Anal. Calcd for $C_9H_7ClO_4$: C, 50.37; H, 3.29; Cl, 16.52; OCH_3, 16.02. Found: C, 50.32; H, 3.36; Cl, 16.30; OCH_3, 15.92.

3-Chloro-2-hydroxy-4,6-dimethoxybenzoic Acid (XIV).—To a solution of 2 g (8.75 mmoles) of 7-chloro-4,6-dimethoxycoumaran-3-one (IX) in 700 ml of anhydrous acetone, 8 g of powdered $KMnO_4$ was added. The mixture was stirred at room temperature for 24 hr, and the resulting brown solid obtained by filtration was washed with acetone, dried at 120° for 15 min, and ground with 40 ml of 10% NH_4OH solution. The filtrate and washing were combined and added to 100 g of crushed ice, and this mixture was carefully acidified with concentrated H_2SO_4. The gelatinous-type precipitate was filtered off, dried, and recrystallized from ethyl acetate. The resulting tan needles (0.51 g) melted at 222.0–223.0° dec in accordance with the literature.[9]

7-Chloro-4-ethoxy-6-methoxycoumaran-3-one (XV).—To a mixture of 30 g of anhydrous K_2CO_3 and 4.29 g (0.020 mole) of 7-chloro-4-hydroxy-6-methoxycoumaran-3-one (X) in 120 ml of dimethylformamide, a solution of ethyl bromide (3.27 g, 0.030 mole) in 40 ml of dimethylformamide was added. The reaction mixture was slowly heated to 65° and maintained at this temperature for 5 hr. It was then added to 800 ml of ice water, and the resulting red precipitate was washed with water. Recrystallization from aqueous ethanol gave orange-red needles (3.1 g, 63.9%); after recrystallization from 95% ethanol, a melting point of 180.7–182.2° dec was obtained; λ_{max}^{EtOH} 210 mμ (ε 18,927), 235 (18,200), 286 (19,656), 322 (5096); $\lambda_{max}^{CHCl_3}$ 5.88 μ (C=O).

Anal. Calcd for $C_{11}H_{11}ClO_4$: C, 54.45; H, 4.57; Cl, 14.61. Found: C, 54.58; H, 4.58; Cl, 14.70.

7-Chloro-4-ethoxy-6,2′-dimethoxy-6′-methylgris-2′-ene-3,4′-dione (XVI) was prepared from 10.16 g (0.030 mole) of 7-chloro-4-hydroxy-6,2′-dimethoxy-6′-methylgris-2′-ene-3,4′-dione (V) according to the procedure used in the synthesis of XV. The white solid product (10.1 g, 91.7%) crystallized from benzene–ether in white needles: mp 213.0–213.5°; $[\alpha]^{26}D$ +322.26° (*c* 1.523, acetone); λ_{max}^{EtOH} 218 mμ (ε 23,109), 235 (22,925), 291 (23,659), 328 (5685); $\lambda_{max}^{CHCl_3}$ 5.85 (C=O), 6.02 μ (COC=C); lit.[4] mp 211–213°, $[\alpha]D$ +324°.

3-Chloro-6-ethoxy-2-hydroxy-4-methoxybenzoic Acid (XVII). A. From the Oxidation of 7-Chloro-4-ethoxy-6-methoxycoumaran-3-one (XV).—Compound XV (2.0 g, 8.24 mmoles) was oxidized by the procedure described for oxidation of IX. The product (0.47 g), recrystallized from ethyl acetate, melted at 210.0–211.7° dec; λ_{max}^{KBr} 3.15 (OH), 3.77 (bonded OH), 5.92 μ (C=O).

Anal. Calcd for $C_{10}H_{11}ClO_5$: C, 48.70; H, 4.50; Cl, 14.38. Found: C, 48.62; H, 4.55; Cl, 14.29.

B. From the Oxidation of 7-Chloro-4-ethoxy-6,2′-dimethoxy-6′-methylgris-2′-ene-3,4′-dione (XVI).—A solution of 8.0 g (0.022 mole) of XVI in 1.8 l. of anhydrous acetone was treated with 32 g of powdered $KMnO_4$ by the procedure described for the oxidation of XV. The acid obtained from this reaction melted at 204.7–206.7° dec after recrystallization from ethyl acetate; mixture melting point with the acid obtained in part A above was 207.7–209.0° dec. The infrared spectrum (in KBr) was superimposable on that of the acid obtained in part A.

3-Chloro-6-ethoxy-2-hydroxy-4-methoxybenzanilide (XVIII) was prepared in the customary manner from 0.40 g of 3-chloro-6-ethoxy-2-hydroxy-4-methoxybenzoic acid (XVII) and 1 ml of aniline. Recrystallization from benzene yielded 0.092 g of silky white needles, mp 210.0–210.5°, λ_{max}^{KBr} 3.03 (NH, OH) and 6.08 μ (NC=O).

Anal. Calcd for $C_{16}H_{16}ClNO_4$: C, 59.73; H, 5.01; Cl, 11.02; N, 4.35. Found: C, 59.68; H, 5.30; Cl, 11.08; N, 4.53.

7-Chloro-6,2′-dimethoxy-4-(*p*-methoxybenzyloxy)-6′-methylgris-2′-ene-3,4′-dione (I).—A benzene solution of freshly prepared and vacuum dried (at 25°) crude *p*-methoxybenzyl bromide (XI, prepared from 3.45 g (0.025 mole) of anisyl alcohol) was added slowly to a stirred mixture of 6.77 g (0.020 mole) of anhydrous 7-chloro-4-hydroxy-6,2′-dimethoxy-6′-methylgris-2′-ene-3,4′-dione (V), 25 g of anhydrous K_2CO_3, and 200 ml of anhydrous acetone. After the reaction mixture was refluxed for 16 hr, the solid separated by filtration was washed with two 40-ml portions of boiling acetone and the filtrate and washings were combined and concentrated to dryness. The resulting solid product (8.5 g, 92.5%) was recrystallized from dioxane–absolute ethanol; it melted at 201.6–202.2° dec; $[\alpha]^{26}D$ +246.32° (*c* 1.224, dioxane); λ_{max}^{EtOH} 231 mμ (ε 36,712), 292 (22,027), 335 (6425); $\lambda_{max}^{CHCl_3}$ 5.82 (C=O), 6.0 μ (COC=C).

Anal. Calcd for $C_{24}H_{23}ClO_5$: C, 62.82; H, 5.05; Cl, 7.73. Found: C, 62.69; H, 4.83; Cl, 8.02.

7-Chloro-4-[3-(N,N-diethylcarbamoyl)benzyloxy]-6,2′-dimethoxy-6′-methylgris-2′-ene-3,4′-dione (II) was prepared from V (3.39 g, 0.010 mole) and XII (3.0 g, 0.011 mole) by the procedure described for the synthesis of I. The crude product (4.7 g, 89.0%), recrystallized from benzene, gave white crystalline plates: mp 191.0–192.0°; $[\alpha]^{26}D$ +215.41° (*c* 1.012, acetone); λ_{max}^{EtOH} 214 mμ (ε 35,641), 235 (29,569), 292 (21,912), 330 (5808); $\lambda_{max}^{CHCl_3}$ 5.85 (C=O), 6.02 μ (COC=C).

Anal. Calcd for $C_{28}H_{30}ClNO_7$: C, 63.69; H, 5.73; Cl, 6.72; N, 2.65. Found: C, 63.61; H, 5.81; Cl, 6.61; N, 2.51.

7-Chloro-6,2′-dimethoxy-4-(3,7-dimethyl-6-octenyl-1-oxy)-6′-methylgris-2′-ene-3,4′-dione (III) was prepared from V (6.8 g, 0.020 mole) and XIII (4.6 g, 0.021 mole) by the procedure described for the synthesis of I except that dimethylformamide was employed as the solvent and the reaction temperature was held at 25° for 1 hr and 70° for 4 hr. The crude product (7.8 g, 80.0%) crystallized from 80% methanol in the form of white crystalline plates: mp 136.5–137.5°; $[\alpha]^{26}D$ +252.33° (*c* 0.988, acetone); λ_{max}^{EtOH} 218 mμ (ε 24,327), 235 (23,135), 291 (22,658), 327 (5963); $\lambda_{max}^{CHCl_3}$ 5.82 (C=O), 6.02 μ (COC=C).

Anal. Calcd for $C_{26}H_{33}ClO_5$: C, 65.47; H, 6.97; Cl, 7.43. Found: C, 65.42; H, 6.91; Cl, 7.60.

7-Chloro-6-methoxy-4-(*p*-methoxybenzyloxy)coumaran-3-one (VI) was prepared from X (2.15 g, 0.010 mole) and XI (2.61 g, 0.013 mole) by the procedure described for the synthesis of III. The solid product (3.1 g, 92.6%) was recrystallized from dioxane giving the analytical sample: mp 182.6–183.2° dec; λ_{max}^{EtOH} 232 mμ (ε 26,446), 285 (17,408), 322 (5021); $\lambda_{max}^{p\text{-Dioxane}}$ 236 mμ (ε 23,768), 283 (18,914), 317 (5858); λ_{max}^{KBr} 5.87 μ (C=O).

Anal. Calcd for $C_{17}H_{15}ClO_5$: C, 60.99; H, 4.52; Cl, 10.59. Found: C, 60.94; H, 4.76; Cl, 10.55.

7-Chloro-4-[3-(N,N-diethylcarbamoyl)benzyloxy]-6-methoxycoumaran-3-one (VII) was prepared from X (2.15 g, 0.010 mole) and XII (2.97 g, 0.011 mole) by the procedure described for the synthesis of III. The product (2.9 g, 71.8%) was recrystallized from ethyl acetate giving cream-colored microcrystalline needles: mp 141.0–143.0° dec; λ_{max}^{EtOH} 208 mμ (ε 37,157), 235 (26,252), 286 (19,790), 320 (6866); $\lambda_{max}^{CHCl_3}$ 5.87 (C=O), 6.18 μ (NC=O).

Anal. Calcd for $C_{21}H_{22}ClNO_5$: C, 62.45; H, 5.49; Cl, 8.78; N, 3.47. Found: C, 62.69; H, 5.46; Cl, 9.00; N, 3.50.

7-Chloro-6-methoxy-4-(3,7-dimethyl-6-octenyl-1-oxy)coumaran-3-one (VIII) was prepared from X (2.15 g, 0.010 mole) and XIII (2.63 g, 0.012 mole) by the procedure described for the synthesis of III. The product (2.1 g, 59.5%) was recrystallized from methanol, yielding the analytical sample: mp 75.2–76.0°; λ_{max}^{EtOH} 209 mμ (ε 20,643), 235 (18,349), 285 (18,173), 320 (4940); $\lambda_{max}^{CHCl_3}$ 5.85 μ (C=O).

Anal. Calcd for $C_{19}H_{25}ClO_4$: C, 64.67; H, 7.14; Cl, 10.05. Found: C, 64.67; H, 7.05; Cl, 10.05.

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The Synthesis of *p*-Guanidinobenzamidines

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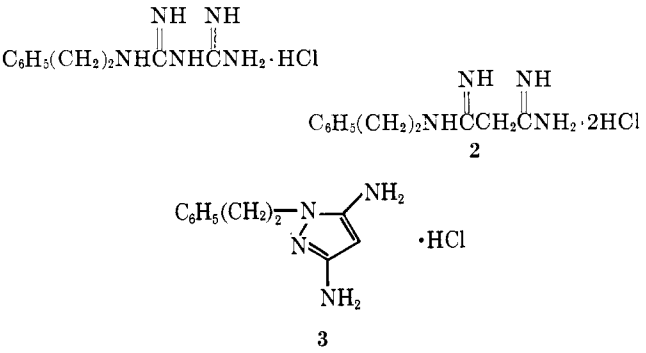
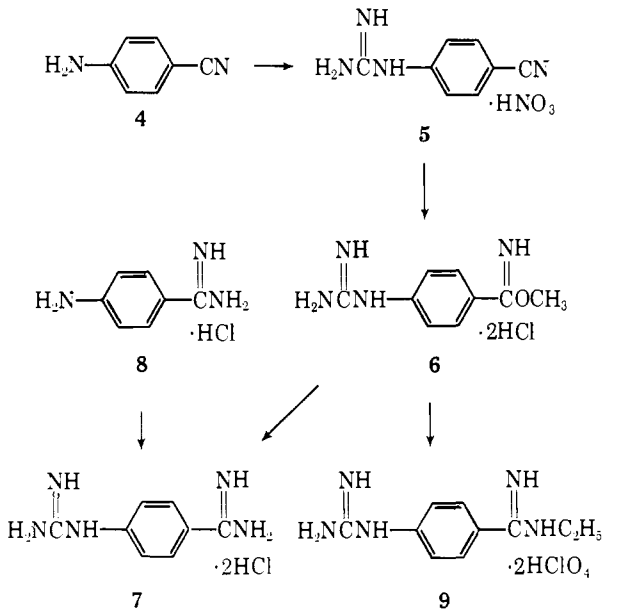
Phenethylbiguanide hydrochloride (**1**) is a clinically effective drug for the control of selected cases of diabetes.[1] We have sought to develop for hypoglycemic

(1) J. Pomeranze, H. Fuji, and G. T. Muratoff, *Proc. Soc. Exptl. Biol. Med.*, **95**, 193 (1957).



testing novel chemical systems which incorporate features of the biguanide skeleton and have already reported the syntheses of phenethylmalonamidine dihydrochloride (**2**)[2] and 3,5-diamino-1-phenethylpyrazole hydrochloride (**3**).[3] In this communication we describe the synthesis of some salts of *p*-guanidinobenzamidines, a system which can be construed as a biguanide in which a *p*-phenylene group has been inserted between the guanyl and guanidino moieties. The specific examples synthesized are the parent compound **7** and the *p*-guanidinobenzamidines, **9** and **15**, isomeric with phenethylbiguanide.

The parent *p*-guanidinobenzamidine dihydrochloride was synthesized by two routes starting from either *p*-aminobenzonitrile or *p*-aminobenzamidine hydrochloride. Thus, *p*-aminobenzonitrile (**4**) was allowed to react with cyanamide in acidic medium to provide *p*-guanidinobenzonitrile nitrate (**5**). After liberation from the salt, the free base was converted to methyl

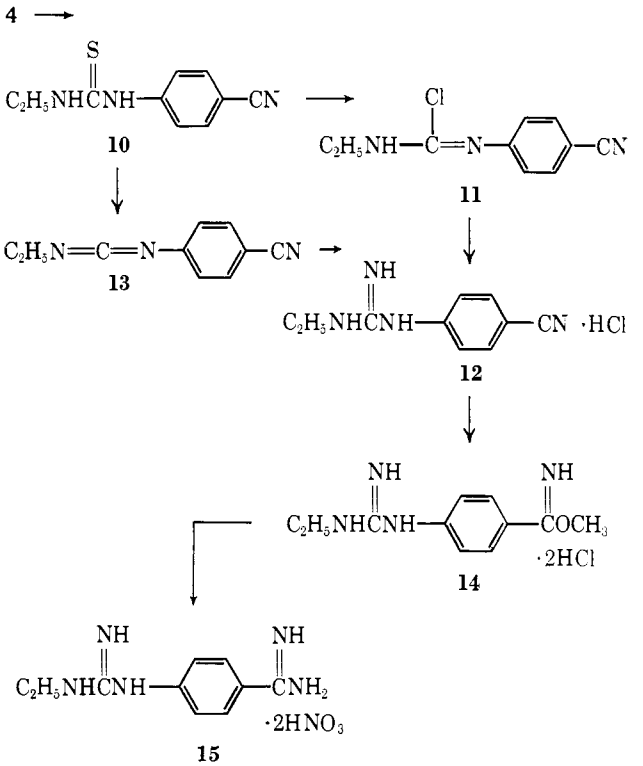


p-guanidinobenzimidate dihydrochloride (**6**) with methanolic hydrogen chloride. The imidate salt **6** formed *p*-guanidinobenzamidine dihydrochloride (**7**) when treated with ammonia. In the alternative synthesis, *p*-aminobenzamidine hydrochloride (**8**) was converted to **7** with aqueous cyanamide. Reaction of **6** with ethylamine yielded *p*-*N*-ethylamidinophenylguanidine, isolated as the diperchlorate **9**, one of the isomers of phenethylbiguanide.

(2) W. J. Fanshawe, V. J. Bauer, E. F. Ullman, and S. R. Safir, *J. Org. Chem.*, **29**, 308 (1964).

(3) W. J. Fanshawe, V. J. Bauer, and S. R. Safir, *ibid.*, **29**, 942 (1964).

The reaction of ethyl cyanamide with **4** and with **8** failed. Therefore, a different route for the synthesis of the other isomer, **15**, was required. *p*-Aminobenzonitrile (**4**) was allowed to react with ethyl isothiocyanate to provide 1-*p*-cyanophenyl-3-ethyl-2-thiourea (**10**), which was converted to N-*p*-cyanophenyl-N'-ethylchloroformamidine (**11**) with thionyl chloride. The reaction of **11** with ammonia provided the *p*-guanidinobenzonitrile salt **12**. When the preparation of **11** proved to be capricious, another route was devised. Desulfurization of **10** with mercuric oxide gave N-*p*-cyanophenyl-N'-ethylcarbodiimide (**13**), which was converted to **12** with ammonia. The transformation of **12** to 1-*p*-amidinophenyl-3-ethylguanidine dinitrate (**15**) by means of the intermediate imidate salt **14** proceeded smoothly.



The *p*-guanidinobenzamidine salts **7**, **9**, and **15** were administered as suspensions in 0.5% sodium carboxymethylcellulose solution orally at 250 mg/kg to normal chicks and intraperitoneally at 200 mg/kg to normal rats. Blood glucose levels, estimated as "reducing sugar" content by the method of Hoffman as modified for the Technicon Auto-Analyzer,[4] were not depressed significantly below controls when determined at 2 hr after dosing for chicks and 3 hr after dosing for rats.

Experimental Section[5]

***p*-Guanidinobenzonitrile Nitrate (5).**—A solution of 100 g (0.85 mole) of *p*-aminobenzonitrile, 425 ml of ethanol, 170 ml of 8 *N* nitric acid, and 75 ml of 50% aqueous cyanamide (Aero® Cyanamide-50, American Cyanamid Co.) was heated under reflux for 6 hr. Then the solution was treated with 5 g of charcoal,

(4) W. S. Hoffman, *J. Biol. Chem.*, **120**, 51 (1937). The animal testing was carried out by Drs. C. Boshart, S. Gordon, and E. Tocus of these laboratories.

(5) Melting points were determined in a Hershberg apparatus and are uncorrected. Microanalyses were performed by Mr. L. M. Brancone and staff. The syntheses of **5** and **6** were first developed by Mr. P. T. MacGregor and Dr. M. J. Weiss of these laboratories.

filtered, and stored at 5° overnight. The solid which separated was collected and dried at 120° in a vacuum oven. The product consisted of 55 g (29%) of colorless prisms, mp 238–240°.

p-Guanidinobenzonitrile.—To a boiling solution of 39.1 g (0.18 mole) of **5** in 500 ml of water was added a solution of 7.0 g (0.18 mole) of NaOH in 25 ml of water. Upon cooling, colorless crystals, 18.8 g (65%), mp 200–203°, separated. A sample was recrystallized three times from ethanol, affording colorless prisms, mp 216–217° dec.

Anal. Calcd for $C_8H_8N_4$: C, 59.98; H, 5.03; N, 34.98. Found: C, 60.09; H, 5.18; N, 34.60.

Methyl p-Guanidinobenzimidate Dihydrochloride (6).—To 200 ml of cold saturated methanolic HCl in a pressure bottle was added 30 g of *p*-guanidinobenzonitrile. The mixture was shaken at room temperature for 24 hr. The solid was collected, washed with ether, and dried, affording 44 g (88%) of colorless crystals, mp 287–288° dec. The material was used without purification.

p-Guanidinobenzamidine Dihydrochloride (7). A.—A solution of 1.0 g (3.8 mmoles) of methyl **6** and 10 ml of cold saturated methanolic NH_3 was allowed to stand at room temperature for 5 hr. The solvent was removed on a steam bath under a stream of nitrogen leaving a colorless solid residue. Three recrystallizations from water provided 0.31 g (33%) of colorless needles, mp 293° dec.

Anal. Calcd for $C_8H_{12}Cl_2N_6$: C, 38.41; H, 5.23; Cl, 28.34; N, 28.00. Found: C, 38.20; H, 5.48; Cl, 27.93; N, 27.77.

B.—A solution of 13.6 g (0.08 mole) of *p*-aminobenzamidine hydrochloride,[6] 32.0 ml of 3 *N* ethanolic HCl, 80 ml of water, and 6.2 ml (0.075 mole) of 50% aqueous cyanamide was heated under reflux for 6 hr. The solvent was removed under reduced pressure on a steam bath, and the oily residue was triturated with ethanol. The residual solid amounted to 9.7 g (52%) of colorless crystals, mp 291–297°. Recrystallization from water gave 3.6 g of product, mp 295–296° dec, undepressed upon admixture with a sample prepared as in method A, above.

p-N-Ethylamidinophenylguanidine Diperchlorate (9).—A solution of 100 ml of methanol, 25 ml of ethylamine, and 10.0 g (0.038 mole) of methyl *p*-guanidinobenzimidate dihydrochloride was stored in a pressure bottle at room temperature for 12 hr. The solvent was removed under reduced pressure, and the residual oil was treated with 40 ml of 3 *N* ethanolic HCl. The solid which separated amounted to 8.80 g of colorless crystals, mp 250–260°. This solid was dissolved in 10 ml of water, and 7 ml of 70% $HClO_4$ was added. The precipitate which formed consisted of 8.80 g (57%) of colorless crystals, mp 211–212°. Three recrystallizations from water provided the analytical sample, mp 213–214°.

Anal. Calcd for $C_{10}H_{17}Cl_2N_5O_8$: C, 29.57; H, 4.22; Cl, 17.46; N, 17.24. Found: C, 30.11; H, 4.61; Cl, 17.21; N, 17.50.

1-p-Cyanophenyl-3-ethyl-2-thiourea (10).—A solution of 5.90 g (0.05 mole) of *p*-aminobenzonitrile, 4.35 g (0.05 mole) of ethyl isothiocyanate, and 20 ml of dimethyl sulfoxide was heated on a steam bath for 4 hr. The dark solution was poured into 250 ml of water, and the solid, mp 93–105°, which separated was collected. Two crystallizations from benzene gave 6.25 g (61%) of fine colorless needles, mp 132–133°.

Anal. Calcd for $C_{10}H_{11}N_3S$: C, 58.53; H, 5.40; N, 20.48; S, 15.59. Found: C, 58.55; H, 5.40; N, 20.35; S, 15.42.

In other runs, a crystalline modification, mp 116–117°, was obtained and employed with equal success in subsequent reactions.

N-p-Cyanophenyl-N'-ethylchloroformamidine (11).—To a cold solution of 4.90 g (0.024 mole) of 1-*p*-cyanophenyl-3-ethyl-2-thiourea in 50 ml of glyme was added 1.8 ml (2.9 g, 0.024 mole) of thionyl chloride. A solid immediately separated, then became oily, and after stirring for 2 days, solidified to 6.0 g of a pale yellow powder, mp 120–129° dec. A sample was recrystallized from acetonitrile for analysis, affording pale yellow crystals, mp 130–140° dec.

Anal. Calcd for $C_{10}H_{10}ClN_3$: C, 57.83; H, 4.85; Cl, 17.08; N, 20.23. Found: C, 58.16; H, 4.81; Cl, 15.95; N, 20.49.

1-p-Cyanophenyl-3-ethylcarbodiimide (13).—A suspension of 2.05 g (0.01 mole) of 1-*p*-cyanophenyl-3-ethyl-2-thiourea, 4.32 g (0.02 mole) of mercuric oxide, and 100 ml of ether was shaken for 8 hr. The mixture was filtered, and the solvent was distilled under reduced pressure leaving a colorless oil, which was used without purification. The infrared spectrum exhibits bands at 4.50 (−C≡N) and 4.65 μ (N=C=N).

1-p-Cyanophenyl-3-ethylguanidine Hydrochloride (12). A.—To a cold saturated solution of NH_3 in 250 ml of dioxane was added with stirring 25 g (0.12 mole) of crude N-*p*-cyanophenyl-N'-ethylchloroformamidine. The mixture was stirred at room temperature for 20 hr, heated on a steam bath for 1 hr, and filtered. The filtrate was concentrated under reduced pressure to an oil which was taken up in 30 ml of 3 *N* ethanolic HCl. The solution was concentrated to an oil, which was triturated with acetonitrile. The solid was collected, washed with acetonitrile and ether, and dried, leaving 8.70 g (32%) of colorless crystals, mp 185–186°. A sample was twice recrystallized from ethanol, providing colorless prisms, mp 185–186°.

Anal. Calcd for $C_{10}H_{13}ClN_4$: C, 53.45; H, 5.83; Cl, 15.78; N, 24.93. Found: C, 53.30; H, 6.09; Cl, 15.71; N, 24.69.

B.—Ammonia was bubbled through a solution of N-*p*-cyanophenyl-N'-ethylcarbodiimide (prepared from 19.5 g of 1-*p*-cyanophenyl-3-ethyl-2-thiourea) in 1 l. of ether for 30 min. The white solid which separated was collected and consisted of 8.0 g of the crystalline base. This solid was treated with 20 ml of hot 3 *N* ethanolic HCl. Upon cooling 6.4 g (30% yield, based upon thiourea) of colorless crystals, mp 191–192°, separated. The infrared spectrum of the compound was identical with that of the analytical sample prepared in method A, above.

Methyl p-Ethylguanidinobenzimidate Dihydrochloride (14).—A cold solution of 100 ml of dry ether and 6 ml of methanol was saturated with HCl at 0°, and 1.80 g (0.008 mole) of 1-*p*-cyanophenyl-3-ethylguanidine hydrochloride was added. The mixture was shaken at room temperature in a stoppered pressure bottle for 4 hr, and allowed to stand overnight. The solid which separated was collected, washed with ether, and dried, affording 2.10 g (89%) of an off-white solid, mp 114–120° dec.

1-p-Amidinophenyl-3-ethylguanidine Dinitrate (15).—To 50 ml of cold saturated methanolic NH_3 was added with stirring 5.0 g (0.017 mole) of **14**. After 1 hr at 0° and 2 hr at room temperature, the solid was collected and added to 25 ml of saturated aqueous $NaNO_2$. Colorless crystals, mp 180–185°, separated. Two recrystallizations from water provided 3.6 g (64%) of colorless prisms, mp 206–207°. A small portion was twice recrystallized from water, affording the analytical sample, mp 205–206°.

Anal. Calcd for $C_9H_{15}N_7O_6$: C, 36.25; H, 5.17; N, 29.60. Found: C, 36.33; H, 5.44; N, 29.81.

(6) F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 412 (1961).

The Chemical Structure of a Cocarcinogen and of Phorbol Isolated from Croton Oil

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In a recent paper Arroyo and Holcomb[1] confirmed our earlier findings[2,3] on the isolation and identification of the cocarcinogenic principle A1 ($C_{36}H_{56}O_8$) from croton oil. Compound A1 is one of eight cocarcinogens so far isolated as pure compounds and characterized chemically as well as biologically.[4,5] By partial synthesis A1 has been identified[6] as one of two possible

(1) E. R. Arroyo and J. Holcomb, *J. Med. Chem.*, **8**, 672 (1965).

(2) E. Hecker, H. Bresch, and Ch. von Szczepanski, *Angew. Chem. Intern. Ed. Engl.*, **3**, 227 (1964); E. Hecker and H. Bresch, *Z. Naturforsch.*, **20b**, 216 (1965).

(3) E. Hecker, H. Bresch, and J. G. Meyer, Abstracts of Papers, 1st World Fat Congress, Hamburg, 1964, p 176; see also *Fette, Seifen, Anstrichmittel*, **67**, 78 (1965).

(4) E. Hecker, H. Kubinyi, and H. Bresch, *Angew. Chem. Intern. Ed. Engl.*, **3**, 747 (1964); E. Hecker and H. Kubinyi, *Z. Krebsforsch.*, **67**, 176 (1965).

(5) E. Clarke and E. Hecker, *Naturwiss.*, **52**, 446 (1965); *Z. Krebsforsch.*, **67**, 192 (1965).

(6) H. Kubinyi, Ph.D. Thesis, University of Munich, 1964; E. Hecker, H. Kubinyi, H. U. Schairer, Ch. von Szczepanski and H. Bresch, *Angew. Chem. Intern. Ed. Engl.*, **4**, 1072 (1965).