Synthesis of Some New Mesoionic Heterocycles

(Miss) Vineeta Taneja, (Mrs.) Madhu Anand, (Miss) C. L. Gupta,
(Mrs.) S. B. Gupta and R. L. Mital*

Department of Chemistry, University of Rajasthan,
Jaipur-302004, India

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The synthesis of various substituted 1-hydroxy-2-chloroacetyl-6-thia-10b-aza-2a-azoniaaceanthrylene hydroxide inner salt, 1-hydroxy-6-thia-10b-aza-2a-azoniaaceanthrylene hydroxide inner salt, 1-hydroxy-2-piperidinoacetyl-6-thia-10b-aza-2a-azoniaaceanthrylene hydroxide inner salt is described. The ir is also included.

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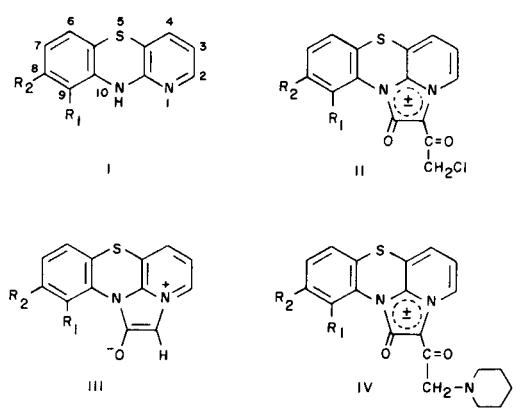
Azaphenothiazines are used as antipsychotic [1], antitumor [1,2], enthelmintic [3-5], CNS-depressant [3,5], antibacterial [3,5], antihistaminic [6], and sedative [7] agents. In the present investigation we synthesized some new heterocyclic compounds from 8/9-substituted-azaphenothiazines which contain a mesoionic ring.

The synthesis of 10-chloroacetyl-1-azaphenothiazine was the initial key step in making one of the several series of phenothiazine compounds [8] of potential therapeutic value. It is well known that phenothiazine can be chloroacetylated under a variety of conditions to yield 10-chloroacetylphenothiazine [9]. However, treatment of 1-azaphenothiazine [10] in such standard reactions did not produce the desired 10-chloroacetyl-1-azaphenothiazine, nor indeed any identifiable product. The preparation of 1-hydroxy-2-chloroacetyl-6-thia-9-bromo-10-chloromethyl-10b-aza-2a-azoniaaceanthrylene hydroxide inner salt (II) was initiated by condensation of 10*H*-9-bromo-10-chloromethyl-1-azaphenothiazine (I) by chloroacetic anhydride and chloroacetic acid in dry dioxane. The product II on treatment with piperidine and *N,N*-dimethylformamide gives III.

The structure of all these compounds were confirmed by their analytical and spectral data. The ir spectra of the compounds shows some characteristic peaks indicating the presence of a particular group.



where I, II, III, IV, a, R_1 = Cl, R_2 = H
b R_1 = CH_3, R_2 = H
c R_1 = H, R_2 = Br

EXPERIMENTAL

Melting points were determined in sealed evacuated capillary tubes and are uncorrected. Infrared spectral measurements were carried out on Perkin Elmer 577 grating infrared spectrometer using potassium bromide disks.

Chloroacetylation of 10*H*-9-Chloro-1-azaphenothiazine.

A stirred mixture of 10*H*-9-chloro-1-azaphenothiazine (58.50 g, 0.25 mole), chloroacetic anhydride (54.0 g, 0.32 mole), chloroacetic acid (75.0 g, 0.79 mole) in 250 ml of dry dioxane was refluxed for an hour. The hot mixture was poured into 11 ml of hot water and the precipitate was collected and washed with warm 95% ethanol until the washings were colourless. The product 1-hydroxy-2-chloroacetyl-6-thia-10-chloro-10b-aza-2a-azoniaaceanthrylene hydroxide inner salt (IIa) was obtained as a fluffy, yellow green solid, mp 300°; ir (potassium bromide): γ 1640 (C=O), 1340 (CN), 740 cm^{-1} (C-Cl).

Anal. Calcd. for $C_{15}H_8Cl_2N_2O_2S$: C, 51.28; H, 2.28. Found: C, 51.10; H, 2.35.

In a similar manner 1-hydroxy-2-chloroacetyl-6-thia-10-methyl-10b-aza-2a-azoniaaceanthrylene hydroxide inner salt (IIb) mp 288°; ir (potassium bromide): γ 1660 (C=O), 1442, 1380 (CH asymmetric and symmetric deformation vibrations of CH_3 group), 1370 cm^{-1} (CN).

Anal. Calcd. for IIb $C_{16}H_{11}ClN_2O_2S$: C, 58.00; H, 3.32. Found: C, 57.89; H, 3.15.

1-Hydroxy-2-chloroacetyl-6-thia-9-bromo-10b-aza-2a-azoniaaceanthryene hydroxide inner salt (IIc) mp > 300° was prepared similarly: ir (potassium bromide): γ 1665 (C=O), 1330 (CN), 540 cm^{-1} (C-Br).

Anal. Calcd. for IIc $C_{15}H_8BrClN_2O_2S$: C, 45.45; H, 2.02. Found: C, 45.40; H, 2.12.

The chloroacetylation of 10*H*-9-chloro-1-azaphenothiazine was attempted under basic conditions in a number of modifications. The best yield (40%) was obtained when a stirred mixture of 10*H*-9-chloro-1-azaphenothiazine (1 mole), chloroacetylchloride (2 moles), and excess potassium carbonate was refluxed for 3 hours in dioxane. The yield was unpredictable and the product was impure. After many recrystallisations from glacial acetic acid, the same fluffy yellow green solid, mp IIa 300°. In a similar way IIb mp 288° and IIc mp > 300° were prepared.

Hydrolysis of the Chloroacetylation Product.

1-Hydroxy-2-chloroacetyl-6-thia-10-chloro-10b-aza-2a-azonia aceanthrylene hydroxide inner salt (IIa) was added to a mixture of concentrated hydrochloric acid (5 ml) and glacial acetic acid (15 ml) and refluxed for 15 minutes. The reaction mixture was made basic with sodium hydroxide solution and the resultant precipitate was collected. Recrystallisation from 95% ethanol yielded 1-hydroxy-6-thia-10-chloro-10b-aza-2a-azoniaaceanthrylene hydroxide inner salt (IIIa) as a buff coloured solid, mp 229°. The average yield was approximately 50%.

In a similar manner 1-hydroxy-6-thia-10-methyl-10b-aza-2a-azoniaaceanthrylene hydroxide inner salt (IIIb) mp 215° and 1-hydroxy-6-thia-9-bromo-10b-aza-2a-azoniaaceanthrylene hydroxide inner salt (IIIc) mp 265° were prepared.

Anal. Calcd. for IIIa $C_{13}H_7ClN_2OS$: C, 56.78; H, 2.55. Found: C, 56.61; H, 2.40.

Anal. Calcd. for IIIb $C_{14}H_{10}N_2OS$: C, 66.14 H, 3.98. Found: C, 66.10; H, 4.00.

Anal. Calcd. for IIIc $C_{13}H_7BrClN_2OS$: C, 43.94; H, 1.97. Found: C, 43.80; H, 1.89.

Reaction of the Chloroacetylation Product with Piperidine.

A stirred mixture of 1-hydroxy-2-chloroacetyl-6-thia-10-chloro-10b-aza-2a-azoniaaceanthrylene hydroxide inner salt (IIa) (0.07 mole), piperidine (18.8 g, 0.22 mole) and *N,N*-dimethylformamide (200 ml) was heated on a boiling water bath for an hour. After cooling overnight in a refrigerator, the resultant precipitate was collected and washed with water. The filtrate and washings were poured into 11 ml of water previously made alkaline (sodium carbonate) and the mixture filtered. The total solid collected was combined and recrystallised (propanol) to yield fine yellow needle crystals (18.0 g) mp 200°. This was shown to be 1-hydroxy-2-piperidinoacetyl-6-thia-10-chloro-10b-aza-2a-azoniaacenthrylene hydroxide inner salt (IVa).

In the similar manner 1-hydroxy-2-piperidineacetyl-6-thia-10-methyl-10b-aza-2a-azoniaaceanthrylene hydroxide inner salt (IVb) mp 198° and 1-hydroxy-2-piperidinoacetyl-6-thia-9-bromo-10b-aza-2a-azon iaaceanthrylene hydroxide inner salt (IVc) mp 253° were prepared.

Anal. Calcd. for IVa $C_{20}H_{18}ClN_3O_2S$: C, 60.00; H, 4.50. Found: C, 60.18; H, 4.41.

Anal. Calcd. for IVb $C_{21}H_{21}N_3O_2S$: C, 66.49; H, 5.54. Found: C, 66.39; H, 5.44.

Anal. Calcd. for IVc $C_{20}H_{18}BrN_3O_2S$: C, 54.05; H, 4.05. Found: C, 54.00; H, 4.00.

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