134.35, 133.92, 132.92, 130.61, 58.49, 54.91, 50.82, 49.35, and 38.73 ppm; calcd *m/e* 260.1565, found 260.1569.

Pentaene **28a** proved not to be crystalline: ^{13}C NMR ($CDCl_3$) exhibits most intense peaks at 133.60, 132.75, 131.91, 57.74, 56.76, 48.96, and 37.72 ppm; calcd *m/e* 260.1565, found 260.1569.

Monoene **29b** was obtained crystalline: mp 70.5 °C (after sublimation); ^{13}C NMR ($CDCl_3$) 142.33, 126.41, 54.49, 53.31, 52.23, 49.37, 46.67, 45.91, 44.67, 43.65 (2 C), 34.48, 33.02, 32.32 (2 C), 31.67 (2 C), 30.97, 30.59, and 26.28 ppm; calcd *m/e* 268.2197, found 268.2196.

Anal. Calcd for $C_{20}H_{28}$: C, 89.49; H, 10.51. Found: C, 89.42; H, 10.74.

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Registry No.—**2,** 57700-83-1; **3,** 57760-88-0; **5,** 57700-82-0; **6,** 57760-87-9; **7,** 59938-99-7; **8,** 59939-00-3; **10,** 59981-13-4; **12,** 59939-01-4; **13,** 60018-67-9; **14,** 59939-02-5; **17,** 59939-03-6; **18,** 59981-14-5; **19,** 59939-04-7; **23,** 57700-86-4; **27,** 57700-87-5; **28a,** 59939-05-8; **28b,** 59953-49-0; MTAD, 13274-43-6.

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lin-Benzoguanine. Synthesis by Two Independent Methods

Gene E. Keyser and Nelson J. Leonard*

Roger Adams Laboratory, University of Illinois, Urbana, Illinois 61801

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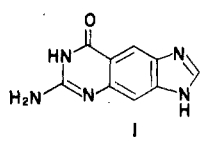
lin-Benzoguanine, 6-aminoimidazo[4,5-*g*]quinazol-8-one (1), has been synthesized by two independent methods, both starting with an intact central benzenoid ring. In one route, the substituted benzimidazole moiety was elaborated before closure of the pyrimidine ring. In the other, the substituted quinazolone was synthesized prior to imidazole ring closure. The title compound is fluorescent and represents a version of guanine that has been widened by 2.4 Å.

Recent work in these laboratories has centered on the synthesis and biochemical implications of benzologs of the purine bases,[1] specifically *lin*-benzoadenine (**2**). We have



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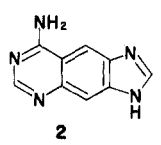

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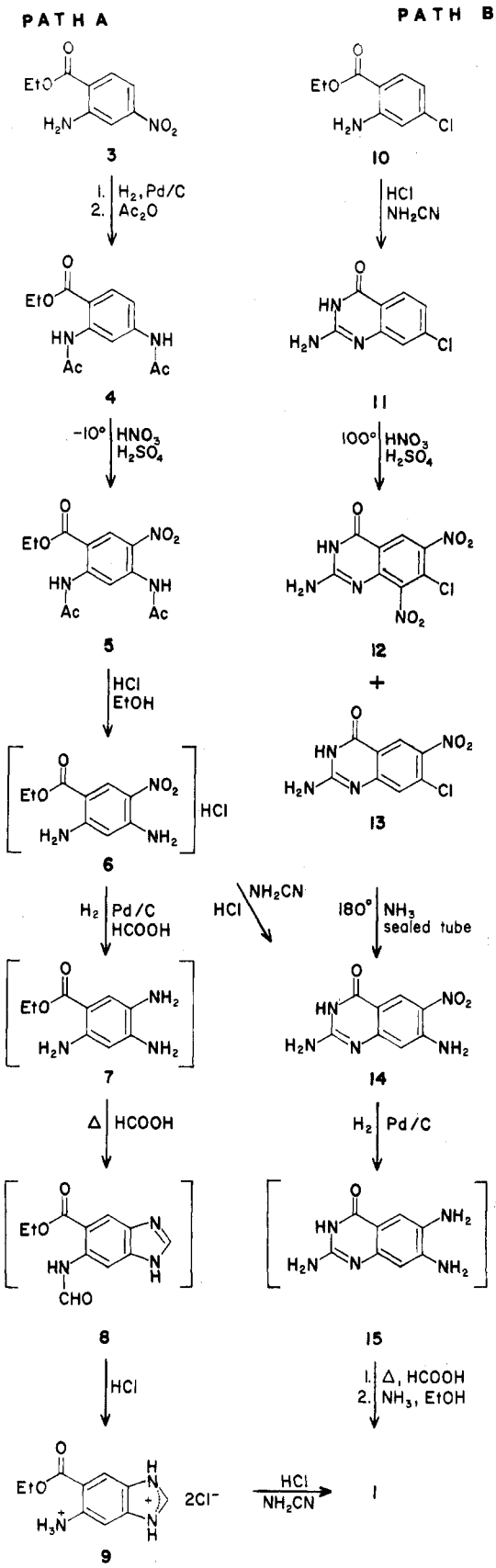
extended this series to include *lin*-benzoguanine, 6-aminoimidazo[4,5-*g*]quinazol-8-one (1), and report here its synthesis by two independent methods. The syzygial nature of these two pathways allows specific substitution in either the imidazole or the pyrimidine portions of the system toward the conclusion of the respective sequences. In the route of primary interest, path A, the extensive use of acyl and hydrochloride derivatives of tri- and tetrasubstituted aromatics avoided some of the problems foreseen[1] in the discussion of synthetic approaches to the "stretched-out" bases. Path A, however, does not easily allow for the unequivocal substitution at the 3 position (analogous to 9 in guanine), which is needed for assignment of the desired site of ribosidation by comparison of uv spectra. Thus, a second route, path B, was established by modification of the procedure used for *lin*-benzoadenine, which provides unequivocal substitution of the 3 position by nucleophilic aromatic substitution of a modified 4-quinazolone.

Path A has the decided advantage of allowing the synthesis of a variety of purine analogues in one step from a common benzimidazole intermediate. The addition of isocyanates, isothiocyanates, and substituted cyanamides, analogous to the preparation of substituted quinazolines and pyrimidones,[2] should lead to benzologs of xanthines, 2-thioxanthines, and N^2-alkyl and 1-alkylguanines, respectively. The use of substituted cyanamides may be limited by the ambiguity of substitution, but this could be avoided by use of 2-alkylthiohypoxanthine intermediates.

Results and Discussion

Path A. Compound **3** was easily obtained by esterification of 4-nitroanthranilic acid in 95% yield. Reduction of **3** with hydrogen over Pd/C followed by acetylation with acetic anhydride afforded **4** in 94% yield. Nitration of **4** to give **5** was best accomplished at −10 °C with concentrated sulfuric acid and fuming nitric acid, the low temperature being necessary to prevent hydrolysis of the acyl groups of the product. Compound **5** was subjected to a series of reactions without isolation of the intermediates to give **9** in 85% yield. First, the acyl protecting groups were removed by heating in ethanolic HCl to give **6,** which proved to be unstable to air on long standing, even as its hydrochloride salt. Dissolution of **6** in 98% formic acid, followed by reduction with hydrogen over Pd/C and heating, gave **8,** which was identified by its NMR spectrum. Unfortunately, the formyl group was cleaved on prolonged standing,[3] both in air and under a nitrogen atmosphere, to give a mixture of fluorescent products. Cleavage of the formyl group with retention of purity, however, could be accomplished by heating with ethanolic HCl to afford the di-



hydrochloride **9**. Heating **9** in a large excess of ethanolic cyanamide resulted in the precipitation of **1** as the free base in 98% yield. Purification could be accomplished by neutralizing a hot solution of the base in 1 M HCl with ammonia, although this method led to the incorporation of NH_4Cl in the gel sometimes formed.[4] A more crystalline-like solid could be obtained by dissolution of the base in boiling 98% ethanol saturated with HCl, followed by evaporative cooling with a stream of nitrogen. This approach to **1** does not require purification by recrystallization at any stage.

Table I. Technical Fluorescence Emission and Excitation Data

Compd	pH	Emission[d]	Excitation
1	1.0[a]	426	248, 257, 270, 283, 332[e]
	6.8[b]	403, 380 (sh)	256, 290, 340[f]
	13.0[c]	410	256, 268, 316, 356[g]
9	1.0[a]	442	
	6.8[b]	456	
	13.0[c]	434	

[a] 0.1 M HCl. [b] 0.05 M phosphate. [c] 0.1 M NaOH. [d] Excitation at 332 nm. [e] Emission fixed at 426 nm. [f] Emission fixed at 403 nm. [g] Emission fixed at 410 nm.

Preliminary work shows that good results can be expected in making a series of imidazo[4,5-*g*]quinazol-8-ones variously substituted in the 6 and 7 positions. Specifically, *lin*-benzoxanthine, characterized by its mass spectrum and uv spectra, has been made by adding an excess of KNCO to an aqueous solution of **9** adjusted to pH 4 with 1 M HCl. The product was easily isolated by filtration.

Path B. Alternative to its preparation from **3**, *lin*-benzoguanine may be prepared from **10**, in a method very similar to the preparation of *lin*-benzoadenine.[1] Compound **10** was obtained by esterification of 4-chloroanthranilic acid. Treatment of **10** with cyanamide, analogous to the conversion of **9** to **1**, netted **11** in 89% yield. Nitration of **11** was interesting in that the amount of dinitrated product **12** could be controlled by limiting the amount of fuming nitric acid added to the sulfuric acid solution of **11**; excellent yields of mononitrated product **13** could thereby be obtained. Displacement of the Cl in **13** with ammonia was accomplished in 85% yield using ammonia saturated butanol at 180 °C in a sealed tube. The reduction of **14** with hydrogen over Pd/C followed by heating in formic acid gave **1** in 86% yield; treatment with ethanolic ammonia was necessary to remove small amounts of side products, presumably formylated derivatives of **1**.

Although yields and conditions have not been optimized, path B is hampered by the need for purification in the latter stages of preparation. Specific substitution at the 3 position of compound **1** during the chloro-displacement stage may be accomplished by the use of aliphatic amines, directly analogous to work done in the *lin*-benzoadenine series, to provide uv models for studies of the site(s) of ribosidation.

Determination of the pK_a's of **1** in 66% DMF gave values in agreement with the idea that it behaves more like separate quinazolone and benzimidazole moieties than as a purine base. Assignments of these values are $pK_a < 2.0$ (pyrim $-$ H^+), $pK_a \simeq 4.5$ (imid $-$ H^+), $pK_a \simeq 9.5$ (pyrim $-$ H^+), $pK_a \geq 11.0$ (imid $-$ H^+). The uv spectra of **1**, shown in Figure 1, show marked changes in going from acidic through neutral to basic media in accord with these assignments. Compound **1** and its immediate precursor **9** are fluorescent, a fact which may be of some significance in later studies of the substrate properties of **1**, or cofactors related to it, in enzymatic reactions; a summary of the technical fluorescence spectra is given in Table I.

The same basic concept of stretching the molecule by 2.4 Å that guided us in our investigation of the biological activity in the *lin*-benzoadenosine series[5] suggests extension of the present *lin*-benzoguanine series to include the riboside, ribotide, and related derivatives.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary

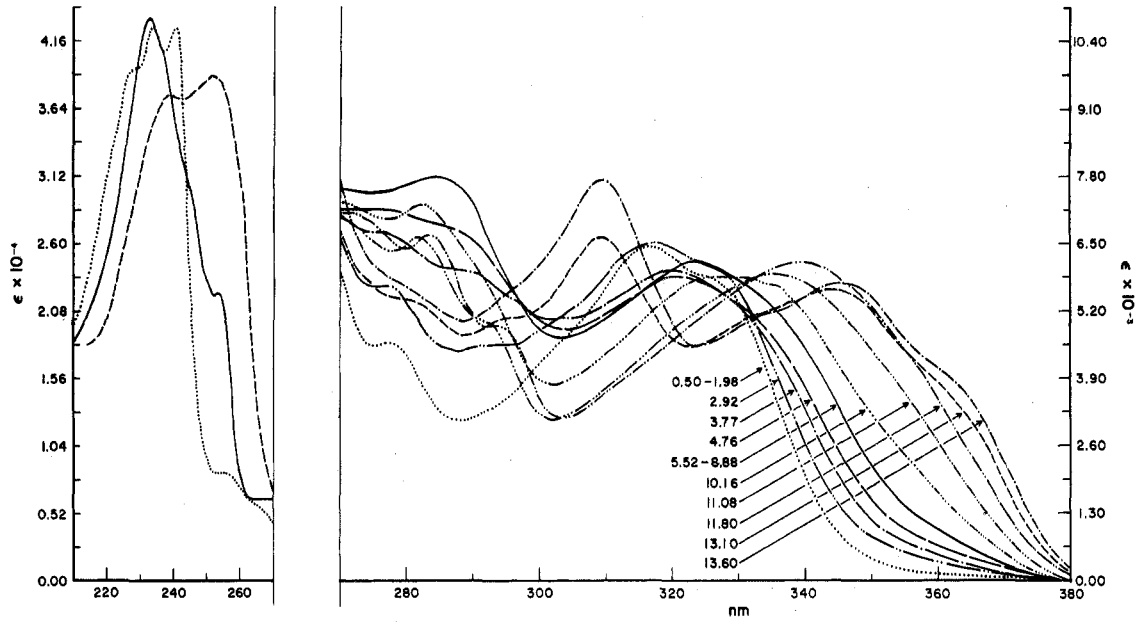


Figure 1. Ultraviolet spectra of *lin*-benzoguanine as a function of pH.

melting point apparatus and are corrected. Nuclear magnetic resonance spectra were recorded on a Varian A-60 or HA-100 spectrophotometer using tetramethylsilane as an internal standard. Mass spectra were run on a Varian-MAT CH-5 spectrometer coupled with a 620i computer and a Statos recorder. Ultraviolet absorption spectra were obtained on a Beckman Acta M VI spectrophotometer. Fluorescence emission and excitation spectra were measured on a Hitachi Perkin-Elmer MPF-2A fluorescence spectrophotometer. All buffer solutions were checked to ensure the absence of absorption or emission in the region of interest. Microanalyses were performed by Mr. Josef Nemeth and staff, who also weighed samples for quantitative ultraviolet absorption studies.

Ethyl 4-Nitroanthranilate (3). A solution of 4-nitroanthranilic acid (50.0 g, 275 mmol) in absolute ethanol (1 l.) was saturated with HCl and heated at reflux for 24 h. The solution was concentrated in vacuo to 200 ml, poured into 200 ml of saturated $NaHCO_3$ solution, and extracted with chloroform (10 × 200 ml). The chloroform extracts were dried ($MgSO_4$), and the solvent was removed in vacuo to afford **3** (55.0 g, 95% yield), mp 94 °C (lit.[6] mp 94 °C).

Ethyl 2,4-Diacetamidobenzoate (4). A solution of ethyl 4-nitroanthranilate (15.0 g, 71.4 mmol) in absolute ethanol (150 ml) was hydrogenated at 3 atm over 1.0 g of 5% Pd/C during 30 min. The catalyst was removed by filtration and washed with absolute ethanol (50 ml), and the solvent was removed from the filtrate in vacuo. Acetic anhydride (200 ml) was added, the solution was heated at reflux for 1–2 h under nitrogen, then the solvent was removed in vacuo and 200 ml of ice water added. The mixture was stirred until no large particles remained and filtered, and the white solid was dried in vacuo at 60 °C to afford analytically pure **4** (10.1 g, mp 196 °C). Concentration of the filtrate to 25% of its original volume followed by addition of 25 ml of ethanol and refrigeration resulted in precipitation of additional product (7.6 g, total yield 94%): mp 195–196 °C; NMR ($CDCl_3$) δ 1.40 (t, 3, CH_3), 2.15 (s, 3, CH_3CO), 2.20 (s, 3, CH_3CO), 4.32 (q, 2, CH_2), 7.9 (m, 2, ArH), 8.4 (m, 1, ArH), 8.9 (br s, 1, NH), 11.15 (br s, 1, NH).

Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.04; H, 6.12; N, 10.55.

Ethyl 2,4-Diacetamido-5-nitrobenzoate (5). Ethyl 2,4-diacetamidobenzoate (16.0 g, 6.06 mmol) was added to a solution of fuming HNO_3 (25 ml) and concentrated H_2SO_4 (32 ml) at −10 to −5 °C in 0.5-g portions at 10-min intervals. After addition was complete, the solution was stirred for 3.5 h, or until no starting material remained by TLC (silica gel, 5% EtOH–$CHCl_3$). The clear solution was added to an ice–salt water mixture dropwise.[7] The resulting mixture was refrigerated at −20 °C for 1 h and filtered, and 12.5 g of crude yellow-orange crystals were collected (67% yield), mp 150–160 °C. The analytical sample was obtained by dissolution in absolute ethanol and precipitation with water: mp 163 °C; NMR ($CDCl_3$) δ 1.40 (t, 3, CH_3), 2.20 (s, 3, CH_3CO), 2.28 (s, 3, CH_3CO), 4.15 (q, 2, CH_2), 8.85 (s, 1, ArH), 10.0 (s, 1, ArH), 10.5 (br s, 1, NH), 11.3 (br s, 1, NH).

Anal. Calcd for $C_{13}H_{15}N_3O_6$: C, 50.48; H, 4.89; N, 13.59. Found: C, 50.41; H, 4.89; N, 13.83.

The crude material may be used as is for deacetylation and reduction because the impurity consists of deacetylated product.

6-Amino-5-carboethoxybenzimidazole Dihydrochloride (9). A solution of ethyl 2,4-diacetamido-5-nitrobenzoate (3.0 g, 9.7 mmol) in absolute ethanol (100 ml) was saturated with HCl and heated at reflux for 20 min under nitrogen. The mixture was reduced to 10% of its original volume in vacuo and saturated with HCl at 0 °C. The precipitate was removed by filtration and dissolved immediately in formic acid (97%, 100 ml). The solution was hydrogenated at 3 atm H_2 over 0.2 g of 5% Pd/C during 30 min. The catalyst was removed by filtration and the solution heated at reflux for 1 h. The solvent was removed in vacuo and 100 ml of absolute ethanol was added. Repetition of the saturation, heating, concentration, cold saturation procedure above yielded 2.3 g of analytically pure **9** (85% yield): NMR (D_2O) δ 1.55 (t, 3, CH_3), 4.60 (q, 2, CH_2), 7.82 (s, 1, ArH), 8.60 (s, 1, ArH), 9.48 (s, 1, Im CH); MS *m/e* 205 (M^+ for $C_{10}H_{11}N_3O_2$); mp >300 °C.

Anal. Calcd for $C_{10}H_{13}Cl_2N_3O_2$: C, 43.18; H, 4.71; N, 15.11. Found: C, 42.90; H, 4.65; N, 15.03.

6-Aminoimidazo[4,5-*g*]quinazol-8-one (1) from 9. To a mixture of 5-carboethoxy-6-aminobenzimidazole dihydrochloride (1.0 g, 3.6 mmol) in absolute ethanol (100 ml) heated at reflux was added cyanamide (7.6 g, 180 mmol) in 10 equal portions over a period of 6 h. The mixture was heated for an additional 2 h, concentrated to 50% of its original volume, and cooled to 0 °C. The precipitate was filtered and washed with cold water (20 ml), cold absolute ethanol (20 ml), and anhydrous ether (100 ml) to afford 0.71 g of white solid (98% yield, mp >300 °C). Purification, if needed, could be accomplished by dissolution in boiling 1 M HCl, followed by neutralization with ammonia. Alternatively, purification could be achieved by dissolution in 98% ethanol saturated with HCl at reflux, followed by cooling under a stream of nitrogen to afford the dihydrochloride of **1**: NMR (1 M NaOD/D_2O) δ 7.48 (s, 1), 8.18 (s, 1), 8.25 (s, 1); uv λ_{max} (0.1 M NaOH) 238 nm (ε 37 600), 254 (39 500), 280 (sh), 296 (sh), 310 (6500), 345 (5600), 374 (sh), λ_{max} (0.1 M Na_2CO_3 buffer pH 10.3), 234 nm (ε 40 800), 270 (7270), 283 (7000), 324 (5700); λ_{max} (0.05 M phosphate pH 6.8) 233 nm (43 600), 254 (22 600), 270 (6900), 285 (7250), 324 (5900); λ_{max} (0.1 M NH_4HCO_2 buffer, pH 2.8) 235 nm (sh), 240 (ε 43 400), 266 (sh), 277 (sh), 290 (sh), 317 (5800), 329 (sh); λ_{max} (0.1 M HCl) 228 nm (sh), 234 (ε 42 850), 240 (45 200), 256 (8950), 267 (sh), 278 (3650), 316 (6200), 325 (sh); MS *m/e* 201 (M^+ for $C_9H_7N_5O$); ir (KBr) (free base) 3300, 3100 (br) (NH), 1700, 1650, 1625 cm^{-1} (C=N and C=O).

Anal. Calcd for $C_9H_9Cl_2N_5O$: C, 39.43; H, 3.31; Cl, 25.87; N, 25.55. Found: C, 39.51; H, 3.49; Cl, 25.87; N, 25.33.

Ethyl 4-Chloroanthranilate (10). The esterification of 4-chloroanthranilic acid essentially according to the directions for **3** afforded **10** (89% yield), mp 40–41 °C (lit.[8] mp 41 °C, 50% yield).

2-Amino-7-chloro-4-quinazolone (11). To a solution of ethyl 4-chloroanthranilate (20 g, 100 mmol) in absolute ethanol (200 ml) heated at reflux was added concentrated HCl (10 ml) and cyanamide

(42 g, 1 mol) in 10 equal portions over a period of 24 h, another 10 ml of concentrated HCl being added after 20 h. The heterogeneous solution was cooled to 0 °C and filtered after standing for 6 h. The white solid was washed with cold water (25 ml), cold ethanol (25 ml), and anhydrous ether (100 ml), to afford analytically pure **11** (as the ⅓ hydrate)[9] (18.0 g, 89% yield): mp >300 °C; NMR [$(CD_3)_2SO$] δ 6.0–7.0 (br s, 1, NH), 7.0 (d of d, 1, 6-ArH, J = 8, 2 Hz), 7.15 (d, 1, 8-ArH, J = 2 Hz), 7.80 (d, 1, 5-ArH, J = 8 Hz), 8.0–10.0 (br s, 2, NH_2); MS m/e 195 (M^+ for $C_8H_6ClN_3O$).

Anal. Calcd for $C_8H_6ClN_3O \cdot \frac{1}{3}H_2O$: C, 47.65; H, 3.33; N, 20.84. Found: C, 47.93; H, 3.23; N, 20.75.

2-Amino-7-chloro-6-nitro-4-quinazolone (13). To a solution of 2-amino-7-chloro-4-quinazolone (1.0 g, 5.1 mmol) in concentrated H_2SO_4 (5 ml) at −10 °C (acetone–ice) was added 0.25 ml (1.2 equiv) of fuming HNO_3. The solution was heated on a steam bath for 10 min, then poured onto 200 ml of ice. The mixture was filtered to afford 1.0 g of **13** after drying at 100 °C in vacuo. On standing at 0 °C, 0.3 g of **13** as its $\frac{1}{2}H_2SO_4$ salt crystallized, analytically pure (96% total yield): mp >300 °C; NMR of free base [$(CD_3)_2SO$] δ 7.67 (s, 1, ArH), 8.2 (br s, 1, NH), 8.55 (s, 1, ArH), 10.1 (br s, 2, NH_2); MS m/e 240 (M^+ for $C_8H_5ClN_4O_3$).

Anal. Calcd for $C_8H_5ClN_4O_3 \cdot \frac{1}{2}H_2SO_4$: C, 33.18; H, 2.09; N, 19.35. Found: C, 33.33; H, 2.10; N, 19.38.

2-Amino-7-chloro-6,8-dinitro-4-quinazolone (12) and 13. The above reaction was repeated using 0.5 ml (2.4 molar equiv) of fuming HNO_3. A yellow-red solid (1.4 g) was collected; hot filtration of the undissolved material from AcOH gave 0.38 g of **13**, identical with that isolated above (NMR and TLC, 20% ethanol, ½% AcOH in $CHCl_3$). Concentration and cooling of the AcOH gave analytically pure **12** (0.99 g, 68% yield): mp >300 °C; NMR [$(CD_3)_2SO$] δ 7.5 (br s, 2, NH_2), 8.62 (s, 1 ArH), 11.72 (s, 1, NH); MS m/e 285 (M^+ for $C_8H_4ClN_5O_5$).

Anal. Calcd for $C_8H_4ClN_5O_5$: C, 33.64; H, 1.41; N, 24.52. Found: C, 33.68; H, 1.45; N, 24.26.

2,7-Diamino-6-nitro-4-quinazolone (14). A sealed tube containing 2-amino-7-chloro-6-nitro-4-quinazolone (0.42 g, 1.75 mmol) in ammonia-saturated butanol (20 ml at 0 °C) was heated at 180 °C for 24 h.[10] The solution was cooled to −20 °C, filtered, and washed with cold butanol (50 ml, −20 °C), triturated and washed with water (3 × 100 ml), and repurified from 90% AcOH, then from boiling 10% HCl, neutralized hot with concentrated NH_4OH, to afford **14** (0.330 g, 85% yield): mp >300°; NMR [$(CD_3)_2SO$] δ 6.55 (s, 1, ArH), 6.90 (br s, 2, NH_2), 7.42 (s, 2, NH_2), 8.0–9.5 (br s, 1, NH), 8.55 (s, 1, ArH); MS m/e 221 (M^+ for $C_8H_7N_5O_3$).

An analytical sample was obtained by sublimation (240 °C, 0.01 mmHg) followed by recrystallization of the HCl salt from 20% HCl.

Anal. Calcd for $C_8H_8ClN_5O_3$: C, 37.29; H, 3.13; N, 27.18. Found: C, 37.42; H, 3.09; N, 26.85.

6-Aminoimidazo[4,5-*g*]quinazol-8-one (1) from 14. A solution of 2,7-diamino-6-nitro-4-quinazolone (0.10 g, 0.45 mmol) in formic acid (97%, 60 ml) was hydrogenated at 3 atm H_2 over 0.010 g of 10% Pd/C during 30 min. The catalyst was removed by filtration and the solution was heated at reflux for 2 h, after which the solvent was removed in vacuo. The pink residue was dissolved in 0.1 M HCl by heating, treated with decolorizing charcoal, and precipitated by addition of concentrated NH_4OH followed by cooling. Preliminary purification could be achieved by stirring with ammonia-saturated ethanol at 25 °C. The white solid was removed by filtration and further purified by acid–base precipitation, yield 0.078 g (86%). The product was identical with that prepared from **9** by TLC, uv, and NMR.

2,7-Diamino-6-nitro-4-quinazolone (14) from 5. A solution of ethyl 2,4-diacetamido-5-nitrobenzoate (0.005 g) in absolute ethanol (5 ml) was saturated with HCl and heated at reflux for 20 min under nitrogen. Cyanamide was added to the solution and heating was continued for 36 h, at which time TLC (silica gel, EtOH–AcOH–$CHCl_3$) showed the formation of a compound identical with **14**.

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Registry No.—**1**, 60064-29-1; **1** 2HCl, 60064-30-4; **3**, 55204-24-5; **4**, 60064-31-5; **5**, 60064-32-6; **9**, 60064-33-7; **10**, 60064-34-8; **11**, 20198-18-9; **12**, 60064-35-9; **13**, 60064-36-0; **13** $\frac{1}{2}H_2SO_4$, 60064-37-1; **14**, 60064-38-2; **14** HCl, 60064-39-3; 4-nitroanthranilic acid, 619-17-0; 4-chloroanthranilic acid, 89-77-0.

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(9) Drying over P_2O_5 in vacuo or at 140 °C in vacuo gave no decrease in the water content.
(10) More concentrated solutions of starting material in butanol are not advisable, as they tend to lead to the formation of many side products.

Functionalization of a Steroidal C-18 Angular Methyl Group Using a 21,20-Chlorohydrin

George R. Lenz

Division of Chemical Research, Searle Laboratories, P.O. Box 5110, Chicago, Illinois 60680

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The preparation of a 3-keto-4-ene-21,20-chlorohydrin is described. Irradiation of its nitrite ester **7** furnished the C-18 nitroso compound **8**, which was converted into the oxime **10**. Selective acetylation of the oxime allowed oxidation of the C-20 alcohol to the chloro ketone **12**, and subsequent replacement of the C-21 chlorine by an acetoxy group to form **13**. All attempts at cleaving the oxime to generate the free 18-aldehyde failed. Elimination of acetic acid from the oxime acetate furnished 18-nitrilodeoxycorticosterone **15**. Oxidation of the oxime **10**, or the lead tetraacetate–iodine reaction on the chlorohydrin **5**, furnished the 21-chloro-18→20-lactone **16**, which was reduced to the 18,20β-diol **18**. Selective acetylation at C-18 allowed the oxidation of the C-20 alcohol to form 18-acetoxyprogesterone which was subsequently converted into 18-hydroxydeoxycorticosterone acetate.

Ever since the elucidation of the structure of aldosterone as an 18-aldehyde, the functionalization of the angular methyl group at C-18 has posed a fascinating synthetic challenge. The most convenient synthesis of aldosterone was reported by Barton and involved the photolysis of corticosterone acetate 11β-nitrite to form aldosterone oxime.[1] At about the same time, Pappo described the synthesis of 18-hydroxyprogesterone (**1**) and 18-hydroxydeoxycorticosterone (**2**) from con-