Lakeside Laboratories, Division of Colgate-Palmolive Company

Morphanthridines III (1). 6-Basic Substituted Morphanthridines

Alexander E. Drukker, Claude I. Judd and Donald D. Dusterhoft

The reaction of hydrazines and amines with 6-chloromorphanthridine was investigated. Grignard coupling of aminoalkyl halides with 6-chloromorphanthridine afforded 6-aminoalkylmorphanthridines. Cyclization of 6-(2-chloroethylamino)morphanthridine yielded the new ring system 5'*H*-imidazo[5,6-a]dibenz[b,e]azepine, which was aminoalkylated by generation of the 11-position anion with butyllithium, followed by treatment with a tertiary aminoalkyl halide.

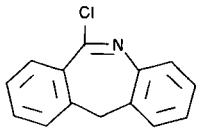
We have recently reported on the synthesis of 11-aminoalkyl- (1) and 11-aminoalkylidene-5,6-dihydromorphanthridines (2). Although a few 6-alkyl- and 6-arylmorphanthridines had previously been described in the literature (3), only after our work on the preparation of 6-basic substituted morphanthridines was completed did references appear describing 6-aminoalkylaminomorphanthridines (4). This prompts us to submit at this time the details of our own investigation in this area.

The readily available 5,6-dihydro-6-morphanthridone (5) was converted to 6-chloromorphanthridine (I) by treatment with phosphorus pentachloride. Analogous to the known alkylation of *N*-phenylbenzimidyl chloride with Grignard compounds (6), treatment of 6-chloromorphanthridine (I) with 3-dimethylaminopropylmagnesium chloride or 3-(*N*-methyl-*N*-benzylamino)propylmagnesium chloride in tetrahydrofuran (7) yielded the corresponding 6-aminoalkylmorphanthridines IIa and IIb.

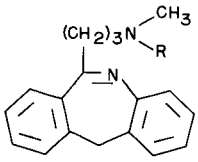
Treatment of 6-chloromorphanthridine (I) with alcoholic hydrazine hydrate afforded 6-hydrazinomorphanthridine (IIIb), isolated and characterized as the oxalate salt. The method of Backeberg (8) was used for the preparation of 6-aminomorphanthridine (IIIa), namely heating of 6-chloromorphanthridine (I) with an amine (in this case ammonia) in phenol or cresol as the solvent. The amino alcohol, 6-(2-hydroxyethylamino)morphanthridine (IIIc), was similarly prepared, and was converted into the chloride hydrochloride (IV). Liberation of the base was followed by spontaneous ring closure to yield the previously unreported ring system 5'*H*-imidazo-[5,6-a]dibenz[b,e]azepine (V). The same compound V was obtained in low yield by thermal dehydration of IIIc.

Aminoalkylation of V in the 11-position, which is analogous to the aminoalkylation of 5-substituted dihydromorphanthridines (I), was effected by treating V with a hexane solution of butyllithium to generate the 11-position anion, followed by alkylation with a tertiary aminoalkyl halide to give VIa and VIb.

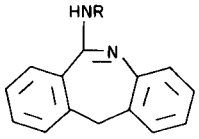
The infrared spectrum of the amino alcohol (IIIc) shows a strong band at 6.5 μ, which resembles the "amide II" band of non-cyclic secondary amides as described by Bellamy (9). This suggests that these compounds can exist in tautomeric equilibrium between the two possible C=N forms, and perhaps, involves hydrogen bonding stabilization from either OH or NH. In addition, the appearance in the spectrum of IIIa of bands at 2.88 and 2.89 μ, which is an unusually small difference in wavelength for a NH_2 group, together with bands at 6.05 and 7.20 μ (amidine II), lends further support to this possibility.



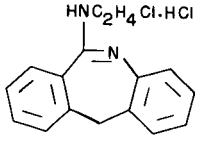
I



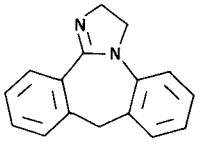
II a, R=CH_3
b, R=CH_2Ph



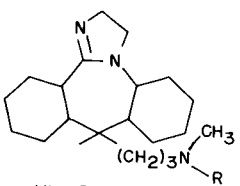
III a, R=H
b, R=NH_2
c, R=C_2H_4OH



IV



V



VI a, R=CH_3
b, R=H

Comparison of the infrared spectrum of the amino alcohol (IIIa) with that of the cyclization product (V) shows disappearance of bands at 3.05 μ and 3.7 μ (bonded OH and strongly hydrogen bonded NH) on cyclization. Furthermore, bands at 7.25, 7.59 and 7.91 μ seem to be characteristic for the imidazodibenzazepine ring system.

In the ultraviolet region, the morphanthridines showed a λ infl. at 224-226 mμ and a λ max at 244-249 mμ, while the imidazodibenzazepines showed a λ infl. at 229-231 mμ and a λ max at 256-266 mμ, with a corresponding decrease in molecular extinction value.

EXPERIMENTAL

All melting points were determined in a Thomas-Hoover capillary melting point apparatus, calibrated against standards. Infrared spectra were determined as Nujol mulls with a Beckman IR-8 infrared spectrophotometer, and ultraviolet spectra were measured in ethanol solution with a Beckman DK-2A spectrophotometer.

6-Chloromorphanthridine (I) (4).

A mixture of 20.9 g. (0.1 mole) of 5,6-dihydro-6-morphanthridone and 29 g. of phosphorus pentachloride was heated to 130° for 2 hours. The mixture became liquid and phosphorus oxychloride started to reflux. Fractionation in vacuum gave 20.45 g. (90%) of a viscous oil, b.p. 162° (0.2 mm.).

Anal. Calcd. for $C_{14}H_{10}ClN$: C, 73.85; H, 4.43; Cl, 15.57; N, 6.15. Found: C, 73.64; H, 4.39; Cl, 15.65; N, 6.18.

6-Hydrazinomorphanthridine (IIIb).

To a solution of 50 ml. of 85% hydrazine hydrate in 500 ml. of ethanol was added 11.4 g. (0.05 mole) of 6-chloromorphanthridine, and the solution was left for two days at room temperature. The solution was concentrated, 500 ml. of water was added, the resulting gum was extracted with benzene, the benzene solution was extracted with dilute hydrochloric acid, and the aqueous solution was made basic with potassium hydroxide to give 11.15 g. (100%) of product, which was converted in ethanolic solution to the hydrogen oxalate, which was recrystallized from aqueous methanol; m.p. 203°, λ max 244 (ϵ, 10,400), 284 mμ (ϵ, 7,690).

Anal. Calcd. for $C_{16}H_{16}N_3O_4$: C, 61.33; H, 4.83; N, 13.41; oxalic acid 28.74. Found: C, 61.10; H, 4.72; N, 13.38; oxalic acid, 28.96.

6-(3-Dimethylaminopropyl)morphanthridine (IIa).

To a Grignard solution, prepared from 27.9 g. (0.23 mole) of 3-dimethylaminopropyl chloride and 5.6 g. of magnesium (0.23 atom) in 200 ml. of tetrahydrofuran (T.H.F.) was added dropwise a solution of 25.8 g. (0.116 mole) of 6-chloromorphanthridine in 200 ml. of T.H.F. After stirring for 24 hours at room temperature, 24 ml. of saturated ammonium chloride was added, the precipitate was filtered, and the filtrate was concentrated. The residue was dissolved in chloroform, extracted with *N* hydrochloric acid, and the aqueous solution was made alkaline with potassium hydroxide, extracted with ether, the ether extracts dried over potassium carbonate, filtered, concentrated, and distilled to yield 6.5 g. (20%) of a yellow viscous oil, b.p. 150° (0.1 mm.).

Anal. Calcd. for $C_{19}H_{22}N_2$: N, 10.06. Found: N, 9.78.

This base was converted to the hydrogen oxalate in alcoholic solution to give a salt of m.p. 161°, λ infl. 223 (ϵ, 19,500), 244 mμ (ϵ, 8,450), λ max 311 mμ (ϵ, 3,720).

Anal. Calcd. for $C_{21}H_{14}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.24; H, 6.49; N, 7.68.

Similarly prepared was 6-(3-*N*-benzyl-*N*-methylaminopropyl)morphanthridine hydrogen oxalate (IIb), m.p. 189-192°, λ infl. 224 (ϵ, 20,400), 244 mμ (ϵ, 8,920), λ max 310 mμ (ϵ, 3,730).

Anal. Calcd. for $C_{27}H_{26}N_2O_4$: C, 72.96; H, 6.36; N, 6.32. Found: C, 73.10; H, 6.51; N, 6.32.

6-Aminomorphanthridine (IIIa).

Into a stirred solution of 45.6 g. (0.2 mole) of 6-chloromorphanthridine in 200 g. of phenol was passed at 100° dry ammonia for 6 hours. The phenol was removed by distillation and the residue was taken up in benzene. Shaking this benzene solution with 5% aqueous hydrochloric acid precipitated the hydrochloride of 6-aminomorphanthridine, which was filtered and recrystallized from 2-propanol to give a monohydrate, which was dehydrated by heating *in vacuo* at 110° to afford 29.3 g. (59%) of the hydrochloride, m.p. 204-206°, λ infl. 224 mμ (ϵ, 15,880), λ max 247 (ϵ, 10,580), 284 mμ (ϵ, 7,240).

Anal. Calcd. for $C_{14}H_{13}ClN_2$: C, 68.71; H, 5.35; Cl, 14.49; N, 11.46. Found: C, 68.77; H, 5.35; Cl, 14.48; N, 11.31.

6-(2-Hydroxyethyl)morphanthridine (IIIc).

To 122 g. (2 moles) of aminoethanol in 250 g. of phenol was added 28.4 g. (0.124 moles) of 6-chloromorphanthridine and the mixture was stirred 14 hours at 160°. Most of the excess of phenol and aminoethanol was distilled in vacuum, and the residue was treated with dilute sodium hydroxide. The solid residue was extracted with 250 ml. of dichloromethane, the organic solution extracted with 250 ml. of *N* hydrochloric acid, and the aqueous extract was made alkaline with potassium hydroxide. The product was filtered and recrystallized from 500 ml. of ethanol to yield 13.8 g. (44.5%) of 6-(2-hydroxyethylamino)morphanthridine, m.p. 205-207°, λ infl. 226 mμ (ϵ, 17,160), λ max 248-249 (ϵ, 11,420), 294-295 mμ (ϵ, 7,820).

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.17; H, 6.39; N, 11.10. Found: C, 76.21; H, 6.17; N, 11.09.

6-(2-Chloroethylamino)morphanthridine Hydrochloride (IV).

A solution of 11.6 g. (0.0417 mole) of 6-(2-hydroxyethylamino) morphanthridine in 300 ml. of chloroform was acidified with dry hydrochloric acid. To this salt was added 11.6 g. of thionyl chloride, the solution was refluxed for 3 hours, concentrated, and the residue was recrystallized from 400 ml. of petroleum ether (boiling range 90 to 100°) to afford 10.3 g. (79%) of product, m.p. 184-186°.

Anal. Calcd. for $C_{16}H_{16}Cl_2N_2$: C, 62.55; H, 5.25; Cl, 23.08; N, 9.13. Found: C, 62.32; H, 5.26; Cl, 23.63; N, 9.05.

5'*H*-Imidazo[5,6-a]dibenz[b,e]azepine (V).

A solution of 52 g. (0.17 mole) of 6-(2-chloroethylamino) morphanthridine hydrochloride in 2 l. of methanol was treated with 84 ml. of 5 *N* sodium hydroxide, and the solution was refluxed for 3 hours, concentrated, diluted with water, extracted with ether, the ethereal solution was dried over potassium carbonate, filtered and concentrated to yield 32 g. (81%) of the cyclization product, m.p. 162-163°, λ infl. 229 mμ (ϵ, 13,930), λ max 256 (ϵ, 8,120), 295 mμ (ϵ, 6,830).

Anal. Calcd. for $C_{16}H_{14}N_2$: C, 82.01; H, 6.03; N, 11.96. Found: C, 82.07; H, 6.18; N, 11.79.

11-(3-Dimethylaminopropyl)-5'*H*-imidazo[5,6-a]dibenz[b,e]azepine (VIa).

To a solution of 11.7 g. (0.05 mole) of 5'*H*-imidazo[5,6-a]dibenz[b,e]azepine in 250 ml. of T.H.F. was added 40 ml. of butyllithium solution in 150 ml. of ether at room temperature. The dark green solution was stirred 5 hours, followed by dropwise addition of a solution of 6.1 g. (0.05 mole) of 3-dimethylaminopropyl chloride in 25 ml. of ether. The solution was stirred 20 hours at room temperature, 25 ml. of water was added, the organic layer was separated, dried over potassium carbonate, filtered, concentrated, and the residue was distilled to afford 11.35 g. (70%) of base, b.p. 220° (1.2 mm.), λ infl. 230-231 mμ (ϵ, 12,700), λ max 260 (ϵ, 8,780), 293 mμ (ϵ, 7,120).

Anal. Calcd. for $C_{21}H_{25}N_3$: C, 78.96; H, 7.89; N, 13.15. Found: C, 78.74; H, 8.11; N, 13.15.

Similarily prepared was 11-(1-methyl-4-piperidyl)-5'*H*-imidazo-[5,6-a]dibenz[b,e]azepine, b.p. 200° (0.05 mm.), λ infl. 231 mμ (ϵ, 14,370), λ max 259-260 (ϵ, 9,580), 292-293 mμ (ϵ, 7,330).

Anal. Calcd. for $C_{22}H_{25}N_3$: C, 79.70; H, 7.60; N, 12.68. Found: C, 80.00; H, 7.62; N, 12.60.

11-(3-Methylaminopropyl)-5'*H*-imidazo[5,6-a]dibenz[b,e]azepine (VIb).

To a solution of 11.7 g. (0.05 mole) of 5'*H*-imidazo[5,6-a]dibenz-[b,e]azepine in 150 ml. of T.H.F. was added 40 ml. (0.06 mole) of butyllithium solution in 150 ml. of ether at room temperature. After 4 hours stirring, a solution of 9.9 g. (0.05 mole) of 3-(*N*-benzyl-*N*-methylamino)propyl chloride in 25 ml. of ether was added dropwise, and the solution was stirred 20 hours at room temperature. Water (25 ml.) was added. The organic layer was separated, dried over potassium carbonate, filtered, and concentrated to give 20 g. of crude 11-(3-*N*-benzyl-*N*-methylaminopropyl)-5'*H*-imidazo[5,6-a]dibenz-[b,e]azepine. Part (17 g.) of this oil was refluxed for 20 hours with 100 ml. of benzene and 5.42 g. of ethyl chloroformate. Water was added, the organic layer was separated, dried over potassium carbonate, filtered and concentrated to yield 14.3 g. of the carbamate, part of which (9.1 g.) was hydrolyzed by refluxing for 12 hours with a solution of 12.1 g. of barium hydroxide octahydrate in 200 ml. of

ethylene glycol. The mixture was poured into water, filtered, the filter residue and filtrate were extracted with benzene, the benzene extracts were dried over potassium carbonate, filtered, concentrated and distilled to yield 2.5 g. (31%) of product, b.p. 155° (0.05 mm.), λ infl. 231 (ε, 13,340), 288-289 mμ (ε, 6,060), λ max 260 mμ (ε, 9,700).

Anal. Calcd. for $C_{20}H_{23}N_2$: C, 78.65; H, 7.59; N, 13.76. Found: C, 78.35; H, 7.68; N, 13.72.

REFERENCES

(1) Part II, Alexander E. Drukker and Claude I. Judd, *J. Heterocyclic Chem.*, 2, 283 (1965).

(2) Alexander E. Drukker and Claude I. Judd, *ibid.*, 2, 276 (1965).

(3) W. F. Short, C. I. Broderick, and M. L. Donaldson, British Patent 696,473 (1953); 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); F. Hunzicker, F. Künzle, O. Schindler and J. Schmutz, *Helv. Chim. Acta*, 47, 1163 (1964).

(4) G. Stille, H. Lauener, E. Eichenberger, F. Hunzicker, and J. Schmutz, *Arzneimittel-Forsch.*, 15, 841 (1965); Belgian Patent 649,284 (1964); British Patent 1,006,156 (1965).

(5) L. H. Werner, S. Ricca, E. Mohacsi, A. Rossi, and V. P. Arya, *J. Med. Chem.*, 8, 74 (1965).

(6) M. Busch and M. Fleischmann, *Ber.*, 43, 2553 (1910).

(7) A. Marxer, *Helv. Chim. Acta*, 24, 217 (1941).

(8) O. G. Backeberg and J. L. C. Marais, *J. Chem. Soc.*, 181 (1942).

(9) L. J. Bellamy, "The Infrared Spectra of Complex Molecules", 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1962, p. 216.

Received March 10, 1966 Milwaukee, Wisconsin 53201