Purine *N*-Oxides: XXXVII. Derivatives from 6-Chloropurine 3-Oxide (I)

Alfredo Giner-Sorolla

Division of Cell Biochemistry, The Sloan-Kettering Institute for Cancer Research
New York, New York 10021

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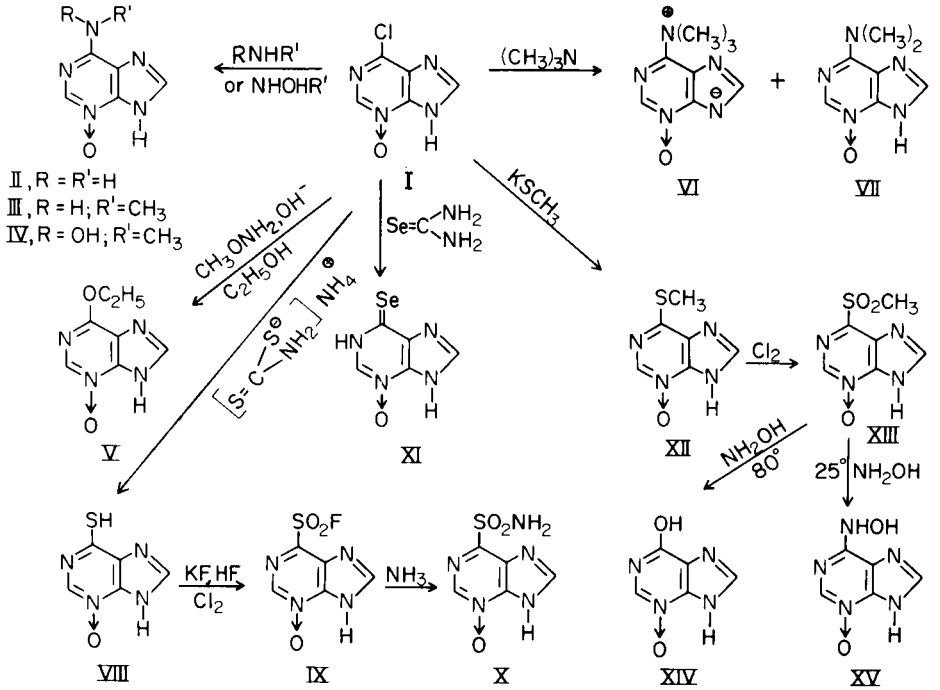
Interaction of 6-chloropurine 3-oxide with several amines led to 6-substituted purine 3-oxides. 6-Chloropurine 3-oxide and selenourea gave 6-selenopurine 3-oxide. 6-Mercaptopurine 3-oxide, prepared from the 6-chloro derivative and ammonium dithiocarbonate, was transformed with chlorine and hydrogen fluoride into 6-purinesulfonyl fluoride 3-oxide which upon ammonolysis afforded purine-6-sulfonamide 3-oxide. Methanethiol and 6-chloropurine 3-oxide yielded the known 6-methylthiopurine 3-oxide, which by treatment with chlorine was oxidized to 6-methylsulfonylpurine 3-oxide. Reaction of the latter with hydroxylamine led to an improved synthesis of 6-hydroxylaminopurine 3-oxide, which by interaction with manganese dioxide was transformed into 6-nitrosopurine 3-oxide.

Several 6-substituted purine 3-oxide derivatives have been prepared from 6-chloropurine 3-oxide (2) with the hope of improving the chemotherapeutic index of the parent compounds. Among the substituents, the 6-trimethylammonium group was chosen because 6-trimethylammonium purine chloride (3) was found to inhibit transplantable tumors in animals (3b); it has been tested clinically (4). 6-Selenopurine was found to be as active as 6-mercaptopurine against mouse leukemia (5), but was less effective in other animal tumors, presumably because of its instability (6). 6-Selenopurine 3-oxide, prepared from the 6-chloro analog, proved to be more stable in aqueous solutions than 6-selenopurine itself. Sulfonamido purines have been reported to possess antitumor activity in mice (7). Purine-6-sulfonamide 3-oxide was accordingly synthesized to study the biological effect of the *N*-oxide



SCHEME I.

function.

Synthetic Studies.

6-Chloropurine 3-oxide (I) was prepared by oxidation of 6-chloropurine in an improvement of the previously reported method (2). Reaction of I with ammonia, methylamine, methylhydroxylamine, gave the 3-oxides of adenine (II) (8), 6-methylaminopurine (III) and 6-*N*-methylhydroxylaminopurine (IV) respectively (Scheme 1). When compound I reacted with ethanolic methoxyamine, 6-ethoxypurine 3-oxide (V) was formed by alkali catalyzed substitution. Interaction of I and trimethylamine gave a mixture of purine-6-trimethylammonium betaine 3-oxide (VI) and 6-dimethylaminopurine 3-oxide (VII). The known (9) 6-mercaptopurine 3-oxide (VIII) was conveniently prepared from I and ammonium dithiocarbamate: upon treatment of VIII with potassium fluoride, hydrofluoric acid, and chlorine, by the Robins and Beaman method (7), 6-purinesulfonyl fluoride 3-oxide (IX) was obtained, which upon ammonolysis gave purine-6-sulfonamide 3-oxide (X).

Treatment of I with selenourea afforded 6-selenopurine 3-oxide (XI) which was reduced to purine with Raney nickel. Aqueous solutions of XI were more stable than those of the parent compound.

Reaction of I with methanethiol led to the previously reported (9) 6-methylmercaptopurine 3-oxide (XII). Treatment of XII with chlorine in aqueous methanol (10) gave a convenient preparation of the known 6-methylsulfonylpurine 3-oxide (XIII) (8). Refluxing of XIII with hydroxylamine resulted in the formation of hypoxanthine 3-oxide (XIV) (8). 6-Hydroxylaminopurine 3-oxide (11) (XV) was presumably formed, but a reducing hydrolysis may occur in which compound XV is transformed to XIV with simultaneous reduction of the *N*-oxide (XV) yielding 6-hydroxylaminopurine. A similar reduction by hydroxylamine was previously observed with 6-chloropurine 3-oxide (I) which gave 6-hydroxylaminopurine (11). Reaction of XIII with hydroxylamine at 25° afforded a reproducible synthesis of 6-hydroxylaminopurine 3-oxide (XV) (12). Oxidation of compound XV led to 6-nitrosopurine 3-oxide (XVI).

EXPERIMENTAL (13)

6-Chloropurine 3-Oxide (I).

6-Chloropurine (14) (I, 10.5 g., 0.145 mole) was suspended in ether (750 ml.) and *m*-chloroperbenzoic acid (85-90%) (105 g.) was added. After stirring in the dark for 3 weeks, the thick suspension was filtered and washed with ether. The crude product was extracted with ether in a Soxhlet for 3 days; from the ether solution upon evaporation, 6-chloropurine (2.0 g.) was recovered. The product remaining in the thimble was 6-chloropurine 3-oxide (2) (I), (8.2 g., 88%), m.p. 160° (explodes when inserted at 150°), of sufficient purity for synthetic use. An analytical sample was obtained by dissolving I in cold dilute aqueous ammonia, treatment with charcoal and neutralization with glacial acetic acid.

Reaction of 6-Chloropurine 3-Oxide (I) and Ammonia.

A solution of 6-chloropurine 3-oxide (I, 1.0 g., 6.2 mmoles) in concentrated aqueous ammonia (20 ml.) containing ammonium chloride (15) (0.1 g.) was heated in a glass lined, high-pressure reaction vessel at 100° for 24 hours. The reaction mixture was concentrated to 10 ml. by heating at ordinary pressure, treated with charcoal, filtered and the filtrate evaporated to dryness *in vacuo*. The residue was washed with water and ethanol to yield a crystalline product, m.p. 350° (0.60 g., 66%) which showed a single spot by paper chromatography with the same R_f values and uv spectra as adenine 3-oxide (II) (8a).

6-Methylaminopurine 3-Oxide (III).

6-Chloropurine 3-oxide (I, 1.0 g., 6.2 mmoles) was added slowly to a stirred solution of 40% methanolic methylamine (30 ml.) and kept at 25° for 3 days. The resulting solution was treated with charcoal, filtered and evaporated to dryness *in vacuo*. The residue was washed with 70% aqueous ethanol to yield 0.68 g. (70%) short needles, m.p. 240° dec. An analytical sample was obtained by repeated washing with 70% aqueous ethanol; λ max *p*H 1.0 291 nm (29.8 x 10^3); λ max *p*H 6.0, 228 (26.2 x 10^3) and 300 nm (29.2 x 10^3); λ max *p*H 10.0, 233 (17.4 x 10^3) and 297 nm (13.0 x 10^3).

Anal. Calcd. for $C_6H_7N_5O$: C, 43.63; H, 4.27; N, 42.41. Found: C, 43.53; H, 4.23; N, 42.47.

6-*N*-Methylhydroxylaminopurine 3-Oxide (IV).

A solution of 6-chloropurine 3-oxide (I, 0.51 g., 3 mmoles) in 95% aqueous ethanol (10 ml.) containing methylhydroxylamine (from methylhydroxylamine hydrochloride (1.67 g., 20 mmoles) and potassium hydroxide (1.4 g.) in ethanol, *p*H adjusted to *ca.* 9) was treated with charcoal, filtered and the solution kept at 25° for 18 hours. The resulting precipitate was filtered, repeatedly washed with 70% ethanol and dried to yield 0.45 g. (83%) of short colorless needles, m.p. 195° (exploded when inserted at 190°); λ max *p*H 0.0, 295 nm (17.8 x 10^3); λ max *p*H 3.0, 230 (10.0 x 10^3) and 300 nm (15.8 x 10^3); λ max *p*H 6.0, 233 (13.9 x 10^3) and 310 nm (16.2 x 10^3); λ max *p*H 10.0, 234 (10.5 x 10^3) and 335 nm (13.3 x 10^3).

Anal. Calcd. for $C_6H_7N_5O_2$: C, 39.78; H, 3.89; N, 38.66. Found: C, 39.77; H, 3.87; N, 38.73.

Compound IV was extremely photosensitive; it rapidly turned blue-green when exposed to light. Treatment of IV with a suspension of Raney nickel in boiling water gave a solution with uv spectra and R_f values identical to those of 6-*N*-methylhydroxylaminopurine (15).

Reaction of 6-Chloropurine 3-Oxide (I) and Trimethylamine.

A solution of 6-chloropurine 3-oxide (I, 3.5 g., 0.02 mole) in 25% methanolic trimethylamine (100 ml.) was stirred for 18 hours at 25°. The resulting precipitate was collected, washed with ethanol and dried to yield 2.45 g. (61%) of a pale cream crystalline product m.p. 195° dec. Repeated recrystallization of a sample from 90% aqueous ethanol gave rhomboidal plates of purine 6-trimethylammonium betaine 3-oxide (VI) m.p. 202° dec.; λ max *p*H 0, 224 (19.6 x 10^3) and 295 nm (10.3 x 10^3); *p*H 4.0, λ max 224 (27.2 x 10^3) and 303 nm (7.8 x 10^3); at *p*H 10.0, λ max 230 (27.8 x 10^3) and 310 nm (8.5 x 10^3).

Anal. Calcd. for $C_8H_{12}N_5O$: C, 49.47; H, 6.23; N, 36.06.

Found: C, 49.77; H, 5.74; N, 36.34.

From the filtrate of the preparation of VI described above, upon evaporation *in vacuo* at 25°, a solid was obtained. The residue was suspended in a little ethanol and filtered to yield 6-dimethylaminopurine 3-oxide (VII), 0.43 g. (12%) of colorless long needles, m.p. 276° dec. Recrystallization from 90% aqueous ethanol gave colorless threads or thin needles, m.p. 276° dec.; λ max *p*H 0, 216 (21.8 x 10^3) and 294 nm (35.9 x 10^3); λ max *p*H 6.0, 230 (12.1 x 10^3) and 305 nm (16.6 x 10^3); *p*H 10.0, 234 (15.7 x 10^3) and 302 nm (16.0 x 10^3).

Anal. Calcd. for $C_7H_9N_5O$: C, 46.92; H, 5.06; N, 39.09. Found: C, 46.62; H, 4.93; N, 38.82.

Compounds VI and VII (10 mg. each) were suspended in water (5 ml.) and Raney nickel (50 mg.) was added. After boiling for 30 minutes the suspensions were filtered, the nickel washed with boiling water and the respective combined filtrates evaporated to dryness *in vacuo*. The residue showed uv spectra and R_f values identical to those of a sample of purine-6-trimethylammonium betaine (3b) and 6-dimethylaminopurine (16) respectively.

Reaction of 6-Chloropurine 3-Oxide (I) with Methoxyamine.

A solution of methoxyamine (prepared from methoxyamine hydrochloride (8.35 g., 0.1 mole) in 90% aqueous ethanol (75 ml.) and sufficient amount of 10% ethanolic potassium hydroxide to bring the *p*H of the solution to 9) was added to a suspension of 6-chloropurine 3-oxide (I, 1.7 g., 10 mmoles) in ethanol (25 ml.) and the mixture was refluxed for 3 hours. The solution was neutralized with glacial acetic acid and evaporated to dryness under reduced pressure. The residue was suspended in cold water to yield 1.05 g. (58%) of a crystalline product, m.p. 240° (efferv.). An analytical sample was prepared by solution of the crude material in 0.1 *N* potassium hydroxide, treatment with charcoal and neutralization with glacial acetic acid to yield colorless rhombi, m.p. 250° (efferv.) of 6-ethoxypurine 3-oxide (V); λ max *p*H 0.0, 264 nm (13.9 x 10^3); λ max *p*H 5.0, 225 (24.7 x 10^3), and 282 (10.9 x 10^3); λ max *p*H 12.0, 276 nm (9.1 x 10^3).

Anal. Calcd. for $C_7H_8N_4O_2$: C, 46.66; H, 4.48; N, 31.10. Found: C, 46.62; H, 4.47; N, 31.01.

This product was identical to 6-ethoxypurine 3-oxide prepared by refluxing compound I (0.17 g., 1 mmole) and 5% ethanolic solution of sodium ethoxide (10 ml.) for 3 hours, evaporating to dryness, adding of water (5 ml.), and neutralizing the solution with glacial acetic acid.

6-Mercaptopurine 3-Oxide (VIII) from 6-Chloropurine 3-Oxide (I).

Ammonium dithiocarbonate (12 g., 0.11 mole) was added to a suspension of 6-chloropurine 3-oxide (I, 8.2 g., 0.048 mole) in ethanol (200 ml.) and heated with stirring at 60° for 2 hours. The mixture was cooled, filtered, the yellow precipitate washed with ethanol and dried to yield 5.9 g. (73%) of 6-mercaptopurine 3-oxide (VIII) (9) light yellow needles, m.p. 230° dec.

6-Selenopurine 3-Oxide (XI).

A solution of selenourea (0.26 g., 2.2 mmoles) in ethanol (20 ml.) was added to a suspension of 6-chloropurine 3-oxide (I, 0.34 g., 2 mmoles) in ethanol (20 ml.) and the mixture refluxed for two hours with stirring. The resulting precipitate was filtered when hot, washed with boiling ethanol and the combined filtrates evaporated to dryness under reduced pressure. The residue was suspended in water (10 ml.), the *p*H adjusted to 7 with solid sodium bicarbonate and the suspension collected by filtration. The precipitate was dissolved in 2% sodium carbonate solution at 60°, treated with charcoal, filtered, and the filtrate acidified with glacial acetic acid. The resulting precipitate was washed with water and dried *in vacuo* to yield short orange prisms (0.33 g., 77%) m.p. 298° (efferv. when inserted at 290°); λ max *p*H 3 228 (9.5 x 10^3), 347 (16.2 x 10^3); *p*H 7 λ max 233 (10.1 x 10^3), 343 (13.3 x 10^3); *p*H 12 λ max 215 and 287 nm (unstable).

Anal. Calcd. for $C_5H_4N_4OSe \cdot \frac{1}{4}H_2O$: C, 27.35; H, 2.07; N, 25.52; Se, 35.96. Found: C, 27.35; H, 2.93; N, 25.77; Se, 36.40.

When 6-selenopurine 3-oxide (XI, 10 mg.) was boiled in water (3 ml.) and Raney nickel (50 mg.) for 15 minutes, a solution was obtained with uv spectra and R_f values identical to those of purine.

Aqueous solutions of XI (1.95 mg.) in water (250 ml.) at *p*H 5.5 were kept at 37°. After 6 hours no appreciable change in O.D. was observed at λ max 228 and 348 nm.

Purine-6-sulfonyl Fluoride 3-Oxide (IX).

6-Mercaptopurine 3-oxide (VIII, 0.90 g., 5.3 mmoles) was suspended in a solution containing methanol (5 ml.), 48% aqueous hydrofluoric acid (8 ml.) and potassium fluoride dihydrate (8 g.). The mixture was cooled at -5° and chlorine gas was rapidly bubbled in at -5° to 0° for 30 minutes, after which the uv spectrum of a sample neutralized with sodium bicarbonate showed complete transformation. The resulting suspension was collected, washed with a little ice water, and suspended in a cold 10% sodium acetate solution (10 ml.). The suspension was filtered and washed with cold water, carefully pressed dry, and kept *in vacuo* over phosphorus pentoxide overnight; yield, 0.64 g. (55%) of a yellow crystalline product, m.p. 160° (dec. when inserted at 150°). A sample of this material was repeatedly recrystallized from ethanol to yield thin pale yellow prisms, m.p. 160° dec.; λ max (water, *p*H 5.5) 234, 301, 330 nm (unstable).

Anal. Calcd. for $C_5H_3N_4FSO_3$: C, 27.53; H, 1.39; N, 25.68; F, 8.71; S, 14.70. Found: C, 27.46; H, 1.43; N, 25.80; F, 8.60; S, 14.58.

A sample of purine-6-sulfonyl fluoride 3-oxide (IX, 10 mg.) was reduced by boiling with Raney nickel (50 mg.) in water (3 ml.) for 30 minutes. The resulting solution had uv spectra and R_f values identical to those of purine-6-sulfonic acid (17).

Purine-6-sulfonamide 3-Oxide (X).

Purine-6-sulfonyl fluoride 3-oxide (IX, 0.70 g., 3.2 mmoles) was poured slowly with stirring into liquid ammonia (20 ml.). The suspension was stirred for 30 minutes and then the ammonia was allowed to evaporate. The residue was taken up with water (10 ml.), a few drops of concentrated aqueous ammonia added, treated with charcoal, filtered and neutralized with glacial acetic acid. The resulting crystalline precipitate was washed with water and dried, 0.26 g. (38%), m.p. 250° (explodes when inserted at 240°).

An analytical sample was obtained by repeated treatment with dilute aqueous ammonia, charcoal, and neutralization with glacial acetic acid, and subsequent washing with water and ethanol. Colorless prisms were obtained, m.p. 360° dec.; λ max *p*H 2, 232 (20.8 x 10^3); 320 (12.9 x 10^3); *p*H 10, 231 (23.8 x 10^3); 318 nm (9.2 x 10^3).

Anal. Calcd. for $C_5H_5N_5O_3S$: C, 27.90; H, 2.32; N, 32.55; S, 14.88. Found: C, 27.82; H, 2.36; N, 32.41; S, 15.11.

6-Methylmercaptopurine 3-Oxide (XII).

Methanethiol (5 ml., 0.1 mole) was added at 0° to a solution of 6-chloropurine 3-oxide (I, 3.0 g., 18 mmoles) in *N* potassium hydroxide (30 ml.). The mixture was stirred at 0° for 1 hour, then at 25° for 3 hours. After treatment with charcoal, the *p*H of the solution was adjusted to 4 by addition of glacial acetic

acid. The crystalline precipitate which appeared was collected, washed with a little cold water, and dried to yield 1.75 g. (51%) of a crystalline product m.p. 245-247°, with uv spectra and R_f values identical to those of 6-methylmercaptopurine 3-oxide (9).

6-Methylsulfonylpurine 3-Oxide (XIII).

6-Methylmercaptopurine 3-oxide (XII) (2.0 g., 10.8 mmoles) was suspended in 30% aqueous methanol (50 ml.), cooled at 5° and chlorine gas bubbled therein for 20 minutes at temperature range between 5° and 15°. The mixture was kept at 25° for 20 minutes and then cooled. The resulting precipitate was collected by filtration and washed with cold water and ether to yield 2.15 g. (92%) of a crystalline product, m.p. 196-198°, identical to 6-methylsulfonylpurine 3-oxide (8a). (R_f values, uv and ir spectra.)

Reaction of 6-Methylsulfonylpurine 3-Oxide (XIII) with Hydroxylamine.

A. At Reflux Temperature.

A suspension of 6-methylsulfonylpurine 3-oxide (XIII, 1 g., 4.5 mmoles) in 0.6 *M* ethanolic hydroxylamine (500 ml.) was refluxed for 6 hours. The resulting precipitate was washed with water and ethanol to yield 0.21 g. (29%) of hypoxanthine 3-oxide (XIV) (8). The mother liquid showed the uv spectrum of 6-hydroxylaminopurine (18).

B. At 25°.

A solution of 6-methylsulfonylpurine 3-oxide (XIII, 2.0 g., 9 mmoles) in 0.6 *M* ethanolic hydroxylamine (900 ml.) was stirred at 25° for 72 hours. The resulting precipitate was collected, suspended in water (20 ml.) and the *p*H of the suspension adjusted to 5 with glacial acetic acid. The precipitate was collected by filtration, washed with water and ethanol and dried to yield 1.1 g. (73%) of a product identical to 6-hydroxylaminopurine 3-oxide (XV) (11).

6-Nitrosopurine 3-Oxide (Disodium Salt) (XVI).

A supersaturated solution of 6-hydroxylaminopurine 3-oxide (XV) (167 mg., 1 mmole) (prepared by solution of XV in *N* hydrochloric acid (2.5 ml.), dilution in water (50 ml.) and careful addition of sodium bicarbonate to *p*H 7) was treated with active magnesium dioxide (19) (0.50 g.). The reaction mixture was stirred at 25° for one hour and filtered through Celite. The filtrate was concentrated under reduced pressure to *ca.* 3 ml., neutralized with sodium acetate and the resulting precipitate washed with 70% aqueous ethanol to yield a red crystalline substance m.p. $>300°$; λ max *p*H 5.5 (water), 230 and 410 nm (unstable) (20).

Anal. Calcd. for $C_5H_3N_5O_2Na_2$: C, 28.45; H, 1.43; N, 33.18; Na, 21.79. Found: C, 28.26; H, 1.77; N, 32.58; Na, 22.04.

Compound XVI decomposed when treated with a 20% aqueous acetic acid solution. A solution of XVI (10 mg.) in *M* ethanolic hydroxylamine (10 ml.) was stirred at 25° for 24 hours; the resulting solution showed uv and R_f values identical to those of 6-nitrosopurine (21). Similar reduction of an *N*-oxide with hydroxylamine has been described above (*cf.* 11).

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(12) The reaction of purine-6-sulfonic acid 3-oxide (8a,11) with ethanolic hydroxylamine gave yields of XV up to *ca.* 60% (11). These yields were obtained when the starting material was made by sodium sulfite treatment of I, which was obtained by chlorination of the mercapto derivative VIII. The latter compound was prepared from 7-aminothiazolo[5,4-*d*]pyrimidine 6-oxide according to Brown *et al.* (9). However, when purine-6-sulfonic acid 3-oxide was made from 6-chloropurine by oxidation as described above, the reaction with ethanolic hydroxylamine was very slow, the yields in 6-hydroxylaminopurine 3-oxide (XV) were very poor; occasionally the reaction did not occur. To secure a reproducible route from XV we have either used the method detailed here (I → XII → XIII → XV) which gave an overall yield in XV of 45%, or the following procedure: The mercapto derivative VIII was oxidized with potassium permaganate to purine-6-sulfonic acid 3-oxide, according to Scheinfeld *et al.* (8a) and then treated with hydroxylamine solution as indicated in ref. 11. The overall yield in XV was 60%.

(13) Ultraviolet absorption spectra were determined with a Beckman DU model. Ascending paper chromatography was run on Whatman No. 1 paper in the following solvent systems: concentrated ammonium hydroxide-water-isopropyl alcohol (10:20:70); 1-butanol-water-acetic acid (50:25:25); and 1 *M* ammonium acetate-ethanol (30:70). Melting points were determined with a Thomas Hoover melting point apparatus and the temperatures corrected. Analyses were performed by Spang Microanalytical

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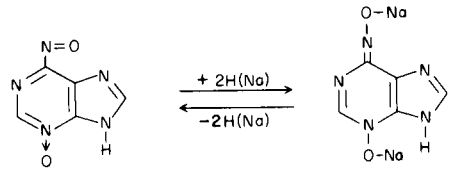
(20) The instability of the compound in aqueous solution did not allow the isolation of the free base. To account for the elementary analysis (double determination) the following formulation for XVI could be written:



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