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Aminocyclanols, II[1,2]:

# Stereochemical Studies on a New Ciramadol Analogue by NMR-Spectroscopy

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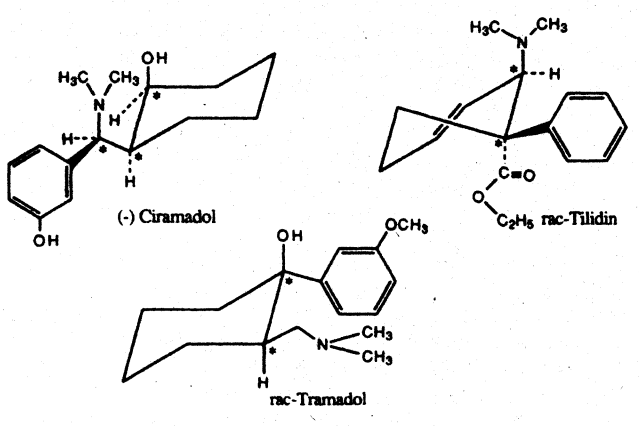
The absol. configuration of a Ciramadol analogue obtained from (-)-menthone is established by $^1$H-NMR-, simulated NMR-, COSY-90-, and NOE-measurements. The final compound 2-(α-1-pyrrolidino)benzyl-4-isopropyl-1-methyl-cyclohexan-3-one (**4b**), *e.g.*, has 1*R*,2*S*,4*S*,11*S*-configuration due to stereoselective *Michael*-type addition of pyrrolidine to the pertinent benzylidene intermediate **3**.

**Aminocyclanole, 2. Mitt.: Stereochemische Untersuchungen an einem neuen Analogon des Ciramadols durch NMR-Spektroskopie**

Die absol. Konfiguration einer Ciramadol-analogen Verbindung aus (-)-Menthon wurde durch $^1$H-NMR-, simulierte NMR-, COSY-90- und NOE-Untersuchungen geklärt. Danach hat die als Beispiel untersuchte Verbindung 2-(α-1-Pyrrolidino)benzyl-4-isopropyl-1-methyl-cyclohexan-3-on (**4b**) 1*R*,2*S*,4*S*,11*S*-Konfiguration, die durch eine stereoselektive *Michael*-analoge Addition des Pyrrolidins an die entspr. Benzyliden-Verbindung **3** entsteht.

Ciramadol, Tilidin, and Tramadol are aminocyclanoles of clinical importance as opiat analgesics (Scheme 1)[3-8]. - The mixture of *E* and *Z* isomers of 1*R*,4*S*-2-benzylidene-4-isopropyl-1-methyl-cyclohexan-3-one (**2** + **3**) has been prepared by *Claisen-Schmidt*-type condensation of (-)-menthone with benzaldehyde[1,2]. The quantitative ratio of these isomers was determined by gc with ms-detection to be *E* 68% and *Z* 31%[1,2]. If one of these components is dissolved in $Et_2O$ containing a few drops of conc. HCl isomerisation to the *E*/*Z* mixture of this composition occurs. Only the *E* isomer of this mixture reacts with various cyclic amines to yield aminocyclanone type compounds (Scheme 2). These compounds show higher opiat analgesic activity than the aminocyclanol compound Tramadol and Morphine and can be reduced to the pertinent aminocyclanols[1,2].




**Schema 1:** Ciramadol, Tilidin, and Tramadol

In this study we have elucidated the absol. configuration of 2-(α-1-pyrrolidino)benzyl-4-isopropyl-1-methyl-cyclohexan-3-one (**4b**) as an example by $^1$H-NMR techniques.

2-α-(aminobenzyl)menthones **3** have four asymmetric C-atoms. As a result, there should be eight pairs of enantiomers. The starting compound (-)-menthone of known absol. configuration has two chiral centers (1*R*,4*S*), $[\alpha]_D$ = -24°. Therefore, the absol. configurations at C-2 and C-11 have to be established. The diastereoselectivity for the amine addition at C-11 of the *E*-(-)-2-benzylidene-menthone (**3**) is quite high, because tlc analyses of the crude product and its $^1$H-NMR spectrum show only one isomer.

In the $^1$H-NMR spectrum of **4b** the doublet at 4.1 ppm (J = 11.5 Hz) results from 11-H coupled with 2-H. The dd at 3.5 ppm arises from 2-H coupled with 1-H and 11-H ($J_{2\text{-}11}$ = 11.5 Hz; $J_{2\text{-}1}$ = 4.7 Hz). The region 3.0-4.1 ppm has been used for NMR simulation. Several sets of J values were used to obtain the simulated NMR spectra. Long-range couplings were neglected. The spectrum with $J_{2\text{-}11}$ = 11.5, $J_{1\text{-}11}$ = 0, $J_{1\text{-}2}$ = 4.8 Hz fits the actual NMR spectrum, whilst the combination $J_{2\text{-}11}$ = 4.8, $J_{1\text{-}11}$ = 0.0, $J_{1\text{-}2}$ = 11.5 Hz does not.

These results indicate that the methyl group on C-1 is axial and 1-H is oriented equatorially. 2-H stands in axial position and the aminobenzyl group at C-2 equatorially. The angle between 2-H and 11-H is near to 180°. A speculative rationalization of the formation of the β-amino ketones **4** is shown in Scheme 2.

COSY-90 and NOE measurements have been performed under the assumption that the absol. configuration at C-1 and C-4 remain *R* and *S*, respectively. The doublet of 2-H coupling with 1-H with J = 4.7 Hz indicates an angle of about 45°. NOE experiments confirm an axial position of 2-H, because saturating the signal of 2-H induces a strong NOE for 1-H (Tab. 1) (and only a weak NOE on 11-H). In

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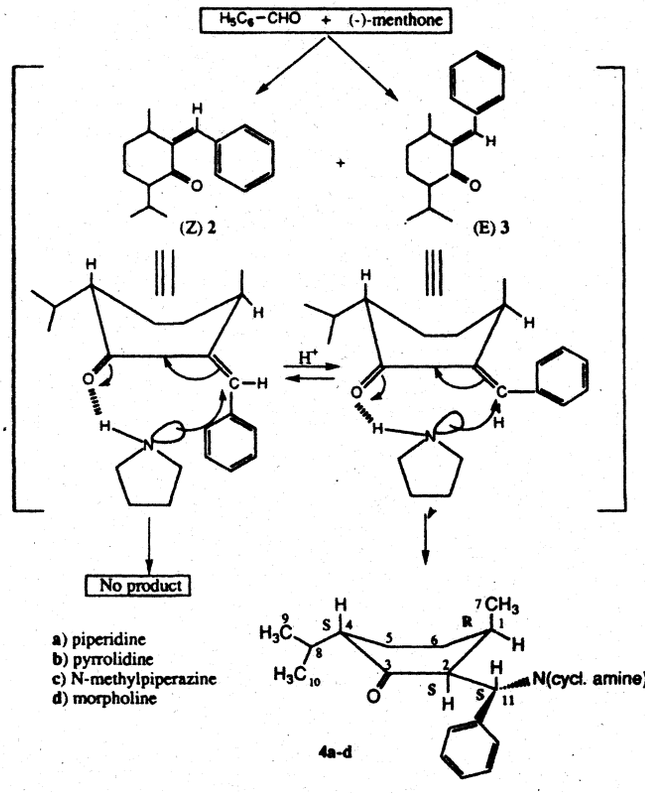
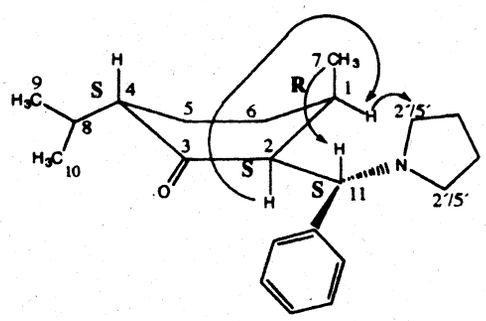



**Schema 2:** Speculative reaction mechanism

the difference spectrum, the relation resulting from integration of the signals of 1-H and 11-H is 6:1 (equatorial position of 2-H should afford a relation being nearly the same for both protons, because nearly identical distances for 1-H/2-H and 2-H/11-H (ca. 3 Å) are shown by the pertinent *Dreiding* model). 2-H and 11-H are arranged *trans* to each other. If there were a *s-cis* arrangement the NOE-effects should be of equal intensity or even opposite. Irradiation onto 1-H causes a five times stronger NOE-effect at 2-H than at 11-H. If 1-H were arranged axially the NOE-effect at 11-H should be larger than that at 2-H as it can be seen from *Dreiding* models. *S*-configuration at C-11 is highly probable, because there is an NOE of 1-H effecting the 2'- and 5'-pyrrolidine protons (further non-relevant NOE's are not cited) (Scheme 3).

Morever, saturating the resonances of 2-H caused intensive NOE amplification of the ortho-H's of the phenyl ring



**Schema 3:** Main NOE effects

and of the 2'-H/5'-H's of the pyrrolidine increment. These NOE measurements demonstrate a *trans* position of 2-H and 11-H. This is corroborated by a $^3J$ value of 11.5 Hz for the doublet of 11-H. The connectivities of 2-H and 11-H are established by a COSY spectrum. COSY-90 and COSY-long-range experiments confirm the structure shown in Scheme 3.

Saturation of C-1-$CH_3$ resonances leads to a strong enhancement of the signals of 1-H and 11-H, whilst there is no NOE for 2-H. If 2-H were arranged equatorially, the distance between 11-H and the $CH_3$ group should be > 3.5 Å, so excluding an NOE. Moreover, in this case there should be an NOE between the methyl protons and 2-H (distance about 2 Å).

From these experiments we conclude that the absol. configuration at C-2 is *S* and that there is a favoured conformation having 2-H and 11-H *trans* to each other.

## Experimental Part

2-(α-Aminobenzyl)-menthones **4** were prepared as reported[1,2].- $^1$H-NMR spectra for simulation - see above - were recorded at 20°C on a Bruker AC-80 MHz FT-NMR in $CDCl_3$, TMS as internal standard, using the PANIC program.- Chemical shifts in δ (ppm).

$^1$H-NMR, 400 MHz, $CDCl_3$ (TMS) 23°C of **4b** (Bruker ARX 400): δ = 0.65 (d, J = 6.7 Hz, 3H, 9-$CH_3$ or 10-$CH_3$), 0.77 (d, J = 6.8 Hz, 3H, 10-$CH_3$ or 9-$CH_3$), 0.84 (d, J = 7.1 Hz, 3H, 7-$CH_3$), 1.48-1.62 (m, 5H, 1 menthone-H, 3'-$CH_2$, 4'-$CH_2$), 1.75-1.80 (m, 1H, menthone-H), 1.85-1.93 (sept, J = 6.7 Hz, 1H, 8-H), 1.95-2.07 (m, 3H, menthone-H), 2.27-2.44 (m, 4H, 2'-$CH_2$, 5'-$CH_2$), 2.79 (br., 1H, 1-H), 3.38 (dd, J = 4.7 Hz, J = 11.5 Hz, 1H, 2-H), 4.11 (d, J = 11.5 Hz, 1H, 11-H), 7.09-7.29 (m, 5 arom. H).

**Tab. 1:** NOE effect of 2-(α-pyrrolidino)benzyl-4-isopropyl-1-methylcyclohexan-3-one (**4b**)

| NOE of | | |
|---|---|---|
| 1-H | to | 11-H (w), 2-H (s), 2'-H / 5'-H (s), 7-$CH_3$ (s) and menthone ring |
| 2-H | to | 11-H (w), 1-H (s), 2'-H / 5'-H'(s), o-phenyl-Hs (s), 7-$CH_3$ (s) |
| 11-H | to | 1-H (w), 2-H(w), 2'-H / 5'-H (s), o-phenyl-H's (s) and 7-$CH_3$ (s) |
| 7-$CH_3$ | to | 1-H (s), 11-H (s) and menthone ring (s) |
| 9- / 10-$CH_3$ | to | 4-H (s) and menthone ring (s) |
| 4-H | to | 9-$CH_3$ / 10-$CH_3$ (s) and menthone ring (s) |

w: weak, s: strong

COSY-90 and NOE experiments were performed on a Bruker ARX 400. The COSY-90 data were recorded with IK and 256 points in the $t_2$ and $t_1$ dimensions, respectively. NOE spectra were recorded using NOEMUL pulse program. The data size was 32 K.

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