Derivatives of Morphanthridine[1]

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The Schmidt reaction products of monosubstituted anthraquinones were studied. The resulting mixtures of isomeric morphanthridine-6,11-diones were separated by crystallization and the structure of some of the isomers was determined. Reduction of morphanthridine-6,11-dione gave 6-morphanthridone and 5,6-dihydromorphanthridine. The 5-dialkylaminoalkyl derivatives of morphanthridine-6,11-dione and of 6-morphanthridone showed interesting antispasmodic activity; 5-(2-imidazolinylmethyl)-5,6-dihydromorphanthridine was of particular interest because of its effect on aconitine-induced cardiac arrhythmias.

Substitution of tricyclic ring systems with dialkylaminoalkyl groups has yielded numerous compounds of clinical value, *e.g.*, the phenothiazine derivatives, imipramine, and related compounds. During the past years a great number of derivatives of tricyclic ring systems have been studied for possible biological effects and especially for psychotherapeutic activity. This field has recently been reviewed by Jucker.[2]

The present paper describes derivatives of morphanthridine substituted in the 5-position by a dialkylaminoalkyl group or a 2-imidazolin-2-ylmethyl group. Protiva, *et al.*,[3] Martin,[4] and Habicht[4,5] have described derivatives of 5,6-dihydromorphanthridine substituted at the 5-position, and Winthrop, *et al.*,[6] reported derivatives substituted at the 11-position with a dialkylaminoalkyl group.

The starting material for our investigations was morphanthridine-6,11-dione (I) a compound first reported in 1912[7] and subsequently prepared by other methods.[8a-f] Morphanthridine-6,11-dione was most conveniently prepared by the Schmidt reaction from anthraquinone.[8d] This procedure was also applicable for the preparation of halo-, alkyl-, and alkoxy-substituted morphanthridine-6,11-diones. Only low yields of these products could be obtained by the procedure of Wolfram and Hausdörfer[8a] whereby N-(substituted phenyl)phthalimides are rearranged at elevated temperatures in the presence of aluminum chloride to the corresponding morphanthridine-6,11-diones.

Chloro-, methyl-, and methoxy-substituted morphanthridine derivatives were included in this study as such substituents have often been found to influence the pharmacological activity markedly. These were obtained by subjecting 1- and 2-chloro-, 1- and 2-methyl-, and 1- and 2-methoxyanthraquinones to the Schmidt reaction. The directing influence of these groups was not very specific and mixtures of at least two isomeric morphanthridine-6,11-diones were obtained. The main components of these mixtures could be separated by careful fractional crystallization (Table I). The exception was 1-methoxyanthraquinone which gave mainly 1-methoxymorphanthridine-6,11-dione in a yield of 63%. Morphanthridine-6,11-dione itself was obtained in 77% yield. Yields for the other diones are given in Table I. The structure of some of these substituted morphanthridine-6,11-diones was determined by hydrolysis to the amino acids II (Table II), which occurred readily with dilute sodium hydroxide. The amino acids were then deaminated by means of diazotization and reduction with hypophosphoric acid[9] to the corresponding 2-benzoylbenzoic acids III (Table III). The position of the substituent was determined either by comparison with an authentic sample of the corresponding substituted 2-benzoylbenzoic acid or was based on infrared and n.m.r. spectral data. By considering the position of the substituent in the 2-benzoylbenzoic acid derivative and whether a 1- or 2-substituted anthraquinone had served as starting material, it was possible to establish the position of the substituent in the morphanthridine-6,11-dione. The results are given in Table I.

Caronna, *et al.*,[8e] reported that when 1- and 2-chloroanthraquinone are subjected to the Schmidt reaction, predominantly 4-chloro- and 3-chloromorphanthridine-6,11-dione, respectively, are obtained. The results obtained under our conditions differed (Table I) from the findings of Caronna, *et al.*[8e] Kränzlein[8b] had previously prepared 3-methylmorphanthridine-6,11-dione by reaction of phthalic anhydride with *m*-acetotoluidide under Friedel Crafts conditions, hydrolysis of the acetamido group and ring closure. This reaction sequence was not applicable to acetanilide, *o*-, *m*-, or *p*-chloroacetanilide, or 2,4- and 3,4-dichloroacetanilide.[8b]

We also studied a new approach to the morphanthridine ring system which might have been useful for the preparation of substituted morphanthridines, *i.e.*, ring closure of the tosylate of N-benzylanthranilic acid chloride VI with aluminum chloride. However, only tarry products were obtained when this reaction was carried out.

Structure of the 2-Benzoylbenzoic Acids. 2-(4-Tolyl)benzoic acid, 4′-ethyl-2-benzoylbenzoic acid, and 2′- and 4′-methoxy-2-benzoylbenzoic acid could

(1) Reported in part at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept. 1963. See also G. H. Werner, U. S. Patent 2,973,354 (February 28, 1961). The alternate chemical name for morphanthridine is 11H-dibenz[*b,e*]azepine.

(2) E. Jucker, *Angew. Chem. Intern. Ed.*, **2**, 495 (1963).

(3) M. Borovička and M. Protiva, *Chem. Listy*, **51**, 1544 (1957); M. Protiva, M. Borovička, V. Bach, Z. Votava, J. Stránková, and Z. Horáková, *Experientia*, **13**, 291 (1957); M. Protiva, *et al.*, Czechoslovakian Patents 86,610 (1958) and 88,128 (1958); *Chem. Abstr.*, **54**, 2373*f*, 2382*d* (1960).

(4) H. Martin and E. Habicht, U. S. Patent 2,861,987 (November 25, 1958); *Chem. Abstr.*, **53**, 7215*e* (1959).

(5) E. Habicht and H. Moeller, U. S. Patent 3,038,896 (June 12, 1962); *Chem. Abstr.*, **59**, 2800*h* (1963).

(6) S. O. Winthrop, M. A. Davis, F. Herr, J. Stewart, and B. Gandley, *J. Med. Pharm. Chem.*, **5**, 1190 (1962).

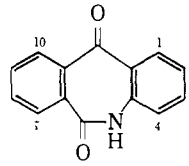
(7) Aktiengesellschaft für Anilin Fabrikation, German Patent 258,345 (1912); *Chem. Abstr.*, **7**, 2836 (1913).

(8) (a) A. Wolfram and E. Hausdörfer, German Patent 551,250 (1932); *Chem. Abstr.*, **26**, 4341 (1932); (b) P. Kränzlein, *Ber.*, **70**, 1952 (1937); (c) H. Elsner and H. Batz, German Patent 837,537 (1952); *Chem. Abstr.*, **54**, 25716 (1960); (d) G. Caronna and S. Palazzo, *Gazz. chim. ital.*, **83**, 533 (1953); (e) *ibid.*, **84**, 1135 (1954); (f) D. D. Emrick and W. E. Truce, *J. Org. Chem.*, **26**, 1329 (1961).

(9) N. Kornblum, *Org. Reactions*, **2**, 262 (1944).

TABLE I

MORPHANTHRIDINE-6,11-DIONES DERIVED FROM ANTHRAQUINONES

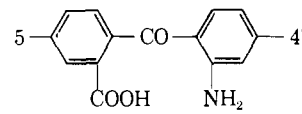


Anthraquinone substituent	Morphanthridinedione substituent	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	Yield, %
H	H[a,b]	246–248	$C_{14}H_9NO_2$							77
1-Cl	7-Cl	271–273	$C_{14}H_8ClNO_2$	65.25	3.13	5.44	65.33	3.34	5.47	10
	1-, 4-, or 10-Cl	210–212					65.08	2.84	5.78	3.7
2-Cl	8-Cl	234–235					65.67	3.19	5.57	7.5
	2-, 3-, or 9-Cl	216–220					65.34	3.18	5.21	7.5
1-CH_3	10-CH_3	230–232	$C_{15}H_{11}NO_2$	75.93	4.67	5.90	75.64	4.92	5.95	19
	1-, 4-, or 7-CH_3	217–219					75.82	4.63	5.66	23
2-CH_3	3-CH_3[c]	260–264					75.95	4.67	5.82	20
	8-CH_3	204–207					75.62	4.70	5.77	17.5
2-C_2H_5	3-C_2H_5	178–180	$C_{16}H_{13}NO_2$	76.47	5.21	5.57	76.67	5.30	5.51	22
1-OCH_3	1-OCH_3	254–255	$C_{15}H_{11}NO_3$	71.14	4.37	5.53	71.34	4.25	5.18	63
2-OCH_3	3-OCH_3	258–259					71.10	4.43	5.85	22
	2-, 8-, or 9-OCH_3	235–236					71.06	4.70	5.66	>5

[a] Ref. 7. [b] Ref. 8. [c] Ref. 8b.

TABLE II

2-(2-AMINOBENZOYL)BENZOIC ACIDS DERIVED FROM MORPHANTHRIDINE-6,11-DIONES



Morphanthridinedione substituent	2-(2-Aminobenzoyl)benzoic acid Substituent	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
H	H[a,b]	195	$C_{14}H_{11}NO_3$						
7-Cl	6-Cl	189–192	$C_{14}H_{10}ClNO_3$	60.99	3.66	5.12	60.97	3.92	4.94
8-Cl	5-Cl	168–170					61.60	3.76	
10-CH_3	3-CH_3	148–150	$C_{15}H_{13}NO_3$	70.56	5.13	5.49	70.79	5.25	
3-CH_3	4'-CH_3[c]	180–182					70.21	5.02	5.42
8-CH_3	5-CH_3	192–194					70.64	5.25	5.43
1-OCH_3	6'-OCH_3	207–208	$C_{15}H_{13}NO_4$	66.41	4.83	5.16	66.27	4.91	5.15
3-OCH_3	4'-OCH_3	258 ring closes					66.30	4.73	5.29

[a] Ref. 7. [b] Ref. 8. [c] Ref. 8b.

be identified by mixture melting point with authentic samples of these acids. 6-Chloro-2-benzoylbenzoic acid was reported by Newman and Scheurer[10] as melting at 90–117°. Our material melted at 110–116°. The infrared spectrum showed mono- and 1,2,3-trisubstituted benzene, and strong bonded OH absorption at 3270 cm.$^{-1}$. There were no strong acid bands in the 2600-cm.$^{-1}$ area, but the carbonyl band was found at 1754 cm.$^{-1}$. The n.m.r.[11] spectrum did not show a distinct low-field proton signal which would correspond to the proton α to the carboxyl group. In addition, the carboxylic acid proton signal which falls between 623 and 704 c.p.s. in other 2-benzoylbenzoic acids was absent. These findings are consistent with the lactol structure of 6-chloro-2-benzoylbenzoic acid (VII). The structure of the 5-chloro-2-benzoylbenzoic acid was assigned on the basis of the following data. The infrared spectrum showed a monosubstituted benzene ring and a 1,2,4-trisubstituted benzene ring. In the n.m.r. spectrum, the low-field proton signal corresponding to the proton α to the carboxyl group fell at 479.6 c.p.s. as a doublet with J = 2.0 c.p.s. This indicated a proton at the 4-position and a substituent at the 5-position. In addition, the possibility of the compound being 4-chloro-2-benzoylbenzoic acid[12] (m.p. 174–177°) was ruled out by mixture melting point with an authentic sample, a marked depression (149–152°) being noted.

The structure of the 3-methyl-2-benzoylbenzoic acid was established by mixture melting point with an

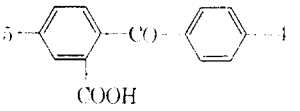
(10) Table III, ref. a.

(11) All spectra were determined in deuteriochloroform at 60 Mc. using a Varian A-60 spectrometer. Chemical shifts were determined using tetramethylsilane as the internal standard and are reported in c.p.s.

(12) C. Eggerer and H. Meyer, *Monatsh.*, **34**, 83 (1913).

TABLE III

2-BENZOYLBENZOIC ACIDS DERIVED FROM MORPHANTHRIDINE-6,11-DIONES



Morphanthridine-6,11-dione	2-Benzoylbenzoic acid	M.p., °C	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
7-Cl	6-Cl[a]	110–116	$C_{14}H_9ClO_3$	64.49	3.48	64.68	3.49
8-Cl	5-Cl	172–174				64.60	3.58
10-CH_3	3-CH_3[b]	160–165				74.56	5.34
3-CH_3	4'-CH_3[c]	135–137	$C_{15}H_{12}O_3$	74.98	5.04	74.96	5.04
8-CH_3	5-CH_3[d]	148–152				74.97	5.17
3-C_2H_5	4'-C_2H_5[e]	127–129	$C_{16}H_{14}O_3$	75.56	5.55	75.84	5.45
1-OCH_3	2'-OCH_3[f]	145–146	$C_{15}H_{12}O_4$	70.30	4.72	70.40	4.59
3-OCH_3	4'-OCH_3[g]	145–146				70.29	4.89

[a] M. S. Newman and P. Scheurer, *J. Am. Chem. Soc.*, **78**, 5004 (1956). [b] M. S. Newman and C. D. McCleary, *ibid.*, **63**, 1537, 1542 (1941). [c] H. Limpricht, *Ann.*, **299**, 300 (1898). [d] M. Hayashi, *J. Chem. Soc.*, 1513 (1930). [e] G. F. Lewenz and K. T. Serijan, *J. Am. Chem. Soc.*, **75**, 4087 (1953). [f] B. P. Geyer, *ibid.*, **64**, 2226 (1942). [g] W. R. Orndorff and L. Kelly, *ibid.*, **44**, 1518 (1922). Although the 2'- and 4'-methoxy-2-benzoylbenzoic acids had identical melting points, a marked depression in a mixture melting point was found.

authentic sample. Although this sample melted somewhat higher (170–172°), no depression was found. Further confirmation for this structural assignment was obtained by n.m.r. data, and the infrared spectra were also practically identical.

In the n.m.r. spectrum of 5-methyl-2-benzoylbenzoic acid the low-field proton signal (α to the carboxyl group) was at 464.5 c.p.s. and was a broad singlet with half-width = 3.3 c.p.s. suggesting coupling with a *meta* proton and possibly *para*. These data are consistent with the suggested structure. The methyl signal was at 143 c.p.s. The infrared spectrum showed a mono- and a 1,2,4-trisubstituted benzene ring. The melting point of this compound is also consistent with that reported in the literature for the 4- and 5-methyl-2-benzoylbenzoic acid, *i.e.*, 145 and 150°, respectively.[12]

Reduction of morphanthridine-6,11-dione with copper chromite,[14] zinc, and ammonia[8f] or with palladium on charcoal in glacial acetic acid gave 6-morphranthridone (IV). Treatment of either morphanthridine-6,11-dione[11] (I) or 6-morphanthridone (IV) with lithium aluminum hydride gave 5,6-dihydromorphanthridine (V). Reduction of chloro-substituted morphanthridine-6,11-diones, either catalytically or with lithium aluminum hydride, led to some loss of halogen making it difficult to isolate pure products. Alkylation of morphanthridine-6,11-dione (I) and 6-morphanthridone (IV) with 3-dimethylaminopropyl chloride in the presence of sodamide gave 5-(3-dimethylaminopropyl)-morphanthridine-6,11-dione (VIIIa) and 5-(3-dimethylaminopropyl)-6-morphanthridone (VIIIb), respectively. The other derivatives of I and IV given in Table IV were prepared in the same way. As a by-product in the alkylation of morphanthridine-6,11-dione with 3-dimethylaminopropyl chloride, the ring-open compound IX, 2-[2-(3-dimethylaminopropylamino)benzoyl]benzoic acid, was also formed. This material may have been produced by hydrolysis during the work-up.

Reduction of VIIIa with lithium aluminum hydride gave 5-(3-dimethylaminopropyl)-5,6-dihydromorphanthridine (X) in a low yield. Considerably higher yields of X were obtained by reduction of the corresponding 6-morphanthridone derivative (VIIIb). This compound (X) has previously been prepared by Protiva,[3] *et al.*, either by direct alkylation of 5,6-dihydromorphanthridine or by lithium aluminum hydride reduction of 5-dimethylaminoacetyl-5,6-dihydromorphanthridine. Reaction of X with methyl iodide gave the dimethiodide (Table IV, **19**). 5,6-Dihydro-5-(2-imidazolin-2-ylmethyl)morphanthridine (XII) (Table IV, **21**) was prepared by cyanomethylation of 5,6-dihydromorphanthridine, followed by reaction with 1,2-diaminoethane.[15] The related compounds (**22**–**24**) were prepared from the cyanomethyl derivative (XI) by reaction with 1,3-diaminopropane, 1,2-diaminopropane, and 1,4-diaminobutane. The 1-methyl-2-imidazolinylmethyl derivative (Table IV, **25**) was obtained by alkylation of **21** with methyl iodide.

Biological Results.—The compounds were tested by our Division of Macrobiology. The 5-dialkylaminoalkyl derivatives of morphanthridine-6,11-dione and 6-morphanthridone were found to possess good antispasmodic activity, *i.e.*, direct inhibitory action on the smooth muscle of the small intestine. In this test the derivatives of morphanthridinedione exhibited greater activity. The quaternized derivative (**14**) was less active than the unquaternized compound. Most interesting as an antispasmodic was 5-(3-dimethylaminopropyl)morphanthridine-6,11-dione (**9**). This compound was only weakly anticholinergic; however, in the anesthetized and unanesthetized dog with a surgically prepared Thiry-Vella loop at 1 mg./kg. i.v., it produced an immediate marked decrease in tonal activity of the small intestine,[16] lasting for more than 1 hr. The compound was also administered orally to unanesthetized dogs, with a surgically prepared Thiry-Vella loop, in capsules at 2.5–30 mg./kg. after feeding.[16] A marked reduction of peristalsis was noted.

[13] Table III, ref. *a*.

[14] G. Wittig, G. Closs, and L. Mindermann, *Ann. Chem.*, **594**, 89 (1955).

[15] M. Hartmann and S. Snader, U. S. Patent 2,560,115 (September 10, 1951).

[16] W. E. Barrett, R. Weis, and V. J. Pleasure, *Am. J. Digest. Diseases*, in press.

CHART I

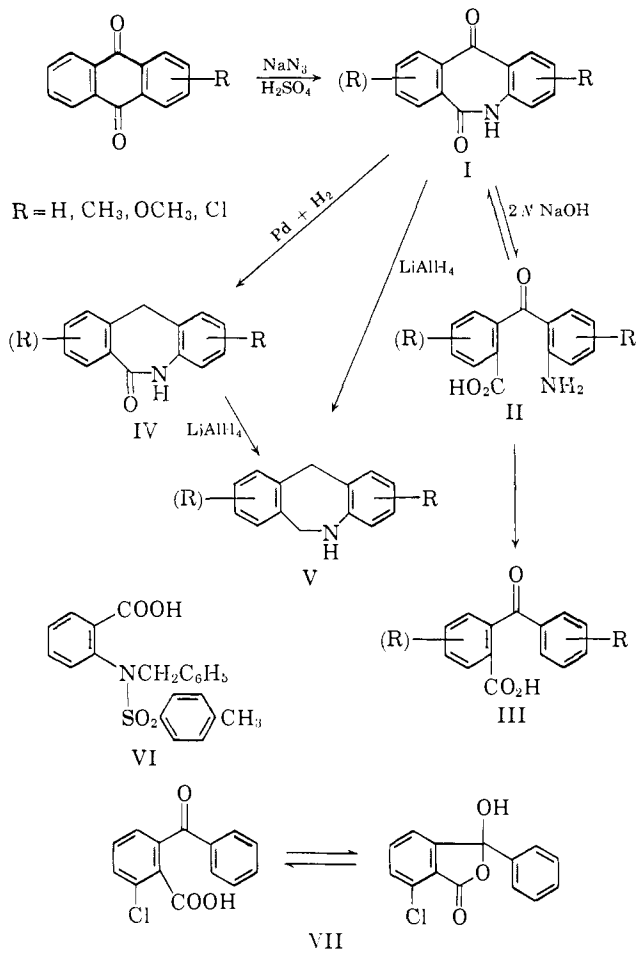
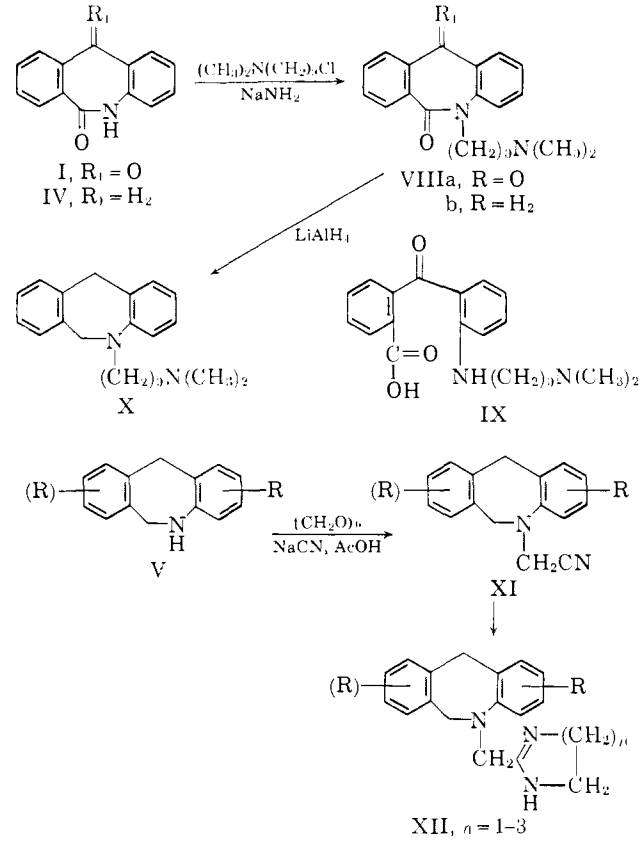


CHART II



Adiphenine was three to four times less effective in this test.

5,6-Dihydro-5-(2-imidazolin-2-ylmethyl)morphanthridine (**21**) and the related compounds **22–28** and **30** showed a marked effect on aconitine-induced ventricular fibrillation of the isolated feline heart. The corresponding derivatives of morphanthridine-6,11-dione and 6-morphanthridone were only weakly active. Perfusion of the heart with physiological Ringers solution containing 0.022 γ/ml. of aconitine nitrate induced ventricular fibrillation in 18 min. In this test the criterion for judging the effectiveness of the compound was the measurement of the time from the start of the aconitine perfusion until the onset of ventricular fibrillation. Quinidine sulfate was used as a standard. Compound **21** was 3–4 times as potent as quinidine sulfate in this test. Enlarging the imidazoline ring to a six- or seven-membered ring (**22** and **23**) decreased the activity. Introduction of a methyl group in the imidazoline ring in position 1 or 4 (**25** and **24**) had little effect on the antiarrhythmic activity. Substitution in the 5,6-dihydromorphanthridine nucleus by a methyl, methoxy, or chloro group in the compounds studied (**26–28** and **30**) also had only a slight effect.

Compound **19**, a dimethiodide, was found to have an intense, long-lasting hypotensive effect due to ganglionic blockade. None of the compounds tested had any effect on the central nervous system, nor could we confirm under our test conditions the intense antihistaminic effect claimed for compound **17** by Protiva,[3] *et al.*

Experimental[17]

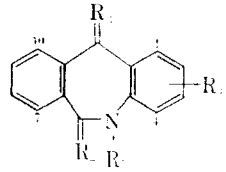
3- and 8-Methylmorphanthridine-6,11-dione (I). **General Procedure.**—A mixture of 600 ml. of concentrated sulfuric acid and 200 ml. of methylene chloride was cooled to 15°, 126 g. (0.57 mole) of 2-methylanthraquinone was added, followed by 43.8 g. (0.67 mole) of sodium azide, added in small portions over a 1-hr. period at 20–25°. The reaction mixture was stirred at room temperature for 3 hr., allowed to stand overnight, and then poured over a mixture of ice and water. The crude product was filtered off, washed with water, and dried. It was recrystallized by dissolving in 4.8 l. of toluene at reflux. On cooling, 65 g. of material, m.p. 205–248°, crystallized. Recrystallization from dimethylformamide gave 27.5 g. of 3-methylmorphanthridine-6,11-dione, m.p. 260–264°, yield 20%. On concentrating the toluene filtrate to approximately 2 l. and cooling, 43.2 g. of material, m.p. 178–186°, was obtained. Recrystallization from dioxane gave 24 g. of 8-methylmorphanthridine-6,11-dione m.p. 203–204°, yield 17.5%. Further recrystallization raised the melting point to 204–207°.

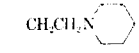
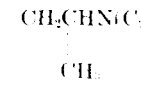
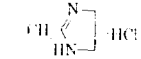
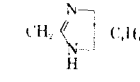
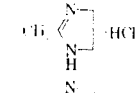
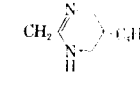
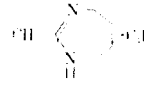
The Schmidt reaction products of 1-methyl- and 1- and 2-chloroanthraquinone were also worked up using toluene and dimethylformamide as solvents for recrystallizing and separating the isomeric diones. The reaction product of 1-methoxyanthraquinone was recrystallized from a mixture of dimethylformamide and ethanol, that for 2-methoxyanthraquinone, and 2-ethylanthraquinone from ethanol.

Hydrolysis of Morphanthridine-6,11-diones.—A suspension of 5.4 g. 3-methylmorphanthridine-6,11-dione in 50 ml. of 2 *N* NaOH was heated on the steam bath for 45 min. On cooling, the sodium salt of 2-(2-amino-4-methylbenzoyl)benzoic acid separated. It was dissolved by adding 30 ml. of water. The reaction mixture was acidified with dilute HCl to pH 6, whereupon the amino acid precipitated. It was filtered off and recrystallized from methanol; yield 3.6 g., m.p. 180–182°, of 2-(2-amino-4-methylbenzoyl)benzoic acid. The identical procedure was used to hydrolyze the other substituted morphanthridine-6,11-diones investigated. In the case of the 2-(2-amino-4-ethylbenzyl)benzoic acid, the crude amino acid was deaminated directly.

(17) Melting points are uncorrected.

TABLE IV



Compd.	B	B	R_1	R_2	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1	H	O	H_2	H	202–204°	$C_{17}H_{13}NO$						
2	H	O	H_2	3-CH_3	234–238	$C_{18}H_{15}NO$	80.69	5.86	6.27	80.63	6.08	5.98
3	H	O	H_2	8-CH_3	176–179	$C_{18}H_{15}NO$	80.69	5.86		80.83	6.19	
4	H	H_2	H	H	128–130°	$C_{17}H_{15}N$						
5	H	H_2	H_2	3-CH_3	93–95	$C_{18}H_{17}N$	86.08	7.22	6.69	85.84	7.39	6.43
6	H	H_2	H_2	8-Cl	136–138	$C_{17}H_{14}ClN$	73.20	5.27	Cl, 15.44	72.65	5.18	Cl, 16.29
7	H	H_2	H_2	1-OCH_3	104–105	$C_{18}H_{15}NO$	79.97	6.71	6.22	79.68	6.70	5.73
8	H	H_2	H_2	3-C_2H_5	Oil	$C_{18}H_{17}N$	86.05	7.65	6.25	85.75	7.62	6.12
9	$(CH_2)_3N(CH_3)_2 \cdot HCl$	O	O	H	170–172	$C_{19}H_{20}N_2O_2 \cdot HCl$	66.18	6.14	8.12	66.19	6.21	8.12
10		O	O	H	210–212	$C_{24}H_{22}N_2O_2 \cdot HCl$	68.00	6.25	7.55	68.20	6.38	7.55
11		O	O	H	213–215	$C_{21}H_{24}N_2O_2 \cdot HCl$	67.64	6.76	7.52	67.53	6.81	7.51
12		O	O	H	>300°	$C_{18}H_{14}N_2O_2 \cdot HCl$	63.25	4.72	Cl, 10.37	63.29	4.99	Cl, 10.39
13	$(CH_2)_3N(CH_3)_2 \cdot HCl$	O	H_2	H	236–239	$C_{19}H_{22}N_2O \cdot HCl$	68.97	7.00		68.77	7.25	
14	$(CH_2)_3N^+(CH_3)_2Cl^- \cdot H_2O$	O	H_2	H	166–170	$C_{20}H_{25}ClN_2O + H_2O$	66.19	7.50	7.72	66.55	7.64	7.34
15	$CH_2CH_2N(C_2H_5)_2 \cdot HCl$	O	H_2	H	208–210	$C_{20}H_{20}NO \cdot HCl$	70.85	7.84	7.51	70.67	8.13	7.59
16		O	H_2	H	180 dec.	$C_{17}H_{13}NO \cdot C_4H_4O_4$	64.85	5.19	10.31	64.82	5.29	10.49
17	$(CH_2)_3N(CH_3)_2 \cdot HCl$	H_2	H_2	H_2	181–183	$C_{19}H_{24}N_2 \cdot HCl$						
18	$CH_2CH_2N(CH_3)(C_2H_5)_2 \cdot I$	H_2	H_2	H	215–217°	$C_{21}H_{29}IN_2$	57.80	7.00	6.42	57.77	7.44	6.10
19	$(CH_2)_3N^+(CH_3)_3I^- \cdot CH_3Cl$	H_2	H_2	H	185–187	$C_{21}H_{30}I_2N_2$	44.69	5.35		44.37	5.34	
20	$-CH_2CN$	H_2	H_2	H	96–98	$C_{16}H_{12}N_2$	82.01	6.02	14.96	82.10	6.29	12.00
21		H_2	H_2	H	245–247	$C_{18}H_{16}N_2 \cdot HCl$	68.87	6.42	13.39	68.91	6.62	13.26
22		H_2	H_2	H	169	$C_{18}H_{20}N_2 \cdot C_4H_4O_4$	67.79	6.18	10.31	67.43	6.14	10.14
23		H	H_2	H	190 dec.	$C_{20}H_{20}N_2 \cdot C_4H_4O_4$	68.58	6.46	9.97	68.24	6.39	9.89

24		H_2	H_2	H	193–195	$C_{19}H_{21}N_3 \cdot HCl$	69.60	6.76	12.82	69.23	6.80	12.65
25		H_2	H_2	H	206–207	$C_{19}H_{21}N_3 \cdot HI$	54.42	5.29	10.02	54.63	5.38	9.69
26		H_2	H_2	3-CH_3	234–236	$C_{19}H_{21}N_3 \cdot C_4H_4O_4$	67.79	6.18	10.31	67.77	6.35	9.89
27		H_2	H_2	1-, 4-, or 7-CH_3	239–241	$C_{18}H_{21}N_3 \cdot HCl$	69.60	6.76	12.82	69.49	6.92	12.78
28		H_2	H_2	8-Cl	250 dec.	$C_{18}H_{18}ClN_3 \cdot HCl$	62.08	5.50	12.07	61.94	5.80	11.75
29		H_2	H_2	1-OCH_3	117–118	$C_{21}H_{23}N_3O$	77.25	6.10	10.60	77.27	6.28	10.77
30		H_2	H_2	1-OCH_3	254–255	$C_{19}H_{21}N_3O \cdot HCl$	66.36	6.45	12.22	66.31	6.51	12.18

[a] Ref. 14. [b] Maleate. [c] Ref. 3.

Deamination of 2-(2-Aminobenzoyl)benzoic Acids.—To a mixture of 2.7 ml. of concentrated HCl and 12 ml. of water, 3.0 g. of 2-(2-amino-4-methylbenzoyl)benzoic acid was added. After cooling to 0°, a solution of 0.82 g. of sodium nitrite in 7.5 ml. of water was added dropwise at 0 to 5°. After the diazotization was completed, the solution was filtered and added to a solution of 10.5 ml. of 50% hypophosphorous acid in 7.5 ml. of water. The reaction mixture was kept in an ice bath for 1 hr., then stored in the refrigerator overnight. During this period a precipitate formed which crystallized. It was filtered off and recrystallized twice from aqueous alcohol; yield 0.8 g. of 2-(4-toluyl) benzoic acid. For analysis it was recrystallized from toluene and sublimed *in vacuo*.

N-Benzyl-N-*p*-tosylanthranilic Acid (VI).—To a solution of 29.1 g. (0.1 mole) of N-*p*-tosylanthranilic acid[18] in 9 g. of NaOH dissolved in 100 ml. of water, 100 ml. of ethanol, and 0.5 g. of KI were added. The solution was refluxed while 25.3 g. of benzyl chloride (0.2 mole) was added dropwise. The reaction mixture was refluxed for 16 hr., alkaline reaction being maintained by occasional addition of 10% aqueous NaOH solution. After cooling, the ethanol was removed *in vacuo*, the aqueous phase was extracted with ethyl acetate and acidified. An oil precipitated which crystallized. After recrystallization from a mixture of ethyl acetate and hexane, VI melted at 164–166°; yield 26 g.

Anal. Calcd. for $C_{21}H_{19}NO_4S$: C, 66.12; H, 5.02; N, 3.67. Found: C, 66.22; H, 4.84, N, 3.65.

6-Morphanthridone (IV). General Procedure.—A suspension of 111.6 g. of morphanthridine-6,11-dione in 2 l. of glacial acetic acid was hydrogenated in a 4 l. Magna-Dash autoclave with 10 g. of 10% palladium on carbon at 75–80° and 10.5 kg./cm.^{2}. After 5.5 hr. the required amount of hydrogen had been taken up. The reaction mixture was cooled, the catalyst was filtered off, and the solution was concentrated *in vacuo*. On addition of 30 ml. of ether to the residue, the 6-morphanthridone crystallized. It was filtered off and recrystallized from 2 l. of ethyl acetate; yield 53 g. (50%). The identical procedure was used to prepare 3- and 8-methyl-6-morphanthridone.

5,6-Dihydromorphanthridine (V). General Procedure.[19]—With stirring, 187.5 g. of lithium aluminum hydride (4.94 moles) was added gradually to 3.6 l. of dry tetrahydrofuran. After 30 min. 334 g. of morphanthridine-6,11-dione (1.5 moles) was added over 1 to 1.5 hr. without external cooling. The reaction mixture was refluxed for 4 hr. and stirred at room temperature overnight, 400 ml. of water was then cautiously added. Following the addition, the slurry was refluxed for 30 min. and filtered hot. The filter cake was washed thoroughly with methylene chloride and the washings were combined with the tetrahydrofuran filtrate. The filtrate was concentrated *in vacuo*, the residue was dissolved in 2 l. of ethanol at reflux and filtered to remove unreacted starting material. The filtrate was cooled and the 5,6-dihydromorphanthridine was filtered off; yield 198.5 g., m.p. 127–129°.

5,6-Dihydromorphanthridine (V) from 6-Morphanthridone.—A suspension of 15 g. of lithium aluminum hydride (0.4 mole) in 700 ml. of dry ether was stirred for 0.5 hr., then 42 g. of 6-morphanthridone (0.2 mole) was added over a 2-hr. period. The reaction mixture was stirred for 16 hr. at room temperature, and worked up by adding in sequence 45 ml. of ethyl acetate, 15 ml. of water, 30 ml. of 15% NaOH solution, and 45 ml. of water. The slurry was filtered and the filtrate was dried and concentrated *in vacuo*. The residue was recrystallized from 2-propanol; yield 20 g., m.p. 128–130°.

Alkylation of Morphanthridine-6,11-dione. General Procedure. 5-(3-Dimethylaminopropyl)morphanthridine-6,11-dione (VIIIa).—To a mixture of 111.5 g. of morphanthridine-6,11-dione (0.5 mole) and 750 ml. of dimethylformamide, 35.5 g. of a 55% suspension of sodamide (0.5 mole) in toluene was added, whereupon a clear yellow solution formed. After stirring for 30 min., 67 g. of 3-dimethylaminopropyl chloride dissolved in 400 ml. of toluene was added. The reaction mixture was heated to 50–60° for 7.5 hr., allowed to stand overnight, then filtered and concentrated *in vacuo*. The oily residue was treated with 500 ml. of water and 500 ml. of ethyl acetate. Some solids (19 g.) separated, were filtered off (m.p. 200–238°), and were identified as impure starting material. The ethyl acetate solution was dried

(18) F. Ullman and H. Bleier *Ber.*, **35**, 4273 (1902).

(19) Procedure worked out by Dr. J. A. Nelson, Developmental Research Division.

and concentrated, and the residue was redissolved in 300 ml. of ethyl acetate. On addition of a solution of HCl in ethyl acetate, 5-(3-dimethylaminopropyl)morphanthridine-6,11-dione hydrochloride precipitated and crystallized slowly. It was filtered off, dissolved in 500 ml. of water and filtered to remove an additional amount (4 g.) of starting material. The aqueous solution was made alkaline with 2 *N* NaOH and the base was extracted with ethyl acetate. The hydrochloride was reprepared and recrystallized from 2-propanol; yield 86 g., m.p. 170–172°. On standing, yellow solids crystallized from the aqueous alkaline solution from which the base had been extracted. This material was identified as 2'-(3-dimethylaminopropylamino)-2-benzoylbenzoic acid (IX) and was filtered off, washed with water, and recrystallized from ethanol. It was converted to the hydrochloride by warming with an alcoholic solution of HCl for 30 min. The solution was concentrated and the residue was triturated with ethyl acetate. The crystalline hydrochloride, after recrystallization from a mixture of ethanol and acetone, melted at 232–234° and was slightly hygroscopic.

Anal. Calcd. for $C_{19}H_{22}N_2O_3 \cdot HCl$: C, 62.89; H, 6.39; N, 7.72. Found: C, 62.87; H, 6.63; N, 7.33.

Alkylations using piperidinoethyl chloride and 2-diethylaminopropyl chloride were carried out using the identical procedure. The alkylation with 2-chloromethyl-2-imidazoline was worked up differently as the product was very insoluble. The reaction mixture was filtered and concentrated *in vacuo*. The residue was extracted with ethyl acetate and 2-propanol at reflux. The insoluble material was washed with water, then extracted with a small volume of dimethylformamide, washed with ethanol, and dried. The 5-(2-imidazolinylmethyl)morphanthridine-6,11-dione (**12**) melted at 261–263°, the hydrochloride over 300°; yield 8.5%.

Alkylation of 6-Morphanthridone. General Procedure. 5-(3-Dimethylaminopropyl)-6-morphanthridone (VIIIb).—A mixture of 25.8 g. of 6-morphanthridone (0.12 mole), 4.7 g. of sodamide (0.12 mole) and 180 ml. of toluene was refluxed for 3 hr. with stirring. A solution of 15.5 g. of 3-dimethylaminopropyl chloride (0.126 mole) in 85 ml. of toluene was added and refluxing was continued for 3.5 hr. After cooling, the reaction mixture was filtered and concentrated. The residue was distilled *in vacuo*; yield 33 g., b.p. 190–200° (0.7 mm.). Part of this material (5.0 g.) was converted to the hydrochloride which after recrystallization from 2-propanol melted at 236–239°; yield 4.5 g. (Table IV, **13**) The methochloride was prepared by heating a solution of 4 g. of the base in 30 ml. of methanol containing 5 g. of methyl chloride to 60° for 1 hr. in a sealed tube and recrystallizing the product from a mixture of 2-propanol and ethyl acetate; yield 3.2 g., m.p. 166–170° (Table IV, **14**).

5-(3-Dimethylaminopropyl)-5,6-dihydromorphanthridine. General Procedure.—To a stirred mixture of 200 ml. of ether and 4.56 g. of lithium aluminum hydride (0.12 mole), 11.76 g. of 5-(3-dimethylaminopropyl)-6-morphanthridone (0.04 mole) dissolved in 30 ml. of ether was added and allowed to react for 16 hr. at room temperature. The reaction mixture was worked up by adding in sequence with stirring 6.8 ml. of ethyl acetate, 2.3 ml. of water, 4.6 ml. of 15% NaOH, and 6.8 ml. of water, filtering and concentrating the filtrate. The residue was distilled *in vacuo*; yield 9.0 g., b.p. 175–180° (0.7 mm.).

Anal. Calcd. for $C_{19}H_{24}N_2$: C, 81.38; H, 8.62; N, 9.62. Found: C, 81.39; H, 8.71; N, 9.66.

The dimethiodide was obtained by warming a solution of 4.5 g. 5-(3-dimethylaminopropyl)-5,6-dihydromorphanthridine (0.016 mole) in 13 ml. of dimethylformamide with 4.3 g. of methyl iodide (0.03 mole) for 2 hr. to 32–37°. The solution was cooled and 200 ml. of ether was added. The dimethiodide (**19**) crystallized and was filtered off. After recrystallization from a mixture of methanol and 2-propanol it melted at 185–187°, yield 4.0 g.

5-Cyanomethyl-5,6-dihydromorphanthridine (XI). General Procedure.—A solution of 39.2 g. of 5,6-dihydromorphanthridine (0.2 mole) was cooled to 10°, 6.2 g. of paraformaldehyde (0.2 mole) was added followed by the dropwise addition of a solution of 11.8 g. of NaCN (0.24 mole) in 40 ml. of water. The temperature was kept at 10–20° for 2 hr., then at 25° for 1 hr., and finally at 45–55° for 3 hr. After this period 8.5 ml. of 37% aqueous formaldehyde solution was added slowly, the temperature was kept at 35–40° for 1 hr., and then 10 ml. of water was added. After standing at room temperature for 16 hr., the aqueous supernatant solution was decanted. The crude crystalline nitrile was dissolved in 350 ml. of benzene with warming. The benzene solution was dried and concentrated, the residue was triturated with hexane and allowed to crystallize; yield 36.5 g., m.p. 96–98° (Table IV, **20**). The 5-cyanomethyl derivatives of 1-methoxy- and 3-ethyl-5,6-dihydromorphanthridine were prepared identically. The 3-ethyl derivative was not obtained crystalline. The 5-cyanomethyl derivatives of 3- and 1-, 4-, or 7-methyl- and 8-chloro-5,6-dihydromorphanthridine were used directly as crude products.

5-(2-Imidazolin-2-ylmethyl)-5,6-dihydromorphanthridine (XII). General Procedure.—A mixture of 187 g. of 5-cyanomethyl-5,6-dihydromorphanthridine (0.8 mole), 57 g. of 1,2-diaminoethane (0.95 mole), and 1.8 ml. of carbon disulfide (added slowly) was heated in an oil bath to 90–108° (inside temperature) for 6 hr. During this period ammonia was evolved slowly. The reaction mixture was diluted with 70 ml. of ethanol and concentrated *in vacuo*; this was repeated using 70 ml. of ethyl acetate to remove unchanged 1,2-diaminoethane. The residue was dissolved in 500 ml. of ethyl acetate, treated with Norit and filtered. The hydrochloride was prepared by acidifying the solution with anhydrous HCl; it separated in crystalline form from the ethyl acetate solution and was filtered off. The hydrochloride was recrystallized by dissolving in 2.2 l. of ethanol at reflux, filtering to remove a small amount of insoluble material, and adding 2.5 l. of ethyl acetate to the warm solution. On standing, the product crystallized. After a second recrystallization, 121.5 g. (48% yield) of hydrochloride, m.p. 245–247°, was obtained.

The corresponding tetrahydropyrimidinyl derivative (**22**) was prepared by the same reaction. In this case the maleate was prepared. It crystallized in pure form on treatment with acetone; 41% yield. The maleate of the tetrahydro-1,3-diazepinyl derivative (**23**) was obtained in a yield of 21% after recrystallization from ethanol.

The hydriodide of the 1-methyl-2-imidazolinylmethyl derivative (**25**) was obtained by treating 2 g. of 5-(2-imidazolin-2-ylmethyl)-5,6-dihydromorphanthridine dissolved in 10 ml. of ethanol with 2 ml. of methyl iodide at room temperature. After 4 hr. the solution was concentrated, and the residue was triturated twice with ethyl acetate, then dissolved in acetone. On cooling, the hydriodide crystallized. After two recrystallizations from ethanol it melted at 206–207°, yield 1.0 g.

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