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Short Communication

Synthesis of a *C*-Nor-morphin-6-ene by Radicalic Isomerization of a Cyclopropyl Moiety

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Summary. By desulfurization with Raney nickel, the dithioacetal of 7,14-cyclodihydrocodeinone affords a *C*-nor-morphinene derivative apparently by radicalic isomerization.

Keywords. *C*-Normorphinans; *C*-Normorphinenes; Desulfurization; Radicalic isomerization.

Synthese eines *C*-Nor-morphin-6-ens durch radikalische Cyclopropan-Isomerisierung (Kurze Mitt.)

Zusammenfassung. Ausgehend von 7,14-Cyclodihydrocodeinon ist über das Dithioacetal ein *C*-Nor-morphinen durch Desulfurierung mit Raney-Nickel zugänglich. Der Mechanismus der Bildung wird diskutiert.

The development of novel opioid analgesics is still of current interest. It is noteworthy that pharmacological data of opioids, which carry a five-membered ring C, are rare [1]. The approach to 14-methyl substituted derivatives has been reported by *Fleischhacker* and *Klement via* the cyclopropyl ketone **1** which is available in a seven step route from thebaine [2, 3]. At that time, attempts to obtain the 6,7-unsaturated derivative **3** have been unsuccessful; neither *Bamford-Stevens* reaction of the tosyl hydrazone of **2a**, nor dehydration of **2b** (or **2c**) or dehydromesylation of **2d** afforded **3**. At present, in another context, the synthesis of **3** could be achieved.

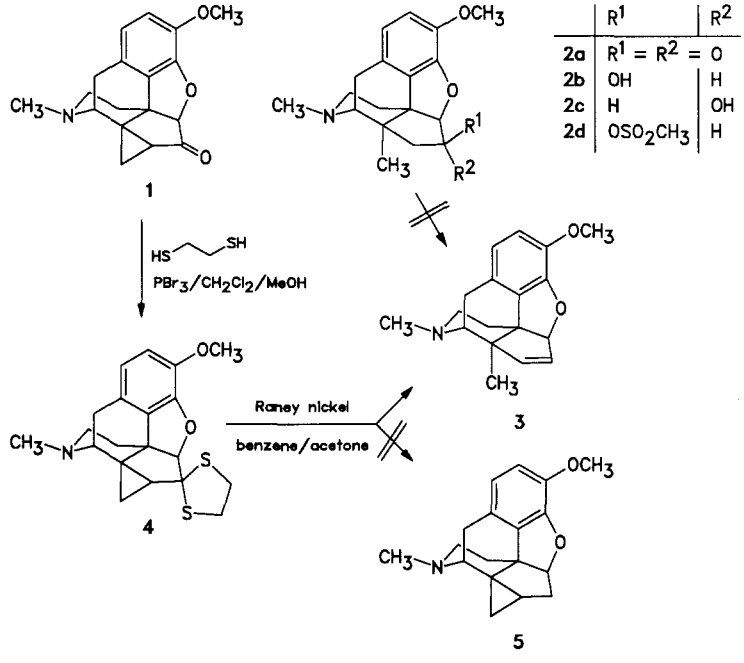
Investigations on the reactivity of the cyclopropane moiety in **1** towards nucleophiles should also include the preparation of **5** which, in contrast to **1**, does not possess an activated cyclopropane ring. With regard to the acid-sensitivity of **1**, the access to **5** could not be performed by *Clemmensen* reduction of the carbonyl group. Thus, it was planned to generate the dithioacetal **4** to yield the methylene function by reductive cleavage.

The desulfurization of dithioacetals with Raney nickel is well known as a mild method which allows to reduce even α,β-unsaturated ketones to the corresponding olefins [4, 5, 6]. The dithioacetal **4** was obtained in good yield by treatment of **1** with 1,2-ethanedithiol, in presence of phosporus tribromide in dichloromethane/methanol as solvents [7, 8]. Desulfurization by heating of **4** with Raney nickel in a

solvent mixture of benzene and acetone did, however, not afford **5**, but led to a substance which showed the signals of a double bond in the ^{1}H NMR spectrum and whose spectral data were in full accordance with the proposed structure of the hitherto unknown compound **3**.

The mechanism of Raney reactions probably is of the free-radical type. Therefore, the formation of **3** seems to proceed *via* isomerization of radicalic intermediates. Alternatively, a thermal isomerization of **5** to give **3** can be excluded, because isomerizations like these usually require drastic reaction conditions [9, 10]. Moreover, **5** could never be detected (as intermediate) in reaction mixtures of the described Raney nickel reduction. On the other hand, it is known that activated cyclopropyl moieties are cleaved under more moderate conditions [5].

Ketone **1**, with an activated cyclopropane ring, is stable when treated with Raney nickel. Thus, it can be excluded that **5**, being less reactive than **1**, undergoes ring cleavage under the same conditions.



	R^1	R^2
2a	$R^1 = R^2 = O$	
2b	OH	H
2c	H	OH
2d	OSO_2CH_3	H

Experimental

Melting points: Kofler hot stage apparatus, uncorrected. IR-spectra: Perkin-Elmer 298; ^{1}H-spectra: Varian EM 390, Bruker AC 80; Elemental analyses: performed by Dr. J. Zak, Institut für Physikalische Chemie der Universität Wien; Flash chromatography: Silicagel 60.

(5S,9R,13R,14R)-4,5-Epoxy-6,6-(1,2-ethylendithio)-3-methoxy-14,17-dimethyl-C-nor-morphinan (**4**)

To a solution of 300 mg (1 mmol) of 7,14-cyclo-dihydrocodeinone **1** in abs. dichloromethane (30 ml) and abs. methanol (5 ml), 0.5 ml (6 mmol) of 1,2-ethanedithiol were added. After cooling the solution to $-20\,^\circ$C, 0.1 ml (1.2 mmol) of phosphorus tribromide were added dropwise. The cooling bath was removed, and the solution was stirred for 2 h. Finally, the reaction mixture was added to a solution of 1.0 g NaOH in 100 ml of water and extracted with dichloromethane (3 × 20 ml). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo*, affording 305 mg (81%) of **4** as yellow oil.

^{1}H-NMR ($CDCl_3$): $\delta = 6.76$, 6.67 (AB-system, 2H, $J = 9.0$ Hz, 1-H, 2-H), 4.37 (s, 1H, 5-H), 3.89 (s, 3H, OCH_3), 3.30, 3.27 (s, s, 2H, 2H, S–CH_2–CH_2–S), 2.46 (s, 3H, NCH_3). MS (*m/z*): 373 (M^+).

(5S,9R,13R,14R)-4,5-Epoxy-3-methoxy-14,17-dimethyl-C-nor-morphinan-6-ene (**3**)

In a solvent mixture of acetone (20 ml) and benzene (20 ml) were dissolved 300 mg (0.8 mmol) of **4**. After addition of Raney nickel (prepared from 2 g alloy according to Ref. [6]: the catalyst was warmed for 1 h at 60 °C and then extensively washed with water until neutral reaction of the eluent), the reaction mixture was refluxed for 24 h. The catalyst was filtered off, and the filtrate was concentrated *in vacuo*. The residue was redissolved in dichloromethane, washed with brine, and dried over Na_2SO_4. Evaporation *in vacuo* yielded a colorless oil which was purified by flash chromatography (eluent: petroleum ether/ethyl acetate = 9 + 1). The product crystallized on seeding to yield 140 mg (61%) of **3**. m.p.: 142–143 °C (ethyl acetate). ^{1}H-NMR: $\delta = 6.66$, 6.52 (AB-system, 2H, $J = 8$ Hz, 1-H, 2-H), 6.20 (d, 1H, $J = 6$ Hz, 6-H), 5.41 (d, $J = 1$ Hz, 5-H), 5.33 (dd, $J = 6$ Hz, $J = 1$ Hz, 7-H), 3.84 (s, 3H, OCH_3), 2.39 (s, 3H, NCH_3), 1.36 (s, 3H, 14-CH_3). MS (*m/z*): 283 (M^+). Anal.: calcd. for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94; found: C, 76.14; H, 7.41; N, 4.97.

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