120. *Some αββ-Triarylacrylonitriles, αββ-Triarylacrylic Acids, and their Derivatives.*

By Ng. Ph. Buu-Hoï and Jean Lecocq.

A number of diaryl ketones have been condensed in the presence of sodamide with various arylacetonitriles to give *αββ*-triarylacrylonitriles, which could be converted by alkaline hydrolysis into *αββ*-triarylacrylic acids through the corresponding amides. In some instances, both of the required stereoisomeric forms of the dissymetric nitriles could be isolated. Many of the substances described have been found to be rather oestrogenic and are now under test for other physiological properties.

In the course of a search for oestrogenic compounds which may also act as growth-inhibitors for malignant tumours, as does diethylstilboestrol, our attention has been directed to substances related to triphenylethylene; moreover, it has recently been observed that certain oestrogens of the same type may also interfere with the experimental production of tumours by carcinogenic hydrocarbons (Lacassagne, Buu-Hoï, and Rudali, 1946). For these reasons, triphenylethylene derivatives, and particularly the related nitriles were deemed worthy of a detailed investigation.

The most convenient way to prepare triarylacrylonitriles (I) is the condensation of diaryl ketones with the sodio-derivatives of arylacetonitriles (cf. Bodroux, *Bull. Soc. chim.*, 1911, **9**, 758):

$$\mathrm{CAr'Ar''O} + \mathrm{Ar{\cdot}CH_2{\cdot}CN} \longrightarrow \mathrm{CAr'Ar''{:}CAr{\cdot}CN}\ \text{(I.)} + \mathrm{H_2O}$$

Bodroux prepared triphenyl-, αβ-diphenyl-, β-*p*-tolyl-, and αβ-diphenyl-β-(α′-naphthyl)-acrylonitrile (the last in very low yields), but he ignored the possibility that when unsymmetrical diaryl ketones are used, two stereoisomeric nitriles may be produced. We have extended his reaction to a number of diversely substituted diaryl ketones and arylacetonitriles, and thus obtained a series of triarylacrylonitriles, some of which were obtained in the two required stereoisomeric forms. In accordance with Koelsch's observations upon the properties of stereoisomeric triarylacrylic acids (*J. Amer. Chem. Soc.*, 1932, **54**, 2487), we have found that the *trans-* are generally far more soluble than the *cis*-compounds, and that the latter easily undergo extensive stereomutation under the influence of heat.

All of these nitriles are highly crystalline substances which, with one exception (see p. 644), give deep violet halochromic colorations with pure sulphuric acid. Mild treatment with alcoholic alkalis results in formation of the corresponding amides, which also dissolve in sulphuric acid with a deep halochromic coloration.

On treating triphenylacrylonitrile with a boiling solution of potassium hydroxide in amyl alcohol, Bodroux (*loc. cit.*) obtained the amide, but failed to effect further hydrolysis. We have found that complete hydrolysis is achieved by long heating with very concentrated alkali. This method of preparing triphenylacrylic acid is far more convenient than either carboxylation of triphenylvinylmagnesium bromide (Koelsch, *J. Amer. Chem. Soc.*, 1932, **54**, 2045) or treatment of a sulphuric solution of the amide with sodium nitrite (Heyl and Meyer, *Ber.*, 1895, **28**, 2785). Using the same procedure, we also obtained from ββ-diphenyl-α-*p*-anisylacrylonitrile (*cis*-form) an acid which was identical with *trans*-ββ-diphenyl-*p*-anisylacrylic acid prepared by another method by Koelsch (*loc. cit.*). The presence of many methoxyl groups does not appear to interfere with the saponification process, for we obtained α-phenyl-ββ-di-*p*-anisylacrylic acid without difficulty by that method. Application of Bouveault's process to the saponification of *ββ-diphenyl-α-*p*-tolylacrylamide* afforded a small yield of the corresponding *acid.*

When fluorenone was added to an ethereal solution of the sodio-derivative of phenylacetonitrile, a violent reaction took place, accompanied by formation of an abundant precipitate; after hydrolysis, however, only fluorenone and phenylacetonitrile could be isolated, these compounds being recovered almost quantitatively. An attempt to condense anthraquinone with phenylacetonitrile failed similarly.

EXPERIMENTAL.

Triphenylacrylic Acid.—A mixture of triphenylacrylonitrile (5 g.), sodium hydroxide (15 g.) and *iso*amyl alcohol (50 g.) containing a few drops of water was heated under reflux for 72 hours and then poured into water; the aqueous layer was separated, freed from traces of amyl alcohol by a short boiling, and acidified with dilute hydrochloric acid. The flocculent precipitate (1·5 g.) was collected by suction, thoroughly washed with water, and crystallised twice from aqueous acetic acid; slender colourless prisms, m. p. 213°, were thus obtained.

*αβ-Diphenyl-β-*p*-tolyacrylamide.*—αβ-Diphenyl-β-p-tolyacrylonitrile, m. p. 123° (3·1 g.) (Bodroux, *loc. cit.*), was heated during one hour with a solution of sodium hydroxide (10 g.) in *iso*amyl alcohol (35 g.) containing a few drops of water. On cooling, the mixture yielded colourless crystals of *αβ-diphenyl-β-*p*-tolyacrylamide* (3 g.); after recrystallisation from 50% aqueous acetic acid, it formed microscopic glinting needles, m. p. 208—210° (Found: N, 4·5. $C_{22}H_{19}ON$ requires N, 4·4%).

*ββ-Diphenyl-α-*p*-tolylacrylonitrile.*—A mixture of *p*-tolylacetonitrile (5 g.), dissolved in anhydrous ether (50 c.c.), and freshly prepared sodamide (2 g.) was gently refluxed until evolution of ammonia had ceased, and the brownish-red solution was slowly treated with benzophenone (5 g.) dissolved in ether. A violent reaction set in immediately; after it had subsided, heating was continued for a further hour, the reaction mixture poured into ice-water, the organic layer collected and dried (Na_2SO_4), and the solvent distilled off. The brownish-red oil which remained crystallised partly on standing overnight; the solid was filtered off, and, after recrystallisation from acetic acid, slender colourless prisms (6 g.), m. p. 153°, were obtained (Found: N, 4·4. $C_{22}H_{17}N$ requires N, 4·7%), giving a deep violet colour with sulphuric acid. The *amide* formed almost colourless needles, m. p. 216°, from aqueous acetic acid (Found: N, 4·4. $C_{22}H_{19}ON$ requires N, 4·4%).

A solution of the above amide (1·1 g.) in pure sulphuric acid (15 g.) was slowly treated with sodium nitrite (0·3 g.) under ice-cooling; the resulting mixture was kept at room temperature for 24 hours, and then poured into water. The reddish precipitate was collected, thoroughly washed with water, and extracted with an aqueous solution of sodium carbonate. The alkaline filtrate was acidified with dilute hydrochloric acid, and the precipitate recrystallised from aqueous acetic acid. *ββ-Diphenyl-α-*p*-tolylacrylic acid* (0·5 g.) was thus obtained as fine, almost colourless needles, m. p. 237—238°, which gave with sulphuric acid an intense green coloration which rapidly became violet and finally red (Found: C, 84·2; H, 5·6. $C_{22}H_{18}O_2$ requires C, 84·0; H, 5·7%).

*ββ-Diphenyl-α-*m*-tolylacrylonitrile.*—*m*-Tolylacetonitrile (7 g.), dissolved in ether, was treated with sodamide (2·5 g.) and then with benzophenone (4 g.) exactly as in the foregoing example. After standard treatment, the *nitrile* (5 g.) crystallised from aqueous acetic acid in brilliant, colourless prisms, m. p. 122° (Found: N, 4·6%). The corresponding *amide* formed colourless needles, m. p. 177°, from aqueous acetic acid (Found: N, 4·2%).

*β-Phenyl-αβ-di-*p*-tolylacrylonitrile.*—This was similarly formed from *p*-tolylacetonitrile (6·7 g.) in ether, sodamide (2·5 g.), and *p*-methylbenzophenone (8 g.). The thick yellowish oily *nitrile* first obtained, solidified after distillation (b. p. 235°/3·5 mm.), and formed almost colourless prisms, m. p. 114—115°, from acetic acid (Found: N, 4·2%). The corresponding *amide* formed a colourless micro-crystalline powder from aqueous acetic acid, m. p. 237° (Found: N, 4·2%).

*αβ-Diphenyl-β-*p*-chlorophenylacrylonitrile.*—The sodio-derivative prepared from phenylacetonitrile (7·6 g.) and sodamide (3 g.) was allowed to react with *p*-chlorobenzophenone (10 g.) in ether. After standard treatment, a *nitrile* (10 g.) was obtained (from acetic acid) as very feebly yellow prisms, m. p. 139—140°, which were rather soluble in ether, and were therefore probably the *trans*-form (Found: N, 4·6. $C_{21}H_{14}NCl$ requires N, 4·4%).

*β-Phenyl-β-*p*-chlorophenyl-α-*p*-tolylacrylonitrile.*—The reaction between the sodio-derivative of *p*-tolylacetonitrile (from 8·5 g. of nitrile and 3 g. of sodamide) and *p*-chlorobenzophenone (10 g.) afforded after standard treatment an extremely viscous oil which slowly solidified after vacuum distillation (10 g.) (b. p. 245°/4 mm.). It crystallised from aqueous acetic acid as a bright yellow microcrystalline powder, m. p. 147—148° (Found : N, 4·1. $C_{22}H_{16}NCl$ requires N, 4·2%). The corresponding *amide* formed tiny, colourless needles, m. p. 197°, from aqueous acetic acid (Found : N, 3·8 $C_{22}H_{18}ONCl$ requires N, 4·0%).

*αβ-Diphenyl-β-*p*-anisylacrylonitriles.*—Phenylacetonitrile (6 g.) in ether was treated with sodamide (2·5 g.) and then with *p*-methoxybenzophenone (8·7 g.), heating being prolonged during 2 hours. The reaction mixture was poured into ice-water, and the abundant yellow precipitate thus obtained was collected by filtration and, crystallised twice from acetic acid, cis-*αβ-diphenyl-β-*p*-anisylacrylonitrile* (9 g.), formed pale yellowish prisms, m. p. 166° (Found : N, 4·3. $C_{22}H_{17}ON$ requires N, 4·5%). The filtrate was evaporated under diminished pressure, and the residue, which solidified on standing with some drops of acetic acid, gave on recrystallisation from the same solvent, trans-*αβ-diphenyl-β-*p*-anisylacrylonitrile* (1 g.) as almost colourless needles, m. p. 124—125° (Found : N, 4·2%). The ratio *cis* : *trans* obviously depended on the quality of the sample of sodamide used in the condensation, for in another experiment using an old specimen of this reagent, only the *trans*-isomer was obtained. cis-trans-*Conversion* : The *cis*-isomer was heated in a vacuum, and the glassy distillate (b. p. 245°/4 mm.) crystallised from aqueous acetic acid in tiny, almost colourless prisms, the m. p. (126—128°) of which was not depressed by admixture with a sample of the *trans*-nitrile prepared as above.

*αβ-Diphenyl-β-*p*-anisylacrylamides.*—(a) cis-*Isomer.* When heated for 3 hours with a solution of sodium hydroxide (7·5 g.) in aqueous amyl alcohol (25 g.), the foregoing *cis*-nitrile (2·5 g.) afforded an *amide*, which crystallised from aqueous acetic acid in yellow prisms, m. p. 196—198° (Found : N, 4·1. $C_{22}H_{19}O_2N$ requires N, 4·2%). (b) trans-*Isomer.* From a sample of the *trans*-nitrile, an *amide* was similarly obtained in yellow needles, m. p. 176—180° (Found : N, 4·2%) deeply depressed upon admixture with the foregoing amide.

*ββ-Diphenyl-α-*p*-anisylacrylonitrile.*—Reaction of *p*-methoxyphenylacetonitrile (6 g.) with sodamide (2 g.) was slow, and required freshly distilled samples of nitrile as well as an active sodamide. Heating was prolonged for 3 hours after ammonia had ceased to be evolved, and an ethereal solution of benzophenone (5 g.) was added. After a further hour's refluxing and standard treatment of the deep red mixture, the *nitrile* (5 g.) was obtained from acetic acid as short yellow needles, m. p. 149° (Found : N, 4·2%). The *amide* crystallised from aqueous acetic acid in slender prisms, m. p. 198°(Found : N, 4·4%).

*β-Phenyl-αβ-di-*p*-anisylacrylonitrile* (trans-*Form*).—The viscous yellow oil obtained from the sodio-derivative of *p*-methoxyphenylacetonitrile (7·5 g.) and *p*-methoxybenzophenone (7 g.) did not crystallise spontaneously, and was therefore submitted to vacuum-distillation. A glassy resin, b. p. 260°/4·5 mm., was thus obtained, which readily solidified on standing overnight with a few drops of acetic acid. After recrystallisation from the same solvent, slightly yellow needles, m. p. 122—125°, were obtained (7·5 g.), which were very easily soluble in ether as expected of the trans-*form* (Found : N, 4·0. $C_{23}H_{19}O_2N$ requires N, 4·1%). The trans-*amide* crystallised from dilute acetic acid in yellow prisms, m. p. 243° (Found : N, 3·7. $C_{23}H_{21}O_3N$ requires N, 3·9%).

*α-Phenyl-ββ-di-*p*-anisylacrylonitrile.*—Phenylacetonitrile (6 g.) in ether (50 c.c.) was treated with sodamide (2·5 g.) and then with a suspension of 4 : 4′-dimethoxybenzophenone (10 g.) in ether. After decomposition with ice-water, the crystals which separated were redissolved in hot acetic acid (charcoal). On cooling, the *nitrile* (10 g.) was obtained in microscopic, faintly yellow needles, m. p. 159° (Found : N, 4·2%).

A mixture of the foregoing nitrile (7 g.), sodium hydroxide (21 g.), and aqueous amyl alcohol (70 g.) was refluxed during 3 hours; the *amide* which separated on cooling was recrystallised from 50% aqueous acetic acid, giving slender needles, m. p. 209° (Found : N, 4·0%). When the heating was prolonged for 3 days, the acid was obtained; it formed yellow needles from acetic acid, m. p. 169°, as given by Koelsch (*loc. cit.*).

*α-*p*-Tolyl-ββ-di-*p*-anisylacrylonitrile.*—*p*-Tolylacetonitrile (6·7 g.) in ether (50 c.c.) was treated with sodamide (2·5 g.) and then with 4 : 4′-dimethoxybenzophenone (10 g.). After an hour's boiling, the reaction mixture was poured into ice-water; a large quantity of unchanged ketone was precipitated, and was filtered off. The filtrate was dried (Na_2SO_4) and afforded, after evaporation of the solvent and crystallisation from 80% aqueous acetic acid, slender needles of the *nitrile* (7 g.), m. p. 110—111° (Found : N, 4·2. $C_{24}H_{21}O_2N$ requires N, 3·9%), giving a deep violet coloration with pure sulphuric acid. The corresponding *amide* formed yellow needles, m. p. 213°, from aqueous acetic acid (Found : N, 3·9. $C_{24}H_{23}O_3N$ requires N, 3·7%).

*αβ-Diphenyl-β-*3 : 4*-dimethoxyphenylacrylonitriles.*—Phenylacetonitrile (7·6 g.) was successively treated with sodamide (3 g.) and with a suspension of 3 : 4-dimethoxybenzophenone (11·2 g.) in ether. After addition of water, the solid which separated was collected by suction and recrystallised from acetic acid. The cis-*nitrile* (8 g.) was thus obtained as slender yellow prisms, m. p. 181° (Found : N, 4·0. $C_{23}H_{19}O_2N$ requires N, 4·1%). The ethereal filtrate was dried (Na_2SO_4), the solvent removed, and the solid residue recrystallised from aqueous acetic acid, giving the trans-*nitrile* (2 g.) as almost colourless needles, m. p. 143—145°, readily soluble in ether (Found : N, 4·1%). On alkaline saponification, both isomers gave the same *amide*, crystallising from aqueous acetic acid in slender yellow needles, m. p. 198° (Found : N, 4·1. $C_{23}H_{21}O_3N$ requires N, 3·9%); as it is generally assumed that the *trans*-compounds are the more stable towards heat, it may be inferred that this is the *trans*-amide.

*αβ-Diphenyl-β-*2 : 4*-dimethoxyphenylacrylonitrile.*—Phenylacetonitrile (7 g.) in ether was treated successively with sodamide (2·3 g.) and an ethereal suspension of 2 : 4-dimethoxybenzophenone (10 g.). After decomposition of the reaction mixture, a precipitate (6 g.) was obtained. Recrystallisation from 90% acetic acid gave microscopic yellow prisms, m. p. 146—148° (sintering at 142°) (Found : N, 4·2%). This *substance* could be distilled without isomerisation (b. p. 235°/0·4 mm.).

*α-Phenyl-ββ′-bis-(*p*-dimethylaminophenyl)acrylonitrile.*—The action of Michler's ketone (15 g.) upon the sodio-derivative of phenylacetonitrile (9·2 g. of nitrile with 3·5 g. of sodium amide) afforded a deep coloured semi-solid suspension which was treated with ice-water. The yellow precipitate obtained was chiefly composed of recovered ketone, and was removed by filtration. The filtrate was concentrated, and the deposited solid recrystallised from ethanol. The *amino-nitrile* (0·5 g.) thus obtained formed deep yellow silky needles, m. p. 185°, which did not give any coloration with sulphuric acid (Found: N, 11·1. $C_{25}H_{25}N_3$ requires N, 11·4%).

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THE LABORATORY OF ORGANIC CHEMISTRY,
ÉCOLE POLYTECHNIQUE, PARIS.

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