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

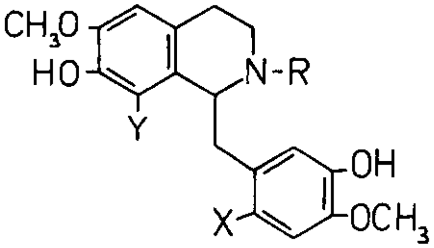
Csaba Szántay*, Gábor Blaskó, Marietta Bárczai-Beke, Gábor Dörnyei
and Lajos Radics

Institute of Organic Chemistry, Technical University, H-1111 Budapest
Gellért tér 4, Hungary and Central Research Institute for Chemistry,
Hungarian Academy of Sciences

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 Brossi[1] 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 ^{1}H-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-ethoxycarbonyl[2] and N-formyl-norreticulines[3]. 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°C [2], ^{1}H-NMR ($CDCl_3$+DMSO-d_6): δ 1,24 (t, 3H, CH_3), 3,80 (s, 6H, 2xOCH_3), 5,18-5,37 (m, 1H, C_1-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)].



1	R	X	Y
a	H	H	H
b	H	Br	H
c	$CO_2C_2H_5$	H	H
d	$CO_2C_2H_5$	Br	H
e	$CO_2C_2H_5$	Cl	H
f	$CO_2C_2H_5$	Cl	Cl
g	CHO	H	H
h	CHO	Br	H
i	CHO	Cl	H

Chlorination of **1c**, at the same temperature, gave **1e** and **1f** in the ratio 4:1. Separation of the two products (**1e**, **1f**) was achieved by preparative TLC on Kieselgel PF_{254} (Merck) plate, in benzene-chloroform-triethylamine (3:6:2) eluating system. **1e** [m.p.: 215-216°C, IR (KBr): 3350 cm^{-1} (OH), 1670 cm^{-1} (N-C=O), ^{1}H-NMR ($CDCl_3$+DMSO-d_6): δ 1,02 (t, 3H, CH_3), 3,84 (s, 6H, 2xOCH_3), 5,18-5,36 (m, 1H, C_1-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)]; **1f** [m.p.: 224-226°C, IR(KBr): 3300 cm^{-1} (OH), 1665 cm^{-1} (N-C=O), ^{1}H-NMR ($CDCl_3$+DMSO-d_6): δ 1,10 (t, 3H, CH_3), 3,87 (s, 3H, OCH_3), 3,92 (s, 3H, OCH_3), 5,56-5,71 (m, 1H, C_1-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 **1e**, while **1f** could be detected in traces only.

Direct bromination of N-formyl-norreticuline (**1g**) at -20°C proceeds quantitatively. The 6'-bromo compound[4] (**1h**) 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 arrangements[5].

Treatment of the crude mixture of the **1h** rotamers with ethyl acetate resulted in a crystalline mass consisting of the pure *cis*-**1h**[6]. On the other hand the *trans*-**1h** 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*-**1h** has a sharp melting point at 226-227°C, the *trans*-**1h** 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*-**1h**, and at 1680 cm^{-1} in that of the *trans*-**1h** 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 **1h** in DMSO-d_6 (δ)

	cis-**1h**	*trans*-**1h**
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*-**1h**: *trans*-**1h** 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 temperature[7]. At elevated temperatures the predominance of the *cis* form in the equilibrium mixture is increased; the *cis*-**1h**: *trans*-**1h** 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 value[8] 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 **1g** at -45°C afforded **1i** selectively. Also consisting of two N-formyl rotamers, this product exhibited physico-chemical and spectroscopic properties resembling to those of **1h**. [^{1}H-NMR (CDCl$_3$+DMSO-d$_6$): δ 3,64 (s, 6H, 2xOCH$_3$) 4,5-4,72 (m, 0,4H, C$_1$-H) 5,17-5,38 (m, 0,6H, C$_1$-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 **1i** rotamers with methanol resulted in a crystalline mass consisting of the pure *cis*-**1i**[6] [m.p. 222-223°C, IR KBr : 1670 cm^{-1} (N-C=O)]. The *trans*-**1i** was obtained by preparative TLC. The N-C=O absorption of this rotamer can be found at 1690 cm^{-1}.

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