135. *Organo-lead Compounds. Part III.* N-*Trialkylplumbisulphonamides.*

By B. C. Saunders.

A large variety of lead compounds of a new type, $RSO_2{\cdot}NR'{\cdot}PbR''_3$, has been prepared by two methods. They are highly crystalline, stable, compounds and all possess powerful sternutatory properties; many of them are intolerable at a concentration of 1 : 10^7. They are, therefore, more potent than the simpler trialkyl-lead salts already described in this series of papers. The most effective are N-*tri*-n-*propylplumbimethane*- and *tri*-n-*propylplumbibenzene-sulphonamide.*

In 1940 McCombie and Saunders reported to the Ministry of Supply a new type of compound, namely, N-*triethylplumbitoluene*-p-*sulphonamide,* $C_6H_4Me{\cdot}SO_2{\cdot}NH{\cdot}PbEt_3$ (I), a colourless, stable, crystalline compound, recrystallisable from benzene and several other non-polar solvents. We prepared it in 73% yield by heating the sodio-derivative of toluene-*p*-sulphonamide with triethyl-lead chloride in alcohol :

$$C_6H_4Me{\cdot}SO_2{\cdot}NH\boxed{Na + Cl}PbEt_3 = \underset{\text{(I.)}}{C_6H_4Me{\cdot}SO_2{\cdot}NH{\cdot}PbEt_3} + NaCl$$

The compound had the lead content required for the formula (I) and was decomposed by passage of gaseous hydrogen chloride into its suspension in ether, giving pure toluene-*p*-sulphonamide and diethyl-lead dichloride. The latter was almost certainly a secondary product, the primary product being triethyl-lead chloride which is known to give the dichloride when its dilute ethereal solution is kept in the presence of excess of hydrogen chloride. Cleavage of (I) is therefore expressed as :

$$C_6H_4Me{\cdot}SO_2{\cdot}NH{\cdot}PbEt_3 + HCl \longrightarrow C_6H_4Me{\cdot}SO_2{\cdot}NH_2 + PbEt_3Cl$$

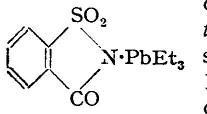
Examined as a sternutator by spraying its alcoholic solution, the sulphonamide (I) proved to be the most effective lead sternutator tested till then, being considerably more potent than the trialkyl-lead salts described in Parts I and II (*J*., 1949, 919, 2983). It was intolerable at a concentration of 1 : 10^7. Similar syntheses gave N-*triethylplumbibenzenesulphonamide, tri*-n-*propylplumbitoluene*-p-*sulphonamide, and tri*-n-*propylplumbibenzenesulphonamide,* all stable crystalline compounds and, as expected, the introduction of the tri-*n*-propyl grouping increased the sternutatory action (see Part I, *loc. cit.*). For example, tri-*n*-propylplumbibenzenesulphonamide was a particularly powerful sternutator and at a concentration of 1 : 10^7 all the observers were forced to leave the testing-chamber after an exposure of only 40 seconds (sternutatory grade, 3; cf. Part I). In addition to its action on the nose, throat, chest, and gums, the compound produced irritation on the fingers and faces of some of the workers who undertook its preparation, particularly on a large scale.

In efforts to simplify the preparation it was found (1941) that mixing cold alcoholic solutions of tri-*n*-propyl-lead hydroxide and benzenesulphonamide and then adding water precipitated *N*-tri-*n*-propylplumbibenzenesulphonamide, practically pure even before recrystallisation, and in almost quantitative yield :

$$PbPr_3{\cdot}OH + C_6H_5{\cdot}SO_2{\cdot}NH_2 = C_6H_5{\cdot}SO_2{\cdot}NH{\cdot}PbPr_3 + H_2O$$

This method had wide application and gave excellent yields, particularly when the sulphonamide was markedly " acidic."

A variety of compounds of the type $R{\cdot}SO_2{\cdot}NR'{\cdot}PbR''_3$ was then prepared in which R = Me, Ph, $o\text{-}C_6H_4Me$, $p\text{-}C_6H_4Me$, or $p\text{-}NH_2{\cdot}C_6H_4$, R′ = H, Ph, $p\text{-}C_6H_4Cl$, or $p\text{-}C_6H_4Br$, and R″ = Et or Pr^n. These were, without exception, powerful sternutators, the most effective being *tri*-n-*propylplumbimethanesulphonamide,* $Me{\cdot}SO_2{\cdot}NH{\cdot}PbPr_3$, which was extremely unpleasant at a concentration of 1 : $2{\cdot}5 \times 10^7$ (sternutatory grade 3^+). In addition, its lower molecular weight and high solubility in alcohol and other organic solvents increased its applicability.



(III.)

Saccharin reacted readily in cold alcohol with triethyl-lead hydroxide, giving o-*sulphobenzoic triethylplumbi-imide* (III). This and the corresponding *tri*-n-*propyl* derivative, like the acylic sulphonamides, were powerful sternutators, being intolerable at a concentration of 1 : 10^7 after only 1½ minutes. Even at this high dilution a " sweet taste " was noticed by the observers.

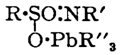
In Parts I and II we reported that an unsaturated grouping intensified the physiological action of an organo-lead compound. For example, triethyl-lead acrylate and tri-*n*-propyl-lead acrylate were more potent than the corresponding saturated salts. In view of the fact that the sulphonamide grouping also increases sternutatory action, it was decided to combine the two " active " groups in one molecule. We accordingly prepared N-*triethylplumbiethylenesulphonanilide*, $CH_2{=}CH{\cdot}SO_2{\cdot}NPh{\cdot}PbEt_3$, by the action of triethyl-lead chloride on the *sodio*-derivative of ethylenesulphonanilide. This sodium salt was soluble in alcohol and reacted smoothly. In this instance a purer product was obtained than when triethyl-lead hydroxide and the free ethylene sulphonanilide were used, as the latter anilide did not appear to be sufficiently acidic to react completely with the hydroxide. Although *N*-triethylplumbiethylenesulphonanilide gave an almost intolerable atmosphere at a concentration of 1 : 10^7, it did not show the expected increased potency compared with the simpler compounds.

As an example of a compound containing two $-SO_2{\cdot}NR{\cdot}PbR'_3$ groupings in the molecule, we prepared *methanedi*-(N-*triethylplumbisulphonanilide*) (IV), a powerful sternutator, but not exhibiting outstanding properties.

It should be pointed out that no definite chemical evidence has been produced to decide between formulæ (V) and (VI) for these compounds. Both would account for the cleavage by

$CH_2(SO_2{\cdot}NPh{\cdot}PbEt_3)_2$ (IV.)

$R{\cdot}SO_2{\cdot}NR'{\cdot}PbR''_3$ (V.)



$$\begin{array}{l} R{\cdot}SO{:}NR' \\ \quad | \\ \ \ O{\cdot}PbR''_3 \end{array}$$

(VI.)

hydrogen chloride into the parent sulphonamide and the trialkyl-lead chloride. The point could be decided by *X*-ray analysis, and it is hoped that this will be undertaken in the near future.

EXPERIMENTAL.

N-*Triethylplumbitoluene*-p-*sulphonamide*.—Toluene-*p*-sulphonamide (3·4 g.) was dissolved in alcohol, and sodium (0·5 g.) was added. The white flaky precipitate produced was filtered off, washed with alcohol, and dried. To this sodio-derivative (1·93 g.), suspended in alcohol, triethyl-lead chloride (3·3 g.) was added and the whole heated under reflux for 20 minutes. The product was then cooled and filtered, and to the filtrate water was added until the solid *triethylplumbitoluene*-p-*sulphonamide* crystallised out. After being washed with water, dried, and recrystallised from benzene, it had m. p. 127° (Found : Pb, 44·53. $C_{13}H_{23}O_2NSPb$ requires Pb, 44·6%).

Cleavage by hydrogen chloride. (*a*) Triethylplumbitoluene-*p*-sulphonamide was suspended in a *large* volume of ether, and dry hydrogen chloride passed in. The substance dissolved and, after saturation, the solution was set aside. Diethyl-lead dichloride separated (Found : Pb, 62·2. Calc. for $C_4H_{10}Cl_2Pb$: Pb, 61·9%).

(*b*) Triethylplumbitoluene-*p*-sulphonamide was suspended in the *minimum* volume of ether and treated as in (*a*). A lead-free solid separated rapidly and had m. p. 138°. It was shown to be toluene-*p*-sulphonamide.

N-*Triethylplumbibenzenesulphonamide*.—Prepared as above, but by use of molecular quantities of sodiobenzenesulphonamide and triethyl-lead chloride, and recrystallised from benzene, the *sulphonamide* had m. p. 132° (Found : Pb, 45·9. $C_{12}H_{21}O_2NSPb$ requires Pb, 46·0%).

N-*Tri*-n-*propylplumbitoluene*-p-*sulphonamide*.—Sodiotoluene-*p*-sulphonamide (3·6 g.) was suspended in alcohol and tri-*n*-propyl-lead chloride (6·5 g.) was added. Subsequent treatment as above, and recrystallisation from light petroleum (b. p. 80—100°) gave the *amide*, m. p. 100—101° (Found : Pb, 41·1. $C_{16}H_{29}O_2NSPb$ requires Pb, 40·9%).

N-*Tri*-n-*propylplumbibenzenesulphonamide*.—(*a*) Prepared and purified as in the preceding paragraph, N-*tri*-n-*propylplumbibenzenesulphonamide* (73%, crude) had m. p. 96° (Found : Pb, 41·6. $C_{15}H_{27}O_2NSPb$ requires Pb, 42·1%).

(*b*) To an alcoholic solution of tri-*n*-propyl-lead hydroxide (from 3·7 g. of the chloride) was added an alcoholic solution of benzenesulphonamide (1·6 g.). Water was added, and after 10 minutes the product was filtered off. 118 G. of crude but almost pure material were recrystallised, yielding 101 g. of the pure sulphonamide, m. p. 93·5—94·5°. 5 C.c. of alcohol dissolved 3·2 g. of the sulphonamide at 15°, and after 6 days the substance was reprecipitated unchanged (m. p. 93·5—94·5°) by the addition of water.

Tripropylplumbitoluene-*p*-sulphonamide, triethylplumbibenzenesulphonamide, and triethylplumbitoluene-*p*-sulphonamide were also prepared by method (*b*), from the calculated quantities of hydroxide and sulphonamide.

N-*Triethylplumbimethanesulphonamide*.—Methanesulphonamide (0·95 g.) was dissolved in hot benzene and mixed with triethyl-lead hydroxide (3·11 g.) dissolved in benzene. The mixture was heated under reflux for 30 minutes on a water-bath. After cooling, a very small quantity of a solid separated and was recrystallised from aqueous alcohol; this decomposed at 197° (Found: Pb, 56·2%). To the filtrate light petroleum was added to precipitate the white crystalline *triethylplumbimethanesulphonamide* which, recrystallised from benzene–light petroleum (b. p. 60—80°), had m. p. 97° (Found: Pb, 53·4. $C_7H_{19}O_2NSPb$ requires Pb, 53·4%).

N-*Tri*-n-*propylplumbimethanesulphonamide*.—Freshly prepared moist silver oxide (2·8 g.) was suspended in benzene and a small quantity of alcohol added. To this was added tripropyl-lead chloride (3·7 g.) dissolved in benzene, and the mixture shaken and then filtered. The filtrate was added to methanesulphonamide (0·95 g.) dissolved in hot benzene, and the procedure of the previous experiment then followed. The *amide* had m. p. 67° (Found: Pb, 48·1. $C_{10}H_{25}O_2NSPb$ requires Pb, 48·2%).

N-*Triethylplumbimethanesulphonanilide*.—Benzene solutions of methanesulphonyl chloride (3·42 g.) and aniline (5·52 g.) were mixed. After 20 minutes, light petroleum (b. p. 40—60°) was added, and the precipitated mixture of aniline hydrochloride and methanesulphonanilide was boiled with benzene and filtered. To the benzene filtrate, light petroleum was added. Methanesulphonanilide, m. p. 100°, separated (Found: C, 49·5; H, 5·6. Calc. for $C_7H_9O_2NS$: C, 49·1; H, 5·3%). The methanesulphonanilide (0·85 g.), dissolved in alcohol, was added to triethyl-lead hydroxide (1·55 g.) and set aside for 30 minutes. The white crystalline *triethylplumbimethanesulphonanilide* which separated on the addition of water was recrystallised from benzene–light petroleum (b. p. 40—60°), and had m. p. 115·5° (Found: Pb, 44·1. $C_{13}H_{23}O_2NSPb$ requires Pb, 44·6%).

N-*Triethylplumbisulphanilamide*.—A solution of sulphanilamide (1·72 g.) in alcohol was added to a solution of triethyl-lead hydroxide (3·12 g.) in alcohol. After 30 minutes the mixture was filtered, and to the filtrate water was added. The colourless *triethylplumbisulphanilamide* which separated was recrystallised from alcohol and then had m. p. 171° (Found: Pb, 43·9. $C_{12}H_{22}O_2N_2SPb$ requires Pb, 44·55%).

N-*Tri*-n-*propylplumbisulphanilamide*.—Prepared similarly, the alcoholic solution of the hydroxide being made by shaking the chloride (3·7 g.) in alcohol with moist silver oxide (2·8 g.) for 10 minutes before filtration, *tri*-n-*propylplumbisulphanilamide* had m. p. 101° after recrystallisation from benzene (Found: Pb, 40·9. $C_{15}H_{28}O_2N_2SPb$ requires Pb, 40·9%).

o-*Sulphobenzoic Triethylplumbi-imide*.—A solution of triethyl-lead hydroxide (3·11 g.) in alcohol was added to an alcoholic solution of saccharin (1·8 g.). After 30 minutes the mixture was cooled in ice-water, and water added until a turbidity was produced. On scratching of the vessel, a white solid separated which was recrystallised from a mixture of benzene and light petroleum (b. p. 60—80°). The *lead* derivative was thus obtained as colourless needles, m. p. 135°, containing nitrogen and sulphur (Found: Pb, 44·4. $C_{13}H_{19}O_3NSPb$ requires Pb, 44·1%).

The compound was dissolved in ether and dry hydrogen chloride passed in. Crystals of saccharin separated and, on storage, diethyl-lead dichloride gradually separated from the filtrate.

o-*Sulphobenzoic Tri*-n-*propylplumbi-imide*.—Prepared from alcoholic solutions of tripropyl-lead hydroxide (from the chloride) and saccharin, and recrystallised from benzene–light petroleum (b. p. 60—80°), the *imide* had m. p. 130° (Found: Pb, 39·4. $C_{16}H_{25}O_3NSPb$ requires Pb, 40·0%).

N-*Triethylplumbitoluene*-p-*sulphonanilide*.—Prepared from the sulphonanilide (2·51 g.) and triethyl-lead hydroxide (3·12 g.) in alcohol, and recrystallised from aqueous alcohol, the *sulphonanilide* had m. p. 134° (Found: Pb, 37·8. $C_{19}H_{27}O_2NSPb$ requires Pb, 38·35%).

N-*Tri*-n-*propylplumbitoluene*-p-*sulphonanilide*.—Prepared similarly to the corresponding sulphanilamide, from the chloride (3·7 g.) and the sulphonanilide (2·51 g.), and recrystallised from aqueous alcohol, this *anilide* had m. p. 104° (Found: Pb, 35·0. $C_{22}H_{33}O_2NSPb$ requires Pb, 35·6%).

N-*Triethylplumbitoluene*-o-*sulphonamide*.—Prepared from toluene-*o*-sulphonamide and triethyl-lead hydroxide, and recrystallised from aqueous alcohol, the *amide* had m. p. 133° (Found: Pb, 44·6. $C_{13}H_{23}O_2NSPb$ requires Pb, 44·6%).

N-*Triethylplumbitoluene*-p-*sulphon*-p′-*chloroanilide*.—Prepared from alcoholic solutions of toluene-*p*-sulphon-*p*′-chloroanilide and triethyl-lead hydroxide, the *lead* derivative was recrystallised from benzene and light petroleum, and had m. p. 111·5° (Found: Pb, 36·05. $C_{19}H_{26}O_2SNClPb$ requires Pb, 36·1%).

N-*Tri*-n-*propylplumbitoluene*-p-*sulphon*-p′-*chloroanilide*, m. p. 123° (Found: Pb, 33·5. $C_{22}H_{32}O_2NSClPb$ requires Pb, 33·6%), and *triethylplumbitoluene*-p-*sulphon*-p′-*bromoanilide*, m. p. 117° (from benzene) (Found: Pb, 33·15. $C_{19}H_{26}O_2NSBrPb$ requires Pb, 33·48%), were similarly prepared.

Sodium Ethane-1 : 2-*disulphonate* (cf. *Annalen*, 1886, **148**, 96, and *J.*, 1922, 120).—The calculated quantities of ethylene dibromide and sodium sulphite ($7H_2O$) were heated under reflux with the minimum amount of water needed to dissolve the sulphite. After 3 hours, the mixture was evaporated to crystallisation, and the solid obtained was dried at 120°. Yield, 75%.

Ethanedisulphonyl Chloride.—To the crude sodium salt, phosphorus pentachloride (2 mols.) was added, and the reaction completed by careful warming. The phosphorus oxychloride was distilled off at 15 mm. and the residue ground with ice and extracted with ether. The ethereal extract was dried (Na_2SO_4) and evaporated. The product, recrystallised from light petroleum (b. p. 100—110°), had m. p. 91° (yield 55%).

Ethylenesulphonanilide.—The above sulphonyl chloride (25 g.) was dissolved in ether (30 c.c.), and aniline (31 g.), also in ether (20 c.c.), was added. (If excess of aniline was used, side-reactions took place.) Heat was evolved, and when the addition was complete the mixture was boiled until no more sulphur dioxide was evolved. The precipitated aniline hydrochloride was filtered off and washed with ether. The ethereal solutions were extracted with hydrochloric acid and dried (Na_2SO_4), the ether was distilled off, and the residue recrystallised from alcohol; it had m. p. 69° (yield 55%).

Sodioethylenesulphonanilide.—Ethylenesulphonanilide (11 g.) was dissolved in aqueous sodium hydroxide solution (25 c.c.; 10%) by warming. The solution was filtered and cooled in ice, and the crystalline precipitate which formed was filtered off and dried on a porous plate. This product was washed with ether, again filtered, and dried *in vacuo* over concentrated sulphuric acid.

The crude product was readily soluble in alcohol, but was recrystallised by adding a small quantity of light petroleum (b. p. 60—80°) to a hot alcoholic solution, filtering this solution while hot and then cooling it in ice. The crystalline *sodioethylenesulphonanilide* was dried *in vacuo* over calcium chloride.

The yield of pure product was 2 g. (16%) (Found : C, 46·6; H, 3·9; N, 7·1. $C_8H_8O_2NSNa$ requires C, 46·8; H, 3·9; N, 7·5%). The compound was readily soluble in water or alcohol, slightly soluble in acetone, and insoluble in ether, chloroform, or benzene. When the compound was heated slowly the m. p. was sharp (69°; this is the m. p. of the original ethylenesulphonanilide). On further heating of the sodio-derivative, fusion was followed by decomposition and charring, and finally a white residue of sodium sulphate remained.

An aqueous solution, on acidification with dilute sulphuric acid, gave a white precipitate of the original sulphonanilide (m. p. 69°).

N-*Triethylplumbiethylenesulphonanilide*.—Triethyl-lead chloride (1·2 g.) in alcohol (10 c.c.) and sodioethylenesulphonanilide (0·75 g.) in alcohol (10 c.c.) were mixed and kept at room temperature for 15 hours. Sodium chloride (0·2 g., theoretical yield) was filtered off, and the filtrate poured into water. The white precipitate which separated was filtered off, washed with water, and dried *in vacuo*. The crude *lead* derivative recrystallised as colourless leaflets from light petroleum (b. p. 100—120°) (Found : N, 3·0. $C_{14}H_{23}O_2NSPb$ requires N, 2·95%) (yield 1 g., 55%). When heated gradually, it melted sharply at 116°. When heated in the open in bulk it decomposed with a mild explosion.

Methanedisulphonyl Chloride.—Methanedisulphonic acid was prepared from acetylene and fuming sulphuric acid by the method of Schroeter (*Annalen*, 1919, **418**, 183). To the dehydrated acid (20 g.), phosphorus pentachloride (48 g.) was added in small quantities. When the addition was complete, the mixture was heated on a water-bath for 15 minutes and then the phosphorus oxychloride was distilled off at 42°/20 mm. The residue on distillation at 143°/20 mm. gave the pure disulphonyl chloride (20 g., 83%).

Methanedisulphonanilide.—Aniline (9·3 g.) in benzene (50 c.c.) was added to methanedisulphonyl chloride (5·3 g.) in benzene (35 c.c.). The mixture was boiled under reflux for 10 minutes, cooled, shaken with sodium hydroxide (4 g.) in water (25 c.c.), and filtered through sintered glass to remove a slight precipitate. The aqueous layer was separated, extracted with more benzene, and then acidified with dilute hydrochloric acid. The precipitate was purified by repeated dissolution in dilute sodium hydroxide solution, washing with benzene, and reacidification. The disulphonanilide thus obtained (3·8 g., 50%) was dried *in vacuo* over solid potassium hydroxide and paraffin wax.

Methanedi-(N-*triethylplumbisulphonanilide*).—Triethyl-lead hydroxide (2 g.) was added to methanedisulphonanilide (1 g.) in a mixture of water (10 c.c.) and alcohol (10 c.c.), and heated till clear. The solution was filtered while hot, and on cooling colourless crystals were obtained and recrystallised from aqueous alcohol. *Methane di*-(N-*triethylplumbisulphonanilide*) was obtained as long colourless needles, insoluble in water, soluble in alcohol and in hot benzene. The compound did not melt, but sintered at 71° and decomposed at 180° with effervescence. For lead analysis (see Part I, *loc. cit.*) the compound was first decomposed by nitric acid in a sealed tube (Found : Pb, 44·9. $C_{25}H_{42}O_4N_2S_2Pb_2$ requires Pb, 45·4%).

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