AN EFFICIENT SYNTHESIS OF CHLOROETHYLCLONIDINE

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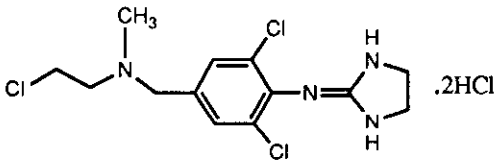
Abstract- An efficient pathway for the preparation of chloroethylclonidine dihydrochloride (**1**) is described.

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]



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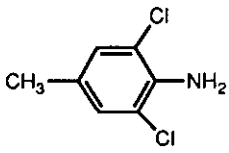

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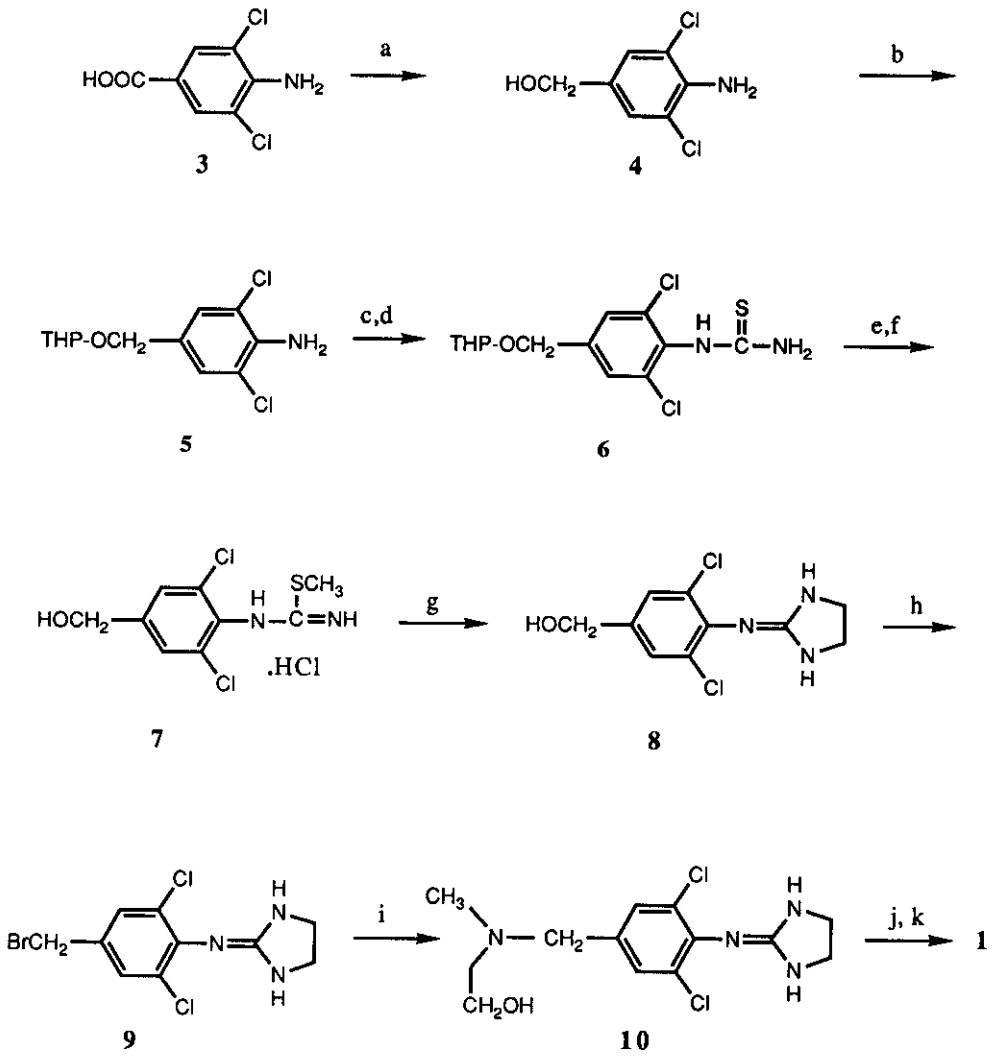
The original synthesis of **1**, reported by Rouot and Leclerc in 1978, begins with 2,6-dichloro-4-methylaniline (**2**).[3] Compound (**2**) is no longer commercially available but may be prepared by chlorination of *N*-acetyl-*p*-toluidine.[4] The reported synthesis involves the construction of the 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, C_2H_5OH, 130°C (54 % from **6**); (h) $SOBr_2$, $ClCH_2CH_2Cl$, 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 %).

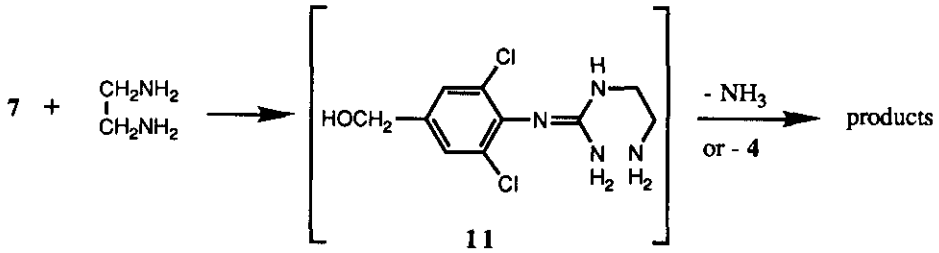
Table 1

Compound	mp (°C)	Ir (cm^{-1})	^{1}H-Nmr (300 MHz) (δ)
1	262		(CD_3OD) 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_2Cl), 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_2OH), 5.55 (br s, 1H, NH), 7.30 (m, 2H, Ar-H's)
8	205-207	-	(CD_3OD) 3.32 (s, 4H, N-CH_2's), 4.33 (s, 2H, Ar-CH_2O), 7.14 (s, 2H, Ar-H's)
9	259-261	-	(CD_3OD) 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_3OD) 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 CH_3I 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 ethylene-diamine 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 loose either ammonia or the aniline enroute to the imidazoline ring.



11

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 $SOBr_2$ 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 ^{1}H-nmr (Table 1). The CHN analyses for selected compounds are: **6**: Anal. Calcd. for $C_{13}H_{16}N_2O_2Cl_2S$: 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 $C_9H_{10}N_2OCl_2S$: 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 $C_{13}H_{17}N_4Cl_3.2HCl$: 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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