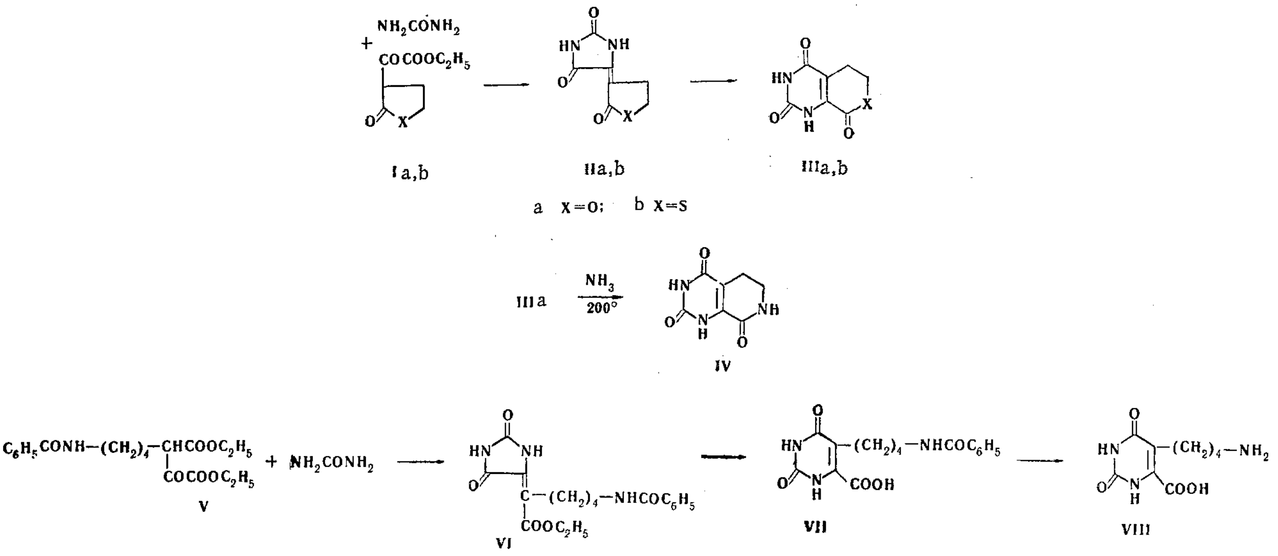
SYNTHESIS OF ω-SUBSTITUTED 5-ALKYLOROTIC ACIDS

A. Ya. Berlin and I. A. Korbukh

UDC 547.854.9.07

The lactone of 5-β-hydroxyethylorotic acid, the thiolactone of 5-(δ-mercaptoethyl)orotic acid, and 5-(δ-benzamidobutyl)orotic acid were synthesized from substituted 5-carbethoxymethylenehydantoins obtained by the condensation of urea with α-ethoxalyl derivatives of γ-butyrolactone, γ-thiobutyrolactone, and ethyl ε-benzamidocaproate. The lactam of 5-(β-aminoethyl)orotic acid was synthesized by the ammonolysis of the lactone of 5-(β-hydroxyethyl)orotic acid. The acid hydrolysis of 5-(δ-benzamidobutyl)orotic acid gave 5-(δ-aminobutyl)orotic acid.

Continuing our investigation of the synthesis of analogs of the bases of nucleic acids [1], we have obtained 5-alkylorotic acid derivatives containing hydroxy, mercapto, and amino groups in the ω-position of the alkyl radical.



α-(Hydantoin-5-ylidene)-γ-butyrolactone (IIa) was synthesized from α-ethoxalyl-γ-butyrolactone (Ia) [2] by condensation with urea. Its thio analog (IIb) was similarly obtained from α-ethoxalyl-γ-thiobutyrolactone (Ib) [3]. The structures of the substituted hydantoins were confirmed by the IR spectra, which have a characteristic maximum at 1780-1800 cm^{-1} (ν_{CO}). By refluxing with aqueous alkali, hydantoins II were converted, respectively, to the lactone of 5-(β-hydroxyethyl)orotic acid (IIIa) and the thiolactone of 5-(β-mercaptoethyl)orotic acid (IIIb). There is a characteristic maximum in the carbonyl absorption region at 1730-1740 cm^{-1} in the IR spectra of the orotic acid derivatives. The lactam of 5-(β-aminoethyl)orotic acid (IV) was obtained by bubbling ammonia gas at 200° into a solution of lactone IIIa in ethylene glycol. The starting compound for the synthesis of 4-(δ-aminobutyl)orotic acid (VIII) was ethyl α-ethoxalyl-ε-benzamidocaproate (V) [4], the condensation of which with urea gave 5-(1-carbethoxy-5-

---

Institute of Experimental and Clinical Oncology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1280-1282, September, 1971. Original article submitted September 30, 1970.

benzamidopentylidene)hydantoin (VI), which was further converted to 5-(δ-benzamidobutyl)orotic acid (VII) by refluxing with aqueous alkali. The benzoyl group in the latter was removed by hydrolysis with concentrated hydrochloric acid.

EXPERIMENTAL

α-(Hydantoin-5-ylidene)-γ-butyrolactone (IIa). A stream of dry hydrogen chloride was bubbled in the course of 1 h at 100° into a solution of 18.6 g (0.1 mole) of Ia and 6 g (0.1 mole) of urea in 7 ml of glacial acetic acid. A crystalline precipitate began to form immediately, and the pasty reaction mixture was transferred to a porcelain dish and allowed to stand for several days. It was then treated with water, and the crystalline precipitate was removed by filtration and recrystallized from water to give 10 g (55%) of IIa with mp 288-290° (dec.). Found %: C 46.4; H 3.4; N 15.6. $C_7H_6N_2O_4$. Calculated %: C 46.2; H 3.4; N 15.4.

α-(Hydantoin-5-ylidene)-γ-thiobutyrolactone (IIb). This compound [14 g (71%)] was similarly obtained from 20.2 g (0.1 mole) of Ib and 6 g (0.1 mole) of urea in 7 ml of glacial acetic acid and had mp 251-253° (dec., from alcohol). Found %: C 42.7; H 3.0; N 14.1; S 16.4. $C_7H_6N_2O_3S$. Calculated %: C 42.4; H 3.1; N 14.1; S 16.2.

Lactone of 5-(β-Hydroxyethyl)orotic Acid (IIIa). A solution of 5 g of IIa and 10 g of KOH in 100 ml of water was refluxed with stirring for 3 h. The mixture was cooled and acidified with hydrochloric acid until it gave a strongly acid reaction to Congo, and the precipitate was removed by filtration and recrystallized from alcohol to give 4 g (80%) of IIIa with mp 317-318° (dec.). Found %: C 46.0; H 3.5; N 15.5. $C_7H_6N_2O_4$. Calculated %: C 46.2; H 3.3; N 15.4.

Thiolactone of 5-(β-Mercaptoethyl)orotic Acid (IIIb). A solution of 3 g of IIb and 20 g of KOH in 150 ml of water was refluxed under nitrogen for 3 h, cooled, and acidified with hydrochloric acid until it gave a strongly acid reaction to Congo. The precipitate was removed by filtration and recrystallized from water acidified with hydrochloric acid to give 2.1 g (70%) of IIIb with mp 300-302° (dec.). Found %: C 42.5; H 3.3; N 14.2; S 16.2. $C_7H_6N_2O_3S$. Calculated %: C 42.4; H 3.1; N 14.1; S 16.2.

Lactam of 5-(β-Aminoethyl)orotic Acid (IV). A strong current of ammonia gas was bubbled at 200° in the course of 6 h into a solution of 4 g of IIIa in 40 ml of ethylene glycol. The mixture was cooled, diluted with water, and acidified with dilute hydrochloric acid. The precipitate was removed by filtration and recrystallized from water to give 1.5 g (37%) of IV, which decomposed above 350°. Found %: C 46.5; H 4.0; N 23.2. $C_7H_7N_3O_3$. Calculated %: C 46.4; H 3.9; N 23.2.

5-(1-Carbethoxy-5-benzamidopentylidene)hydantoin (VI). A stream of dry hydrogen chloride was passed at 100° for 1 h into a mixture of 18 g (about 0.05 mole) of impure V, 3 g (0.05 mole) of urea, and 3.5 ml of glacial acetic acid. The viscous mass was allowed to stand for several days. It was then treated with water, and the crystalline precipitate was removed by filtration and recrystallized from aqueous alcohol to give 3 g (17%) of a product with mp 189-190°. Found %: C 60.2; H 5.9; N 11.9. $C_{18}H_{21}N_3O_5$. Calculated %: C 60.2; H 5.9; N 11.7.

5-(δ-Benzamidobutyl)orotic Acid (VII). A solution of 2 g of VI in 20 ml of 10% aqueous potassium hydroxide was refluxed for 3 h, cooled, and acidified with dilute hydrochloric acid. The precipitate was removed by filtration and recrystallized from water to give 1 g (54%) of VII with mp 250-252° (dec.). Found %: C 58.0; H 5.4; N 12.8. $C_{16}H_{17}N_3O_5$. Calculated %: C 58.0; H 5.2; N 12.7.

5-(δ-Aminobutyl)orotic Acid (VIII). A 1 g sample of VII in 110 ml of concentrated hydrochloric acid was refluxed for 10 h, and the resulting solution was evaporated to dryness in vacuo. Water (50 ml) was added to the residue, and it was again evaporated to dryness. Recrystallization of the residue from water gave 0.6 g (88%) of VIII with mp 298-300° (dec.). Found %: C 47.5; H 5.9; N 18.2. $C_9H_{13}N_3O_4$. Calculated %: C 47.6; H 5.8; N 18.5.

The microanalyses were performed under the direction of A. D. Chinaeva.

LITERATURE CITED

1. A. Ya. Berlin and I. A. Korbukh, Khim. Geterotsikl. Soedin., 397 (1971).
2. F. Korte and H. Machleidt, Ber., 90, 2150 (1957).
3. F. Korte and K.-H. Löhmer, Ber., 90, 1290 (1957).
4. D. E. Flyd and S. E. Miller, J. Org. Chem., 16, 1764 (1951).