Reactions of Thiols and Thioethers. Part I. An Analogue of the Mannich Reaction involving Thiols, Formaldehyde, and Active Methylene or Methylidyne Compounds.

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A new reaction is described in which indole, antipyrine, and 2-naphthol each give sulphur analogues (I), (II), and (III) of Mannich bases on treatment with formaldehyde and thiols. The products have been characterised by direct comparison with compounds formed from Mannich bases or their quaternary derivatives and thiols in the known manner and also by desulphurisation with Raney nickel.

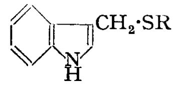
The primary step in the new reaction is shown probably to be addition of formaldehyde to the thiol to form an alkyl- or aryl-thiomethanol.

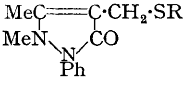
Interaction of 1-dimethylaminomethyl-2-naphthol and excess of toluene-ω-thiol at the boiling point results in a good yield of 1-methyl-2-naphthol, the thiol probably acting as a reducing agent.

Pyrolysis of 1-benzylthiomethyl-2-naphthol gives a 44% yield of 1-methyl-2-naphthol, and α-benzylthiomethyldeoxyanisoin (V) decomposes on distillation into toluene-ω-thiol and α-methylenedeoxyanisoin (VI).

ALTHOUGH the Mannich reaction (Blicke, " Organic Reactions," John Wiley & Sons, Inc., New York, 1942, Vol. I, p. 303 *et seq.*; Mannich, U.S.P. 1,824,676) has been fairly extensively investigated, there appears to be only one recorded example in which an analogous reaction involving thiols in place of amines (Sebrell, U.S.P. 2,150,463) has been attempted. This describes the condensation of a mercaptobenzothiazole, formaldehyde, and a phenol in the presence of a catalyst such as sodium hydroxide. Resinous products of unknown composition were obtained.

The reaction $R^1R^2R^3CH + CH_2O + R^4SH \longrightarrow R^1R^2R^3C{\cdot}CH_2{\cdot}SR^4 + H_2O$, where $R^1R^2R^3CH$ represents a compound containing an active methylene or methylidyne group and R^4 is an alkyl or aryl radical, has now been found to proceed smoothly and satisfactorily with indole, antipyrine, and 2-naphthol under conditions very similar to those necessary for optimum yields of the analogous Mannich bases. The weak bases indole and antipyrine, for example, undergo the new reaction in acid medium while the weakly acidic 2-naphthol reacts only under basic conditions, the products formed being the sulphides, (I), (II), and (III).


(I)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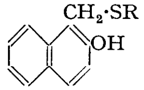
(III)

Unlike the analogous Mannich bases, these compounds do not possess a basic group and thus proved more difficult to isolate. Several unsucessful attempts were made to isolate the sulphides *via* their mercuric chloride complexes.

Indole, aqueous 40% formaldehyde, and ethane-, propane-, *n*-butane-, or toluene-ω-thiol condensed in acetic acid at room temperature during 6 days. Vacuum-distillation of the products gave the desired sulphides (I; R = Et, Pr^n, Bu^n) in yields of about 25%. The benzyl compound (I; R = CH_2Ph), however, was formed in only 14% yield whilst in the case of thiophenol no similar product could be isolated. The low yields may be attributed to decomposition during distillation and to the formation of by-products during the reaction. Attempts to improve the yields by omission of acetic acid, or by its replacement by triethylamine, inhibited the reaction completely.

Paraformaldehyde, antipyrine, and each of the above-mentioned thiols, except ethanethiol, condensed in aqueous acetic acid at 100° in 23—47 hr. The products (II; R = Ph or CH_2Ph) were obtained in yields of about 80%, and the *n*-propyl and *n*-butyl compounds were formed in yields of 42% and 62% respectively. Ethanethiol, probably because of its low boiling point, did not react satisfactorily under the above conditions. The desired sulphide (II; R = Et) was obtained in 17% yield, however, from a mixture of ethanethiol, aqueous 40% formaldehyde, and antipyrine in aqueous acetic acid which had been allowed to stand for 14 days at room temperature. Here, too, reaction failed in a medium made alkaline with triethylamine.

2-Naphthol, aqueous 40% formaldehyde, and each of the thiols in alcoholic solution failed to react at room temperature during 6 days. However, addition of triethylamine caused exothermic reaction and after six days at room temperature the desired sulphides (II; R = Et, Pr^n, Bu^n, Ph, and CH_2Ph) were obtained in 76—89% yields. Only about half these yields were obtained after 3 days' reaction under the same conditions.

It would seem reasonable that the new reaction takes a course analogous to that of the Mannich reaction and, although the mechanism of the latter remains in some doubt, it appears likely (Bodendorf and Koralewski, *Arch. Pharm.*, 1933, **271**, 101; Lieberman and Wagner, *J. Org. Chem.*, 1949, **14**, 1001; Alexander and Underhill, *J. Amer. Chem. Soc.*, 1949, **71**, 4014) that the primary step in the reaction with secondary amines is the union with formaldehyde to give an amino-methanol: $R^1R^2NH + CH_2O \longrightarrow R^1R^2N{\cdot}CH_2{\cdot}OH$. This may then give rise to the carbonium ion $R^1R^2N{\cdot}\overset{+}{C}H_2$, which subsequently attacks the active methylidyne or methylene group (Lieberman and Wagner, *loc. cit.*). Similarly, the first step in the new reaction is probably addition of formaldehyde to the thiol to give a substituted thio-methanol: $RSH + CH_2O \longrightarrow RS{\cdot}CH_2{\cdot}OH$. Support would be provided if the alkyl- or aryl-thiomethanol gave the desired sulphide (I), (III), or (III) in similar yield when used in the reaction in place of the thiol and formaldehyde. This has been confirmed for phenylthiomethanol and antipyrine (78% yield), and for ethylthiomethanol and 2-naphthol (82% yield).

An alternative mechanism involving union of formaldehyde with the active methylidyne or methylene group: $R^1R^2R^3CH + CH_2O \longrightarrow R^1R^2R^3C{\cdot}CH_2{\cdot}OH$, although less likely, cannot be excluded as the primary process. It is improbable, however, for antipyrine, as its 4-hydroxymethyl derivative is unlikely to be produced under the acidic conditions employed (Duquénois and Métais, *Bull. Soc. chim.*, 1949, 415).

In order to confirm the structures and to compare the relative yields, some of the sulphides were prepared by treating the methiodides of the corresponding Mannich bases with a thiol in methanolic sodium methoxide solution (cf. Atkinson, Poppelsdorf, and

Williams, *J.*, **1953**, 580) or by heating the Mannich base with a thiol when the quaternised Mannich base was not easily accessible (cf. Gill, James, Lions, and Potts, *J. Amer. Chem. Soc.*, 1952, **74**, 4923). In this connection, tetramethylammonium iodide was obtained in considerable amount in an attempt to quaternise 1-dimethylaminomethyl-2-naphthol with methyl iodide in chloroform (cf. the interaction of methyl iodide or methyl sulphate with gramine; Geissman and Armen, *ibid.*, p. 3916; Schöpf and Thesing, *Angew. Chem.*, 1951, **63**, 377).

In an attempt to prepare 1-benzylthiomethyl-2-naphthol (III; $R = CH_2Ph$) by heating 1-dimethylaminomethyl-2-naphthol with three mols. of toluene-ω-thiol under reflux until evolution of dimethylamine had ceased (5½ hr.), distillation of the resultant mixture gave a 92% yield of 1-methyl-2-naphthol. This compound was probably produced by the reduction of the Mannich base by the toluene-ω-thiol (cf. Cornforth, Cornforth, and Robinson, *J.*, 1942, 682). In this event, the simultaneous formation of dibenzyl disulphide by oxidation of the thiol might be expected. When the reaction was carried out in an atmosphere of nitrogen, to avoid the possibility of aerial oxidation of the thiol at the elevated temperature, stilbene, hydrogen sulphide, and sulphur were formed in addition to 1-methyl-2-naphthol. Thus, the intermediate formation of dibenzyl disulphide might be inferred since this compound readily decomposes to stilbene when heated, as observed by Fromm and Achert (*Ber.*, 1903, **36**, 539). The course of the reaction may be more complex because of the possibility of the intermediate formation of the benzyl sulphide (III; $R = CH_2Ph$). This compound (prepared by the new reaction) did in fact decompose during 5½ hr. at 210—215°, giving a 44% yield of 1-methyl-2-naphthol. Formation of the methylnaphthol in this instance may be explained by an oxidation–reduction process whereby one molecule of the sulphide is reduced at the expense of another.

It was subsequently found that 1-benzylthiomethyl-2-naphthol could, in fact, be made from equimolecular amounts of 1-dimethylaminomethyl-2-naphthol and toluene-ω-thiol at 150°.

The structures of representative compounds of types (I), (II), and (III) were also confirmed by desulphurisation by Raney nickel to the corresponding methyl compounds (Mozingo, Wolf, Harris, and Folkers, *J. Amer. Chem. Soc.*, 1943, **65**, 1013).

In ancillary experiments, α-benzylthiomethyldeoxyanisoin (V), formed in 85% yield from α-dimethylaminomethyldeoxyanisoin methiodide (IV) and sodium benzyl sulphide, decomposed on distillation into toluene-ω-thiol and α-methylenedeoxyanisoin (VI). Heating (VI) with piperidine gave a base, the hydrochloride of which proved identical with the Mannich base hydrochloride obtained from deoxyanisoin, paraformaldehyde, and piperidine hydrochloride. The structure (VI) was therefore confirmed.

(IV) $Ar{\cdot}CH(CH_2{\cdot}NMe_3^{+}\}I^{-}){\cdot}CO{\cdot}Ar$ $Ar{\cdot}CH(CH_2{\cdot}S{\cdot}CH_2Ph){\cdot}CO{\cdot}Ar$ (V)

(VI) $Ar{\cdot}C(:CH_2){\cdot}CO{\cdot}Ar$ ($Ar = p\text{-}MeO{\cdot}C_6H_4$)

The behaviour of (V) on heating recalls that of some Mannich base hydrochlorides (cf., *inter alia*, Mannich and Heilner, *Ber.*, 1922, **55**, 356; Mannich and Lammering, *ibid.*, p. 3510).

The new sulphides form colourless, almost odourless, crystalline solids. The melting points decrease from ethyl to the higher homologues, and that of the phenyl is higher than that of the benzyl compound.

The chemical properties of these sulphides will be described in a later communication.

EXPERIMENTAL

Light petroleum refers to the fraction of b. p. 40—60°.

Preparation of 3-*Alkyl- and* 3-*Aryl-thiomethylindoles* (I).—(*a*) Gramine (17·4 g., 0·1 mole) was added to a cooled solution of sodium (2·8 g., 0·12 g.-atom) and the thiol (0·12 mole) in anhydrous methanol (200 ml.). Methyl sulphate (12·6 g., 0·1 mole) was then cautiously added in two portions. After the exothermic reaction had abated, the mixture was heated under reflux whilst protected from atmospheric moisture until evolution of trimethylamine had ceased (*ca.* 20 hr.), then poured into water and extracted with ether (2 × 100 ml.). The combined extracts were washed in succession with water, 10% hydrochloric acid (to remove unchanged gramine), water, saturated sodium hydrogen carbonate solution, and with water. The dried ($MgSO_4$) ethereal solution was evaporated to dryness, yielding the crude sulphide.

(*b*) Aqueous 40% formaldehyde (8·2 ml., 0·11 mole) was added to indole (11·7 g., 0·1 mole), the thiol (0·12 mole), and acetic acid (15 ml.). A slight exothermic reaction ensued after a short while and a clear, homogeneous solution resulted. This was kept at room temperature for 6 days and then shaken with ether (100 ml.). The ethereal solution was washed with water (2 × 50 ml.), saturated aqueous sodium hydrogen carbonate until free from acid, and finally with water (50 ml.). After drying ($MgSO_4$) and evaporation of the solvent, a syrup was obtained which yielded the sulphide on vacuum-fractionation.

(*c*) Gramine (1·74 g., 0·01 mole) and the thiol (0·01 mole) were heated together in an oil-bath at 150—160° until evolution of dimethylamine was complete (*ca.* 45 min.). The product usually crystallised and gave the pure sulphide on recrystallisation.

The *sulphides* are recorded in Table 1; they formed colourless leaflets. When produced by the different methods they had identical m. p.s and unchanged mixed m. p.s.

4-*Dimethylaminomethylantipyrine Methiodide.*—Glacial acetic acid (75 ml.) was added to cooled aqueous 33% (w/v) dimethylamine (75 ml., 0·5 mole), and the solution added to antipyrine (94·0 g., 0·5 mole). The mixture was then treated with aqueous 40% formaldehyde (41·0 ml., 0·55 mole), an exothermic reaction setting in after stirring for a short while, giving a homogeneous solution. The mixture was kept at room temperature for 3 days and then poured into cold water (500 ml.). The resulting solution was extracted with chloroform (3 × 100 ml.), and the aqueous layer made alkaline to phenolphthalein with 40% aqueous sodium hydroxide. The Mannich base was extracted with chloroform (3 × 150 ml.) and the dried ($MgSO_4$) extracts were evaporated to *ca.* 250 ml. and chilled. Methyl iodide (31·0 ml., 0·5 mole) was cautiously added (vigorous exothermic reaction) and the mixture heated under reflux for 30 min., then kept overnight at 0°. The *methiodide* separated as a colourless solid (154 g., 80%); after being washed with a little chloroform and ether, it had m. p. 218° (Found: C, 46·5; H, 5·9; N, 10·4; I^-, 32·9. $C_{15}H_{22}ON_3I$ requires C, 46·5; H, 5·7; N, 10·85; I^-, 32·8%).

TABLE 1. 3-*Alkyl- and* 3-*aryl-thiomethylindoles* (I).

Comparison of yields (%).

Method of prep.	R =	Et	Pr^n	Bu^n	Ph	Ph·CH$_2$
(*a*)		63 [a]	74 [a]	67 [a]	—	—
(*b*)		24	26	23	—	14
(*c*)		—	—	—	78	87

[a] These yields take recovered gramine into account.

R	Crystd. from	M. p.	Found (%) C	H	N	S	Formula	Required (%) C	H	N	S
Et	Pet [f]	51·5° [b]	69·2	6·7	7·3	16·6	$C_{11}H_{13}NS$	69·0	6·8	7·3	16·8
Pr^n	Pet	46·5 [c]	70·4	7·5	6·8	15·8	$C_{12}H_{15}NS$	70·2	7·4	6·8	15·6
Bu^n	Pet	42·5 [d]	71·4	7·9	6·4	15·0	$C_{13}H_{17}NS$	71·2	7·8	6·4	14·6
Ph	1, EtOH 2, Pet	84	74·9	5·4	6·0	13·8	$C_{15}H_{13}NS$	75·3	5·5	5·9	13·4
Ph·CH$_2$ [g] ...	1, EtOH 2, Pet	74 [e]	—	—	—	—	—	—	—	—	—

[b] B. p. 180—184°/3 mm. [c] B. p. 160—166°/0·5 mm. [d] B. p. 168—172°/0·7 mm. [e] B. p. 186—190°/2 mm. [f] Light petroleum. [g] Found: N, 5·6. Calc. for $C_{16}H_{15}NS$: N, 5·5%.

Preparation of 4-*Alkyl- and -Aryl-thiomethylantipyrines* (II).—(*a*) The thiol (0·06 mole) and 4-dimethylaminomethylantipyrine methiodide (19·35 g., 0·05 mole) were added in turn to a cooled solution of sodium (1·4 g., 0·06 mole) in anhydrous methanol (100 ml.). The mixture was heated under reflux whilst protected from atmospheric moisture until evolution of trimethylamine ceased (48—72 hr.), and then evaporated to dryness. Extraction of the residue with hot benzene followed by concentration of the extract and slow addition of light petroleum gave the crude sulphide which crystallised.

(*b*) A mixture of antipyrine (9·4 g., 0·05 mole), the thiol (0·06 mole), paraformaldehyde (2·25 g., 0·075 mole), acetic acid (7·5 ml.), and water (5·0 ml.) was heated on the steam-bath at 100° for 23 hr. (47 hr. for propanethiol). The cooled product was dissolved in chloroform (100 ml.), and the solution washed in succession with water, saturated sodium hydrogen carbonate solution until free from acid, and again water. After being dried ($MgSO_4$) the solution was evaporated to dryness at atmospheric pressure and the residue heated at 100°/100 mm. for 15 min. and then at 100°/0·5 mm. for 30 min. The residual oil was dissolved in dry benzene (15 ml.) and the crude sulphide precipitated by the addition of light petroleum. After chilling at 0°, the solid was collected, washed with a little light petroleum, and dried *in vacuo* at room temperature. Purification of the benzyl and phenyl compounds was accomplished by direct crystallisation at this stage, but it was necessary first to extract the crude butyl and propyl sulphides with light petroleum. The crude compounds obtained by evaporation of these extracts were then purified directly by crystallisation.

4-*Ethylthiomethylantipyrine*. A solution of antipyrine (18·8 g., 0·1 mole), ethanethiol (8·9 ml., 0·12 mole), and aqueous 40% formaldehyde (8·2 ml.) in acetic acid (15 ml.) and water (6 ml.) was kept at room temperature for 14 days. The product was worked up as above except that the crude oil was distilled *in vacuo* and the fraction of b. p. 184°/0·5 mm. collected. The *sulphides* are listed in Table 2 and formed colourless prisms.

TABLE 2. 4-*Alkyl- and* 4-*aryl-thiomethylantipyrines* (II).

		Comparison of yields (%).[a]				
Method of prepn.	R =	Et	Pr^n	Bu^n	Ph	Ph·CH$_2$
(*a*)		85	84	84	91	84
(*b*)		17	42	62	80	83

[a] Calc., in case of method *a*, on methiodide used.

R	Crystd. from	M. p.	Found (%) C	H	N	S	Formula	Required (%) C	H	N	S
Et	H_2O	97° [c]	63·8	7·0	10·4	11·9	$C_{14}H_{18}ON_2S$	64·1	6·9	10·7	12·2
Pr^n	C_6H_6–Pet [b]	64—65	64·9	7·0	10·5	11·4	$C_{15}H_{20}ON_2S$	65·2	7·3	10·1	11·6
Bu^n	Pet	53·5—54	66·2	7·2	9·7	11·3	$C_{16}H_{22}ON_2S$	66·2	7·6	9·7	11·0
Ph	MeOH–H_2O (2 : 1)	102—103	69·4	5·8	9·0	10·3	$C_{18}H_{18}ON_2S$	69·7	5·8	9·0	10·3
Ph·CH$_2$...	MeOH–H_2O (2 : 1)	100	70·0	6·4	9·0	10·2	$C_{19}H_{20}ON_2S$	70·4	6·2	8·6	9·9

[b] Light petroleum. [c] B. p. 184°/0·5 mm.

Preparation of 1-*Alkyl- and -Aryl-thiomethyl-2-naphthols* (III).—Aqueous 40% formaldehyde (8·2 ml.) was added to a mixture of 2-naphthol (14·4 g., 0·1 mole), the thiol (0·11 mole), ethanol (10 ml.), and triethylamine (5·0 ml.). An exothermic reaction ensued after the mixture had been shaken for a short while, and the 2-naphthol dissolved. After being kept at room temperature for 6 days the mixture was dissolved in ether (100 ml.), washed with water (2 × 50 ml.), dried ($MgSO_4$), and evaporated to dryness at atmospheric pressure, and the residue was heated at 100°, first at 100 mm. for 15 min., then for 30 min. at 0·5 mm. The resulting oil crystallised and contained *ca.* 90% of the sulphide, which was purified by crystallisation from a suitable solvent.

The *sulphides* prepared in this way are listed in Table 3. They formed colourless prisms.

TABLE 3. 1-*Alkyl- and* 1-*aryl-thiomethyl-2-naphthols* (III).

R	Yield (%)	Crystd. from	M. p.	Found (%) C	H	Formula	Reqd. (%) C	H
Et [a]	89	Pet	52—52·5°	71·5	6·4	$C_{13}H_{14}OS$	71·5	6·5
Pr^n	89	Pet	49·5	72·7	6·9	$C_{14}H_{16}OS$	72·4	6·9
Bu^n	87	Pet	48	73·0	7·4	$C_{15}H_{18}OS$	73·1	7·4
Ph	76	Toluene	126—127	76·9	5·2	$C_{17}H_{14}OS$	76·7	5·3
Ph·CH$_2$ ...	86	*cyclo*Hexane	89	77·1	5·7	$C_{18}H_{16}OS$	77·2	5·8

[a] Found: S, 14·3. $C_{13}H_{14}OS$ requires S, 14·7%.

1-*Benzylthiomethyl-2-naphthol from* 1-*Dimethylaminomethyl-2-naphthol and Toluene-ω-thiol*.—1-Dimethylaminomethyl-2-naphthol (2·01 g., 0·01 mole) and toluene-ω-thiol (1·24 g., 0·01 mole) were heated for 1 hr. in an oil-bath at 150°. A brown gum was obtained on cooling, which on crystallisation from benzene–light petroleum gave a light brown solid (2·27 g.), m. p. 79—80°. Repeated extraction with boiling light petroleum removed the sulphide. Evaporation of the combined extracts produced almost colourless prisms (2·04 g., 73%), m. p. and mixed m. p. 89° (Found: S, 11·8. Calc. for $C_{18}H_{16}OS$: S, 11·4%).

Interaction of 1-*Dimethylaminomethyl*-2-*naphthol and Excess of Toluene*-ω-*thiol*.—(*a*) 1-Dimethylaminomethyl-2-naphthol (10·06 g., 0·05 mole) and toluene-ω-thiol (18·6 g., 0·15 mole) were heated under reflux for 5½ hr. Evolution of dimethylamine was then complete. The product was distilled *in vacuo* and the fraction of b. p. 115—130°/0·9 mm. collected. It solidified and crystallised from benzene–light petroleum as very pale yellow needles (7·3 g., 92%), m. p. 110° (mixed m. p. with 1-methyl-2-naphthol, 110—111°).

(*b*) The same quantities of reactants were used but the mixture was heated under reflux for 2½ hr. with a stream of dry nitrogen passing through the boiling solution. Evolution of dimethylamine was rapid at first and ceased at the end of the reaction period. Some hydrogen sulphide was also evolved. The reaction product solidified on cooling and was dissolved in and ether (120 ml.). The solution was extracted with 10% aqueous sodium hydroxide (2 × 50 ml.), and the alkaline extract filtered from a small quantity of sulphur, cooled, and made acid to Congo-red with hydrochloric acid. An oil separated which, after being stirred and cooled, gave a brown solid (6·38 g.), m. p. 99—100°. This was crystallised in succession from benzene–light petroleum, *cyclo*hexane, aqueous ethanol (charcoal), and hot water, to give 1-methyl-2-naphthol, as colourless needles (5·3 g., 67%), m. p. and mixed m. p. 111°.

The ethereal solution, after being extracted with alkali, was dried ($MgSO_4$) and evaporated to dryness, producing a solid which, after crystallisation from ethanol (charcoal), was dissolved in excess ethanol. Successive crops of crude stilbene were obtained (total 2·77 g.) on stepwise evaporation of the solution. (No attempt was made to isolate more stilbene from the mother liquors.) Recrystallisation from ethanol afforded flat, colourless prisms (2·62 g.), m. p. 125°, mixed m. p. 124—125°. The ultra-violet absorption spectrum was identical with that of stilbene.

Pyrolysis of 1-*Benzylthiomethyl*-2-*naphthol* (III; R = $Ph\cdot CH_2$).—The benzyl sulphide (10·0 g.) was heated for 5½ hr. at 210—215°. A little hydrogen sulphide was evolved. Distillation of the dark brown product *in vacuo* gave a fraction, b. p. 95—110°/0·3 mm., solidifying to a yellow solid (3·6 g.). Crystallisation from benzene–light petroleum gave almost colourless fine needles (2·5 g.), m. p. 111°. The mixed m. p. with 1-methyl-2-naphthol was 111° (Found : C, 83·9; H, 6·4. Calc. for $C_{11}H_{10}O$: C, 83·5; H, 6·4%).

Attempted Preparation of 1-*Dimethylaminomethyl*-2-*naphthol Methiodide*.—Methyl iodide (3·1 ml.) was added to a cooled solution of 1-dimethylaminomethyl-2-naphthol (10·06 g., 0·05 mole) in chloroform (20 ml.), causing an immediate opalescence. The mixture was heated under reflux for 1 hr., an equal volume of dry ether added to the cooled mixture, and heating under reflux continued for a further 30 min. After cooling, the supernatant liquid was decanted and the gummy residue dissolved in hot methanol. On chilling, the solution deposited colourless crystals of tetramethylammonium iodide (3·79 g.), m. p. >300°. A sample was recrystallised first from methanol, then from water (Found : N, 6·8; I^-, 62·5. Calc. for $C_4H_{12}NI$: N, 7·0; I^-, 63·1%). The filtrate gave a brown, uncrystallisable gum on evaporation to dryness.

Desulphurisation of the Sulphides (I; R = Bu^n), (II; R = Et), *and* (III; R = Et).—The method of Mozingo, Wolf, Harris, and Folkers (*J. Amer. Chem. Soc.*, 1943, **65**, 1013) was used, 98% ethanol being the medium in which the desulphurisations were carried out. The corresponding methyl compounds were obtained : Skatole (62%), m. p. and mixed m. p. 96°, after two crystallisations from light petroleum (Found : N, 10·4. Calc. for C_9H_9N : N, 10·7%); 4-methylantipyrine (56%), m. p. 80° (from *cyclo*hexane) (Found : C, 71·4; H, 6·6. Calc. for $C_{12}H_{14}ON_2$: C, 71·3; H, 7·0%); 1-methyl-2-naphthol (75%), m. p. 110° (from benzene–light petroleum) (Found : C, 83·2; H, 6·5. Calc. for $C_{11}H_{10}O$: C, 83·5; H, 6·4%).

α-*Dimethylaminomethyldeoxyanisoin Hydrochloride*.—Deoxyanisoin (25·6 g., 0·1 mole), dimethylamine hydrochloride (9·8 g., 0·11 mole), paraformaldehyde (4·5 g., 0·15 mole), and glacial acetic acid (52 ml.) were heated under reflux for 1 hr. and then evaporated to dryness *in vacuo*. The gum thus obtained was extracted with ether (2 × 50 ml.) and dissolved in boiling ethanol (100 ml.). Crystallisation began after concentration of the solution to *ca.* 100 ml., and was completed by cooling, addition of ether (150 ml.) with stirring, and chilling at 0° for 1 hr. The solid, recrystallised from ethanol–ether, afforded the colourless *hydrochloride* (24·1 g., 69%), m. p. 172° (Found : C, 65·1; H, 6·6; N, 4·0; Cl^-, 10·4. $C_{19}H_{24}O_3NCl$ requires C, 65·3; H, 6·6; N, 4·0; Cl^-, 10·2%). The free *base* was obtained by the action of alkali on the hydrochloride and separated as an oil which, on cooling and trituration with light petroleum, gave a colourless crystalline solid, m. p. 61° (Found : C, 72·7; H, 7·1; N, 4·5. $C_{19}H_{23}O_3N$ requires C, 72·8; H, 7·35; N, 4·5%).

The *methiodide* (IV) of the base was prepared in chloroform and crystallised from methanol as a colourless solid (76%), m. p. 190° (decomp.) (Found : C, 52·5; H, 5·7; N, 3·0; I^-, 28·0. $C_{20}H_{26}O_3NI$ requires C, 52·8; H, 5·7; N, 3·1; I^-, 27·9%).

α-Benzylthiomethyldeoxyanisoin (V).—α-Dimethylaminomethyldeoxyanisoin methiodide (13·65 g., 0·03 mole) was added to a solution of sodium benzyl sulphide (0·033 mole) in anhydrous methanol (100 ml.). The mixture was heated under reflux until the evolution of trimethylamine was complete (84 hr.) and then evaporated to dryness, first at atmospheric pressure, then *in vacuo*. Hot benzene extraction of the semi-solid residue, followed by evaporation to dryness of the extract *in vacuo*, gave a viscous yellow oil (11·65 g.) which crystallised during several weeks at room temperature. Crystallisation of the solid from ethanol gave colourless prisms of the *benzyl sulphide* (10·0 g. 85%), m. p. 83·5°. Two further recrystallisations from ethanol raised the m. p. to 87° (Found : C, 73·2; H, 6·0; S, 8·4. $C_{24}H_{24}O_3S$ requires C, 73·4; H, 6·2; S, 8·2%).

Decomposition of α-Benzylthiomethyldeoxyanisoin.—The benzyl sulphide (8·0 g.) decomposed on attempted distillation *in vacuo*. The fraction (3·4 g.), b. p. 182—184°/0·2 mm., formed an almost colourless oil which crystallised. Crystallisation from ethanol gave *α-methylenedeoxyanisoin* (VI) as colourless prisms, m. p. 58° (Found : C, 76·0; H, 5·8. $C_{17}H_{16}O_3$ requires C, 76·1; H, 6·0%).

α-Piperidinomethyldeoxyanisoin Hydrochloride.—(*a*) Prepared in a similar way to the Mannich dimethylamino-base hydrochloride, this *salt* was obtained as colourless prisms (56%), m. p. 184° after crystallisation from ethanol–ether (Found: C, 67·8; H, 7·25; N, 3·9; Cl^-, 9·0. $C_{22}H_{28}O_3NCl$ requires C, 67·8; H, 7·24; N, 3·6; Cl^-, 9·1%).

(*b*) α-Methylenedeoxyanisoin (2·00 g., 0·0075 mole) and piperidine (4·0 ml., 0·041 mole) were heated at 100° for 14 hr. Excess of piperidine was then removed *in vacuo* and the cooled residual orange oil washed by decantation with water (2 × 10 ml.). The oil was dissolved in benzene (30 ml.) and washed with water (15 ml.). After being dried ($MgSO_4$), the benzene solution was saturated with dry gaseous hydrogen chloride and evaporated to half its bulk at atmospheric pressure. Cooling and scratching afforded pale buff crystals of α-piperidinomethyldeoxyanisoin hydrochloride (2·90 g.), m. p. 180—183°. Crystallisation from ethanol–ether gave very small, almost colourless prisms (2·20 g., 76%), m. p. 183—184°, mixed m. p. 184° (Found : N, 3·9%).

Interaction of Ethylthiomethanol and Antipyrine.—Triethylamine (2·5 ml.) was added to a mixture of 2-naphthol (7·2 g., 0·05 mole), ethylthiomethanol (Levi, *Gazzetta*, 1932, **62**, 775) (5·1 g., 0·055 mole), ethanol (5 ml.), and water (5 ml.). A very slight exothermic reaction ensued, all the 2-naphthol dissolved, and the mixture separated into two layers. After being kept at room temperature for 6 days with occasional shaking, the mixture was worked up as before, to give pale yellow prisms of 1-ethylthiomethyl-2-naphthol (8·9 g., 82%), m. p. and mixed m. p. 52°.

Interaction of Phenylthiomethanol and Antipyrine.—A mixture of antipyrine (9·4 g., 0·05 mole), phenylthiomethanol (Levi, *loc. cit.*) (7·7 g., 0·055 mole), acetic acid (7·5 ml.), and water (5·0 ml.) was heated at 100° for 23 hr. Working up afforded colourless rectangular prisms of 4-phenylthiomethylantipyrine (12·05 g., 78%), m. p. and mixed m. p. 102—103°.

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