chymotrypsin at *p*H 7.6, and less readily by crystalline trypsin at *p*H 7.6. The pepsin digest contained 1 mg. of crystalline pepsin and 10 mg. of the respective products per 2 cc. of hydrochloric acid resulting in a *p*H of 1.6. The chymotrypsin and the trypsin digests contained 2 mg. of proteinase and 10 mg. of the respective synthetic products per cc. of the 0.1 *M* phosphate buffer of *p*H 7.6. The temperature was 37°. The incubation time was 20 minutes. For the measurement of proteolysis the Folin–Ciocalteu phenol reagent was employed using tyrosine as the standard as described by Northrop and associates.[12] These results are summarized in Table III. All the products, with the exception of zein, were used in the form of suspensions when digested by chymotrypsin and trypsin at *p*H 7.6. When 1 mg. of crystalline pepsin was added to 10 mg. of the synthetic products in a volume of 2 cc. the breakdown into small-size peptides was almost complete in 20 minutes at 37°. This did not take place with chymotrypsin and with trypsin when 2 mg. of each of the enzymes was used in the digests. There was only a small precipitate formed on the addition of 5% trichloroacetic acid to the digest. The trichloroacetic acid-soluble products gave a pink biuret test.

TABLE III

HYDROLYSIS OF THE SYNTHETIC (DIALYZED) PRODUCTS BY PROTEINASES

Source of product	Tyrosine liberated, mg. By pepsin	By chymotrypsin	By trypsin
Egg albumin	0.24	0.10	0.06
Bovine serum albumin	.17	.10	.08
Zein	.22	.18	.04
Blood fibrin	.28	.12	.09

Acknowledgments.—The author is grateful to Dr. S. J. Circle and Dr. M. MacKenzie of Columbia University, for the molecular weight estimations; to Dr. R. T. Major and Dr. J. J. Mayernik of Merck and Company, Inc., for the microbiological amino acid assays; to Dr. J. R. Weisiger of the Rockefeller Institute for Medical Research, for the free α-amino nitrogen determinations; and to Mr. P. P. Mazzella of this Laboratory for skillful technical assistance.

STATEN ISLAND, N. Y.

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[12] J. H. Northrop, M. Kunitz and R. M. Herriott, "Crystalline Enzymes," Columbia University Press, New York, N. Y., 1948.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF G. D. SEARLE AND COMPANY]

The Preparation of Some 2,3-Diaryl-2-pentenenitriles by the Knoevenagel Condensation

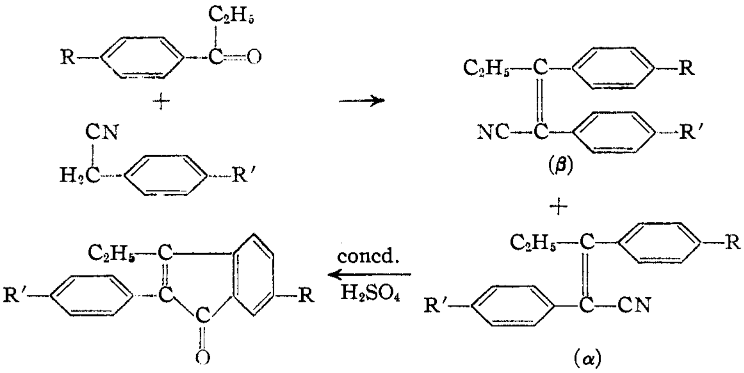
BY KURT RORIG

2,3-Diphenyl-2-pentenenitrile (I), 2-phenyl-3-(*p*-methoxyphenyl)-2-pentenenitrile (II), and 2,3-bis-(*p*-methoxyphenyl)-2-pentenenitrile (III) were prepared by the condensation of the appropriate arylacetonitrile and aryl ethyl ketone. Either sodamide in an aromatic solvent (toluene or xylene) or sodium methoxide in methanol effected these condensations. Both *cis*- and *trans*-2,3-diaryl-2-pentenenitriles were obtained from these reactions. The *trans* structure has been unequivocally assigned to the higher melting, less soluble 2,3-diphenyl-2-pentenenitrile (Iα) by virtue of its facile conversion to the known 3-ethyl-2-phenylindone (IV). Hydrogenation of I with Adams catalyst gave 2,3-diphenylvaleronitrile. With sodamide in boiling xylene, homoanisonitrile has been found to undergo autocondensation to give α,β-bis-(*p*-methoxyphenyl)-acrylonitrile.

Although condensations of aromatic aldehydes or diaryl ketones with arylacetonitriles are well known, aryl alkyl ketones have not been successfully used in such reactions. For example, the condensation of acetophenone with phenylacetonitrile in the presence of sodamide has been reported to fail.[1]

We have found that propiophenone and phenylacetonitrile do not react in the presence of acetic acid and ammonium acetate (the Cope conditions[2]). However, this condensation was effected by sodamide or sodium methoxide. In this manner 2,3-diphenyl-2-pentenenitrile (I) and its ring methoxylated analogs (II and III) were prepared.

Of these reactions, the sodamide-induced preparation of 2,3-diphenyl-2-pentenenitrile (I) was the one most thoroughly studied to achieve optimum conditions. This condensation was effected in maximum yield by heating equimolar amounts of the reactants in refluxing xylene. More than one equivalent of sodamide, or the lower reaction temperature obtained with benzene or ether as the solvent,[3] decreased the yield.



I, R = R′ = H
II, R = OCH_3; R′ = H
III, R = R′ = OCH_3

Two isomers (α and β) were obtained from these condensations. Trituration with petroleum ether

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[1] F. Bodroux, *Bull. soc. chim.*, [4] **9**, 726, 758 (1911); *Compt. rend.*, **152**, 1594 (1911).

[2] A. C. Cope, C. M. Hofmann, C. Wyckoff and E. Hardenbergh, THIS JOURNAL, **63**, 3453 (1941).

[3] The sodamide used was a dry-packed commercial preparation. With freshly prepared sodamide, the optimum reaction temperature may well be lower.

or recrystallization from acetic acid served to separate a solid isomer from an oil consisting principally of the lower-melting geometrical isomer.

When the solid 2,3-diphenyl-2-pentenenitrile (Ia) was heated in concentrated sulfuric acid,[4] there was obtained 3-ethyl-2-phenylindone[5] (IV), presumably by hydration followed by cylization. The oily 2,3-diphenyl-2-pentenenitrile (Iβ) did not give this indone (IV) on treatment with sulfuric acid. Therefore the *cis* relationship of the 3-phenyl group to the nitrile group is established for the solid 2,3-diphenyl-2-pentenenitrile (Iα). A similar rigorous proof for the *cis* relationship of cyano to the 3-aryl groups of the solid pentenenitriles, IIα and IIIα, was not possible because the activating methoxy groups induced ring sulfonation under conditions of indone formation. However, the lower solubility and higher melting points of the solid isomers IIα and IIIα strongly suggest the *trans* configuration for these molecules, *i.e.*, the aryl groups are *trans* to one another.

In the hydrogenation of 2,3-diphenyl-2-pentenenitrile in the presence of Adams catalyst, reduction of the ethylenic bond was accompanied by some reduction of the cyano group. The only product isolated from this reduction mixture was the high-melting racemic 2,3-diphenylvaleronitrile previously prepared by the 1,4-addition of ethylmagnesium bromide to α,β-diphenylacrylonitrile.[6]

The attempted condensation of homoanisonitrile and *p*-methoxypropiophenone with commercial sodamide in refluxing xylene resulted in recovery of nearly all the starting ketone and in formation of a substantial amount of a solid melting at 107–108°. This proved to be identical with a sample of α,β-bis-(*p*-methoxyphenyl)-acrylonitrile prepared by condensing anisaldehyde with homoanisonitrile.[7]

The mechanism of this unexpected formation of α,β-bis-(*p*-methoxyphenyl)-acrylonitrile from two molecules of homoanisonitrile with over-all loss of three hydrogens and a cyano group is still uncertain.[8]

Finally the desired 2,3-bis-(*p*-methoxyphenyl)-2-pentenenitrile (III) was obtained, though in poor yield, by using freshly prepared sodamide at the lower temperature of boiling toluene as the condensing agent.

Experimental

The 2,3-Diphenyl-2-pentenenitriles (a) Sodamide Condensation.—A suspension of 39 g. (1 mole) of commercially available, dry-packed sodamide[9] in 400 ml. of xylene was placed under a nitrogen atmosphere in one-liter three-necked, round-bottom flask equipped with a mercury-sealed Hershberg stirrer, reflux condenser, and dropping funnel. Approximately one-fifth of a total of 117 g. (1 mole) of phenylacetonitrile was added from the dropping funnel. The mixture was then heated to reflux to initiate formation of sodiophenylacetonitrile. The remainder of phenylacetonitrile was then added as rapidly as the exothermic reaction permitted. To this sodiophenylacetonitrile, an insoluble greenish-brown sludge, was added at the reflux temperature at a rate consistent with the exothermic effect 134 g. (1 mole) of propiophenone. The reaction mixture then changed to a deep-red color and became quite pasty. After stirring at reflux for 2.5 hours, the cooled mixture was cautiously decomposed and neutralized with 200 ml. of water and 60 g. of glacial acetic acid. After dilution with 600 ml. of ether to facilitate separation of the aqueous layer, the organic layer was dried over potassium carbonate, decolorized with charcoal, and stripped of solvent. Upon distillation there was obtained a forerun of 60 g. of unreacted starting materials, a main fraction of 123 g., b.p. 140–180° (1 mm.), and a tarry residue of 28 g. Redistillation of the main fraction afforded 113 g. of mixed isomeric 2,3-diphenyl-2-pentenenitriles, b.p. 120–124° (0.3 mm.).

Anal. Calcd. for $C_{17}H_{15}N$: N, 6.00. Found: N, 5.93, 5.92.

The semi-solid distillate was heated and slurried with 330 ml. of petroleum ether (b.p. 28–38°). Upon cooling and filtering, 18.4 g. of colorless white crystals, m.p. 100–103.5°, were obtained. After two recrystallizations from 75% aqueous acetic acid the pure solid 2,3-*trans*-diphenyl-2-pentenenitrile (Iα), m.p. 109–110°, was obtained.

Anal. Calcd. for $C_{17}H_{15}N$: C, 87.51; H, 6.48; N, 6.00. Found: C, 87.37; H, 6.61; N, 5.93.

The petroleum ether solution from which the above solid had been obtained was evaporated and distilled to give 77 g. of a thick yellowish oil, b.p. 122–125° (0.3 mm.), n^{25}_{D} 1.5911. This is principally 2,3-*cis*-diphenyl-2-pentenenitrile (Iβ).

Anal. Calcd. for $C_{17}H_{15}N$: C, 87.51; H, 6.48; N, 6.00. Found: C, 87.06; H, 6.55; N, 5.58.

(b) **Sodium Methoxide Condensation.**—To 30 g. (0.56 mole) of sodium methoxide dissolved in 200 ml. of methanol was added 59 g. (0.5 mole) of phenylacetonitrile and 67 g. (0.5 mole) of propiophenone. After 3.5 hours reflux, the homogeneous red solution was diluted with one liter water, neutralized with sulfuric acid and extracted with ether. The ethereal layer was dried over potassium carbonate and distilled at 0.1 mm. pressure. There was obtained an initial fraction of 62 g. of mixed unreacted starting materials; the desired fraction of 37 g., b.p. 125–135°; and a tarry residue of 10 g. The semi-crystalline second fraction was triturated with petroleum ether (b.p. 28–38°) to give 10 g. of crystals, m.p. 92–97°. This was crystallized from 18 ml. of 80% aqueous acetic acid to give 6.8 g. of 2,3-*trans*-diphenyl-2-pentenenitrile (Iα), m.p. 108–109°. The petroleum ether filtrate was distilled to give 23 g. of oily 2,3-*cis*-diphenyl-2-pentenenitrile (Iβ), b.p. 117–119° (0.1 mm.), n^{25}_{D} 1.5922.

3-Ethyl-2-phenylindone (IV).—Two grams of crystalline 2,3-*trans*-diphenyl-2-pentenenitrile (Iα), was dissolved in 11 ml. of concentrated sulfuric acid and heated to 90°. This solution, after cooling to 55° in the next 5 minutes, was poured into 150 ml. water. The initially formed orange oil crystallized on overnight standing. It was then filtered, washed and recrystallized from 75% aqueous acetic acid to give 1.2 g. of crystals, m.p. 75–84°. After two recrystallizations the orange 3-ethyl-2-phenylindone melted 97.0–98.5°.

Anal. Calcd. for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 87.17; H, 5.97.

This compound has been reported to melt at 97–98°.[5]

2,3-Diphenylvaleronitrile.—Sixty grams of the oily 2,3-diphenyl-2-pentenenitrile (Iβ) was purified by refluxing briefly in 200 ml. of absolute ethanol with 3 g. of Raney nickel. The filtered solution of Iβ was hydrogenated with 1.0 g. of Adams platinum oxide catalyst at 50° and 40 p.s.i. until one equivalent of hydrogen had been taken up (11 hours). The solution, which contained a substantial amount of ammonia, was filtered and evaporated to give 57.5 g. of light-yellow oil. A small quantity (0.9 g.) of basic organic material was extracted with 10% hydrochloric acid from an ethereal solution of the reduction product. The neutral hydrogenation product was then distilled at 0.1 mm. pressure to give 32.5 g. of yellow oil, b.p. 110–115°, 6.0 g. of oil, b.p. 115–120°, and 12 g. of viscous residue. The two distilled fractions became semi-crystalline upon standing several hours. The higher boiling 6.0 g. fraction gave 0.70 g. of 2,3-diphenyl-2-pentenenitrile (Iα), m.p. 106–107°. A mixture of this with an authentic speci-

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[4] P. Pfeiffer, H. Behr, H. Kübler and H. Rüping, *J. prakt. Chem.*, **121**, 87 (1929).

[5] R. L. Frank, H. Eklund, J. W. Richter, C. R. Vanneman and A. N. Wennerberg, This Journal, **66**, 3 (1944).

[6] E. P. Kohler, *Am. Chem. J.*, **36**, 392 (1906).

[7] J. B. Niederl and A. Ziering, This Journal, **64**, 886 (1942).

[8] Further work intended to elucidate this reaction mechanism is in progress.

[9] Obtained from the Farchan Laboratories, of Cleveland, Ohio.

men, melting 109–110°, melted at 106–109°. The 32.5 g. lower-boiling fraction of distillate was recrystallized from 100 ml. of petroleum ether (b.p. 60–71°) to give 4.2 g. of crude 2,3-diphenylvaleronitrile, m.p. 102–104°. After two recrystallizations from absolute ethanol this substance melted 106.5–108.0°. The melting point of this sample, m.p. 106.5–108.0, with admixed 2,3-diphenyl-2-pentenenitrile, m.p. 108–109°, was 101–103°. Two further recrystallizations from absolute ethanol, one recrystallization from glacial acetic acid, and a vacuum sublimation gave an analytical sample of 2,3-diphenylvaleronitrile, m.p. 110.5–112.5°.

Anal. Calcd. for $C_{17}H_{17}N$: C, 86.76; H, 7.28; N, 5.95. Found: C, 86.34; H, 7.18; N, 5.70.

This compound has been previously reported by Kohler[6] to melt at 115°.

2-Phenyl-3-(*p*-methoxyphenyl)-2-pentenenitriles.—The preparation of these isomeric nitriles proceeded exactly as described under the "sodamide condensation" above. From 58.5 g. (0.5 mole) of phenylacetonitrile, 19.5 g. (0.5 mole) of commercial sodamide,[9] and 82 g. (0.5 mole) of *p*-methoxypropiophenone[10] there was obtained 65 g. of mixed isomeric 2-phenyl-3-(*p*-methoxyphenyl)-2-pentenenitriles, b.p. 138–143° (0.2 mm.), which set to a semi-solid sludge on standing.

Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.09; H, 6.51; N, 5.32; OCH_3, 11.78. Found: C, 81.93; H, 6.61; N, 5.32; OCH_3, 11.65.

This semi-crystalline distillate was recrystallized from glacial acetic acid to give 30.3 g. of massive, colorless prisms, m.p. 97–100°. A second crop of 9.8 g. of the same material, m.p. 83–97° was obtained on diluting the acetic acid liquors with water. Three recrystallizations from glacial acetic acid gave the pure *trans*-2-phenyl-3-(*p*-methoxyphenyl)-2-pentenenitrile (IIα), m.p. 104.5–105.5°.

Anal. Calcd. for $C_{18}H_{17}NO$: N, 5.32; OCH_3, 11.78. Found: N, 5.30; OCH_3, 11.86.

The oily residue from acetic acid recrystallization, which contained the *cis* isomer (IIβ) was not further purified.

2-Phenyl-3-(*p*-hydroxyphenyl)-2-pentenenitrile.—Five grams of *trans*-2-phenyl-3-(*p*-methoxyphenyl)-2-pentenenitrile was refluxed for 18 hours in a solution of 36 ml. of glacial acetic acid and 19 ml. of 48% hydrobromic acid. The dark brown reaction mixture, after dilution with 400 ml. of water, was extracted with ether. The oil remaining after evaporation of the dried ether extract was taken up in a minimum of warm benzene, treated with activated charcoal, and cooled to give 1.65 g. of brown crystals, m.p. 145–149°. A second recrystallization from benzene gave 1.20 g. of tan crystals, m.p. 163–167°. This solid was dissolved in 100 ml. 1% sodium hydroxide, decolorized with charcoal, and reprecipitated with carbon dioxide to give 0.92 g. of pure white powdery 2-phenyl-3-(*p*-hydroxyphenyl)-2-pentenenitrile, m.p. 172–173°.

Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.90; H, 6.07; N, 5.62. Found: C, 82.29; H, 6.00; N, 5.46.

Homoanisonitrile.—This was made from anisyl alcohol *via* *p*-methoxybenzyl chloride. Major revision of the method of Shriner and Hull[11] resulted in consistently higher yields of homoanisonitrile obtained with minimal effort.

Anhydrous hydrogen chloride was bubbled rapidly for 2 hours into a solution of 660 g. (4.8 moles) of anisyl alcohol in 3 l. of thiophene-free benzene. The exothermic reaction heated the solution to 80° in that time. The benzene layer was then separated from 120 ml. of concentrated hydrochloric acid which had formed, and distilled at water-pump pressure to remove the benzene. The residual crude *p*-methoxybenzyl chloride, dissolved in 1650 ml. of dioxane, was added over a 70-minute period to a boiling solution of 940 g. (14.4 moles) of potassium cyanide in 870 ml. of water contained in a 5 l., three-necked flask equipped with an efficient stirrer, reflux condenser and addition funnel. After 2.5 hours of further reflux, the condenser was set for downward distillation and 1500 ml. of distillate was collected. The residue was then diluted with one liter of water and extracted with three 1.5-l. portions of benzene. Upon removal of benzene and distillation there was obtained 508 g. of crude product, b.p. 108–125° (0.5 mm.). Redistillation gave 496 g. (71%) of homoanisonitrile, b.p. 105–108° (0.5 mm.), $n^{25}\mathrm{D}$ 1.5324.

2,3-Bis-(*p*-methoxyphenyl)-2-pentenenitrile (III).—A toluene suspension of sodio homoanisonitrile was made by the general method of Hancock and Cope[12] from 11.5 g. of sodium, 300 ml. of liquid ammonia and 75 g. (0.51 mole) of homoanisonitrile. To this suspension at 50° was added 82 g. (0.5 mole) of *p*-methoxypropiophenone. External heating rapidly brought the mixture to reflux temperature. A moderate exothermic effect was noted when the temperature reached 65°. The very black mixture which soon became quite viscous was refluxed for 40 minutes. The reaction mixture when worked up in the usual manner gave a heavy oil from which 60 g. of starting materials were recovered by distillation at 0.2 mm. The semi-crystalline residue, weighing 65 g., was not distillable at 0.2 mm. pressure because of excessive decomposition. The residue was therefore dissolved in 180 ml. boiling glacial acetic acid, treated with 5 g. of decolorizing charcoal, filtered and cooled. There was obtained from the acetic acid only one fully crystalline crop of 5 g., m.p. 125–130°. This when recrystallized from 20 ml. of glacial acetic acid gave one crop of 4.0 g., m.p. 131–132° and a second crop of 0.4 g., m.p. 129–131°. A sample of 2,3-*trans*-bis-(*p*-methoxyphenyl)-2-pentenenitrile recrystallized twice from acetic acid and once from ethanol melted at 131.5–132.5°.

Anal. Calcd. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.78; OCH_3, 21.16. Found: C, 77.96; H, 6.58; N, 4.90; OCH_3, 20.69.

α,β-Bis-(*p*-methoxyphenyl)-acrylonitrile from Homoanisonitrile.—This reaction was set up exactly as described under the "Sodamide condensation" above. Seventy-five grams (0.51 mole) of homoanisonitrile was added to a refluxing suspension of 20 g. (0.51 mole) of commercial sodamide[9] in xylene over a 25-minute period. When then 84 g. (0.51 mole) of *p*-methoxypropiophenone was added to this mixture in a 5-minute period, the reaction became so black and unpromising in appearance that it was immediately cooled and worked up in the usual manner.[13] There was obtained by distillation of the crude organic mixture a first fraction of 80 g. of liquid, b.p. 91–95° (0.15 mm.). Although homoanisonitrile also boils in this range, this liquid was shown to be *p*-methoxypropiophenone by the absence of nitrogen and the following elemental analysis.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37; OCH_3, 18.90. Found: C, 72.98; H, 7.43; OCH_3, 18.51.

Five grams of this recovered ketone gave 4.6 g. of *p*-methoxypropiophenone semicarbazone, m.p. 176–177° (lit. m.p. is 172–173°).[14]

The second fraction of 55 g. was redistilled to give 37.5 g. of solid, b.p. 194–214° (0.2 mm.). This was recrystallized from glacial acetic acid to give 10.3 g. of α,β-bis-(*p*-methoxyphenyl)-acrylonitrile, m.p. 107–108°.

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28; OCH_3, 23.39. Found: C, 77.05; H, 5.70; N, 5.28; OCH_3, 22.75.

A mixture of this α,β,-bis-(*p*-methoxyphenyl)-acrylonitrile, m.p. 107–108°, with an authentic sample, m.p. 107–108°, prepared[7] from anisaldehyde and homoanisonitrile, melted at 107–108°.

SKOKIE, ILLINOIS

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[10] W. Bradley and R. Robinson, *J. Chem. Soc.*, 2360 (1926).

[11] R. L. Shriner and C. J. Hull, *J. Org. Chem.*, **10**, 230 (1945).

[12] E. M. Hancock and A. C. Cope, *Org. Syn.*, **25**, 25 (1945).

[13] The odor of hydrogen cyanide was apparent when the reaction mixture was decomposed and acidified.

[14] O. Wallach and F. J. Pond, *Ber.*, **28**, 2717 (1895).