[CONTRIBUTION FROM THE LABORATORY OF APPLIED ORGANIC CHEMISTRY, RESEARCH COUNCIL OF ISRAEL]

Studies in Selective Toxicity. I. Syntheses of *N*-Alkylbenzenesulfonanilides

M. NEEMAN AND A. MODIANO

Received February 17, 1956

N-Alkyl benzenesulfonanilides with halogen substituents in the *para*-positions of both phenyl radicals have been prepared. Two homologous series of N-*n*-alkylbenzenesulfonanilides showed oscillation of melting points and of solubility in kerosene between homologs with even and odd numbers of carbon atoms in the alkyl radical up to C_5. Dimorphism was shown by some of the compounds. The U.V. spectra of several compounds are reported. The homologs up to C_8 showed biological activity as DDT synergists.

N-Methyl- and N-ethyl-4-chlorobenzenesulfon-4′-chloroanilide have been tested for synergistic activity with DDT.[1,2] They showed biological activity, but appear to be of no practical value due to their negligible solubility in kerosene, which is the solvent commonly used for the formulation of DDT solutions, and their low solubility in the aromatic hydrocarbons used in emulsion concentrates of DDT.

Two series of N-*n*-alkyl-4-bromo- and 4-chlorobenzenesulfon-4′-chloro-anilides have been prepared with *n*-alkyl radicals up to dodecyl. One compound with a branched N-alkyl radical (XI, R = isoamyl), and one with a β-chloroalkyl radical (XXIV, R = β-chloroethyl) were also prepared.

The solubility in kerosene of the compounds of both series increased from 4-chlorobenzenesulfon-4′-chloroanilide to a maximum for the N-*n*-heptyl compound XIV, and from 4-bromobenzenesulfon-4′-chloroanilide to the N-*n*-hexyl compound XIII (Fig. 1 and Fig. 2). In both series, oscillation of the solubility in kerosene was observed between homologs with an even and an odd number of carbon atoms in the N-alkyl radical, up to *n*-amyl. The solubility of the compounds in benzene and xylene increased very rapidly on increase of the N-*n*-alkyl radical. The solubility of the compounds in ketones (acetone, butanone) was very high, and that in water was extremely low.

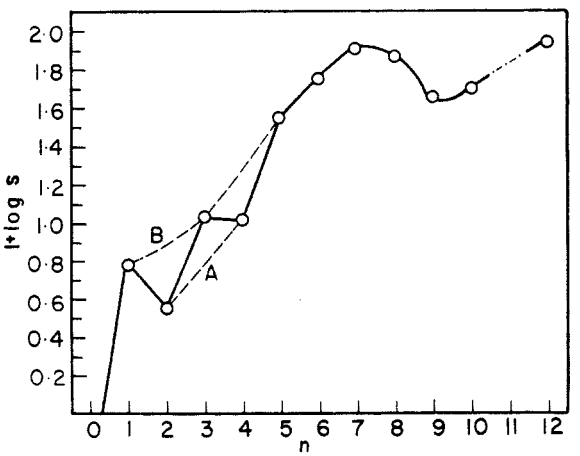


FIG. 1.—THE SOLUBILITY IN KEROSENE OF HOMOLOGOUS N-*n*-ALKYL-4-CHLOROBENZENESULFON-4′-CHLOROANILIDES AT 20°. THE LOGARITHMIC SOLUBILITY log s *versus* the number of carbon atoms n in the N-*n*-alkyl radical.

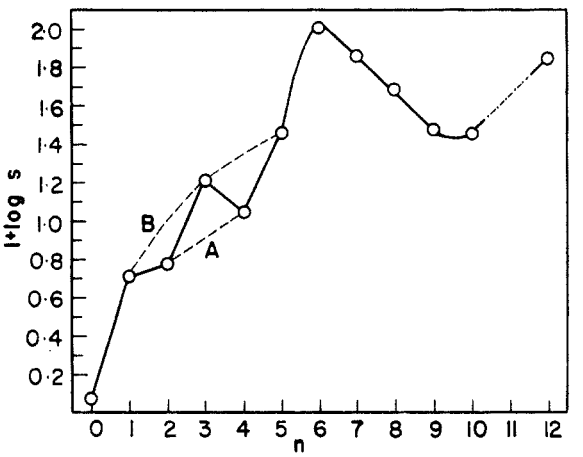


FIG. 2.—THE SOLUBILITY IN KEROSENE OF HOMOLOGOUS N-*n*-ALKYL-4-BROMOBENZENESULFON-4′-CHLOROANILIDES AT 20°. THE LOGARITHMIC SOLUBILITY log s *versus* the number of carbon atoms n in the N-*n*-alkyl radical.

The melting points in both homologous series showed oscillation between homologs with an even and an odd number of carbon atoms in the N-*n*-alkyl radical up to R = *n*-amyl. The separate curves of melting points of the even-numbered homologs were higher than those of the odd-numbered ones when plotted against the number of carbon atoms in the alkyl radical.

The curves of the reciprocal of the absolute temperature of the melting points $\frac{1}{T_m}$ *versus* the number n of carbon atoms in the N-*n*-alkyl radicals of the compounds (Fig. 3 and Fig. 4) were very similar to the corresponding curves of the logarithm of the solubility in kerosene log s *versus* n (Fig. 1 and Fig. 2).

The melting points observed for 4-chlorobenzenesulfon-4′-chloroanilide and the N-ethyl compound III were considerably higher than those reported by Speroni.[1,2] The first compound had a m.p. of 145.4–146° and appears to be identical with that

(1) Speroni, *Chimica, e industria (Milan)*, **34**, 391 (1952).
(2) Speroni, Losco, Santi, and Peri, *Chimie & industrie*, **69**, 658 (1953).

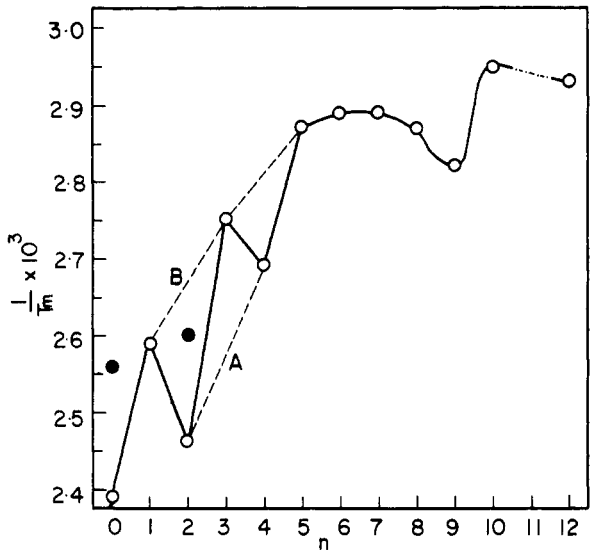


FIG. 3.—MELTING POINTS OF HOMOLOGOUS N-*n*-ALKYL-4-CHLOROBENZENESULFON-4′-CHLOROANILIDES. THE RECIPROCAL ABSOLUTE TEMPERATURE OF MELTING $\frac{1}{T_m}$ *versus* the number of carbon atoms n in the N-*n*-alkyl radical. FULL CIRCLES REPRESENT LOWER-MELTING DIMORPHOUS FORMS.

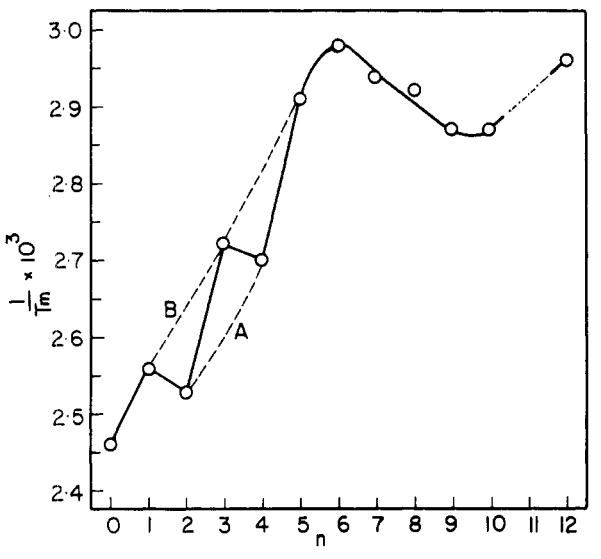


FIG. 4.—MELTING POINTS OF HOMOLOGOUS N-*n*-ALKYL-4-BROMOBENZENESULFON-4′-CHLOROANILIDES. THE RECIPROCAL ABSOLUTE TEMPERATURE OF MELTING $\frac{1}{T_m}$ *versus* the number of carbon atoms n in the N-*n*-alkyl radical.

described by Baxter and Chattaway,[3] who reported m.p. 148°. It depressed considerably (by 28°) the melting point (148°) of 4-chlorophenylsulfone; thus, the suggestion of Speroni[2] that Baxter and Chattaway's product may have been that sulfone, is untenable. Methylation of both the high-melting, and Speroni's lower-melting form (m.p. 118°) of 4-chlorobenzenesulfon-4′-chloroanilide with dimethyl sulfate in aqueous sodium hydroxide, yielded an identical N-methyl derivative I of m.p. 112.5°. Moreover, the U.V. spectra of our unalkylated and N-methylated compounds (in 95% ethanol) were closely similar (Table II). Thus, the two forms of 4-chlorobenzenesulfon-4′-chloroanilide are obviously dimorphic.

Dimorphism was also shown by the next higher even-numbered homolog III (X = Cl, R = ethyl). Speroni[1] obtained a low-melting form, m.p. 111–113°, by reaction of N-ethyl-4-chloroaniline with 4-chlorobenzenesulfonyl chloride, while alkylation of 4-chlorobenzenesulfon-4′-chloroanilide with diethyl sulfate gave in the present study a product of m.p. 133°.

In neither case was it possible to convert the higher-melting forms into the lower-melting ones by changing the solvent or the conditions of crystallization.

Similar cases of dimorphism among 4-toluenesulfon-4′-halogenoanilides have been reported by Ratcliffe.[4] Dimorphism is also a likely cause of the disagreement in melting points reported for certain N-alkyl-benzenesulfonanilides.[5,6]

The compounds I to IV (X = Cl or Br, R = methyl or ethyl) have been prepared by alkylation of the corresponding benzenesulfonanilide with dimethyl or diethyl sulfate in aqueous sodium hydroxide (Method A). Higher alkyl radicals were introduced by means of the appropriate alkyl tosylates in 10 or 20% aqueous sodium hydroxide at 95 to 125° (Method B). The preparation of N-alkyl-4-toluenesulfonanilides by a similar procedure has been reported.[7] The compounds proved difficult to hydrolyze by acid or alkali.

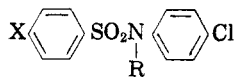
Biological activity. The N-alkylbenzenesulfonanilides were tasteless and odorless. They showed slight or no biological activity by themselves, when tested on mammals and insects: compounds VIII, XIV, XVI, and XVII showed no effect on rats at 500 mg./kg. (in aqueous suspension, by stomach tube or intraperitoneal injection).[8] Only two of the compounds tested by spraying of kerosene solutions against DDT-resistant house flies showed slight activity.[9] High activity was, however, observed when the compounds were tested for synergistic activity with DDT against DDT-resistant house flies.[10] All compounds, up to and including the *n*-octyl homolog, were active. The isoamyl analog XI was inactive, and the β-chloroethyl derivative XXIV showed activity. Characteristic curves were

(3) Baxter and Chattaway, *J. Chem. Soc.*, **107**, 1823 (1915).

(4) Ratcliffe, *J. Chem. Soc.*, 1140 (1951).
(5) Halberkann, *Ber.*, **54**, 1833 (1921).
(6) Witt and Uermenyi, *Ber.*, **46**, 300, 304 (1913).
(7) Klamann, Hofbauer, and Drahowzal, *Monatsh.*, **83**, 870 (1952).
(8) H. Meyer, private communication.
(9) G. G. Mer, private communication.
(10) Neeman, Modiano, Mer, and Cwilich, *Nature*, in press (preliminary note).

TABLE I

N-ALKYLBENZENESULPHOANILIDES



	X	R	Yield Method	Yield %	Crystal Form	M.P., °C. (corr.)	Formula	Analyses Calc'd C	Calc'd H	Found C	Found H
I	Cl	CH_3	B	83	Short columns	112.5	$C_{13}H_{11}Cl_2NO_2S$	49.37	3.51	49.36	3.58
II	Br	CH_3	B	80	Monoclinic columns	117.4	$C_{13}H_{11}BrClNO_2S$	43.28	3.07	43.24	3.02
III	Cl	C_2H_5	B	92	Orthorhombic columns	133	$C_{14}H_{13}Cl_2NO_2S$	50.92	3.97	50.77	4.04
IV	Br	C_2H_5	B	80	Hexagonal columns	123.2	$C_{14}H_{13}BrClNO_2S$	44.87	3.49	45.23	3.35
			C	86							
V	Cl	n-C_3H_7	C	76	Small needles	90.9	$C_{15}H_{15}Cl_2NO_2S$	52.33	4.39	52.17	4.33
VI	Br	n-C_3H_7	C	80	Prismatic needles	94.1	$C_{15}H_{15}BrClNO_2S$	46.35	3.89	46.11	4.02
VII	Cl	n-C_4H_9	C	56	Needles	99	$C_{16}H_{17}Cl_2NO_2S$	53.63	4.78	53.65	4.63
VIII	Br	n-C_4H_9	C	64	Intertwined needles	97.5	$C_{16}H_{17}BrClNO_2S$	47.72	4.25	47.68	4.60
IX	Cl	n-C_5H_{11}	C	50	Small needles	75.5	$C_{17}H_{19}Cl_2NO_2S$	54.84	5.14	54.85	5.35
X	Br	n-C_5H_{11}	C	44	Small needles	71.5	$C_{17}H_{19}BrClNO_2S$	48.99	4.60	49.34	4.89
XI	Br	iso-C_5H_{11}	C	78	Needles	89.8	$C_{17}H_{19}BrClNO_2S$	48.99	4.60	48.84	4.72
XII	Cl	n-C_6H_{13}	C	86	Short needles	73.1	$C_{18}H_{21}Cl_2NO_2S$	55.96	5.48	55.78	5.30
XIII	Br	n-C_6H_{13}	C	71	Monoclinic prisms	63.4	$C_{18}H_{21}BrClNO_2S$	50.18	4.92	50.33	5.23
XIV	Cl	n-C_7H_{15}	C	80	Hexagonal platelets	72.6	$C_{19}H_{23}Cl_2NO_2S$	57.00	5.79	57.01	5.78
XV	Br	n-C_7H_{15}	C	85	Needles	67	$C_{19}H_{23}BrClNO_2S$	51.30	5.21	51.11	4.99
XVI	Cl	n-C_8H_{17}	C	96	Columns	75.2	$C_{20}H_{25}Cl_2NO_2S$	57.97	6.08	58.29	6.18
XVII	Br	n-C_8H_{17}	C	75	Columns	68.5	$C_{20}H_{25}BrClNO_2S$	52.35	5.49	52.35	5.39
XVIII	Cl	n-C_9H_{19}	C	80	Needles	79.5	$C_{21}H_{27}Cl_2NO_2S$	58.87	6.35	58.70	6.60
XIX	Br	n-C_9H_{19}	C	96	Needles	76.4	$C_{21}H_{27}BrClNO_2S$	53.34	5.76	53.60	6.02
XX	Cl	n-$C_{10}H_{21}$	C	45	Small needles	66.1	$C_{22}H_{29}Cl_2NO_2S$	59.72	6.60	59.76	6.79
XXI	Br	n-$C_{10}H_{21}$	C	52	Needles	74.6	$C_{22}H_{29}BrClNO_2S$	54.27	6.00	54.52	6.10
XXII	Cl	n-$C_{12}H_{25}$	C	85	Small needles	68.2	$C_{24}H_{33}Cl_2NO_2S$	61.26	7.07	61.50	7.04
XXIII	Br	n-$C_{12}H_{25}$	C	70	Small needles	65	$C_{24}H_{33}BrClNO_2S$	55.97	6.46	56.16	6.61
XXIV	Br	CH_2CH_2Cl	C	40	Orthorhombic columns	107	$C_{14}H_{12}BrCl_2NO_2S$	41.10	2.96	41.25	3.22

obtained when the biological response was plotted against the number of carbon atoms in the *n*-alkyl radical for each of the two homologous series. These curves differed greatly for various methods of application. By topical application of the synergists with DDT in dilute benzene solutions to DDT-resistant house flies, the N-methyl compounds I and II were the most active in each series. When tested by a method of short duration contact of flies with residual deposits of the synergist and of DDT,[11] the compounds I and XIV (X = Cl, R = methyl and R = *n*-heptyl), and XII (X = Br, R = *n*-hexyl), showed maximum activity in their respective series. The correlation of biological factors such as "intrinsic synergistic activity", and "availability" by pick-up from deposits and cuticular penetration, in relation to chemical structure and physical properties of the compounds, will be the subject of a forthcoming paper.[10]

TABLE II

ABSORPTION CHARACTERISTICS OF BENZENESULFONANILIDES IN 95% ETHANOL

	λ_{max}, mμ	log ϵ_{mol}
4-CHLOROBENZENESULFON-4′-CHLOROANILIDE	227.5	4.31
-N-Methyl	227.5	4.52
-N-Ethyl	229	4.23
-N-*n*-Heptyl	228	4.22
4-BROMOBENZENESULFON-4′-CHLOROANILIDE	232.5	4.35
-N-Methyl	233	4.29
-N-*n*-Nonyl	236	4.11

EXPERIMENTAL

Method A. Preparation of benzenesulfonanilides. 4-Halogenobenzenesulfonyl chloride (0.2 mole) was condensed with 4-chloroaniline (0.2 mole) by mixing the reactants at 70° and adding an equivalent amount of 0.7 *N* aqueous sodium hydroxide with stirring over 30 minutes. After another 30 minutes at 70°, the product was filtered off, washed with dilute hydrochloric acid and water, and recrystallized from 95% ethanol. Chlorobenzenesulfon-4′-chloroanilide had m.p. 145.4–146° (corr.).

Anal. Calc'd for $C_{12}H_9Cl_2NO_2S$: C, 47.47; H, 3.00. Found: C, 47.62; H, 3.31.

4-Bromobenzenesulfon-4′-chloroanilide had m.p. 135.5° (corr.). Previously reported m.p. 134°[12] and m.p. 138°[3].

Anal. Calc'd for $C_{12}H_9BrClNO_2S$: C, 41.55: H, 2.63. Found: C, 41.56; H, 2.79.

Method B. Alkylation of benzenesulfonanilides with dialkyl (methyl and ethyl) sulfates. The benzenesulfonanilide (0.04 mole) was dissolved in 10% aqueous sodium hydroxide (0.042 mole) and the dialkyl sulfate (0.042 mole) was added with stirring at 25° over a period of 30 minutes. The N-alkylbenzenesulfonanilide began to precipitate a few minutes after addition of the dialkyl sulfate started. After an additional hour at 40°, the product was filtered off and recrystallized from 95% ethanol.

Method C. Alkylation of benzenesulfonanilides with alkyl tosylates. The benzenesulfonanilide (0.04 mole) was dis-

(11) Mer and Davidovici, *Parasitology*, **40**, 87 (1950).

(12) Marvel and Smith, *J. Am. Chem. Soc.*, **45**, 2696 (1923).

solved in 10 or 20% aqueous sodium hydroxide (0.04 mole). The alkyl tosylate was added with stirring at room temperature, and the reaction mixture was heated to 95–125° for 1 to 3 hours. After cooling, the reaction mixture was poured onto ice, whereupon the solid N-alkylbenzenesulfonanilide separated. This substance was filtered off, triturated with dilute aqueous sodium hydroxide and with water, and recrystallized from ethanol or aqueous ethanol.

Attempted hydrolysis of an N-alkylbenzenesulfonanilide. N-*n*-octyl-4-bromobenzenesulfon-4'-chloroanilide was recovered unchanged after refluxing for 70 hours with an excess of 25% aqueous hydrochloric acid or for 40 hours with 10% aqueous sodium hydroxide.

Solubility determinations. Solubilities were determined at 20°. The kerosene used was a commercial product produced by the Haifa refineries, which complied with Israel Standard No. 100. It had a specific gravity 60° F/60° F of 0.7928; an I.B.P. of 156° C. and a F.B.P. of 261° C. (by the test method ASTM D 86/52): an olefin plus aromatic content of 19.2% by vol. (I.P. 145/55); a bromine number of 1.7 (I.P. 129/53); a calculated aromatic content of 17.5% by vol. (I.P. 128/55T); a specific refractivity of 0.5608 (I.P. 60/53), and an Abel flash point of 43° C. (I.P. 33/55).

U.V. absorption measurements. Measurements were made in 95% ethanol solution with a Beckman model D.U. quartz spectrophotometer. Readings were obtained at 2.5 mμ intervals.

Acknowledgment. Thanks are due to Professor E. D. Bergmann for his constant encouragement and advice; to Professor G. G. Mer and Drs. R. Cwilich, H. Meyer, and A. S. Tahori for biological tests; to Mrs. H. Feilchenfeld and Mrs. L. Adam for U. V. spectra; and to Mrs. M. Goldstein and Mrs. S. Mayer for microanalyses.

P. O. Box 5192
JERUSALEM, ISRAEL