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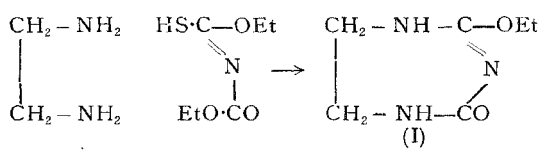
CONTENTS.

FORMATION OF HETEROCYCLIC COMPOUNDS FROM ETHYL CARBETHOXYTHIOCARBAMATE[1]

By Praphulla Chandra Guha and Shanker Rao A. Saletore.

Ethyl carbethoxythiocarbamate, $CO_2Et{\cdot}NH{\cdot}CS{\cdot}OEt$, was prepared by Delitsch (*J. pr. Chem.*, 1874, **9**, 464) by the action of ammonium sulphocyanide on chlorocarbonic ester in presence of alcohol. It contains two active ester groups—so, it was thought worth while to utilise this compound as a reagent for building up various types of heterocyclic compounds containing nitrogen, by condensing it with different kinds of organic bases, and to compare these results with those obtained by one of us (P.C.G., *J. Indian Chem. Soc.*, 1929, **6**, 65) in investigating the action of organic bases on a similar ester, namely, diethylxanthic formic ester, $CO_2Et{\cdot}CS{\cdot}OEt$. With this object in view, the action of ethylenediamine, *o*-phenylenediamine, hydrazine hydrate, phenylhydrazine, 4-phenyl- and 4-*p*-tolylthiosemicarbazides, di-*p*-tolylaminoguanidine, carbamide, thiocarbamide, aniline, *o*- and *p*-toluidines, *α*- and *β*-naphthylamines and benzidine upon ethyl carbethoxythiocarbamate has now been studied.

A molecule of the thiocarbamate reacting in the *cis*-thiol form with one molecule of ethylenediamine gives rise to 2-ethoxy-7-keto-tetrahydro-1 : 3 : 6-heptatriazine, thus :—

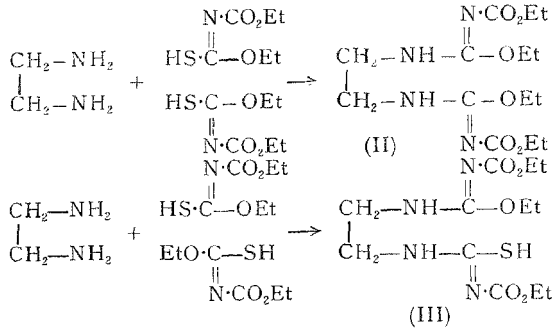


(I)

Together with this heptatriazine, which forms the major portion

[1] Reprinted from the *Journal of the Indian Chemical Society*, 1929, **6**, 565.

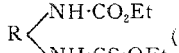
of the reaction product, there are formed two open-chain compounds, (II) and (III), the formation of which evidently depends on the fact that ethyl carbethoxythiocarbamate reacts with the diamine in the following two different ways :



The compound (II) does not contain sulphur and is insoluble in alkali; whereas compound (III) contains sulphur and possesses mercaptanic properties. With *o*-phenylenediamine, the reaction proceeds to yield mainly the sulphur-free heptatriazine compound

 (IV), analogous to compound (I).

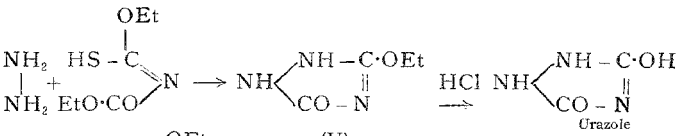
Diethylxanthic formic ester reacts with ethylene- and *o*-phenylene-diamines to yield the corresponding monothiodiurethanes,

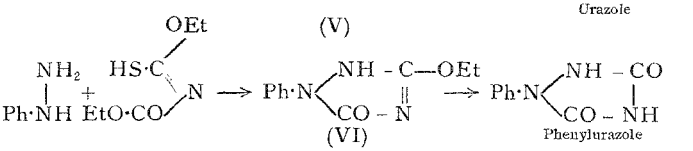
 (R = phenylene and ethylene), which suffer internal condensation yielding phenylene and ethylene ureas and thioureas (*J. Indian Chem. Soc.*, 1929, **6**, 68).

It might be mentioned in this connection that this is not the first occasion on which seven-membered ring compounds from 1 : 2-diamines have been made. Meyer prepared *o*-phenylenemalonamide from *o*-phenylenediamine and malonic acid or ester (*Annalen*, 1903, **327**, 14, 26; 1906, **347**, 34, 45). Thiele and Steimmig prepared a seven-membered compound from *o*-phenylenediamine and acetylacetone (*Ber.*, 1907, **40**, 955). Ethylene and *o*-phenylene biguanides

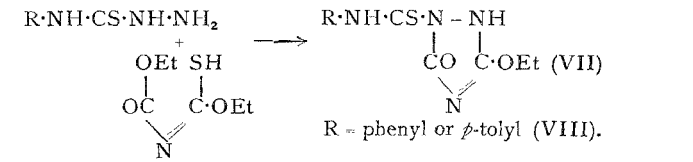
(Ziegelbauer, *Monatsh.*, 1896, **17**, 648; Dittler, *Monatsh.*, 1908, **29**, 645) are obtained from ethylene- and *o*-phenylenediamines and dicyandiamides. Guha and De (*J. Indian Chem. Soc.*, 1926, **3**, 41) prepared a large number of heptatriazine compounds from *o*-aminophenylhydrazine.

A new method for the preparation of urazole derivatives has been found in the action of ethyl carbethoxythiocarbamate on hydrazine and phenylhydrazine: the reactions evidently proceed thus:



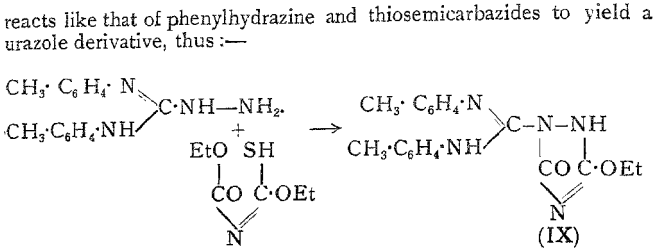


4-Phenyl- and 4-*p*-tolylthiosemicarbazides react with ethyl carbethoxythiocarbamate to yield 1 : 3 : 4-triazole derivatives, which in a sense may be regarded as urazoles.



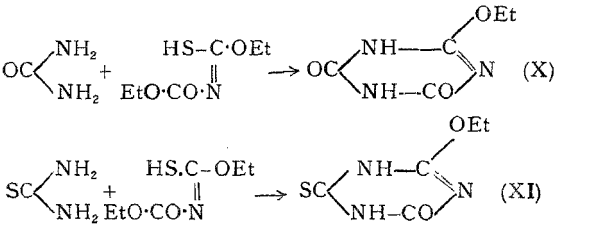
A close examination of the above reaction will reveal the fact that for the formation of these urazole derivatives the hydrazine part of the semicarbazides only takes an active part; to this extent these reactions resemble the formation of urazole derivatives from hydrazine and phenylhydrazine mentioned earlier. An analogous case is to be found in the action of semicarbazide and thiosemicarbazide upon acetoacetic ester as studied by De (*J. Indian Chem. Soc.*, 1926, **3**, 30). The action of ditolylaminoguanidine on the thiocarbamate has also been studied with the result that in this case also the hydrazino-part of the guanidine

reacts like that of phenylhydrazine and thiosemicarbazides to yield a urazole derivative, thus :—



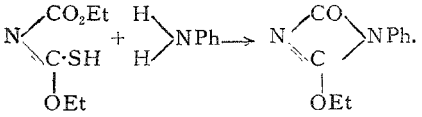
Diethylxanthic formic ester, however, reacts with phenylhydrazine and 4-R-thiosemicarbazides to yield the corresponding carboxylic esters Ph·NH·NH·CS·OEt and RNH·CS·NH·NH·CO_2Et, respectively (*ibid*, pp. 66, 72).

Urea and thiourea react with ethyl carbethoxythiocarbamate to yield 6-ethoxy-2 : 4-dioxy-1 : 3 : 5-triazine (X) and the corresponding thio-compound (XI) respectively, thus :

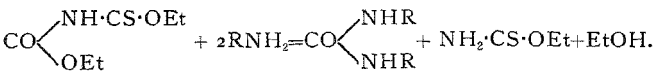


Oxy-derivaties of 1 :3 :5-triazines have been synthesised by Pinner (*Ber.*, 1890, **23**, 2919; 1892, **25**, 1424), Ephraim (*Ber.*, 1897, **30**, 2009), and Rapperfort (*Ber.*, 1901, **34**, 1900) by the action of phosgene on aryl amidines. 2 :4-Dioxy-1 : 3 :5-triazines have been prepared by Nencki (*Ber.*, 1876, **9**, 234), Kolb (*J. pr. Chem.*, 1894, **49**, 97), Ostrogorich (*Annalen*, 1895, **288**, 318; *Gazzetta*, 1897, **27**, 2, 41) by heating acetylurethane with urea (or acetylurea with urethane). 2 :4 :6-Trioxy-1 :3 :5-triazine (cyanuric acid) and its oxy- and *N*-alkyl derivatives are also known (Meyer and Jacobson, " Lehrbuch der organischen Chemie," Vol. I, Part 2, pp. 1331–1336). 2 :4 : 6-Trimercapto-1 :3 :5-triazine (trithiocyanuric acid) was prepared by Troger and Hornung (*J. pr. Chem.*, 1898, **57**, 357) and by Johnson and Menge (*J. Amer. Chem. Soc.*, 1904, **32**, 362, 370).

By analogy with the formation of ring-compounds as described above, it was expected that ethyl carbethoxythiocarbamate might react with aromatic amines to yield four-membered heterocyclic compounds with alternate carbon and nitrogen atoms according to the following scheme:—

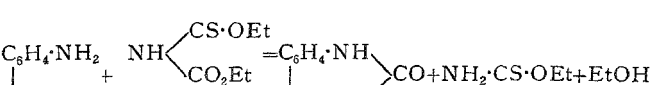


But actually the reaction has been found to proceed in quite a different manner giving rise to *sym*-disubstituted ureas, thus :—



(XII to XVI)

Benzidine similarly gives carbonylbenzidine, but as it contains two amino-groups in the same molecule, one molecule of the thiocarbamate reacts with one molecule of it, thus :—



Diethylxanthic formic ester reacts with aromatic amines to yield the corresponding thiodicarbomonothiodiarylamides, NHR·CS·S·CO·NHR (Guha and Dutt, *ibid*, p. 65).

EXPERIMENTAL.

Ethyl carbethoxythiocarbamate required for these experiments was conveniently prepared in quantity by the method of Delitsch (*J. pr. Chem.*, 1874, **10**, 118). As described by him, the substance is obtained as pale *yellow* prismatic crystals, m. p. 43° ; whereas, according to Doran (*J. Chem. Soc.*, 1896, **69**, 334) the ester comes out from solutions in rosettes of *yellowish* needles, m. p. 44–45°. We, however, found that repeated crystallisation from light petroleum yielded a

pure *white* product which was needle-shaped and melted at 46°. The substance could also be purified more easily by treating the potassium salt with dilute hydrochloric acid in aqueous solution.

The *potassium* derivative was prepared by dissolving the crude ethyl carbethoxythiocarbamate (160 g.) in cold absolute alcohol and adding a concentrated alcoholic solution of caustic potash under ice cooling till there was no more separation of solid. The salt was filtered on the pump, washed with cold alcohol and crystallised from 92 per cent. alcohol; m. p. 225°, yield, 120 g. It is soluble in water and hot alcohol.

Ethyl carbethoxythiocarbamate was isolated from the potassium salt by dissolving the latter in the minimum quantity of water and adding dilute hydrochloric acid. The pale yellow precipitate was crystallised from petroleum (b. p. 60–80°) as white crystalline needles, m. p. 46°, easily soluble in alcohol and ether and also in hot water (Found: N, 7·8; S, 17·89. $C_6H_{11}O_3NS$ requires N, 7·9; S, 18·08 per cent.).

Methyl Derivative.— The potassium salt of the thiocarbamate in alcoholic solution was heated on the water-bath with a slight excess of methyl iodide under reflux for about half an hour when crystals of potassium iodide separated. After filtration, the solution was made free from any excess of methyl iodide by heating on the water-bath, and water was then added when an oily product separated, which solidified on cooling and crystallised from dilute alcohol; m. p. 32–33°. It is extremely soluble in alcohol (Found: N, 7·4. $C_7H_{13}O_3NS$ requires N, 7·32 per cent.).

The *benzyl* derivative was obtained by heating an alcoholic solution of the potassium salt (5 g.) and benzyl chloride (3 g.) for two hours on a water-bath. The precipitated potassium chloride was removed and the filtrate freed from alcohol. The residual oily product was then taken up in ether, washed with water, dried over calcium chloride and the ether distilled. The white solid thus obtained was crystallised from petroleum (b. p. 60–80°) in plates, m. p. 45–46°. It is readily soluble in alcohol (Found: N, 5·3. $C_{13}H_{17}O_3NS$ requires N, 5·24 per cent.).

Reaction with Ethylenediamine: *Formation of Compounds* (I), (II) *and* (III).—On mixing ethyl carbethoxythiocarbamate (6 g.) with ethylenediamine (3 g.) a vigorous reaction took place with development of much heat and liberation of sulphuretted hydrogen. The hot molten mass solidified on cooling. This was treated with a dilute solution of caustic alkali, when a portion dissolved. The residue was

boiled with alcohol (95 per cent.) and filtered. On being cooled, the filtrate deposited a white crystalline product (I) which was recrystallised from alcohol in needles, m. p. 218°. It is soluble in hydrochloric acid from which it is precipitated by alkali; it is sparingly soluble in hot water. It was proved to be free from sulphur (Found: N, 26·8, $C_6H_{11}O_2N_3$ requires N, 26·7 per cent.).

Treatment with Hydrochloric acid.—The compound I (3 g.) was heated on a water-bath with 30–40 c. c. of 6*N*-hydrochloric acid when there was noticed a copious evolution of gas. On cooling, however, only 0·2 g. of a white crystalline solid separated which, after re-crystallisation from dilute alcohol, melted at 225° and was found to be insoluble in acids but soluble in alkalis. It contains 19·5 per cent. of nitrogen which agrees fairly well with the formula of ethylene dicarbamic acid.

Compound (II).—Further concentration of the mother-liquor from the above gave rise to a small quantity of a white crystalline product (m. p. 101–102°) insoluble in alkalis. It crystallises easily from alcohol and does not contain sulphur (Found: N, 15·8. $C_{14}H_{26}O_6N_4$ requires N, 16·1 per cent.). As the amount of the product was small, no further work could be done on it.

Compound (III).—The alkali extract of the reaction mixture, on being treated with dilute hydrochloric acid, precipitated a white flocculent solid, which redissolved on addition of more acid. It was obtained from the acid solution by careful addition of sodium carbonate solution and was crystallised from water in needles, m. p. 123° (Found: C, 44·23; H, 6·92; N, 16·9; S, 9·59. $C_{12}H_{22}O_5N_4S$ requires C, 43·11; H, 6·58; N, 16·8; S, 9·58 per cent.).

2-*Ethoxy*-4 : 5-*benzo*-7-*keto*-*tetrahydro*-1 : 3 : 6-*heptatriazine* (IV).—Ethyl carbethoxythiocarbamate (6 g.) was condensed with *o*-phenylenediamine (3·6 g.) as described in the previous experiment with this modification, that for completing the reaction, the mixture was heated for about half an hour on the water-bath. But in this case only one product was obtained, which crystallised slowly from dilute acetic acid. It was very difficultly soluble in alcohol, easily in glacial acetic acid and almost insoluble in most other organic solvents. It does not contain sulphur and melts at about 330°; yield, 5 g. (Found: N, 20·48. $C_{10}H_{11}O_2N_3$ requires N, 20·48 per cent.).

3-*Keto*-5-*ethoxy*-*dihydro*-1 : 2 : 4-*triazole* (V).—Ethyl carbethoxythiocarbamate (3 g.) was mixed with hydrazine hydrate (1 g.) when there was a considerable development of heat and liberation of sulphuretted hydrogen. The product, at first a liquid, partially

solidified when it was heated on the water-bath from two to three hours, by which time the evolution of sulphuretted hydrogen ceased. The product was next boiled with alcohol and filtered. The filtrate on cooling yielded a white substance, which was crystallised from the same solvent in needles, m. p. 170–172°. It is moderately soluble in cold water and alcohol and excessively so in hot water. It does not contain sulphur (Found: N, 32·11. $C_4H_7O_2N_3$ requires N, 32·5 per cent.). On boiling for a long time with water or for a short time with hydrochloric acid, the ethoxyurazole is hydrolysed to urazole, m. p. 244°.

3-*Keto*-2-*phenyl*-5-*ethoxy*-*dihydro*-1 : 2 : 4-*triazole* (VI).—When phenylhydrazine (2 g.) was added to ethyl carbethoxythiocarbamate (3·5 g.) there was evolution of sulphuretted hydrogen even in the cold. The mixture was then heated on the water-bath under reflux for nearly two hours, by which time the liberation of sulphuretted hydrogen completely ceased, and a solid product was seen to have been formed. It was cooled and filtered on the pump, washed with a little alcohol and crystallised from the least quantity of alcohol in needles, m.p. 150–151°. Yield, 0·5 g. (Found: N, 20·23. $C_{10}H_{11}O_2N_3$ requires N, 20·48 per cent.). It is very soluble in alcohol and water and does not contain sulphur. When heated with hydrochloric acid for a few minutes, it is converted into Pinner's phenylurazole, m. p. 263°.

3-*Keto*-2-*carbothiophenylamino*-5-*ethoxydihydro*-1 : 2 : 4-*triazole* (VII).—On heating 4-phenylthiosemicarbazide (4 g.) with the thiocarbamate (4 g.) under reflux in an oil-bath at 140°, sulphuretted hydrogen was evolved. After three hours' heating the action subsided. The molten mass solidified on cooling when it was triturated with cold alcohol and crystallised twice from the same solvent in glistening white needles, m. p. 246–248°. Yield, 3 g. (Found: N, 20·92. $C_{11}H_{22}O_2N_4S$ requires N, 21·2 per cent.).

3-*Keto*-2-*carbothio*-p-*tolylamino*-5-*ethoxydihydro*-1 : 2 : 4-*triazole* (VIII).—Ethyl carbethoxythiocarbamate was condensed with 4-*p*-tolylthiosemicarbazide just as in the case of 4-phenylthiosemicarbazide, and a product with similar properties melting at 186–187° was obtained. It was however found to be more soluble in alcohol (Found: N, 20·23. $C_{12}H_{14}O_2N_4S$ requires N, 20·14 per cent.).

2-*Di*-p-*tolylamidino*-3-*keto*-5-*ethoxydihydro*-1 : 2 : 4-*triazole* (IX).—Di-*p*-tolylaminoguanidine (2·5 g.) was heated with the thiocarbamate (1·8 g.) without any solvent for about half an hour when the mixture solidified. The solid after filtration and washing with alcohol was crystallised from the same solvent in rectangular plates, m. p. 229–230°. Yield, 2 g. It is soluble in alcohol and in hydrochloric acid (Found: N, 19·75. $C_{19}H_{21}O_2N_5$ requires N, 19·94 per cent.). On heating with

hydrochloric acid for some time, it passed into solution, which yielded on neutralisation with dilute caustic soda solution a solid substance. On crystallisation from alcohol it was obtained in short fine needles, m. p. 256–257° (decomp.).

2-Ethoxy-4 : 6-diketo-3 : 4 : 5 : 6-tetrahydro-1 : 3 : 5-triazine (X).—Urea (1·2 g.) and the thiocarbamate (3·5 g.) were heated together when sulphuretted hydrogen was evolved. After 3–4 hours' heating the molten mass became turbid; when cooled in ice and scratched with a glass rod, a solid separated. This was filtered, washed carefully with alcohol and then crystallised from dilute alcohol in minute white needles, m. p. 171–173°. Yield, 0·9 g. (Found : N, 27·63. $C_5H_7O_3N_3$ requires N, 27·4 per cent.). It is soluble in water and alcohol and is free from sulphur.

2-Ethoxy-4-thio-6-keto-3 : 4 : 5 : 6-tetrahydro-1 : 3 : 5-triazine (XI).—Thiourea (1·5 g.) dissolved in the least quantity of water and a few drops of alcohol was heated with the thiocarbamate (3·5 g.) till sulphuretted hydrogen was no longer liberated. The pasty liquid, on cooling and scratching with a glass rod, gave rise to a small amount of a white solid, which crystallised from alcohol. The product shrinks at 110° and melts at 150°. Repeated crystallisation did not alter the m. p. It is soluble in water and alcohol. Yield, 0·5 g. (Found : N, 24·14. $C_5H_7O_2N_3S$ requires N, 24·2 per cent.).

Reaction with Aniline : Formation of Diphenylurea (XII).—Ethyl carbethoxythiocarbamate (3 g.) was heated with aniline (1·5 g.) under reflux for an hour, when there was effervescence with the liberation of a gas smelling of mercaptans. The flask was cooled when white crystals were found to have been formed, which were filtered on the pump, washed with benzene, dried and crystallised from absolute alcohol in white glistening needles, m. p. 235° (Found : N, 13·29. $C_{13}H_{12}ON_2$ requires N, 13·25 per cent.). The substance was proved to be diphenylurea by taking its mixed m. p. with an authentic sample prepared from urea and aniline (Baeyer, *Annalen*, 1864, **131**, 252).

Reaction with p-*Toluidine : Formation of Di*-p-*tolylurea* (XIII).—Ethyl carbethoxythiocarbamate was condensed with *p*-toluidine when a white product was obtained; m. p. 270° (Found : C, 74·83; H, 6·3; N, 11·71. $C_{15}H_{16}ON_2$ requires C, 75·0; H, 6·7; N, 11·7 per cent.).

Reaction with o-*Toluidine* (XIV).—o-Toluidine in a like manner gave the corresponding di-*o*-tolylurea as white crystalline needles from alcohol, m. p. 246–247° (Found : N, 11·8. $C_{15}H_{16}ON_2$ requires N, 11·7 per cent.).

Reaction with α- and β-Naphthylamines : Formation of (XV) *and* (XVI).—When a mixture of ethyl carbethoxythiocarbamate (2 g.) and

α-naphthylamine (3 g.) was heated at 160°, there was effervescence. The heating was continued for an hour during which time the reaction was complete and the molten product was found to have become solid. A small quantity of the adhering tarry product was removed by triturating it several times with benzene and hot alcohol and it was finally crystallised from glacial acetic acid; m. p. 295–296° (Found : N, 8·9. $C_{21}H_{16}ON_2$ requires N, 8·97 per cent.).

Similarly, with β-naphthylamine the corresponding di-β-naphthylurea was obtained crystallising from glacial acetic acid in needles, m. p. 309–310°.

As there seems to be considerable difference in the melting points ascribed to $\alpha\alpha'$-dinaphthylurea [Delbos, *Annalen*, 1847, **64**, 370; Zinnin, *Annalen*, 1859, **108**, 229; Schiff, *Ber.*, 1879, **12**, 385; Huhn, *Ber.*, 1885, **19**, 2405 (m. p. 270°); Young, *J. Chem. Soc.*, 1897, **71**, 1201 (284–286°); Vittenet, *Bull. Soc. Chim.*, 1874, **21**, 950 (314–315°); Walther and Wldkowski, *J. pr. Chem.*, 1898, **59**, 278 (295–296°)] as also in those of the corresponding $\beta\beta'$-compound [Huhn (293°); Walther and Wldkowski (300°); Young, *J. pr. Chem.*, 1899, **60**, 256 (289–290°); Vittenet (309–310°); Ekstrand, *Ber.*, 1887, **20**, 1360 (286°)], these two compounds were prepared by two different methods, namely, those of Vittenet and of Young. The products obtained were carefully freed from adhering impurities and were repeatedly crystallised from glacial acetic acid. The α-compound obtained by either method melted at 295–296° and the β-compound at 309–310°. The mixed m. p. of these substances taken with the corresponding substances prepared by our method from the thiocarbamate showed no lowering.

Reaction with Benzidine: *Formation of Carbonylbenzidine* (XVII). —The thiocarbamate (1 mol.) was heated with benzidine (mol. and a little more) when after a time a solid separated, which was filtered, washed with alcohol and dried. It is very sparingly soluble in alcohol and acetic acid and is insoluble in all other common organic solvents. Hence, the substance could not be crystallised. It becomes brown at 250° and blackens at about 300°. Yield, 3 g. (Found : N, 13·85. $C_{13}H_{10}ON_2$ requires N, 13·33 per cent.). This compound was prepared by Michler and Zimmermann (*Ber.*, 1881, **14**, 2178) by the action of phosgene on benzidine and properties similar to those of our compound were attributed by them to it.

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Department of Organic Chemistry,
Indian Institute of Science,
Bangalore.

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