toluene, or when heated considerably below its melting point). Data regarding properties and yields of the amino acids synthesized are given in Table III. The general procedure for the preparation of the amino acids is presented in the Experimental Section, together with any significant variations.

Experimental Section

α-Bromohydrocinnamic Acids.—The aniline (0.05 *M*) was dissolved in acetone (100 ml), concentrated hydrobromic acid (16 ml of "48%") was added, and the mixture was cooled to 3–5° and stirred while diazotized beneath the surface with 10.0 ml of 5.00 *F* sodium nitrite. Acrylic acid (50 ml) was added, the mixture was cooled to 0–5°, cuprous bromide was added (amounts are recorded in Table I), the solution was stirred, and the temperature was regulated so that nitrogen was evolved at a reasonable rate.[3] When nitrogen evolution ceased the mixture was concentrated *in vacuo* on steam to remove acetone and the bulk of acrylic acid and water; the residue was treated with water (200 ml) and stored at 0° for 24 hr. An organic residue, oil or solid, was separated, washed twice with water (50-ml portions), dissolved in water (100 ml) by addition of a slight excess of sodium hydrogen carbonate, filtered if necessary, extracted with chloroform (50 ml) and ether (50 ml), stirred with carbon (2 g), filtered, and acidified with concentrated hydrobromic acid. The mixture was extracted with benzene (300 ml), and the benzene layer was washed with water (25 ml), boiled to *ca.* 100 ml, and concentrated *in vacuo*. In most cases the residues solidified wholly or in part. In two cases (α-bromo-*o*-cyano- and α-bromo-*o*-methylhydrocinnamic acids) it was necessary to streak samples of oils on glass in order to induce crystallization; the samples crystallized in 24 hr and were used to seed the bulk of the materials, which then crystallized in a short time. The α-bromo acids were pressed out on tile or between filter papers, and the substances recovered are in certain instances reported as crude yields in Table I; in any case they were purified by one crystallization from formic acid, and these yields are given in Table I. For analysis they were crystallized twice more from formic acid. One substance (α-bromo-*m*-methylhydrocinnamic acid) did not crystallize under a variety of conditions attempted. For purification the oil was boiled with a small amount of formic acid and chilled, the formic acid layer was separated, and the oil was dried. For analysis this process was repeated twice. Formation and purification of α-bromo-*o*-carboxyhydrocinnamic acid required different conditions because of the ease with which this substance loses hydrogen bromide to afford the lactone 1-oxo-3-chromancarboxylic acid.[8]

Cinnamic Acids.—Samples of the purified α-bromohydrocinnamic acids (*ca.* 1 g) were heated with a saturated solution of potassium hydroxide in methanol (10 ml) under gentle reflux for 3–4 min, a part of the methanol was removed, and the mixture was diluted with enough water to dissolve all solid, made strongly acidic with concentrated hydrobromic acid, and stored at 0° for 24 hr. A solid was filtered, washed with cold water (10-ml portions) until the washings were free of halide, and crystallized from aqueous methanol. α-Bromo-*p*-ethoxycarbonylhydrocinnamic acid gave *p*-carboxycinnamic acid when treated in this manner. The α-bromo acid was converted to *p*-ethoxycarbonylcinnamic acid under different conditions.[5] α-Bromo-*o*-ethoxycarbonyl- and α-bromo-*o*-carboxyhydrocinnamic acids gave 1-oxo-3-isochromancarboxylic acid under several sets of conditions.

Phenylalanines.—The α-bromohydrocinnamic acid (0.01 *M*) was dissolved in concentrated ammonium hydroxide (100 ml), the mixture was kept at 0° for 24 hr and then at 23–25° for 48 hr and concentrated to dryness on a steam bath over a 3–5-hr period, and the residue was washed with ice water (5 ml). The solid was treated with a slight excess of 0.1 *F* hydrobromic acid and with water (100 ml), heated to 60°, cooled, and filtered, the filter was washed with water (25 ml) (the cinnamic acids on the filter were recovered and purified in some cases, see footnote *s* in Table III), the combined aqueous filtrates were extracted with chloroform (50 ml) and with ether (50 ml) and concentrated to dryness *in vacuo*, the residue was treated with a slight excess of concentrated ammonia and concentrated on steam to dryness, and a solid was filtered and washed with cold methanol (5-ml portions) until the washings were free of halide. The amino acids thus obtained were crystallized twice from aqueous methanol and then dried at 110° *in vacuo* over potassium hydroxide for analysis. When this process was carried out with α-bromo-*p*-ethoxycarbonylhydrocinnamic acid a mixture of cinnamic acids and α-amino acids was obtained. (Analytical results indicate *ca.* 30% of ester and 70% of amide functions on the amino acids.) When the α-bromo acid was refluxed for 6 hr with concentrated ammonium hydroxide a mixture of *p*-carbamoylphenylalanine and *p*-carbamoylcinnamic acid was isolated and separated. α-Bromo-*o*-carboxyhydrocinnamic acid gave only 1-oxo-3-isochromancarboxylic acid under all conditions tried.

Registry No.—Cinnamic acid (*m*-CH_3CO), 18910-23-1; cinnamic acid (*p*-CH_3CO), 18910-24-2; cinnamic acid (*p*-$CONH_2$), 18910-25-3; phenylalanine (*p*-CN), 18910-26-4; phenylalanine (*p*-CH_3CO), 18910-27-5; phenylalanine (*p*-$CONH_2$), 18910-28-6.

(8) The reaction was run at 28–30°. The mixture was allowed to evaporate at 23–25° in a large crystallizing dish for 48 hr, the residue was treated with 200 ml of ice–water, stirred, and stored at 5° for 24 hr, and a tan solid was filtered, washed twice with water (50-ml portions), air dried, dissolved in a minimum amount of refluxing ether, and treated with 4 vol of 60–71° petroleum ether. After 10 min the solution was filtered, concentrated to remove ether and part of the petroleum ether, and stored at 0° for 24 hr. A solid was filtered, washed with petroleum ether (50 ml), and dried to give 32% analytically pure α-bromo-*o*-carboxyhydrocinnamic acid. When all filtrates and residues to this point were combined and concentrated to dryness and the remaining material was boiled with water (100 ml) for 1 hr and chilled, a solid was filtered which after drying proved to be 5 g of crude 1-oxo-3-isochromancarboxylic acid. This substance, crystallized three times from water and then once from formic acid, melted at 157–158°. E. Bamberger and W. Lodter [*Ber.*, **26**, 1833 (1893)] reported mp 153.5°. *Anal.* Calcd for $C_{10}H_8O_4$: C, 62.5; H, 4.2; neut equiv, 192. Found: C, 62.3; H, 4.2; neut equiv, 194. A mixture with phthalideacetic acid was completely melted by 130°.

Convenient Synthesis of 2-Fluoroadenine[1]

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2-Fluoroadenine has been found to be a feedback inhibitor of purine synthesis.[2] Because of this activity and other general biochemical interest in this compound[3,4] and its nucleosides[5–7] it was desirable to develop a convenient method for its preparation.

Montgomery and Hewson[4] synthesized 2-fluoroadenine *via* diazotization of 2,6-diaminopurine in fluoroboric acid (Schiemann reaction), followed by purification using Celite column chromatography and water crystallization to give a 0.7% yield of pure material. In a modification of their synthesis[4] they obtained a higher yield (6%) by means of a sequence

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involving benzylation of 2,6-diaminopurine, then Schiemann reaction followed by ether extraction of 9-benzyl-2-fluoroadenine, and finally removal of the benzyl group with metallic sodium in liquid ammonia.

In view of existing precedents for the introduction of fluorine into aromatic systems by way of diazotization in anhydrous hydrogen fluoride,[8] it was decided to apply this method to 2,6-diaminopurine even though no such reactions of aminopurines were found in the literature. We found the addition of solid sodium nitrite to a solution of 2,6-diaminopurine in anhydrous hydrogen fluoride to be a facile and convenient procedure resulting in a 22% yield of pure 2-fluoroadenine. The product is a hygroscopic powder with the extent of hydration dependent upon crystalline structure, purity, and external atmospheric conditions.

Experimental Section

The ultraviolet spectra were determined using a Cary Model 11 spectrophotometer. Paper chromatograms were performed by the descending technique on Whatman No. 1 paper, using ultraviolet light for visualization.

2-Fluoroadenine.—To 150 ml of magnetically stirred anhydrous hydrogen fluoride (Matheson) in a polyethylene beaker immersed in an ice bath was added in portions 50.0 g (0.30 mole) of 2,6-diaminopurine hydrate.[9,10] Sodium nitrite (23.0 g, 0.33 mole) was added in portions to the stirred mixture at 0° over a 75-min period. The mixture was stirred for an additional 5 min and then purged with nitrogen for 20 min at 0°. The ice bath was removed, and the nitrogen purge continued. After evaporation of the hydrogen fluoride, the weight of 2-fluoroadenine was 74.0 g. This material was shown to contain approximately 30% ash. The ash level was reduced to below 0.3% by treating the product with distilled water (50 ml/g) five times in a Waring Blendor. To remove residual color, the product (19.0 g) was further purified by dissolving it in 11.5 l. of boiling water, treating the solution with 20 g of Darco KB, filtering, and concentrating the filtrate to dryness *in vacuo*. The residue was treated with water in the Blendor, ground, washed with ether, and air dried to give 11.2 g (22%) of analytically pure 2-fluoroadenine. Paper strip chromatography and ultraviolet absorption data corresponded with the reported values.[4]

Registry No.—2-Fluoroadenine, 18916-91-1.

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A Convenient Synthesis of Hydroxymethyldiphenylphosphine Oxide and Substituted α-Hydroxybenzyldiphenylphosphine Oxides

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There are several routes for the preparation of hydroxymethyldiphenylphosphine oxide and its α-substituted derivatives. Those based on diphenylphosphine[2-5] (eq 1 and 2) have the obvious disadvantage

$$Ph_2PH \xrightarrow{PhCHO} Ph_2PCH(OH)Ph \xrightarrow{AcOOH} Ph_2P(O)CH(OH)Ph \quad (1)$$

$$Ph_2PH \xrightarrow{PhCHO,\ HCl} [Ph_2P(CH(OH)Ph)_2]Cl \xrightarrow{OH^-} Ph_2P(O)CH(OH)Ph \quad (2)$$

that an oxidatively unstable, malodorous starting material that requires prior preparation is used. Miller and coworkers[6,7] prepared various α-mono- and disubstituted α-hydroxymethyldiorganophosphine oxides by the base-catalyzed addition of secondary phosphines oxides to aldehydes and ketones (eq 3). The drawback

$$R_2P(O)H + R'CHO \xrightarrow{NaOEt} R_2P(O)CH(OH)R' \quad (3)$$
$$R = PhCH_2,\ n\text{-}C_8H_{17},\ Ph$$

of this procedure is that it requires prior preparation of the secondary phosphine oxide. Finally, a more direct route, reported much earlier by Conant and coworkers[8] and confirmed by Miller *et al.*,[6] involves the reaction of diphenylchlorophosphine with benzaldehyde in glacial acetic acid. This procedure, however, appears to give only poor (27% in the case of benzaldehyde) yields of product.

We have found that compounds of the type $Ph_2P(O)CH_2OH$, $Ph_2P(O)CH(OH)Ar$ (Ar = Ph, *p*-ClC_6H_4, *p*-MeC_6H_4 and *p*-$NO_2C_6H_4$) and $Ph_2P(O)CH(OH)CCl_3$ may be prepared very simply and in good yield by the reaction of the commercially available diphenylchlorophosphine,[9] the respective aldehyde and concentrated hydrochloric acid. With *p*-anisaldehyde, the product isolated was the α-chloro derivative (eq 4). The corresponding α-hydroxy compound was prepared, however, when diphenylphosphine oxide in aqueous sulfuric acid was substituted for diphenylchlorophosphine in hydrochloric acid. This α-hydroxy compound was converted into the α-chloro compound on reaction with hydrochloric acid (eq 5 and 6). The greater lability

$$Ph_2PCl + p\text{-}MeOC_6H_4CHO \xrightarrow{HCl} Ph_2P(O)CH(Cl)C_6H_4OMe\text{-}p \quad (4)$$

$$Ph_2P(O)H + p\text{-}MeOC_6H_4CHO \xrightarrow{H_2SO_4} Ph_2P(O)CH(OH)C_6H_4OMe\text{-}p \quad (5)$$

$$Ph_2P(O)CH(OH)C_6H_4OMe\text{-}p \xrightarrow{\text{concd HCl}} Ph_2P(O)CH(Cl)C_6H_4OMe\text{-}p \quad (6)$$

of the hydroxy group in the *p*-anisaldehyde adduct might be expected on the basis of resonance forms which can be drawn for the electron releasing methoxy group.

We believe the general reaction is one which proceeds

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