishable and n.m.r. spectra virtually identical).

A solution of (7) (0.16 g) and 49% hydrobromic acid (3.3 cm^3) was heated under reflux for 3 days. Work-up as above gave the product (16) (0.04 g), and t.l.c. (MeOH) showed the presence of the compound thought to be its diastereoisomer. These two products were also found (t.l.c.) when a solution of (7) (0.15 g) and fluoroboric acid was stirred at 100—110 °C.

A solution of (7) (0.15 g), BF_3–ether complex (1.5 cm^3), and trifluoroacetic acid (1.5 cm^3) was heated under reflux for 3 days. On t.l.c. a single spot appeared over *ca.* 48 h, after which spots with lower R_F values became significant. The major component (18) (identical with that first detected by t.l.c.) was partially purified by column chromatography on silica gel ($CHCl_3$–MeOH, 4 : 1 v/v) and then by t.l.c. ($CHCl_3$–MeOH); τ 2.6—3.6 (9 H, m, ArH), and 6.2—8.4 [*ca.* 22 H, including a singlet at 6.2 (=C–CH_2–NPh) and a triplet at 6.55 (=C–CH–N)]; *m/e* 374 (weak, $M^{+\cdot}$), 267 (M — 4-HO·C_6H_4·CH_2), 106, 91, and 77.

A solution of (7) (0.15 g) and fluorosulphonic acid (3 cm^3) was stirred at room temperature for 1.5 h. Work-up as above and column chromatography on silica gel ($CHCl_3$–MeOH, 4 : 1 v/v) gave a colourless oil (46 mg) thought to be the isomer (19) [τ 2.1—3.6 (9 H, m, ArH), 6.08 (*ca.* 3 H, s, OMe), and 6.3—8.6 (*ca.* 20 H, m, including t at 6.45 for =C–CH–N)]. No further reaction occurred when this compound was stirred with fluorosulphonic acid for 22 h.

By the method of Noyes *et al.*,[9] a mixture of the compound (7) (0.25 *g*) and iodine (0.16 g) in spectroscopic grade hexane (20 cm^3) was irradiated with a 500-W lamp while it was agitated by a slow stream of dry N_2. T.l.c. after 6 h showed only starting material. Dry benzene (5 cm^3) was added to increase the proportion of (7) in solution, but t.l.c. after a further 7 h showed only starting material.

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