Further Studies on N-Arylsulfonyl-N′-alkylureas

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Three new series of N-arylsulfonyl-N′-alkylureas, where the aryl group is alkylmercapto-, acyl-, or trifluoromethylphenyl, have been prepared for evaluation as hypoglycemic agents. Pharmacological testing of the compounds showed that high activity is possessed by members of each series and that, in general, the highest activity is found where the N-alkyl substituent is cyclohexyl or cycloheptyl.

The previously reported studies in these laboratories on N-arylsulfonyl-N′-alkylureas[1] as blood sugar agents have now been extended to an investigation of the structure–activity relationships of three series of substituted phenyl compounds. The preparation of the alkylmercaptophenyl derivatives in which both the S-alkyl and N-alkyl substituents were varied was based on the promising activity of N-(4-methylmercaptophenylsulfonyl)-N′-cyclohexylurea.[1] The 4-acetyl compounds were prepared since there appeared to be two possible routes[2] for their detoxication by the mammalian organism involving either oxidation or reduction of the acetyl moiety. The former route would lead to a carboxyl group as has been found in the case of N-(4-methylphenylsulfonyl)-N′-*n*-butylurea (tolbutamide),[3] while the reductive path would yield hydroxyalkyl derivatives which will be discussed later. The third series investigated contained a trifluoromethyl substituent. The metabolic stability of this group in various compounds[4] suggested the inclusion in these studies of a sulfonylurea having this group as a substituent in a phenyl ring.

The compounds were prepared either by (A) reaction between an arylsulfonylamide and an alkyl isocyanate or (B) reaction of an arylsulfonylcarbamate with an amine. The procedure used for the latter reaction was modified from that reported in our earlier work.[1] It was found to be advantageous to carry out the reaction in toluene using a 10% excess of the amine rather than pyrolyzing the amine salt of the carbamate after its formation in a three- to four-fold excess of the amine. In some cases using method B, the product seemed to be contaminated with some of the amine salt of the product. This could be eliminated easily by acidifying the first dilute ethanol crystallization with 5% hydrochloric acid. In subsequent crystallizations the use of ethanol was either avoided or the amount of heating in the presence of ethanol was kept to a minimum. This was based on the finding that in the purification of a large run[5] of N-(4-methylmercaptophenylsulfonyl)-N′-cyclohexylurea, two hours of heating in ethanol converted almost half of the material to the carbamate. This may have been due in part to some residual hydrochloric acid, but a definite deterioration of purity of the product was noted after prolonged heating with ethanol in the absence of any acid.[5]

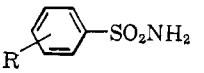
The sulfone of N-(4-methylmercaptophenylsulfonyl)-N′-cyclohexylurea was prepared readily when the sulfide was treated with hydrogen peroxide. Attempts at preparation of a sulfoxide in a similar manner using the theoretical amounts of sodium periodate or hydrogen peroxide were unsuccessful and only starting material was isolated. It was found, however, that one equivalent of hydrogen peroxide converted 4-methylmercaptobenzenesulfonamide to the sulfoxide in 75% yield. The sulfonylurea then was prepared by reaction of this amide with cyclohexyl isocyanate. The resulting N-(4-methylsulfinylphenylsulfonyl)-N′-cyclohexylurea was of special interest because it was shown[6] to be identical with a metabolite of the methylmercapto compound isolated after the latter had been administered to dogs.

Catalytic reduction, using 5% palladium on carbon, converted N-(4-acetylphenylsulfonyl)-N′-cyclohexylurea to the corresponding α-hydroxyethyl derivative in 74% yield. It was mentioned earlier that this conversion of the ketone to an alcohol was one of the possible metabolic routes for the acetyl derivatives. The α-hydroxyethyl compound was shown[6] to be the same as the metabolite isolated after administration of N-(4-acetylphenylsulfonyl)-N′-cyclohexylurea to dogs. It is puzzling that application of a similar catalytic reduction procedure to N-(4-acetylphenylsulfonyl)-N′-*n*-hexylurea led to complete reduction of the acetyl to an ethyl group. There is no ready explanation for this variation in results.

The hypoglycemic activity of the compounds in Tables II, III, and IV was determined by administering the substances to normal, fasted rats and measuring blood glucose at intervals up to seven hours after administration. Activity was calculated as a hypoglycemic score as previously described by Root.[7] For the purpose of this paper the mean hypoglycemic score for a dose of 100 mg./kg. administered to each of six rats was determined. The scale of activity used here would give N-(4-methylphenylsulfonyl)-N′-*n*-butylurea a value of ++ and N-(4-chlorophenylsulfonyl)-N′-*n*-propylurea (chloropropamide) a value of 4 plus. The compounds in Table I were not tested for hypoglycemic activity since studies of other sulfonamides had shown them to have no effect on blood glucose levels.

(1) F. J. Marshall and M. V. Sigal, Jr., *J. Org. Chem.*, **23**, 927 (1958).
(2) R. T. Williams, "Detoxication Mechanisms," 2nd ed., J. Wiley and Sons, Inc., New York, N. Y., 1959, p. 321 and pp. 336-338.
(3) L. H. Louis, S. S. Fajans, J. W. Conn, W. A. Struck, J. B. Wright and J. L. Johnson, *J. Am. Chem. Soc.*, **78**, 5701 (1956).
(4) For a general discussion see H. L. Yale, *J. Med. Pharm. Chem.*, **1**, 121 (1959).
(5) Unpublished studies, these Laboratories.
(6) J. S. Welles, M. A. Root, and R. C. Anderson, *Proc. Soc. Exp. Biol. Med.*, **107**, 583 (1961).
(7) M. A. Root, M. V. Sigal, Jr., and R. C. Anderson, *Diabetes*, **8**, 7 (1959).

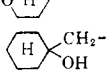
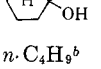
TABLE I

ARYLSULFONAMIDES 

R	Yield, %	M.p., °C.	Recryst. solvent	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
3-CH_3CO	27	135–138	Dil. ethanol	$C_9H_9NO_3S$	48.23	4.55	7.03	48.34	4.65	7.14
4-C_2H_5CO	33	127–129	Water	$C_9H_{11}NO_3S$	50.69	5.20	6.57	50.96	5.25	6.43
4-n-C_3H_7CO	17	105–108	Dil. ethanol	$C_{10}H_{13}NO_3S$	52.84	5.77	6.16	53.52	5.63	6.22
4-i-C_3H_7S	7	112–113.5	Benzene-pet. ether (b.r. 60–71°)	$C_9H_{13}NO_2S_2$			6.06			6.11

TABLE II

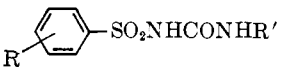
4-ALKYLMERCAPTOPHENYLSULFONYLUREAS, $RSC_6H_4SO_2NHCONHR'$

R	R′	Yield, %	M.p., °C.	Recryst. solvent	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H	Hypoglycemic activity[c]
CH_3	3-$CH_3O(CH_2)_3$	68	109–111	Dil. acetone	$C_{12}H_{18}N_2O_4S_2$	45.25	5.69	45.52	5.65	++
CH_3	n-C_5H_{11}	57	106–108	Dil. ethanol	$C_{13}H_{20}N_2O_3S_2$	49.30	6.37	49.76	6.67	+
						N, 8.86		N, 8.76		
CH_3	2-C_5H_{11}	70	114–116	Dil. acetone	$C_{13}H_{20}N_2O_3S_2$	49.30	6.37	49.00	7.03	++
						N, 8.86		N, 9.03		
CH_3	n-C_6H_{13}	80	132–133	Dil. acetone	$C_{14}H_{22}N_2O_3S_2$	50.89	6.41	51.34	6.61	+
CH_3	cyclo-C_5H_9	89	177–179	Dil. acetone	$C_{13}H_{18}N_2O_3S_2$	49.67	5.77	50.10	5.96	++++
						N, 8.91		N, 8.91		
CH_3	cyclo-C_7H_{13}	73	166–168	Dil. acetone	$C_{15}H_{22}N_2O_3S_2$	52.58	6.48	52.67	6.29	++++
CH_3		67	210–211	Dil. acetone	$C_{13}H_{18}N_2O_4S_2$	47.25	5.48	47.40	5.45	+++
CH_3		40	132–134	Dil. acetone	$C_{15}H_{22}N_2O_4S_2$	50.25	6.18	50.31	6.08	++
C_2H_5	n-C_4H_9[b]	47	117–119	Dil. acetone	$C_{13}H_{20}N_2O_3S_2$	49.30	6.38	49.24	6.49	++
C_2H_5	cyclo-C_6H_{11}[b]	70	182–184	Dil. acetone	$C_{15}H_{22}N_2O_3S_2$	52.63	6.47	52.72	6.73	+++
i-C_3H_7	n-C_4H_9[b]	35	138.5–139.5	Dil. ethanol	$C_{14}H_{22}N_2O_3S_2$	50.88	6.71	51.06	6.29	++
i-C_3H_7	cyclo-C_6H_{11}[b]	20	187.5–188.5	Dil. acetone	$C_{16}H_{24}N_2O_3S_2$	53.92	6.79	54.23	6.70	+++

[a] 1-Aminomethylcyclohexanol was prepared in 54% yield by lithium aluminum hydride (2 moles) reduction of cyclohexanone cyanohydrin (1 mole) in ether. The preparation of this compound has been reported previously by M. W. Goldberg and H. Kirchensteiner, *Helv. Chim. Acta*, **26**, 288 (1943), by catalytic reduction of the cyanohydrin. Their yield was 30%. [b] Prepared by method A. All other compounds in this Table were prepared by method B. [c] For explanation of symbols, see text.

TABLE III

N-TRIFLUOROMETHYLPHENYLSULFONYLUREAS



R	R′	Yield, %	M.p., °C.[e]	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Hypoglycemic activity[f]
4-CF_3	n-C_3H_7[a,b,d]	81	140–142	$C_{11}H_{13}F_3N_2O_3S$	42.58	4.22	9.03	42.33	4.23	9.42	++
4-CF_3	n-C_4H_9[b,c]	40	120–122	$C_{12}H_{15}F_3N_2O_3S$	44.44	4.66	8.64	44.63	5.37	8.75	+
4-CF_3	cyclo-C_6H_{11}[b,c]	40	166–169	$C_{14}H_{17}F_3N_2O_3S$	47.99	4.89	8.00	48.19	4.89	8.38	++++
3-CF_3	cyclo-C_6H_{11}[c]	71	128–131	$C_{14}H_{17}F_3N_2O_3S$	47.99	4.89	8.00	48.16	4.61	7.76	+
4-CF_3	cyclo-C_7H_{13}[a]	69	149–151	$C_{15}H_{19}F_3N_2O_3S$	49.44	5.26	7.69	49.44	5.26	7.79	++++

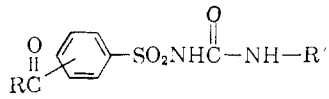
[a] Prepared by method B. The other compounds were prepared by method A. [b] Since completion of this investigation these compounds have been reported by Y. G. Perron, M. H. Pindell, L. B. Crast, and L. C. Cheney, *J. Med. Pharm. Chem.*, **4**, 41 (1961). [c] Since reported by H. L. Yale and F. Sowinski, *J. Org. Chem.*, **25**, 1824 (1960). [d] See B. Blank, F. A. Farina, J. F. Kerwin, and H. Saunders, *J. Org. Chem.*, **26**, 1551 (1961). [e] All compounds were recrystallized from dilute ethanol. [f] For explanation of symbols see text.

In all three series, when the aryl substituent was in the *para* position, the N′-cyclohexyl or N′-cycloheptyl derivatives gave good activity. From the activities observed with these substituents, it is obvious that the presence of the trifluoromethylphenylsulfonyl group does not necessarily produce poor activity. This finding made it all the more surprising that the trifluoromethyl analog of N-(4-methylphenylsulfonyl)-N′-*n*-butylurea and of the very active N-(4-chlorophenylsulfonyl)-N′-*n*-propylurea showed considerably lowered potency. The importance of the position of the substituent in the benzene ring was demonstrated by the greatly decreased activity found when the trifluoromethyl or acetyl group was shifted from the *para* to the *meta* position.

Some interesting results were obtained when the metabolites, N-(4-methylsulfinylphenylsulfonyl)-N′-cyclohexylurea and N-[4-(α-hydroxyethyl)phenylsulfonyl]-N′-cyclohexylurea, were tested for hypoglycemic activity after oral administration to rats. The former was only 40% as active as the parent methylmercapto derivative. In the second case, reduction of the ketone

TABLE IV

ACYLPHENYLSULFONYLUREAS



4-RCO R	R′	Yield, %	M.p., °C.[d]	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Hypoglycemic activity[h]
CH_3	C_2H_5	43	161–162[b]	$C_{11}H_{14}N_2O_4S$	48.87	5.22	10.37	49.04	5.21	10.34	+
CH	n-C_3H_7[c]	19	167–168	$C_{12}H_{16}N_2O_4S$	50.69	5.68	9.84	51.13	5.52	9.91	+
CH_3	n-C_4H_9[a,c]	69	147–149	$C_{13}H_{18}N_2O_4S$	52.33	6.08	9.39	52.06	6.01	9.39	++
CH_3	2-C_4H_9	40	155–156[e]	$C_{13}H_{18}N_2O_4S$	52.33	6.08	9.39	52.43	5.98	9.20	+
CH_3	-C_4H_9	39	139–141	$C_{13}H_{18}N_2O_4S$	52.33	6.08	9.39	52.58	6.15	9.26	+
CH_3	t-C_4H_9	73	150–151	$C_{13}H_{18}N_2O_4S$	52.33	6.08	9.39	52.41	6.13	9.24	++
CH_3	3-CH_3-2-C_4H_8	89	148–149	$C_{14}H_{20}N_2O_4S$	S, 10.27		8.97	S, 10.30		8.83	+++
CH_3	n-C_5H_{11}	61	156–157[e]	$C_{14}H_{20}N_2O_4S$	53.83	6.44	8.97	54.08	6.72	8.74	+++
CH_3	2-C_5H_{11}	44	151–152	$C_{14}H_{20}N_2O_4S$	53.83	6.44	8.97	53.61	6.26	8.80	++++
CH_3	3-C_5H_{11}	90	168–169	$C_{14}H_{20}N_2O_4S$	S, 10.27		8.97	S, 10.29		8.82	+
CH_3	t-C_5H_{11}	48	127–129	$C_{14}H_{20}N_2O_4S$	53.83	6.44	8.97	53.96	6.44	8.70	+++
CH_3	cyclo-C_5H_9	62	171–172	$C_{14}H_{18}N_2O_4S$	54.17	5.84	9.03	54.34	6.04	9.08	+++
CH_3	4-CH_3-2-C_5H_{10}	72	185–186	$C_{15}H_{22}N_2O_4S$	55.19	6.79	8.58	55.14	6.67	8.25	++
CH_3	n-C_6H_{13}	51	160–161	$C_{15}H_{22}N_2O_4S$	55.19	6.79	8.58	55.61	6.87	8.28	+
CH_3	2-C_6H_{13}	69	154–155	$C_{15}H_{22}N_2O_4S$	S, 9.82		8.58	S, 9.76		8.31	+
CH_3	3-C_6H_{13}	79	154–155	$C_{15}H_{22}N_2O_4S$	55.19	6.79	8.58	55.23	6.66	8.49	+
CH_3	cyclo-C_6H_{11}[c]	46	175–177	$C_{15}H_{20}N_2O_4S$	55.54	6.21	8.64	55.66	6.58	8.31	++++
CH_3	5-hexen-2-yl	65	149–150[f]	$C_{15}H_{20}N_2O_4S$	S, 9.89		8.64	S, 10.00		8.77	+++
CH_3	cyclo-$C_6H_{11}CH_2$	82	149–150	$C_{16}H_{22}N_2O_4S$	S, 9.46		8.28	S, 9.19		8.70	+++
CH_3	n-C_7H_{15}	60	166–167	$C_{16}H_{24}N_2O_4S$	56.44	7.11	8.23	56.59	7.35	8.28	0
CH_3	3-C_7H_{15}	90	152–153	$C_{16}H_{24}N_2O_4S$	56.44	7.11	8.23	56.24	7.43	8.18	0
CH_3	4-C_7H_{15}	88	163–165	$C_{16}H_{24}N_2O_4S$	56.44	7.11	8.23	56.83	7.23	8.26	+
CH_3	cyclo-C_7H_{13}	77	155–156	$C_{16}H_{22}N_2O_4S$	S, 9.46		8.28	S, 9.08		8.54	+++
CH_3	n-C_8H_{17}	70	143–144	$C_{17}H_{26}N_2O_4S$	S, 9.04		7.92	S, 8.61		8.04	+
CH_3	3-($CH_3O(CH_2)_3$	68	141–143	$C_{13}H_{18}N_2O_5S$	49.64	5.77	8.91	50.14	5.85	8.71	+
CH_3	2,2-($C_2H_5O)_2C_2H_3$	9	115–116[g]	$C_{15}H_{22}N_2O_6S$	50.28	6.18		50.27	6.34		+
CH_3		41	187–188	$C_{14}H_{18}N_2O_5S$	51.52	5.56	8.59	51.81	5.63	8.38	+
CH_3	$C_6H_5CH_2$	23	149–151	$C_{16}H_{16}N_2O_4S$	57.81	4.85	8.43	58.35	4.94	8.35	+
C_2H_5	n-C_4H_9[a]	57	144–146	$C_{13}H_{20}N_2O_4S$	53.83	6.45	8.97	54.28	6.37	8.72	++
C_2H_5	cyclo-C_6H_{11}[a]	59	177–179	$C_{15}H_{22}N_2O_4S$	56.78	6.55	8.28	57.16	6.27	8.05	++++
n-C_3H_7	cyclo-C_6H_{11}[a]	80	172–174	$C_{16}H_{24}N_2O_4S$	57.93	6.86	7.95	57.86	6.65	7.68	+++
3-RCO											
CH_3	n-C_4H_9[a]	78	146–148[c]	$C_{12}H_{18}N_2O_4S$	52.33	6.08	9.39	55.20	6.06	9.19	+
CH_3	cyclo-C_6H_{11}[a]	59	152–154	$C_{14}H_{20}N_2O_4S$	55.54	6.21	8.64	55.50	6.33	8.61	+

[a] Prepared by method A. All other compounds in this table were prepared by procedure B. [b] Recrystallized from EtOAc–pet. ether (b.p. 60–71°). [c] Since completion of this work these compounds have been reported by B. Blank, F. A. Farina, J. F. Kerwin and H. Saunders, *J. Org. Chem.*, **26**, 1551 (1961). [d] Unless otherwise noted, recrystallized from dil. ethanol. [e] Recrystallized from ethanol. [f] Recrystallized from dil. acetone. [g] Recrystallized from $CHCl_3$–pet. ether (b.p. 60–71°). [h] For explanation of symbols, see text.

to the alcohol did not result in any loss of activity.

More detailed pharmacological and clinical reports have been published elsewhere.[8]

Experimental

Sulfonamides (Table I)—The acyl- and trifluoromethylbenzenesulfonamides were prepared from the sulfonyl chlorides obtained by treatment of a diazonium chloride with sulfur dioxide in essential accordance with the procedure of Meerwein and coworkers.[9] Benzene was used as an immiscible solvent in the preparation of the sulfonyl chlorides.

The alkylmercaptobenzenesulfonamides were prepared as in our earlier work[1] by chlorosulfonation and addition of the resulting crude sulfonyl chloride to concentrated ammonium hydroxide. The isopropylmercapto compound was prepared in very poor yield by this method and when benzyl phenyl sulfide was used, no sulfonamide was obtained.

Ethyl N-arylsulfonylcarbamates were prepared by the procedure given in the report of our previous investigation.[1]

Ethyl N-(4-acetylphenylsulfonyl)carbamate was obtained in 92% yield and was crystallized from dilute ethanol to m.p. 124–126°.

Anal. Calcd. for $C_{11}H_{13}NO_5S$: C, 48.70; H, 4.83; N, 5.16. Found: C, 48.88; H, 4.96; N, 5.44.

Ethyl N-(4-trifluoromethylphenylsulfonyl)carbamate melted at 91–93° (from benzene-petroleum ether; b.p. 60–71°). The yield was 43%.

Anal. Calcd. for $C_{10}H_{10}F_3NO_4S$: C, 40.44; H, 3.39; N, 4.71. Found: C, 40.71; H, 3.60; N, 5.02.

N-Arylsulfonyl-N′-alkylureas. Method A.—A mixture of 0.05 mole of a sulfonamide and 0.15 mole of anhydrous potassium carbonate in 100 ml. of dry acetone was stirred and refluxed for 1.5 hr. At this temperature there was then added at a dropwise rate, a solution of 0.075 mole of the appropriate alkyl isocyanate in 20 ml. of dry acetone. After stirring and refluxing overnight, the mixture was cooled and filtered. The solid residue was dissolved in 375 ml. of water. The crude product was isolated by acidification with concd. hydrochloric acid and was purified as indicated in the tables.

(8) For a preliminary report on one of the compounds, N-(4-acetylphenylsulfonyl)-N′-cyclohexylurea (acetohexamide), see G. E. Maha, W. R. Kirtley, M. A. Root, and R. C. Anderson, *Diabetes*, **11**, 83 (1962). See also R. S. Radding, L. R. Kern, and J. C. Owens, *Metabolism, Clin. and Exptl.*, **11**, 411 (1962).

(9) H. Meerwein, G. Dittmar, R. Göllner, K. Hafner, F. Mensch and O. Steinfort, *Chem. Ber.*, **90**, 841 (1957).

Method B.—To a warm solution of 0.02 mole of an ethyl N-arylsulfonylcarbamate in 75 ml. of toluene was added, dropwise, with stirring, a solution of 0.022 mole of the desired amine in 25 ml. of toluene. The mixture was refluxed for 3 hr. and cooled. If the product crystallized, it was isolated by filtration; otherwise, the toluene was removed under reduced pressure. The product was crystallized from dilute ethanol, with acidification with 5% hydrochloric acid just prior to cooling. Further purification was carried out as indicated in the tables.

4-Methylsulfinylbenzenesulfonamide.—To a solution of 12 g. (0.05 mole) of 4-methylmercaptobenzenesulfonamide in 200 ml. of acetic acid was added, portionwise, 5.7 g. (0.05 mole) of 30% hydrogen peroxide. After heating at about 60° for 24 hr. the mixture was taken to dryness under reduced pressure and the residue was crystallized 3 times from dilute ethanol to give 8.3 g. (75%) of product melting at 177–179°.

Anal. Calcd. for $C_7H_9NO_3S_2$: C, 38.34; H, 4.15. Found: C, 38.10; H, 4.34.

N-(4-Methylsulfinylphenylsulfonyl)urea.—Six grams (0.027 mole) of 4-methylsulfinylbenzenesulfonamide was converted to the sulfonylurea by Method A. Purification from dilute acetone gave 5 g. (54%) of product melting at 173–175°

Anal. Calcd. for $C_{14}H_{20}N_2O_4S_2$: C, 48.82; H, 5.85; N_1 8.13. Found: C, 49.20; H, 5.93; N, 8.00.

N-(4-Methylsulfonylphenylsulfonyl)-N′-cyclohexylurea.—A mixture of 2 g. (0.006 mole) of N-(4-methylmercaptophenylsulfonyl)-N′-cyclohexylurea and 15 ml. of 30% hydrogen peroxide in 10 ml. of acetic acid was warmed for 30 min. on a steam bath. The crystalline material which separated on cooling weighed 1.7 g.. Crystallizations from dilute ethanol gave 1.3 g. (59%) of product melting at 196–198°.

Anal. Calcd. for $C_{14}H_{20}N_2O_5S_2$: C, 46.65; H, 5.59; N, 7.77. Found: C, 46.96; H, 5.74; N, 7.35.

N-[4-(α-Hydroxyethyl)phenylsulfonyl]-N′-cyclohexylurea.—A solution of 20.0 g. (0.616 mole) of N-(4-acetylphenylsulfonyl)-N′-cyclohexylurea, 100 ml. of absolute ethanol and 150 ml. of dioxane was reduced catalytically using initially 2.0 g. of 5% palladium on carbon under an initial hydrogen pressure of 2.8 kg./cm.^{2} As the reaction proceeded the adsorption of hydrogen became quite slow. At this point an additional 2.0 g. of catalyst was added and the reaction then proceeded to completion. The catalyst was removed by filtration and the filtrate evaporated to dryness *in vacuo*. The product, after three recrystallizations from dilute ethanol, melted at 136–137°, yield 14.7 g. (74%).

Anal. Calcd. for $C_{15}H_{22}N_2O_4S$: C, 55.19; H, 6.79; N, 8.58. S, 9.86. Found: C, 55.16; H, 6.86; N, 8.09; S, 9.16.

N-(4-Ethylphenylsulfonyl)-N′-n-hexylurea.—Hydrogenation of 2 g. (0.006 mole) of N-(4-acetylphenylsulfonyl)-N′-*n*-hexylurea was carried out in 200 ml. of ethanol using 1 g. of 5% palladium on carbon as a catalyst with an initial hydrogen pressure of 2.8 kg./cm.^{2}. Hydrogen uptake was complete in 15–20 min., and, after filtering, the ethanol was removed under reduced pressure. The residue crystallized on standing and two crystallizations from dilute acetone gave 5 g. (29%) of product melting at 107–109°. An analytical sample melted at 108–110°. Infrared analysis did not show the presence of an OH and was consistent for an ethyl substituent.

Anal. Calcd. for $C_{15}H_{24}N_2O_3S$: C, 57.65; H, 7.75; N, 8.96; O, 15.35. Found: C, 57.64; H, 7.57; N, 9.04; O, 15.59.

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Monoamine Oxidase Inhibitors. The Synthesis and Evaluation of a Series of Substituted Alkylhydrazines

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A series of aryloxy-, arylthio-, and arylaminoalkylhydrazines has been prepared and evaluated as *in vitro* and *in vivo* inhibitors of monoamine oxidase. Many of the compounds are powerful inhibitors, the most active being (1-methyl-2-phenoxyethyl)hydrazine.

In 1952, Zeller and co-workers[1] found iproniazid to be a powerful and specific inhibitor of the enzyme monoamine oxidase and much suggestive evidence has been subsequently presented to support the thesis that the pharmacological and clinical effects of this drug may be explained in terms of monoamine oxidase inhibition. An exhaustive study by Zeller's group of the structural features necessary for monoamine oxidase inhibition led to the discovery that simple alkylhydrazines were considerably more potent than iproniazid.[2] This, together with the reported high activity of α-methylphenethylhydrazine[3] led us to examine some related aryloxyalkylhydrazines as potential inhibitors of monoamine oxidase.

2-Phenoxyethylhydrazine and 3-phenoxypropylhydrazine were first prepared by Gabriel in 1914 by reaction of the appropriate phenoxyalkyl bromide with hydrazine.[4] 2-Phenoxyethylhydrazine was examined and found to be a potent inhibitor of monoamine oxidase whereas 3-phenoxypropylhydrazine was much less active. It was thus of interest to investigate the relationship between structure and activity in this class of compound, and this paper describes the synthesis and evaluation as monoamine oxidase inhibitors of a series of substituted hydrazines of general formula $ArX(CH_2)_nCH(Y)NHNH_2$, in which variations are made in the aryl group, the alkyl chain (n and Y varied) and the linking group X.

Experimental

Chemistry.—The substituted hydrazines were prepared by the method of Gabriel[4] from the corresponding bromide by reaction with hydrazine in boiling ethanol. In most instances they were colorless liquids which, on a small scale, could be distilled under reduced pressure in a nitrogen atmosphere with only slight decomposition. Occasionally, however, complete decomposition occurred during distillation, a hazard which appeared to be somewhat dependent upon batch size. The bases were rather

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