

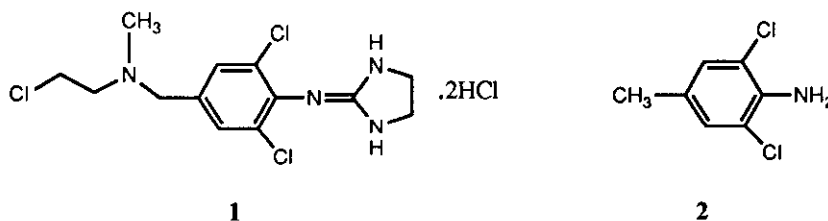
AN EFFICIENT SYNTHESIS OF CHLOROETHYLCLONIDINE

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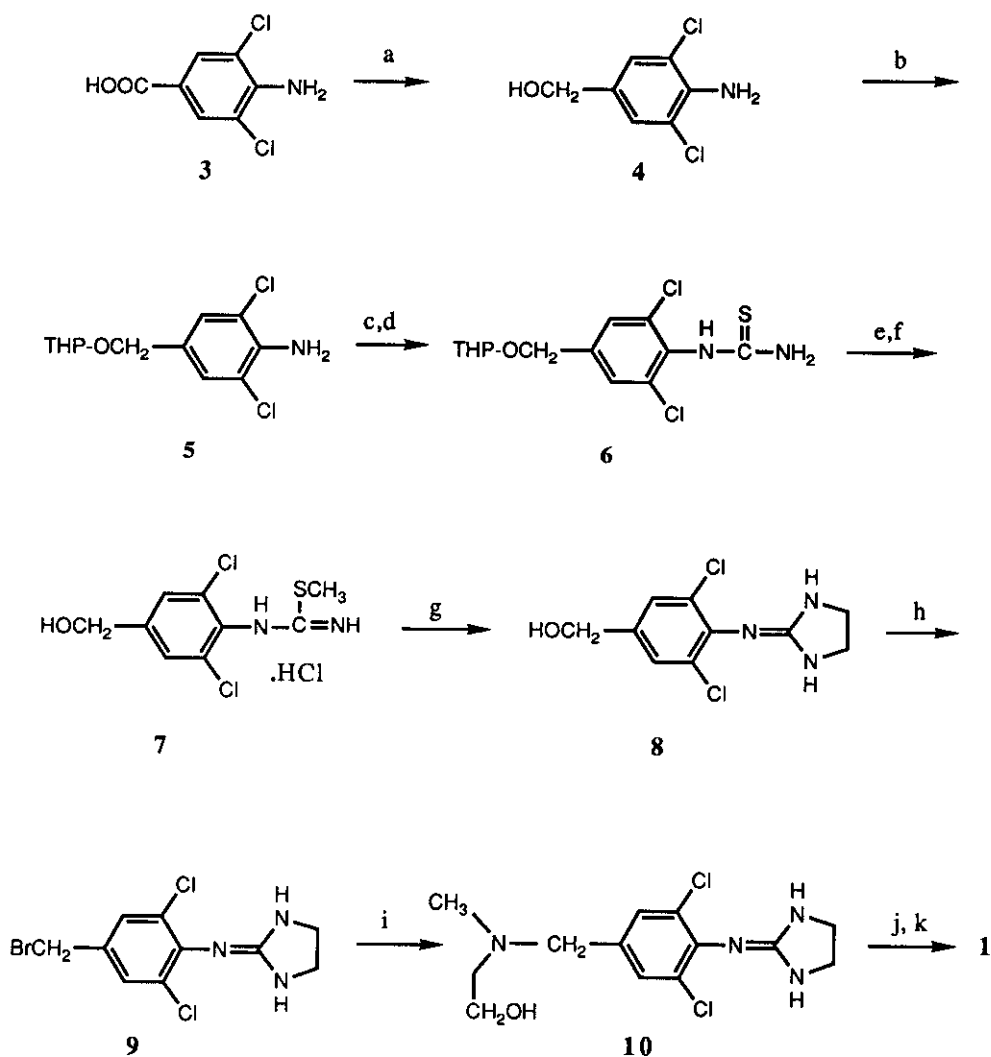
Abstract- An efficient pathway for the preparation of chloroethylclonidine dihydrochloride (**1**) is described.

Chloroethylclonidine (**1**) is a pharmacologically useful ligand for the α -adrenergic receptor, which was initially developed as an α -adrenoreceptor stimulant with prolonged activity.¹ The ability of compound (**1**) to inactivate α -adrenergic receptor binding sites in rat brain made it more useful in differentiating pharmacological properties of subpopulations of α_1 -adrenergic receptors.²



The original synthesis of **1**, reported by Rouot and Leclerc in 1978, begins with 2,6-dichloro-4-methylaniline (**2**).³ Compound (**2**) is no longer commercially available but may be prepared by chlorination of *N*-acetyl-*p*-toluidine.⁴ The reported synthesis involves the construction of the iminoimidazoline ring followed by benzylic bromination with NBS and introduction of the side chain.³ Bromination at this late stage necessitated a protection-deprotection sequence of the imidazoline ring which rendered the overall synthesis inefficient. Hence we embarked on the development of a more efficient synthesis of **1** in multigram quantities from a readily available starting material. The results of this effort are communicated here. Our synthesis as presented in Scheme I started from 4-amino-3,5-dichlorobenzoic acid (**3**) which was reduced with diborane to the alcohol (**4**). The THP protected amine (**5**) was then converted to the thiourea (**6**) *via* reaction with benzoyl isothiocyanate followed by alkaline hydrolysis. Two of

Scheme I*



- * Key: (a) BH_3 , THF; (b) Dihydropyran, *p*-TsOH, CH_2Cl_2 ; (c) Ph-CO-NCS, acetone (70 % from 3); (d) 10% aq. NaOH; (e) CH_3I , CH_3OH ; (f) convert to free base and then to HCl salt; (g) Ethylenediamine, $\text{C}_2\text{H}_5\text{OH}$, 130°C (54 % from 6); (h) SOBr_2 , $\text{ClCH}_2\text{CH}_2\text{Cl}$, reflux; (i) 2-Methylaminoethanol, DMF, -10°C ; (j) convert to free base and then to HCl salt (50 % from 8); (k) SOCl_2 , 65°C (87 %).

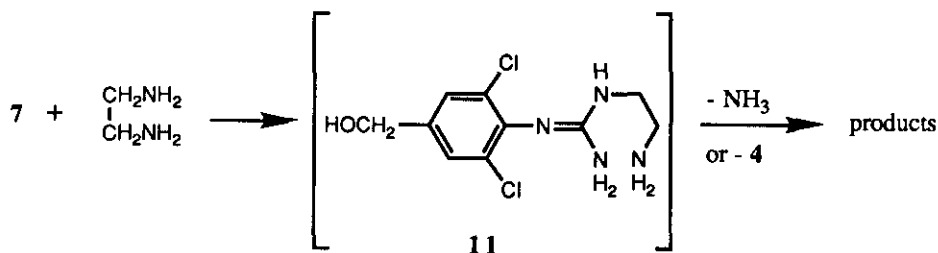
Table 1

Compound	mp (°C)	Ir (cm ⁻¹)	¹ H-Nmr (300 MHz) (δ)
1	262		(CD ₃ OD) 2.96 (s, 3H, N-CH ₃), 3.65 (br s, 2H, N-CH ₂), 3.83 (s, 4H, imidazoline-CH ₂ 's), 4.05 (t, 2H, CH ₂ Cl), 4.53 (br s, 2H, Ar-CH ₂ -N) 7.89 (s, 2H, Ar-H's)
4	118-120	3200	(CDCl ₃) 1.65 (br s, 1H, OH), 4.45 (br s, H, NH ₂), 4.53 (s, 2H, CH ₂), 7.2 (s, 2H, Ar-H's)
5	-	3380, 3480	-
6	170-171	-	(CDCl ₃ , DMSO-d ₆) 1.69(m, 6H, 3,4,5-H (THP)), 3.55 (m, 1H, 6-H (axial) (THP), 3.85 (m, 1H, 6-H (eq) (THP), 4.47 (d, 1H, 1-H (THP)), 4.73 (m, 2H OCH ₂), 6.95 (br s, 2H, NH ₂), 7.40 (s, 2H, Ar-H's), 9.06 (br s, 1H, NH)
7	133-135	3180	(CDCl ₃ , DMSO-d ₆) 2.51 (s, 3H, SCH ₃), 4.54 (s, 2H, CH ₂ OH), 5.55 (br s, 1H, NH), 7.30 (m, 2H, Ar-H's)
8	205-207	-	(CD ₃ OD) 3.32 (s, 4H, N-CH ₂ 's), 4.33 (s, 2H, Ar-CH ₂ O), 7.14 (s, 2H, Ar-H's)
9	259-261	-	(CD ₃ OD) 3.8 (s, 4H, imidazoline-CH ₂ 's), 4.33 (s, 2H, Ar-CH ₂ -O), 7.66 (s, 2H, Ar-H's)
10	272-273	-	(CD ₃ OD) 2.94 (s, 3H, N-CH ₃), 3.32 (t, 2H, N-CH ₂), 3.83 (s, 4H, imidazoline-CH ₂ 's), 3.93 (t, 2H, CH ₂ -O), 7.85 (s, 2H, Ar-H's)

these three steps proceeded in near quantitative yields.

For the construction of the required iminoimidazoline ring we followed the method of Rouot and co-workers.⁶ Thus compound (6) was methylated with CH₃I in methanol to the S-methylthiourea (7). During this reaction the THP group was also cleaved, presumably catalyzed by HI, to the THP-methyl ether. When the free base of compound (7) was treated with ethylenediamine in ethanol in a pressure bottle, only a small amount of the desired cyclized product (8) was obtained while the major product was found to be the starting amine (4). However, when the

hydrochloride salt of *S*-methylthiourea (7) was employed instead, the desired iminoimidazoline (8) was obtained as the major product while the formation of the aniline (4) was also suppressed. The generation of the aniline could be explained by the presence of an intermediate such as 11 which could lose either ammonia or the aniline enroute to the imidazoline ring.



Conversion of the alcohol (8) to the benzyl bromide (9) was then accomplished, without the need for protection of the imidazoline ring, by treatment with SOBr₂ in dichloroethane. The required amination of 11 with 2-methylaminoethanol occurred efficiently when the reaction was carried out in dry DMF at -10 °C. Conversion to the free base and formation of the HCl salt preceded treatment with thionyl chloride leading to 1.

REFERENCES AND NOTES

- ⊕ This manuscript is submitted in commemoration of the 70 th Birthday of Dr. Arnold Brossi.
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 7. The new compounds and key intermediates were characterized by ir and ¹H-nmr (Table 1). The CHN analyses for selected compounds are: 6: Anal. Calcd. for C₁₃H₁₆N₂O₂Cl₂S: C, 46.57; H, 4.81; N, 8.36; S, 9.56. Found: C, 46.66; H, 4.81; N, 8.37; S, 9.61. 7: Anal. Calcd. for C₉H₁₀N₂OCl₂S: C, 40.77; H, 3.80; N, 10.56; S, 12.09. Found: C, 40.56; H, 3.76; N, 10.46; S, 12.22. 10: Anal. Calcd. for C₁₃H₁₇N₄Cl₃.2HCl: Found: C, 38.21; H, 4.69; N, 13.71; Cl, 43.38. Found: C, 38.39; H, 4.67; N, 13.56; Cl, 43.56.

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