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A NEW SYNTHETIC ROUTE TO TROPANE ALKALOIDS. PSEUDOTROPINE AND TROPACOCAINE

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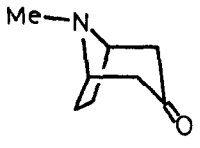
Summary: Pseudotropine and tropacocaine have been synthesized by a facile route involving the [4 + 2] nitroso cycloaddition followed by internal S_N2 displacement.

The tropane class of alkaloids have continued to elicit the unabated interests among organic chemists because of their pharmacological significance, and a great deal of work has been done on the stereochemical and synthetic problems.[1] Since a superb approach to tropinone (1) was devised by Robinson,[2] a number of syntheses of some tropanes have been reported.[1] However, except for two instances of new approach to tropane alkaloids,[3,4] efficient methods for the preparation of natural products are limited. We herein report a facile new route to the naturally occurring tropane alkaloids, pseudotropine (3) and tropacocaine (4). The approach employs a Diels-Alder cycloaddition of cyclohepta-1,3-dienes with nitroso compounds followed by an intramolecular C-N bond formation. Interestingly, a survey of the literature revealed that there are the only Diels-Alder cycloaddition of the seven-membered ring with the nitroso compound.[5]



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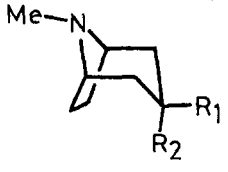


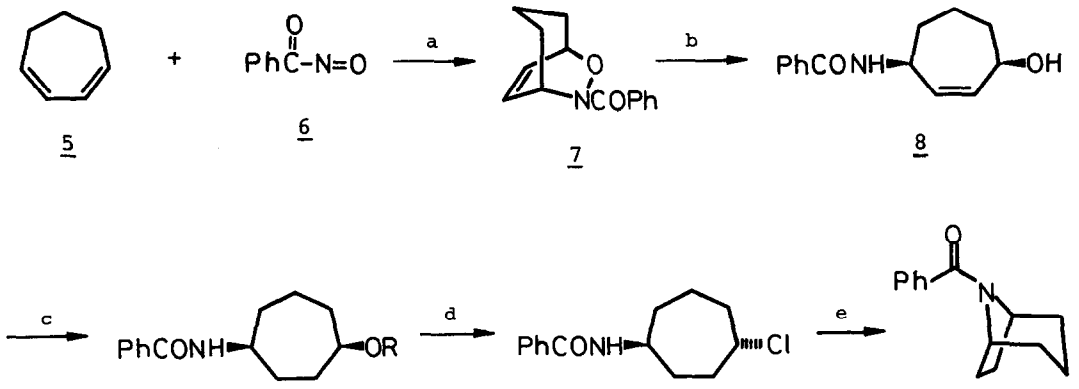
2 R_1 = H, R_2 = OH
3 R_1 = OH, R_2 = H
4 R_1 = OCOPh, R_2 = H

The model study for constructing the tropane skeleton is outlined in Scheme I. The sequence was initiated by the reaction of cyclohepta-1,3-diene (5) with nitroso compound 6, generated *in situ* from *N*-benzoylhydroxylamine and tetrapropylammonium periodate,[6] affording the [4 + 2] cycloadduct 7, mp 101-102 °C, in 65% yield. Reductive N-O bond cleavage of 7 with sodium amalgam in ethanol (Na_2HPO_4, 0 °C) generated the unsaturated amide alcohol 8, mp 157-159 °C, in 77% yield. Hydrogenation of 8 over palladium on carbon in methanol gave the saturated amide alcohol 9 (84%), mp 143.5-145 °C, which was treated

with thionyl chloride (Et_3N, $CHCl_3$, r.t., 14 h) to furnish the chloride 11 (76%), mp 157-159 °C. Compound 9 was also converted to the mesylate 10 (Et_3N, $CHCl_3$, -20 °C, 5 min) in 88% yield, mp 124-126 °C.

Although cyclization of the mesylate 10 using a variety of strong bases was unsuccessful, desired *N*-benzoyl nortropane (12), mp 93.5-95 °C (lit.[7] mp 94-95 °C), was obtained in 87% yield, when the chloride 11 was treated with potassium *tert*-butoxide in a 1:1 HMPA-benzene solution at room temperature for 15 h. This transformation presumably involves an internal S_N2 process, and hence the cyclization may have occurred preferentially in the *trans*-amide 11 rather than *cis*-amide 10 since the benzoylamino group in 11 is correctly disposed for a backside displacement of the anionic leaving group.

Scheme I



5 + 6 → 7 → 8

9 R = H
10 R = Ms

11

12

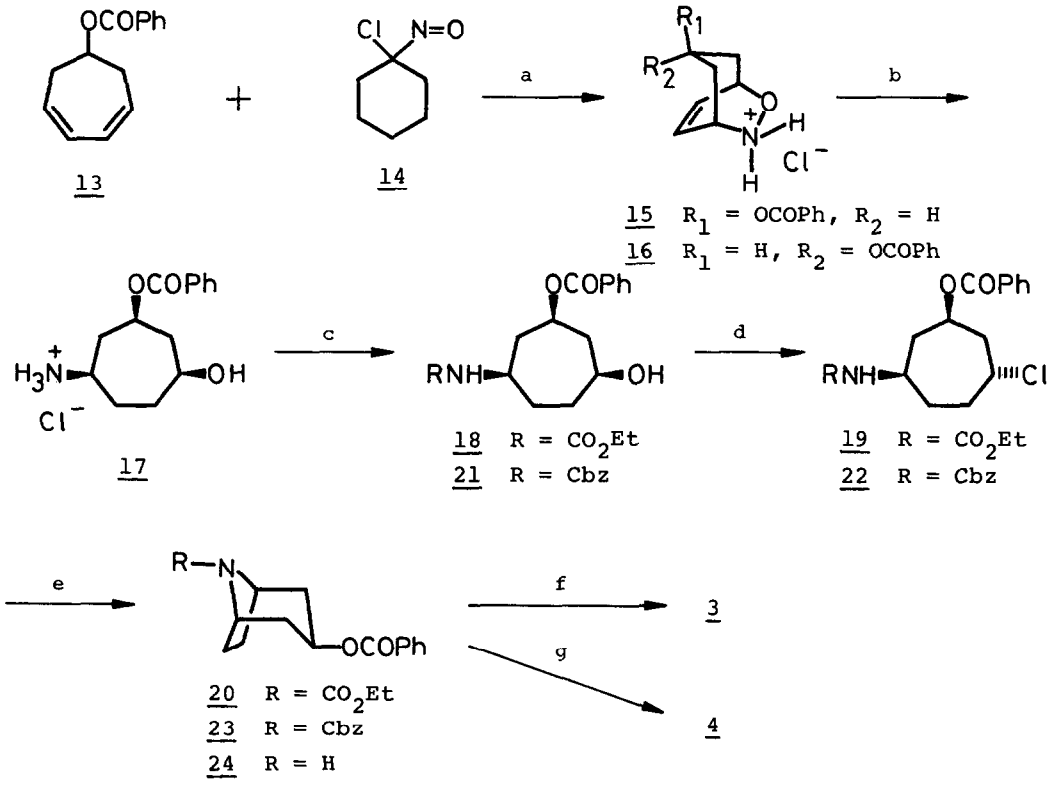
(a) $CHCl_3$-DMF, r.t. (b) Na-Hg, Na_2HPO_4, EtOH, 0 °C (c) H_2, Pd-C, MeOH
(d) $SOCl_2$, Et_3N, $CHCl_3$ (e) t-BuOK, HMPA-benzene, r.t.

Thus having developed the method for the preparation of the tropane based on nitroso cycloaddition, we sought to apply this to the synthesis of naturally occurring tropane alkaloids. Attempted cycloaddition of cyclohepta-3,5-dienyl benzoate (13), prepared in three steps from cycloheptatriene,[8] with the nitroso compound 6 under the same conditions noted above for the preparation of the cycloadduct 7 was not successful.

We then turned to application of 1-chloro-1-nitrosocyclohexane (14)[9] as the dienophile. Thus the reaction of 13 with 14 in a carbon tetrachloride-ethanol (3:2) solution at -20 °C for 2 weeks generated a 79:21 mixture (by 270-MHz ^1H NMR) of the oxazabicyclononene hydrochlorides 15 and 16, respectively (total yield: 72%). The major cycloadduct 15, mp 187-188 °C (decomp), which was read-

ily separable from 16 because of only slight solubility and the ease of crystallization, was converted to pseudotropine (3) as outlined in Scheme II.[10] Thus catalytic hydrogenation (Pd-C, MeOH) of 15 gave the amino alcohol hydrochloride 17, mp 212-214 °C (decomp), in quantitative yield, which was then subjected to selective *N*-acylation (EtOCOCl, aq. Na_2CO_3, $CHCl_3$, 0 °C → r.t.) furnishing the carbamate 18, mp 120-122 °C, in 84% yield. Chlorination of 18 with thionyl chloride (pyridine, $CHCl_3$, 0 °C → reflux) gave 19 (oil) in 55% yield. Construction of the tropane skeleton was effected by intramolecular cyclization of 19 in the similar way described above for the synthesis of *N*-benzoyl nortropane (12). Thus, 19 was treated with potassium *tert*-butoxide in 1:1 benzene-HMPA at 0-5 °C for 2 h to afford 20 as an oil in 46% yield. Reduction of 20 with $LiAlH_4$ provided pseudotropine (3), mp 108-109 °C (lit.[11] mp 108-109.5 °C); picrate, mp 258-259 °C (decomp) (lit.[12] mp 258-259 °C (decomp)), in 67% yield. The ^{13}C NMR data for synthetic 3 was identical with those reported in the literature.[13]

Scheme II



(a) CCl_4-EtOH (3:2), -20 °C, 2 weeks (b) H_2, Pd-C, MeOH (c) EtOCOCl or $PhCH_2OCOCl$, aq. Na_2CO_3, $CHCl_3$, 0 °C → r.t. (d) $SOCl_2$, Py., $CHCl_3$, 0 °C → reflux (e) *t*-BuOK, benzene-HMPA, 0-5 °C (f) $LiAlH_4$, THF, reflux (g) i) H_2, Pd-C, MeOH ii) HCO_2H, HCHO, reflux

A Alternatively, with 17 in hand, we attempted to utilize the above sequence in the synthesis of tropacocaine (4). Benzyloxycarbonylation of 17 in the usual way gave the carbamate 21, mp 114-116 °C, in 96% yield. Chlorination of 21 with thionyl chloride in the same manner described for the peparation of 19 yielded 22 in 36% yield.[14] The base induced cyclization of 22 under the same conditions used for 19 was effected to yield 23 in 75% yield. Deprotection by catalytic hydrogenation (Pd-C, MeOH) converted 23 into *N*-nortropacocaine (24) which subsequently underwent Eschweiler-Clarke reaction (HCHO, HCO_2H, reflux) to provide desired tropacocaine (4), picrate, mp 238-241 °C (decomp) (lit.[15] mp 240-242 °C), in 71% yield from 23. Synthetic 4 had the identical ^{13}C NMR data with those reported in the literature.[16]

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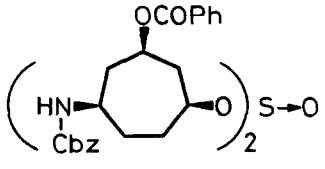

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