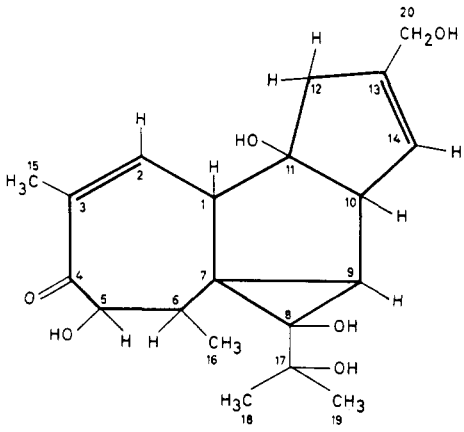
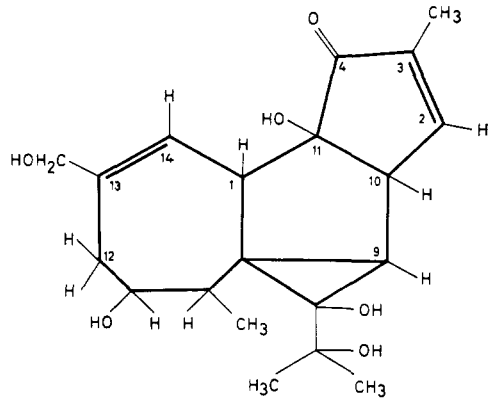


(I)



(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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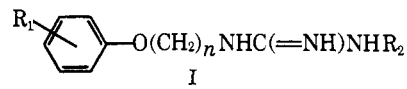
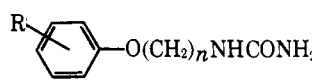
Previously we have described series of aryloxyalkylguanidines[2] (I, R_2 = H) and aminoguanidines[1] (I, R_2 = NH_2) which are compounds displaying marked activity in blocking the sympathetic nervous system and are antiinflammatory agents particularly when the aryl group is 2,6-xylyl [I, R_1 = 2,6-$(CH_3)_2$]. 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-



I



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-

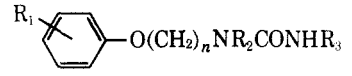
(1) Previous paper: G. J. Durant, G. M. Smith, R. G. W. Spickett, and S. H. B. Wright, *J. Med. Chem.*, **9**, 22 (1966).

(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).

(3) S. Gabriel, *Chem. Ber.*, **47**, 3029 (1914).

TABLE I

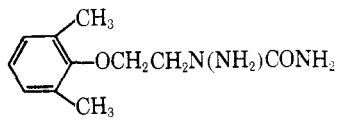
ARYLOXYALKYLUREAS AND RELATED STRUCTURES



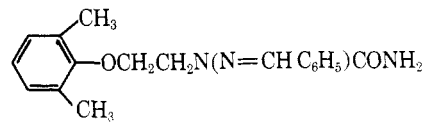
No.	R_1	n	R_2	R_3	Mp, °C	Recrystn solvent[a]	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
1	2,6-$(CH_3)_2$	2	H	H	142–143	BP	$C_{11}H_{16}N_2O_2$	63.43	63.36	7.75	8.02	13.46	13.43
2	2,6-$(CH_3)_2$	3	H	H	109–111	B	$C_{12}H_{18}N_2O_2$	64.84	64.67	8.16	8.32	12.60	12.71
3	2,6-$(CH_3)_2$	4	H	H	106–109	B	$C_{13}H_{20}N_2O_2$	66.07	66.18	8.53	8.47	11.86	12.12
4	4-Cl	2	H	H	159.5–162	IP	$C_9H_{11}ClN_2O_2$	50.47	50.64	5.18	5.13	13.08	13.39
5	2,6-$(CH_3)_2$	2	H	1-$C_{10}H_7$	192–194	E	$C_{21}H_{22}N_2O_2$	75.42	75.39	6.63	6.92	8.38	8.52
6	2,6-$(CH_3)_2$	4	H	C_6H_5CO	107–109	E	$C_{20}H_{24}N_2O_2$	70.56	70.28	7.11	7.19	8.23	8.06
7	2,6-$(CH_3)_2$	2	NH_2	H	112.5–115	T	$C_{11}H_{17}N_3O_2$	59.17	59.43	7.68	7.75	18.82	18.96
8	2,6-$(CH_3)_2$	2	$C_6H_5CH{=}N$	H	152–155	EW	$C_{18}H_{21}N_3O_2$	69.43	69.38	6.80	6.72	13.50	13.58

[a] BP = benzene–petroleum ether (60–80°), B = benzene, IP = isopropyl alcohol–petroleum ether (60–80°), E = ethanol, T = toluene, EW = ethanol–water.

nate which occurs at the secondary nitrogen atom to yield 2-methylsemicarbazide[4] and contrasts with the reaction of 2-(2,6-xylyloxy)ethylhydrazine with 2-methyl-2-thiopseudourea which reacts at the primary nitrogen atom.[4,5] The semicarbazide readily yielded the semicarbazone IV with benzaldehyde showing the presence of a primary amino function and thereby indicating the 2-substituted semicarbazide structure III. These and related compounds synthesized are listed in Table I.



III



IV

Biological Activity.—None of the compounds examined had sympathetic blocking activity in the nictitating membrane assay in the cat.[2] The compounds were also examined for antiinflammatory activity in a rat paw edema assay using yeast as irritant[6] and in the ultraviolet erythema test.[7] The semicarbazide derivative **7** was active in the latter test (0.1 times phenylbutazone) but other compounds were devoid of significant activity in these assays at 200 mg/kg. In anticonvulsant tests **7** had activity of the order 0.1 times diphenylhydantoin in the electroshock seizure assay[8] and the ureas **1**, **2**, and **3** were also slightly active (of the order 0.02–0.03 times diphenylhydantoin). Further evidence of central nervous system effects for these compounds was obtained from dose-range toxicity studies in mice, the ureas **1**, **2**, and **3** giving indications of general CNS depression (loss of righting reflex at approximately 250 mg/kg *po* with LD_{50} values >1000 mg/kg).

Replacement of the strongly basic guanidine moiety in aryloxyalkylguanidines by the less basic urea function would appear to decrease the peripheral biological effects of these compounds but there is some evidence of activity in the central nervous system.

Experimental Section[9]

3-(2,6-Xylyloxy)propylurea.—A solution of 3-(2,6-xylyloxy)-propylamine hydrochloride (10.0 g, 0.046 mole) in water (20 ml) was added to a solution of KCNO (3.77 g, 0.046 mole) in water (10 ml), and the mixture was heated on the steam bath for 30 min. After cooling, the solid was separated and recrystallized from benzene yielding the pure product (9.2 g, 90% yield), mp 109–111°.

1-(1-Naphthyl)-3-[(2-2,6-xylyloxy)ethyl]urea (5).—1-Naphthyl isocyanate (5.1 g, 0.030 mole) was added to 2-(2,6-xylyloxy)-ethylamine (5.0 g, 0.030 mole) in benzene (10 ml). The resultant mixture was heated on the steam bath for 20 min and cooled, and the precipitated urea was separated and recrystallized from ethanol (8.1 g, 80% yield), mp 192–194°.

1-Benzoyl-3-[4-(2,6-xylyloxy)butyl]urea (6).—A mixture of 4-(2,6-xylyloxy)butylurea (2.96 g, 0.013 mole) and benzoyl chloride (1.64 g, 0.012 mole) was heated on the steam bath for 2 hr and set aside overnight at room temperature. The crystalline product was separated and recrystallized from ethanol yielding 1.8 g (44% yield) of **6**, mp 106–107°.

2-[2-(2,6-Xylyloxy)ethyl]semicarbazides (7).—A mixture of 2-(2,6-xylyloxy)ethylhydrazine hydrochloride[2] (4.3 g, 0.020 mole) and KCNO (1.9 g, 0.022 mole) in water (20 ml) was boiled under reflux for 30 min and then cooled. Crystallization occured and the product was separated and recrystallized from toluene yielding **7** (3.5 g, 78.5% yield), mp 112.5–115°.

1-Benzylidene-2-[2-(2,6-xylyloxy)ethyl]semicarbazide (8).—the semicarbazide (3.2 g, 0.014 mole) and benzaldehyde (1.68 g, 0.016 mole) in ethanol (80 ml) were boiled underre flux for 1 hr, concentrated to half volume, and diluted with a little water. Crystallization occurred affording **8** (2.7 g, 61% yield), mp 152–153°.

Acknowledgments.—The authors would like to thank Dr. R. G. Spickett for his interest and encouragement. Microanalytical data were supplied by Mr. M. Graham of the Analytical Department and biological results by our colleagues in the Pharmacology Department of these laboratories to whom we express our sincere thanks.

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(5) J. Augstein, S. M. Green, A. R. Katritsky, and A. M. Monro, *J. Med. Chem.*, **8**, 395 (1965).

(6) (a) J. Selitto and H. O. Randall, *Federation Proc.*, **13**, 403 (1954); (b) H. Selye, *Brit. Med. J.*, **2**, 1129 (1949).

(7) C. V. Winder, J. Wax, V. Burr, M. Been, and C. E. Rosiere, *Arch. Intern. Pharmacodyn.*, **116**, 261 (1958).

(8) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exptl. Therap.*, **106**, 319 (1952).

(9) Melting points were recorded using an Electrothermal apparatus comprising a gas-heated block and a thermometer calibrated for stem exposure.