Anal. Calcd. for $C_{14}H_{15}NS$: C, 73.32; H, 6.59; N, 6.11. Found: C, 73.31; H, 6.67; N, 6.25. Picrate: M.p. 171°. Calcd. for $C_{29}H_{18}N_4O_7S$: C, 52.40; H, 3.96; N, 12.22. Found: C, 52.46; H, 3.79; N, 12.53. 2,6-Dimethyl 4-benzylmercaptopyrylium Perchlorate.—

To a solution of 0.50 g. of 2,6-dimethyl-4-benzylmercaptopyrylium iodide in hot water were added 5 ml, of 70% aqueous sodium perchlorate. The product separated on cooling. It was recrystallized from methanol; yield 0.40 g. (87%), m.p. 145–146° (dec.).¹³

(13) Anker and Cook⁵ report 136

Summary

1. 2,6-Dimethyl-4-thiopyrone reacts with active alkylating agents to give substituted mercaptopyrylium salts.

2. The structure of some of the pyrylium salts has been established by converting them to the corresponding lutidines of known structure.

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Studies in Phenanthridine Chemistry

By JACOB FINKELSTEIN AND SEYMOUR M. LINDER

During an investigation into the structural relationship between Antergan and N-substituted dihydrophenanthridines,1 which was also reported upon by Huttrer,² some phenanthridine derivatives were made for pharmacological and chemothera-peutic screening. The purpose of this paper is to record some observations on the application of standard reactions to phenanthridines.

The most readily obtainable phenanthridines, 6-methylphenanthridine and phenanthridone³ were used as starting materials, and the derivatives synthesized may be classified into five groups: I prepared directly from 6-methylphenanthridine; II from 6-phenanthridinecarboxaldehyde; III from phenanthridone; IV from 6-bromophenanthridine; and V from 6-chloromethylphenanthridine.



Since phenanthridine may be considered as a derivative of quinoline or isoquinoline, the 6methyl group should be active and resemble quinaldine in the type of reactions it may undergo. We found that under the conditions of the Mannich reaction, 6-methylphenanthridine reacted with paraformaldehyde and dimethylamine hydrochloride, to give 6-(β -dimethylaminoethyl)-phenanthridine in good yield. Other secondary amines react similarly.

It was also found that a hydrogen of the methyl group of 6-methylphenanthridine is sufficiently active to undergo the Schmid-Karrer⁴ modification of the Ziegler⁵ reaction to form 6-chloromethylphenanthridine identical with that prepared by cyclizing chloroacetyl-o-aminodiphenyl as described by Morgan and Walls.6 When 6-chloromethylphenanthridine reacted with isopropylamine, benzylamine, benzylisopropylamine, dimethylamine, piperidine and morpholine, the corresponding

secondary and tertiary amines were obtained. It was also found that benzyl tertiary amines of this type could be obtained by benzylation of the secondary amines. However, another method was investigated without satisfactory results. Gilman, et al.,⁷ showed that any halides react with lithium dialkylamides to yield the corresponding tertiary amines and, on occasion, may be preferred over the reaction of RX with a secondary amine. Horning and Bergstrom⁸ also found that lithium dialkylamides react with aryl halides and, in addition, with *n*-butyl bromide, while the lower halides failed. When 6-chloromethylphenanthridine reacted with lithium benzylisopropylamide, only 1,2-di-(6-phenanthridyl)-ethane was isolated, indicating that the halogen is too reactive and undergoes a Wurtz type of reaction. A N-phenan-thridylmethyl-*p*-toluenesulfonamide could not be prepared by treating 6-chloromethylphenanthridine and *p*-toluenesulfonamide. Instead, only the N,Ndiphenanthridylmethyl-p-toluenesulfonamide was formed. When an N-substituted-p-toluenesulfonamide, as benzyl, was treated with 6-chloromethylphenanthridine, the expected alkylation reaction took place with the formation of N-benzyl-N-phenanthridylmethyl - p - toluenesulfonamide, a substance capable of further syntheses after removal of the benzyl group. Other reactions resulting in the replacement of the chlorine group of 6-chloromethylphenanthridine included the preparation of ethers such as, for example, 6-diethylaminoethoxymethylphenanthridine, and of phenanthridineacetonitrile, a versatile compound for further synthetic reactions.

Phenanthridone, being an amide, was N-alkyl-ated by Graebe and Wander⁹ by adding an alkyl halide to the potassium salt. The reaction is rather general and, under the same conditions with β -diethylaminoethyl chloride, the 5-(β -diethylaminoethyl)-phenanthridone was obtained.

Ritchie¹⁰ was first to prepare 6-phenanthridinecarboxaldehyde and describe some of its properties. An important reaction which this compound undergoes is the reductive aldehyde-amine condensation. With both β -diethylaminoethylamine and β -ami-

- 8) Horning and Bergstrom. ibid., 67, 2110 (1945).
- (9) Graebe and Wander, Ann., 276, 245 (1893).

⁽¹⁾ Finkelstein and Linder, THIS JOURNAL, 72, 3282 (1950).

⁽²⁾ Huttrer, *ibid.*, **71**, 4147 (1949).
(3) Numbered according to "The Ring Index" by Patterson and Capell.

⁽⁴⁾ Schmid and Karrer, Helv. Chim. Acta, 29, 573 (1946).

⁽⁵⁾ Ziegler, et al., Ann., 551, 80 (1942).

⁽⁶⁾ Morgan and Walls, J. Chem. Soc. 2117 (1931).

⁽⁷⁾ Gilman, et al., THIS JOURNAL, 67, 2106 (1945).

⁽¹⁰⁾ Ritchie, J. Proc. Roy. Soc., N. S. Wales, 78, 134–186 (1945).

noethylmorpholine with hydrogen and Raney nickel, the expected secondary amine was obtained. In certain cases, this may be a better method for preparing this type of secondary amine than the previously discussed method of employing 6-chloromethylphenanthridine with amines.

For amino compounds substituted directly on the ring, 6-bromophenanthridine reacted with amines. With primary amines the expected product was obtained, but with secondary amines, where one of the substituents was benzyl, the reaction failed. Nevertheless, the tertiary base could be prepared by benzylation of the intermediate secondary amine.

Biological Results¹¹

All the numbered compounds in the experimental section were tested against experimental infections *in vivo*. These experiments included bacterial infections, *e.g.*, hemolytic streptococci, pneumococci and *Salmonella schottmüelleri*, one protozoan infection (*Tryp. equiperdum*) and two viral infections (murine poliomyelitis Col. SK and influenza type A). In a few instances, a spirochetal infection with *Borrelia novyi* was included. The repeated subcutaneous or oral administration of these compounds exerted in no case any curative effect on the above mentioned infections.

All compounds, except XII, are poor spasmolytics. Compound XII is somewhat less active than Syntropan but considerably more toxic. None of the compounds had any antihistamine effect.

Experimental

I. 6-(β -Dimethylaminoethyl)-phenanthridine (VI).— While a solution of 1.5 g. of paraformaldehyde and 4.1 g. of dimethylamine hydrochloride in 75 cc. of alcohol was refluxed, a solution of 9.7 g. of 6-methylphenanthridine⁶ in 50 cc. of alcohol was added over a period of 30 minutes, and then the solution was refluxed for one hour. The alcohol was distilled off, and the residue was made alkaline with dilute sodium hydroxide solution. The resulting oil was taken up in ether, dried and upon saturation with dry hydrogen chloride produced a precipitate which was recrystallized from methanol-ether, and found to be hygroscopic. When warmed with ethanol and dissolved with just enough methanol to effect solution, the addition of a few drops of ether produced crystallization; yield 9.5 g.; m. p. 152-154°.

Anal. Caled. for $C_{17}H_{18}N_{2}$:2HCl·1.5H₂O: C, 58.29; H, 6.62; N, 8.00. Found: C, 58.28; H, 7.03; N, 7.94.

6-Chloromethylphenanthridine.—A mixture of 19.3 g. of 6-methylphenanthridine⁶ in 200 cc. of carbon tetrachloride, 13.3 g. of N-chlorosuccinimide, and 1.2 g. of benzoyl peroxide was refluxed for 3 hours during which time a crystalline product was formed. The solvent was distilled off, and the residue was treated with water to dissolve the succinimide. The insoluble product was recrystallized from ligroin b. p. $60-72^{\circ}$ and decolorized by carbon. The filtrate deposited the 6-chloromethylphenanthridine upon cooling, m. p. 129-131°. With an authentic sample, prepared as by Morgan and Walls,⁶ the melting point was not depressed.

Anal. Calcd. for $C_{14}H_{10}NC1$: C, 73.90; H, 4.43; N, 6.15. Found: C, 73.79; H, 4.12; N, 6.16.

6-(β -1-Piperidylethyl)-phenanthridine (VII).—A solution of 19.3 g. of 6-methylphenanthridine⁶ in 200 cc. of alcohol was added to a stirred, refluxing solution of 8.5 g. of piperidine in 60 cc. of alcohol containing an equivalent of hydrogen chloride and 3.0 g. of paraformaldehyde in the course of 30 minutes and then refluxed for an additional hour. The solution was concentrated and the residue made alkaline. The solid which precipitated was dissolved in ether and this solution was saturated with dry hydrogen chloride. The salt obtained was recrystallized from methanol. In a sealed tube the melting point was $173-176^{\circ}$.

Anal. Caled. for $C_{20}H_{22}N_{2}$ ·2HCl: C, 66.10; H, 6.66; N, 7.70. Found: C, 65.39; H, 6.16; N, 8.20.

II. 6-(β -4-Morpholinylethylaminomethyl)-phenanthridine (VIII).—To a solution of 10.3 g. of 6-phenanthridinecarboxaldehyde,¹⁰ 9.1 g. of β -aminoethylmorpholine was added. There was an immediate reaction, accompanied by the liberation of heat, production of red color, and complete disappearance of the aldehyde. The solution was then hydrogenated at 50 lb. pressure, employing Raney nickel catalyst. The reduction was complete after 2.5 hours. The solvent was distilled and the residue was diluted with water and extracted with ether. The ethereal solution was saturated with dry hydrogen chloride and the precipitated salt collected, m. p. 180–185°. The product obtained had m. p. 201–203° by recrystallization first from 95% alcohol, then from absolute alcohol.

Anal. Calcd. for $C_{20}H_{23}N_3O.2HC1.1.5H_2O$: C, 57.00; H, 6.69; N, 10.00; for $C_{20}H_{23}N_3O.2HC1.2H_2O$: C, 55.82; H, 6.79; N, 9.80. Found: C, 56.22; H, 6.18; N, 10.35.

6-(β -Dimethylaminoethylaminomethyl)-phenanthridine. —Following the above procedure, 14 g. of β -phenanthridinecarboxaldehyde was allowed to react with 12 g. of β -dimethylaminoethylamine and reduced in the presence of Raney nickel. The trihydrochloride was recrystallized from a methanol-ether mixture, m. p. 240° dec.

Anal. Calcd. for $C_{18}H_{21}N_{8}$ ·3HCl·H₂O: C, 53.15; H, 6.44; N, 10.33. Found: C, 53.13; H, 6.35; N, 10.41.

III. 5-(β -Diethylaminoethyl)-6(5H)-phenanthridone (IX).—A mixture of 20 g. of phenanthridone¹² and 30 g. of potassium hydroxide was heated in a casserole and stirred until a uniform melt was obtained. After cooling, the salt was broken up and reacted with 27.2 g. of β -diethylaminoethyl chloride in a sealed tube at 150° for 5 hours. The contents of the tube were triturated with dilute hydrochloric acid and filtered; yield 30.5 g. The product was first recrystallized from a methanol-ether mixture and then twice from methanol, m. p. 193-195°.

Anal. Caled. for C₁₉H₂₂N₂O·HCl·¹/₂H₂O: C, 67.20; H, 7.12; N, 8.24. Found: C, 67.41; H, 6.61; N, 8.32.

6-(β -4-Morpholinylethylamino)-phenanthridine (X).—A mixture of 8.0 g. of 6-bromophenanthridine¹³ and 7.3 g. of β -aminoethylmorpholine was heated in a sealed tube at 120° for 3 hours. The residue was broken up with dilute hydrochloric acid and was made alkaline with sodium hydroxide solution. The gummy precipitate was filtered, dissolved in alcohol and the solution treated with dry hydrogen chloride. The crystalline salt thus produced was collected and dried; yield 9.8 g. It was recrystallized from methanol and dried at 100° in vacuo, m.p. 258-260° dec.

Anal. Cacld. for $C_{19}H_{21}N_3O$ ·2HC1: C, 60.00; H, 6.09; N, 11.05. Found: C, 59.78; H, 5.61; N, 10.89.

6-(β -Dimethylaminoethylamino) - phenanthridine.—A mixture of 8.5 g. of 6-bromophenanthridine and 4.3 g. of β -dimethylaminoethylamine was heated at 120° for 2 hours. The product was extracted with dilute hydrochloric acid and the combined extracts were made alkaline. The liberated oil was converted into its hydrochloride and recrystallized from alcohol; dried at 100°, m. p. 251–254°.

Anal. Caled. for C₁₇H₁₉N₃·2HCl·1.5H₂O: C, 55.90; H, 6.62; N, 11.50. Found: C, 55.98; H, 6.27; N, 11.60.

6-(N,N- β -Dimethylaminoethyl-benzylamino) -phenanthridine.—A solution of 3 g. of 6-(β -dimethylaminoethylamino)-phenanthridine dihydrochloride was made alkaline with dilute sodium hydroxide and the precipitate was extracted with ether. After drying, 1.4 g. of benzyl chloride was added to the ethereal solution and kept at room temperature. The crystals were collected and treated with dilute sodium hydroxide. The insoluble product formed was dissolved in alcohol and treated with an excess of alcoholhydrochloric acid. After standing at 0°, feathery needles were produced, which were purified by several recrystallizations from alcohol, m. p. 350–356° dec.

Anal. Calcd. for $C_{24}H_{26}N_3$ ·2HCl·2H₂O: C, 61.90; H, 6.92; N, 9.02. Found: C, 61.31; H, 6.23; N, 8.88.

⁽¹¹⁾ The authors are indebted to Drs. R. Schnitzer and E. Grunberg for the chemotherapeutic studies and to Dr. Lowell O. Randall for the pharmacological results.

⁽¹²⁾ Walls, J. Chem. Soc., 1405 (1935).

⁽¹³⁾ Walls, ibid., 104 (1934).

IV. 6-(Dimethylaminomethyl)-phenanthridine (XII).— In a scaled tube a mixture of 2.2 g. of 6-chloromethylphenanthridine and 1 g. of dimethylamine in 75 cc. of benzene was heated at 100° for 16 hours. The benzene was distilled off; the residue was then made alkaline with dilute sodium hydroxide and extracted with ether. The ether was distilled in order to remove unreacted dimethylamine. The remaining oil was once again dissolved in ether, dried over potassium hydroxide, filtered and the ethereal solution was saturated with dry hydrogen chloride at 0°, to produce 3 g. of the dihydrochloride as a yellow precipitate. The product was recrystallized from 50 cc. of boiling alcohol; m. p. 198-200°.

Anal. Caled. for $C_{16}H_{16}N_{2}$ ·2HCl: C, 62.18; H, 5.86; N, 9.06. Found: C, 61.63; H, 5.61; N, 8.94.

6-(**Isopropylaminomethyl**)-**phenanthridine** (**XIII**).—This compound was prepared according to the above described procedure. The product was recrystallized from a mixture of methanol-ether, m. p. $209-210^{\circ}$.

Anal. Caled. for $C_{17}H_{18}N_2 \cdot 2HCl^{1/2}H_2O$: C, 61.45; H, 6.37; N, 8.43. Found: C, 61.18; H, 6.43; N, 8.21.

Isopropyl-(di-6-phenanthridylmethyl)-amine.—In one preparation of the above compound there appeared a crystalline product at the interface during the ethereal extraction. This was separated and purified by recrystallization from benzene, m. p. $203-205^{\circ}$. Its analysis corresponded with that expected for the reaction of two moles of 6-chloromethylphenanthridine with one mole of isopropylamine.

Anal. Caled. for C₃₁H₂₇N₃: C, 84.33; H, 6.17; N, 9.54. Found: C, 84.23; H, 6.24; N, 9.48.

N,N-Di-(phenanthridylmethyl)-p-toluenesulfonamide.— A solution of 8.6 g. of p-toluenesulfonamide in 2 g. of sodium hydroxide dissolved in 40 cc. of water was refluxed for 3 hours with a solution of 11.3 g. of 6-chloromethylphenanthridine in 200 cc. of acetone and then concentrated to a small volume *in vacuo* and filtered. After washing the precipitate with water, it was stirred for 15 minutes with 100 cc. of acetone to remove starting material. The product was dried and recrystallized from benzene twice, m. p. 160- 161° .

Anal. Calcd. for $C_{55}H_{27}N_3SO_2$: C, 76.00; H, 4.92; N, 7.60. Found: C, 76.06; H, 5.03; N, 7.38.

None of the monosubstituted sulfonamide seemed to have formed.

6-(4-Morpholinylmethyl)-phenanthridine (XIV).—A mixture of 4.5 g. of 6-chloromethylphenanthridine, 2 g. of morpholine, 25 cc. of benzene, and 5 g. of powdered potassium carbonate was refluxed for 5 hours. After cooling, water was added and the benzene layer separated. It was then extracted with several portions of dilute hydrochloric acid, and the combined extracts were made alkaline with dilute sodium hydroxide solution. The precipitate was taken up in ether, dried over potassium hydroxide, filtered and saturated with dry hydrogen chloride in the cold. The salt was filtered and recrystallized from a methanol-ether mixture; yield 4 g.; m. p. 211–216° dec.

Anal. Calcd. for $C_{18}H_{18}N_2O.2HCI$: C, 61.55; H, 5.74. Found: C, 61.11; H, 5.51.

6-(**N**-**Piperidylmethyl**)-**phenanthridine** (**XV**).—A mixture of 4.5 g. of 6-chloromethylphenanthridine, 2 cc. of piperidine, and 5 g. of powdered potassium carbonate in 25 cc. of benzene was refluxed for 5 hours. After cooling, the benzene solution was extracted with dilute hydrochloric acid, and the extract was made alkaline with sodium hydroxide solution. The precipitate was dissolved in ether, dried over potassium hydroxide, and saturated with dry hydrogen chloride. The hydrochloride thus produced was filtered and dried; yield 3.3 g. It was then recrystallized from methanol.

Anal. Calcd. for $C_{19}H_{20}N_2$:2HCl.¹/₂H₂O: C, 63.67; H, 6.47; N, 7.82. Found: C, 63.85; H, 7.23; N, 7.73.

6-(**Benzylaminomethyl**)-**phenanthridine**.—A mixture of 2.3 g. of 6-chloromethylphenanthridine and 3 g. of benzylamine in 25 cc. of decalin was refluxed for two hours and cooled. The benzylamine hydrochloride produced was filtered. The filtrate was concentrated at 1 mm. in a bath at 80°. The small amount of remaining oil was dissolved in ether, dried over potassium hydroxide, filtered, and saturated with dry hydrogen chloride. The salt produced was then recrystallized from butanol-ether mixture, m. p. $201-203^{\circ}$.

Anal. Caled. for $C_{21}H_{18}N_2$ ·HCl·H₂O: C, 71.47; H, 6.00; N, 7.94. Found: C, 71.38; H, 6.04; N, 8.02.

1,2-Di-(6-phenanthridyl)-ethane.—A solution of phenyl lithium, prepared in the usual manner from 1.8 g. of lithium and 19 g. of bromobenzene, was added to a solution of 15 g. of benzylisopropylamine in 100 cc. of dry xylene. The color changed from light brown to cherry red. After stirring for 0.5 hour, a solution of 23 g. of 6-chloromethylphenanthridine in 200 cc. of xylene was added. A green solution formed, and when the ether was distilled off, while stirring, a yellow precipitate was obtained. The xylene mixture was then refluxed for 3 hours. After cooling and filtering, the 16 g. of product was first recrystallized from 250 cc. of nitrobenzene, then from piperidine, and obtained as lustrous yellow crystals, m. p. 280-282°, which were dried *in vacuo* at 100°.

Anal. Calcd. for $C_{28}H_{20}N_2$: C, 87.47; H, 5.24; N, 7.29. Found: C, 87.54; H, 4.66; N, 7.18.

N-Benzyl-N-(6-phenanthridylmethyl)-p-toluenesulfonamide.—A suspension of 13 g. of N-benzyl-p-toluenesulfonamide in 150 cc. of water containing an equivalent amount of sodium hydroxide and 11.3 g. of 6-chloromethylphenanthridine in 150 cc. of acetone was refluxed for 6 hours. The acetone was then removed by distillation and, upon cooling the residue, crystals were obtained; yield 16.8 g. The compound was recrystallized from butanol, m. p. 147-148° and dried *in vacuo* at 80°.

Anal. Caled. for $C_{28}H_{24}N_2SO_2$: C, 74.30; H, 5.35; N, 6.19. Found: C, 74.34; H, 5.10; N, 5.95.

6-(β -Dimethylaminoethoxymethyl)-phenanthridine (XVI).—A mixture of 9 g. of 6-chloromethylphenanthridine, 7.1 g. of β -dimethylaminoethanol and 5 g. of powdered potassium carbonate was refluxed for 12 hours. The mixture was treated with dilute hydrochloric acid, filtered, and the filtrate made alkaline. The base was dissolved in ether, dried and saturated with dry hydrogen chloride. The salt formed was dried *in vacuo*; yield 7.5 g., m. p. 158–166°. The product was recrystallized three times from alcoholether, m. p. 190–191°.

Anal. Calcd. for $C_{18}H_{20}N_2O$ ·2HCl·H₂O: C, 61.54; H, 6.89; N, 8.00. Found: C, 61.34; H, 6.03; N, 8.28.

6-Cyanomethylphenanthridine.—A solution of 27 g. of 6chloromethylphenanthridine in 400 cc. of hot alcohol was stirred and refluxed while a solution of 7.8 g. of potassium cyanide in 25 cc. of water was added dropwise during 0.5 hour. After being refluxed for 7 hours, approximately 300 cc. of alcohol was distilled and the residue diluted with water. The precipitate was filtered. When treated with a large amount of hot alcohol, approximately 4 g. of a high melting (217-223°) product was obtained. The alcoholic mother liquor was concentrated to the point of crystallization, and approximately 14 g. of a compound was isolated, m. p. 95-103°. After two recrystallizations from alcohol, the nitrile was obtained pure, m. p. 105-108°.

Anal. Caled. for $C_{15}H_{10}N_9$: C, 82.52; H, 4.63; N, 12.82. Found: C, 82.55; H, 4.98; N, 12.78.

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Summary

Some reactions of 6-methyl, 6-chloromethyl, 6formyl and 6-bromophenanthridine as well as of phenanthridone are described.

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