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Synthesis of Certain Tricyclic Quinoline Derivatives as Potential Antiamebal Agents (I)

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Synthesis of the fused tricyclic systems, 1,2,3,3a,4,5-hexahydropyrrolo[1,2a]quinoline (I) and 2,3,4,4a,5,6-hexahydro 1*H*-benzo[*c*]quinolizine (II), each bearing an ethoxyl substituent on the benzene ring, has been achieved. The compounds combine certain structural features of the alkaloid emetine and of 8-quinolinols.

As a part of a continuing study of fused tricyclic systems based on the quinoline nucleus and possessing certain structural features present in emetine and in 8-quinolinols, 9-ethoxy-1,2,3,3a,4,5-hexahydropyrrolo[1,2a]quinoline (I) and 10-ethoxy-2,3,4,4a,5,6-hexahydro 1*H*-benzo[*c*]quinolizine (II) were required. The starting material for both I and II, 8-ethoxyquinaldine (III), was reported by Vaidya and Cannon (2) to have a melting point of 52-53°. However, the material obtained in the present study by the method of Vaidya and Cannon, upon recrystallization from ether, showed a melting point of 76-78°. Preparation of I was attempted utilizing a method applied by Prelog and Metzler (3) in the pyridine system. Reduction of IV to V was attempted using tin and hydrochloric acid (4); sodium and ethanol (5); and hydrogen in the presence of platinum oxide (6). Best results were obtained using the catalytic method of reduction. Compound V was extremely unstable in air, turning black within a short time. It could be stored for some weeks in light-proof, air tight containers. When V was treated with hydrobromic acid according to the procedure of Prelog and Metzler (3), VI was not obtained; rather, V was dehydrated and the ether cleaved to a product which on the basis of spectral and elemental analytical data is concluded to be 8-hydroxy-2-allyl-1,2,3,4-tetrahydroquinoline hydrobromide (VII). Löffler and Flügel (7) isolated an analogous dehydration product in the piperidine series as a side product in the treatment of 2-(3-hydroxypropyl)-piperidine with concentrated sulfuric acid. Successful cyclodehydration of V to I was attained by use of a mixture of concentrated sulfuric and glacial acetic acids (7) or of phosphorus pentoxide in dry xylene. The latter reagent provided a more satisfactory reaction.

Attempts were made to prepare II by a method analogous to that leading to I. When the lithium derivative of 8-ethoxyquinaldine (III) was treated with trimethylene oxide, the starting heterocycle was recovered unchanged. The lithium derivative of III

was treated with 1-bromo-3-chloropropane to form 10-ethoxy-1,2,3,4-tetrahydrobenzo[*c*]quinolizinium bromide (VIII) in one step. VIII was reduced catalytically to II.

EXPERIMENTAL (8)

8-Ethoxy-2-(3-hydroxypropyl)quinoline (IV).

8-Ethoxyquinaldine (III) (2) (18.7 g., 0.1 mole) dissolved in a minimum amount of anhydrous ether (260 ml.) was added dropwise with stirring over 0.5 hour to a solution of *n*-butyl lithium (67 ml. of 1.65 *M*) in hexane (Foot Mineral Co.), while bubbling nitrogen through the mixture. The resulting dark red solution was cooled in an ice-salt mixture, and a solution of 11 g. (0.25 mole) of ethylene oxide in 100 ml. of anhydrous ether was added dropwise with stirring under a stream of nitrogen. Approximately half of the ether was removed on a steam bath; 75 ml. of benzene was added to the residue and the remainder of the ether was removed. The resulting mixture was refluxed 2 hours, then it was cooled, treated with ice, and was extracted repeatedly with ether. The combined ethereal extracts were reduced in volume on a steam bath, washed with water, and were dried over anhydrous sodium sulfate. The ether was removed, and the dark syrupy residue was distilled at 140-160° (0.5 mm.); a heavy orange syrup resulted, which on cooling and agitating deposited white solid material. This solid material was collected on a filter, washed with ether, and recrystallized from 2-propanol. The resulting white acicular crystals showed m.p. 92-93°. Yield, 10.9 g. (47%). An infrared spectrum (Nujol) showed peaks at 2.95 μ (OH); 9.5 μ (C-O stretching of an alcohol); and at 8.0 and 9.7 μ (C-O-C stretching of an ether).

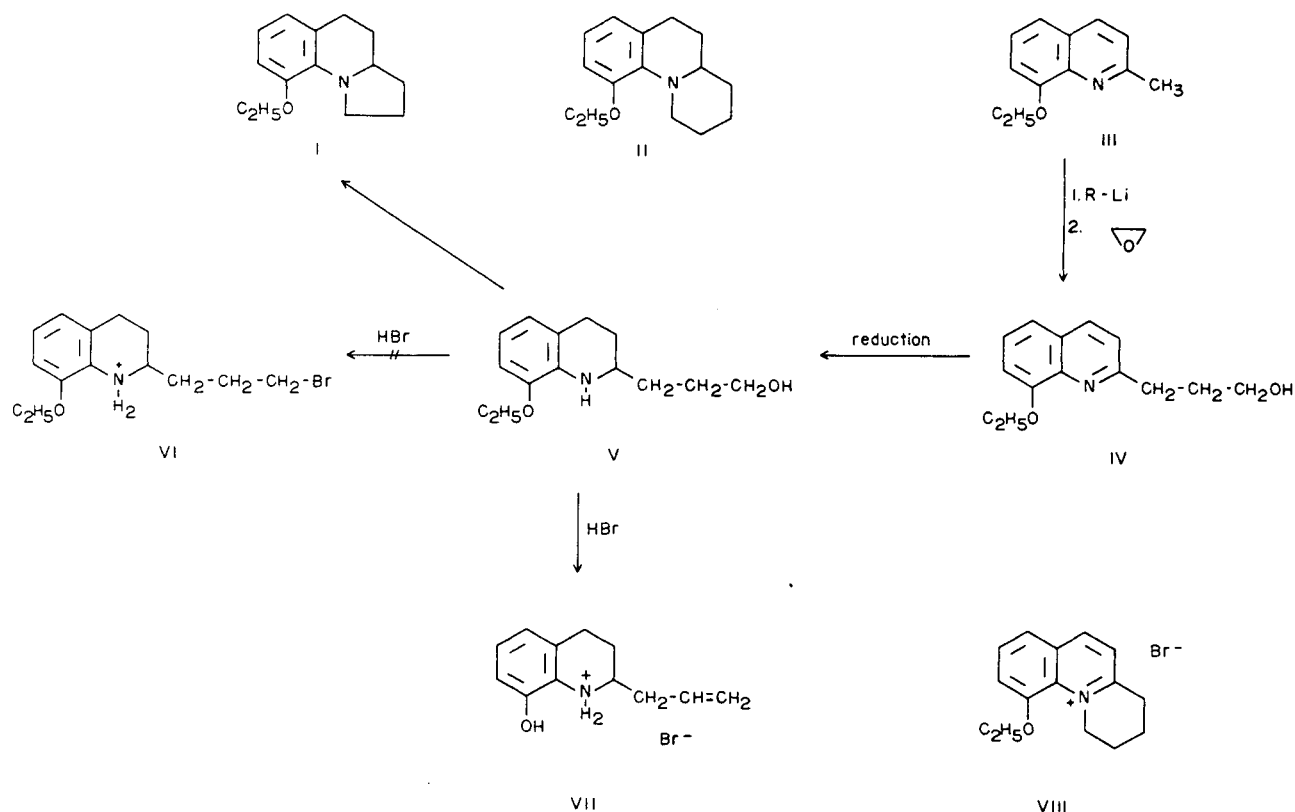
Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.75; H, 7.41; N, 6.06. Found: C, 72.24; H, 7.14; N, 5.97.

A picrate salt crystallized from ethanol as yellow needles, m.p. 135.5-136.5°.

Anal. Calcd. for $C_{20}H_{20}N_4O_6$: C, 52.18; H, 4.38; N, 12.17. Found: C, 52.19; H, 4.79; N, 11.98.

8-Ethoxy-2-(3-hydroxypropyl)-1,2,3,4-tetrahydroquinoline (V).

Compound IV (11.5 g., 0.05 mole) in 200 ml. of anhydrous, acetone-free methanol was reduced in a Parr model 3910 hydrogenation apparatus in the presence of 0.2 g. of platinum oxide, at room temperature and a maximum pressure of 40 p.s.i.g. Approximately 4 hours was required for the calculated amount of hydrogen to be absorbed. The catalyst was removed on a filter and the filtrate was concentrated on a steam bath under a stream of nitrogen. The residue of thick, yellowish liquid was distilled, yielding 11.35 g. (96%)



of a viscous white liquid, b.p. 180° (0.5 mm.); n_D^{24} 1.5546, d_4^{25} 1.247. An infrared spectrum (carbon tetrachloride) showed a peak at 2.95μ (N-H stretching broadened by associated O-H stretching). A picrate salt of V recrystallized from ethanol, m.p. $167-168.5^{\circ}$.

Anal. Calcd. for $C_{20}H_{24}N_4O_3$: C, 51.70; H, 5.22; N, 12.07. Found: C, 52.07; H, 5.13; N, 11.89.

8-Hydroxy-2-allyl-1,2,3,4-tetrahydroquinoline Hydrobromide (VII).

Compound V (2.0 g., 0.0085 mole) was neutralized with dilute hydrobromic acid and the resulting mixture was evaporated to dryness. The crude hydrobromide salt was sealed in an ampul containing 15 ml. of 68% hydrobromic acid and the ampul was maintained at 120° for 5 hours. The contents of the ampul were transferred to a flask from which the volatile components were removed under reduced pressure. The dark brown, viscous residue was mixed with 5 ml. of acetone and was kept in a refrigerator overnight. A brown solid separated which was collected on a filter and was recrystallized from acetone, m.p. $272-277^{\circ}$. Subsequent crystallization from absolute ethanol gave m.p. $283-286^{\circ}$ (decomp.). Yield, 0.50 g. (22%). The infrared spectrum (potassium bromide) showed peaks at 2.90μ (free phenolic OH); 3.20μ (phenolic O-H stretching); 3.85μ (secondary amine salt); 6.10μ (C=C stretching); 7.35 and 7.53μ (O-H deformation); and 11.0μ (CH_2 wagging for terminal vinyl group). The material gave a deep red-orange color with ferric chloride test solution.

Anal. Calcd. for $C_{12}H_{16}BrNO$: C, 53.36; H, 5.97; Br, 29.56; N, 5.16. Found: C, 53.49; H, 6.26; Br, 28.79; N, 4.97.

9-Ethoxy-1,2,3,4,5-hexahydropyrrolo[1,2a]quinoline (I).

Method A.

Compound V (10.0 g., 0.0425 mole) was refluxed for 3.5 hours with a mixture of 6 ml. of glacial acetic acid and 13 ml. of concentrated sulfuric acid. The resulting solution was permitted to cool, was made alkaline with sodium hydroxide, diluted to 100 ml. with water, and was extracted repeatedly with ether. The ether was removed from the combined extracts on a steam bath and the remaining dark, semisolid material was distilled, b.p. 120° (0.75 mm.). Yield, 7.20 g. (78%) of a yellowish liquid. The infrared spectrum was identical with that of the product of Method B.

Method B.

A mixture of 10.0 g. (0.0425 mole) of V, 20.0 g. of phosphorus pentoxide, and 140 ml. of sodium-dried xylene was raised to 135° over 3 hours, and the mixture was refluxed for 20 hours. After cooling, the xylene layer was decanted and the solvent was removed under reduced pressure. The residue and the residue from the reaction flask were made strongly alkaline with concentrated sodium hydroxide solution and were extracted repeatedly with ether. The combined ether extracts were concentrated on a steam bath, and the remaining dark blue liquid was distilled, yielding 7.85 g. (85%) of a lemon-yellow, mobile liquid, b.p. 130° (0.55 mm.); n_D^{22} 1.5655, d_4^{22} 1.093. The infrared spectrum (carbon tetrachloride) showed no absorption between 2.5 and 3.2μ (N-H, O-H). The nmr spectrum (neat) demonstrated a triplet centered at 1.22δ (3 protons); a multiplet centered at 1.69δ (6 protons); a multiplet centered at 2.59δ (2 protons); a multiplet centered at 3.17δ (2 protons); a quartet centered at 3.72δ (2 protons); a very broad multiplet lying between 3.5 and 4.0δ (1 proton); and a singlet centered at 6.50δ (3 protons). A picrate salt of I recrystallized from ethanol, m.p. $180-182^{\circ}$.

Anal. Calcd. for $C_{20}H_{22}N_4O_3$: C, 53.81; H, 4.93; N, 12.55. Found: C, 53.87; H, 4.71; N, 12.54.

A hydrobromide salt of I recrystallized from acetone, m.p. $182-183^{\circ}$.

Anal. Calcd. for $C_{14}H_{20}BrNO$: C, 56.36; H, 6.76; Br, 26.77; N, 4.70. Found: C, 56.73; H, 6.72; Br, 24.98; N, 4.62.

A picrolonate (3) salt of I recrystallized from ethanol, m.p. $165-166^{\circ}$.

Anal. Calcd. for $C_{24}H_{27}N_5O_3$: C, 59.85; H, 5.65; N, 14.54. Found: C, 59.42; H, 5.73; N, 14.52.

10-Ethoxy-1,2,3,4-tetrahydrobenzo[c]quinolizinium Bromide (VIII).

To an efficiently stirred and cooled solution of 18.7 g. (0.1 mole) of 8-ethoxyquinolizidine (III) (2) in 250 ml. of anhydrous ether was added 0.1 mole of *n*-butyl lithium in hexane. Stirring was continued for 0.5 hours, then 15.8 g. (0.1 mole) of freshly distilled 1-bromo-3-chloropropane (Aldrich Chemical Co.) in 100 ml. of anhydrous ether was added in a slow stream. Sodium-dried benzene (200 ml.) was added, and the mixture was refluxed 8 hours. The solvents were removed under reduced pressure; 50 ml. of water was added to the residue and the resulting mixture was extracted repeatedly with ether. The combined ether extracts were evaporated under reduced pressure; the resulting black oil was taken up in 50 ml. of benzene and this solution was heated in a pressure bottle at 79° for 100 hours. The

contents of the bottle, on cooling, deposited a black solid which was collected on a filter and was recrystallized several times from 2-propanol (charcoal). Yield, 4.33 g. (14%) of white crystals, m.p. 211-212° (decomp.). A nmr spectrum (deuterium oxide) demonstrated a triplet centered at 1.00 δ (3 protons); a multiplet centered at 1.48 δ (4 protons); a multiplet centered at 2.92 δ (2 protons); a quartet centered at 3.66 δ (2 protons); a multiplet centered at 4.47 δ (2 protons); a multiplet centered at 7.00 δ (3 protons); a doublet centered at 7.15 δ (1 proton); and a doublet centered at 7.95 δ (1 proton).

Anal. Calcd. for $C_{15}H_{18}BrNO$: C, 58.46; H, 5.88; Br, 25.93; N, 4.55. Found: C, 58.67; H, 5.86; Br, 25.64; N, 4.67.

10-Ethoxy-2,3,4,4a,5,6-hexahydro-1H-benzo[c]quinolizine Hydrobromide (II).

A modification of the method of Bradsher and Desai (9) was employed. VIII (1.30 g., 0.0042 mole) in 100 ml. of anhydrous methanol was hydrogenated in the presence of 0.1 g. of platinum oxide at an initial pressure of 40 p. s. i. g. When absorption of hydrogen ceased (approximately 2 hours), the solution was filtered and the filtrate was concentrated under reduced pressure. The viscous brown residue was taken up in a minimum amount of methanol and crystallization was induced by dropwise addition of ether. The resulting crystalline material was recrystallized repeatedly from 2-propanol (charcoal) to yield 0.884 g. (67%) of a white, microcrystalline solid, m.p. 214-215°. An infrared spectrum (potassium bromide) showed a broad peak at 4.05 μ ($N-H^+$ stretching). A nmr spectrum (deuterium oxide) demonstrated a triplet centered at 0.93 δ (3 protons); a broad multiplet centered at 1.50 δ (8 protons); a multiplet centered at 2.45 δ (2 protons); a multiplet centered at 3.10 δ (2 protons); a quartet centered at 3.70 δ (2 protons); a broad multiplet lying between 3.5

and 4.0 δ (1 proton); and a multiplet centered at 6.62 δ (3 protons).

Anal. Calcd. for $C_{15}H_{22}BrNO$: C, 57.69; H, 7.10; N, 4.49. Found: C, 57.88; H, 7.20; N, 4.27.

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