$C_{14}H_{30}N_2O_6P_2$: C, 40.39; H, 7.26; N, 6.73; P, 14.88. Found: C, 40.37; H, 7.34; N, 6.70; P, 14.96.

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4-(Phenylsulfonyl)carboxylic Acids

Formation of Clathrate (Inclusion) Compounds by 4-Phenyl-4-(phenylsulfonyl)valeric Acid

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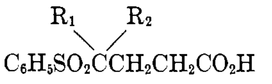
4-Phenyl-4-(phenylsulfonyl)valeric acid forms inclusion compounds with molecules such as ethyl ether, chloroform, carbon tetrachloride, cyclohexane, benzene, toluene, and benzene-heptane. The clathrates lose the volatile component when they are ground, heated under vacuum, or allowed to stand. Three other 4-(phenylsulfonyl)-carboxylic acids examined did not form clathrates.

Clathrate compounds are formed with a number of organic molecules by 4-phenyl-4-(phenylsulfonyl)valeric acid, 4, which we synthesized during the course of another investigation.



$$C_6H_5SO_2C(R_1)(R_2)CH_2CH_2CO_2H$$

Compound		Compound	
1	$R_1 = R_2 = H$	3	$R_1 = C_6H_5$, $R_2 = H$
2	$R_1 = CH_3$, $R_2 = H$	4	$R_1 = C_6H_5$, $R_2 = CH_3$

Accordingly, we report its preparation and properties, as well as those of the related 4-(phenylsulfonyl)carboxylic acids, 1, 2, and 3.

We use "clathrate" in the generic sense, as does *Chemical Abstracts*, to designate inclusion compounds of either the channel or caged type. The classification of inclusion compounds has not been standardized (*4*), but it has been the practice of some authors (*3*, *4*, *7*, *9*) to reserve the word clathrate for the caged structures only.

DISCUSSION

A variety of compounds, both organic and inorganic, are known to act as "host" molecules having crystal structures with channels or cages of the proper geometry to trap and hold firmly certain "guest" molecules (*1*, *4*). The geometry of the arrangement, rather than chemical bonding, is responsible for the stability of the resulting inclusion or clathrate compounds. Apparently, sulfones such as 4 have not previously been reported to act as host molecules. However, 4 is also a substituted valeric acid and in this structural feature does resemble desoxycholic and apocholic acids which have long been known to form inclusion compounds of the channel type, the choleic acids, with many types of smaller molecules (*1*, *9*). In Table I are listed the clathrates formed when 4 is crystallized from various solvents. No attempt was made to establish any limits of size or geometry for the guest molecule, and whether the inclusion compounds are of the channel or caged type is not known.

Positive identification of the guest molecules in the inclusion compounds was complicated by the problem of getting pure 4 to use as a starting material. The compound will not crystallize without the inclusion of a guest, and separation of the volatile component from the clathrate is accomplished only with difficulty and with the risk of accompanying decomposition of 4 itself (vide infra). Water was excluded as a component by the lack of its characteristic absorption bands in the infrared and near infrared.

Positive identification was achieved in the case of the benzene–heptane solvent by careful vacuum heating of the clathrate and collecting the distillate in a cold trap. Infrared analysis of the distillate showed it to be an approximately 40–60 mix-

Table I. Clathrate Compounds from 4

Crystallizing solvent	Neutralization equiv of clathrate[a]	Moles guest/ mole 4[b]
Ethyl ether	374	0.76
Carbon tetrachloride	400	0.53
Toluene	363	0.49
Benzene	355	0.47
Benzene–cyclohexane	363	0.54[c]
Benzene–*n*-heptane	360	[d]
Chloroform-*n*-heptane	440	1.0[e]

[a] Values given are averages of several trials. The expected range of values is ca. ±2% from the average (greatest range with CCl_4 and $CHCl_3$) and includes the imprecision of titrating small samples. [b] Calculated from the neutralization equivalent. [c] Guest is C_6H_{12}. [d] Guest is ca. 40-60 C_6H_6-C_7H_{16}. [e] Guest is $CHCl_3$.

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ture of benzene and heptane. Identification of the guest molecules in the clathrates from 4 and chloroform–heptane, toluene, and cyclohexane–benzene was accomplished by nmr. In those cases in which pure 4 and a pure solvent were used, the neutralization equivalent (n.e.) alone reflects the composition of the clathrate.

Although the mole ratios in the clathrates are nearly ratios of small integers for the combinations studied, individual samples may deviate considerably from the values shown in Table I, especially if they are dried at elevated temperature under vacuum, or are allowed to stand for long periods, and it is uncertain whether any preference for integral ratios of host to guest actually exists. Most other clathrates known have no such preference (*2*), although an exception is found in some choleic acids (*4*).

Compound 4 has two crystal habits. One crystallizes from solvents in needles as a clathrate compound; the other, less distinctly crystalline, is formed when the clathrates are allowed to stand for long periods or are heated below the decomposition point of 4 under vacuum, or are subjected to shearing forces as in grinding. The melting points of the clathrates are indistinct and vary with the conditions of measurement. Melting usually begins at about 70°C and can be completed at 80° or 90°C if the sample is freshly prepared and has not been ground. If any of the second crystal form is present, however, some solid may remain up to ca. 115–16°C, the melting point of nonclathrated 4. Both crystal forms have the same solid-state ir spectra, except for some shifting of bands in the 12–15-μ region.

Complete removal of the guest molecules occluded by 4 is difficult. The neutralization equivalent of a typical clathrate can be lowered by heating under vacuum, but the unexpectedly low decomposition temperature of 4 itself requires the use of the mildest possible conditions. Best results were obtained when the clathrate compound was heated in a 95–100°C oil bath under 0.07-mm pressure for 6 hr. The resulting product melted at 113–14°C and had a neutralization equivalent of 326, only slightly above the theoretical value of 318 for 4-phenyl-4-(phenylsulfonyl)valeric acid. A drying period of only 2 hr under the same conditions resulted in removal of only about half of the volatile component. Substantially longer drying periods or the use of even a slightly higher temperature (110°C) resulted in decomposition of 4 with attendant loss of weight and reduction of the neutralization equivalent to less than the theoretical value.

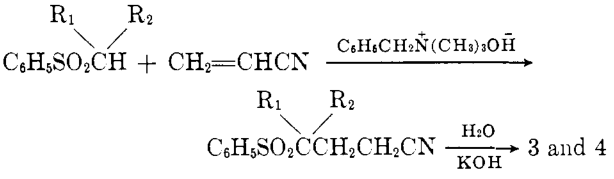
Spontaneous loss of the volatile-included molecule from the clathrates occurs slowly in a closed container and more rapidly in the open air, although the rate in either case varies with the nature of the guest molecule (Table II). Loss of the guest is accompanied by conversion to the higher-melting crystal form. The last three entries in the table show how grinding increases the rates of these processes. None of the other 4-(phenylsulfonyl)butyric acids prepared showed any tendency to form inclusion compounds.

Table II. Effect of Standing on Clathrates

Guest	Initial n.e.	Standing period[a]	Final n.e.	Final mp, °C[b]
$C_6H_5CH_3$	363	19 Mos. CC	342	115–16
$CHCl_3$	435	23 Mos. CC	321	114–15
C_6H_6–C_7H_{16}	360	19 Mos. CC	351	113–16
C_6H_6–C_7H_{16}	361	19 Mos. CC	342	113–15
C_6H_6–C_7H_{16}	363	15 Days OA	361	No change
CCl_4	417	8 Days OA	403	No change
$CHCl_3$	434	8 Days OA	433	No change
$CHCl_3$	434	126 Days OA	330	112–13
$(C_2H_5)_2O$	372	6 Days OA	359	. . .
$(C_2H_5)_2O$	372	9 Days OA	344	110–13
C_6H_6–C_7H_{16}	363	1 Day OA[c]	359	65–113
C_6H_6–C_7H_{16}	363	6 Days OA[c]	339	. . .
C_6H_6–C_7H_{16}	363	12 Days OA[c]	337	112–14

[a] OA = open air, CC = closed container. [b] Melting points of all clathrates were similar initially and covered a broad range (vide supra). [c] Sample ground after the initial n.e. was measured.

The syntheses of 3 and 4 were carried out according to Scheme 1. Yields were good in the preparation of 4 where only one cyanoethylation product was possible, but much lower for 3 where cyanoethylation gave a mixture of mono- and dinitriles that was difficult to purify. Compounds 1 and 2 were prepared by the displacement of a halide ion from a suitably substituted carboxylic acid derivative by sodium benzenesulfinate, followed by hydrolysis to the acid. This method proved inferior to the previously described synthesis of 1 (*6*). Attempts to use these methods for the preparation of other analogs of 4 having the phenylsulfonyl group attached to a quaternary carbon atom—i.e., $R_1 = R_2 = CH_3$ and $R_1 = R_2 = C_6H_5$—were unsuccessful.



$$C_6H_5SO_2CH(R_1)(R_2) + CH_2{=}CHCN \xrightarrow{C_6H_5CH_2\overset{+}{N}(CH_3)_3\overset{-}{O}H} C_6H_5SO_2C(R_1)(R_2)CH_2CH_2CN \xrightarrow[KOH]{H_2O} 3 \text{ and } 4 \qquad (1)$$

Compound	
3	$R_1 = C_6H_5$, $R_2 = H$
4	$R_1 = C_6H_5$, $R_2 = CH_3$

EXPERIMENTAL

Melting points were taken on a Fisher-Johns apparatus and are corrected. Infrared and ultraviolet spectra were recorded on Beckman IR-5 and Beckman DK-2A spectrophotometers, respectively. Nmr spectra were obtained on a Varian T60 instrument.

Ethyl 4-(Phenylsulfonyl)valerate. A mixture of 31.2 grams (0.149 mole) of ethyl 4-bromovalerate (Sapon Chem. Co.), 25.0 grams (0.152 mole) of sodium benzenesulfinate (Aldrich), and 120 ml of *N,N*-dimethylformamide was stirred at 40–50°C for two days, then at 120–5°C for 6 hr. The mixture was filtered, then distilled under water pump vacuum to remove the solvent. Water was added to the residue, and the organic materials were extracted with chloroform. The chloroform solution was washed with water, dried over potassium carbonate, and distilled. The residue was subjected to vacuum distillation (0.15 mm, bath at 95–100°C), which removed a liquid carbonyl compound (λ_{max} 1770 cm^{-1}), probably γ-valerolactone, then trituration with 30–60°C petroleum ether, which removed some phenyl disulfide.

The remaining material, 26 grams of an amber, viscous, undistillable liquid, could not be purified further; however, thin-layer chromatography (tlc) showed it to be free of major impurities, and the ir spectrum was consistent with that expected for ethyl 4-(phenylsulfonyl)valerate: λ_{max} (liquid film) μ 3.27, 3.36, 3.41 (all CH str), 5.77 (C=O str), 6.31 (ar C=C str), 6.90, 7.24, 7.65, and 8.70 (—SO_2—), 9.18, 9.74, 13.65, and 14.45 (CH out of plane def.).

4-(Phenylsulfonyl)valeric Acid, 2. A solution of 19.8 grams of KOH and 25 grams of ethyl 4-(phenylsulfonyl)valerate in 20 ml of water and 100 ml of methanol was heated at reflux until a sample no longer gave any milkiness when diluted with water (1^3/$_4$ hr). The methanol was evaporated under a current of air, 150 ml of water was added, and the mixture then extracted with ether. The water layer was acidified with HCl, saturated with sodium bicarbonate, and extracted with ether. Acidification of the water layer gave a yellow oil which was extracted with ether. The solution was dried over sodium sulfate, and the ether evaporated under a current of air. After the residual oil had stood under a current of air for four days it had all solidified to a waxy solid (9.0 grams).

Crystallization of the crude acid from a carbon tetrachloride–benzene mixture gave 6.4 grams (29%) of pale yellow needles, mp 74–75°, neutralization equivalent 242 (theory = 242). Crystallization from several other solvent mixtures also gave a product with the predicted neutralization equivalent. The analytical sample crystallized in white needles from benzene–carbon tetrachloride and benzene–heptane mixtures and melted at 76–76.5°C: $\lambda_{\max}$ ($CHCl_3$) μ 2.37 (free OH), 5.83 (C=O), 6.31 (ar C=C), 6.91, 7.07, 7.65, and 8.70 (—SO_2—), 9.20, 14.52 (CH out of plane def.). Anal. Calcd. for $C_{11}H_{14}O_4S$: C, 54.53; H, 5.82; S, 13.23. Found: C, 54.65; H, 5.76; S, 13.38.

4-Phenyl-4-(phenylsulfonyl)butyronitrile. To a stirred solution of 45.0 grams (0.194 mol) of benzyl phenyl sulfone (*5*) and 11.6 grams of benzyltrimethylammonium hydroxide (35% in methanol) in 310 ml of acetonitrile was added 10.5 grams (0.198 mol) of acrylonitrile over a 15-min period while the temperature was maintained at 32–5°C. The solution was stirred at room temperature for 18 hr, neutralized with dilute hydrochloric acid, and the acetonitrile removed by distillation under water pump vacuum. Addition of water to the residue precipitated a yellowish solid which was collected by filtration. After two crystallizations from ethanol, using activated charcoal, the product, 65 grams, was still pale yellow and melted at 88–90°C. The major portion was used for hydrolysis to the acid without further purification, and a small sample was crystallized repeatedly from petroleum ether–benzene and alcohol solvents to prepare the analytical sample, mp 104–05°C: $\lambda_{\max}$ ($CHCl_3$) μ 4.45 (CN), 6.31 (ar C=C), 6.68, 6.90, 7.61, and 8.67 (—SO_2—), 9.18, 14.36, and 14.56 (CH out of plane def.). Anal. Calcd. for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30; N, 4.91; S, 11.23. Found: C, 67.08; H, 5.57; N, 4.94; S, 11.16.

4-Phenyl-4-(phenylsulfonyl)butyric Acid, 3. A solution of 59.0 grams of impure 4-phenyl-4-(phenylsulfonyl)butyronitrile, 41 grams of potassium hydroxide in 41 ml of water, and 205 ml of methanol was heated at reflux for 36 hr. At this time dilution of a sample with water still produced milkiness, thought to be due to benzyl phenyl sulfone in the starting material. Evaporation of the methanol under a current of air, dilution with water, filtration, and acidification with concentrated hydrochloric acid cast down an oil which solidified when the mixture was chilled overnight. The crude acid was crystalized from an ethanol–water mixture to give 11 grams of 3, mp 155–6°C. The analytical sample, white prisms, melted at 156–6.5°, $\lambda_{\max}$ (mull) μ 5.86 (C=O), 6.31 and 6.68 (ar C=C), 7.60 and 8.70 (—SO_2—), 7.71, 8.11, 9.20, 9.55, 12.40, 13.48, 13.94, 14.21, 14.48. Neutralization equivalents of the acid after isolation from a variety of solvents were within experimental error of the theoretical value. Anal. Calcd. for $C_{16}H_{16}O_4S$: C, 63.14; H, 5.30; S, 10.53. Found: C, 63.17; H, 5.14; S, 10.40.

4-Phenyl-4-(phenylsulfonyl)valeronitrile. A solution of 215 grams (0.875 mole) of phenyl 1-phenylethyl sulfone (*8*) and 42 ml of benzyltrimethylammonium hydroxide (35% in methanol) in 1770 ml of acetonitrile was treated with 55.3 grams (1.04 mole) of acrylonitrile, and the product was isolated in the manner described above for compound 3. After one crystallization from ethanol (needles) the product weighed 190 grams (73%) and melted at 126–8°C. The analytical sample melted at 129–30°C, $\lambda_{\max}$ (mull) μ 4.44 (CN), 7.72 and 8.68 (—SO_2—), 9.35, 12.58, 13.17, 13.73, 14.46. Anal. Calcd. for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68; S, 10.71. Found: C, 68.22; H, 5.88; N, 4.48; S. 11.01.

4-Phenyl-4-(phenylsulfonyl)valeric Acid, 4, and Clathrates. Hydrolysis of 4-phenyl-4-(phenylsulfonyl)valeronitrile was carried out as described above for 4-phenyl-4-(phenylsulfonyl)butyronitrile. A refluxing period of 16 hr was employed. After evaporation of the methanol, the alkaline solution was diluted with water and acidified with concentrated hydrochloric acid. The 4 which precipitated as a gummy viscous liquid was taken up in ether, and the ether solution was washed with water and dried over calcium sulfate. Distillation of the ether, finishing under water pump vacuum, left a gummy product that gradually solidified on long standing to a tough gluelike solid. Equivalent results were obtained when other solvents were used for the extraction step.

The crude 4 thus isolated could be crystallized from a number of solvent systems to give clathrate compounds such as those described in Table I. The clathrates melted over a wide range, while the nonclathrate crystal form melted at 115–16° C; $\lambda_{\max}$ ($CHCl_3$) μ 5.82 (C=O), 7.66 and 8.67 (—SO_2—), 8.14, 9.33, and (mull) 12.44, 12.81, 13.08, 13.72, 14.44; nmr ($CDCl_3$ soln), ppm 1.74 singlet (3H, CH_3), 2.0–3.0 multiplet (4H, CH_2CH_2), 7.30 singlet (5H, C_6H_5C), 7.38 singlet (5H, $C_6H_5SO_2$), 8.64 singlet (1H, CO_2H).

As a standard procedure the clathrates prepared from 4 were collected on a suction filter and dried overnight in a desiccator under house vacuum (ca. 60 torr). Neutralization equivalents were measured in a 50–50 alcohol–water solvent using a phenolphthalein indicator.

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