in brain–heart infusion (BHI) broth (Difco 0037-01-6) at 36 °C. Twofold dilutions of the stock solution (2000 μg/mL) of the test compound were made in BHI agar to obtain the test concentration ranging from 200 to 0.005 μg/mL. The plate was inoculated with approximately 10^4 organisms. It was then incubated at 36 °C for 18 h. The minimal inhibitory concentration (MIC) was the lowest concentration of the test compound that yielded no visible growth on the plate.

Acknowledgment. We thank the staff of the microbiological team for biological testings, Akiyo Claiborne for her expert technical assistance, and the staff of the Analytical Department for microanalyses.

Registry No. **3**, 86483-51-4; **4**, 615-20-3; **5**, 102614-42-6; **6**, 102614-43-7; **7**, 102614-44-8; **7** (free base), 102614-48-2; **8**, 102614-45-9; **9**, 102614-46-0; **10**, 102614-47-1; **10** (free base), 102614-49-3; **11**, 98106-13-9; **12**, 98106-14-0; **13**, 98106-25-3; **14**, 98106-26-4; *N*-carbethoxypiperazine, 120-43-4; *N*-methylpiperazine, 109-01-3; *N*-acetylpiperazine, 13889-98-0.

Anticonvulsant Activity of 2- and 3-Aminobenzanilides

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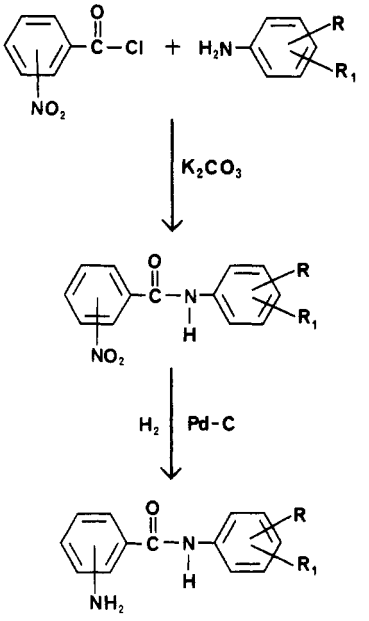
A series of 2- and 3-aminobenzanilides derived from ring-alkylated anilines were prepared and evaluated for anticonvulsant activity. These benzanilides were prepared in the course of studies designed to determine the relationship between the benzamide structure and anticonvulsant effects. The compounds were tested in mice against seizures induced by maximal electroshock (MES) and pentylenetetrazole and in the rotorod assay for neurologic deficit. The 3-aminobenzanilide derived from 2,6-dimethylaniline, **21**, was the most potent anti-MES compound, with an ED50 of 13.48 mg/kg and a protective index of 21.11 (PI = TD50/ED50). The activity profile for **21** compares favorably with that for phenobarbital and phenytoin.

Recent reports[1,2] from this laboratory described the anticonvulsant activity for numerous 4-aminobenzamides of alkyl- and arylamines. Several of these amides show a high level of protection against maximal electroshock (MES) induced convulsions in animal models. These compounds are less effective against subcutaneous pentylenetetrazole (scMet) induced convulsions, and the profile of anticonvulsant activity and toxicity for the more potent analogues resembles that for phenobarbital and phenytoin.

Structurally, some of the simplest compounds possessing anticonvulsant properties are carboxylic acids and their amides.[3] Valproic acid is perhaps the best known example of this class of compounds.[4] Half the dose of valproic acid amide has been shown[5] to be as effective as the dose of valproic acid. Various reports[6,7] have described the anticonvulsant effects of substituted cinnamamides. Cinromide, 3-bromo-*N*-ethylcinnamamide, has been evaluated as a broad-spectrum anticonvulsant and has a reported anti-MES ED50 of 60 mg/kg when administered intraperitoneally (ip) in mice.[7] Several derivatives of 3-phenyl-2-piperidinone have been shown to possess anti-MES and anti-scMet activity in animal models.[8]

The unique behavioral profile produced in animals by substituted benzamide neuroleptics such as metoclopramide has generated considerable interest in recent years.[9]

Scheme I



The benzamide neuroleptics are useful in the treatment of schizophrenia and appear to exert their neuroleptic action selectively at a subpopulation of the D-2 type dopamine receptors.[10] The aminobenzanilides reported in this paper were prepared in an effort to determine the optimal disubstitution pattern in the aminobenzoyl moiety and are a continuation of our studies on the relationship between benzamide structure and anticonvulsant activity.

Results and Discussion

A series of 2- and 3-aminobenzanilides were prepared and evaluated for anticonvulsant activity. The study was conducted in an effort to further elucidate the relationship between benzamide structure and anticonvulsant activity. Previous studies[1,2] demonstrated the potent anticonvulsant properties of several 4-aminobenzamides. The amino-

(1) Clark, C. R.; Wells, M. J. M.; Sansom, R. T.; Norris, G. N.; Dockens, R. C.; Ravis, W. R. *J. Med. Chem.* **1984**, *27*, 779.
(2) Clark, C. R.; Sansom, R. T.; Lin, C.-M.; Norris, G. N. *J. Med. Chem.* **1985**, *28*, 1259.
(3) Murray, W. J.; Kier, L. B. *Med. Chem. (Academic Press)* **1977**, *15*, 591.
(4) Meunier, G.; Carrey, G.; Mennier, Y.; Eymard, P.; Aimard, M. *Therapie* **1963**, *18*, 435.
(5) Carrey, G.; Boucherle, A.; Lebreton, S.; Benoit-Guyod, J. L.; Boitard, M. *Therapie* **1964**, *19*, 917.
(6) Br. Patent 663 903; *Chem. Abstr.* **1957**, *46*, 6336.
(7) Perchalski, R. J.; Karas, B. J.; Wilder, B. J. In *Antiepileptic Drugs*, 2nd ed.; Woodbury, D. M., Penry, J. K., Pippenger, C. E., Eds.; Raven: New York, 1982; Chapter 72, p 817.
(8) Brouillette, W. J.; Grunewald, G. L. *J. Med. Chem.* **1984**, *27*, 202.
(9) Blaney, F. E.; Clark, M. S. G.; Gardner, O. V.; Hadley, M. S.; Middleton, D.; White, T. J. *J. Med. Chem.* **1983**, *26*, 1747.
(10) Jenner, P.; Marsden, C. D. *Acta Psychiatr. Scand., Suppl.* **1984**, *69*, 109.

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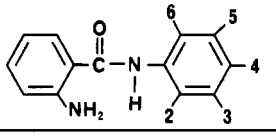
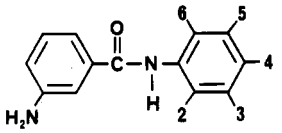
Table I. Physical Properties of 2-Aminobenzanilides[a]



compd	substituent position 2	3	4	5	6	mp, °C	yield,[b,c] %	formula	anal.
1	H	H	H	H	H	125–127	59	$C_{13}H_{12}N_2O$	C, H, N
2	CH_3	H	H	H	H	104–106	51[d]	$C_{14}H_{14}N_2O$	C, H, N
3	H	CH_3	H	H	H	118–119	53	$C_{14}H_{14}N_2O$	C, H, N
4	H	H	CH_3	H	H	148–150	56	$C_{14}H_{14}N_2O$	C, H, N
5	CH_3	CH_3	H	H	H	133–135	56	$C_{15}H_{16}N_2O$	C, H, N
6	CH_3	H	CH_3	H	H	138–139	59	$C_{15}H_{16}N_2O$	C, H, N
7	CH_3	H	H	CH_3	H	155–156	48	$C_{15}H_{16}N_2O$	C, H, N
8	CH_3	H	H	H	CH_3	134–135	50	$C_{15}H_{16}N_2O$	C, H, N
9	H	CH_3	CH_3	H	H	115–116	53	$C_{15}H_{16}N_2O$	C, H, N
10	H	CH_3	H	CH_3	H	160–162	51	$C_{15}H_{16}N_2O$	C, H, N
11	$CH(CH_3)_2$	H	H	H	H	149–151	56	$C_{16}H_{18}N_2O$	C, H, N
12	$CH(CH_3)_2$	H	H	H	CH_3	115–117	46[d]	$C_{17}H_{20}N_2O$	C, H, N
13	$CH(CH_3)_2$	H	H	H	CH_2CH_3	137–139	53[d]	$C_{18}H_{22}N_2O$	C, H, N

[a] The infrared and nuclear magnetic resonance (^1H) spectra were consistent with structural assignments. [b] Yield based on the recovery of recrystallized product. [c] Recrystallized from C_6H_6 unless noted otherwise. [d] Recrystallized from C_6H_6–petroleum ether.

Table II. Physical Properties of 3-Aminobenzanilides[a]



compd	substituent position 2	3	4	5	6	mp, °C	yield,[b,c] %	formula	anal.
14	H	H	H	H	H	124–125	65[d]	$C_{13}H_{12}N_2O$	C, H, N
15	CH_3	H	H	H	H	143–144	67	$C_{14}H_{14}N_2O$	C, H, N
16	H	CH_3	H	H	H	95–97	61	$C_{14}H_{14}N_2O$	C, H, N
17	H	H	CH_3	H	H	160–161	56	$C_{14}H_{14}N_2O$	C, H, N
18	CH_3	CH_3	H	H	H	174–175	64	$C_{15}H_{16}N_2O$	C, H, N
19	CH_3	H	CH_3	H	H	178–180	56	$C_{15}H_{16}N_2O$	C, H, N
20	CH_3	H	H	CH_3	H	175–177	53	$C_{15}H_{16}N_2O$	C, H, N
21	CH_3	H	H	H	CH_3	200–202	55	$C_{15}H_{16}N_2O$	C, H, N
22	H	CH_3	CH_3	H	H	116–118	51	$C_{15}H_{16}N_2O$	C, H, N
23	H	CH_3	H	CH_3	H	142–144	50	$C_{15}H_{16}N_2O$	C, H, N
24	$CH(CH_3)_2$	H	H	H	H	128–123	55	$C_{16}H_{18}N_2O$	C, H, N
25	$CH(CH_3)_2$	H	H	H	CH_3	174–176	57	$C_{17}H_{20}N_2O$	C, H, N
26	$CH(CH_3)_2$	H	H	H	CH_2CH_3	208–209	68	$C_{18}H_{22}N_2O$	C, H, N

[a] The infrared and nuclear magnetic resonance (^1H) spectra were consistent with structural assignments. [b] Yield based on the recovery of recrystallized product. [c] Recrystallized from C_6H_6 unless noted otherwise. [d] Recrystallized from C_6H_6–petroleum ether.

Table III. Physical Properties for the Intermediate Nitrobenzanilides

compd[a]	mp,[b] °C	yield,[c] %	compd[a]	mp,[b] °C	yield,[c] %
1a	152–153	68	**14a**	150–152	86
2a	174–176	63	**15a**	151–152	85
3a	145–147	60	**16a**	115–118	81
4a	146–148	57	**17a**	159–161	61
5a	177–179	62	**18a**	171–172	82
6a	163–165	58	**19a**	165–166	81
7a	173–175	61	**20a**	188–189	91
8a	209–210	68	**21a**	191–192	87
9a	152–154	61	**22a**	181–183	77
10a	164–166	57	**23a**	177–179	54
11a	152–154	49	**24a**	129–131	76
12a	148–150	62	**25a**	174–176	75
13a	154–157	59	**26a**	213–215	75

[a] The compound numbers correspond to the substitution pattern for those in Tables I and II. [b] All compounds recrystallized from C_6H_6. [c] Yield based on the recovery of recrystallized product.

benzanilides reported herein were prepared according to well-known synthetic procedures (Scheme I). The intermediate nitrobenzanilides were obtained from 2- or 3-nitrobenzoyl chloride and the appropriate alkylaniline under basic conditions.[11] The resulting nitrobenzanilides were crystalline solids showing carbonyl absorption in the infrared spectrum at approximately 1685 and 1675 cm^{-1} for the 2-nitro- and 3-nitrobenzanilides, respectively. The aromatic nitro group was reduced by low-pressure catalytic hydrogenation, and the physical properties of the resulting aminobenzanilides are reported in Tables I and II. Physical data for the intermediate nitrobenzanilides are reported in Table III.

Table IV. Anticonvulsant Activity of 2-Aminobenzanilides

compd[c]	MES[a] 30 min	MES[a] 4 h	scMet[a] 30 min	scMet[a] 4 h	tox[a,b] 30 min	tox[a,b] 4 h
1	2	–	–	–	1	–
2	2	1	1	–	2	–
5	–	–	1	–	1	–
6	1	1	1	–	1	–
8	2	1	2	–	2	–
12	1	–	–	–	–	–

[a] 4 = activity at 30 mg/kg, 3 = activity at 100 mg/kg, 2 = activity at 300 mg/kg, 1 = activity at 600 mg/kg, – = no activity at 600 mg/kg. [b] Determined by the rotorod procedure. [c] Compounds **3**, **4**, **7**, **9–11**, and **13** were inactive at 600 mg/kg.

(11) Sonntag, N. O. V. *Chem. Rev.* **1953**, *52*, 237.

Table V. Anticonvulsant Activity of 3-Aminobenzanilides

	MES[a]		scMet[a]		tox[a,b]	
compd[c]	30 min	4 h	30 min	4 h	30 min	4 h
14	3	2	2	1	2	1
15	3	2	2	–	2	1
16	3	1	2	1	2	1
17	2	2	–	–	–	1
18	1	–	–	–	–	–
21	4	3	–	–	1	1
22	1	–	1	–	–	–
23	2	2	2	–	1	1
24	2	1	–	–	2	1
25	1	2	–	–	–	–
26	2	1	–	–	–	–

[a] 4 = activity at 30 mg/kg, 3 = activity at 100 mg/kg, 2 = activity at 300 mg/kg, 1 = activity at 600 mg/kg, – = no activity at 600 mg/kg. [b] Determined by the rotorod procedure. [c] Compounds 19 and 20 were inactive at 600 mg/kg.

Results of the initial anticonvulsant and toxicity evaluation of the aminobenzanilides are reported in Tables IV and V. The preliminary screening was done at doses of the test compounds from 30 mg/kg up to 600 mg/kg administered ip in mice and evaluated against MES-induced seizures and scMet-induced convulsions and in the rotorod assay for neurologic deficit. The time of peak anticonvulsant activity was not established and toxicities are only estimated. The intermediate nitrobenzanilides were essentially inactive in the anticonvulsant tests. The results of the anticonvulsant screening for the 2-aminobenzanilides (Table IV) show only slight activity for a few compounds with the majority showing no toxicity or activity at doses up to 600 mg/kg. Compounds 2 and 8 showed marginal activity when given in doses of 300 mg/kg; however, this activity was not considered sufficient to warrant determination of quantitative anticonvulsant data.

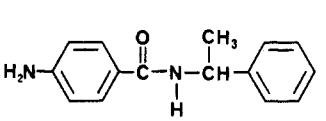
The 3-aminobenzanilides were considerably more active than the 2-aminobenzanilides in the initial anticonvulsant screen. Table V shows that most of the compounds prevented MES-induced convulsions at nontoxic doses; however, scMet activity when present occurred at toxic dose levels. The unsubstituted compound, 14, and the monomethylated benzanilides 15 and 16 showed anti-MES activity at doses of 100 mg/kg 30 min after administration. These three compounds presented very similar activity profiles in all test procedures. All animals (four out of four) dosed at 300 mg/kg displayed rotorod toxicity for each of the three compounds. Thus, these initial studies suggested a low protective index (PI = TD50/ED50) for all these compounds.

Dimethylation of the aniline ring reduced anticonvulsant activity, compared to 14, in all cases except the 2,6-dimethyl analogue 21. Compound 21 showed anti-MES activity 30 min after administration of a dose of 30 mg/kg, and anti-MES activity remained at 4 h after administration of 100 mg/kg. No rotorod toxicity was observed in any of the animals dosed at either level. The *o*-isopropyl compounds 24–26 showed anti-MES activity when given at a dose of 300 mg/kg; however, toxicity was also observed at this dose.

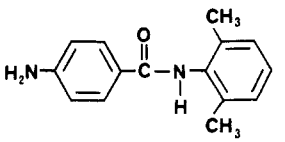
The preliminary screening results indicate that compound 21 has the most anticonvulsant potential of the 2-amino- and 3-aminobenzanilides examined. These preliminary results also allow for some conclusions concerning the structure–activity relationship (SAR) for aminobenzanilides. In a parallel series of 4-aminobenzanilides,[2] anti-MES activity was observed at a dose of 100 mg/kg in 10 of 13 of the substituted anilides. Activity at this level was observed in 4 of 13 3-aminobenzanilides and 0 of 13 2-aminobenzanilides. Thus, in general, the order of anticonvulsant activity of the aminobenzanilides corresponds to the ring substitution pattern of 4-amino > 3-amino > 2-amino.

From the anti-MES screening results, compounds 15 and 21 were chosen for quantitative evaluation against MES-induced convulsions. Table VI shows the results of this study as well as the values obtained for some prototype anticonvulsants in the same test procedures. Compound 15 gave an anti-MES ED50 of 44.47 mg/kg and a TD50 of 108.54, yielding a PI of 2.44. Compound 21 was found to be more active and less toxic than 15. The anti-MES ED50 of 13.48 mg/kg for 21 with a TD50 of 284.57 mg/kg resulted in a PI of 21.11. Thus, 21 shows a high level of anticonvulsant activity and a wide therapeutic window as indicated by the high PI.

Compound 21 is the most promising anticonvulsant compound observed in this study, and its activity can be compared to that of standard prototype anticonvulsant drugs. Compounds 27 and 28 have been identified in previous reports[1,2] as two of the more potent 4-aminobenzamides observed in our studies. Comparative data



27



28

for 27, 28, phenobarbital, phenytoin, and valproic acid are given in Table VI. The anti-MES activity of 21 is intermediate between that of 27 and 28, being slightly more potent than 27, and approximately one-fifth the potency of 28. Compound 28 is the most potent aminobenzamide observed thus far in our studies. Although 21 is less potent than 28, it is also much less toxic, yielding a higher PI than either 27 or 28. The anti-MES activity of 21 is also similar to that of phenobarbital and phenytoin with 21 again showing less rotorod toxicity than either compound. Compounds 21 and 15 showed no anti-scMet activity, which is consistent with previous studies[2] on the 4-aminobenzanilides.

This study together with the information from previous work[2] allows for some general SAR conclusions for these aminobenzanilides. The pattern of substitution in the aminobenzoyl moiety is important for activity, with the

Table VI. Quantitative Anticonvulsant Activity of Selected Aminobenzanilides

		MES		scMet	
compd	TD50[a,b]	ED50[b]	PI[c]	ED50[b]	PI[c]
15	108.54 (105.81–111.38)[d]	44.47 (36.90–54.22)[d]	2.44		
21	284.57 (118.57–579.14)	13.48 (9.90–15.52)	21.11		
27	170.78 (153.02–189.96)	18.02 (13.41–21.43)	9.5	41.72 (38.83–46.00)	4.1
28	15.01 (13.27–16.88)	2.60 (2.18–3.07)	5.77		
phenobarbital	69.01 (62.87–72.89)	21.78 (14.99–25.52)	3.17	13.17 (15.87–15.95)	5.24
phenytoin	65.46 (52.49–72.11)	9.50 (8.13–10.44)	6.89		
valproic acid	424.84 (368.91–450.40)	271.66 (246.97–337.89)	1.57	148.59 (122.64–177.02)	2.87

[a] Rotorod procedure. [b] Doses are in mg/kg. [c] PI = protective index = TD50/ED50. [d] 95% confidence limits.

4-aminobenzanilides showing the highest potency and the 2-aminobenzanilides the least. The 2,6-dimethylaniline derivative is the most potent anti-MES agent in both the 4- and 3-aminobenzanilides. Furthermore, although no quantitative data were measured in the 2-amino series of compounds, the 2,6-dimethylaniline derivative was one of the more active compounds in this group.

Experimental Section

Melting points were determined in open glass capillaries using a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded in chloroform solutions in matched sodium chloride cells or as fluorocarbon mulls by use of a Beckman 4230 spectrophotometer. All ^1H NMR spectra were measured in $CDCl_3$ on a Varian T-60A spectrometer with an internal standard of tetramethylsilane. Elemental analyses (C, H, N) were performed by Atlantic Microlab Inc., Atlanta, GA, and the results obtained were within ±0.4 of the calculated percentage. The following experimental procedures are representative of the general procedures used to synthesize all of the compounds. Experimental data for the 2-amino- and 3-aminobenzanilides are provided in Tables I and II.

Nitrobenzanilides. A solution of the appropriate alkylaniline (0.03–0.07 mol) in 35 mL of tetrahydrofuran was added to 200 mL of 20% (w/v) aqueous potassium carbonate contained in a 1-L three-necked flask equipped with a magnetic stirrer, reflux condenser, addition funnel, and a heating mantle. A solution of nitrobenzoyl chloride (2-fold molar excess) in 35 mL of tetrahydrofuran was added dropwise, and the resulting mixture was refluxed for 12 h and maintained at or above pH 8 during the reaction period. The solution was then cooled to room temperature and extracted with chloroform (3 × 100 mL). The extracts were combined, dried over magnesium sulfate, and evaporated. The resulting residues were purified by recrystallization from benzene.

Aminobenzanilides. A solution of 5.0 g of the appropriate nitrobenzanilide in tetrahydrofuran or absolute ethanol was added to a Paar hydrogenation bottle along with 250 mg of 5% palladium on carbon. The mixture was subjected to low-pressure hydrogenation (45 psi) for 3 h, and the contents of the bottle were filtered through Celite. The filtrate was evaporated and the resulting residue was purified by recrystallization from benzene or benzene–petroleum ether (30–60 °C) mixtures.

Pharmacology. Initial anticonvulsant evaluation of these compounds was conducted using at least three dose levels (30, 100, 300 mg/kg) and in some cases a fourth dose of 600 mg/kg. All tests were performed using male Carworth Farms number-one mice. Test solutions of all compounds were prepared in 30% polyethylene glycol 400, and animals were dosed intraperitoneally 30 min prior to testing.

MES seizures were elicited with a 60-cycle alternating current of 50-mA intensity delivered for 0.2 s via corneal electrodes. A drop of 0.9% saline was instilled in the eye prior to application of electrodes. Abolition of the hind limb tonic extension component of the seizure was defined as protection in the MES test.

The scMet seizure threshold test was conducted by administration of 85 mg/kg of pentylenetetrazole as a 0.5% solution in the posterior midline. Protection in this test was defined as a failure to observe a single episode of clonic spasms of at least 5-s duration during a 30-min period following administration of the test compound.

Neurological deficit was measured in mice by the use of the rotorod test. The dosed animal was placed on a 1-in.-diameter knurled plastic rod rotating at 6 rpm. Neurologic toxicity was defined as the failure of the animal to remain on the rod for 1 min. The median anticonvulsant potency (ED50) and toxicity (TD50) were determined by the graphical method.

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Registry No. 1, 4424-17-3; **1a**, 2385-27-5; 2, 4943-85-5; **2a**, 2385-25-3; 3, 22312-62-5; **3a**, 50623-64-8; 4, 32212-38-7; **4a**, 50623-00-2; 5, 35703-71-0; **5a**, 102630-94-4; 6, 21132-02-5; **6a**, 102630-95-5; 7, 102630-80-8; **7a**, 102630-96-6; 8, 13922-38-8; **8a**, 13922-37-7; 9, 102630-81-9; **9a**, 102630-97-7; 10, 102630-82-0; **10a**, 102630-98-8; 11, 102630-83-1; **11a**, 102630-99-9; 12, 102630-84-2; **12a**, 102631-00-5; 13, 102630-85-3; **13a**, 102631-01-6; 14, 14315-16-3; **14a**, 2243-73-4; 15, 14315-20-9; **15a**, 102631-02-7; 16, 14315-23-2; **16a**, 69754-50-3; 17, 14315-26-5; **17a**, 6911-92-8; 18, 102630-86-4; **18a**, 102631-03-8; 19, 102630-87-5; **19a**, 102631-04-9; 20, 102630-88-6; **20a**, 102631-05-0; 21, 14635-96-2; **21a**, 102631-06-1; 22, 102630-89-7; **22a**, 102631-07-2; 23, 102630-90-0; **23a**, 102631-08-3; 24, 102630-91-1; **24a**, 102631-09-4; 25, 102630-92-2; **25a**, 102631-10-7; 26, 102630-93-3; **26a**, 102631-11-8; aniline, 62-53-3; 2-methylaniline, 95-53-4; 3-methylaniline, 108-44-1; 4-methylaniline, 106-49-0; 2,3-dimethylaniline, 87-59-2; 2,4-dimethylaniline, 95-68-1; 2,5-dimethylaniline, 95-78-3; 2,6-dimethylaniline, 87-62-7; 3,4-dimethylaniline, 95-64-7; 3,5-dimethylaniline, 108-69-0; 2-isopropylaniline, 643-28-7; 2-isopropyl-6-methylaniline, 5266-85-3; 2-isopropyl-6-ethylaniline, 53443-93-9; 2-nitrobenzoyl chloride, 610-14-0; 3-nitrobenzoyl chloride, 121-90-4.

3,17β-Dihydroxy-20,21-epoxy-19-norpregna-1,3,5(10)-trienes: Synthesis, Rearrangement, Cytotoxicity, and Estrogen-Receptor Binding

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Diastereoisomers of 3,17β-dihydroxy-20,21-epoxy-19-norpregna-1,3,5(10)-triene have been prepared as potential antitumor agents. Both isomers undergo the base-catalyzed Payne rearrangement. The isomers were cytotoxic to mammalian cells in culture and were able to displace [^3H]estradiol from binding sites in rat uterine cytosols with $^1/_7$ and $^1/_{70}$ the potency of estradiol. The reasons for this difference are discussed.

Estrogen analogues bearing an alkylating function have been synthesized by several groups in attempts to obtain "receptor-carried cytotoxic agents" active against estrogen-dependent tumors.[1-3] Unfortunately, introduction of the alkylating function into an estrogen often leads to a loss of estrogen-receptor affinity.[4]

It is known from structure–activity studies that the estrogen receptor is relatively tolerant to substitutions at the estrogen 17α-position. Thus ethynylestradiol has a

(1) Chagonda, L. S.; Lockey, P. M.; Marples, B. A.; Traynor, J. R. *Steroids* **1984**, *43*, 283.
(2) Katzenellenbogen, J. A.; McGorrin, R. J.; Tatec, T.; Kempton, R. J.; Carlson, K. E.; Kinder, D. H. *J. Med. Chem.* **1981**, *24*, 435–450.
(3) Leclercq, G.; Henson, J.-C. *Cancer Treat. Rep.* **1978**, *62*, 1255–1257.
(4) *Cytotoxic Estrogens in Hormone Receptive Tumors*; Raus, J., Martens, H., Leclercq, G., Eds.; Academic: London, 1980.

0022-2623/86/1829-1537$01.50/0