Reactions of Thiols and Sulphides. Part II. Some Reactions of Sulphur Analogues of Mannich Bases.*

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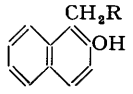
Displacement and alkylating reactions of sulphur analogues of Mannich bases derived from 2-naphthol, indole, and antipyrine occur with decreasing facility in the order given, probably owing to differences in the ease of formation of a conjugated unsaturated intermediate by initial elimination of a thiol. In contrast to the poor alkylating properties reported for phenolic Mannich bases, the sulphur analogue 1-ethylthiomethyl-2-naphthol alkylates smoothly a wide range of compounds, being the first active phenolic alkylating agent of general synthetic value. Some reactions of the β-ketonic sulphide β-ethylthio-β-phenylpropiophenone are described.

Except for the alkali- or acid-cleavage into a thiol and an unsaturated compound (see, *e.g.*, Behagel and Ratz, *Ber.*, 1939, **72**, 1257; Cason and Wanser, *J. Amer. Chem. Soc.*, 1951, **73**, 142) there are few reports of reactions involving sulphur analogues of Mannich bases. Nicolet (*J. Amer. Chem. Soc.*, 1931, **53**, 3066) reported that phenylhydrazine displaced thio-*p*-cresol from β-phenyl-β-*p*-tolylthiopropiophenone to form 1 : 3 : 5-triphenylpyrazoline; Böhme and Mundlos (*Chem. Ber.*, 1953, **86**, 1414) recorded the interaction of ethyl α-methylthiomethylacetoacetate with phenylhydrazine and with urea to yield methanethiol with a pyrazoline and a pyramidone derivative respectively. Only two examples of alkylation have been found: Cardwell (*J.*, 1949, 715) reported that thia*cyclo*hexan-4-one methiodide and a variety of compounds possessing a reactive methylene group gave products of the type $MeS{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH_2R$, and that impure ethylthiobutan-3-one methiodide alkylated ethyl 2-oxo*cyclo*pentanecarboxylate to form ethyl 7-oxo-octane-1 : 4-dicarboxylate in small yield.

In Part I (*loc. cit.*) the preparation was described of sulphur analogues of Mannich bases derived from 2-naphthol, indole, and antipyrine by reaction with thiols and formaldehyde. The representative products 1-ethylthiomethyl-2-naphthol (I; R = SEt), 3-ethyl- and 3-benzyl-thiomethylindole (II; R = SEt and $S{\cdot}CH_2Ph$), 4-ethylthiomethylantipyrine and its



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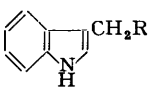

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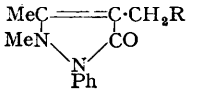

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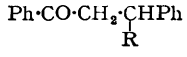

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sulphone (III; R = SEt and SO_2Et), and also β-ethylthio-β-phenylpropiophenone (IV; R = SEt) have now been studied, particularly in regard to their displacement reactions and to their alkylating propensity, in which their analogy to Mannich bases has been further extended. The sulphide (I; R = SEt) proved to be highly reactive; in all cases examined reaction occurred smoothly with displacement of ethanethiol. The Mannich bases (I; R = piperidino and morpholino) were obtained in 85% and 58% yield respectively on 2 hours' heating with piperidine or morpholine in a current of nitrogen, a reaction comparable to that of piperidine or morpholine with 1-dimethylaminomethyl-2-naphthol (Snyder and Brewster, *J. Amer. Chem. Soc.*, 1948, **70**, 4230). Thiol exchange took place readily on similar treatment of (I; R = SEt) with thiophenol or toluene-ω-thiol (yields, 65% and 41% respectively).

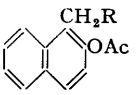
The alkaline catalysis of the reaction between phthalimide and Mannich bases (Atkinson, *J.*, 1954, 1329) was paralleled with the sulphur analogues. Phthalimide and the sulphide (I; R = SEt), heated *in vacuo* in the presence of a catalytic quantity of potassium hydr-

* The paper entitled "Reactions of Thiols and Thioethers. Part I" (*J.*, 1954, 1124) is Part I of this series.

oxide, gave 1-phthalimidomethyl-2-naphthol in 61% yield. Succinimide behaved similarly (65% yield).

With hot aqueous-ethanolic sodium cyanide, the sulphide (I; R = SEt) gave a mixture of 2-hydroxy-1-naphthylacetic acid and 1-cyanomethyl-2-naphthol, but not the amide. This contrasts with Brewster's observation (Thesis, Illinois, 1948) that 1-dimethylaminomethyl-2-naphthol yielded a mixture of di-(2-hydroxy-1-naphthyl)methane and the acid (I; R = CO_2H) on similar treatment. The nitrile gave an 80% yield of the acid on hydrolysis with aqueous sodium hydroxide.

It was expected, in view of its action on phenolic Mannich bases (cf., *inter al.*, Auwers, *Annalen*, 1906, **344**, 102; Bruson and MacMullen, *J. Amer. Chem. Soc.*, 1941, **63**, 270), that



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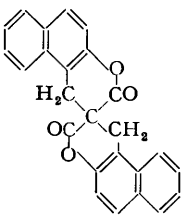

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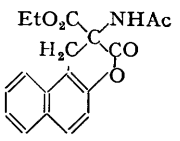


(VII)

acetic anhydride would convert the sulphide (I; R = SEt) into the diacetoxy-derivative (V; R = OAc), but at 100° or at reflux temperature it yielded only the monoacetyl derivative (V; R = SEt).

Although Lieberman and Wagner (*J. Org. Chem.*, 1949, **14**, 1001) were able to condense 1-morpholinomethyl-2-naphthol with dibenzoylmethane under *acid* conditions there seems to be no other example of a successful condensation of a phenolic Mannich base with a compound containing a reactive methylene or methylidyne group. Dalgliesh (*J. Amer. Chem. Soc.*, 1949, **71**, 1697) and Eliel (*ibid.*, 1951, **73**, 43), for example, both reported failure in such attempts.

The sulphide (I; R = SEt) was used successfully, however, to alkylate 2-nitropropane, ethyl malonate, ethyl acetamidomalonate, indole, antipyrine, *p*-cresol, *p*-benzylphenol, and 2-naphthol under alkaline conditions and in reasonable yield.

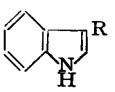
Heating the sulphide with an excess of 2-nitropropane and one mol. of powdered sodium hydroxide gave 1-(2-methyl-2-nitropropyl)-2-naphthol (I; R = $CMe_2 \cdot NO_2$) in 56% yield. Reaction with ethyl malonate gave a high-melting product which, from its elementary analysis, molecular weight, and the fact that it was recovered unchanged after being heated under reflux with hydrochloric acid, appeared to be the *spiro*-lactone (VI) although the malonic ester was present in 200% excess. Production of this lactone recalls the formation of dihydrocoumarin by distillation of ethyl β-*o*-hydroxyphenylpropionate (Pschorr and Einbeck, *Ber.*, 1905, **38**, 2069).

Ethyl acetamidomalonate and the sulphide (I; R = SEt) under similar conditions gave a mixture of the lactone (VII) and diethyl 2-hydroxy-1-naphthylmethylacetamidomalonate [I; R = $C(NHAc)(CO_2Et)_2$] in proportions of 3 : 1 approximately. Boiling ethanol converted the lactone (VII) into this ester, which lost ethanol above its melting-point to re-form the lactone. It is interesting to note that lactams bearing a formal resemblance to the lactones (VI) and (VII) were obtained by Herz, Dittmer, and Cristol (*J. Amer. Chem. Soc.*, 1948, **70**, 504) by treating 2-dimethylaminomethylpyrrole with ethyl malonate or acetamidomalonate in boiling toluene or xylene in the presence of catalytic quantities of sodium hydroxide.

Hydrolysis and decarboxylation of the lactone (VII) by hot hydrochloric acid gave β-(2-hydroxy-1-naphthyl)alanine.

Indole and antipyrine were easily alkylated by the sulphide (I; R = SEt), the products (VIII) and (IX) being formed in 52% and 82% yields respectively. Interaction of 2-naphthol and gramine (II; R = NMe_2) also yielded the indole derivative (VIII), thus confirming its structure. Similarly, heating the sulphide *in vacuo* with *p*-cresol, *p*-benzyl-

phenol, or 2-naphthol afforded respectively the (2-hydroxy-1-naphthylmethyl)phenols in good yield. Reactions of this type might provide an easy route to otherwise difficultly accessible xanthens by the elimination of water between neighbouring hydroxyl groups. Heating the sulphide with thioacetamide and a catalytic quantity of potassium hydroxide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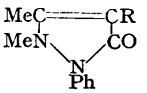
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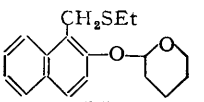
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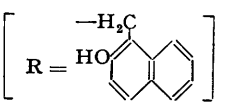


gave di-(2-hydroxy-1-naphthylmethyl) sulphide, a reaction analogous to that observed with ketonic Mannich bases (Gill, James, Lions, and Potts, *J. Amer. Chem. Soc.*, 1952, **74**, 4923).

A further analogy between the sulphide and phenolic Mannich bases (see, *e.g.*, Auwers, *Ber.*, 1903, **36**, 1878; Auwers and Dombrowski, *Annalen*, 1906, **344**, 280), is that in boiling alkali the sulphur compound decomposed to yield di-(2-hydroxy-1-naphthyl)methane but in small yield.

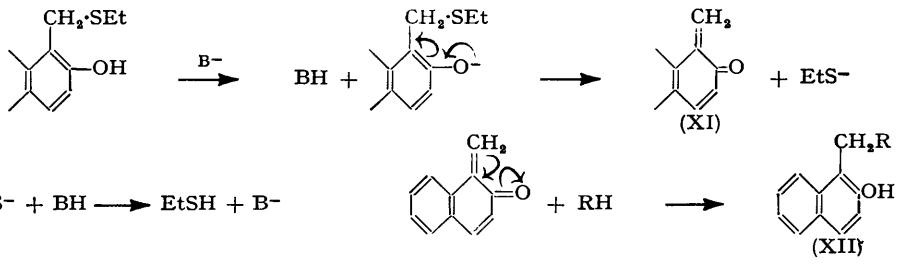
In view of the high reactivity of the sulphide (I; R = SEt), the homologues (I; R = SPr^n, SBu^n, SPh, and SCH_2Ph) described in Part I (*loc. cit.*) were not studied further. They would probably be less reactive owing to the lower volatility of the thiol to be displaced.

3-Ethylthiomethylindole (II; R = SEt) proved to be far less reactive, not only than the naphthol compound described above, but also than its nitrogen analogue gramine (II; R = NMe_2). For example, the ethylthiomethylindole gave only 8% of 3-piperidinomethylindole when heated with piperidine for 24 hours, though a catalytic quantity of potassium hydroxide increased the yield to 49%; phthalimide and the indole (II; R = SEt) together with potassium hydroxide gave only 15% of 3-phthalimidomethylindole (cf. Atkinson, *loc. cit.*). Condensation could not be effected with ethyl acetamidomalonate, thiophenol, or 2-nitropropane.

Snyder and Pilgrim (*J. Amer. Chem. Soc.*, 1948, **70**, 3770) showed that gramine gave a 1 : 4 mixture of 3-indolylacetamide and 3-indolylacetic acid when heated with excess of aqueous-ethanolic sodium cyanide for 80 hr. Under these conditions, the sulphur analogue (II; R = SEt) gave a 1 : 2 mixture of the same amide and acid. The benzyl derivative (II; R = S·CH_2Ph) was less reactive: with phthalimide it gave only an 8% yield of the phthalimido-derivative (II; R = phthalimido), probably owing to the lower volatility of toluene-ω-thiol. In the antipyrine series, 4-ethylthiomethylantipyrine (III; R = SEt) was found to be unreactive towards piperidine, aqueous-ethanolic sodium cyanide, and methanolic sodium thiophenoxide. The derived sulphone (III; R = SO_2Et) also failed to react with either piperidine or methanolic sodium thiophenoxide.

Heating the β-ketonic sulphide (IV; R = SEt) with excess of piperidine or thiophenol in a current of nitrogen gave ethanethiol and, respectively, β-phenyl-β-piperidinopropiophenone (IV; R = piperidino) and β-phenyl-β-phenylthiopropiophenone (IV; R = SPh). Substantially no thiol exchange occurred with toluene-ω-thiol, however, showing once again the discrepancy between this thiol and the more acidic thiophenol.

It is considered probable that the above reactions take place in two main stages: elimination of thiol from the sulphide under the catalytic influence of a base (B^-) to form a conjugated unsaturated compound, followed by 1 : 4-addition of the reagent to the unsaturated intermediate. *E.g.*:



It is necessary to postulate the primary decomposition of the sulphide (I; R = SEt) to account for the easy elimination of thiol under the influence of a catalytic quantity of alkali. In this case the unsaturated product (XI) could not be isolated, probably because of polymerisation since an almost sulphur-free resin was obtained. A similar result has been reported by Auwers and Bullman (*Ber.*, 1926, **59**, 2719) in a reaction which might have been expected to yield an analogue of (XI). It is well known, on the other hand, that unsaturated compounds are readily produced by thiol elimination from β-ketonic sulphides. When a reagent (RH) which can undergo 1 : 4-addition to a conjugated unsaturated intermediate to form a stable product is present at the same time, however, the final product (XII) is obtained. Support for these hypotheses is afforded by the observation that the acetyl (V; R = SEt) and the tetrahydropyranyl (X) derivative do not undergo the elimination, displacement, or alkylating reactions unless the conditions are such to remove the protecting grouping. Thus, the base-stable tetrahydropyranyl derivative was recovered unchanged after treatment with piperidine or aqueous-ethanolic sodium cyanide, while the acetyl compound underwent hydrolysis in the presence of piperidine and then gave the normal reaction product (I; R = piperidino); but the acetyl compound failed to react with thiophenol, which reacts very readily with the unacetylated naphthol (I; R = SEt).

Similarly, the structural inability of 4-ethylthiomethylantipyrine (III; R = SEt) or its sulphone to form a conjugated unsaturated derivative probably accounts for their lack of reactivity. The poor reactivity of the alkylthiomethylindoles (II; R = SEt and SCH_2Ph) in both displacement and alkylating reactions may be due to the slowness of the thiol-elimination stage, for with the indole Mannich bases, from which amine elimination is known to be rapid, reactions of this type occur smoothly and with good yield.

Experimental

Reactions of 1-*Ethylthiomethyl*-2-*naphthol* (I; R = SEt).—(a) *With piperidine or morpholine.* The sulphide (Part I, *loc. cit.*) (2·18 g., 0·01 mole) and the base (0·05 mole) were heated under reflux for 2 hr. with a stream of dry nitrogen passing through the boiling solution. Addition of water to the cooled mixture precipitated the crude product. One crystallisation from ethanol (charcoal) gave colourless platelets of 1-piperidinomethyl- (85%), m. p. and mixed m. p. 93—94° (Found: N, 5·8. Calc. for $C_{16}H_{19}ON$: N, 5·8%), and 1-morpholinomethyl-2-naphthol (58%), m. p. and mixed m. p. 116—117° (Found: N, 5·7. Calc. for $C_{15}H_{17}O_2N$: N, 5·8%).

(b) *With thiophenol or toluene-*ω*-thiol.* The sulphide (0·01 mole) and the thiol (0·05 mole) were heated together at 130° for 2 hr. in dry nitrogen. Excess of thiol was then removed *in vacuo* and the residue purified by crystallisation, giving colourless prisms of 1-phenylthiomethyl- (65%) (from toluene), m. p. and mixed m. p. 126—127°, and 1-benzylthiomethyl-2-naphthol (41%) (from *cyclo*hexane) m. p. and mixed m. p. 89°.

(c) *With phthalimide.* The sulphide (0·01 mole), phthalimide (1·47 g., 0·01 mole), and powdered potassium hydroxide (*ca.* 40 mg.) were heated together *in vacuo* at 180° for 1 hr. Evolution of gas appeared to have ceased after 40 min. Trituration of the cooled, dark brown, gummy residue with hot ethanol containing acetic acid (5 drops) gave the crude derivative (2·59 g.). Crystallisation from ethanol gave pure 1-phthalimidomethyl-2-naphthol (1·85 g., 61%), m. p. 203°, mixed m. p. 202—203° (Found: N, 4·6. Calc. for $C_{19}H_{13}O_3N$: N, 4·6%).

(d) *With succinimide.* A mixture of the sulphide (4·37 g., 0·02 mole), succinimide (2·97 g., 0·03 mole), and potassium hydroxide (*ca.* 80 mg.) was heated under reflux *in vacuo* (15 cm.) at 150° until evolution of ethanethiol had ceased (1 hr). The brown residue separated from aqueous ethanol containing acetic acid (9 drops) as a sticky brown solid (4·64 g.), which after being twice crystallised from *iso*propanol (charcoal) afforded colourless prisms of 1-*succinimidomethyl*-2-*naphthol* (3·29 g., 65%), m. p. 141° (Found: C, 70·3; H, 5·3; N, 5·5. $C_{15}H_{13}O_3N$ requires C, 70·6; H, 5·1; N, 5·5%).

(e) *With aqueous-ethanolic sodium cyanide.* The sulphide (5·00 g., 0·023 mole) was added to sodium cyanide (5·60 g., 0·115 mole) in hot ethanol (44·5 c.c.) and water (11 c.c.), and the mixture refluxed for 80 hr. Water (56 c.c.) was added, and the solution treated with charcoal and evaporated *in vacuo* until all the ethanol had been removed. Addition of excess of powdered solid carbon dioxide with stirring to the aqueous residue precipitated a brown solid (2·45 g.). This was crystallised from ethanol containing a little ether, then from aqueous ethanol (char-

coal), yielding buff leaflets, m. p. 173° (pre-heated bath). Recrystallisation from aqueous ethanol gave 1-*cyanomethyl*-2-*naphthol* (1·21 g., 29%), m. p. 177° (pre-heated bath at 170°) (Found: C, 78·7; H, 5·1; N, 7·7. $C_{12}H_9ON$ requires C, 78·7; H, 5·0; N, 7·6%). Its *benzoyl* derivative formed colourless prisms, m. p. 143°, from ethanol (Found: C, 79·0; H, 4·8; N, 4·9. $C_{19}H_{13}O_2N$ requires C, 79·4; H, 4·6; N, 4·9%).

The filtrate from the crude nitrile was cooled and made acid to Congo-red with hydrochloric acid. A yellow crystalline precipitate was formed which was purified by dissolving it in dilute aqueous sodium carbonate and acidifying the filtered solution (charcoal) with hydrochloric acid, giving 2-hydroxy-1-naphthylacetic acid (1·34 g., 29%), m. p. 146° (Found: C, 70·9; H, 4·9. Calc. for $C_{12}H_{10}O_3$: C, 71·3; H, 5·0%).

(f) *With acetic anhydride.* The sulphide (5·00 g.), heated with acetic anhydride (5·8 c.c.) for 3 hr. at 100° or 3½ hr. under reflux, afforded only the *acetyl* derivative (V; R = SEt) as colourless prisms, m. p. 82°, from ethanol (Found: C, 69·5; H, 6·1; S, 12·2. $C_{15}H_{16}O_2S$ requires C, 69·2; H, 6·2; S, 12·3%).

(g) *With 2-nitropropane.* A mixture of the sulphide (5·00 g.,) freshly distilled 2-nitropropane (20 c.c.), and sodium hydroxide (0·92 g.) was heated under reflux with a stream of dry nitrogen passing through the boiling reactants. The mixture became almost solid after 1 hr. and a further quantity (10 c.c.) of 2-nitropropane was added to facilitate ebullition. After a further 1½ hours' heating, evolution of ethanethiol appeared to have ceased. The mixture was cooled, acidified with 10% aqueous acetic acid (25 c.c.), and shaken with ether (100 c.c.). The ether layer was washed with water (4 × 35 c.c.) and evaporated, first at atmospheric pressure and then *in vacuo*, giving a dry brown residue which afforded pale-buff plates, m. p. 172—173° (decomp.), after being twice crystallised from toluene. A further crystallisation from 90% ethanol gave 1-(2-*methyl*-2-*nitropropyl*)-2-*naphthol* (I; R = $CMe_2{\cdot}NO_2$) (3·12 g., 56%), m. p. 175—176° (decomp.) (Found: C, 68·1; H, 6·3; N, 6·0. $C_{14}H_{15}O_3N$ requires C, 68·5; H, 6·2; N, 5·7%). The *acetyl* derivative crystallised from ethanol as prisms, m. p. 105° (Found: N, 4·8. $C_{16}H_{17}O_4N$ requires N, 4·9%).

(h) *With ethyl malonate.* Ethyl malonate (4·81 g., 0·03 mole), the sulphide (0·02 mole), and potassium hydroxide (*ca.* 80 mg.) were heated under reflux *in vacuo* for 1 hr. at 160—170°. The cooled semisolid product was ground with a little ethanol containing acetic acid (9 drops), yielding a pale yellow solid (2·95 g.). Crystallisation was effected by dissolving it in a small quantity of dimethylformamide and adding excess of ethanol; this gave colourless needles of spiro-3 : 3′-*bis*-(3 : 4-*dihydro*-5 : 6-*benzocoumarin*) (VI) (2·57 g., 68%), m. p. 314° [Found: C, 79·0; H, 4·4; *M* (Rast), 344. $C_{25}H_{16}O_4$ requires C, 78·9; H, 4·2%; *M*, 380]. This compound was recovered unchanged after crystallisation from ethanol or after being heated under reflux for 17 hr. with 20% hydrochloric acid.

(i) *With ethyl acetamidomalonate.* Ethyl acetamidomalonate (15·19 g., 0·07 mole), the sulphide (15·28 g., 0·07 mole), and a catalytic quantity of potassium hydroxide were heated under reflux *in vacuo* (15 cm.) for 1 hr. at 190—200°. Evolution of gas had then ceased. The dark brown product was heated under reflux with ethanol (200 c.c.) for 30 min. and the solution cooled to 0°, to give a pale-buff solid (A) (10·80 g.), m. p. 222—224°. A second fraction (B) (3·29 g.), m. p. 178—179°, was obtained from the mother-liquors by evaporation. Fraction (A), crystallised from aqueous dimethylformamide and then from dimethylformamide–ethyl acetate, gave 3-*acetamido*-3-*ethoxycarbonyl*-3 : 4-*dihydro*-5 : 6-*benzocoumarin* (VII) (9·72 g., 42%), prisms, m. p. 226° (Found: C, 66·2; H, 5·2; N, 4·1. $C_{18}H_{17}O_5N$ requires C, 66·1; H, 5·2; N, 4·3%). Fraction (B) after repeated crystallisation from ethanol afforded prisms of *diethyl* 2-*hydroxy*-1-*naphthylmethylacetamidomalonate* [I; R = $C(NHAc)(CO_2Et)_2$] (2·16 g., 8·3%), m. p. 183·5—184° (decomp.) (Found: C, 64·2; H, 6·3; N, 3·8. $C_{20}H_{23}O_6N$ requires C, 64·3; H, 6·2; N, 3·8%). Heating this compound above its m. p. resulted in evolution of ethanol and formation of a solid, m. p. 222—223°, not depressed on admixture with the lactone (VII).

Prolonged treatment of the lactone with hot ethanol re-formed the pure ester [I; R = $C(NHAc)(CO_2Et)_2$], m. p. and mixed m. p. 183·5—184°.

(j) *With indole.* Indole (2·34 g., 0·02 mole), the sulphide (0·02 mole), and a catalytic quantity of potassium hydroxide were heated at 150°/15 cm. for 1 hr. Evolution of ethanethiol, fairly rapid at first, had then ceased. Crystallisation of the residue from toluene (5 c.c.)–*cyclo*hexane (10 c.c.), and then xylene (charcoal) gave a pink solid, m. p. 145·5—149·5°. Recrystallisation from xylene followed by fractional crystallisation from aqueous ethanol afforded colourless prisms of 3-(2-*hydroxy*-1-*naphthylmethyl*)*indole* (VIII) (2·84 g., 52%), m. p. 151—152° (Found: C, 83·4; H, 5·8; N, 4·9. $C_{19}H_{15}ON$ requires C, 83·5; H, 5·5; N, 5·1%).

(k) *With antipyrine.* A mixture of antipyrine (3·76 g., 0·02 mole), the sulphide (0·02 mole), and potassium hydroxide (*ca.* 80 mg.) was heated *in vacuo* first for 1 hr. at 150—160°, then for a further 2 hr. at 190—200°, after which the reaction appeared complete. Crystallisation of the product from methanol (charcoal) gave colourless prisms of 4-(2-*hydroxy*-1-*naphthylmethyl*)-*antipyrine* (IX) (5·66 g., 82%), m. p. 201° (Found: C, 76·4; H, 5·9; N, 8·0. $C_{22}H_{20}O_2N_2$ requires C, 76·7; H, 5·9; N, 8·15%). The *acetyl* derivative crystallised from aqueous ethanol as prisms, m. p. 133—134° (Found: C, 74·5; H, 5·9; N, 7·0. $C_{24}H_{22}O_3N_2$ requires C, 74·6; H, 5·7; N, 7·25%).

(l) *With* p-*cresol.* *p*-Cresol (3·24 g., 0·03 mole), the sulphide (0·02 mole), and potassium hydroxide (*ca.* 80 mg.) were refluxed for 1 hr. at 155—160°/15 cm. Trituration of the hot residue with toluene (20 c.c.) gave a crude product (2·52 g., 48%), m. p. 221—223°, which was recrystallised in turn from glacial acetic acid (charcoal) and aqueous *iso*propanol to form small colourless needles of 1-(2-*hydroxy*-5-*methylbenzyl*)-2-*naphthol*, m. p. 227—228° (decomp.) (bath preheated at 220°) (Found: C, 82·4; H, 5·7%; active H, 1·7 atoms. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%; active H, 2·0 atoms). The *dibenzoyl* derivative crystallised from ethyl acetate as prisms, m. p. 194° (Found: C, 80·8; H, 4·8. $C_{32}H_{24}O_4$ requires C, 81·3; H, 5·1%).

(m) *With* p-*benzylphenol.* The reaction was carried out as described for *p*-cresol. The crude product, m. p. 216—218° (decomp.), crystallised from *iso*propanol and then recrystallised from glacial acetic acid (charcoal) as pale pink prisms of 1-(5-*benzyl*-2-*hydroxybenzyl*)-2-*naphthol* (2·88 g., 38%), m. p. 220·5° (decomp.; bath preheated at 210°) (Found: C, 84·2; H, 5·6%; active H, 2·3 atoms. $C_{24}H_{20}O_2$ requires C, 84·7; H, 5·9%; active H, 2·0 atoms). Its *dibenzoate* formed colourless prisms, m. p. 189—190°, from ethyl acetate–ethanol (Found: C, 82·9; H, 5·1. $C_{38}H_{28}O_4$ requires C, 83·2; H, 5·1%). The *bis*-3 : 5-*dinitrobenzoate* was obtained as small yellow prisms, m. p. 251—252°, from ethyl acetate (Found: C, 62·6; H, 3·5; N, 7·7. $C_{38}H_{24}O_{12}N_4$ requires C, 62·6; H, 3·3; N, 7·7%).

(n) *With* 2-*naphthol.* A mixture of the sulphide (0·02 mole), 2-naphthol (2·88 g., 0·02 mole), and potassium hydroxide (*ca.* 80 mg.) was heated for 1 hr. at 150—160°/15 cm. A vigorous gas evolution took place and the mixture solidified after 30 min. The cooled residue was triturated with toluene and crystallised twice from glacial acetic acid, to give colourless needles of di-(2-hydroxy-1-naphthyl)methane (4·59 g., 77%), m. p. and mixed m. p. 200° (Found: C, 83·8; H, 5·5. Calc. for $C_{21}H_{16}O_2$: C, 84·0; H, 5·4%).

(o) *With thioacetamide.* The sulphide (0·01 mole), thioacetamide (0·83 g., 0·011 mole), and potassium hydroxide (*ca.* 40 mg.) were heated *in vacuo* at 135—140° for 45 min. Crystallisation of the residue from ethanol containing acetic acid (5 drops), then from toluene, afforded almost colourless prisms of *di*-(2-*hydroxy*-1-*naphthylmethyl*) *sulphide* (0·76 g.), m. p. 160° (Found: C, 75·8; H, 5·5; S, 9·45. $C_{22}H_{18}O_2S$ requires C, 76·3; H, 5·2; S, 9·3%).

(p) *With sodium hydroxide.* The sulphide (0·02 mole), dissolved in a solution of sodium hydroxide (1·38 g.) in water (10 c.c.), was heated under reflux for 1 hr. Addition of water (45 c.c.) followed by treatment with excess of powdered solid carbon dioxide precipitated a greenish-brown gum and a little solid. The mixture was extracted with ether (100 c.c.), and the extract washed with water, dried ($MgSO_4$), and evaporated, finally *in vacuo*. Crystallisation of the dry residue from toluene gave colourless needles of di-(2-hydroxy-1-naphthyl)methane (0·78 g.), m. p. and mixed m. p. 200° (Found: C, 83·7; H, 5·6. Calc. for $C_{21}H_{16}O_2$: C, 84·0; H, 5·4%).

When a mixture of the sulphide (0·03 mole) and powdered potassium hydroxide (*ca.* 120 mg.) in the absence of water was heated under reflux *in vacuo* at 170—180°, ethanethiol was smoothly eliminated. Reaction appeared to be complete after 2 hr. However, only indefinite or polymeric material was isolated.

Hydrolysis of 1-*Cyanomethyl*-2-*naphthol.*—1-Cyanomethyl-2-naphthol (0·5 g.) was heated under reflux with sodium hydroxide (0·6 g.) in water (4·0 c.c.) until evolution of ammonia had ceased (4 hr.). The solution was then treated with charcoal and saturated with sulphur dioxide, to give a pale-cream solid (0·51 g.). This was dissolved in dilute sodium carbonate solution, filtered (charcoal), and reprecipitated by excess of dilute hydrochloric acid, giving colourless plates of 2-hydroxy-1-naphthylacetic acid (0·44 g., 80%), m. p. 147°, mixed m. p. 146—147° (Found: C, 70·9; H, 5·1. Calc. for $C_{12}H_{10}O_3$: C, 71·3; H, 5·0%).

β-(2-*Hydroxy*-1-*naphthyl*)*alanine* [I; R = $CH(NH_2)\cdot CO_2H$].—3-Acetamido-3-ethoxycarbonyl-3 : 4-dihydro-5 : 6-benzocoumarin (VII) (3·27 g., 0·01 mole), concentrated hydrochloric acid (10·0 c.c.), and water (7·5 c.c.) were refluxed for 18 hr., after which the solution was evaporated to dryness *in vacuo*. The residue was treated with water (15 c.c.) and evaporated to dryness again, and this operation was repeated. The product was suspended in hot water (50 c.c.) and

dissolved by the addition of the minimum of 10% aqueous sodium hydroxide. Neutralisation (pH 6) with hydrochloric acid precipitated a grey solid (1·52 g.) which was dissolved in hot dilute sodium carbonate, filtered (charcoal), and reprecipitated by careful addition of dilute hydrochloric acid, giving an almost colourless product (1·15 g.). This was washed free from chloride ions with water and crystallised from 15% aqueous ammonia (charcoal), affording almost colourless plates of the pure *amino-acid* (1·06 g., 46%), m. p. 286—288° (decomp.) (bath preheated at 278°) (Found: C, 67·1; H, 5·5; N, 6·4. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·7; N, 6·1%).

Reaction of Gramine with 2-Naphthol.—Gramine (1·74 g., 0·01 mole), 2-naphthol (0·01 mole), and potassium hydroxide (*ca.* 40 mg.) were heated *in vacuo* at 160° for 30 min. The initially vigorous reaction then appeared to have ceased. Fractional crystallisation of the dark product from aqueous ethanol containing acetic acid (5 drops) gave colourless prisms of 3-(2-hydroxy-1-naphthylmethyl)indole (VIII) (1·24 g., 45%), m. p. and mixed m. p. 151—152° (Found: N, 5·0. Calc. for $C_{19}H_{15}ON$: N, 5·1%).

Reactions of 3-Ethylthiomethylindole (II; R = SEt).—(a) *With piperidine.* 3-Ethylthiomethylindole (Part I, *loc. cit.*) (2·00 g.), piperidine (10 c.c., 9·65 mol.), and potassium hydroxide (*ca.* 40 mg.) were refluxed for 24 hr. Excess of piperidine was then removed *in vacuo*, the residue dissolved in a small quantity of toluene, and the solution evaporated to dryness. The semi-solid product was dissolved in ether (20 c.c.) and the solution extracted with 3% hydrochloric acid (5 × 20 c.c.). After being treated with charcoal the combined acid extracts were made alkaline (phenolphthalein) with 10% aqueous sodium hydroxide, to give colourless prisms of 3-piperidinomethylindole (1·09 g., 49%), m. p. 159°, mixed m. p. 159—160° (Found: N, 12·8. Calc. for $C_{14}H_{18}N_2$: N, 13·1%). Omission of catalyst reduced the yield to 7·6%.

(b) *With phthalimide.* The sulphide (3·83 g., 0·02 mole), phthalimide (0·02 mole), and potassium hydroxide (*ca.* 80 mg.) were heated at 180°/15 cm. for 2½ hr., after which the initially vigorous reaction appeared to have ceased. The cooled residue was extracted with ether (2 × 20 c.c.), and the undissolved portion (2·78 g.) stirred for a short time with cold 10% aqueous sodium hydroxide. Crystallisation of the residual solid from ethanol gave pale buff prisms of 3-phthalimidomethylindole (0·85 g., 15·4%), m. p. and mixed m. p. 182—183°. A 7·8% yield was obtained when 3-benzylthiomethylindole (Part I, *loc. cit.*) (0·02 mole) was substituted for (II; R = SEt) in the foregoing reaction.

(c) *With aqueous-ethanolic sodium cyanide.* 3-Ethylthiomethylindole (5·00 g.) was refluxed with sodium cyanide (4·60 g.) in ethanol (51·5 c.c.) and water (12·9 c.c.) for 80 hr. Water (46 c.c.) was then added and the mixture warmed until all solid had dissolved. After being treated with charcoal the solution was concentrated at reduced pressure until all the ethanol had been removed. The product was kept at 0° overnight and afforded a sticky, light brown solid (2·41 g.) which recrystallised from ethanol–ether (charcoal) to give 3-indolylacetamide (0·95 g., 21%), m. p. 148—150° (Found: N, 15·9. Calc. for $C_{10}H_{10}ON_2$: N, 16·1%). The filtrate from the crude amide was made acid (Congo-red) by hydrochloric acid. Almost pure 3-indolylacetic acid (1·90 g., 42%), m. p. 63—165°, was precipitated. Crystallisation from ethylene dichloride containing a little ethanol gave pure acid, m. p. 167—168° (Found: N, 8·3%; equiv., 176. Calc. for $C_{10}H_9O_2N$: N, 8·0%; equiv., 175).

Attempted Reactions of 4-Ethylthiomethylantipyrine (III; R = SEt).—The sulphide (Part I, *loc. cit.*) was heated under reflux with (*a*) piperidine for 2 hr. in a current of nitrogen, (*b*) aqueous ethanolic sodium cyanide for 80 hr., and (*c*) methanolic sodium thiophenoxide for 72 hr. Substantially unchanged 4-ethylthiomethylantipyrine was recovered.

4-Ethylsulphonylmethylantipyrine (III; R = SO_2Et).—This *sulphone*, prepared in 50% yield by permanganate oxidation of the sulphide (III; R = SEt) in acetic acid, crystallised from methanol as colourless rods, m. p. 172—173° (Found: N, 9·6; S, 11·0. $C_{14}H_{18}O_3N_2S$ requires N, 9·5; S, 10·9%).

Reactions of β-Ethylthio-β-phenylpropiophenone.—(a) *With piperidine.* β-Ethylthio-β-phenylpropiophenone (Kipnis and Ornfelt, *J. Amer. Chem. Soc.*, 1946, **68**, 2104) (5·41 g., 0·02 mole) and piperidine (10 c.c., 0·1 mole) were heated under reflux for 1 hr. with a stream of dry nitrogen passing through the solution, then kept at 0° overnight. The precipitated β-piperidino-β-phenylpropiophenone crystallised from light petroleum (b. p. 60—80°) as needles (4·51 g., 77%), m. p. 94°, not depressed on admixture with an authentic sample (Georgi and Schwyzer, *J. pr. Chem.*, 1912, **86**, 273) (Found: N, 4·7. Calc. for $C_{20}H_{23}ON$: N, 4·8%).

(b) *With thiophenol.* Thiophenol (5·50 g., 0·05 mole) and β-ethylthio-β-phenylpropiophenone (2·70 g., 0·01 mole) were heated under nitrogen for 1 hr. at 130°. Excess of thiophenol was then removed *in vacuo*. The residual solid was twice crystallised from ethanol, giving colourless

needles of β-phenyl-β-phenylthiopropiophenone (2·84 g., 89%), m. p. 120—121°, not depressed on admixture with a specimen prepared by Ruhemann's method (*J.*, 1905, **87**, 461). The original ethylthio-compound was recovered substantially unchanged when toluene-ω-thiol was used in this reaction.

1-*Ethylthiomethyl*-2-*naphthyl Tetrahydro*-2′-*pyranyl Ether* (X).—To 1-ethylthiomethyl-2-naphthol (40·0 g.) in dry ether (650 c.c.), dihydropyran (70·7 g.) (freshly distilled from solid sodium hydroxide) was added. After thorough mixing, concentrated hydrochloric acid (15 drops) was added, and the whole kept at room temperature for 6 days. The solution was washed with aqueous 5% sodium hydroxide (3 × 200 c.c.) and then water (2 × 200 c.c.), filtered, and evaporated to dryness. The oily residue was heated at 100°/100 mm. for 30 min., and then at 100°/1 mm. for 30 min., giving a pale orange oil (35·2 g.) which crystallised. From ethanol–light petroleum (b. p. 40—60°) it afforded a crude solid (19·5 g., 35%), m. p. 51—52°. Three further crystallisations from light petroleum (b. p. 40—60°) followed by one from ethanol gave the *ether* (X) as colourless prisms, m. p. 58° (Found: C, 71·1; H, 7·0; S, 10·9. $C_{18}H_{22}O_2S$ requires C, 71·5; H, 7·3; S, 10·6%).

Piperidine (10 c.c.) and the ether (X) (2·00 g.) were heated under reflux for 3 hr. Excess of piperidine was then removed *in vacuo* and the residue crystallised from light petroleum (b. p. 40—60°), to give the unchanged ether (1·98 g.), m. p. and mixed m. p. 58°.

The ether (X) (3·02 g., 0·01 mole) was refluxed with sodium cyanide (2·30 g.) in ethanol (25·8 c.c.) and water (6·5 c.c.) for 80 hr. Water (23 c.c.) was then added and the mixture concentrated *in vacuo* until all the ethanol had been removed. Colourless prisms of the unchanged ether (2·94 g.), m. p. and mixed m. p. 58°, were deposited on cooling.

Thiophenol (4·23 g.) and the acetyl derivative (V; R = SEt) (2·00 g.) were heated for 2 hr. at 120—130° with a stream of dry nitrogen passing through the reaction mixture. Excess of thiophenol was removed *in vacuo* and the residue crystallised from ethanol, to give colourless prisms of the unchanged acetyl compound (1·96 g.), m. p. and mixed m. p. 82°.

Reaction of the Sulphide (V; R = SEt) *with Piperidine*.—Piperidine (3·9 g.) was added to the acetyl derivative (V; R = SEt) (2·0 g.) whereupon all the solid dissolved with the evolution of heat. The solution was heated under reflux for 2 hr. under nitrogen, ethanethiol being steadily evolved. Excess of piperidine was then removed *in vacuo* and the residue crystallised from ethanol, to yield almost colourless plates of 1-piperidinomethyl-2-naphthol (1·56 g.), m. p. and mixed m. p. 93—94°.

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