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2-MERCAPTO-4 : 5-DIPHENYLIMIDAZOLE DERIVATIVES AS POSSIBLE SYMPATHOMIMETICS

BY

VIVEKANANDA BHATT, M., BALAKRISHNA HARIHARA IYER

AND

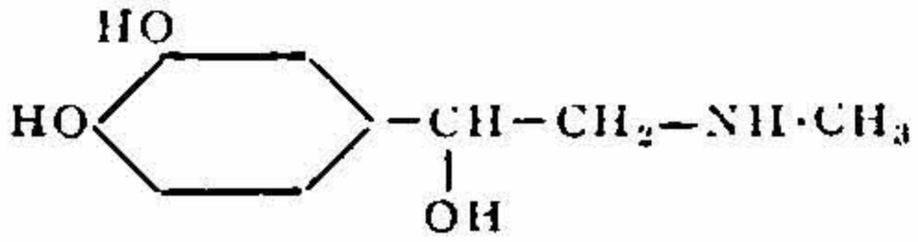
PRAPHULLA CHANDRA GUHA

E. V. GANAPATI IYER, B.Sc.
Chairman of Editorial Board

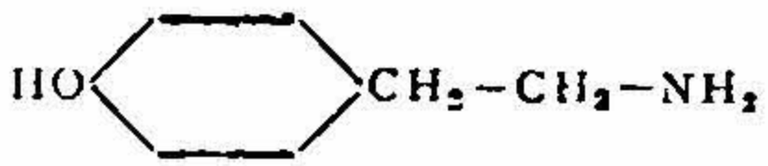
2-MERCAPTO-4 : 5-DIPHENYLIMIDAZOLE DERIVATIVES AS POSSIBLE SYMPATHOMIMETICS*

By Vivekananda Bhatt, M., Balkrishna Harihara Iyer and Praphulla Chandra Guha

Oliver and Schaefer (*J. Physiol.*, 1894, **16**, 1; 1895, **18**, 230) discovered the blood pressure raising property of suprarenal (adrenal) glandular extracts. Abel and Crawford (*Bull. Johns-Hopkins Hosp.*, 1897, **8**, 151) separated the active principle—Epinephrine as they called it—by means of the insoluble benzoyl derivative. It was obtained in the crystalline state by Takamine (*Am. J. Pharm.*, 1901, **73**, 523; *Therapeutic Gazette*, 1901, **25**, 221) and by Aldrich (*Am. J. Physiol.*, 1901, **5**, 457; *J. Am. Chem. Soc.*, 1905, **27**, 1074) almost simultaneously. The labours of Krukenberg (*Virchow's Archives*, 1885, **101**, 542); Moore (*J. Physiol.*, 1895, **17**, *Proc.* March 16) and v. Furth (*Monatsh*, 1903, **24**, 261; *Ber.*, 1904, **37**, 1388) and others (Pauly, *Ber.*, 1903, **36**, 2944; Jowett *J. Chem. Soc.*, 1904, **85**, 192) led to the elucidation of the structure of adrenaline (A) which was confirmed by Stolz (*Ber.*, 1904, **37**, 4149; *Ger. Pat.*, **157**, 300) and Dakin (*Proc. Roy. Soc.*, London, 1905, **76 B**, 491–498) by synthesis.



(A)



(B)

Following the discovery that extracts of putrid meat (Abelous, Ribaut, *et al.*, *Compt. rend. soc. biol.*, 1906, **58**, 463, 530) and placenta (Dixon and Taylor, *B.M.J. II*, **107**, 1150) possess the property of raising the blood pressure, Barger, Dale and others (Barger and Dale, *J. Physiol.*, 1909, **38**, *Proc. Physiol. Soc.* 1909, XIII; Barger and Walpole, *ibid.*, 1909, **38**, 343; Rosemheim *ibid.*, 1909, **38**, 337; Dale and Dixon, *ibid.*, 1909, **39**, 25); isolated, a series of amines from both sources. The pharmacological studies of the various amines thus isolated showed that *β-p*-hydroxyphenylethylamine (B) (tyramine) was the most powerful amongst them. Its close resemblance to adrenaline both in physiological properties and chemical structure was soon recognised.

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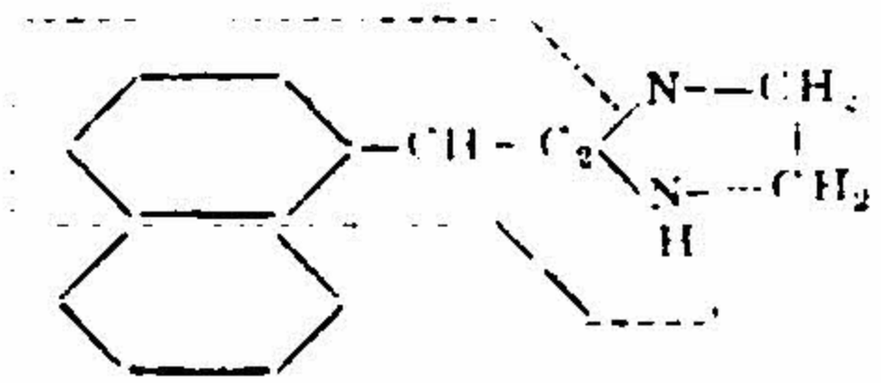
* A preliminary note on this subject was published in *Current Science* June 1948, **17**, 184–5.

Examining about forty amines having well defined pressor action Barger and his colleagues (*J. Physiol.*, 1910, **41**, 19) came to the conclusion that "....the optimum constitution of a fatty aromatic amine for the production of sympathomimetic action is that which is found in adrenaline itself, *viz.*, a benzene ring and a side chain of two carbon atoms of which the second bears the amino group". This is known as *β-phenylethylamine rule.*

The physiologically active imidazole derivatives that occur both in plant and animal products, *e.g.*, alkaloids like pilosine and pilocarpine, amino acids like histidine, and histamine which is found in ergot extracts, have attracted great attention. A number of 2-alkylaryl and 2-alkyl heterocyclic imidazole derivatives have been prepared and some of them, notably privine—2-α-napthylmethylimidazoline (C) -which has been introduced into clinical practice as a vasoconstrictor have been found to be active pressors. (Scholz, *J. Ind. Engg. Chem.*, 1945, 37, 120).



(C)

It will be noticed from formula (C) that privine possesses a β-phenylethyl amine skeleton as indicated by the enclosure in dotted lines.

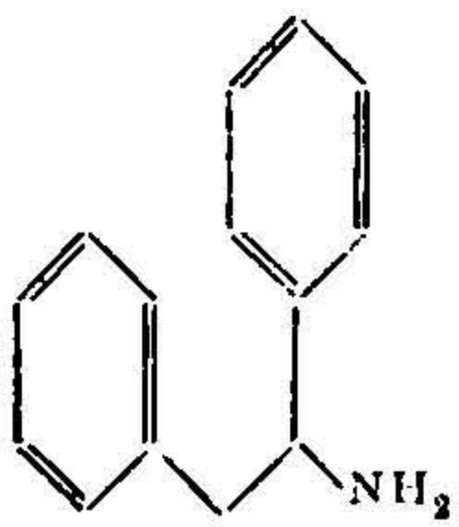
Smirk and McGeorge (*Lancet*, 1942, II, **243**, 301) have discovered that *s*-methylisothioureasulphate can successfully be used to overcome fall of blood pressure in spinal anæsthesia, even when adrenaline proves to be of little avail.

With a view to studying the pharmacological effect of compounds having all these structural factors, *viz.*, (i) β-phenylethylamine structure, (ii) alkylisothiourea residue and (iii) imidazole ring, in one and the same compound and also to testing the effect of different alkyl or aryl groups attached to sulphur of the mercaptanic group, eight new 2-mercapto-4:5-diphenylimidazole derivatives and twelve new 2-mercapto-1-aryl-4:5-diphenylimidazole derivatives have now been synthesised (*vide* Table).

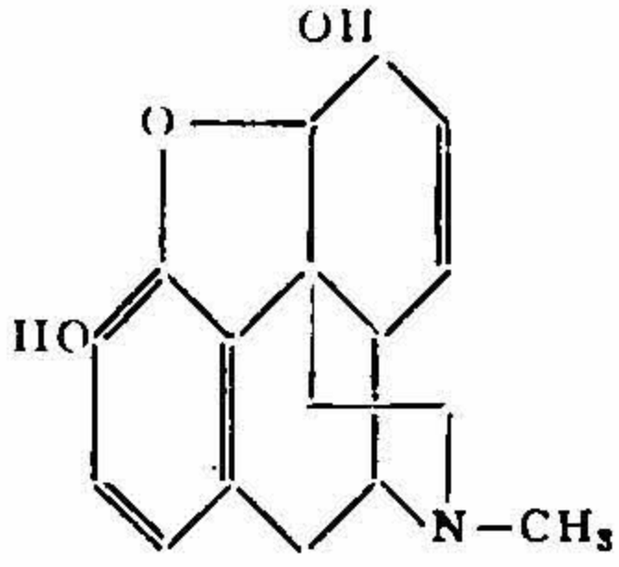
From a scrutiny of the structure (F) it will be seen that there is present in it the β-phenylethylamine skeleton and an alkyl isothiourea residue with nitrogen atoms common to both and forming an imidazole ring. The presence of the two phenyl groups in the 4 and 5 positions of the imidazole ring may be regarded as furnishing two β-phenylethyl amine residues.

It may be of interest to note that about 12 per cent. of the total organic sulphur of peptides and proteins of the blood serum is contained in substances derived from thioiminazoles (Lefevre and Rangier, *Compt. rend.*, 1942, **214**, 774; *Bull, soc. chim. biol.*, 1943, **25**, 292).

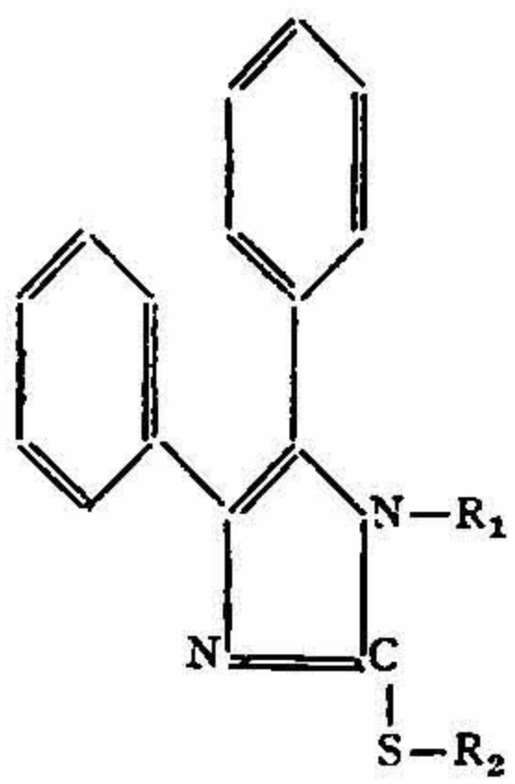
4: 5-Diphenylimidozole derivatives have other points of interest. Dodds and coworkers (*Proc. Roy. Soc., London*, 1944, **132 B**, 119) found that diphenylethylamine derivatives possess morphine-like activity which they ascribe to the structural propinquity of diphenylethylamine (D) to morphine (E).



(D)

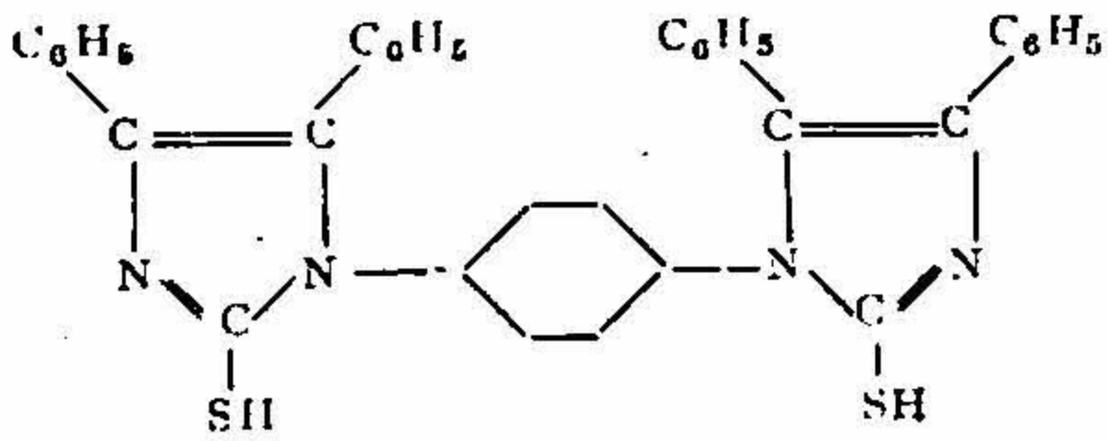


(E)



(F)

N-Aryl derivatives of 2-mercapto-4: 5-diphenylimidazoles, described in literature were prepared by heating benzoin, N-substituted thiourea and alcohol in sealed tubes at 180–190° for 4 hours (Anschutz and Schwickerath, *Annalen*, 1895, **284**, 9; Muller, *ibid.*, 1895, **284**, 25). Biltz and Krebs (*Annalen*, 1912, **391**, 195) prepared 2-mercapto-4 : 5-diphenylimidazole by fusing together benzoin and thiourea. We extended this method to mono substituted thioureas and developed a general method for the preparation of 1-aryl-2-mercapto-4: 5-diphenylimidazoles, by fusing equimolecular quantities of N-substituted thiourea and benzoin in the neighbourhood of 200° C. Two mols. of benzoin reacted with one mole of *p*-phenylenedithiourea to give (XX) having the formula (G).

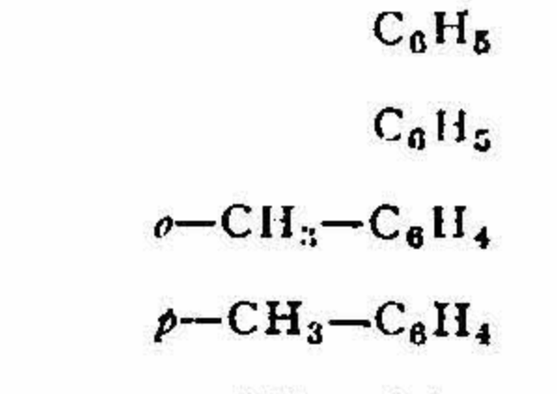


(G)

2-Mercapto-4: 5-diphenyl-imidazole derivatives are either sparingly soluble or insoluble in common solvents except pyridine. They yield alkali metal salts which are generally soluble in alcohol and hot water.

The thioethers have been prepared by the usual method, *viz.*, by refluxing the alkali-metal salts with the appropriate alkyl or aryl halides in alcoholic solution.

In the Table below is listed twenty analogues and derivatives of 2-mercapto-4: 5-diphenyl-imidazole (type F).

No.	R_1	R_2
I	H	$-CH_2-CH_2-CH_3$
II	H	$-CH_2-CH=CH_2$
III	H	$-CH_2-CO-CH_3$
IV	H	$-CH_2-CH_2-OH$
V	H	$-CH_3-COOH$
VI	H	$-CH_2-C_6H_5$
VII	H	$-C_6H_4-NO_2-p$
VIII	H	$-C_6H_2-(NO_2)_3$ 2, 4, 6.
IX	C_6H_5	$-CH_2-CO-CH_3$
X	C_6H_5	$-C_6H_3(NO_2)_2$ 2, 4.
XI	C_6H_5	$-C_6H_2(NO_2)_3$ 2, 4, 6.
XII	$o-CH_3-C_6H_4$	H
XIII	$p-CH_3-C_6H_4$	H
XIV	$p-CH_3-C_6H_4$	$-C_6H_3(NO_2)_2$ 2, 4.
XV	$p-CH_3-C_6H_4$	$-CH_2-C_6H_5$
XVI	$p-CH_3-O-C_6H_4$	H
XVII	$p-CH_3-O-C_6H_4$	$-CH_2-C_6H_5$
XVIII	$p-CH_3-O-C_6H_4$	$-C_6H_2-(NO_2)_3$ 2, 4, 6.
XIX	$p-NO_2-C_6H_4$	H
XX		H

Experimental

2-Mercapto-4 : 5-diphenylimidazole (MDPI) was prepared according to the method of Biltz and Krebs (*loc. cit.*).

2-n-*Propylmercapto*-4 : 5-*diphenylimidazole* (*I*).—The dry sodium salt of 2-mercapto 4 : 5-diphenylimidazole (MDPI) (dried at 110°), freshly distilled *n*-propyliodide (1·5 c.c.) and 90% alcohol (20 c.c.) were heated under reflux in a steam-bath for half an hour when the reaction mixture ceased to react alkaline to litmus. The mixture was poured into water and the solid that separated was filtered; yield (crude) 1·9 g. The product was crystallized from alcohol in shining white needles, m.p. 174°. (Found: N = 9·6; $C_{18}H_{18}N_2S$ requires N = 9·5 per cent.)

2-*Allylmercapto*-4 : 5-*diphenylimidazole* (*II*).—Freshly distilled allyl-bromide (2 c.c.), alcohol (25 c.c.) and sodium salt of MDPI (3·9 g.) were refluxed on a steam-bath till the reaction mixture reacted neutral (½ hour). After three crystallizations from alcohol a substance m.p. 181–2° was obtained; yield 3·2 g. (Found: N, 9·9; $C_{18}H_{16}N_2S$ requires N, 9·6 per cent.)

2-*Acetonylmercapto*-4 : 5-*diphenylimidazole* (*III*).—Dry sodium salt of MDPI (2·6 g.), freshly distilled chloroacetone (2 c.c.) and alcohol (20 c.c.) were heated together for 2½ hours under reflux; yield (crude) 2·7 g. After repeated crystallizations from 50% alcohol and benzene-petrol it was obtained in white felt-like mass of needles, m.p. 150–1°. (Found: N, 9·0; $C_{18}H_{16}ON_2S$ requires N, 9·1 per cent.)

2-*ω-Hydroxyethylmercapto*-4 : 5-*diphenylimidazole* (*IV*).—Sodium salt of MDPI (2·6 g.), ethylene chlorohydrin (1·5 c.c.) and alcohol (20 c.c.) were heated under reflux till the reaction mixture was neutral (3 hours); yield (crude) 1·7 g. (55%). The product was crystallized twice from alcohol; transparent cubes with lemon yellow lustre m.p. 167°. (Found: N, 9·3; $C_{17}H_{16}ON_2S$ requires N, 9·5 per cent.)

2-*Carboxymethylmercapto*-4 : 5-*diphenylimidazole* (*V*).—Freshly distilled chloroacetic acid (1·6 g.), sodium salt of MDPI (2·6 g.) and alcohol (20 c.c.) were refluxed for 1½ hours; yield (crude) 2·8 g. The substance was sparingly soluble in ethyl alcohol, ethylacetate, acetone and methyl alcohol. It was purified by treating with sodiumbicarbonate solution and precipitating with acid. Finally it was crystallized twice from dilute acetic acid; m.p. 216°. (Found: N, 9·0; $C_{17}H_{14}O_2N_2S$ requires N, 9·0 per cent.)

2-*Benzylmercapto*-4 :5-*diphenylimidazole* (*VI*).—Benzylchloride (1·5 c.c.), sodium salt of MDPI (2·6 g.) and alcohol (20 c.c.) were heated till the

reaction mixture was neutral (½ hour). After evaporating to half the original volume the separated solid was filtered and washed with water. Two crystallizations from alcohol yielded felt-like white shining needles; m.p. 185–6°. (Found: N, 8·2; $C_{22}H_{18}N_2S$ requires N, 8·2 per cent.)

2-*p-Nitrophenylmercapto*-4: 5-*diphenylimidazole* (*VII*).—*p*-Nitrochlorobenzene (1·7 g.), alcohol (20 c.c.) and sodium salt of MDPI (2·6 g.) were refluxed for about 60 hours. The product was crystallized from alcohol; yield (crude) 1·9 g. Recrystallization from alcohol yielded yellow glistening needles; m.p. 209°. (Found: N, 11·0; $C_{21}H_{15}O_2N_3S$ requires N, 11·2 per cent.)

2-(2′, 4′, 6′-*Trinitrophenyl mercapto*)-4: 5-*diphenylimidazole* (*VIII*).—Sodium salt of MDPI (2·6 g.) picrylchloride (2·6 g.) and alcohol (20 c.c.) were refluxed for 8 hours. A dark red solid separated on cooling, yield (crude), 3·3 g. The substance was purified by precipitation with water from alcoholic solution, the crystals decomposed with explosive violence when heated quickly in the neighbourhood of 186°; softened near about 250°. (Found: N, 14·6; $C_{21}H_{13}O_6N_5S$ requires N, 15·1 per cent.)

Na-salt of 2-Mercapto-1: 4: 5-triphenylimidazole (MTPI) has now been prepared by the following modification of the method of Anschutz and Schwickerath (*loc. cit.*). A mixture of finely powdered phenylthiurea (3·7 g.) and benzoin (5·25 g.) was heated in an oil-bath with occasional stirring. The clear liquid formed at about 155° frothed up, between 160–170°. The heating was continued till the bath temperature rose to 200°. The hard solid that had formed on cooling was ground well with alcohol. After filtering, the cream coloured solid was washed with alcohol and crystallized from aqueous pyridine to a white product m.p. 290 (decomp.) yield, 6·5 g. (76%). The Na-salt was obtained by grinding the crude product with sodium hydroxide solution (20%). It was crystallized from hot water or dilute alcohol.

2-*Acetonylmercapto*-1: 4: 5-*triphenylimidazole* (*IX*).—Sodium salt of MTPI (1·7 g.), chloroacetone (1 c.c.) and alcohol (30 c.c.) were refluxed together on steam-bath for one hour. The product was crystallized twice from 80% alcohol; yield 1·2 g. (65%) m.p. 153–4°. (Found: N, 7·3; $C_{21}H_{20}ON_2S$ requires N, 7·3 per cent.)

2-(2′, 4′-*Dinitrophenylmercapto*)-1: 4: 5-*triphenylimidazole* (*X*).—A mixture of the sodium salt of MTPI (1·7 g.), alcohol (30 c.c.) and 2, 4-dinitrochlorobenzene (1·2 g.) was heated under reflux for 15 minutes. The separated solid was crystallized from benzene-petrol in yellow shining

crystals; yield (crude) 1·7 g. m.p. 199–200°. (Found: N, 11·5; $C_{27}H_{18}O_4N_4S$ requires N, 11·3 per cent.)

2-(2′, 4′, 6′-*Trinitrophenylmercapto*)-1 : 4 : 5-*triphenylimidazole* (*XI*).—A mixture of the sodium salt of MTPI (1·7 g.), alcohol (30 c.c.) and picryl chloride (1 g.) was heated in an oil-bath for 15 minutes. The product was crystallized from ethylacetate-petrol or chloroform-petrol mixture in dark-red glistening needles, m.p. 205–6° (decomp.); yield 1·4 g. (Found: N, 13·4; $C_{27}H_{17}O_6N_5S$ requires N, 13·0 per cent.)

1-*o*-*Tolyl*-2-*mercapto*-4 : 5-*diphenylimidazole* (*XII*).—The procedure adopted for the preparation was essentially the same as that for MDPI and MTPI. A mixture of benzoin (7 g.) and *o*-tolylthiourea (5·4 g.) was heated in an oil-bath. The clear liquid first formed solidified between 195–210°. The product after treatment with boiling alcohol was heated with NaOH solution. The pasty Na-salt after norite treatment in alcohol and filtration, was treated with hydrochloric acid (1 : 1) and the precipitate (yield: 6 g.) was purified through its potassium salt and finally crystallized from aqueous pyridine, m.p. 288–9° (decomp.). (Found: N, 8·2; $C_{22}H_{18}N_2S$ requires N, 8·2 per cent.)

1-p-*Tolyl*-2-*mercapto*-4 : 5-*diphenylimidazole* (*XIII*).—A mixture of benzoin (5·3 g.), *p*-tolylthiourea (4 g.) was heated in an oil-bath up to 200°, the product was worked up as usual and crystallized from aqueous pyridine as yellow white microcrystalline solid, m.p. 319–320° (decomp.). (Found: N, 8·3; $C_{22}H_{18}N_2S$ requires N, 8·2 per cent.)

2-(2′, 4′-*Dinitrophenylmercapto*)-1-p-*tolyl*-4 : 5-*diphenylimidazole* (*XIV*).—2, 4-Dinitrochlorobenzene (1 g.) potassium salt of (XIII) (1·3 g.) and alcohol (30 c.c.) were refluxed on a water-bath for 2 hours. On cooling, the solid that had separated was filtered off and crystallized from acetone, m.p. 233°, yield 0·7 g. (40%). (Found: N, 11·5; $C_{28}H_{20}O_4N_4S$ requires N, 11·0 per cent.)

2-*Benzylmercapto*-1-p-*tolyl*-4 : 5-*diphenylimidazole* (*XV*).—A mixture of the potassium salt of (XIII) (1·9 g.), benzylchloride (1·5 c.c.) and alcohol (20 c.c.) was refluxed for 4 hours in a water-bath. After cooling, the light yellow crystalline cake was filtered off and crystallized twice from chloroform-alcohol, in white shining prisms, m.p. 191°. (Found: N, 6·8; $C_{29}H_{24}N_2S$ requires N, 6·5 per cent.)

1-p-*Methoxyphenyl*-2-*mercapto*-4 : 5-*diphenylimidazole* (*XVI*).—Finely powdered *p*-methoxyphenylthiourea (6 g.) and benzoin (6·3 g.) were heated together in an oil-bath to 200°. The product was worked up as usual, yield

(crude) 7·5 g. (69%), m.p. 297° (decomp.). (Found: N, 8·1; $C_{22}H_{18}ON_2S$ requires N, 7·8 per cent.)

2-*Benzylmercapto*-1-p-*methoxyphenyl*-4: 5-*diphenylimidazole* (*XVII*).—The sodium salt of XVI (1·9 g.), alcohol (20 c.c.) and benzylchloride (1 c.c.) were refluxed on a steam-bath for 7 hours. The reaction mixture was treated with excess of water and the product after two crystallizations from aqueous pyridine gave a white microcrystalline powder m.p. 161·2°. (Found: N, 6·4, $C_{29}H_{24}ON_2S$ requires N, 6·3 per cent.)

2-(2′, 4′, 6′-(*Trinitrophenylmercapto*)-1-p-*methoxyphenyl*-4: 5-*diphenylimidazole* (*XVIII*).—A mixture of picrylchloride (0·7 g.), sodium salt of XVI (0·7 g.) and alcohol was refluxed on a steam-bath for 1 hour. The dark red solid that had separated on cooling was crystallized twice from chloroform-petrol; yield (crude) 0·7 g.; m.p. 168° (decomp.)

2-*Mercapto*-1-p-*nitrophenyl*-4: 5-*diphenylimidazole* (*XIX*).—*p*-Nitrophenyl thiourea (2·7 g.) and benzoin (2·7 g.) were fused together and heated up to 220°. The powdered solid after being washed with hot alcohol, was crystallized from aqueous pyridine (norite) in micro-crystalline yellow powder, m.p. 284°, yield, 1·5 g. (Found: N, 11·2; $C_{21}H_{15}O_2N_3S$ requires N, 11·3 per cent.)

p-*Phenylene-bis*-1-(2-*mercapto*-4: 5-*diphenylimidazole*) (*XX*).—*p*-Phenylene dithiourea (5 g. prepared more conveniently from *p*-phenylenediaminehydrochloride and ammoniumthiocyanate than by the method given by Billeter and Steiner, *Ber.*, 1887, **20**, 230) and benzoin (12·5 g.) were heated in an oil-bath (200°). The product being insoluble in common organic solvents was purified through the potassium salt. The compound did not melt below 340°, yield 7·3 g. (Found: N, 9·7; $C_{36}H_{26}N_4S_2$ requires N, 9·7 per cent.)

We thank Mr. J. R. Guha for supplying us 20 grammes of *p*-Methoxyphenylthiourea.

Organic Chemistry Laboratories,
Indian Institute of Science,
Bangalore 3.

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