BROMINATION OF α-ERGOCRYPTINE AND OTHER ERGOT ALKALOIDS WITH 3-BROMO-6-CHLORO-2-METHYLIMIDAZO/1,2-b/PYRIDAZINE-BROMINE COMPLEX AS A NEW BROMINATING AGENT

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Abstract - A new and improved bromination of α-ergocryptine and some other ergot alkaloids of the type 1, 2 and 3 using 3-bromo-6-chloro-2-methylimidazo/1,2-b/pyridazine-bromine complex (5) as a new brominating agent, to give purified 2-bromo derivatives in yields up to 81%, is described.

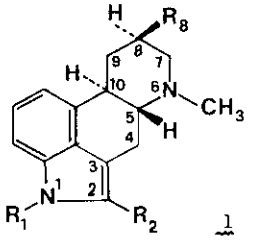
The halogenation of ergot alkaloids of the types 1, 2, and 3 was described many years ago. A number of different halogenating agents, including bromine, pyridine hydrobromide perbromide, N-bromosuccinimide, N-bromophthalimide, N-iodosuccinimide, N,2,6-trichloro-4-nitroacetanilide, t-butylhypochlorite and others in dioxane usually at elevated temperatures has been employed for this purpose [1]. Recently, the clinically important 2-bromo-α-ergocryptine (2; R_1=H, R_2=Br, R_8=4c) has been prepared in 38% yield by bromination of α-ergocryptine with N-bromosuccinimide in dioxane [2]. However, the yields of monobrominated products are relatively low even under optimal experimental conditions, due to the formation of polybromo derivatives, undefined decomposition products, deeply colored resinous material and epimerization at position 8. Moreover, the ergot alkaloids with a peptide side chain can be easily transformed into 12'-O-alkyl derivatives in the presence of alcohols in acidic solutions [1,2].

During our continous interest in the chemistry of azolo-azines with a bridgehead nitrogen atom [3] we observed that some imidazo/1,2-b/pyridazine derivatives form stable, well defined 1:1 complexes with bromine, which can be used as brominating agents for a variety of organic compounds [4].

In this communication we would like to report on the bromination of α-ergocryptine and some other ergot alkaloids with this new brominating agent,

namely, 3-bromo-6-chloro-2-methylimidazo/1,2-b/pyridazine-bromine complex, the compound which has been previously synthesized in our laboratory by bromination of 6-chloro-2-methylimidazo/1,2-b/pyridazine with an excess of bromine in acetic acid [5].

This method has several advantages over the previously reported procedures. The brominating agent is stable in the solution when halogenated hydrocarbons are used as solvents, it is selective and does not lead to large amounts of side products, including those which result from epimerization at position 8. The bromination is carried out at room temperature and is complete in few minutes giving purified 2-bromo derivatives of ergot alkaloids in 50-81% yields. Epimerization at position 8 is minimal due to short reaction time. Usually, 1.2 to 1.5 moles of brominating agent is used per one mole of ergot alkaloid. The excess of brominating agent can be easily decomposed by addition of acetone and ammonium hydroxide, and the product isolated by extraction, column chromatography and/or crystallization from appropriate solvents, to obtain 2-bromo derivatives in pure form. From the reaction mixture 3-bromo-6-chloro-2-methylimidazo/1,2-pyridazine can be isolated. This can be converted back into the brominating agent by treatment with an excess of bromine in acetic acid.



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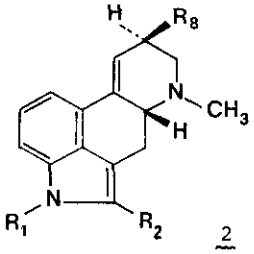

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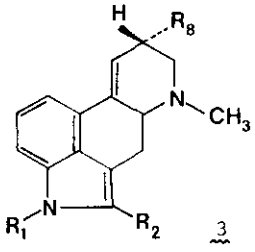

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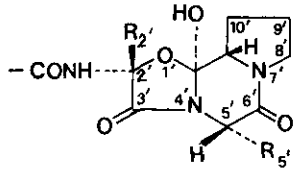
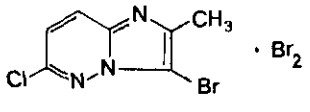


4 a) R_2 = CH_3 R_5 = CH_2Ph
b) R_2 = CH_3 R_5 = $CH_2CH(CH_3)_2$
c) R_2 = $CH(CH_3)_2$ R_5 = $CH_2CH(CH_3)_2$



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The starting compounds which are not commercially available were prepared according to the procedures described in the literature: 6-chloro-2-methylimidazo /1,2-b/pyrazine [6]; 3-bromo-6-chloro-2-methylimidazo/1,2-b/pyridazine [5], 9,10-dihidroergotamine [7], 9,10-dihydro-α-ergosine[7], α-ergosine [8], α-ergosine[9], α-ergocryptine [10], 5R, 8R-lysergic acid diethyl amide[11,12], and 1-methyl-9,10-dihydrolysergic acid methyl ester [13,14].

Preparation of the brominating agent, 3-Bromo-6-chloro-2-methylimidazo/1,2-b/pyridazine-bromine complex (5).

a) A solution of 6-chloro-2-methylimidazo/1,2-b/pyridazine (1.67 g, 0.01 M) in glacial acetic acid (25 ml) is treated dropwise with an excess of bromine at room temperature. The resulting precipitate, which is formed immediately,is collected by filtration and washed with glacial acetic acid (5 ml). The crude product is recrystallized from acetic acid and washed with diethyl ether in order to remove acetic acid, and dried in vacuo at 30° C for one hour. Yield 75-90 %,mp. 217-220°C, lit. mp. 217-220°C [5].

b) 3-Bromo-6-chloro-2-methylimidazo/1,2-b/pyridazine-bromine complex may be regenerated from 3-bromo-6-chloro-2-methylimidazo/1,2-b/pyridazine in the following way. 3-Bromo-6-chloro-2-methylimidazo/1,2-b/pyridazine (0.23 g, 0.00093 M) is dissolved in glacial acetic acid (2 ml) and treated dropwise with bromine (0.00139 M) in glacial acetic acid (1 ml). The work-up procedure is the same as above. Yield 0.38 g (90 %), mp. 217-220°C, lit. mp. 217-220°C, ir spectrum identical with that of an authentic specimen [5].

Bromination of ergot alkaloids. A typical procedure.
2-Bromo-9,10-dihydroergotamine (1; R_1=H, R_2=Br, R_8=4a)

To stirred solution of 9,10-dihydroergotamine (1; R_1=H, R_2=H, R_8=4a) (0.584 g, 0.001 M) dissolved in methylene chloride (20 ml) 3-bromo-6-chloro-2-methylimidazo/1,2-b/pyridazine-bromine complex (5) (0.612 g, 0.0015 M) in methylene chloride (180 ml) is added. The mixture is stirred at room temperature for two minutes, followed by addition of acetone (10 ml) and aqueous ammonium hydroxide (2%, 100 ml). The organic layer is separated and aqueous layer extracted twice with methylene chloride (200 ml each time). The combined extracts are evaporated in vacuo and the dry residue applied to a column containing silicagel (50 g), using a mixture of methylene chloride: ethanol (20:1) as eluent. 3-Bromo-6-chloro-2-methylimidazo/1,2-b/pyridazine (0.23 g) is obtained as the first component. Further elution yields pure 2-bromo-9,10-dihydroergotamine (1; R_1=H, R_2=Br, R_8=4a)(0.33 g, 50%), mp. 198-200°C, lit. mp. 198-199°C [1], $|\alpha|_D^{20}$ =-84° (c=1, pyridine), lit. $|\alpha|_D^{20}$= -87° [1], ir and nmr spectra identical with those of an authentic specimen [1].

Under essentially the same reaction conditions some other ergot alkaloids were brominated. The experimental details are summarized in the Table.

Table. Bromination of Ergot Alkaloids with 3-Bromo-6-chloro-2-methylimidazo/1,2-b/pyridazine·Bromine Complex

Stating compound	Product [a]	Yield [b] [%]	mp. [°C]	lit.mp. [°C] or mol formula	$[\alpha]_D^{20}$	lit. $[\alpha]_D^{20}$
9,10-dihydro-α-ergosine (1; R_1=H, R_2=H, R_8=4b)	2-bromo-9,10-dihydro-α-ergosine (1; R_1=H, R_2=Br, R_8=4b)	69	286-188	$C_{30}H_{38}BrN_5O_5$ [c]	-40° (c=1, methanol)	-
α-ergosine (2; R_1=H, R_2=H, R_8=4b)	2-bromo-α-ergosine (2; R_1=H, R_2=Br, R_8=4b)	31	183-185	$C_{30}H_{36}BrN_5O_5$ [d]	-91,6°	-
α-ergocryptine (2; R_1=H, R_2=H, R_8=4c)	2-bromo-α-ergocryptine (2; R_1=H, R_2=Br, R_8=4c)	75	215-218	202-203 [2]	-98° (c=1, pyridine)	-98,3° (c=1,3; pyridine) [2]
α-ergosinine (3; R_1=H, R_2=H, R_8=4b)	2-bromo-α-ergosinine (3; R_1=H, R_2=Br, R_8=4b)	70	188-190	$C_{30}H_{36}BrN_5O_5$ [e]	+403° (c=1, chloroform)	-
5R, 8R-lysergic acid diethyl amide [2; R_1=H, R_2=H, R_8=$CON(C_2H_5)_2$]	2-bromo-5R, 8R-lysergic acid diethyl amide [2; R_1=H, R_2=Br, R_8=$CONH(C_2H_5)_2$]	73,4 [f]	122-125	120-127 [1]	+17° (c=1, pyridine)	+15° (c=1, pyridine) [1]
1-methyl-9,10-dihydro-lysergic acid methyl ester (1; R_1=CH_3, R_2=H, R_8=$COOCH_3$)	2-bromo-1-methyl-9,10-dihydro-lisergic acid methyl ester (1; R_1=CH_3, R_2=Br, R_8=$COOCH_3$)	65 [g]	166-168	$C_{18}H_{19}BrN_2O_2$ [h]	-94° (c=0,5; chloroform	-

a)
b) Isolated compounds are in all respects (mp., ir and nmr) identical with the compounds cited in the literature.
c) Yield of purified product.
d) Anal.: Calcd. C 57.32%, H 6.09%, Br 12.71%; Found C 57.41%, H 6.62%, Br 12.70%.
e) Anal.: Calcd. C 57.50%, H 5.79%, Br 12.76%; Found C 57.63%, H 6.06%, Br 12.40%.
f) Anal.: Calcd. C 57.50%, H 5.79%, Br 12.76%; Found C 57.59%, H 5.94%, Br 12.68%.
g) After recrystallization of the dry residue from ether.
h) After recrystallization of the dry residue from methanol/water (85:15).
Anal.: Calcd. C 57.30%, H 5.61%, Br 21.18%; Found C 57.45%, H 5.51%, Br 21.20%.

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