A Convenient Synthesis of Purine-6-carboxylic Acid from 6-Methylpurine *via* 6-Styrylpurine

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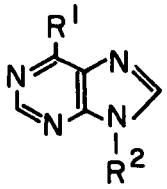
Purine 6-carboxylic acid (III) has been shown to be a useful intermediate for the synthesis of a variety of 6-substituted purine derivatives (2). Purine 6-carboxylic acid was first prepared by hydrolysis of 6-cyanopurine (3) and was later obtained by oxidation of the commercially available 6-methylpurine (4). Direct oxidation of 6-methylpurine (I) with either selenium dioxide or potassium permanganate has given poor yields of the 6-carboxylic acid III (5), but conversion of I to purine-6-methylenepyridinium iodide and oxidation of the latter has given III in 48% overall yield (6), while conversion of I to 6-trichloromethylpurine and hydrolysis of that compound has given 37% of III (7) and conversion of I to purine 6-malonaldehyde and subsequent oxidation has given 18% of III (8). This communication presents a simple procedure which involves the hitherto undescribed 6-styrylpurine as intermediate and which furnishes III in 59% yield from I; the attempted utilization of the procedure for similar oxidation of a 6-methylpurine ribonucleoside derivative is also described.

A study of methods for Knoevenagel-type conversion of 4-methylcinnoline derivatives to the corresponding 4-styryl derivatives showed that almost quantitative yields were obtained by treatment of a cinnoline hydrochloride with benzaldehyde and hydrogen chloride at 160° (9). The electronic similarity of 6-methylpurine and 4-methylcinnoline suggested that the method might be applicable to 6-methylpurine, and it was found that 6-styrylpurine (II) was thereby obtained in 95% yield. Oxidation of 6-styrylpurine with potassium permanganate in aqueous pyridine then furnished a 62% yield of purine 6-carboxylic acid. In order to determine whether these procedures could be utilized to obtain ribonucleosides of purine 6-carboxylic acid, 6-methyl-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-purine (IV) was prepared by condensation of the chloromercuri derivative of I with tri-*O*-benzoyl-D-ribofuranosyl chloride according to the Davoll-Lowy (10) procedure for nucleoside synthesis. Compound IV (64% yield) could be isolated simply and efficiently by precipitation of its dihydrochloride from a solution of the base in benzene; this method could be useful in Davoll-Lowy and related syntheses of many other blocked basic nucleosides by eliminating tedious chromatographic purification of the product. The structure of IV was established by removal of the benzoyl groups with ammonia-ethanol which gave in 50% overall yield a compound identical with 6-methyl-9-β-D-ribofuranosylpurine prepared by condensations of 6-methylpurine with *O*-acetylated ribofuranose intermediates followed by deacetylation (11,12). Attempted condensation of IV with benzaldehyde in the presence of hydrogen chloride was studied at temperatures ranging from 80° to 160° but yielded little material with the properties expected for the desired tribenzoylribosyl-6-styrylpurine.



	R^1	R^2
I	CH_3	H
II	CH=CHPh	H
III	COOH	H
IV	CH_3	tri-O-benzoyl-β-D-ribofuranosyl

EXPERIMENTAL

Paper chromatograms were run by the ascending method on Whatman No. 1 paper. Ultraviolet spectra were determined with a Beckman DU spectrophotometer. Elemental analyses were by J. F. Alicino. Melting points (capillary method) are uncorrected.

6-Styrylpurine (II).

Gaseous hydrogen chloride was passed into a solution of 6-methylpurine (0.5 g.) (Cyclo Chemical Corp., Los Angeles, Calif.) in warm acetone (150 ml.) until precipitation of solid ceased. The white suspension was boiled to expel excess hydrogen chloride, cooled, and the 6-methylpurine hydrochloride collected, washed with acetone, and dried *in vacuo* over sodium hydroxide. A suspension of the hydrochloride in benzaldehyde (15 ml., freshly distilled at 15 mm.) was placed in a bath at 175° and hydrogen chloride bubbled through the mixture. After 10-12 minutes the solid dissolved, and after a further 5 minutes precipitation of a yellow solid commenced. Heating was continued for a further 5

minutes. The cooled mixture was diluted with benzene (20 ml.), and the solid was collected and washed with benzene, then suspended in water at 80° and the *p*H adjusted to 7 with ammonium hydroxide giving 0.79 g. (95% yield) of 6-styrylpurine, m.p. 244-245°. Crystallization from ethanol (25 ml. concentrated to 10 ml.) gave cream needles, 0.6 g., m.p. 246°. The product showed only one ultraviolet-absorbing component (R_f 0.78; compound I had R_f 0.59) on paper chromatograms run in 1-butanol-water (86:14); λ max was 334 nm (ε = 29,700) in ethanol-water (1:1) and 334 nm (ε = 22,600) in ethanol-0.2 *N* sodium hydroxide (1:1).

Anal. Calcd. for $C_{13}H_{10}N_4$: C, 70.25; H, 4.53; N, 25.21. Found: C, 70.45; H, 4.50; N, 24.84.

6-Carboxypurine (III).

A solution of 6-styrylpurine (0.63 g.) in pyridine (20 ml.) and water (5 ml.) was mechanically stirred and treated dropwise at -2 to 0° with a solution of potassium permanganate (1.2 g.) in water (30 ml.). The dark suspension was stirred for 30 minutes at 2-3°, and for 1.5 hours at 25°. Celite filter-aid (0.5 g.) was added, and the mixture brought to *p*H 9 with 5 *N* sodium hydroxide. The solid was collected by filtration, washed with 0.1 *N* sodium hydroxide, and extracted with warm 0.12 *N* sodium hydroxide (20 ml.). The combined pale yellow filtrates were adjusted to *p*H 7 with hydrochloric acid and evaporated to dryness at 20 mm. The residual solid was triturated with ether (50 ml.) to remove benzoic acid, then dissolved in boiling water (250 ml.), and the solution decolorized with charcoal and vacuum-evaporated to 20 ml. The resulting suspension was adjusted to *p*H 2 with hydrochloric acid, giving 6-carboxypurine monohydrate as cream-colored needles (0.32 g., 62% yield; dried 1 hour *in vacuo* at 100°), m.p. 200° dec. [reported (3), 198° dec.], which gave a single spot, R_f 0.03, on a paper chromatogram developed with 1-butanol-water (86:14); λ max 280 nm (in water) (3).

Anal. Calcd. for $C_6H_4N_4O_2.H_2O$: C, 39,57; H, 3.32; N, 30.77. Found: C, 39.30; H, 3.46; N, 30.73.

6-Methyl-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)purine (IV).

To a stirred solution of 6-methylpurine (4.52 g.) in water (500 ml.) containing an equimolar amount of sodium hydroxide and Celite filter-aid (9 g.) was added a solution of mercuric chloride (9.17 g.) in ethanol (100 ml.). The precipitated chloromercuri derivative of 6-methylpurine and the Celite were collected and dried *in vacuo*. The yield of chloromercuri 6-methylpurine was quantitative. To a suspension of the Celite and chloromercuri derivative in boiling xylene (450 ml.) was added a xylene solution of tri-*O*-benzoyl-D-ribofuranosyl chloride (13) prepared from 17.8 g. of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (14), and the mixture was stirred under reflux for 3 hours. Removal of the xylene *in vacuo* yielded a brown glass. A solution of this in chloroform (200 ml.) was filtered from the Celite and extracted with 30% aqueous potassium iodide solution (2 x 50 ml.), and then with water. The orange glass (21.07 g.) obtained by evaporation of the chloroform *in vacuo* was dissolved in benzene (500 ml.) and portion of the solvent was distilled from the filtered solution in order to remove azeotropically traces of water. The solution was treated at 20° with dry hydrogen chloride until precipitation ceased and the suspension was stored overnight at 4° with exclusion of moisture. The solid was collected, washed immediately with dry benzene and dried at 25 mm. over potassium hydroxide, giving 14.13 g. (64%) of the dihydrochloride of IV as a yellowish solid, m.p. 123-125°. In ethanol the compound showed absorption maxima at 230 nm and 261 nm ($A_{261}:A_{230}$ = 1.18) and an inflexion at 280-282 nm ($A_{280}:A_{261}$ = 0.32). Treatment of IV for 7 days at 4° with methanol saturated with ammonia gave a trace of 6-methylpurine and a compound indistinguishable from 6-methyl-9-β-D-ribofuranosylpurine prepared (11,12) from 6-methylpurine and tetra-*O*-acetyl-D-ribofuranose.

Anal. Calcd. for $C_{32}H_{28}N_4O_7.2HCl$: C, 58.98; H, 4.33; N, 8.60; Cl, 10.88. Found: C, 59.51; H, 4.14; N, 8.75; Cl, 10.47.

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