170. *The Preparation of Some* cis-*Azo-compounds.*

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The isolation of *cis*-azobenzene by chromatographic analysis of an irradiated solution of the *trans*-form in petroleum on aluminium oxide is described. Other azo-compounds are shown to form unimolecular isomerides, to which is ascribed a *cis*-configuration. Those which have been isolated are relatively less stable than *cis*-azobenzene, but are separated from the normal form with remarkable ease on the chromatographic column. Attention is drawn to apparent marked differences in lability among closely related azo-compounds and to the insufficiency of existing conceptions and data to account for these differences.

G. S. Hartley has recently announced (*Nature*, 1937, **140**, 281; this vol., p. 633) the isolation of *cis*-azobenzene and the photometric detection of isomerides of some 4-substitued azobenzenes. The present communication on the preparation of several azo-compounds in the *cis*-form was deemed advisable while the work is still admittedly incomplete in order to avoid duplication of results.

The recognition of a *cis*-form of azobenzene analogous to maleic as compared with fumaric acid was, as in the work of Hartley, largely fortuitous and prompted by the observation that many azo-dyes, when submitted to chromatographic analysis, exhibit a serious departure from the normal chromatographic rule according to which a single compound should give only one adsorption band. This behaviour is not limited to azo-compounds, but is shown by dyes of other classes (Ruggli and Jensen, *Helv. Chim. Acta*, 1935, **18**, 624), anthocyanines (Karrer and Strong, *ibid.*, 1936, **19**, 25), etc., and must be generally ascribed at least in part to factors such as varying dispersion of the pigments as well as the possible presence of small amounts of isomeric compounds in the purest commercial dyes.

On investigating this abnormality more closely among the azo-compounds, however, it was noticed that some relatively complex representatives (*e. g.*, azophenols) were chromatographically homogeneous, but an old specimen of " purest " azobenzene, when adsorbed on activated aluminium oxide from petroleum solution, gave a broad diffuse zone in the lower part of the column with a very narrow, sharply defined band of more strongly adsorbed material. The weakly adsorbed component, constituting the bulk of the azobenzene, behaved normally on being washed through the column and immediately readsorbed, giving only the single diffuse zone. The narrow band again appeared, however, if either the solution or the recovered solid was kept in ordinary diffuse light for a few days. By irradiating the solution before a mercury lamp, a considerable proportion of the initial azobenzene was converted, with darkening of the colour of the solution, into more strongly adsorbed material, which was eluted with petroleum–methanol and obtained at once as orange-red crystals, m. p. 71°, from cold petroleum. By performing the irradiation and chromatographic separation in absence of any considerable amounts of air it was shown that the phenomenon is associated only with irradiation and not with oxygenation (the presence of small amounts of azoxy-compounds has in the past led to unsubstantiated claims to have isolated isomeric azo-compounds; cf. H. Hartley and Stuart, J., 1914, **105**, 309). The new compound, which is identical (m. p. and mixed m. p.) with G. S. Hartley's *cis*-azobenzene prepared by a more tedious selective extraction procedure, is deeper in colour both in the solid and in the dissolved state than normal azobenzene, with which it gives large depressions in m. p. (mixed m. p. 35—45°), but reverts to the normal form very slowly at the ordinary temperature, more rapidly when fused, and partly when irradiated. [H. Hartley and Stuart (*loc. cit.*) and also C. V. and R. A. Gortner (*J. Amer. Chem. Soc.*, 1910, **32**, 1294) remark on the deep red colour of their supposed *cis*-isomeride, so it is possible that their product was substantially *cis*-azobenzene contaminated with oxygenated compounds.] Obviously an equilibrium is set up by irradiation, the chromatographic behaviour of normal and the new azobenzene being indistinguishable after a further period of irradiation. Cryoscopic molecular-weight determination in benzene showed the latter form to be unimolecular and therefore truly stereoisomeric with normal azobenzene. (Each of the *cis*-compounds described in this paper could be recovered unchanged when the solution in benzene was evaporated in a vacuum at room temperature after standing for moderate periods, so the possibility of the recorded molecular weights referring to re-formed *trans*-compound is excluded.) Both forms were catalytically reduced to hydrazobenzene, which was reoxidised to the normal form. Although the conditions and nature of the reduction made a quantitative comparison of the rates of reduction somewhat difficult, it seems that under the comparable conditions employed there is little difference between them. Addition compounds of azobenzene and other azo-compounds with polynitro-compounds (trinitrobenzene, trinitrotoluene, styphnic acid, with *cis*- and *trans*-azobenzene, benzeneazo-*p*-toluene, *pp'*-azotoluene, *p*-cyanoazobenzene, from alcoholic solution) did not prove suitable for characterising these stereoisomerides, nor did trustworthy evidence of their formation present itself (cf. Hoffmann and Kirmreuther, *Ber.*, 1910, **43**, 1767).

These early results suggested that the photochemical formation of *cis*-azo-compounds of considerable stability might be a general phenomenon, but at once anomalies appeared which only further work can explain. Thus with the combined irradiation–chromatographic technique a cis-*benzeneazo*-p-*toluene* (the *cis*-configuration in this and the other cases is assigned, in absence of physical evidence, by analogy with azobenzene and on the basis of molecular-weight determinations) was obtained resembling the lower homologue in its relation to the *trans*-isomer. Similarly *pp'*-azotoluene yielded a cis-pp'-*azotoluene*. In these instances and in all other cases where a *cis*-isomer which was sufficiently stable to be obtained substantially free from the *trans*-compound was observed, the solution became perceptibly darker on irradiation; the above substituted azobenzenes were markedly less stable in the *cis*-modification than the unsubstituted compound and readily reverted (in the case of *pp'*-azotoluene after only once melting at 100°) to the stable forms. With *oo'*- and *mm'*-azotoluenes neither the characteristic deepening in colour on irradiation nor the sharp separation of any isomeride on the chromatographic column could be observed and it seems clear that either *cis*-isomerisation does not take place or the isomeride is too labile to admit of isolation. Both of the above alkyl-substituted *cis*-azobenzenes were unimolecular in benzene solution, so simple polymorphism cannot account for the isomerism (cf. Schaum, Schaeling and Klausing, *Annalen*, 1916, **411**, 191). No evidence that benzeneazo-α-naphthalene, αα′- or ββ′-azonaphthalene forms a stable *cis*-isomeride in the same way has yet been obtained.

A number of 4-substituted azobenzenes which are all presumably *trans* in configuration have been subjected to a preliminary examination of their ability to form *cis*-isomerides of sufficient stability to allow of their separation. 4-Hydroxy-, 4-acetoxy-, 4-amino- and 4-acetamido-azobenzenes, when irradiated in benzene or petroleum solution and subsequently chromatographically adsorbed on alumina, furnished some evidence, in the form of an indefinite " tailing " of the main zone or the development of subsidiary zones, of the transient formation of *cis*-isomerides, but in each case only the normal *trans*-modification was recovered. Alkylation of the *p*-hydroxyl group resulted in increased stability of the *cis*-modification, so that methyl and *ethyl* ethers of *cis-p*-benzeneazophenol could be obtained. Solidification of the pure *cis*-forms has not yet been effected, as reversion to the *trans*-forms is rapid and is complete within two days at the ordinary temperature in absence of light, the initially chromatographically homogeneous, deep red oils then solidifying to orange crystalline masses of the *trans*-compounds. *p*-Chloroazobenzene is rather more stable in the *cis*-form, but with substitution of cyanogen for the chlorine all stability apparently disappears and no *cis-p*-benzeneazobenzonitrile has been obtained.

It is clear that the possibility of intermediate quinonoid structures, which might account in part for the permanence of the *trans*-form in benzeneazophenol and *p*-aminoazobenzene, cannot explain the varying behaviour of other 4-substituted azobenzenes and azohydrocarbons.

The ease or impossibility of chromatographic separation of *cis-trans* azo-mixtures does not appear to be influenced to a practical extent by the nature of the aluminium oxide adsorbent. Mild deactivation by washing with water, removal of alkali by washing with phenol or acetic acid solution, or activation by treatment with lime-water (cf. Franck, *Arch. Pharm.*, 1937, 131) did not affect the properties of the separated *cis*-isomerides, although the amount of adsorbent necessarily varied. When adsorbents of even moderate activity were used, the separation from petroleum solution was always remarkably sharp in the sense that the whole of the *trans*-isomeride could usually be washed through the column while the *cis*-zone either remained stationary in the upper part of the column or moved only very slowly down. Chromatographic analysis thus seems to be generally applicable to the separation of *cis-trans* isomerides in the azo-series.

The isomerisation of β-carotene by alumina and the chromatographic isolation of the resulting *ψ*-α-carotene has been effected by Gillam and el Ridi (*Nature*, 1935, **136**, 914; *Biochem. J.*, 1936, **30**, 1735) and the detection of the spontaneous isomerisation of lycopene by its altered chromatogram was noted by Zechmeister and Tuzson (*Nature*, 1938, **141**, 249). In the polyene series the possibility of *cis-trans* isomerism about one or more ethylene linkages is accompanied by the possibility of transposition of the conjugated double bonds. However, there is clearly a similarity between the polyene isomerides and the nitrogenous compounds described in the present communication. It is noteworthy that, though the azo-compounds appear to yield more labile isomerides than olefins, the difference in adsorption affinity caused by the altered configuration of the aromatic nuclei about the azo-group is so great that chromatographic separations of *cis*- and *trans*-azo-compounds are probably at once the simplest and most complete separations of closely related compounds to be effected by this means.

Further work to investigate the generality of this phenomenon (*e. g.*, among azo-dyes) and the chemical properties of *cis*-azo-compounds, and to elucidate the factors influencing the lability of azo-compounds in this respect is in progress.

EXPERIMENTAL.

All the following azo-compounds were purified chromatographically before irradiation by filtration of a dilute (1%) solution in light petroleum through Merck's " Aluminiumoxyd standardisiert nach Brockmann " and recovery of the azo-compound either directly from the filtrate or by elution of the main adsorption zone with petroleum containing 1% of methanol. The irradiation and chromatographic analysis were carried out in each case, except where otherwise stated, in an atmosphere of nitrogen.

cis-*Azobenzene.*—1 G. of *trans*-azobenzene in 50 c.c. of light petroleum was irradiated at a distance of 12—15″ from an unshielded quartz mercury vapour lamp for 30 minutes. The solution, which had become red, was filtered through a column (20 cm.; 2 cm. internal diameter) of Merck's alumina, which was then washed with 100 c.c. of petroleum. All unchanged *trans*-compound was washed through the column, but *cis*-azobenzene remained adsorbed in a very sharp zone 4 cm. in length, beginning at 1 cm. from the upper end of the column. The adsorbed material was eluted from this zone with 150 c.c. of light petroleum containing 1% of methanol, the petroleum filtered and, after removal of methanol by washing with water, dried over sodium sulphate and evaporated in a vacuum below 22°. The crystalline material obtained was recrystallised from a little cold petroleum, giving orange-red plates, m. p. 71°, mixed m. p. with *trans*-azobenzene, 35—45° (Found: C, 79·2; H, 5·65; N, 15·2; *M*, cryoscopic in benzene, 175. Calc. for $C_{12}H_{10}N_2$: C, 79·1; H, 5·5; N, 15·4%; *M*, 182).

Reduction of cis- *and* trans-*Azobenzenes.*—2·00 Mg. of platinum oxide (Adams's catalyst) were suspended in 1 c.c. of alcohol in a Barcroft respirometer so arranged that, when reduction of the catalyst was completed, 2·00 mg. of azobenzene could be brought into contact with the catalyst and reduced. The compensating flask of the apparatus was charged in the same way except that the azobenzene was omitted. The results show that there is no very considerable difference under these conditions in the rates of hydrogenation of the isomers and that reduction proceeds beyond the hydrazo-stage, although there is no difficulty in recognising the completion of the primary rapid reduction.

2·00 Mg. of azo-compound in 0·5 c.c. of alcohol + 2·00 mg. of Adams's catalyst suspended in 1 c.c. of alcohol. Temp. 20°.

Time, mins.		1	2	3	4	5	6	8
Uptake of H, c.mm. at *N.T.P.*	*cis-*	146	189	209	237	—	268	330
	trans-	135	250	308	—	370	410	—

The initial slightly more rapid reduction of the *trans*-isomeride was repeatedly confirmed when the compensating flask of the respirometer contained the second modification. The colourless solutions were filtered after the theoretical volume of hydrogen had been absorbed (246 c.mm.), washed with water, oxidised with air, and extracted with petroleum; the azo-compounds thus obtained were chromatographically indistinguishable from normal *trans*-azobenzene.

cis-*Benzeneazo*-p-*toluene.*—A solution of 0·5 g. of benzeneazo-*p*-toluene in 25 c.c. of petroleum was irradiated at a distance of 12″ from a quartz mercury vapour lamp for 3 hours and filtered through a column of alumina (20 cm.; 1·7 cm. diameter), and the chromatogram washed with 50 c.c. of petroleum. The whole of the unchanged azo-compound passed into the filtrate, leaving the *cis*-compound adsorbed as a layer, 3 cm. long, at the top of the column. The zone was removed, and the remainder of the column used to rechromatograph the solution after it had been concentrated to 25 c.c. and again irradiated for 2 hours. The "cis"-zones were united and worked up as for *cis*-azobenzene. The residue obtained on evaporation was oily, but crystallised, when rubbed, to a deep red solid (m. p. 40°), which had m. p. 42—45° after rapid crystallisation from methanol–water at a low temperature. Yield, 110 mg. (Found: N, 14·4; *M*, cryoscopic in benzene, 181. $C_{13}H_{12}N_2$ requires N, 14·3%; *M*, 196).

Azotoluenes.—*oo*′-Azotoluene was prepared by Vorländer and Meyer's method (*Annalen*, 1901, **220**, 122) (b. p. 210°/5 mm.; recrystallised from alcohol, red prisms, m. p. 55°; yield, 37%), but was more conveniently obtained from *o*-nitrotoluene by the method used for the preparation of *pp*′-azotoluene (yield, 52%). It gave no indication of the ready formation of a stable *cis*-modification.

Long irradiation of the *mm*′-isomer in air gave a small amount of a product, which separated on the chromatographic column as a firmly adsorbed, yellow compound. Elution in the usual way gave stable, long yellow needles, m. p. 59° (from petroleum). The *compound* has the composition of an azoxytoluene, but does not appear to be identical with any of those hitherto known (Found: C, 74·0; H, 6·3; N, 12·45. $C_{14}H_{14}ON_2$ requires C, 74·4; H, 6·25; N, 12·4%). Distillation with iron filings gave a red oil, which soon solidified and after filtering in petroleum solution through a short column of alumina yielded *mm*′-azotoluene, m. p. and mixed m. p. 54°. It is not impossible that the new compound is a (*cis*) stereoisomeride of that hitherto known (m. p. 39°), but it is significant that it has not yet proved possible to convert the new compound into the old. *pp*′-Azotoluene was prepared by the following method: A milky suspension of 90 g. of stannous chloride (dihydrate) in 150 c.c. of water was added slowly, so that the temperature did not exceed 60°, with stirring to 64 g. of sodium hydroxide in 250 c.c. of water. The sodium stannite solution was boiled, 27 g. of *p*-nitrotoluene in 100 c.c. of alcohol added, and the whole shaken. *pp'*-Azotoluene separated in bright orange crystals, which were collected hot after 30 minutes' refluxing and recrystallised from alcohol; m. p. 145°. Yield, 18 g. (85%).

cis-pp'-*Azotoluene*.—A solution of 400 mg. of the *trans*-compound in 100 c.c. of light petroleum was irradiated at a distance of 12" from a mercury lamp for 30 minutes and then chromatographed on a column of Merck's alumina (20 cm., 2 cm. diameter). The *trans*-compound was completely washed through the column with 120—150 c.c. of petroleum. cis-pp'-*Azotoluene* remained adsorbed as a layer 1·5—2 cm. long, beginning 1 cm. from the top of the column. Isolation as for *cis*-azobenzene and crystallisation at 0° from a little petroleum yielded 30 mg. of deep red needles, m. p. 105° (rapid heating), mixed m. p. with the *trans*-compound, 95—100° (Found: C, 79·8; H, 6·55; *M*, cryoscopic in benzene, 220. $C_{14}H_{14}N_2$ requires C, 80·0; H, 6·7%; *M*, 210). After melting, the substance solidified as pure *trans*-azotoluene, m. p. 144°.

p-*Benzeneazophenol*.—Adsorption even on mildly deactivated alumina was too firm from petroleum solution and unsatisfactory from benzene solution. 500 Mg., dissolved in 50 c.c. of benzene, were adsorbed on alumina (25 cm.; 1·7 cm. diameter) and the broad band extending 7 cm. from the top of the column was developed with 50 c.c. of benzene and then with 50 c.c. of benzene + 10 c.c. of alcohol. 300 Mg. of the azo-compound were thus recovered from the filtrate; the remainder stained the whole of the column a uniform orange-yellow colour and was only eluted with alcoholic ammonia. After irradiation of the chromatographically pure product (300 mg. in 50 c.c. of benzene; irradiated for 30 mins. at 12" from the mercury lamp) an orange band, which was distinct from the main, more easily eluted, unchanged azo-compound, was developed on washing the column with ether, but in each case only normal *trans*-benzeneazophenol was recovered. *p*-Benzeneazophenyl acetate behaved similarly, as did also 2 : 4-bisbenzeneazophenol and its acetate.

p-*Aminoazobenzene*.—Purification of the crude product was best effected by running a 1% solution in benzene through a column of alumina and concentrating the filtrate until *p*-aminoazobenzene crystallised (8—10 g. can be treated on a column of Merck's alumina, 20 cm.; 2 cm. diameter). No isomerisation was chromatographically detectable after a 1% solution of benzene had been irradiated for 3 hours at a distance of 12" from the mercury lamp. Acetamidoazobenzene behaved similarly and furnished no evidence of a stable *cis*-isomeride.

p-*Benzeneazophenetole*.—500 Mg., dissolved in 100 c.c. of petroleum, were irradiated and chromatographed. An upper zone (3—4 cm.) of firmly adsorbed material was developed and eluted with 200 c.c. of 1% methanol in petroleum. A deep red oil (55 mg.) was obtained in the usual way (Found: C, 74·3; H, 6·1. $C_{14}H_{14}ON_2$ requires C, 74·4; H, 6·25%). The material became lighter in colour during 2 days and solidified to normal benzeneazophenetole, m. p. 78—79°.

p-*Chloroazobenzene*.—The following modified preparation was found convenient: 25 g. of aminoazobenzene hydrochloride in 700 c.c. of water and 77 c.c. of concentrated hydrochloric acid were diazotised with 7 g. of sodium nitrite in 35 c.c. of water. After 30 minutes the filtered solution was poured into a boiling solution of 14 g. of cuprous chloride in 125 c.c. of concentrated hydrochloric acid and again filtered after 10 minutes. The grey-black mass was washed with hydrochloric acid, caustic soda solution, and water and a benzene extract (150 c.c.) of the residue was filtered through two columns of Merck's alumina. The recovered compound was redissolved in 100 c.c. of warm petroleum, filtered again through an alumina column (25 cm.; 2·5 cm. diameter), and the filtrate concentrated until deep orange needles, m. p. 88—90°, crystallised (yield, 8 g.; 21%) (cf. Mentha and Heumann, *Ber.*, 1886, **19**, 3022).

500 Mg. of the chromatographically pure product in 100 c.c. of petroleum were irradiated for 30 minutes and then chromatographed, the column (20 cm.; 2 cm. diameter; Merck's alumina) being washed with 50 c.c. of petroleum. The zone of *cis*-compound was 2—3 cm. long, beginning 1 cm. from the top of the column. The products of several separations (each *ca.* 30—50 mg.) were worked up together in the usual way. Only a deep red oil was obtained, which solidified after 2 days to *trans*-*p*-chloroazobenzene (Found: C, 66·85; H, 4·1. Calc. for $C_{12}H_9N_2Cl$: C, 66·6; H, 4·2%).

p-*Cyanoazobenzene*.—A diazotised solution of 35 g. of aminoazobenzene was added to potassium cuprocyanide soution at 90° (88 g. of copper sulphate in 400 c.c. of water at 90°, treated with 98 g. of potassium cyanide in 100 c.c. of water). The crude product was collected when cold, washed, and dried on a tile. A benzene extract of the residue (200 c.c.) was passed through three columns of alumina (20 cm.; 2 cm. diameter); the crystalline residue obtained from the filtrate sublimed in a vacuum in pale orange needles, m. p. 120·5°.

Prolonged irradiation in petroleum solution, and chromatographic analysis of the resulting solution gave no indication of isomerisation beyond a tail to the main chromatographic zone which quickly followed the bulk of adsorbed material on development.

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