711. *Studies with Dithizone. Part V.* A Comparison of Routes for the Synthesis of [^{35}S]Dithizones.*

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Of various routes for the synthesis of [^{35}S]dithizones, the action of alkali hydrogen sulphide on 1 : 5-diaryl-3-chloroformazans † shows most promise. The action of bromine (one or more equivalents) on 1 : 5-diphenylformazan gives 3-bromo-1 : 5-di-*p*-bromophenylformazan, also obtained by the bromination of the di-*p*-bromophenylformazan. Di-*p*-bromophenylthiocarbazone ("dibromodithizone") has been prepared by two routes, purified, and characterised.

Studies of the physical chemistry of partition equilibria governing the extraction of traces of metals with diphenylthiocarbazone (III; "dithizone," HDz) have led us to consider the synthesis of this reagent "labelled" with a radioactive isotope (Irving, Bell, and Williams, *J.*, 1952, 357). This would facilitate its determination in either the aqueous or the organic phase whether present as the ion Dz^-, the undissociated molecule HDz, or as complexes $[MDz_m]^{n-m+}$ with an *n*-valent metal. Difficulties and limitations imposed by the customary absorptiometric determination of dithizone might thus be circumvented. In such work a prime consideration is to design the synthesis so as to minimise radiation hazards and to conserve valuable radioactive material. Since in the present paper we restrict ourselves to the introduction of radioactive sulphur, speed of working is of secondary importance and our conclusions would apply analogously to syntheses involving radiocarbon.

Three main synthetic routes to dithizone are available. The first (Fischer, *Annalen*, 1878, **190**, 120) involves the preparation of the phenylhydrazinium salt of β-phenylthiocarbazic acid (I) from phenylhydrazine and carbon disulphide, elimination of hydrogen sulphide by heating, and oxidation of the resulting diphenylthiocarbazide (II). The preparation of the salt (I) is practically quantitative and radio-sulphur could readily be introduced at this stage by use of $C^{35}S_2$; but in stage (I) to (II) half the activity would be lost in volatile products and although these can be recovered the thermal decomposition is not easy to control. The oxidation stage (II) to (III) as usually carried out with methyl-alcoholic potash involves self-oxidation and reduction in which only 25% at most of the original activity is retained. Although overall yields (based on the weight of phenylhydrazine taken) of 50—64% of crude dithizone have been claimed (*Org. Synth.*, **25**,

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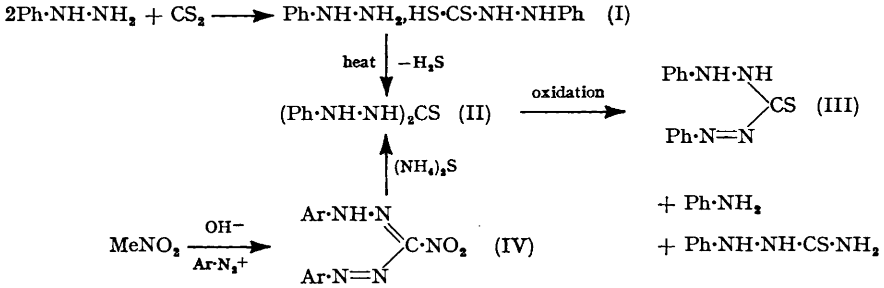
* Part III, *J.*, 1952, 356, Part IV, *J.*, 1952, 1216.

† The nomenclature is based on the Beilstein name "formazan" for $H\overset{1}{N}{:}\overset{2}{N}{\cdot}\overset{3}{C}H{:}\overset{4}{N}{\cdot}\overset{5}{N}H_2$, numbered as shown.—Ed.

p. 28), the further stages of purification needed to prepare a sample suitable for spectrophotometric measurements (cf. Cooper and Sullivan, *Analyt. Chem.*, 1949, **23**, 613; Coope and Kofron, *ibid.*, 1947, **21**, 1135; Sandell, "Colorimetric Determination of Traces of Metals," New York, 1950) may further reduce the yield by a factor of at least 10. We have attempted unsuccessfully to improve the yield in stage (II) to (III) by using other oxidising agents such as mercuric oxide or lead tetra-acetate in glacial acetic acid, and hydrogen peroxide under a variety of conditions.



A second route to dithizone, of special value for the synthesis of its analogues (Hubbard and Scott, *J. Amer. Chem. Soc.*, 1943, **65**, 2390; Oesper and Klingenberg, *J. Org. Chem.*, 1948, **13**, 309), starts with the preparation of a 1 : 5-diaryl-3-nitroformazan * (IV) by coupling an aryldiazonium salt with an alkaline solution of nitromethane. The reduction stage (IV) to (II) is carried out in rather variable yield by using an excess of ammonium sulphide (Bamberger, Padova, and Ormerod, *Annalen*, 1925, **446**, 260), and the final oxidation stage (II) to (III) is identical with Fischer's synthesis. Hubbard and Scott (*loc. cit.*) claim to have obtained 0·2 g. of purified di-β-naphthylthiocarbazone (as III) from 1 g. of the corresponding 1 : 5-diaryl-3-nitroformazan (as IV), but Coope and Kofron (*loc. cit.*), starting with 0·1 g. of material thus purified, found further purification necessary to get a product suitable for spectrophotometric work, their final yield being only 12 mg. From 1 g. of pure 1 : 5-di-*p*-bromophenyl-3-nitroformazan (as IV) we were unable to prepare more than 54 mg. of di-*p*-bromophenylthiocarbazone (as III) pure enough for spectrophotometry. Though more versatile than Fischer's synthesis, that of Bamberger *et al.* appears to present few advantages when over-all yields and general convenience are considered.

The third route exploits the reactivity of an ω-halogen atom in Ar·NH·N:CX·, and in the preparation of 3-bromo-1 : 5-diphenylformazan (IX; X = Br, Ar = Ph) for this purpose (see p. 3540) we were anticipated by Fusco and Romani (*Gazzetta*, 1946, **76**, 419, 439), who obtained dithizone by treating (IX; X = Cl, Ar′ = Ph) with sodium hydrogen sulphide, although full details are unknown. The necessary 3-chloroformazan is obtained by coupling a diazonium solution with dipotassium chloromalonate (VI; R = K), prepared from the chloro-ester (VI; R = Et) which results from the action of sulphuryl chloride on diethyl malonate (V; R = Et). Improvements in detail have enabled us to prepare the desired 3-chloro-1 : 5-diphenylformazan (as IX) pure and in good over-all yield. ω-Chlorodi-β-naphthylformazan (IX; X = Cl, Ar = β-$C_{10}H_7$), obtained similarly, formed a brown crystalline solid of constant m. p. 206—207° after only two recrystallizations from glacial acetic acid.

The conversion of 3-halogenoformazans into dithizones was investigated under a variety of conditions, 10 mg. of chlorodiphenylformazan being used in each case. The yield of pure product was determined by the absorptiometric method described on p. 3541. Typical results were:

Experimental conditions	Temp.	Yield, %
10 Min.' refluxing with excess of NaHS	78°	14·3, 12·0
10 Min.' mechanical shaking with excess of NaHS	18	39·8, 33·3
10 Min.' mechanical shaking with 1 equiv. of NaHS	18	8·4, 11·0

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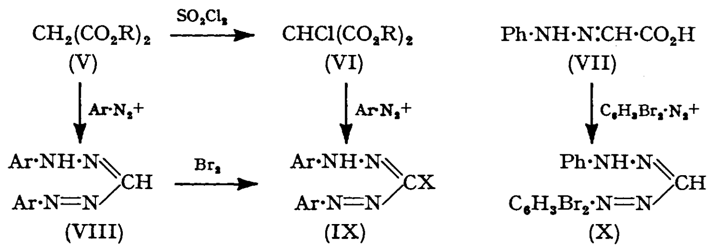
* See footnote on p. 3538 for nomenclature.

To avoid the troublesome preparation of the chlorodiphenylformazan, attempts were made to prepare the bromo-compound * (IX; X = Br, Ar = Ph) by direct bromination



of 1 : 5-diphenylformazan (VIII; Ar = Ph) which is readily prepared from malonic acid (V; R = H) and benzenediazonium chloride (Bamberger and Wheelwright, *Ber.*, 1892, **25**, 3201; von Pechmann and Runge, *Ber.*, 1894, **27**, 2920). With 1 equiv. of bromine the product was a tribromodiphenylformazan, m. p. 214—215°. This was obtained in better yield when 3 equivs. of bromine were used, but all attempts to prepare a less highly substituted product failed. The presence of a reactive 3-bromine atom was established by the ready reaction with sodium hydrogen sulphide to give a thiol closely resembling dithizone.

Phenylhydrazones of aromatic aldehydes generally brominate in the ω-position and in positions *ortho*- and *para*- to the nitrogen of the phenylhydrazine residue (cf. Chattaway, *J.*, 1930, 157), but the tribromodiphenylformazan was shown not to be identical with 3-bromo-1-(2 : 4-dibromophenyl)-5-phenylformazan prepared by the action of bromine on the 1-(2 : 4-dibromophenyl)-5-phenylformazan (X) obtained by the action of 2 : 4-dibromobenzenediazonium chloride on the phenylhydrazone (VII) of glyoxylic acid. Reduction of the tribromodiphenylformazan with stannous chloride in concentrated hydrochloric acid gave *p*-bromoaniline as the sole product and the formulation as 3-bromo-1 : 5-di-*p*-bromophenylformazan (IX; X = Br, Ar = *p*-C_6H_4Br) was established by its identity with the 3-bromination product of di-*p*-bromophenylformazan (VIII; Ar = *p*-C_6H_4Br), obtained by the action of *p*-bromobenzenediazonium chloride upon malonic acid.

The reactive halogen atom of 3-bromo-1 : 5-di-*p*-bromophenylformazan was readily replaced on 15 min.' refluxing in ethanol containing an equivalent amount of sodium hydrogen sulphide. Some reduction to the corresponding thiocarbazide occurred, but the expected di-*p*-bromophenylthiocarbazone (" dibromodithizone," as IX; X = SH, Ar = *p*-C_6H_4Br) was readily obtained by aerial oxidation and isolated after acidification as a blue-black solid, m. p. 145—147°. It closely resembles dithizone in its reactions, dissolving in ammonia or aqueous alkalis to give orange solutions and in organic solvents to give green solutions which give coloured complexes when shaken with aqueous solutions of zinc, lead, mercury, or silver. In carbon tetrachloride the absorption spectrum shows a principal maximum at 629 mμ ($\varepsilon = 30{,}600$) and a subsidiary maximum at 452 mμ. It closely resembles that of dithizone with maxima at 635 mμ ($\varepsilon = 32{,}500$) and 462 mμ. The expected similarity to dithizone throws doubt on the " dibromodithizone " prepared by Hubbard and Scott (*loc. cit.*) by reduction of 1 : 5-di-*p*-bromophenyl-3-nitroformazan (as IV) and described as a solid, m. p. 125°, like di-β-naphthylthiocarbazone insoluble in aqueous ammonia, and " possessing low tinctorial power." We have repeated Hubbard and Scott's preparation with some improvements in detail and obtained from 1 g. of the nitrophenylformazan 54 mg. of pure di-*p*-bromophenyldithiocarbazone identical in m. p. and absorption spectrum with the authentic specimen obtained from 3-bromo-1 : 5-di-*p*-bromophenylformazan.

Although the molecular extinction coefficient of dithizone or its analogues can be obtained directly by measuring the absorbancy of a suitably dilute solution of known concentration, yet any impurities in the sample will lead to spurious low values since the diarylthiocarbazones absorb more strongly in the visual region than their oxidation pro-

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* In agreement with Fusco and Romani (*loc. cit.*, p. 429) we find that the action of an aryldiazonium solution on bromomalonic acid gives a halogen-free product.

ducts or structurally related substances. However, the mercury complexes are found to have negligible absorption at the long-wave maximum of the corresponding reagent, so that the absorbancy at this wave-length of a mixture of metal complex and free dithizone serves as a measure of the latter. Thus, if the initial absorbancy A_0 of v ml. of a dithizone solution of concentration c moles/l. is reduced to A_x after x μg. of mercuric ions (a deficiency) have been made to react quantitatively with it to give the complex of formula $HgDz_2$ (cf. Irving, Andrew, and Risdon, *J.*, 1949, 541), we have

$$A_0 = \varepsilon cl; \quad \varepsilon = 10^5vl(A_0 - A_x)/x \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and

$$c = A_0x/10^5vl(A_0 - A_x) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where l is the length of the optical cell used and ε is the molecular extinction coefficient of dithizone at the wave-length used. A linear plot of A_x against x for various amounts of mercury is used to obtain the slope $(A_0 - A_x)/x$, whence the extinction coefficient ε is calculated by equation (1). This procedure has been used for dithizone itself (Cooper and Sullivan, *loc. cit.*) but is capable of wider application. Conversely, knowing A_0, A_x, and x, we can determine the weight of pure dithizone in a solution of known volume from equation (2) without the need for the extensive purification and direct weighing of microgram samples. In this way the amount of pure material in samples which had been subjected to several stages of purification by extraction or crystallization could be determined, and typical overall yields are quoted below.

Dithiocarbazone formed	Starting material	Yield, %
Phenyl	3-Chloroformazan	39·8, 33·3
p-Bromophenyl	3-Bromoformazan	3·9
	Nitroformazan	5·6
β-Naphthyl	3-Chloroformazan	2·8
	Nitroformazan	2·5 [a]

[a] Following Scott and Hubbard (*loc. cit.*) and Coope and Kofron (*loc. cit.*). Percentages refer to spectrophotometrically pure material.

The direct synthesis of diarylthiocarbazides from thiocarbonyl chloride and phenylhydrazine (Heller, *Annalen*, 1891, **263**, 269) or bromo- or nitro-phenylhydrazines (Dyson, *J.*, 1937, 1358) eliminates the thermal decomposition stage (I) to (II) of Fischer's synthesis but the yields have not been investigated, since the preparation of $C^{35}S_2Cl_2$ would be exceedingly troublesome. All the syntheses proposed hitherto involve a stage of oxidation from thiocarbazide to thiocarbazone. Poor yields can generally be traced to loss of material or the introduction of by-products removable only with difficulty at this point. A direct synthesis from phenylthiosemicarbazide and nitrosobenzene failed. The most promising route to [^{35}S]diarylthiocarbazones appears to be through the 1 : 5-diaryl-3-chloroformazan, though, save for the diphenyl compound, the yields are poor. A practical disadvantage in the use of [^{35}S]dithizone is the weakness of the β-rays emitted which preclude the use of liquid counting.

EXPERIMENTAL

Preparation of 3-*Bromo*-1 : 5-*di*-p-*bromophenylformazan* ("*Tribromodiphenylformazan*") (as IX; X = Br, Ar = *p*-C_6H_4Br).—(a) *By bromination of diphenylformazan.* Diphenylformazan (as VIII) (4·5 g., 1 mol.) in glacial acetic acid (25 ml.) was treated gradually with bromine (9·6 g., 2 mols.) in the cold. The mixture became warm and 3-*bromo*-1 : 5-*di*-p-*bromophenylformazan* separated immediately as a black solid. It was collected, washed with cold ethanol, and air-dried; after two recrystallizations from aqueous dioxan it formed minute orange crystals, m. p. 214—215° (Found : C, 33·6; H, 2·0; Br, 52·7; N, 12·1. $C_{13}H_9N_4Br_3$ requires C, 33·9; H, 2·0; Br, 52·0; N, 12·2%). A solution in concentrated hydrochloric acid (1 g. in 10 ml.) was boiled with stannous chloride (2 g.) till colourless. After the mixture had been made alkaline, *p*-bromoaniline was distilled in steam. The acetyl derivative (m. p. 167—168·5°; from water) and the benzoyl derivative (m. p. 202—203°) did not depress the m. p.s of authentic specimens.

(b) *By* ω-*bromination of* 1 : 5-*di*-p-*bromophenylformazan.* When a diazonium solution prepared from *p*-bromoaniline (35 g.) was added to a cooled aqueous solution of malonic acid (10·4 g.), 1 : 5-di-*p*-bromophenylformazan (as VIII; Ar = *p*-C_6H_4Br) separated as a dark red solid, which was collected, dried, and recrystallized from aqueous dioxan (Found: N, 14·8; Br, 42·3. Calc. for $C_{13}H_{10}N_4Br_2$: N, 14·7; Br, 41·9%). The m. p. of our product, 177—178°, is much higher than that of Busch and Wolbring's preparation (114—115°; from aqueous acetic acid; *J. pr. Chem.*, 1905, **71**, 366). This may be due to polymorphism which is not uncommon among derivatives of diphenylformazan, although Hunter and Roberts (*J.*, 1941, 820) showed that for many cases of alleged "isomerism" in this series, differences of physical properties could usually be attributed to different degrees of purification. Complete elimination of the tarry by-products which have a profound influence on the m. p. is more readily effected with aqueous dioxan mixtures than with aqueous acetic acid mixtures.

When a solution of di-*p*-bromophenylformazan in glacial acetic acid was treated with bromine (1 equiv.) in the cold, 3-bromo-1 : 5-di-*p*-bromophenylformazan separated as a dark brown solid which after two recrystallizations from aqueous dioxan melted at 213—214° and did not depress the m. p. of the "tribromodiphenylformazan" described above.

Preparation of 1-(2 : 4-*Dibromophenyl*)-5-*phenylformazan* (X).—(i) The phenylhydrazone of glyoxylic acid (prepared by electrolytic reduction of a saturated aqueous solution of oxalic acid: cf. Tafel and Friedrichs, *Ber.*, 1900, **33**, 2209; 1904, **37**, 3188) had m. p. 136° (from aqueous ethanol) (Busch and Meussdörffer, *J. pr. Chem.*, 1907, **75**, 121 report 137°). This phenylhydrazone (VII; 2·25 g.) in water (50 ml.) containing sodium hydroxide (2 g.) was treated at 0° with a diazonium solution prepared from 2 : 4-dibromoaniline (3·94 g., 1 equiv.). 1-(2 : 4-*Dibromophenyl*)-5-*phenylformazan* (X), which separated, formed orange-red crystals, m. p. 198—200° after several crystallisations from benzene–acetone (Found: N, 14·6; Br, 41·7. $C_{13}H_{10}N_4Br_2$ requires N, 14·7; Br, 41·9%).

Bromination of (X) gave a product, m. p. 270°, which was not identical with the tribromination product from diphenylformazan. Owing to its insolubility in common solvents, this compound was not further investigated.

Preparation of 1 : 5-*Diaryl*-3-*chloroformazans*.—Diethyl malonate (50 g.) and sulphuryl chloride (45·6 g.) were heated under reflux for 1 hr. Fractionation gave diethyl chloromalonate (VI; R = Et), b. p. 113°/10 mm. This chloro-ester (25 g.) in ethyl alcohol (30 ml.) was treated in the cold with a solution of potassium hydroxide (16·6 g.) in ethyl alcohol (70 ml.). Potassium chloromalonate (VI; R = K) rapidly separated. It was collected and washed well with alcohol, and all traces of solvent were removed by keeping the solid salt under vacuum for several days. Potassium chloromalonate (22 g.) in water (100 ml.) containing sodium acetate (40 g.) was treated at 0° (mechanical stirrer) with a diazonium solution prepared from 27 g. of aniline hydrochloride. A dark red, granular precipitate slowly separated, and after being kept overnight this was collected and dried. Recrystallization from ethanol gave 3-chloro-1 : 5-diphenylformazan as dark red needles, m. p. 150—151° (Fusco and Romani, *loc. cit.*, report 153°). Complete removal of alcohol from the potassium chloromalonate before coupling increased the yield by reducing the amount of tarry by-products obtained when Fusco and Romani's preparative details are followed.

3-Chloro-1 : 5-di-β-naphthylformazan (25 g., 70%) was prepared similarly from potassium chloromalonate (21·4 g.) and a diazonium solution from β-naphthylamine (31·5 g.). It formed dark brown crystals, m. p. 206—207°, from acetic acid (Fusco and Romani give 213—214°).

Preparation of Di-p-*bromophenylthiocarbazone*.—(a) *From* 3-*bromo*-1 : 5-*di*-p-*bromophenylformazan*. A solution of sodium hydrogen sulphide, prepared by saturating a solution of sodium (0·023 g.) in ethyl alcohol (10 ml.) with dry hydrogen sulphide, was refluxed for 15 min. with "tribromodiphenylformazan" (0·46 g.). The initial orange colour became pale green, and after the mixture had cooled air was drawn through it until the rapid colour change to deep orange indicated the formation of the sodium salt of the expected thiocarbazone. On addition of excess of dilute hydrochloric acid di-*p*-bromophenylthiocarbazone separated as an almost black solid. The crude material (0·5 g.) was dissolved in carbon tetrachloride (50 ml.) and shaken with a mixture of ammonia (*d* 0·88; 50 ml.) and doubly-distilled water (450 ml.). Most of the dibromodithizone passed into the aqueous phase as the orange-coloured ion. The organic phase was rejected, and the aqueous solution washed with three successive portions of carbon tetrachloride (20 ml.). The aqueous extract was then kept at 0—5° while being cautiously made acid, and the dibromodithizone which then separated was dissolved in pure chloroform (20—30 ml.) and transferred to a beaker placed in a vacuum desiccator which contained calcium chloride and a small heating coil. The latter was used to maintain a temperature of about 25° while the solvent was evaporated under greatly reduced pressure. Completely dry *di*-p-*bromophenylthiocarbazone* which remained could be further purified by dissolving it in a small volume of pure chloroform and adding light petroleum. It formed bluish-black crystals with a coppery reflex, m. p. 145—147° (Found: C, 37·5; H, 2·5; Br, 38·7. $C_{13}H_{10}N_4Br_2S$ requires C, 37·7; H, 2·4; Br, 38·6%).

(b) *From* 1 : 5-*di*-p-*bromophenyl*-3-*nitroformazan*.—The 1 : 5-diarylnitroformazan (1 g., m. p. 156—158°; cf. Hubbard and Scott, *loc. cit.*) was suspended in ethyl alcohol (25 ml.) and saturated alternately with ammonia and hydrogen sulphide until the completion of the reduction was shown by the change of colour from red to yellow and by the disappearance of particles of starting material. No attempt was made to isolate the product, but 10 ml. of 5% alcoholic potassium hydroxide were added, and the mixture heated for a few minutes, a deep orange colour then being seen. The mixture was cooled and acidified; dibromodithizone separated and was purified as previously described. The yield of pure material, m. p. 146—148°, was 0·056 g.

The Molecular Extinction Coefficient of Di-p-*bromophenylthiocarbazone*.—10 ml. of a dilute solution of the purest dibromodithizone available (~6·5 mg./l.) in carbon tetrachloride were equilibrated with 10 ml. of a solution of x μg. of mercuric ion in 0·1N-sulphuric acid. The absorbancy (1-cm. cell) at 635 mμ was measured with a Beckman Model DU spectrophotometer. For the linear plot of absorbancy against x a slope of 0·0306 per μg. of Hg^{++} was found, whence $\varepsilon = 30,600$. This checks absolutely with the value calculated from the absorbancy (0·825) of a solution in carbon tetrachloride containing 11·16 mg./l. In this solvent $\lambda_{\text{min.}} = 525$ mμ ($\varepsilon_{\text{min.}} = 7,200$) and the subsidiary $\lambda_{\text{max.}} = 463$ mμ ($\varepsilon = 20,030$).

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