79. *ω-Bromo-*o*-cyanostyrenes and Related Compounds.*

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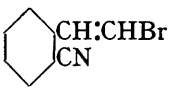
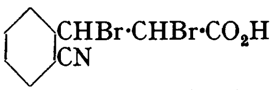
The two *o*-cyanocinnamic acids have been converted into the two *ω-bromo-*o-*cyanostyrenes*, the higher-melting form being obtained in especially good yield. These two styrene derivatives differ considerably in chemical activity. Related compounds, including *ω-bromo-*p-*cyanostyrene*, have been prepared.

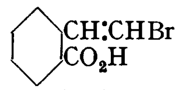
ω-BROMO-*o*-CYANOSTYRENES (I) have been prepared with a view to the synthesis of 1-substituted *iso*quinolines (following paper), and the non-synthetic aspects of the work are now recorded. *trans-o*-Cyanocinnamic acid (Davies and Poole, J., 1927, 2661) yields with bromine vapour at the ordinary temperature αβ-dibromo-β-*o*-cyanophenylpropionic acid (II*A*), m. p. 203—204° (Linstead and Noble, J., 1937, 936, record m. p. 184—186°). This with steam in the presence of sodium acetate gives cis-*ω-bromo-*o-*cyanostyrene* (I), m. p. 30°, though only in 34% yield. Similar treatment of *allo*- or *cis-o*-cyanocinnamic acid (Edwards, J., 1926, 815) gives αβ-dibromo-β-*o*-cyanophenylpropionic acid (II*B*), m. p. 154—155°. This on mere boiling with water gives a 75% yield of *trans*-ω-bromo-*o*-cyanostyrene, m. p. 86°. Helberger and von Rebay (*Annalen*, 1937, **531**, 279) prepared ω-bromo-*o*-cyanostyrene (m. p. 87°) from (II*B*) by the action of pyridine.



(I.)



(II*A*.) and (II*B*.)



(III.)

The two ω-bromo-*o*-cyanostyrenes show considerable differences in chemical activity. Some bromine is removed as hydrogen bromide from the *cis*-isomer by boiling for 1 minute with alcoholic N-sodium hydroxide, and *o*-cyanophenylacetylene can be isolated: all the bromine is readily removed by more prolonged treatment. The *trans*-form loses only a portion of its bromine when refluxed with alcoholic alkali for 8 hours, the main products being *ω-bromostyrene-*o*-carboxylic acid* (III) and its *acid amide*; the latter is more readily obtained by the action of hydrogen peroxide and alkali on *trans*-ω-bromo-*o*-cyanostyrene. Greater activity of the *cis*- than of the *trans*-antimeride has already been noted with the ω-bromostyrenes and especially with the ω-bromo-*p*-nitrostyrenes (Dann, Howard, and Davies, J., 1928, 606). The striking activity of *cis*-ω-bromo-*o*-cyanostyrene seems to be restricted to the action of alkali, for aniline or piperidine in boiling benzene is relatively inert. The *cis*-form is readily converted by the action of light into a mixture, from which much *trans*-ω-bromo-*o*-cyanostyrene can be separated partly by crystallisation and partly by the destruction of the labile *cis*-form with alkali.

In the preparation of (I) on a large scale where (II) is not isolated in a pure state, its stereochemical homogeneity largely depends on the conditions of bromination of the parent *o*-cyanocinnamic acid. For example, when the *cis*-acid (m. p. 137°) is brominated in hot acetic acid, the final product (I) is a mixture of the *cis*- and the *trans*-form in poor yield, whereas the *trans*-form is obtained stereochemically pure and in much greater yield when the bromination is carried out with bromine in a desiccator. The same changes in the bromination conditions of *trans-o*-cyanocinnamic acid bring about a similar variation in the proportion of the geometrical isomers of (I), though here the *cis*-form in the absence of bright light contains a relatively small proportion of the *trans*-form. In the higher temperature method of bromination it is probable that, perhaps through the agency of hydrogen bromide, some interconversion of the *o*-cyanocinnamic acids takes place. Some such change is particularly likely in view of the occurrence of such side reactions as the production of ammonium bromide, which indicates the presence of hydrogen bromide during the reaction.

The two dibromo-acids (II*A*) and (II*B*) recall the high-melting *meso*-dibromosuccinic acid formed by the bromination of fumaric acid and the low-melting *r*-dibromosuccinic acid formed from maleic acid (for a discussion of this and related instances, see Frankland, J., 1912, **101**, 673). The analogy between (II*A*) and (II*B*) and the two dibromosuccinic acids is not perfect, because both forms of (II) have potential optical activity owing to the asymmetry of the molecule rendering complete internal compensation impossible. Accordingly no attempt has been made to resolve either acid.

The assumption is made throughout this work (and also that of Dann, Howard, and Davies, *loc. cit.*) that the higher-melting of a pair of geometrical isomerides is the *trans*-form, but actual proof of these probable configurations is lacking. The assumption, however, is supported by the often observed "preferential *trans*-elimination rule" described by Frankland (*loc. cit.*, p. 687). For example, *trans*-*o*-cyanocinnamic acid (m. p. 256°) *via* (II*A*) gives *cis*-ω-bromo-*o*-cyanostyrene, m. p. 30°, and *cis*-*o*-cyanocinnamic acid (m. p. 137°) *via* (II*B*) gives *trans*-ω-bromo-*o*-cyanostyrene, m. p. 86°. It is known that the *cis*-forms of cinnamic, *p*-methylcinnamic, and *o*-methoxycinnamic acids, unlike the biologically inactive *trans*-forms, have a powerful growth-promoting action on plants as shown by the pea test (Koepfli, Thimann, and Went, *J. Biol. Chem.*, 1938, **122**, 766, 769). The test with the two cinnamic acids has been confirmed in this University. Peas do not respond at all to the high-melting *o*-cyanocinnamic acid, and the positive response with the low-melting (*cis*-) form is so slight that it is hardly significant. Accordingly, this possible biological test of spatial configuration cannot yet be relied upon.

The properties of the *cis*-form of (I) made it desirable to check the possibility that it was 1-bromo*iso*quinoline and not the desired styrene. Accordingly, *ω-bromo-*p*-cyanostyrene*, in which such cyclic formation is impossible, was examined: it resembles the *cis*-*o*-compound.

EXPERIMENTAL.

*αβ-Dibromo-β-*o*-cyanophenylpropionic Acid, m. p.* 154—155°.—*o*-Cyano*allo*cinnamic acid (43·2 g.) was powdered and spread in thin layers in a vacuum desiccator over a slight excess of bromine (40·5 g.; 13·5 c.c.). The pale yellow powder (79 g.; 95%) obtained after 5 days in the dark crystallised from toluene in colourless prisms, m. p. 154—155° (decomp.) (Found: equiv., 332·8. Calc. for $C_{10}H_7O_2NBr_2$: equiv., 332·9). The titrated solution, when left overnight with a slight excess of N/50-sodium hydroxide, deposited long fine needles of ω-bromo-*o*-cyanostyrene, m. p. 86°. [The isomeric acid on treatment with 10% or 25% potassium hydroxide solution gives a mixture of α-bromo-β-*o*-cyanophenylacrylic acid and *o*-cyanophenylpropiolic acid (Linstead and Noble, *loc. cit.*).] When more than a slight excess of bromine was used in the bromination, the product was a dark viscous mass, which continually lost bromine in a vacuum, evolved bromine copiously on boiling with water, and was apparently an addition compound of bromine with the cyano-group. In all brominations by this method some hydrogen bromide was perceptible except when the *o*-cyanocinnamic acid was pure and dry.

trans-*ω-Bromo-*o*-cyanostyrene.*—αβ-Dibromo-β-*o*-cyanophenylpropionic acid (16 g.; m. p. 154—155°) was heated with water (200 c.c.), and the product distilled in steam. *trans*-ω-Bromo-*o*-cyanostyrene (7·5 g.; 75%) crystallised from alcohol or light petroleum in colourless needles, m. p. 86°, having a very faint hyacinth-like odour (Found: Br, 39·0. Calc. for C_9H_6NBr: Br, 38·5%).

*αβ-Dibromo-β-*o*-cyanophenylpropionic Acid, m. p.* 203—204°.—*o*-Cyano*allo*cinnamic acid (8 g.), when brominated (7·5 g. of bromine) in a desiccator as described above, yielded 15·1 g. (98%) of a buff powder, which crystallised from much water in colourless needles and from toluene in colourless prisms; m. p. in a previously heated bath, 203—204° (decomp.) (Found: C, 35·4; H, 2·4; equiv., 332·75. Calc. for $C_{10}H_7O_2NBr_2$: C, 36·0; H, 2·1%; equiv., 332·9). The same acid was also isolated, in almost quantitative yield, when *o*-cyanocinnamic acid (m. p. 256°) was brominated in hot glacial acetic acid, and most of the acetic acid then removed by distillation.

cis-*ω-Bromo-*o*-cyanostyrene.*—αβ-Dibromo-β-*o*-cyanophenylpropionic acid (10 g.; m. p. 203—204°) was dissolved in a solution of sodium acetate in water (250 c.c.), and the product distilled in steam. The oil in the distillate solidified in ice (yield, 2·1 g.; 34%) and then separated from aqueous alcohol in colourless needles with a hyacinth-like odour, m. p. 30° (Found: C, 51·8; H, 2·8. C_9H_6NBr requires C, 51·9; H, 2·9%). The b. p. was not definite, some isomerism taking place, but the main fraction boiled at 108—118°/0·5 mm. It was insoluble in water but somewhat soluble in concentrated hydrochloric acid, from which some of the *trans*-form gradually separated at the ordinary temperature.

Conversion of cis- *into* trans-ω-*Bromo*-o-*cyanostyrene by the Action of Light.*—When the pure *cis*-form (m. p. 30°) (or preferably the crude mixture, m. p. 23—25°, obtained in the preceding experiment) was exposed in thin layers to bright sunlight for 3½ hours, it became semi-solid even though the temperature was above 50°. A yield of about 50% of the high-melting form was obtained by crystallisation of the product from light petroleum (b. p. 60—80°).

The conversion of the *trans*-isomer into a mixture of the two forms was brought about much more slowly, both with the pure compound and when a solution in benzene was exposed to sunlight for 32 hours, the temperature being 55—65°.

Action of Alkali on the ω-*Bromo*-o-*cyanostyrenes.*—*The* cis-*form, m. p.* 30°. The inital action of sodium hydroxide in dilute ethyl alcohol was to form *o*-cyanophenylacetylene, m. p. 75° (Linstead and Noble, *loc. cit.*, record m. p. 76°). The styrene was boiled with the above reagent for 1 minute, nitric acid and silver nitrate solution added, and the silver bromide at once removed from the hot solution; the filtrate, after cooling and standing for about 1 minute, deposited the *silver* salt of *o*-cyanophenylacetylene in sparingly soluble, colourless needles, which puffed vigorously but did not explode on heating and reacted vigorously with a bright flash with nitric acid (Found: Ag, 45·9. C_9H_4NAg requires Ag, 46·15%). The separation of this silver salt from the solution should be quickly carried out, as silver fulminate, which resembles it in appearance, often crystallises when the solution is kept for a few minutes. The presence of silver fulminate in the precipitate can be detected without detonation by its rapidly becoming violet or violet-brown in light, the cyanophenylacetylene salt being much more stable.

cis-ω-Bromo-*o*-cyanostyrene lost all its bromine when boiled for 3½ hours with excess of sodium hydroxide in aqueous methyl alcohol. An ethereal extract of the product yielded a bromine-free oil insoluble in alkali, and the aqueous layer contained sodium acetophenone-*o*-carboxylate. The acid had m. p. 114—115° and was identified by the method of mixed melting points and by the m. p. 211° of its *p*-nitrophenylhydrazone (Davies and Poole, J., 1927, 2662).

The trans-*form, m. p.* 86°. 3·0 G. in methyl alcohol (50 c.c.) were refluxed for 8 hours with 2N-sodium hydroxide (40 c.c.). The solution, on cooling, deposited ω-*bromostyrene*-o-*carboxyamide* (0·95 g.), m. p. 203—204°, and more of this, together with oily material, was obtained by extraction with ether. When the ether-extracted aqueous layer was acidified, 0·125 g. (m. p. 159°) of the acid (III) separated; the filtrate from this yielded on repeated extraction with ether a small quantity of acetophenone-*o*-carboxylic acid. ω-*Bromostyrene*-o-*carboxylic acid* (III) crystallised from alcohol in small needles with a very fine sheen, m. p. 160°. The bromine was very inert, and the acid did not decolorise potassium permanganate solution as quickly as cinnamic acid (Found: equiv. 229. $C_9H_7O_2Br$ requires equiv., 227).

ω-Bromostyrene-*o*-carboxyamide, readily soluble in hot alcohol and anisole, sparingly soluble in boiling benzene and cold alcohol, forms colourless needles, m. p. 203—204° (Found: Br, 35·2. C_9H_8ONBr requires Br, 35·4%). It is more readily made by heating *trans*-ω-bromo-*o*-cyanostyrene with perhydrol and a trace of sodium hydroxide solution above 86° for about 30 minutes, with vigorous agitation and with frequent renewal of hydrogen peroxide and the trace of alkali; the solid obtained is crystallised from alcohol.

When a mixture (m. p. about 23°) of the two forms of ω-bromo-*o*-cyanostyrene is boiled for a few minutes with alcoholic alkali, much of the *trans*-form is left owing to the inertia of its bromine atom. Because of this inertia, attempts to make the silver salt of *o*-cyanophenylacetylene from the *trans*-form failed.

p-*Cyanocinnamic Acid.*—*p*-Cyanobenzaldehyde (Moses, *Ber.*, 1900, **33**, 2624) (0·13 g.) was dissolved in pyridine, a slight excess of malonic acid added together with 2 drops of piperidine, and the mixture heated until carbon dioxide ceased to be evolved. The cooled product was poured into dilute hydrochloric acid; the precipitate obtained (0·08 g.) separated from glacial acetic acid in colourless crystals, m. p. 253° (Moses gives 248—249°). This is probably the *trans*-form, since the stable form is almost invariably obtained by the usual methods of synthesis.

αβ-Dibromo-β-*p*-cyanophenylpropionic acid was obtained as a pale yellow powder (0·13 g.), m. p. 179—182°, when *p*-cyanocinnamic acid (0·08 g.) was exposed to the vapour of bromine (0·1 g.) in a desiccator in the dark for 4 days.

ω-*Bromo*-p-*cyanostyrene.*—αβ-Dibromo-β-*p*-cyanophenylpropionic acid (0·1 g.) was dissolved in sodium acetate solution, and the product distilled in steam. The opaque distillate, placed in a refrigerator, deposited fine colourless needles with a faint odour of hyacinths, m. p. 47·5° after recrystallisation from light petroleum (yield, 0·02 g.) (Found: Br, 38·9. C_9H_6NBr requires Br, 38·5%). This is probably the *cis*-form, since (1) the *p*-cyanocinnamic acid is almost certainly the *trans*-form, and (2) a portion of the styrene, after being exposed to sunlight in a silica tube for 18 hours and then crystallised from light petroleum, had m. p. 86° after softening at about 50°, indicating a partial change into a higher-melting form.

The authors thank Miss Norma Smith for the biological testing of the cinnamic and the *o*-cyanocinnamic acids, and Miss Winifred Bibby and Mr. J. L. Osborne for assistance in the chemical work.

THE UNIVERSITY OF MELBOURNE. [*Received, November* 17*th*, 1938.]