

STUDIES AIMING AT THE SYNTHESIS OF MORPHINE I.
SEPARATION AND CHARACTERIZATION OF THE AMIDE ROTAMERS OF 6'-HALOGENO-
N-FORMYL-NORRETICULINES

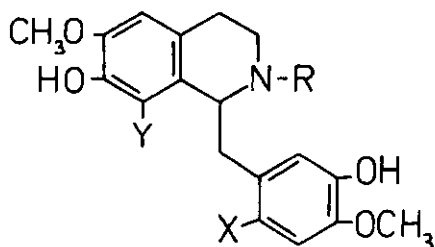
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Abstract - *Via* direct halogenation of N-substituted norreticulines, number of 6'-halogeno derivatives were prepared. The physical and spectroscopic properties of the successfully separated crystalline rotamers of both 6'-bromo- and 6'-chloro-N-formyl-norreticuline were studied.

In connection with their recent studies on N-substituted norreticuline derivatives, constituting potential intermediates for the total synthesis of morphine, Rice and Brossi¹ noted the separation of the two amide rotamers of 6'-bromo-N-formyl-norreticuline on TLC plates and observed a high barrier to interconversion through ¹H-NMR. This communication has prompted us to report the results of our related studies, carried out coincidentally with Ref.(1), that provide further important details about these interesting molecules.

The products described below were obtained by direct bromination or chlorination of N-ethoxycarbonyl² and N-formyl-norreticulines³. The reactions were carried out in dichloromethane solutions at low temperatures. Bromination of 1c at -20 °C was found to proceed selectively; the bromine entered the molecule at position C-6', to give 1d [yield 82 %, m.p.: 216-217°C, lit m.p.: 215-217°C², ¹H-NMR (CDCl₃+DMSO-d₆): δ 1,24 (t, 3H, CH₃), 3,80 (s, 6H, 2xOCH₃), 5,18-5,37 (m, 1H, C₁-H), 6,61 (s, 1H), 6,66 (s, 1H), 6,78 (s, 1H), 7,01 (s, 1H) aromatic protons, 8,28 (broad, 1H, OH), 8,60 (broad, 1H, OH)].



<u>l</u>	R	X	Y
a	H	H	H
b	H	Br	H
c	CO ₂ C ₂ H ₅	H	H
d	CO ₂ C ₂ H ₅	Br	H
e	CO ₂ C ₂ H ₅	Cl	H
f	CO ₂ C ₂ H ₅	Cl	Cl
g	CHO	H	H
h	CHO	Br	H
i	CHO	Cl	H

Chlorination of lc, at the same temperature, gave le and lf in the ratio 4:1. Separation of the two products (le, lf) was achieved by preparative TLC on Kieselgel PF₂₅₄ (Merck) plate, in benzene-chloroform-triethylamine (3:6:2) eluating system. le [m.p.: 215-216°C, IR (KBr): 3350 cm⁻¹ (OH), 1670 cm⁻¹ (N-C=O), ¹H-NMR (CDCl₃+DMSO-d₆): δ 1,02 (t, 3H, CH₃), 3,84 (s, 6H, 2xOCH₃), 5,18-5,36 (m, 1H, C₁-H), 6,50 (s, 1H), 6,57 (s, 1H), 6,78 (s, 1H), 6,86 (s, 1H) aromatic protons, 7,80-8,55 (broad, 2H, OH), MS: m/e (%): 375 (0,64), 326 (0,57), 286 (2,0), 284 (7,1), 250 (100), 222 (23), 191 (4,3), 178 (15), 163 (9,3)]; lf [m.p.: 224-226°C, IR(KBr): 3300 cm⁻¹ (OH), 1665 cm⁻¹ (N-C=O), ¹H-NMR (CDCl₃+DMSO-d₆): δ 1,10 (t, 3H, CH₃), 3,87 (s, 3H, OCH₃), 3,92 (s, 3H, OCH₃), 5,56-5,71 (m, 1H, C₁-H), 6,62 (s, 1H), 6,81 (s, 1H), 6,83 (s, 1H) aromatic protons, 7,60-8,15 (broad, 2H, OH), MS: m/e (%): 455 (0,1), 428 (0,1), 426 (0,8), 424 (2,6), 397 (0,1), 395 (0,3), 393 (1,1), 336 (0,5), 334 (1,0), 332 (1,6), 286 (37,3), 284 (100), 258 (5,0), 256 (16,5), 242 (1,5), 240 (5,0), 214 (6,8), 212 (23,4), 199 (6,0), 197 (20,8), 173 (2,6), 171 (7,5), 135 (2,5), 133 (9,8)]. The selectivity of monochlorination could be increased by lowering the temperature. At -45°C, the main product is le, while lf could be detected in traces only.

Direct bromination of N-formyl-norreticuline (lg) at -20°C proceeds quantitatively. The 6'-bromo compound⁴ (lh) revealed itself in two spots on TLC (R_f=0,53 and 0,62, Kieselgel DC Fertigplatte (Merck) chloroform-methanol 10:1) corresponding to the two isomers containing the N-formyl group in different rotational arrangements⁵.

Treatment of the crude mixture of the lh rotamers with ethyl acetate resulted in a crystalline mass consisting of the pure *cis*-lh⁶. On the other hand the *trans*-lh was obtained in crystalline form from the methanolic solution of the carefully evaporated mother liquor.

Further characterization of the isomers has been obtained from physico-chemical and spectroscopic data. While *cis*-lh has a sharp melting point at 226-227°C, the *trans*-lh undergoes morphological change at 150-153°C and melts at 224-227°C. The N=C=O absorption in the solid state IR spectra of the two crystalline rotamers showed significant difference. This absorption appears at 1655 cm⁻¹ in the spectrum of the *cis*-lh, and at 1680 cm⁻¹ in that of the *trans*-lh compound.

The ¹H-NMR spectra displayed characteristic chemical shift differences for the two isomers. The chemical shift values for the pertinent protons are summarized in Table 1.

Table 1. ¹H-NMR data of lh in DMSO-d₆ (δ)

	<i>cis</i> - <u>lh</u>	<i>trans</i> - <u>lh</u>
CHO	8,01 s	7,48 s
C ₅ , -H	6,97 s	7,01 s
C ₁ -H	5,35-5,52	4,59-4,78

The isomeric ratio *cis*-lh: *trans*-lh in DMSO solution at ambient temperatures was 70 : 30. The interconversion of the rotamers was followed by ¹H-NMR methods. Kinetic measurements have shown that, when dissolving any one of the rotamers, the equilibrium value of the isomeric ratio is attained in 20 to 25 min. at room temperature⁷. At elevated temperatures the predominance of the *cis* form in the equilibrium mixture is increased; the *cis*-lh: *trans*-lh ratio at e.g. 95°C was found as 85 : 15. Increasing temperatures gave rise to line-shape phenomena typical for hindered exchange processes. The coalescence of the CHO signals occurs at 170°C (δ 7,75) to give an estimated value⁸ of 94 kJ/mol (22,5 kcal/mol) for the activation free energy of rotamer interconversion. The mass spectra of the rotamers proved identical [MS: m/e (%): 423 (0,1), 421 (0,1) 394 (0,05), 392 (0,05), 341(0,2), 314 (0,05), 312 (0,1), 298 (0,07), 296 (0,07), 286 (0,2), 284 (0,3), 283 (0,2), 217 (0,07), 215 (0,07), 206 (100), 202 (0,1), 200 (0,1), 178 (7), 176 (1,3), 163 (6.), 162 (1), 148 (0,4), 146 (0,4), 135 (1), 134 (1,3)].

Chlorination of lg at -45°C afforded li selectively. Also consisting of two N-formyl rotamers, this product exhibited physico-chemical and spectroscopic properties resembling to those of lh. [$^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{DMSO-d}_6$): δ 3,64 (s, 6H, $2 \times \text{OCH}_3$) 4,5-4,72 (m, 0,4H, $\text{C}_1\text{-H}$) 5,17-5,38 (m, 0,6H, $\text{C}_1\text{-H}$), 6,54 (s, 1H), 6,58 (s, 1H), 6,66 (s, 1H), 6,80 (s, 0,6H), 6,87 (s, 0,4H), aromatic protons, 7,35 (s, 0,4H, CHO), 7,87 (s, 0,6H, CHO), 8,67-9,20 (broad, 2H, OH) MS: m/e (%): 379 (0,8), 377 (3), 350 (0,6), 348 (1,5), 342 (3), 313 (3,7), 243 (0,6), 241 (1,8), 214 (3,5), 212 (11), 206 (100), 199 (2,9), 197 (8,1), 178 (39,6), 173 (14,2), 171 (43,7), 158 (4,5), 156 (13), 130 (8,9), 128 (26,5)]. Treatment of the crude mixture of the li rotamers with methanol resulted in a crystalline mass consisting of the pure *cis*-li⁶ [m.p. $222-223^{\circ}\text{C}$, IR KBr : 1670 cm^{-1} (N-C=O)]. The *trans*-li was obtained by preparative TLC. The N-C=O absorption of this rotamer can be found at 1690 cm^{-1} .

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