Lakeside Laboratories, Division of Colgate-Palmolive Company

Morphanthridines I. 11-Aminoalkylidene- and 11-(4-Piperidylene)-5,6-dihydromorphanthridines

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New methods are described for the preparation of 5,6-dihydro-11-morphanthridone, 5-substituted 5,6-dihydro-11-morphanthridones and nuclear halogenated derivatives. Basic Grignard reagents convert these ketones to carbinols, which through dehydration affords a convenient route to straight chain and cyclic 11-aminoalkylidene derivatives.

The well documented psychopharmacological properties of aminoalkylidene derivatives of dibenzo[a,d]cycloheptatriene (1), 10,11-dihydrodibenzo[a,d]-cycloheptatriene (2), and thioxanthene (3) prompted us to investigate the synthesis of similar derivatives of 5,6-dihydromorphanthridine.

Our initial approach to the desired aminoalkylidene derivatives was through the carbinol Ia, obtained by treatment of 5-methyl-6,11(5*H*)-morphanthridinedione with 3-dimethylaminopropyl magnesium chloride. This carbinol Ia surprisingly resisted all attempts at mild dehydration using such common agents as acetyl chloride in refluxing chloroform or *p*-toluenesulfonyl chloride in pyridine. The infrared spectra of the products of these reactions were consistent with the formation of the respective acetate and tosylate. Similar results have been reported by other workers using the carbinol Ib prepared from 6,11(5*H*)-morphanthridinedione (4). Recently, the dehydration of Ib using polyphosphoric acid has been described (5).

A second method involved treatment of 1-methyl-4-piperidone with 11-lithio-5-methyl-5,6-dihydromorphanthridine (6) which resulted in the formation of the carbinol IIa. Treatment of IIa with acetic anhydride afforded the acetate IIb from which acetic acid could be pyrolytically eliminated by heating to 200-250°C. The product obtained was spectrally identical to an authentic sample of the piperidylene compound III when compared in the infrared.

Our final approach was to investigate the reaction of 5,6-dihydro-11-morphanthridones with aminoalkyl magnesium halides. By analogy with related tricyclic systems such as dibenzo[a,d]cycloheptatrienes (1), 10,11-dihydrodibenzo[a,d]cycloheptatrienes, and thioxanthene (7), we expected that 11-hydroxy-11-aminoalkyl-5,6-dihydromorphanthridines would undergo ready dehydration. Treatment of IV with tertiary aminoalkyl magnesium halides in tetrahydrofuran (8), proceeded normally, affording the carbinols (V), Table I. The aminoalkylidene compounds (VI), Table II, were obtained in almost quantitative yield by treatment of the hydrochloride salts of V with acetyl chloride in refluxing chloroform, or by heating V in concentrated hydrochloric acid.

The synthesis of ketone IVa had previously been reported (9). However, the low yields and technical difficulties associated with this procedure forced us to study alternate methods for the preparation of these ketones. The ready availability of 6,11(5*H*)-morphanthridinedione (VII) (10) suggested its use as a starting material. Blocking of the 11-position carbonyl as the ketal (VIII), methylation to IX, reduction with lithium aluminum hydride to X and hydrolysis, afforded the desired ketones (IV). It was found that the usual conditions for ethylene ketal formation, namely acid catalyzed dehydration by azeotropic distillation of water from a solution of the ketone (VII) and ethylene glycol in benzene or toluene, were ineffective due to the unreactive nature of the 11-position carbonyl and to the limited solubility of the dione in benzene or toluene. This resistance to ketal formation was overcome by heating VII with a large excess of ethylene glycol in the presence of a catalytic amount of *p*-toluenesulfonic acid, while slowly distilling off the excess of ethylene glycol and water.

A single attempt to reverse the sequence and form the 11-ethylene ketal of the 5-methyl dione was unsuccessful.

Alkylation of VIII to yield IX was effected by treatment with sodium amide, followed by addition of methyl iodide. The ketal (X) was obtained by reduction of IX using lithium aluminum hydride, and the ketal blocking group was finally removed by heating X with aqueous alcoholic hydrochloric acid. The ketone IVa proved to be identical with a sample obtained by the method of G. Wittig *et al.*, (9,11).

Alternately, 5,6-dihydro-11-morphanthridones could be prepared by direct oxidation of the 11-position methylene of 5,6-dihydromorphanthridines with chromium trioxide (12), provided that the nitrogen was blocked as the 5-acetyl derivative (XI) (13). Hydrolytic cleavage of the acyl group to XIII followed by alkylation or aralkylation of the 5-lithio intermediate, afforded the ketone XIV. It is worthy of note that sodium hydride or sodium amide catalyzed alkylations were unsuccessful in our hands, probably due to the lack of generation of the desired anion.

Treatment of 5-acetyl-5,6-dihydro-11-morph-

anthridone (XII) with dimethylaminopropyl magnesium chloride resulted in reaction occurring exclusively at the 11-carbonyl position yielding the carbinol, which without purification, was dehydrated to form 5-acetyl-11-dimethylaminopropylidene-5,6-dihydromorphanthridine (XV). Hydrolysis with alkali or acid provided a general and ready route to the 5-unsubstituted compound XVI.

The preparation of 6,11(5*H*)-morphanthridinediones, having a chloro substituent in either of the aromatic rings, has been described (14). Although Schmidt rearrangement of 2-chloroanthraquinone can theoretically give rise to four different isomers, only three have been reported. One isomer, melting at 305°, was formed in low yield, while the major rearrangement products were reported to melt at 216-220° and 234-235° (14b). We have now established the structure of the 305° product as VIIb by direct comparison with an authentic sample obtained in low yield from an aluminum chloride melt of *N*-(4-chlorophenyl)phthalimide (15). Moreover, chlorination of 6,11-(5*H*)-morphanthridinedione with *N*-chlorosuccinimide afforded VIIb in satisfactory yield. We have accepted this as additional evidence in support of our structural assignment, since chlorination of acylanilines with *N*-chlorosuccinimide has been shown to yield the *para* chloro derivative (16).

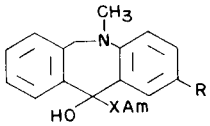
Compounds 4 and 7 (Table II) were prepared from the corresponding *N*-methyl-*N*-benzyl precursors by treatment with an alkyl chloroformate or an alkylthiochloroformate, followed by alkaline hydrolysis of the resulting carbamate (17).

Efforts to prepare the oxime from either ketone IV or XIII were unproductive. The low reactivity of these carbonyl groups can probably best be attributed to the mesomeric effect of the anilino nitrogen, since *N*-acylation increased the reactivity allowing the preparation of the oxime of XII in moderate yield.

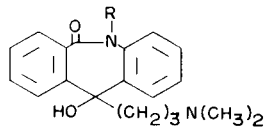
The infrared absorption spectra of the carbinols (Table I) exhibited a strong band near 1020 cm^{-1}, which is to be expected for carbinols with α,β-aryl unsaturation (18) and which was absent in the parent ketones. The ultraviolet spectra of the compounds of Table II exhibited a new band appearing at 225-228 mμ, ε approximately 27,000, indicative of the presence of the conjugated double bond. The only exceptions to this were compound 11, (Table II), which showed a band at 219 mμ, ε 25,000, and compound 12, with a band at 223 mμ, ε 25,490.

TABLE I

5-Methyl-11-Hydroxy-11-Basic Substituted-5,6-Dihydromorphanthridines

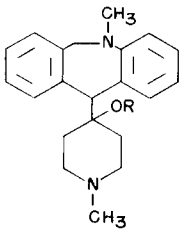


R	X	Am	M.P., °C	Calcd., % C	H	N	Found, % C	H	N
H	$CH_2CH_2CH_2$	$N(CH_3)_2$	133.5-134	77.37	8.44	9.03	77.29	8.46	9.20
Cl	$CH_2CH_2CH_2$	$N(CH_3)_2$	158-160	69.64	7.30	8.12	69.48	7.49	8.06
H	$CH_2CH_2CH_2$	4-Methylpiperazino	143-146.5	75.57	8.54	11.50	75.96	8.27	11.12
H	1-methyl-4-piperidyl		192-196	78.20	8.13	8.69	78.26	7.98	8.67
Cl	1-methyl-4-piperidyl		210-212	70.67	7.06	7.85	70.24	7.11	7.81



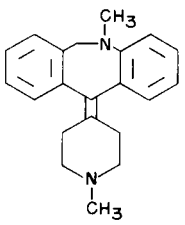
I a, R = CH_3

b, R = H

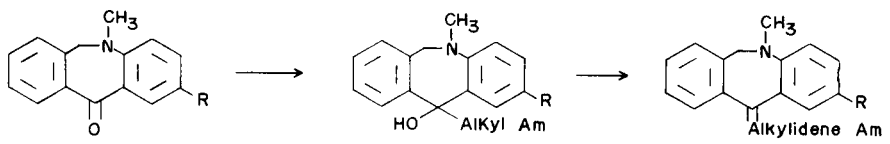


II a, R = H

b, R = $C-CH_3$ (O)



III



IV a, R = H

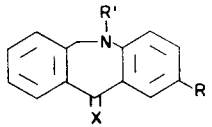
b, R = Cl

V

VI

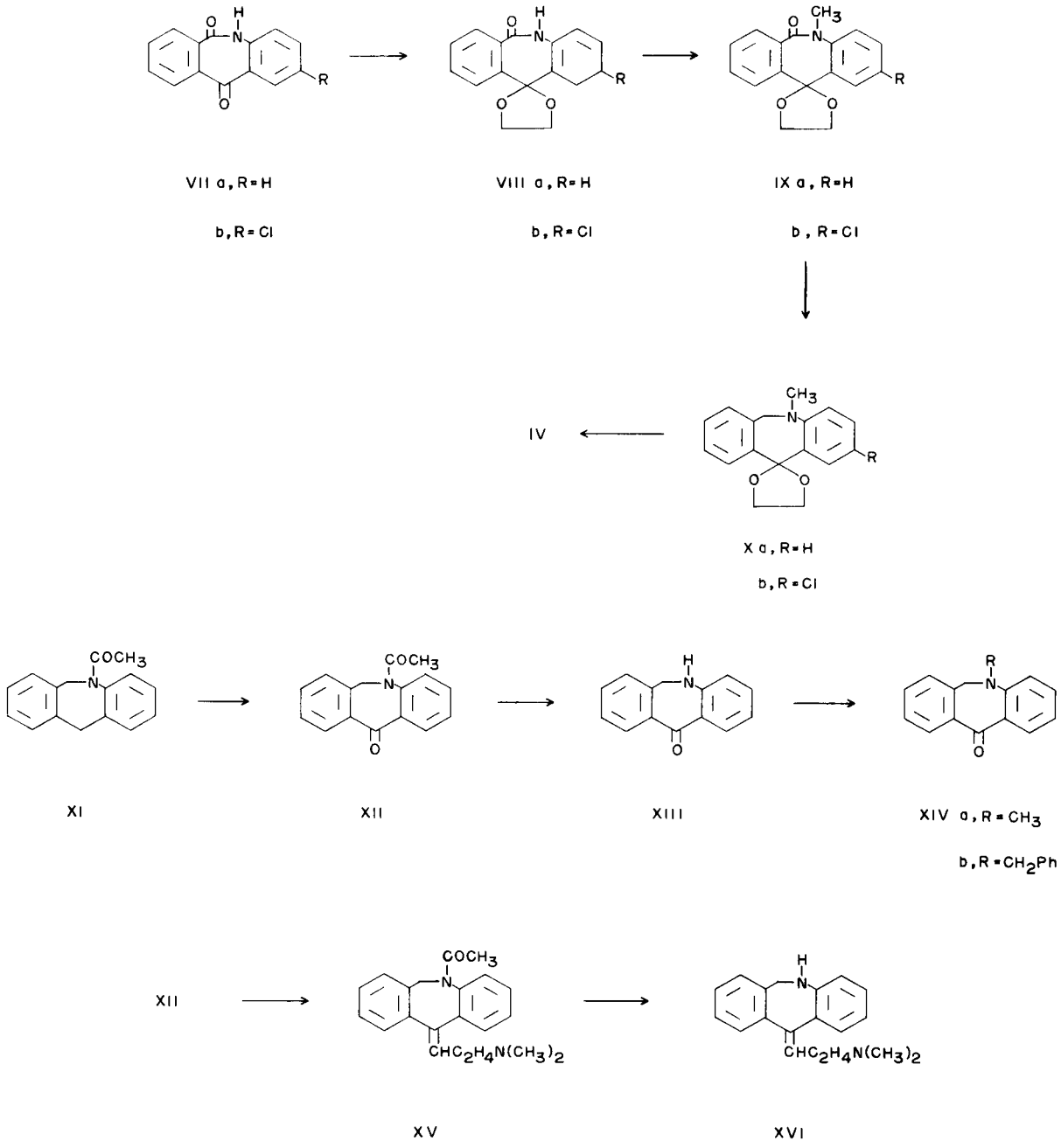
TABLE II

11-Aminoalkylidene[and 11-piperidylene]-5,6-Dihydromorphanthridines



Compound	R	R'	X	B.p., °C(mm.)	Calcd. %/Found% C	H	N	Salt	M.p., °C	Calcd. %/Found% C	H	N
1	H	CH_3	$=CHCH_2CH_2N(CH_3)_2$	165(0.08)				2 hexamate(b, c)	137	59.04 58.98	7.74 7.72	8.61 8.66
2	Cl	CH_3	$=CHCH_2CH_2N(CH_3)_2$	200-210(0.35)				2 HCl	191-193	60.08 59.83	6.30 6.53	7.00 6.96
3	Cl	CH_3	$=CHCHCH_3CH_2N(CH_3)_2$	180-185(0.6)	73.98 74.05	7.39 7.46	8.22 8.00					
4	H	CH_3	$=CHCH_2CH_2NHCH_3$	163-167(0.02)	81.98 81.87	7.97 8.09	10.06 9.80					
5	H	CH_3	$=CHCH_2CH_2N$⟨⟩$N-CH_3$					2 maleate	182-186	64.23 64.04	6.43 6.11	7.26 7.15
6	H	CH_3	$=CHCHCH_3CH_2N(CH_3)CH_2C_6H_5$	214-225(1.8)	84.77 84.65	7.91 7.77	7.32 7.65					
7	H	CH_3	$=CHCHCH_3CH_2NHCH_3$	170-175(0.2)	82.15 81.94	8.27 8.22	9.57 9.65					
8	H	CH_3	$=CHCH_2CH_2N$⟨⟩$N-CH_2C_6H_5$	270(0.7)			6.41 6.78	2 maleate	193-194	67.77 68.15	6.30 6.22	6.41 6.43
9	H	CH_3	=⟨⟩$N-CH_3$	120-123(a)	82.83 82.72	7.97 7.91	9.21 9.16	maleate	145-147	71.41 71.68	6.71 6.68	6.66 6.56
10	H	$CH_2C_6H_5$	=⟨⟩$N-CH_3$	112-113(a)	85.22 85.13	7.42 7.29	7.36 7.20					
11	H	H	$=CHCH_2CH_2N(CH_3)_2$	200-210(1.3)	81.97 81.72	7.97 7.80	10.06 10.30					
12	H	H	=⟨⟩$N-CH_3$					maleate	185	70.92 70.76	6.44 6.20	6.89 6.91

(a) This is a melting point. (b) "Hexamate" = cyclohexylsulfamate. (c) S: Calcd. 9.85; Found, 10.04.



EXPERIMENTAL

Methods.

All melting points were determined in a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared spectra were determined in carbon disulfide solution with a Beckman IR-8 infrared spectrophotometer, and ultraviolet spectra were measured in ethanol solution with a Beckman DK-2A spectrophotometer. In all cases, the major absorption bands corresponded with the assigned structures.

5-Methyl-11-hydroxy-11-(3-dimethylamino)propyl-5,6-dihydro-6-morphanthridone (Ia).

To a Grignard solution, prepared from 40.7 g. (0.35 mole) of 3-dimethylaminopropyl chloride and 8.5 g. (0.35 g. atom) of magnesium in 215 ml. of tetrahydrofuran, was added dropwise at room temperature a solution of 41.5 g. (0.175 mole) of 5-methyl-6,11(5*H*)-morphanthridinedione in 350 ml. of tetrahydrofuran. The dark colored solution was stirred overnight at room temperature, the complex was decomposed by the addition of 50 ml. of saturated ammonium chloride solution, filtered, and concentrated *in vacuo* to give 53 g. of a solid residue. Part of this (24 g.) was dissolved in benzene, extracted with cold dilute hydrochloric acid, the aqueous solution was washed with ether and made alkaline with potassium carbonate. The base was extracted with benzene, concentrated, and the residue was recrystallized from 65 ml. of boiling ethanol to give 17.6 g. (68%) of carbinol (19), m.p. 150-152°.

Anal. Calcd. for $C_{20}H_{24}N_2O_2$: C, 74.05; H, 7.46; N(non-aqueous titration), 4.32; N, 8.64. Found: C, 74.60; H, 7.66; N(non-aqueous titration), 4.50; N, 8.63.

5-Methyl-11-(1-methyl-4-hydroxy-4-piperidyl)-5,6-dihydromorphanthridine (IIa).

To a stirred solution of 66.4 g. (0.318 mole) of 5-methyl-5,6-dihydromorphanthridine in 380 ml. of tetrahydrofuran was added in 25 minutes at 10° a solution of 206 ml. of butyl lithium solution (20) (0.353 mole) in 290 ml. of ether. The dark brown solution was stirred 6 hours at room temperature, followed by dropwise addition in 1 hour of 35.9 g. (0.318 mole) of 1-methyl-4-piperidone in 118 ml. of ether. After 8 hours stirring at room temperature, 200 ml.

of water was added, the organic layer separated, washed with water, dried over drierite, filtered, and concentrated. The residue was distilled to give 44.9 g. of recovered 5-methyl-5,6-dihydromorphanthridine, followed by 24.5 g. (24% or 74%, based on 5-methyl-5,6-dihydromorphanthridine used), b.p. 210-220° (0.15 mm.). Recrystallization from acetonitrile gave a 90% recovery of the solid carbinol, m.p. 152-153°.

Anal. Calcd. for $C_{21}H_{26}N_2O$: C, 78.21; H, 8.13; N, 8.69. Found: C, 78.23; H, 8.16; N, 8.71.

5-Methyl-11-hydroxy-11-(1-methyl-4-piperidyl)-5,6-dihydromorphanthridine.

To a Grignard solution, prepared from 4.86 g. (0.2 g. atom) of magnesium, 26.7 g. (0.2 mole) of 1-methyl-4-chloropiperidine and 175 ml. of tetrahydrofuran was added 22.3 g. (0.1 mole) of 5-methyl-5,6-dihydro-11-morphanthridone in 150 ml. of tetrahydrofuran at room temperature. The solution was stirred overnight, the complex decomposed by addition of 25 ml. of saturated ammonium chloride solution, the precipitate filtered, the filtrate dried over potassium carbonate, filtered, and concentrated. The residue (30.5 g.) was recrystallized several times from acetonitrile to give 14.0 g. (43%) of carbinol, m.p. 192-196°.

Anal. Calcd. for $C_{21}H_{26}N_2O$: C, 78.20; H, 8.13; N, 8.69. Found: C, 78.26; H, 7.98; N, 8.67.

5-Methyl-11-(1-methyl-4-piperidylene)-5,6-dihydromorphanthridine (III).

(Method A.) To a solution of 27 g. (0.0837 mole) of 5-methyl-11-(1-methyl-4-hydroxy-4-piperidyl)-5,6-dihydromorphanthridine in 500 ml. of acetic anhydride was added 19 g. of *p*-toluenesulfonic acid. The mixture was kept 5 hours at 100°, the excess of acetic anhydride was removed by distillation, dilute sodium hydroxide was added to the residue, and the dark material formed was extracted with benzene. The benzene solution was washed with water, dried over drierite, filtered, and concentrated *in vacuo* to give 18 g. of crude acetate. This ester was pyrolyzed by heating for 1 hour in a 210° oil bath, during which time acetic acid was liberated and distilled. Distillation of the residue afforded a fraction of 8.1 g., b.p. 180-220° (0.05 mm.) the infrared and ultraviolet spectra of which showed only minor differences from that of the material prepared as described under (b).

Anal. Calcd. for $C_{21}H_{24}N_2$: N, 9.20. Found: N, 8.98.

Method (B). A solution of 14 g. (0.0435 mole) of 5-methyl-11-hydroxy-11-(1-methyl-4-piperidyl)-5,6-dihydromorphanthridine in 170 ml. of chloroform was acidified with gaseous hydrochloric acid until the *p*H reached 1. A solution of 12 g. of acetyl chloride in 60 ml. of chloroform was added dropwise, and the resulting mixture was refluxed for 2.5 hours and concentrated. The gummy residue was dissolved in 150 ml. of water, washed with ether, and the aqueous layer was made alkaline with potassium hydroxide. The resulting oil was extracted with ether, dried over potassium carbonate, filtered, and concentrated to give 13.2 g. (100%) of compound, m.p. 120-123°.

Anal. Calcd. for $C_{21}H_{24}N_2$: C, 82.83; H, 7.97; N, 9.21. Found: C, 82.72; H, 7.91; N, 9.16.

6,11(5*H*)-Morphanthridinedione-11-ethylene ketal (VIIIa).

A mixture of 44.6 g. (0.2 mole) of 6,11(5*H*)-morphanthridinedione, 1250 ml. of ethylene glycol and 0.9 g. of *p*-toluenesulfonic acid was stirred and slowly distilled. Approximately 250 ml. of distillate was collected in 3 hours. The mixture was cooled, neutralized with alcoholic sodium ethylate, and poured into 5 l. of water. The solid was filtered, dried, and recrystallized from ethyl acetate to give 24.0 g. (52.5%) of ketal, m.p. 223-224°.

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.53; H, 4.84; N, 5.28.

2-Chloro-6,11(5*H*)-morphanthridinedione 11-ethylene ketal (VIIIb) was similarly prepared in 53.2% yield. M.P. 269-273°.

Anal. Calcd. for $C_{16}H_{12}ClNO_3$: C, 63.69; H, 4.01; Cl, 11.78; N, 4.64. Found: C, 63.73; H, 3.94; Cl, 11.78; N, 4.49.

2-Chloro-6,11-morphanthridinedione (VIIb).

A solution of 22.3 g. (0.1 mole) of 6,11(5*H*)-morphanthridinedione and 15 g. (0.11 mole) of *N*-chlorosuccinimide in 400 ml. of acetic acid was refluxed 16 hours and cooled to room temperature. The precipitate was filtered and twice recrystallized from 700 ml. of *p*-dioxane to give 8.95 g. (37.5%) of product, m.p. 316-317°.

Anal. Calcd. for $C_{14}H_8ClNO_2$: C, 65.25; H, 3.13; Cl, 13.78; N, 5.43. Found: C, 65.13; H, 3.31; Cl, 13.55; N, 5.70.

5-Methyl-6,11-morphanthridinedione 11-ethylene ketal (IXa).

To a solution of 18.7 g. (0.07 mole) of 6,11(5*H*)-morphanthridinedione 11-ethylene ketal in a mixture of 350 ml. of toluene and 100 ml. of dioxane was added a slurry of 2.72 g. (0.07 mole) of sodamide in 100 ml. of toluene. The mixture was refluxed for 3 hours, cooled, and a solution of 28.4 g. (0.2 mole) of methyl iodide in 50 ml. of toluene was added in 0.5 hour. The mixture was stirred 12 hours at room temperature and heated to reflux for 24 hours. Water (15 ml.) was added to the cooled mixture, the organic layer was separated, dried over potassium carbonate, filtered, and concentrated to give 14.3 g. (63.5%) of product, m.p. 190-191°.

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.51; H, 5.43; N, 4.95.

2-Chloro-5-methyl-6,11-morphanthridinedione 11-ethylene ketal (IXb).

This compound was similarly prepared in 82% yield. M.p. 173-176°.

Anal. Calcd. for $C_{17}H_{14}ClNO_3$: C, 64.66; H, 4.47; Cl, 11.24; N, 4.43. Found: C, 64.56; H, 4.51; Cl, 11.29; N, 4.47.

2-Chloro-5-methyl-5,6-dihydro-11-morphanthridone 11-ethylene ketal (Xb).

A solution of 47.3 g. (0.15 mole) of 2-chloro-5-methyl-6,11-morphanthridinedione 11-ethylene ketal in 250 ml. of tetrahydrofuran was added dropwise to a stirred slurry of 5.5 g. of lithium aluminum hydride in 160 ml. of tetrahydrofuran. The mixture was stirred and refluxed 24 hours, cooled, and 31 ml. of water were added dropwise. The mixture was filtered, the filtrate was concentrated, and the residue was recrystallized from 500 ml. of isopropanol to give 28 g. (61.5%) of the ketal, m.p. 131.5-132°.

Anal. Calcd. for $C_{17}H_{16}ClNO_2$: C, 67.67; H, 5.35; Cl, 11.75; N, 4.64. Found: C, 67.53; H, 5.22; Cl, 11.55; N, 4.66.

5-Acetyl-5,6-dihydromorphanthridine (XI).

To a solution of 39 g. (0.2 mole) of 5,6-dihydromorphanthridine in 500 ml. of benzene was added dropwise 25.6 g. (0.25 mole) of acetyl chloride. The solution was refluxed 2 hours, cooled, stirred with water; the benzene layer was separated and washed with sodium bicarbonate solution and water, dried over potassium carbonate, filtered, and concentrated. The residue was recrystallized from 300 ml. of ethanol to give 45 g. (95%) of acylated base, m.p. 145-147°.

Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.16; H, 6.12; N, 6.02.

5-Acetyl-5,6-dihydro-11-morphanthridone (XII).

Chromium trioxide (8.8 g.) was added in small portions to a solution of 7.12 g. (0.03 mole) of 5-acetyl-5,6-dihydromorphanthridine in 350 ml. of glacial acetic acid. The solution was refluxed 3 hours, concentrated *in vacuo*, the residue was taken up in ether, washed with sodium bicarbonate solution and water, dried over potassium carbonate, filtered, and concentrated to give 6.5 g. (83%) of a yellow solid, m.p. 97-100°.

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.46; H, 5.22; N, 5.58. Found: C, 76.53; H, 5.19; N, 5.64.

5-Acetyl-11-oximino-5,6-dihydromorphanthridine.

A solution of 10.04 g. (0.04 mole) of 5-acetyl-5,6-dihydro-11-morphanthridone, 7 g. (0.1 mole) of hydroxylamine hydrochloride, 100 ml. of pyridine, and 100 ml. of ethanol was refluxed 48 hours. The solution was concentrated and the residue was poured on ice. The solid was collected, taken up in chloroform, the chloroform solution washed with water, 10% hydrochloric acid, and water and dried over sodium sulfate. The solution was filtered and concentrated to give 19 g. of a solid, which was recrystallized from acetonitrile to give 4.4 g. (41%) of oxime, m.p. 222-224°.

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.29; N, 10.52. Found: C, 72.09; H, 5.24; N, 10.55.

5,6-Dihydro-11-morphanthridone (XIII).

A solution of 4 g. (0.016 mole) of 5-acetyl-5,6-dihydro-11-morphanthridone in 87 ml. of 2% alcoholic sodium hydroxide was refluxed 3 hours, concentrated, and diluted with 200 ml. of water. The solid was filtered and recrystallized from 6 ml. of ethanol to give 2.5 g. (75%) of ketone, m.p. 124-125°.

Anal. Calcd. for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.08; H, 5.38; N, 6.89.

5-Methyl-5,6-dihydro-11-morphanthridone (IVa).

(Method A.) To a solution of 10.45 g. (0.05 mole) of 5,6-dihydro-11-morphanthridone in 100 ml. of tetrahydrofuran was added 37 ml. of butyl lithium solution (0.055 mole) in 100 ml. of ether. The orange colored solution was stirred 5 hours at room temperature, followed by the addition of 8.5 g. (0.06 mole) of methyl iodide in 150 ml. of ether. The solution was stirred 12 hours at room temperature, 25 ml. of water was added, the organic layer was separated, washed with water, dried over potassium carbonate, filtered, and the solution was concentrated to give 11.5 g. of an oil, which crystallized

from methanol to give 8.85 g. (80%) of the ketone, m.p. 111-115°.

(Method B.) A solution of 20 g. (0.07 mole) of 5-methyl-6,11-morphanthridinedione 11-ethylene ketal in 250 ml. of tetrahydrofuran was added dropwise to a stirred slurry of 2.7 g. of lithium aluminum hydride in 150 ml. of tetrahydrofuran. The mixture was refluxed 5 hours, cooled, 25 ml. of water was added dropwise, the organic layer was separated, dried over potassium carbonate, filtered, and concentrated to give 28.3 g. of crude 5-methyl-5,6-dihydro-11-morphanthridone 11-ethylene ketal in the form of a very viscous oil. This oil was dissolved in 195 ml. of 85% aqueous ethanol, 15 ml. of 38% aqueous hydrochloric acid was added and the solution was heated 2 hours on a steam bath, cooled, and poured into 1 l. of water. The solid was filtered and recrystallized from methanol to give 8.2 g. (52.5%) of ketone, m.p. 108-110°. A sublimed sample melted at 115°. The ketones prepared according to (A) and (B) were each identical in every respect with a sample prepared according to a published method (9,11).

5-Benzyl-5,6-dihydro-11-morphanthridone.

To 10.45 g. (0.05 mole) of 5,6-dihydro-11-morphanthridone in 100 ml. of tetrahydrofuran was added at 15°, 35 ml. (0.055 mole) of butyl lithium solution in 90 ml. of ether. The mixture, containing a red precipitate, was stirred 2 hours at room temperature, followed by the dropwise addition of 9.4 g. (0.055 mole) of benzyl bromide in 150 ml. of ether. The mixture was stirred 24 hours, 25 ml. of water was added, the organic layer was separated, dried over potassium carbonate, filtered, concentrated, and distilled to give 12.4 g. (83%) of product, b.p. 210° (0.025 mm.). The oil could be crystallized from methanol to give a ketone of m.p. 115-115.5°.

Anal. Calcd. for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68. Found: C, 84.06; H, 5.91; N, 4.70.

2-Chloro-5-methyl-5,6-dihydro-11-morphanthridone (IVb).

To a solution of 55.7 g. (0.185 mole) of 2-chloro-5-methyl-5,6-dihydro-11-morphanthridone 11-ethylene ketal in 650 ml. of ethanol and 85 ml. of water was added, with cooling, 41 ml. of 38% aqueous hydrochloric acid. The reaction mixture was refluxed 2.5 hours, cooled, poured into 1 l. of 1 *N* sodium hydroxide and diluted to 3 l. with water. The solid was filtered and recrystallized from ethanol to give 38 g. (80%) of ketone, m.p. 121-123.5°.

Anal. Calcd. for $C_{15}H_{12}ClNO$: C, 69.91; H, 4.70; N, 5.44. Found: C, 69.99; H, 4.70; N, 5.42.

5-(Alkyl or aralkyl)-11-hydroxy-11-aminoalkyl-5,6-dihydromorphanthridines.

A typical example is the preparation of 2-chloro-5-methyl-11-hydroxy-11-(3-dimethylaminopropyl)-5,6-dihydromorphanthridine. To a Grignard solution, prepared from 1.7 g. (0.07 g. atom) of magnesium and 8.5 g. (0.07 mole) of 1-chloro-3-dimethylaminopropane in 100 ml. of tetrahydrofuran was added at room temperature a solution of 9.0 g. (0.035 mole) of 2-chloro-5-methyl-5,6-dihydro-11-morphanthridone in 100 ml. of tetrahydrofuran. The solution was stirred for 24 hours at room temperature, 13 ml. of saturated ammonium chloride solution was added, the inorganic salt filtered, and the filtrate was concentrated *in vacuo*. The solid residue was recrystallized from methanol to give 8.2 g. (70%) of carbinol, m.p. 151-160°.

Anal. Calcd. for $C_{20}H_{25}ClN_2O$: C, 69.64; H, 7.30; N, 8.12. Found: C, 69.48; H, 7.49; N, 8.06.

5-(Alkyl or aralkyl)-11-aminoalkylidene-5,6-dihydromorphanthridines.

A typical example is the preparation of 2-chloro-5-methyl-11-(3-dimethylamino-2-methyl)propylidene-5,6-dihydromorphanthridine. Into a cooled solution of 10.6 g. (0.03 mole) of 2-chloro-5-methyl-11-hydroxy-11-(3-dimethylamino-2-methylpropyl)-5,6-dihydromorphanthridine in 150 ml. of chloroform was passed dry hydrochloric acid until the *p*H reached 1. A solution of 8.1 g. (0.1 mole) of acetyl chloride in 50 ml. of chloroform was added dropwise, and the resulting solution was refluxed 2 hours, cooled, and concentrated *in vacuo*. The residue was taken up in water, washed with ether, the aqueous solution was made alkaline with potassium hydroxide, the base was extracted with ether, the ethereal extracts were dried over potassium carbonate, filtered, and concentrated. The residue was distilled to give 8.2 g. (80%) of base, b.p. 180-185° (0.6 mm.).

Anal. Calcd. for $C_{21}H_{25}ClN_2$: C, 73.98; H, 7.39; N, 8.22. Found: C, 74.05; H, 7.46; N, 8.00.

11-(3-Dimethylaminopropylidene)-5,6-dihydromorphanthridine.

To a Grignard solution, prepared from 5.35 g. (0.22 g. atom) of magnesium and 26.0 g. (0.22 mole) of 3-dimethylaminopropyl chloride in 300 ml. of tetrahydrofuran was added dropwise a solution of 25.1 g. (0.1 mole) of 5-acetyl-5,6-dihydro-11-morphanthridone in 150 ml. of tetrahydrofuran, and the mixture was stirred overnight at room temperature. Saturated ammonium chloride solution (20 ml.) was added, the mixture was filtered, and the filtrate was concentrated. The residue was extracted with benzene, the benzene layer was extracted with dilute hydrochloric acid, the acid layer was made alkaline with potassium hydroxide and was extracted with chloroform. The chloroform solution was dried over potassium carbonate, filtered, and concentrated to give 18 g. of the crude carbinol. This carbinol was recentrated to give 18 g. of the crude carbinol. This carbinol was redissolved in 250 ml. of chloroform, treated with dry hydrochloric acid until the *p*H reached 1, and a solution of 17 g. of acetyl chloride in 50 ml. of chloroform was added dropwise. The solution was refluxed 2 hours, concentrated, the residue was dissolved in water, the aqueous solution was washed with ether and made alkaline with potassium hydroxide. The oil was extracted with ether, the ethereal solution was dried over potassium carbonate, filtered, and concentrated. The residue was distilled to give 7.7 g. (24%) of 5-acetyl-11-(3-dimethylaminopropylidene)-5,6-dihydromorphanthridine, b.p. 200-210° (0.17 mm.). Part (5.0 g., 0.0156 mole) of this base was refluxed 18 hours with 38% aqueous hydrochloric acid, cooled, and the solution was washed with ether. The solution was then made alkaline with potassium hydroxide and extracted with ether. The ethereal solution was dried over potassium carbonate, filtered, concentrated, and distilled to give 3.3 g. (76%) of a light yellow oil, b.p. 200-210° (1.3 mm.).

Anal. Calcd. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06. Found: C, 81.72; H, 7.80; N, 10.30.

5-Methyl-11-(3-*N*-methylamino-2-methylpropylidene)-5,6-dihydromorphanthridine.

To a solution of 29.0 g. (0.076 mole) of 5-methyl-11[3-*N*-methyl-*N*-benzylamino)-2-methylpropylidene]-5,6-dihydromorphanthridine in 100 ml. of benzene was added 10.4 g. (0.084 mole) of ethyl thiochloroformate, and the solution was refluxed 18 hours. The solution was distilled with steam, the flask residue was dissolved in benzene, the benzene solution was washed with water, dried over potassium carbonate, filtered, and concentrated *in vacuo* to give 28.8 g. of 5-methyl-11-{3-[*N*-methyl-*N*-(*S*-ethylthiocarbonyl)amino]-2-methylpropylidene}-5,6-dihydromorphanthridine, b.p. 217-223° (1.2 mm.). A mixture of 10 g. (0.026 mole) of this thiocarbamate, 200 ml. of ethylene glycol, and 16.8 g. (0.053 mole) of barium hydroxide·8 H_2O was refluxed 8 hours, poured into 500 ml. of water, and filtered. The filtrate was dried over potassium carbonate, filtered, concentrated, and the residue was distilled to give 7.0 g. (91%) of product, b.p. 170-175° (0.2 mm.).

Anal. Calcd. for $C_{20}H_{24}N_2$: C, 82.15; H, 8.27; N, 9.57. Found: C, 81.94; H, 8.22; N, 9.65.

REFERENCES

(1) M. Protiva, V. Hněvsová-Seidlová, Z. J. Vejdělek, I. Jirkovsky, Z. Votava, and J. Metysová, *J. Med. Pharm. Chem.*, 4, 411 (1961).
(2) F. J. Ayd, Jr., *Psychosomatics*, 1, 320 (1960); W. Dorfman, *ibid.*, 1, 153 (1960); P. E. Feldman, *Diseases Nervous System*, 22, 27 (1961); M. Vaisberg and J. C. Saunders, *ibid.*, 22, 334 (1961).
(3) H. C. B. Denber, P. Rajotte, and E. Ross, *Comprehensive Psychiatry*, 1, 380 (1960).
(4) S. O. Winthrop, M. A. Davis, F. Herr, J. Stewart, and R. Gaudry, *J. Med. Pharm. Chem.*, 5, 1199 (1962); U. S. Patent 3,084,155 (1963) and 3,173,913 (1965); British Patent 972,082 (1964).
(5) Belgian Patent 652,938 (1964).
(6) See part II of this series.
(7) U. S. Patent 2,951,082 (1960).
(8) A. Marxer, *Helv. Chim. Acta*, 24, 217 (1941).
(9) G. Wittig, G. Closs, and F. Mindermann, *Ann.*, 594, 89 (1955).
(10) G. Caronna and S. Palazzo, *Gazz. chim. ital.*, 83, 533 (1953).
(11) We thank Professor Dr. G. Wittig for supplying us with a sample.
(12) This reaction is analogous to the oxidation of dibenzo[a,d]-cycloheptadiene as described by M. Avram, I. G. Dinulescu, D. Dinu, G. Mateescu, and C. D. Nenitzescu, *Tetrahedron*, 19, 309 (1963).
(13) J. O. Jilek, J. Pomykáček, E. Svátek, V. Seidlová, M. Rajšner, K. Pelz, B. Hoch, and M. Protiva, *Collection Czech. Chem. Commun.*, 30, 445 (1965).
(14a) U. S. Patent 2,973,354 (1961); French Patent 1,216,631 (1960); Swiss Patent 345,011 (1960); (b) L. H. Werner, S. Ricca, E. Mohacsi, A. Rossi, and V. P. Arye, *J. Med. Chem.*, 8, 74 (1965).
(15) German Patent 551,256 (1932).
(16) R. Stroh, "Methoden der Organischen Chemie", Vol. 5/3, E. Mueller, Ed., George Thieme Verlag, Stuttgart, Germany, 1962, p. 803; N. P. Buu-Hoi, *Rec. trav. chim.*, 73, 197 (1954).
(17) W. B. Wright, Jr., and H. J. Brabander, *J. Org. Chem.*, 26, 4057 (1961); J. Knabe, *Angew. Chem. Internat. Ed.*, 1, 58 (1962); J. Knabe and U. R. Shukla, *Arch. Pharm.*, 295, 690, 871 (1962); K. Stach and F. Bickelhaupt, *Monatsh.*, 93, 896 (1962); F.

Bickelhaupt, K. Stach and M. Thiel, *ibid.*, 95, 485 (1964); U. S. Patent 3,037,047 (1962).
(18) Bellamy, "The Infrared Spectra of Complex Molecules", 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 109.
(19) Treatment of the hydrochloric acid salt with an excess of acetyl chloride in refluxing chloroform gave a product showing a new carbonyl band in the infrared spectrum at 5.65 μ and a new CO stretching band at 7.8 μ, indicating the formation of an acetate ester, with retention of the amide carbonyl band at 6.0 μ.
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