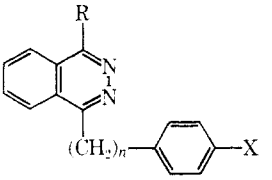
TABLE I: 1-SUBSTITUTED 4-ARYL- (OR 4-ARALKYL-) PHTHALAZINES



No.	R	n	X	Mp, °C	Cryson solvent[a]	Formula	Analyses[b]	Method[c]
1	MeNH	0	H	195–197	A	$C_{15}H_{13}N_3$	C, H, N	C
2	Me_2N	0	H	111–113	B	$C_{16}H_{15}N_3$	C, H, N	C
3	EtNH	0	H	150–151	C–D	$C_{16}H_{15}N_3$	C, H, N	C
4	*n*-PrNH	0	H	103–104	E–D	$C_{17}H_{17}N_3$	C, H, N	C
5	*i*-PrNH	0	H	191–192	A–B	$C_{17}H_{17}N_3$	C, H, N	C
6	$HO(CH_2)_2NH$	0	H	161–163	C	$C_{16}H_{15}N_3O$	C, H, N	D
7	$Me_2N(CH_2)_2NH$	0	H	126–129	A–B	$C_{18}H_{20}N_4$	C, H, N	D
8	$Me_2N(CH_2)_3NH$	0	H	257–259	E	$C_{19}H_{22}N_4 \cdot 2HCl \cdot H_2O$	C, H, Cl, N	B
9	*i*-$PrCH_2NH$	0	H	143–144	C	$C_{18}H_{19}N_3$	C, H, N	B
10	$C_6H_5(CH_2)_2NH$	0	H	147–149	C	$C_{22}H_{19}N_3$	C, H, N	D
11	$C_6H_5CH_2NH$	0	H	219–220	C	$C_{21}H_{17}N_3$	C, H, N	D
12	$[CH_3(CH_2)_3]_2N$	0	H	173–175	A	$C_{22}H_{27}N_3 \cdot HCl$	C, H, Cl, N	D
13	C_3H_5NH[d]	0	H	188–190	C	$C_{17}H_{15}N_3$	C, H, N	D
14	C_5H_9NH[e]	0	H	189–191	E–B	$C_{19}H_{19}N_3$	C, H, N	B
15	$C_6H_{11}NH$[f]	0	H	303–305	F	$C_{20}H_{21}N_4 \cdot HCl$	C, H, N	G
16	C_4H_8N[g]	0	H	106–108	E–D	$C_{18}H_{17}N_3 \cdot 0.25H_2O$[h]	C, H, N	D
17	$C_5H_{10}N$[h]	0	H	152–153	C	$C_{19}H_{19}N_3$	C, H, N	A
18	$C_5H_{10}NO$[i]	0	H	159–160	E–D	$C_{19}H_{19}N_3O$	C, H, N	A
19	C_4H_8NO[j]	0	H	192–194	C	$C_{18}H_{17}N_3O$	C, H, N	D
20	$C_5H_{11}N_2$[k]	0	H	155–158	C	$C_{19}H_{20}N_4$	C, H, N	D
21	$C_{10}H_{13}N_2$[l]	0	H	217–219	F	$C_{24}H_{22}N_4$	C, H, N	D
22	$C_{11}H_{14}NO$[m]	0	H	208–210	C	$C_{25}H_{23}N_3O$	C, H, N	G
23	$C_{11}H_{13}ClNO$[n]	0	H	252–254	F	$C_{25}H_{22}ClN_3O$	C, H, N	G
24	EtO	0	H	91–93	B	$C_{16}H_{14}N_2O$	C, H, N	E
25	*n*-PrO	0	H	71–73	B	$C_{17}H_{16}N_2O$	C, H, N	E
26	*i*-PrO	0	H	102–104	F–D	$C_{17}H_{16}N_2O$	C, H, N	E
27	C_5H_9O[o]	0	H	120–121	B	$C_{19}H_{18}N_2O$	C, H, N	F
28	$C_6H_{11}O$[p]	0	H	111–113	F–D	$C_{20}H_{20}N_2O$	C, H, N	F
29	*i*-PrNH	0	Cl	199–202	F–B	$C_{17}H_{16}ClN_3$	C, H, Cl, N	C
30	$Me_2N(CH_2)_2NH$	0	Cl	265–267	F–G	$C_{18}H_{19}ClN_4 \cdot 2HCl$	C, H, Cl, N	B
31	$Me_2N(CH_2)_3NH$	0	Cl	260–270	F–G	$C_{19}H_{21}ClN_4 \cdot 2HCl$	C, H, Cl, N	B
32	C_3H_5NH[d]	0	Cl	189–191	A	$C_{17}H_{14}ClN_3$	C, H, Cl, N	C
33	EtO	0	Cl	156–157	A–B	$C_{16}H_{13}ClN_2O$	C, H, Cl, N	E
34	*i*-PrO	0	Cl	122–124	B	$C_{17}H_{15}ClN_2O$	C, H, Cl, N	E
35	Cl[q]	0	Cl	190–191	A–B	$C_{15}H_8Cl_2N_2$	C, H, Cl, N	
36	*i*-PrNH	1	H	229–231	F–G	$C_{18}H_{19}N_3 \cdot HCl$	C, H, Cl, N	C
37	$Me_2N(CH_2)_3NH$	1	H	234–236	E–G	$C_{20}H_{24}N_4 \cdot 2HCl$	C, H, Cl, N	B
38	C_3H_5NH[d]	1	H	149–150	A–B	$C_{18}H_{17}N_3$	C, H, N	C
39	*i*-PrO	1	H	91–93	B	$C_{18}H_{18}N_2O$	C, H, N	E

[a] A = EtOAc, B = Skellysolve B (bp 60–80°), C = MeCN, D = H_2O, E = *i*-PrOH, F = EtOH, G = Et_2O. [b] Analytical results obtained for the indicated elements were within ±0.3% of the theoretical values. *Anal.* (compound **16**) H_2O: calcd, 1.61; found, 1.98 (Karl Fischer). [c] See Experimental Section. [d] C_3H_5 = cyclopropyl. [e] C_5H_9 = cyclopentyl. [f] C_6H_{11} = cyclohexyl. [g] C_4H_8N = pyrrolidino. [h] $C_5H_{10}N$ = piperidino. [i] $C_5H_{10}NO$ = 4-hydroxypiperidino. [j] C_4H_8NO = morpholino. [k] $C_5H_{11}N_2$ = 4-methylpiperazino. [l] $C_{10}H_{13}N_2$ = 4-phenylpiperazino. [m] $C_{11}H_{14}NO$ = 4-hydroxy-4-phenylpiperidino. [n] $C_{11}H_{13}ClNO$ = 4-*p*-chlorophenyl-4-hydroxypiperidino. [o] See ref 7.

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Stereoisomeric 2,2′-Bithiiranes

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In the course of the work on bifunctional alkylating agents the title compounds were prepared by reaction of (2*R*:3*R*)-, (2*S*:3*S*)-, and *meso*-1,2:3,4-diepoxybutane[1] with KSCN, a known method[2] for the transformation of epoxides to episulfides. The mechanism of this conversion implies Walden inversions,[2] which in the present case afforded change in configuration at both of the two asymmetrical carbon atoms. The stereoisomeric 2,2′-bithiiranes polymerized readily. Only fresh sublimated samples were free of polymers. For this reason the biological properties of the compounds are not evaluated.

(1) (a) P. W. Feit, *Chem. Ber.*, **93**, 116 (1960); (b) *J. Med. Chem.*, **7**, 14 (1964).

(2) For a review see M. Sander, *Chem. Rev.*, **66**, 297 (1966).

Experimental Section[3]

General Method for the Preparation of (2*R*:2′*R*)-, (2*S*:2′*S*)-, and *meso*-2,2′-Bithiirane.—A cooled solution of KSCN (16 g) in H_2O (50 ml) was added to the 1,2:3,4-diepoxybutane (4.3 g) and the reaction mixture was kept at 3–7° for 1 hr while stirring. After additional stirring for 4.5 hr at 15–20° the precipitated material was filtered off and washed (H_2O) and the filter cake was extracted ($CHCl_3$, 200 ml). The $CHCl_3$ solution was dried (Na_2SO_4) and the solvent was removed *in vacuo* to give the crude product (about 3 g). After one recrystallization from EtOH (15 ml, 99.9%) (under filtration) while avoiding a long heating period, the bithiirane (about 2.3 g) was obtained. The analytical samples were purified by sublimation *in vacuo* (12 mm, 40–50°). The physical properties are listed in Table I.

TABLE I
(2*R*:2′*R*)-, (2*S*:2′*S*)-, AND *meso*-2,2′-BITHIIRANE[a]

Configuration	Mp, °C	$[\alpha]^{20}$, deg ($CHCl_3$) at mμ 365	436	446	578	589
2*R*:2′*R*[b]	80–81	+66.2	−92.6	−89.2	−82.5	−80.3
2*S*:2′*S*	80–80.5	−67.2	+92.1	+89.1	+82.4	+80.0
meso[c]	99–100					

[a] Analytical results obtained for C, H, S were within 0.25% of the theoretical values for the formula $C_4H_6S_2$. [b] Prepared from (2*S*:3*S*)-1,2:3,4-diepoxybutane. [c] Prepared from *meso*-1,2:3,4-diepoxybutane.

(3) H. Gürtler gave technical assistance. Analyses were performed by G. Cornali and W. Egger. Melting points are corrected and were taken in open glass capillaries using a Hershberg apparatus.

Derivatives of 4-Aminobenzenesulfonanilide

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In a search for more potent sulfonamide compounds, we have been preparing a series of derivatives of 4-aminobenzenesulfonanilide; we now wish to report the synthesis of 4-(*p*-nitrobenzenesulfonamido)succinanilic acid and 4-(*p*-aminobenzenesulfonamido)succinanilic acid.

Experimental Section[1]

4-Nitrosuccinanilic Acid.—A mixture of 14 g (0.1 mole) of 4-nitroaniline, 10 g (0.1 mole) of succinic anhydride, 50 ml of anhydrous dioxane, and a few drops of H_2SO_4 was refluxed overnight, cooled, and poured into a 10% solution of Na_2CO_3. The clear solution was stirred for 1 hr and then acidified with AcOH. The yield was 24 g (100%), mp 193–194°.

4-Aminosuccinanilic acid was prepared by the procedure of Landsteiner and Van der Scheer.[2]

4-(*p*-Nitrobenzenesulfonamido)succinanilic Acid.—To a thoroughly stirred mixture of 5.5 g (0.026 mole) of 4-aminosuccinanilic acid and 3 g (0.052 mole) of Na_2CO_3 in 30 ml of H_2O, was slowly added a solution of 5 g (0.026 mole) of *p*-nitrobenzenesulfonyl chloride in 30 ml of dioxane. After addition, the mixture was stirred at room temperature for 30 min and then filtered. The compound was crystallized (Me_2CO–H_2O); yield 70%, mp 216–218°. *Anal.* ($C_{16}H_{15}N_3O_7S$) C, H, N, S.

4-(*p*-Aminobenzenesulfonamido)succinanilic acid was prepared following the same procedure used for 4-aminosuccinanilic acid. There was obtained 2 g (71%) of white flakes, mp 189–190° (Me_2CO–H_2O). *Anal.* ($C_{16}H_{17}N_3O_5S$) C, H, N, S.

The nitro sulfanilamide analog was as effective as sulfanilamide *in vitro* against *Staphylococcus aureus* at 1000 μg/ml; the effective concentration of the amino derivative was 2000 μg/ml. Both compounds had an oral LD_{50} of 1.5 g/kg in rats.[3]

(1) Melting points were taken on a Fisher-Johns block and are uncorrected. Analyses were performed by Microanalytical Laboratory, Oxford, England. The infrared spectra were determined with a Perkin-Elmer 137 and were as expected.

(2) K. Landsteiner and J. Van der Scheer, *J. Exptl. Med.*, 56, 399 (1932).

(3) Personal communication from Dr. N. Ercoli, Instituto de Zoología Tropical, Universidad Central de Venezuela, Caracas, Venezuela.

Preparation of Some ω-N-(Substituted Benzyl)aminoalkylpyridines

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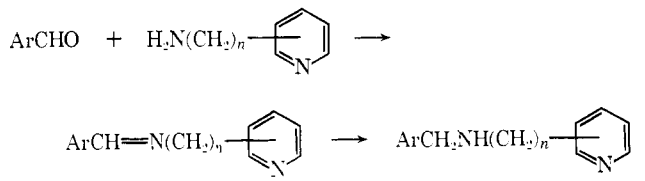
In our earlier paper[1] we reported the preparation of some ω-pyridylalkyl benzamide and benzoate derivatives which showed sedative activity. Continuing our work in this series we now report the preparation of some substituted ω-N-benzylaminoalkylpyridines.



The ω-aminoalkylpyridine was treated in a nonpolar solvent (*e.g.*, benzene, toluene, xylene) with an equivalent amount of an aromatic aldehyde. The resulting Schiff bases were reduced in good yield with $NaBH_4$ in anhydrous EtOH. The products are listed in Table I.

Biological Effects.—According to Dews' method the compounds showed sedative activity against the exciting effect of desoxyephedrine (DOE);[2] some have a strong antihypertensive effect. It appeared that the sedative and antihypertensive activity of our series was affected by the aryl substituent and the position of alkyl chain in the pyridine. The most active compound was 2-[β-(3,4-dimethoxybenzylamino)ethyl]pyridine (**11**). Its most important data are the following therapeutic ratios for action [LD_{50}/ED_{50} (mg/kg)]: decrease of spontaneous motility in the mouse, 15.7 (ip); antagonism against DOE in the mouse, 11.8 (ip); hypotensive activity in the dog, ≫20 (iv).

Experimental Section[3]

2-[β-(3,4-Dimethoxybenzylamino)ethyl]pyridine (11).—3,4-Dimethoxybenzaldehyde (49.8 g, 0.3 mole) in 200 ml of xylene was refluxed with 36.6 g (0.3 mole) of 2-(β-aminoethyl)pyridine for 2 hr in an apparatus equipped with a Marcusson H_2O separatory adapter. During this period 5.4 ml (0.3 mole) of H_2O was collected. The xylene was removed by distillation, the residue was dissolved in 300 ml of anhydrous EtOH, 18 g (0.4 mole) of $NaBH_4$ was added, and the mixture refluxed for 2 hr. The complex was decomposed by the addition of H_2O, the EtOH was removed by distillation, and the residue was extracted three times with 100 ml of C_6H_6. The organic extracts were combined, dried (Na_2SO_4), filtered, and evaporated. The residue was distilled: bp 183–185° (0.05 mm), yield 71.5 g (87%). The oily

(1) O. H. Hankovszky and K. Hideg, *J. Med. Chem.*, 9, 151 (1966).

(2) P. B. Dews, *Brit. J. Pharmacol.*, 8, 46 (1953).

(3) Melting points were obtained on a Boetius apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical values.