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 $C_{10}H_9ClN_3$: 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).

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

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 $NaNO_3$. 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 $C_9H_{17}N_7O_6$: C, 36.25; H, 5.17; N, 29.60. Found: C, 36.33; H, 5.44; N, 29.81.

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).

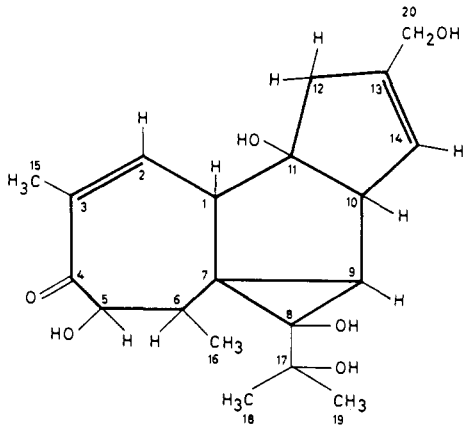
(2) E. Hecker, H. Bresch, and Ch. von Szczepanski, *Angew. Chem. Intern. Ed. Engl.*, **3**, 227 (1964); E. Hecker and H. Bresch, *Z. Naturforsch.*, **20b**, 216 (1965).

(3) E. Hecker, H. Bresch, and J. G. Meyer, Abstracts of Papers, 1st World Fat Congress, Hamburg, 1964, p 476; see also *Fette, Seifen, Anstrichmittel*, **67**, 78 (1965).

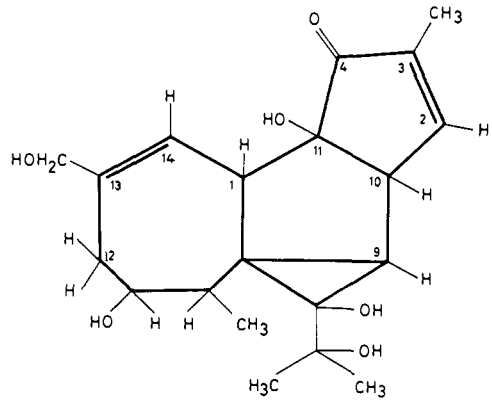
(4) E. Hecker, H. Kubinyi, and H. Bresch, *Angew. Chem. Intern. Ed. Engl.*, **3**, 747 (1964); E. Hecker and H. Kubinyi, *Z. Krebsforsch.*, **67**, 176 (1965).

(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).



(I)



(II)

isomeric diesters of the diterpene parent alcohol phorbol, $C_{20}H_{28}O_6$,[2,3] with acetic and myristic acids. In agreement with chemical and physical data accumulated in our laboratory structure I has been proposed for phorbol,[7] and an entirely different formula discussed by Arroyo and Holcomb[8] has been excluded.[7]

In the above mentioned paper[1] "from the infrared, nmr, ultraviolet, and other evidence at hand" the authors now suggest structure II for phorbol, but they do not relate this structure to retene which they claim to have obtained as a product of dehydrogenation of phorbol,[8] nor do they give any detailed account for essential structural features of II (*e.g.*, the cyclopropane ring, ditertiary glycol). Nevertheless, II contains all structural units from our earlier proposal[7] but the sequences C-2, -3, and -4 and C-14, -13, and -12 of I are being exchanged. From our detailed nmr data[7] (in pyridine-d_5) this exchange of sequences clearly is excluded: spin-decoupling technique definitely establishes the sequence H-9 (1.34 ppm, doublet $J_{9,10}$ = 5.5–6.0 cps), H-10 (3.93 ppm, triplet $J_{9,10}$ = 5.5–6.0, $J_{1,14}$ = 5.5–6.0 cps), and H-14 (6.17 ppm, doublet $J_{1,14}$ = 5.5–6.0 cps) as suggested for I. H-2 (7.88 ppm, multiplet, $J_{1,2}$ = 0.5–1.0, $J_{2,15}$ = 1–2 cps) shows coupling with H-1 and long-range coupling with H-15 but no coupling with H-10. Also H-2 and H-14 can be differentiated: after reduction of the carbonyl group in phorbol with $LiAlH_4$,[7] H-2 is shifted approximately 2 ppm toward higher field. Furthermore the sequence H-9, -10, and -14 can be extended including C-13 and C-20 as in I; after oxidation of the allylic hydroxyl group to the aldehyde in appropriate esters of phorbol, H-14 is being shifted approximately 1 ppm[7] toward lower field. Also a singlet (3.10 ppm)[7] was recorded for H-12 contrary to its position in II but in accordance with its position in I. Also the sequence H-12 and -5 as suggested in II would result in a multiplet for H-5 since we find a doublet (5.03 ppm, J = 10.5–11.0 cps)[7] for H-5 indicating coupling only with H-6, whereas in the case of II at least one additional coupling would be expected.

(7) H. Kubinyi, Ph.D. Thesis, University of Munich, 1964; E. Hecker, H. Kubinyi, Ch. von Szczepanski, E. Härle, and H. Bresch, *Tetrahedron Letters*, 1837 (1965).

(8) E. R. Arroyo and J. Holcomb, *Chem. Ind.* (London), 350 (1965); see also B. L. van Duuren, *ibid.*, 943 (1965).

Biologically Active Guanidines and Related Compounds. III.[1] Some Aryloxyalkylurea Derivatives

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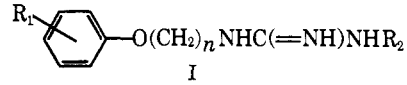
Previously we have described series of aryloxyalkylguanidines[2] (I, R_2 = H) and aminoguanidines[1] (I, R_2 = NH_2) which are compounds displaying marked activity in blocking the sympathetic nervous system and are antiinflammatory agents particularly when the aryl group is 2,6-xylyl [I, R_1 = 2,6-$(CH_3)_2$]. Extending this work, we have investigated the effect of replacing the strongly basic guanidinium residue of these compounds by the weakly basic urea function. Accordingly we report the preparation and biological activity of a series of aryloxyalkylureas (II) and related structures.

2-Phenoxyethylurea (II, R = H; n = 2) was synthesized by Gabriel[3] from 2-phenoxyethylamine hy-



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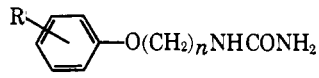

II

drochloride and potassium cyanate, and this method was used in the preparation of 2-(2,6-xylyloxy)ethylurea [II, R = 2,6-$(CH_3)_2$; n = 2] and the higher homologs (n = 3 or 4).

Reaction of 2-(2,6-xylyloxy)ethylhydrazine hydrochloride[1] with potassium cyanate occurred at the secondary nitrogen atom yielding the semicarbazide III. This reaction is in accord with the known reaction of methylhydrazine hydrochloride with potassium cya-

(1) Previous paper: G. J. Durant, C. M. Smith, R. G. W. Spickett, and S. H. B. Wright, *J. Med. Chem.*, **9**, 22 (1966).

(2) D. I. Barron, P. M. G. Bavin, G. J. Durant, I. L. Natoff, R. G. W. Spickett, and D. K. Vallance, *ibid.*, **6**, 705 (1963).

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