A SHORT AND EFFICIENT SYNTHESIS OF C-NOR-DIHYDROCODEINONE - THE ANTIPODE OF GOTO'S SINOMENILONE

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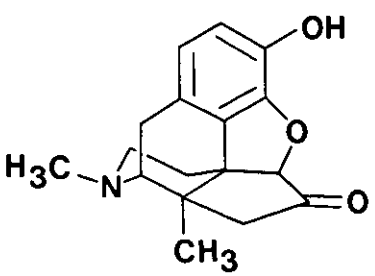
Abstract —— In a four step synthesis, when using dihydrocodeinone, the C-nor-derivative 2 will be obtained in good yields. The reduction of the ringsize is achieved by bromination to the 1,7,7-tribromoketone 4 and heating it in an alkaline solution. Decarbonylation of the α-hydroxy acid 5 and subsequent catalytic hydrogenation of 6 lead to the desired enantiomer of Goto's sinomenilone.

In our group we have for the first time produced a series of 14-alkylmorphine derivatives[1,2] for comparative pharmacological studies. We were also able to include the C-nor-morphine derivative 1 in the studies of structural and activity relations. This compound has beside a five membered ring, a methyl group at the C-14 position as its principal structural element. Since in the comparison of the analgetic effect of dihydromorphinone and 14-methyldihydromorphinone the latter proved to be at least 100 times more active, it became evident that the methyl group produces an extraordinary effectivity increase and



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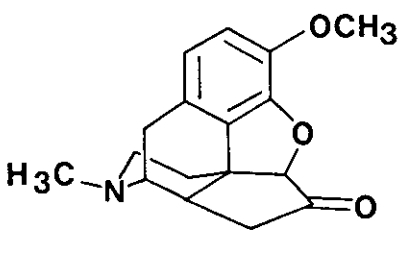

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can be regarded as a pharmakophore substituent[3].

In order to be able to compare morphine and C-nor-morphine derivatives without the result being influenced by the 14-methyl group, we have worked out a short synthesis for the unsubstituted C-nor-dihydrocodeinone 2.

The mirrorimage of our target molecule was first described in 1932 by Goto et al.[4], and named sinomenilone, due to its production out of sinomenine.

We obtained a suitable preliminary stage for reduction of the ring C through the bromination of dihydrocodeinone (3). Comprehensive studies of the bromination reaction described by Gates and Shepard[5] showed that contrary to the claims made by these authors no 1,7-dibromide product could be isolated. Depending on the stoichiometric relations (2-2.3 eq. Br_2) moderate quantities of 7,7-dibromo-dihydrocodeinone and 1,7,7-tribromoketone 4 are produced beside the untransformed 3. When 3 equivalent bromine is used, the compound 4 is produced in good yields.

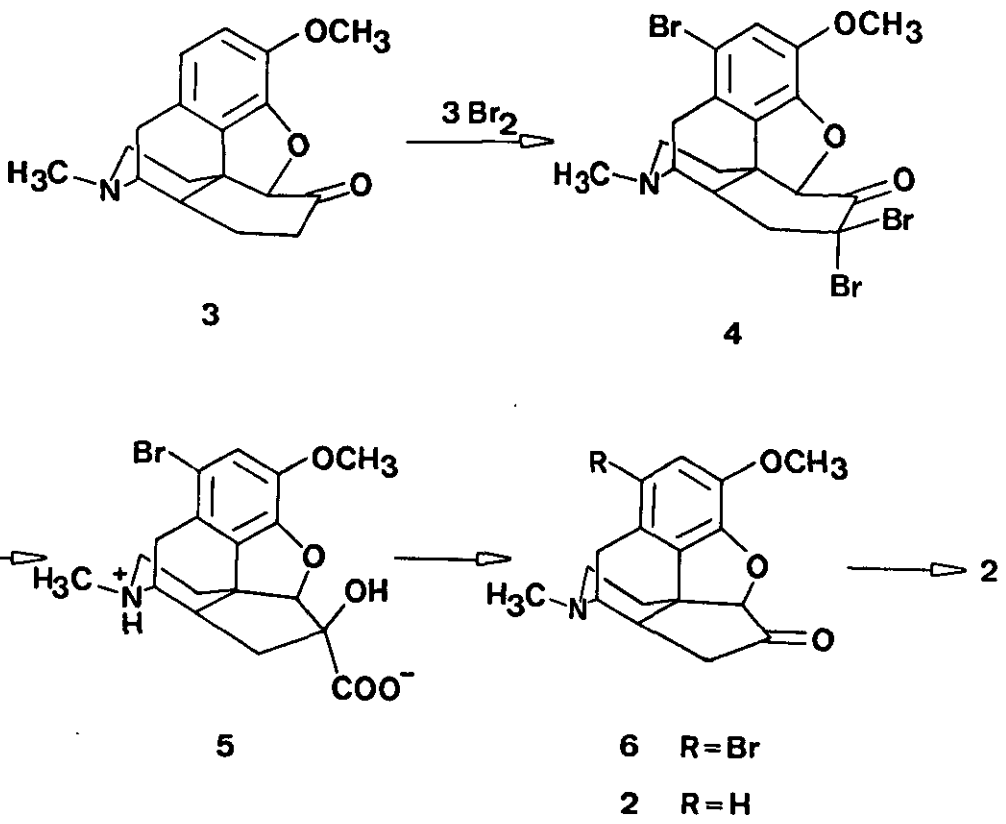
The substitution of the geminal bromine atoms by hydroxyl, when treated with an alkaline solution, produces an unstable diol which eliminates water. In the strong alkaline medium the diketone undergoes benzilic acid rearrangement to 5 and therefore can not be isolated. By treating it with 15% oleum we were able to decarbonilize 5 to ketone 6 with a yield of 56%. An increase of the yield through the use of more concentrated oleum was not possible, nor was the 2-chloro-3-ethylbenzoxazolium tetrafluoroborate suggested by Mukaiyama[6] more productive.

The ketone 6 crystallized well out of methanol, however different fractions showed different melting points. As was spectroscopically shown in the process of crystallization partial hemiacetal development occurred with methanol.

Crystallization of the oily base 6 out of ethanol produced colorless prisms which give the same melting point of 184 °C which found in literature for the enantiomer[4]

By means of catalytic hydrogenation 6 was transformed to the desired 2. For the reason that Goto only achieved a very unsatisfactory yield through the catalytic hydrogenation of the antipode of 6 with $Pd/BaSO_4$, we set the reaction in hydrochloric acid with the more reactive Pd/C as a catalysator and we managed to isolate 2 in a yield of 88%.

The assignment of sinomenilone to a particular structure by Goto in 1932[4] we were able now to confirm on the enantiomer with the aid of modern spectroscopic methods.



EXPERIMENTAL PART[7]

All the melting points are uncorrected. Spectra were determined using the instrumentation indicated. IR-spectra: Perkin-Elmer 237. NMR-spectra (ppm relative to internal TMS): Varian EM-390. Mass spectra (MS): Varian MAT-111.

1,7,7-Tribromodihydrocodeinone (4).

To a stirred solution of dihydrocodeinone (5g, 16.7 mmol) in acetic acid (90 ml) bromine (8.27g, 51.6 mmol) in acetic acid (30 ml) was added over a period of 90 min. After a few minutes a precipitate began to form. The mixture was stirred for 5 h and the solvent was removed under reduced pressure to give the crude hydrobromide of 4. The residue was dissolved in water. The aqueous solution was adjusted to pH 8 and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and evaporated to give a yellow oil of 4 (8.54g, 96%). Crystallization from benzene-pentane gave pale yellow crystals: mp 220 °C with decomp.

IR (KBr): 1753 cm^{-1} (ketone); ^{1}H-NMR ($CDCl_3$): δ=6.93 (s, 1H, 2-H); 5.48 (s, 1H, 5-H); 3.93 (s, 3H, OCH_3); 2.43 (s, 3H, NCH_3). MS: m/e= 533, 535, 537, 539 (1:3:3:1)

1-Bromo-4,5-epoxy-6-hydroxy-3-methoxymorphinan-6-carboxylic Acid (5).

4.HBr (16.2g, 26.2 mmol) was dissolved in warm 4N NaOH (30 ml). After cooling to room temperature 10N NaOH (20 ml) was added. Gradually a brownish precipitate was formed. The mixture was stirred at room temperature overnight. It was adjusted to pH 8 by adding acetic acid. The precipitate of 5 was isolated. The mother liquor was extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and evaporated to give an amorphous solid of 5. The collected crude product was recrystallized from methanol-CH_2Cl_2 to give colorless crystals (6.95g, 65%): mp 280-285°C.
IR (KBr): 1590 cm^{-1} (COO^-), 3425 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$): δ=6.95 (s, 1H, 2-H); 4.73 (s, 1H, 5-H); 3.90 (s, 3H, OCH_3); 2.93 (s, 3H, NCH_3).

1-Bromo-C-nor-dihydrocodeinone (6).

5 (2g, 4.87 mmol) was dissolved in ice-cooled 15% oleum (3 ml) and then warmed to 40 °C. The decarbonylation was complete after 5 h of stirring at this temperature. The brown solution was cooled, diluted with water and basified with 2N Na_2CO_3. The mixture was extracted with benzene. The organic layer was dried and evaporated to give a yellow oil. This crude product was chromatographed on Al_2O_3 using benzene-triethylamine (95+5) to give the ketone 6 (0.99g, 56%). Crystallization from ethanol gave colorless prisms: mp 184 °C.
IR (KBr): 1758 cm^{-1} (ketone); ^{1}H-NMR ($CDCl_3$): δ=6.88 (s, 1H, 2-H); 4.44 (s, 1H, 5-H); 3.83 (s, 3H, OCH_3); 2.47 (s, 3H, NCH_3).

C-Nor-dihydrocodeinone (2).

The bromoketone 6 (150 mg, 0.41 mmol) was hydrogenated in 1N HCl (10 ml) with Pd/C (50 mg) under 1 atm. After absorption of 9.5 ml hydrogen, the mixture was filtered, basified with Na_2CO_3 and extracted with benzene. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Crystallization from ethanol gave colorless prisms of 2 (93mg, 88%): mp 177-179 °C.
IR (KBr): 1752 cm^{-1} (ketone); ^{1}H-NMR ($CDCl_3$): δ=6.65 (AB-signal, 2H, 1-H,2-H); 4.41 (s, 1H, 5-H); 3.84 (s, 3H, OCH_3); 2.43 (s, 3H, NCH_3): MS: m/e= 285 (M^+).
$[\alpha]_D^{27}$ -412° (c 0.55, $CHCl_3$)

REFERENCES

1. W. Fleischhacker and A. Klement, Monatsh. Chem. 1977, 108, 1441.
2. W. Fleischhacker and B. Richter, Chem. Ber. 1979, 112, 2539.
3. W.R. Buckett and W. Fleischhacker, in preparation.
4. K. Goto and K. Takubo, Liebigs Ann. Chem. 1932, 499, 171.
5. M. Gates and M.S. Shepard, J. Amer. Chem. Soc. 1962, 84, 4125.
6. T. Mukaiyama and Y. Echigo, Chem. Lett. 1978 (1), 49.
7. Taken from the diploma thesis of P. T.

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