Pyridoannelation of Hindered Ketones *via* their Nitrogen Derivatives. Synthesis of 5,6,7,8-Tetrahydro-8,9,9-trimethyl-5,8-methanoquinolines from (+)-Camphor

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The transformation of (+)-camphor into (+)-8,9,9-trimethyl- and (+)-2,8,9,9-tetramethyl-5,6,7,8-tetrahydroquinolines **1** and **2** has been accomplished by three different procedures based on the elaboration of imino or enamino intermediates. The values of the rotatory powers for both the compounds are reported.

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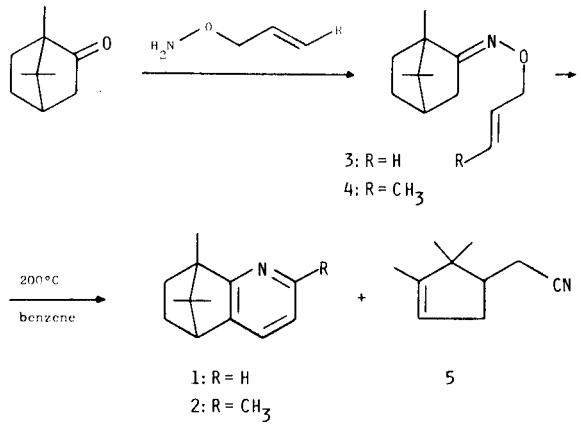
Pyridoannelation is operatively defined as the elaboration of a pyridine nucleus onto an α-methylene carbonyl compound in such a manner that the carbonyl carbon becomes adjacent to the nitrogen in the final product. This kind of synthetic strategy allows the selective synthesis of unambiguously substituted pyridine derivatives and in this respect has been sometimes applied by us to the conversion of chiral aldehydes into optically active alkylpyridines [1].

Pursuing our studies in this field, more recently we focussed our attention on 5,6,7,8-tetrahydroquinolines containing one asymmetric carbon atom in the alicyclic ring [2]. Our interest in these compounds is mainly dictated by the fact that they are the most convenient starting products for the synthesis of the corresponding optically active 2,2'-bipyridines, a new class of chiral ligands for asymmetric reactions [3]. Additionally, chiral tetrahydroquinolines are well suited substrates for the study of the chirooptical properties of the pyridine chromophore: the stiffening of the chiral array determined in the molecule by the ring constraint cuts down drastically the number of the possible conformers that may contribute to the optical activity, resulting in an enhancement of the dissimetry factor and allowing a more reliable attribution of the circular dichroism (c.d.) bands observed [4].

In this paper we report our investigation on the pyridoannelation of (+)-camphor, a typical hindered ketone, to give the two 5,6,7,8-tetrahydro-8,9,9-trimethyl-5,8-methanoquinolines **1** and **2**. In these compounds the bicyclic bridged system adds a further constraint to the aliphatic portion of the molecule and this is expected to result in a higher stereodifferentiating ability of the chiral ligands derived from these pyridines.

Compound **1** had already been prepared by us in connection with a c.d. investigation through thermolysis of (+)-camphor oxime *o*-allyl ether [5]. This preparative method, discovered few years ago by Japanese authors [6], is straightforward for the synthesis of 2,3-cycloalkenopyridines but in the case of camphor derivatives suffers from two strong limitations. First of all, the yields of the reaction are very low and, notwithstanding our efforts, could not be significantly improved in the course of this work (6% in our best run). Secondly, the method is not suited for the preparation of 2-alkylsubstituted derivatives like **2** since pyridine formation is completely prevented when the allyl residue of the substrate bears an alkyl group, as in the case of camphor oxime *O*-crotyl ether (**4**). Actually, heating at 200° for 46 hours this compound brought about the Beckmann fragmentation of the oximino derivative affording as the exclusive reaction product the cyanoolefin **5**, isolated in more than 70% yield.

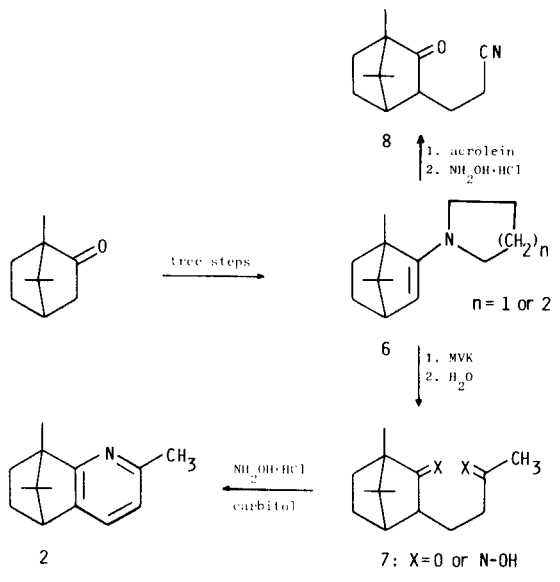
Scheme 1



The structure of **5**, inferred on the basis of ir, nmr and mass spectra, was confirmed by comparison with an authentical sample prepared according to a reported procedure [7]. The same compound albeit in lower amount (60% yield by gc), was identified among the neutral side products formed in the thermolysis of **3** to **1** at 200°, thus indicating that this temperature must be regarded as the upper limit for the thermal stability of these camphor derivatives.

To encompass these difficulties, we turned our attention to a synthetic route that we devised few years ago for the preparation of chiral 2,5-dialkylpyridines [8]. According to

Scheme 2



the procedure reported in Scheme 2, the camphor enamine **6**, readily available through aminolysis of the relevant *N*-nitroimine [9], can be alkylated with the suitable α,β-unsaturated carbonyl compound affording a masked 1,5-dioxocompound to be cyclized to pyridine by treatment with hydroxylamine hydrochloride. Actually, the enamine alkylation took place smoothly with both acrolein and methyl vinyl ketone (MVK), but the structures and even the fate of the adducts were different depending on the nature of the electrophilic olefin employed.

With MVK the pyrrolidino enamine **6** (n = 1) gave in more than 90% yield an adduct, likely the enamino ketone, readily hydrolizable even on exposure to the atmospheric moisture. The hydrolysis product showed ν C=O 1740 and 1710 cm^{-1} in the ir and M^+ = 222 in the mass spectrum, consistent with the structure of the 1,5-diketone **7** (X = O).

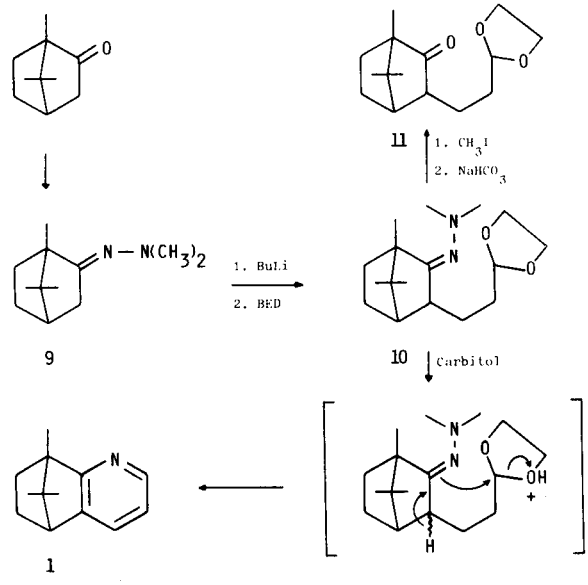
Reaction of the diketone with hydroxylamine hydrochloride in ethanol, either in the presence or not of hydrochloric acid, gave in variable extent the dioxime **7** (X = NOH) which in these conditions did not produce any trace of pyridine **2** but, on prolonging the reaction times, reverted back to camphor oxime. When the same reaction was performed in polar solvents of high boiling point, like ethyl cellosolve or carbitol, the diketone **7** (X = O) could be successfully cyclized to **2**. Even under these conditions the reaction with hydroxylamine hydrochloride took several hours to be completed and the tetrahydroquinoline **2** could be obtained in only moderate yields (25-30%).

The reaction of the enamine **6** (n = 1) with acrolein gave rise to a complex mixture of products and the same result was obtained when the alkylation was performed on the piperidino enamine **6** (n = 2), while we were unable to prepare the still unknown morpholino analogue.

None of the compounds produced in these reactions could be isolated in pure form and surely identified. Nevertheless, a cyclic structure for the acrolein adduct can be confidently suggested on the basis of the lack of the aldehydic proton resonance in the ^{1}H-nmr of the crude reaction product.

Several attempts were performed in order to cyclize either the crude reaction adducts or the relevant hydrolysis products, but the reaction with hydroxylamine hydrochloride failed to give even a trace of the desired pyridine **1**. In most cases, however, processing the neutral extracts during the work up of the reaction mixture allowed to isolate a crystalline product identified as the ketonitrile **8** on the basis of its spectroscopic and analytical data. The same compound was obtained as the main reaction product along with the tetrahydroquinoline **1** (3:1 ratio) in the reaction with hydroxylamine hydrochloride of the keto-acetal **11**, readily prepared by treatment of the methiodide of **10** with aqueous sodium carbonate in a two-phase system (Scheme 3).

Scheme 3



These facts indicate that compound **8** probably originates from the intermediate aldoxime formed in the early stages of the reaction with hydroxylamine hydrochloride, as a consequence of the low reactivity of the sterically hindered keto group. Its formation rules out any possibility to prepare the tetrahydroquinoline **1** according to Scheme 2 even if camphor enamines can be efficiently alkylated by acrolein, because the putative intermediate is more prone to undergo dehydration rather than cyclization.

From this last consideration it follows that a more appropriate synthetic procedure for the preparation of **1** would require the elaboration of an imino derivative of the ketonic rather than the aldehydic carbonyl group. The presence of a good leaving group on the imino nitrogen would be also profitable, facilitating the aromatization of the intermediate dihydropyridine in the cyclization step.

Among the camphor derivatives apt to fit with these requirements, *N,N*-dialkylhydrazones seemed to us the substrates of choice for several reasons. Otherwise from enamines, these compounds are stable and accessible in high yield by direct reaction of camphor with the corresponding hydrazine. Additionally, their α-lithiated derivatives can be easily prepared and are very reactive towards a great variety of electrophiles [10] thus allowing a ready introduction of the suitable three carbon substituent required for the pyridoannelation.

According to Scheme 3, camphor *N,N*-dimethylhydrazone (**9**) was deprotonated with butyllithium and subsequently alkylated at −78° with 2-(2-bromoethyl)-1,3-dioxolane (BED) to give the iminodioxolane **10** in good yield. Heating this compound in acetic acid or in carbitol in the presence of one drop of hydrochloric acid resulted in a clean conversion into the tetrahydroquinoline **1** that could be isolated in pure form in 70-80% yield.

It can be suggested that the formation of the pyridine nucleus occurs through a reaction path involving the opening of the protonated 1,3-dioxolane ring promoted by a nucleophilic attack of the imino nitrogen on the acetalic carbon (Scheme 3). This leads to an intermediate tetrahydropyridine derivative which can attain a facile aromatization through the acid catalyzed elimination of two small molecules, the first of ethylene glycol and the second of dimethylamine.

Since this mechanistic picture seems quite probable even in the absence of direct evidence for the intermediate species, we can draw the conclusion that the overall synthetic sequence is racemization free, as on the other hand could be confidently anticipated simply on the basis of the conservation of the bornane skeleton in the final product. Actually, the values of the optical rotation observed for compound **1** were practically constant in each of the several separate preparations performed by both the allyloxime and the dimethylhydrazone routes. This confirms the absence of racemization in both the synthetic procedures and allows to assume the value $[\alpha]_D^{25}$ +38 (c 2, cyclohexane) as the maximum rotatory power for the tetrahydroquinoline **1**.

Similar arguments hold also in the case of the 2-methyl-substituted analogue **2**, taking into account that the synthetic sequence employed in this case has been previously demonstrated as racemization free. The recorded specific rotation, $[\alpha]_D^{25}$ +25.4 (c 2, cyclohexane) can be then assumed as a reliable value for the maximum rotatory power of the tetrahydroquinoline **2**.

It is worth while to stress that the about 50% overall yield recorded in the dimethylhydrazone mediated conversion of camphor into the tetrahydroquinoline **2** is more than two times higher than those usually obtained by us in the pyridoannelation of carbonyl compounds and this improvement is substantially determined by the very good yield obtained in the last step of the synthesis, the cyclization of the alkylated dimethylhydrazone. This achievement is even more impressive in the present case where a rather hindered substrate is involved and where the final product is afflicted by a considerable strain.

From these considerations, the dimethylhydrazone route appears a valuable synthetic tool for the pyridoannelation of carbonyl compounds and further work is in progress in order to elucidate the potential of this procedure.

EXPERIMENTAL

Boiling points are uncorrected. The gc controls were effected on a Perkin-Elmer 3920-B gas chromatograph, using the columns and the temperature specified. The ir spectra were recorded on a Perkin-Elmer 157 spectrometer. The ^{1}H-nmr spectra at 60 MHz were obtained with a Varian T-60 spectrometer in tetrachloromethane or deuteriochloroform solutions using tetramethylsilane as an internal standard (δ = 0). Mass spectra were measured with a Hitachi Perkin-Elmer RMU-6L spectrometer operating at 70 eV. The optical rotations were taken on a Perkin-Elmer 241 polarimeter in 1 dm tubes. Elemental analyses were performed by a Perkin-Elmer 240-B analyzer.

Materials.

(+)-Camphor ($[\alpha]_D^{20}$ +43.5, c = 10 in ethanol), crotyl bromide, *N,N*-dimethylhydrazine, and 2-(2-bromoethyl)-1,3-dioxolane were commercial products (Fluka AG) and were used without further purification. Acrolein and methyl vinyl ketone (Fluka AG) were stored on 4 Å molecular sieves and distilled just before use. *O*-Allylhydroxylamine hydrochloride was prepared according to Cope, *et al.* [11] (+)-Camphor oxime was obtained by a conventional method. Camphor pyrrolidino- and piperidino-enamine were prepared according to Bondavalli, *et al.* [9].

Camphor Oxime *O*-Allyl Ether (**3**).

A solution of (+)-camphor (3.0 g, 19 mmoles), *O*-allylhydroxylamine hydrochloride (2.47 g, 22 mmoles) in pyridine (10 ml) was heated at 35° for 4 hours and then at 60° for 26 hours. The mixture was cooled and 60 ml of 10% hydrochloric acid and 20 ml of ether were added. The organic layer was separated, washed with water and dried over sodium sulfate. Evaporation of the solvent afforded **3** as a diastereomeric mixture which was used as such in the next reaction, yield 3.74 g (91%); nmr (deuteriochloroform): δ 6.26-5.56 (m, 1 H), 5.40-4.90 (m, 2 H), 4.60-4.26 (m, OCH_2, 2 H); ms: 207 (M^+, 13), 95 (M-112, 100).

Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.3; H, 10.2; N, 6.8. Found: C, 75.1; H, 10.3; N, 6.5.

Camphor Oxime *O*-Crotyl Ether (**4**).

To a stirred solution of sodium ethoxide (0.37 g of sodium in 15 ml of absolute ethanol) a solution of (+)-camphor oxime (2.67 g, 16 mmoles) in absolute ethanol (10 ml) was added. After 10 minutes, crotyl bromide (2.16 g, 16 mmoles) was added and the solution was refluxed for 4.5 hours. After cooling, the mixture was filtered, the filtrate was treated with 30 ml of ether and sodium bromide was removed again by suction. The solvent was evaporated and the oily residue was distilled by bulb-to-bulb to obtain 1.9 g (54% yield) of **4** as a diastereomeric mixture which

was used as such in the next reaction, bp 65-70° (0.03 mm Hg); nmr (deuteriochloroform): δ 5.73-5.53 (m, 2H), 4.53-4.30 (m, OCH_2, 2 H), 1.80-1.60 (m, $CH_3C=$, 3 H).

Anal. Calcd. for $C_{14}H_{23}NO$: C, 76.0; H, 10.5; N, 6.3. Found: C, 75.8; H, 10.5; N, 6.0.

(+) -5,6,7,8-Tetrahydro-8,9,9-trimethyl-5,8-methanoquinoline (**1**).

A solution of crude **3** (7.5 g, 36 mmoles) in dry benzene (40 ml) was heated at 200° for 46 hours in a sealed tube under nitrogen atmosphere. After cooling, the dark reaction mixture was stirred with 10% hydrochloric acid (20 ml) and allowed to settle. The aqueous phase was separated, made alkaline with 10% sodium hydroxide and extracted twice with ether. The combined ether extracts were dried with sodium sulfate and concentrated *in vacuo*. The remaining brown oil was distilled by bulb-to-bulb affording 0.36 g (5.5%) of **1**, bp 130° (11 mm Hg); $[\alpha]_D^{25}$ + 36.8 (c 2.1, cyclohexane); nmr (tetrachloromethane): δ 8.03-7.86 (m, H-2, 1 H), 7.20-7.00 (m, H-4, 1 H), 6.83-6.60 (m, H-3, 1 H), 2.83-2.66 (d, 1 H), 1.26 (s, 3 H), 0.98 (s 3 H), 0.53 (s, 3 H).

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.4; H, 9.1; N, 7.5. Found: C, 83.5; H, 9.3; N, 7.3.

Thermolysis of **4**.

Following the same procedure above described, compound **4** (1.9 g, 8.6 mmoles) in benzene (10 ml) was heated at 200° for 46 hours. After the usual work-up and distillation under reduced presure of the neutral extracts, compound **5** [7] (0.8 g, 62% yield) was isolated, bp 125° (25 mm Hg); ir (neat): 2240 cm^{-1} (C≡N), 1610 cm^{-1} (C=C); nmr (deuteriochloroform): δ 5.15 (m, 1 H), 2.50-2.00 (m, 5 H), 1.55-1.66 (s, 3 H), 1.06 (s, 3 H), 0.80 (s, 3 H).

(+)-3-(3-Oxobutyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**7**, X = 0).

To a stirred solution of camphor pyrrolidino enamine **6** [9] (7.4 g, 36 mmoles) in dry benzene (20 ml), a solution of MVK (2.7 g, 38 mmoles) in dry benzene (10 ml) was added under a nitrogen atmosphere. After 3 hours refluxing, the mixture was fractionally distilled and the product boiling at 141-146° (0.3 mm Hg) was collected. Hydrolysis with 10% hydrochloric acid gave pure **7** (X = 0), (7.8 g, 98% yield), bp 135° (0.3 mm, Hg); $[\alpha]_D^{25}$ +31.0 (c 2.0, cyclohexane); ir (neat): 1740 cm^{-1} (C=O), 1710 cm^{-1} (C=O); nmr (tetrachloromethane): δ 2.71-2.50 (m, 1 H), 2.33-2.00 (m, 2 H), 2.15 (s, 3 H), 1.95-1.85 (m, 1 H), 1.81-1.50 (m, 4 H), 1.32-1.25 (m, 2 H), 0.99 (s, 3 H), 0.88 (s, 3 H), 0.84 (s, 3 H).

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.6; H, 10.0. Found: C, 75.4; H, 10.1.

(+)-2,8,9,9-Tetramethyl-5,6,7,8-tetrahydro-5,8-methanoquinoline (**2**).

A solution of **7** (X = 0) (4.5 g, 20.2 mmoles) and hydroxylamine hydrochloride (2.3 g, 33 mmoles) in diethylenglycol monoethyl ether (70 ml) was refluxed for 24 hours. The cooled mixture was acidified with 10% hydrochloric acid and extracted with ether. The aqueous layer was separated, made alkaline with 10% sodium hydroxide and extracted with ether. The organic extracts were dried over sodium sulfate and the solvent was evaporated. The oily residue was distilled under reduced pressure to yield pure **2** (1.2 g, 30%), bp 85° (0.03 mm Hg); $[\alpha]_D^{25}$ +25.4 (c 2.0, cyclohexane); nmr (tetrachloromethane): δ 7.03 (d, H-4, 1 H, $J_{4,3}$ = 7 Hz), 6.60 (d, H-3, 1 H, $J_{3,4}$ = 7 Hz), 2.70 (d, 1 H), 2.42 (s, 3 H), 1.25 (s, 3 H), 0.96 (s, 3 H), 0.53 (s, 3 H).

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.5; H, 9.5; N, 7.00. Found: C, 83.6; H, 9.4; N, 6.9.

Camphor *N,N*-Dimethylhydrazone (**9**).

A solution of (+)-camphor (22.8 g, 0.2 mole), *N,N*-dimethylhydrazine (27.0 g, 0.45 mole) and a catalytic amount 4-toluenesulfonic acid in absolute ethanol (45 ml) was refluxed for 72 hours. The solvent was removed and the residue taken up with 5% hydrochloric acid and ether. The aqueous layer was separated, made alkaline with a 10% solution of sodium hydroxide and extracted with ether. The organic extracts were dried over sodium sulfate and the solvent was evaporated. Distillation of the residue gave **9** (16 g, 85% yield based on recovered camphor), bp 65° (4 mm Hg); nmr (deuteriochloroform): δ 2.45 (s, 6 H), 1.03 (s, 3 H), 0.97 (s, 3 H), 0.82 (s, 3 H).

Anal. Calcd. for $C_{12}H_{22}N_2$: C, 74.2; H, 11.4; N, 14.4. Found: C, 74.2; H, 11.5; N, 14.2.

3-(3-Ethylenedioxypropyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one *N,N*-dimethylhydrazone (**10**).

A 1.6 *M* solution of butyllithium in *n*-hexane (32 ml) was slowly added under nitrogen to a cooled solution (−75°) of **9** (9.7 g, 50 mmoles) in dry THF (150 ml). The mixture was then warmed to 0° and stirred at this temperature for 0.5 hours. After cooling again to −78°, a solution of 2-(2-bromoethyl)-1,3-dioxolane (9.1 g, 50 mmoles) in dry THF (10 ml) was added and the mixture was allowed to rise slowly to room temperature and stirred for 2 hours. The mixture was hydrolyzed with cold water, extracted with ether and the organic extracts were dried with sodium sulfate. The solvent was evaporated and the oily residue, which contained about 50% of **9** by gc (2 m × 2 mm column packed with 2.5% OV-17 on Chromasorb G 80-100 mesh operating at programmed temperature between 70 and 270°C), was fractionally distilled to give **10** (5.5 g, 66% yield based on recovered **9**), bp 120° (0.03 mm Hg); nmr (deuteriochloroform): δ 4.77 (t, 1 H), 4.00-3.67 (m, 4 H), 2.33 (s, 6 H), 1.00-0.83 (m, 9 H).

Anal. Calcd. for $C_{17}H_{30}N_2O_2$: C, 69.3; H, 10.3; N, 9.5. Found: C, 69.0; H, 10.5; N, 9.2.

3-(3-Ethylenedioxypropyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**11**).

A mixture of **10** (4.7 g, 16 mmoles) and methyl iodide (11.4 g, 80 mmoles) were refluxed for 24 hours. The excess of the halogenide was distilled and the residue was poured into water (50 ml) and extracted twice with *n*-pentane. The aqueous layer was separated and treated with sodium hydrogen carbonate (0.5 g). The alkaline solution was refluxed for 24 hours, extracted with *n*-pentane and the organic extracts dried over sodium sulfate. Evaporation of the solvent and distillation *in vacuo* gave **11** (2.4 g, 60% yield), bp 112° (0.05 mm Hg); nmr (deuteriochloroform): δ 4.80 (t, 1 H), 4.03-3.70 (m, 4 H), 1.03-0.80 (m, 9 H).

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.4; H, 9.6. Found: C, 71.1; H, 9.8.

Conversion of **11** into **1**.

A mixture of **11** (1.8 g, 7.2 mmoles) and hydroxylamine hydrochloride (1.46 g, 21 mmoles) in carbitol (20 ml) was heated at 170° for 1 hour. The mixture was diluted with water (200 ml) and extracted with dichloromethane. The aqueous phase was alkalized with a 10% solution of sodium hydroxide and extracted with ether. Drying with sodium sulfate and evaporation of the solvent gave **1** (0.34 g, 26% yield). Processing the dichloromethane solution afforded 0.95 g (64% yield) of 3-(2-cyanoethyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**8**), mp 64° (*n*-hexane); ir (dichloromethane): 2240 cm^{-1} (C≡N), 1730 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.50 (m, 2 H), 1.06 (s, 3 H), 0.93 (s, 3 H), 0.60 (s, 3 H).

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.1; H, 9.3; N, 6.8. Found: C, 75.8; H, 9.6; N, 6.6.

Direct Conversion of **10** into **1**.

A solution of **10** (2.94 g, 0.01 mole) in carbitol (20 ml) was acidified with a few drops of hydrochloric acid and refluxed for 6 hours. The mixture was alkalized with a 10% solution of sodium hydroxide and extracted with ether. The ethereal phase was dried with sodium sulfate and the solvent was removed. Disillation of the residue under reduced pressure afforded 1.5 g (80% yield) of pure **1** $[\alpha]_D^{25}$ +38.0 (c 2.03, cyclohexane).

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