A convenient synthesis of codeine and morphine*

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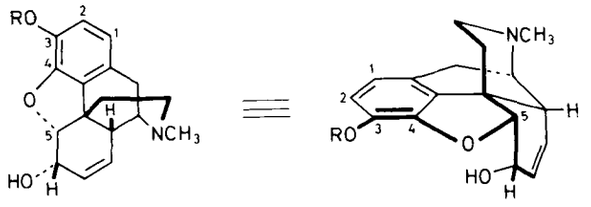
Abstract. Acid-catalysed cyclization of 1-(3,5-dihydroxy-4-methoxybenzyl)-*N*-formyl-1,2,3,4,5,8-hexahydro-6-methoxyisoquinoline (**2c**), where the benzyl group is symmetrically substituted, gave *N*-formyl-2-hydroxynordihydrothebainone (**4c**) exclusively. The 2-hydroxyl substituent could be removed selectively in high yield, *via* the 1-phenyltetrazol-5-yl ether (**4d**), to yield *N*-formylnordihydrothebainone (**4e**). (−)-*N*-Formylnordihydrothebainone (**4e**) was reduced to (−)-dihydrothebainone (**4a**). The conversion of **4a** to codeine (**1b**) and morphine (**1a**) has already been recorded.

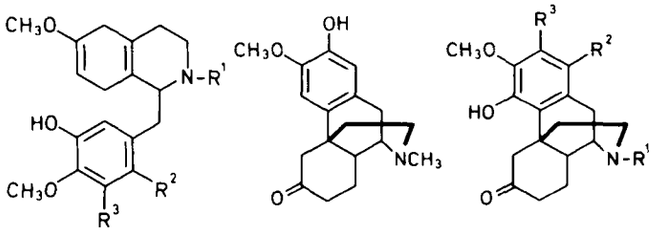
A possible solution of the world drug problem might be to stop the planting of *Papaver somniferum* L. so as to make impossible the illegal production of morphine from opium and its easy conversion into heroine. This method, however, will result in a lack of medicinally useful (−)-morphine (**1a**), (−)-codeine (**1b**), and derivatives. A convenient synthesis of the title compounds thus seems desirable, and we wish to report such a synthesis.



1a R = H, (−)-morphine
1b R = CH_3, (−)-codeine

Two syntheses of morphine and codeine have been described[1,2], but the number of steps involved is great and the yield is low. Furthermore, methods for the formation of the alkaloids have been described, partly on the analogy of the biosynthesis[3,4].

The acid-catalysed ring closure of 1-benzyl-1,2,3,4,5,8-hexahydroisoquinoline derivatives according to *Grewe*[5], although it is elegant and suitable for the production on an industrial scale of useful morphinan derivatives, has not led to a practical synthesis of codeine and morphine. In the acid-catalysed ring closure of 1-(3-hydroxy-4-methoxybenzyl)-1,2,3,4,5,8-hexahydro-6-methoxy-2-methylisoquinoline (**2a**) both *Grewe* et al.[6], with the aid of phosphoric acid, and *Morrison* et al.[7], with the aid of hydrochloric acid, obtained a mixture of the undesirable isomer **3** in a yield of 37% and the suitable intermediate **4a** in a yield of only 3%. The hydroxyl group in position 4 of the morphinan ring system is necessary to bring about later the 4,5-oxygen bridge. Some of us showed in a preceding communication[8] that blocking of the benzyl radical with a methyl group in position 2 leads to an 85% conversion into the morphinan derivative **4b**. In this case the formation of the undesirable isomer is, of course, not possible.



2 **3** **4**

2a $R^1 = CH_3$, $R^2 = R^3 = H$
2b $R^1 = R^2 = H$, $R^3 = OH$
2c R^1 = CHO, $R^2 = H$, $R^3 = OH$

4a $R^1 = CH_3$, $R^2 = R^3 = H$
4b R^1 = CHO, $R^2 = CH_3$, $R^3 = H$
4c R^1 = CHO, $R^2 = H$, $R^3 = OH$
4d R^1 = CHO, $R^2 = H$, $R^3 = OC_7H_5N_4$
4e R^1 = CHO, $R^2 = R^3 = H$

In seeking for a grouping which might be easily removed after the cyclization process, we chose a new approach by using, instead of a substituent in position 2 in the benzyl group, a *hydroxyl group in position 3*. Thus the benzyl group is substituted symmetrically and cyclization can now take place in one way only. This idea was published recently, independently of us, by *De Graw* et al.[9]. These authors did not achieve the desired results.

By means of a Birch reduction we prepared 1-(3,5-dihydroxy-4-methoxybenzyl)-1,2,3,4,5,8-hexahydro-6-methoxyisoquinoline (**2b**) (85%, m.p. 214–215°; ref. 9: 51%, m.p. 198–204°). Formylation of this substance, using ethyl formate, afforded **2c** (88%, m.p. 204–205°), which was cyclized with 80% sulfuric acid in ether to the morphinan derivative **4c** (75%, m.p. 240–241°). In the case of **4c** the hydroxyl group in

* The structures of all new compounds are based on IR, NMR, and mass spectra. Combustion analysis results within 0.3% of theory were obtained for all crystalline products.

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5 *R. Grewe* and *A. Mondon*, Chem. Ber. **81**, 279 (1948).
6 *R. Grewe* and *W. Friedrichson*, Chem. Ber. **100**, 1550 (1967).
7 *G. C. Morrison, R. O. Waite* and *J. Shavel Jr.*, Tetrahedron Letters **1967**, 4055.
8 *H. C. Beyerman, E. Buurman* and *L. Maat*, Chem. Commun. **1972**, 918.
9 *J. I. De Graw, J. C. Christensen, V. H. Brown* and *M. J. Cory*, J. Heterocycl. Chem. **11**, 363 (1974).

position 2 could be converted selectively[10] with 5-chloro-1-phenyltetrazole[11] into the phenyltetrazolyl ether **4d** (79%, m.p. 233–235°). Hydrogenolysis of **4d** with the aid of palladium on carbon in the presence of a base gave *rac.* *N*-formylnordihydrothebainone (**4e**) (83%, m.p. 274–275°), the spectral data (MS, IR, NMR) of which were identical with those of (−)-*N*-formylnordihydrothebainone obtained from natural material[12]. The selective reduction of (−)-*N*-formylnordihydrothebainone to (−)-dihydrothebainone (**4a**) was possible with palladium on carbon as catalyst. The conversion of (−)-dihydrothebainone (**4a**) into (−)-codeine (**1b**) and (−)-morphine (**1a**) has already been recorded[1,13,14].

A repetition of the synthesis with chiral starting material **2b** is of course not essentially different. This work is in progress.

We synthesized compound **2b** starting from (3,5-dihydroxy-4-methoxyphenyl)acetic acid and [2-(3-methoxyphenyl)-ethyl]amine. By condensation of these two compounds (3,5-dibenzyloxy-4-methoxyphenyl)-*N*-(3-methoxyphenethyl)acetamide (95%, m.p. 87–88°) was obtained. Subjection of the latter compound to a Bischler-Napieralski reaction gave 1-(3,5-dibenzyloxy-4-methoxybenzyl-3,4-dihydro-6-methoxyisoquinoline hydrochloride (54%, m.p. 129–130°). The above-mentioned Birch reduction of this compound to *rac.* **2b** was carried out with lithium in liquid ammonia in the presence of *tert*-butanol.

It is also possible to reduce the C=N bond of the Bischler-Napieralski reaction product with sodium tetrahydridoborate. The 1-(3,5-dibenzyloxy-4-methoxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrobromide (60%, m.p. 145–147°) thus obtained, was resolved with the aid of (−)-malic acid. This afforded the (+)-malate [m.p. 155°, dec, $[\alpha]_D$ 15° (*c* 1.5, $CHCl_3$ – CH_3OH 10 : 1)], which after being worked up gave the dextro-rotatory base. From the mother liquor we obtained the (−)-malate, which afforded the leavo-rotatory base.

[10] Trial runs were carried out with compounds **3** and **4a** (with a formyl substituent on the nitrogen atom), respectively, in order to be able to effect the selective ether formation with the 2-OH, in contrast to the sterically hindered 4-OH. On hydrogenolysis with palladium on carbon[11] the desired 1-phenyltetrazol-5-yl ether of **3** (with >N–CHO) gave a near-quantitative deoxygenation to 3-methoxy-6-oxo-*N*-formylmorphinan (m.p. 208–209°).

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[12] (−)-Dihydrothebainone was acetylated and demethylated according to *Von Braun*'s method with the aid of cyanogen bromide, which yielded (−)-nordihydrothebainone {m.p. 188–190°, $[\alpha]_D$ −65° (*c* 1, methanol)}. Formylation with ethyl formate gave (−)-*N*-formylnordihydrothebainone {m.p. 250–255°, dec., $[\alpha]_D$ −182° (*c* 1, methanol)}.

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A stereospecific synthesis of *cis*- and *trans*-1-alkenyl sulfides from 1-alkynyl sulfides and a copper(I) hydride complex or lithium tetrahydridoaluminate

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Abstract. 1-Alkynyl sulfides $R^1C{\equiv}C{-}S{-}R^2$ **1** are easily converted with a copper(I) hydride complex in tetrahydrofuran into *cis*-1-alkenyl sulfides $R^1CH{=}CH{-}S{-}R^2$ **2** in yields >90%. Treatment of compounds **1** with $LiAlH_4$ in the same solvent leads to the isomeric *trans*-1-alkenyl sulfides $R^1CH{=}{=}CH{-}S{-}R^2$ **3** in almost quantitative yield.

Introduction

Since the first preparation of $H_2C{=}CH{-}S{-}C_2H_5$ by *Strömholm*[1] several methods have been reported for the synthesis of 1-alkenyl sulfides[2]. Most of these, however, give rise to mixtures of *cis*- and *trans*-isomers, and separation by distillation is rather difficult. Only a few deal with a stereospecific synthesis of either *cis*- or *trans*-1-alkenyl sulfides.

With respect to the preparation of 1-alkenyl sulfides with the *cis*-geometry the data from the literature are restricted to some special examples. *Truce* et al.[3] found that thiolates add in a *trans* manner to phenylacetylene, yielding *cis*-$C_6H_5CH{=}{=}CH{-}S{-}R$ together with 10–20% of the α-(alkylthio)styrene (compare ref. 4). The latter type of product is even the main one when *alkylacetylenes* are treated with thiolates, and only small amounts (~20 rel. %) of *cis*-1-alkenyl sulfides are found (compare ref. 3).

For the preparation of *trans*-1-alkenyl sulfides three useful methods have been published. *Balĕnović* et al.[5] converted 1-(alkylsulfinyl)-1-(alkylthio)alkanes into *trans*-1-alkenyl sulfides with a stereochemical purity >80% by simply heating.

[1] *D. Strömholm*, Ber. Dtsch. Chem. Ges. **33**, 823 (1900).

[2] *H. J. Boonstra, L. Brandsma, A. M. Wiegman* and *J. F. Arens*, Recl. Trav. Chim. Pays-Bas **78**, 252 (1959) and earlier work cited therein.

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