Investigations of analogous reactions for Me_2SbI, $MeSbI_2$, Me_3As and Me_2AsI are in progress.

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Synthesis of racemic and chiral codeine and morphine *via* the dihydrothebainones. (Chemistry of opium alkaloids, Part XI)*

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Abstract.—Racemic and chiral 1-(3,5-dibenzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (**1**, Scheme) were N-methylated, which gave **2a**. A Birch reduction converted **2a**, *via* **2b**, into the 1,4-diene **3**. Acid-catalysed cyclization of **3** gave the morphinan **4**. Selective removal of the hydroxyl group in position 2, *via* the 1-phenyl-5-tetrazolyl ether (**5**), by hydrogenolysis, yielded (−)-dihydrothebainone (**6**). The conversion of **6** into (−)-codeine and (−)-morphine is known. In this way our preceding synthesis is shortened by two steps.

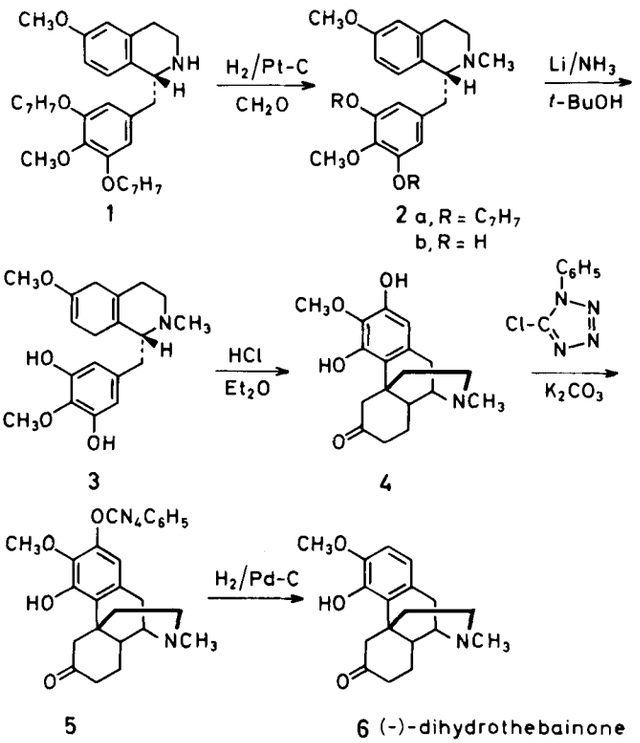
Introduction

Recently we published the details[1] of a previously reported total synthesis of codeine and morphine[2]. Here *N*-formylnordihydrothebainone occupied a key position. The *N*-formyl group was introduced in order (i) to mask the nitrogen, (ii) to promote the acid-catalysed ring closure to the morphinan skeleton, while moreover (iii), by reduction, the desired *N*-methyl compound was obtained[3]. This route produced good yields, but is comparatively long and appeared to admit of shortening.

An investigation into a direct methylation, instead of introduction of the methyl group *via* a formyl group, shows that this is also possible, provided that it is performed before the Birch reduction. The *ortho* positions of the symmetrically substituted 1-benzyl derivative subsequently obtained are found to be sufficiently activated for the acid-catalysed ring closure. The partial etherification of the hydroxyl group in position 2 proceeds more satisfactorily with the *N*-methyl compound. Purification of the last three *N*-methyl intermediates (**3**, **4**, and **5**) was no longer necessary and the synthetic pathway[1,2] could be shortened by two steps, while the overall yield was higher.

Results and discussion

Both racemic and chiral 1-(3,5-dibenzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline[1] (**1**, Scheme) were methylated in order to use a *N*-methylisoquinoline for the acid-catalysed ring closure to the morphinan skeleton. The methylation with formaldehyde and hydrogen in the presence of platinum on carbon to **2a** took place quantitatively, the benzyl ether groups remaining intact. When these benzyl groups are first removed, with the aid of palladium on carbon, by hydrogenolysis, it is found that the *N*-methylation can no longer be performed. This is in contrast with the *N*-formylation, which did not proceed satisfactorily until after splitting-off of the benzyl ether groups, as in the Birch reduction.



Scheme. Synthesis of (−)-dihydrothebainone (**6**).

Negative Cotton effects near 240 and 280 nm in the ORD spectrum of (+)-**1** indicate the (*R*) configuration of the 1-benzylisoquinoline derivative[4], and this product ultimately yields the (−)-dihydrothebainone with the natural absolute configuration. This may also be inferred from the synthesis of the corresponding *N*-formyl derivatives[1]. The synthesis was therefore performed further with the (*R*) compounds; up to and including compound **5**, the racemic compounds were also used.

Racemic- and (*R*)-**2a** were converted into **3** by means of a Birch reduction. With the aid of TLC, it was found that the two benzyl ether groups split off first, considerably more slowly than with the corresponding >NH compound. Addition of *tert*-butanol as proton donor then gave a rapid further reduction to **3**. To enable us to follow the conversions more effectively and for characterization, **2a** was debenzylated to **2b** by means of a hydrogenolysis with the aid of palladium on carbon.

* For Part X, see: reference 1.

[1] *H. C. Beyerman, J. van Berkel, T. S. Lie, L. Maat, J. C. M. Wessels, H. H. Bosman, E. Buurman, E. J. M. Bijsterveld* and *H. J. M. Sinnige*, Recl. Trav. Chim. Pays-Bas **97**, 127 (1978).

[2] *H. C. Beyerman, T. S. Lie, L. Maat, H. H. Bosman, E. Buurman, E. J. M. Bijsterveld* and *H. J. M. Sinnige*, Recl. Trav. Chim. Pays-Bas **75**, 24 (1976).

[3] *H. C. Beyerman, L. van Bommel, L. Maat* and *C. Olieman*, Recl. Trav. Chim. Pays-Bas **95**, 312 (1976).

[4] *M. Shamma*, The Isoquinoline Alkaloids, Academic Press Inc., New York (1972), p. 75.

A treatment of **3** with concentrated hydrochloric acid and ether yielded 2-hydroxydihydrothebainone (**4**) quantitatively, from which the hydroxyl group in position 2 still had to be removed. Here we obtained good results with the aid of the 1-phenyl-5-tetrazolyl ether (**5**). The selectivity in the formation of the ether in position 2 is probably promoted by the (steric) structure of the molecule, the hydroxyl group in position 4 being shielded more effectively than with the corresponding >NCHO compound[5]. Starting from optically active **5**, the removal of the 1-phenyltetrazolyl-5-yloxy substituent in position 2 by a catalytic hydrogenation yielded (−)-dihydrothebainone (**6**) which was identical with (−)-dihydrothebainone prepared from natural material. In the various conversions therefore no racemization occurred.

The conversion of dihydrothebainone to codeine[6,7] and morphine[8] is known.

Experimental part

Combustion analyses were performed by Mr. *H. M. A. Buurmans*. Melting points are uncorrected. ^{1}H NMR spectra were measured with a Varian T-60 spectrometer. Mass spectra were obtained with a Varian 311 A spectrometer by Mrs. *A. H. Knol-Kalkman* and Dr. *P. J. W. Schuyl*. Infrared spectra were recorded with a Perkin Elmer P521 and a Beckman IR 4210 spectrophotometer. Rotations were measured with a Perkin Elmer P141 polarimeter. Optical rotatory dispersion curves were measured with a Spectropol 1 spectropolarimeter (FICA, France). Reactions were checked by TLC on silica (0.25 mm, Merck F254; solvent system: methylene chloride/methanol/4 *N* ammonia 85 : 15 : 2; detection by UV, iodine, and Gibbs' reagent).

(R),(S)- And racemic 1-(3,5-dibenzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (**2a**)

The malate of (*R*)-**1** was prepared as described in reference 1. Treatment of 8.2 g (13 mmol) of (*R*)-**1** (*S*)-malate with ammonia and chloroform yielded the free base. (*R*)-**1**·HBr: $|\alpha|_D^{25}$ +17° (*c* 1.5, 90% acetic acid), ORD (*c* 0.11, ethanol): $|M|_{286}^{15}$ −1000°, $|M|_{270}^{15}$ +500, $|M|_{247}^{15}$ −3100°.

A 37% solution of formaldehyde (10.5 ml) and 1 g of 5% platinum on carbon were added until the oily residue dissolved in 100 ml of methanol. The reaction mixture was hydrogenated for 6 h at 45°C. The catalyst was filtered over hyflo and the solvent was evaporated *in vacuo*, yielding 6.45 g of (*R*)-**2a** (12.7 mmol; 97%) as an oil.

(*R*)-**2a** Was crystallized as the picrate from ethanol: m.p. 72–80°C, calcd. for $C_{39}H_{38}N_4O_{11}\cdot C_2H_5OH$ (784.79): C 62.74; H 5.65; N 7.14, found C 63.0; H 5.5; N 7.5, $|\alpha|_D^{25}$ −27.4° (*c* 0.6, dimethylformamide).

(*S*)-**2a** Picrate from ethanol: m.p. 70–77°C, calcd. for $C_{39}H_{38}N_4O_{11}\cdot C_2H_5OH$ (784.79), found C 63.0; H 5.6; N 7.4, $|\alpha|_D^{25}$ +27.6° (*c* 0.6, dimethylformamide).

Racemic **2a** picrate from ethanol: m.p. 69–74°C, calcd. for $C_{39}H_{38}N_4O_{11}\cdot C_2H_5OH$ (784.79), found C 63.0; H 5.3; N 7.2.

Racemic **2a** picrate was converted into the hydrogen bromide: m.p. 144–146°C, calcd. for $C_{33}H_{35}NO_4\cdot HBr$ (590.55): C 67.11; H 6.15; N 2.37, found C 67.2; H 6.3; N 2.5.

(R)-1-(3,5-Dihydroxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (**2b**)

For further characterization, (*R*)-**2a** was hydrogenated with palladium on carbon as a catalyst to **2b**, which was analysed as the picrate: m.p. 203°C (dec.), calcd. for $C_{25}H_{26}N_4O_{11}$ (558.49): C 53.76; H 4.69; N 10.03, found C 53.8; H 4.8; N 10.0, $|\alpha|_D^{25}$ −14.9° (*c* 1.1, dimethylformamide).

(R)- And racemic 1-(3,5-dihydroxy-4-methoxybenzyl)-1,2,3,4,5,8-hexahydro-6-methoxy-2-methylisoquinoline (**3**)

The reduction was carried out as described in reference 1. Both racemic **3** and (*R*)-**3** were obtained by extraction in a yield of 90%. Racemic **3** was crystallized from methanol/ether: m.p. 190–192°C, calcd. for $C_{19}H_{25}NO_4$ (331.40): C 68.86; H 7.60; N 4.23, found C 68.8; H 7.6; N 4.3.

(*R*)-**3** (3.5 g) could not be crystallized. It was purified by dissolution in a mixture of 75 ml of toluene and 100 ml of cyclohexane, and a dark precipitate was removed. The filtrate was evaporated *in vacuo* and the residue was dissolved in 250 ml of ether. A precipitate, formed at 4°C after 16 h, was removed again. The filtrate yielded 3.3 g of amorphous (*R*)-**3**, which was identical with racemic **3**, according to TLC and ^{1}H NMR.

(R)- And racemic 2-hydroxydihydrothebainone (**4**)

Concentrated hydrochloric acid (20 ml) was added to (*R*)-**3** (2.5 g, 7.5 mmol) dissolved in 30 ml of ether at 0°C. After 1 h at room temperature, the solvents were evaporated *in vacuo*. This treatment was repeated, after which the residue was dissolved in 20 ml of concentrated hydrochloric acid and 30 ml of ether. TLC showed complete cyclization after 24 h at room temperature. The solvents were removed *in vacuo* yielding amorphous (*R*)-**4**·HCl, which was purified by dissolution in 15 ml of methanol and precipitation with 250 ml of ether at 4°C (2.55 g, 7.2 mmol, 96%).

Racemic **4**·HCl was obtained in the same yield and crystallized from ethanol: m.p. 279°C (dec.), M.S.: M^+ 317, fragments 164 and 59 (showing B/C rings *cis*).

(R)- And racemic 2-(1-phenyltetrazol-5-yloxy)dihydrothebainone (**5**)

Potassium carbonate (3.4 g, 6 eq) and 5-chloro-1-phenyltetrazole (810 mg, 1.1 eq) were added to a solution of 1.45 g of (*R*)-**4**·HCl (4.1 mmol) in 40 ml of dimethylformamide in a nitrogen atmosphere. TLC analyses showed that the conversion was complete after 2 h at 70 ± 2°C. Solid material was filtered off, the solvent was evaporated *in vacuo*, and traces of dimethylformamide were removed by treatment with *p*-xylene. The residue was dissolved in 0.1 *N* hydrochloric acid and washed with chloroform. The aqueous layer was made alkaline with ammonia (pH 8) and extracted with chloroform. The chloroform layer was washed with water, dried over magnesium sulfate and evaporated *in vacuo*. This yielded 850 mg of (*R*)-**5** (45%), which according to TLC was identical with racemic **5** (50% yield). An analytical sample of racemic **5** was crystallized from ethanol: m.p. 206°C (dec.), calcd. for $C_{25}H_{27}N_5O_4$ (461.51): N 15.18, found N 15.0, IR: C=O 1703 cm^{-1}, C-(tetrazolyl) 1538 cm^{-1}, m.s.: M^+ 461, fragments 317, 164 and 59.

(−)-*Dihydrothebainone* (**6**)

Crude (*R*)-**5** (267 mg, 0.58 mmol) was converted into the hydrochloride by treatment with hydrogen chloride in ethanol/ether. The precipitate, dissolved in 35 ml of methanol, was hydrogenated at 50–55°C in the presence of 160 mg of 10%-palladium on carbon until complete dissappearence of the starting material (TLC, iodine detection). The reaction mixture was filtered over hyflo and evaporated *in vacuo*. The residue was dissolved in 0.1 *N* HCl and washed with chloroform. The base was liberated as usual, yielding 130 mg of (−)-**6** (75%). The infrared spectrum, the melting point, and the mixed melting point determination showed identity with (−)-dihydrothebainone prepared from natural material. The hydrochloride crystallized from ethanol/ether, $|\alpha|_D^{25}$ −51.4° (*c* 0.6, water), and was, according to infrared spectrum and melting point, identical with the product prepared from natural material {$|\alpha|_D^{25}$ −52.1° (*c* 0.6, water)}.

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[5] *H. C. Beyerman, E. Buurman, T. S. Lie* and *L. Maat*, Recl. Trav. Chim. Pays-Bas **95**, 43 (1976).
[6] *D. D. Weller* and *H. Rapoport*, J. Med. Chem. **19**, 1171 (1976).
[7] *J. A. Lawson* and *J. I. DeGraw*, J. Med. Chem. **20**, 165 (1977).
[8] *K. C. Rice*, J. Med. Chem. **20**, 164 (1977).