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Morphanthridines II. 11-Aminoalkyl-5,6-dihydromorphanthridines

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Butyl lithium converts 5-substituted-5,6-dihydromorphanthridines to the 11-position anion. Treatment of this lithium anion with aminoalkyl halides affords the 11-aminoalkylated derivatives. Catalytic hydrogenation causes reductive cleavage of benzylamino bridge of the morphanthridine ring, a reaction which is used to structurally relate these compounds to the known 11-aminoalkylidene-5,6-dihydromorphanthridines.

Many compounds of clinical value have been obtained by aminoalkylation of tricyclic ring systems. Consequently, the preparation of many 5-substituted 5,6-dihydromorphanthridines (1), 5-substituted 5,6-dihydro-6-morphanthridones (2), and 5-substituted 6,11-morphanthridinediones (3) have been reported. Although the aminoalkylation of the 5,6-dihydromorphanthridine ring system in the 11-position has not been described, several of these compounds are known (4). By analogy with the aminoalkylation of dibenzo[a,d]cycloheptadiene (5), we correctly projected that alkylation of the lithium anion of 5-substituted-5,6-dihydromorphanthridines (I) with tertiary aminoalkyl halides, cyclicaminoalkyl halides, or halopiperidines, should afford the 5-substituted-11-basic substituted-5,6-dihydromorphanthridines (II) in good yield.

The procedure of G. Wittig *et al.*, (6) served well for the preparation of 5-methyl-5,6-dihydromorphanthridine. We found butyl lithium a convenient substitute for phenyl lithium in effecting the rearrangement of *N*-methyl-*N*-phenylisoindolinium iodide. Similarly, *N*-methyl-*N*-(4-chlorophenyl)-isoindolinium iodide yielded the 2-chloro substituted product.

A more versatile and convenient method for the preparation of the parent ring system, 5,6-dihydromorphanthridine (3a, 6, 7), was through reduction of 6,11(5*H*)-morphanthridinedione with lithium aluminum hydride (3a, 6). The alkylation procedure of Wittig *et al.*, (6) was employed to introduce the substituent in the 5-position. This involved preparation of a lithium anion followed by treatment with an alkyl halide. Commercially available butyl lithium in hexane conveniently replaced methyl lithium in this reaction. Alkylation could not be effected, however, if sodium amide or sodium hydride was used instead of methyl lithium or butyl lithium, probably due to the inability to form the required anion.

The alternate synthetic possibility of alkylation prior to reduction was investigated. Treatment of morphanthridine-6,11(5*H*)-dione with sodium amide followed by methyl iodide provided 5-methyl-6,11-(5*H*)-morphanthridinedione. Reduction with lithium aluminum hydride resulted in incomplete reaction affording a mixture of partially reduced products. On the other hand, lithium aluminum hydride reduction of 5-benzyl-5,6-dihydro-6-morphanthridone proceeded satisfactorily affording 5-benzyl-5,6-dihydromorphanthridine in high yield which was in every respect identical to the product obtained by alkylation of the saturated ring.

The alkylation of 5-substituted-5,6-dihydromorphanthridines was effected at room temperature in a solvent mixture of ether and tetrahydrofuran, by the addition of a hydrocarbon solution of butyl lithium, followed by adding an ethereal solution of the aminoalkyl halide.

The secondary amines 5 and 8 (Table I) were prepared from the corresponding tertiary benzylamines 2 and 7. The benzyl group could not be removed by catalytic hydrogenolysis using palladium, because the 5,6-dihydromorphanthridine ring system itself was subject to benzyl cleavage. This was illustrated when hydrogenation of 5-methyl-5,6-dihydromorphanthridine at room temperature in the presence of palladium on carbon, gave a high yield of 2-methyl-2'-methylaminodiphenylmethane (6), which was isolated and identified as its hydrochloride. However, treatment of the *N*-methyl-*N*-benzylaminoalkyl compounds with alkyl chloroformates or alkyl thiochloroformates followed by alkaline hydrolysis of the intermediate carbamates (8), afforded the secondary amines in high yield.

There was ample precedent for our assumption that aminoalkylation of 5-methyl-5,6-dihydromorphanthridine using the butyl lithium generated anion would afford the 11-aminoalkylated products (9). Proof of this was obtained when both catalytic hydrogenation of the aminoalkyl compound (III) and of the aminoalkylidene compound (IV) in the presence of palladium on carbon, afforded the same aniline derivative (V) identified as its dipicrate salt. Since the structure of IV is unambiguous (10), the position of the aminoalkyl group in III is established.

EXPERIMENTAL (11)

N-Methyl-*N*-(4-chlorophenyl)isoindolinium iodide.

To 46.0 g. (0.33 mole) of *N*-methyl-4-chloroaniline was added slowly with stirring 22.5 ml. of 40% aqueous hydrobromic acid. A solution

of 26.4 g. (0.1 mole) of α,α'-dibromo-*o*-xylene in 135 ml. of chloroform was added rapidly and the reaction mixture was stirred and refluxed for 20 hours. The chloroform was distilled, the residue cooled, 165 ml. of water added, and the solution made alkaline with 28 ml. of concentrated ammonia. The solution was extracted three times with 75 ml. portions of ether and reduced in volume to 150 ml. on a steam bath under reduced pressure. It was then heated to 60° and with rapid agitation, 17.5 g. (0.15 mole) of potassium iodide was added in one portion. The solution was cooled and the precipitate collected and dried to yield 21.8 g. (58.7%) of product, m.p. 179-181°C.

Anal. Calcd. for $C_{15}H_{15}ClIN$: C, 48.47; H, 4.07. Found: C, 48.42; H, 4.18.

2-Chloro-5-methyl-5,6-dihydromorphanthridine.

Commercial butyl lithium solution (12) (190 ml., 0.306 mole) in 90 ml. of dry ether was added in 7 hours to a stirred slurry of 105.0 g. (0.283 mole) of *N*-methyl-*N*-(4-chlorophenyl)isoindolinium iodide in 90 ml. of dry ether. The mixture was refluxed for 4 hours, cooled to room temperature, and 200 ml. of water was added dropwise. The solid was removed by filtration, the ethereal layer was separated, dried over potassium carbonate, filtered, and taken to dryness under reduced pressure. The residue (57.7 g.) was distilled and gave 48.4 g. of product distilling at 150-185° (0.06 mm.). The distillate was recrystallized twice from methanol to give 26.9 g. (39%)

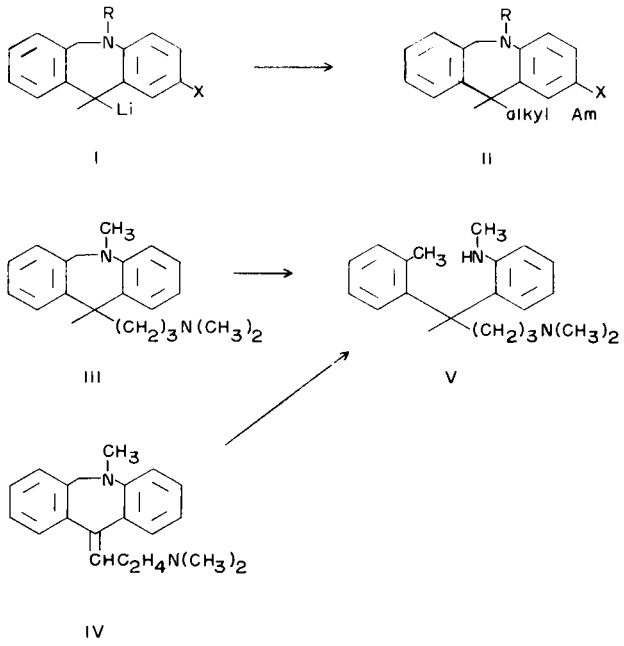
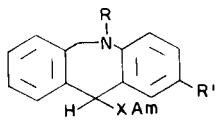


TABLE I

5-Substituted-11-Aminoalkyl-5,6-dihydromorphanthridines



Compound	R	R'	X	Am	B.p., °C(mm.)	Calcd. % / Found % C	H	N	Salt	M.p., °C
1	CH_3	H	$(CH_2)_3$	$N(CH_3)_2$	156-159(0.125)	58.86(f) 58.86(f)	8.03 8.13	8.58 8.53	2C (g, h)	148-149
2	CH_3	H	$(CH_2)_3$	$NCH_3CH_2C_6H_5$	225(0.2)	84.28 84.14	8.16 8.38	7.56 7.63	2C (g)	119 (i)
3	CH_3	H	$(CH_2)_3$	piperidino	190(0.08)	82.58 82.65	9.04 9.11	8.35 8.40	fumarate	184-186 (j)
4	CH_3	H	$(CH_2)_3$	4-methyl-piperazino	195(0.1) (a)	79.03 79.05	8.94 8.85	12.06 11.91		
5	CH_3	H	$(CH_2)_3$	$NHCH_3$	170(0.05) (b)	69.68(f) 69.58(f)	7.12 7.05	7.07 7.19	maleate	126
6	CH_3	H	$CHCH_3CH_2CH_2$	$N(CH_3)_2$	145-147(0.12)	59.43(f) 59.61(f)	8.16 8.19		2C (g)	117
7	CH_3	Cl	$(CH_2)_3$	$NCH_3CH_2C_6H_5$	163-170(0.35)	59.78(f) 59.56(f)	7.28 7.46	7.34 7.41	2C (g)	122-124
8	CH_3	Cl	$(CH_2)_3$	$NHCH_3$		58.84(f) 59.07(f)	6.49 6.54	7.22 7.14	2 HCl	200-204
9	CH_3	Cl	$(CH_2)_3$	piperidino	223(0.2) (c)	74.87 75.17	7.92 7.95	7.59 7.32		
10	CH_3	H	$(CH_2)_3$	4-benzyl-piperazino	260(0.8)	81.84 82.17	8.29 8.39	9.87 10.68		
11	$CH_2C_6H_5$	H	$(CH_2)_3$	piperidino	290(0.5)	84.84 84.91	8.35 8.13	6.82 6.74		
12	$CH_3(CH_2)_3$	H	$(CH_2)_3$	piperidino	250(3.5) (d)	73.13(f) 72.84(f)	8.19 7.88	5.68 5.51	maleate	138
13	CH_3	H	$(CH_2)_2$	piperidino	169(0.05)	82.56 82.36	8.82 8.91	8.76 8.82		
14	CH_3	H	1-methyl-4-piperidyl		162-167(0.1) (e)	82.30 82.39	8.55 8.50	9.14 9.16		

(a) Melting point 69-72°. (b) *Anal.* Calcd. for $C_{13}H_{24}N_2$: N, 9.99. Found: N, 9.81. (c) *Anal.* Calcd. for $C_{23}H_{29}ClN_2$: Cl, 9.61. Found: Cl, 9.45. (d) *Anal.* Calcd. for $C_{26}H_{36}N_2$: N, 7.44. Found: N, 7.88. (e) Melting point 88-89°. (f) Assay of the salt. (g) C = cyclohexylsulfamate. (h) Dihydrochloride (hygroscopic), melting point, approximately 105°. (i) *Anal.* Calcd. for $C_{38}H_{56}N_4O_6S_2$: N, (total) 7.69; N(non-aqueous titration), 3.84. Found: N, (total) 7.74; N(non-aqueous titration), 3.84. (j) *Anal.* Calcd. for $C_{27}H_{34}N_2O_4$: C, 71.97; H, 7.61; N, 6.22. Found: C, 71.61; H, 7.51; N, 6.26.

of product, m.p. 57.5-60.0°.

Anal. Calcd. for $C_{15}H_{14}ClN$: C, 73.91; H, 5.79; N, 5.75. Found: C, 73.68; H, 5.87; N, 5.58.

5-Methyl-6,11(5*H*)-morphanthridinedione.

To 33.5 g. (0.15 mole) of morphanthridine-6,11(5*H*)dione in 250 ml. of dioxane was added with stirring a suspension of 5.85 g. (0.15 mole) of sodium amide in 200 ml. of toluene. The mixture was heated to reflux for 3.5 hours until the evolution of ammonia stopped, cooled to 30°, and a solution of 71 g. (0.5 mole) of methyl iodide in 200 ml. of toluene was added. The mixture was stirred several hours at room temperature, followed by a 9 hour reflux period. After cooling, 60 ml. of water was added, the organic layer was separated, dried over potassium carbonate, filtered, and concentrated. The solid residue was recrystallized from 150 ml. of ethanol to give 25.3 g. (71%) of product, m.p. 93-95°.

Anal. Calcd. for $C_{15}H_{11}NO_2$: C, 75.93; H, 4.67; N, 5.90. Found: C, 75.65; H, 4.81; N, 5.79.

5-Benzyl-5,6-dihydro-6-morphanthridone.

To a solution of 20.9 g. (0.1 mole) of 5,6-dihydro-6-morphanthridone in 200 ml. of dry toluene was added a slurry of 3.9 g. (0.1 mole) of sodamide and the mixture was stirred and refluxed for 3 hours. To the resulting clear solution was added, in 10 min., 51.3 g. (0.3 mole) of benzyl bromide in 100 ml. of toluene and the mixture was heated to reflux for 19 hours, cooled, 50 ml. of water added, the organic layer separated, washed once more with 50 ml. of water and dried over potassium carbonate. After removal of the toluene by distillation there remained 52 g. of residue, which was recrystallized from 300 ml. of hot ethanol. Yield 22.0 g. (73.5%), m.p. 148-150°. Repeated crystallizations from ethanol raised the m.p. to 150-151°.

Anal. Calcd. for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68. Found: C, 84.14; H, 5.47; N, 4.90.

5-Benzyl-5,6-dihydromorphanthridine.

To a slurry of 2.7 g. (0.072 mole) of lithium aluminum hydride in 250 ml. of tetrahydrofuran was added in 0.5 hour a solution of 21.5 g. (0.072 mole) of 5-benzyl-5,6-dihydro-6-morphanthridone in 200 ml. of tetrahydrofuran. The mixture was stirred and heated to reflux for 22 hours, cooled, 10 ml. of water was added to decompose the complex and the inorganic material was removed by filtration. The filtrate was taken to dryness and the residue was distilled. We obtained 13.8 g. (67.5%), b.p. 180-190° (0.12 mm.).

Anal. Calcd. for $C_{21}H_{19}N$: C, 88.38; H, 6.71; N, 4.91. Found: C, 87.99; H, 6.51; N, 4.79.

5-Methyl-5,6-dihydromorphanthridine.

To a solution of 435 g. (2.22 mole) of 5,6-dihydromorphanthridine in 1800 ml. of tetrahydrofuran was added at room temperature 2.35 moles of butyl lithium solution in 1900 ml. of ether. After the solution had been stirred for 5 hours at room temperature a solution of 331 g. (2.33 moles) of methyl iodide in 900 ml. of ether was added in 1.5 hours. The solution was stirred overnight at room temperature, washed with 500 ml. of water, dried over potassium carbonate, filtered, and concentrated. The residue was recrystallized from 2.5 l. of methanol to give 395 g. (84%), m.p. 78-80° (lit. 78-78.5°) (6).

Anal. Calcd. for $C_{15}H_{15}N$: C, 86.06; H, 7.23; N, 6.69. Found: C, 85.86; H, 7.20; N, 6.63.

Similarly prepared were 5-benzyl-5,6-dihydromorphanthridine (*v.s.*) and 5-butyl-5,6-dihydromorphanthridine, b.p. 150° (0.13 mm.).

Anal. Calcd. for $C_{18}H_{21}N$: C, 86.01; H, 8.42; N, 5.57. Found: C, 85.41; H, 8.55; N, 5.55.

5-Alkyl- and 5-aralkyl-11-tertiary aminoalkyl-5,6-dihydromorphanthridines.

A typical example is the preparation of 2-chloro-5-methyl-11-(3-*N*-methyl-*N*-benzylaminopropyl)-5,6-dihydromorphanthridine. Commercial butyl lithium solution (48 ml., 0.073 mole) dissolved in 70 ml. of anhydrous ethyl ether was added dropwise in 0.5 hour to a cooled solution of 17.0 g. (0.07 mole) of 2-chloro-5-methyl-5,6-dihydromorphanthridine dissolved in 100 ml. of tetrahydrofuran, after which the solution was stirred at room temperature for 5 hours. Freshly distilled 1-chloro-3-(*N*-methyl-*N*-benzylamino)propane dissolved in 40 ml. of anhydrous ethyl ether was added dropwise in 0.2 hour with cooling, and the solution was stirred at room temperature for 16 hours after which 21 ml. of water was added. The organic layer was separated, dried, and taken to dryness under reduced pressure. The residue was fractionated to give 22.3 g. (78.5%) of a brown oil, b.p. 163-170° (0.35 mm.). Di-cyclohexylsulfamate. The salt was formed after several days by mixing alcoholic solutions of the base and of hexamic acid, diluted with ethyl ether, and was recrystallized twice from isopropyl alcohol; m.p. 122-124°C.

Anal. Calcd. for $C_{38}H_{56}ClN_4O_6S_2$: C, 59.78; H, 7.28; N, 7.34. Found: C, 59.56; H, 7.46; N, 7.41.

5-Methyl-11-(3-methylaminopropyl)-5,6-dihydromorphanthridine.

A solution of 945 g. (2.55 moles) of 5-methyl-11-(3-*N*-methyl-*N*-benzylaminopropyl)-5,6-dihydromorphanthridine and 347.5 g. (3.2 moles) of ethyl chloroformate in 2700 ml. of benzene were refluxed for 24 hours, concentrated, and distilled to give 855.7 g. (92%) of a viscous oil; b.p. 210° (0.5 mm.).

Anal. Calcd. for $C_{22}H_{28}N_2O_2$: N, 7.95. Found: N, 7.71.

A mixture of 852 g. (2.4 moles) of 5-methyl-11-[3-(*N*-methyl-*N*-carbethoxyamino)propyl]-5,6-dihydromorphanthridine, 1232 g. (3.92 moles) of barium hydroxide, and 8600 ml. of ethylene glycol were stirred and refluxed for 24 hours. The mixture was poured into 35 l. of water, the barium carbonate removed by filtration and both the precipitate and the filtrate washed and extracted with benzene. The combined benzene extracts were concentrated and the residue distilled to give 536 g. (80%) of base, b.p. 180° (0.1 mm.).

Anal. Calcd. for $C_{19}H_{24}N_2$: N, 9.99. Found: N, 9.79.

Hydrogen maleate: The salt was obtained in 72% yield by mixing an alcoholic solution of the base with an alcoholic solution of maleic acid, m.p. 124-126°.

Anal. Calcd. for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.07. Found: C, 69.58; H, 7.05; N, 7.19.

2-Methyl-2'-methylaminodiphenylmethane.

5-Methyl-5,6-dihydromorphanthridine (627 mg.) in 50 ml. of ethanol were hydrogenated in the presence of 750 mg. of 10% palladium on carbon at room temperature. The catalyst was removed by filtration and the filtrate was concentrated. The infrared spectrum indicated the formation of a secondary amine, and was identical with the spectrum of an authentic sample. The base was dissolved in hot 10% hydrochloric acid, refrigerated, and the crystals were collected by filtration. M.p. 186-188° (lit. 185-186°) (6).

Anal. Calcd. for $C_{15}H_{15}ClN$: Cl, 14.31; N, 5.65. Found: Cl, 14.48; N, 5.69.

1-Dimethylamino-4-(2-tolyl)-4-(2-methylaminophenyl)butane.

(A) A solution of 5 g. of 5-methyl-11-(3-dimethylaminopropylidene)-5,6-dihydromorphanthridine (10) in 200 ml. of ethanol was hydrogenated for 24 hours at 50° and 60 lbs. hydrogen pressure in the presence of 5 g. of 10% palladium on carbon. The catalyst was filtered and the filtrate concentrated.

Anal. Calcd. for $C_{20}H_{26}N_2$: N, 9.51. Found: N, 9.21.

A dipicrate salt was prepared in ethanol, which after recrystallization from acetonitrile melted at 171°.

Anal. Calcd. for $C_{32}H_{34}N_8O_{14}$: C, 50.93; H, 4.54; N, 14.85. Found: C, 50.90; H, 4.68; N, 14.65.

(B) A solution of 5.3 g. of 5-methyl-11-(3-dimethylaminopropyl)-5,6-dihydromorphanthridine in 200 ml. of ethanol was hydrogenated 24 hours at 50° and 60 lbs. hydrogen pressure in the presence of 5 g. of 10% palladium on carbon. The catalyst was filtered, and the filtrate was concentrated. The dipicrate salt, when prepared as under (A), had a melting point of 169°. The melting point of the mixture of picrates (A) and (B) was 169°. The infrared and ultraviolet spectra of the bases were identical and showed a band in the infrared at 3.03 μ (NH-group) and maxima at 245, 246, and 295 mμ in the ultraviolet.

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(11) Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are corrected.

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