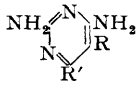
707. *The Preparation of Enol Ethers from Certain β-Keto-nitriles.*

By B. H. Chase and James Walker.

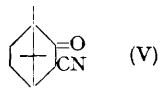
αβ-Unsaturated β-alkoxy-nitriles, the enol ethers of β-keto-nitriles, are intermediates in the synthesis of highly active antimalarials of the 2 : 4-diaminopyrimidine type. Methods for the preparation of such enol ethers are reviewed, and the acid-catalysed etherification of β-keto-nitriles has been studied in detail. Infra-red absorption characteristics of β-keto-nitriles are discussed.

The production of antimalarials of the 2 : 4-diaminopyrimidine type (I), such as the highly active pyrimethamine (2 : 4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine) (II), calls for accessibility of the αβ-unsaturated β-alkoxy-nitriles (III; R″ = alkyl), which are intermediates yielding (I) on condensation with guanidine (Russell and Hitchings, *J. Amer. Chem. Soc.*, 1951, **73**, 3763; Chase, Thurston, and Walker, *J.*, 1951, 3439). These unsaturated nitriles (III) are, of course, enol ethers of the corresponding β-keto-(or β-aldehydo-, when R′ = H) nitriles (IV), and the latter are relatively easy of access by Claisen condensation of esters (*e.g.*, R′·CO_2Et) with appropriate nitriles (R·CH_2·CN), although they (IV) do not themselves react with guanidine to give diaminopyrimidines but yield aminotriazines instead (Russell, Hitchings, Chase, and Walker, *J. Amer. Chem. Soc.*, 1952, **74**, 5403).

(I)



(II; R = *p*-Cl·C_6H_4, R′ = Et)
(VI; R = H, R′ = *p*-Cl·C_6H_4)
(VII; R = R′ = *p*-Cl·C_6H_4)



(V)

(III) R′·C(OR″):CR·CN

(IV*a*) R′·CO·CHR·CN ⟷ R′·C(OH):CR·CN (IV*b*)

Whether alkylation of such β-keto-nitriles (IV) by hitherto conventional methods affords *O*- or *C*-alkylated derivatives obviously depends upon structural factors as well as upon the choice of reagents and conditions of reaction. In the case of 1-cyanoindan-2-one, for example, *O*-methylation takes place with methyl sulphate and *C*-methylation occurs exclusively with sodium methoxide and methyl iodide, yet *O*-ethylation occurs with sodium ethoxide and ethyl iodide (Moore and Thorpe, *J.*, 1908, **93**, 165). By contrast, however, 2-cyanoindan-1-one undergoes exclusive *O*-methylation with sodium methoxide and methyl iodide (Mitchell and Thorpe, *J.*, 1910, **97**, 2278). The sodium salt of 2-cyano*cyclo*hexanone undergoes mainly *C*- but also *O*-alkylation with alkyl halides (von Auwers, *Ber.*, 1928, **61**, 408), and that of 2-cyano*cyclo*pentanone undergoes exclusive *C*-methylation and -ethylation (Best and Thorpe, *J.*, 1909, **95**, 711), yet with 3-cyanocamphor (V) *O*-alkylation apparently predominates over *C*-alkylation under comparable conditions (Haller and Minguin, *Compt. rend.*, 1894, **118**, 690; Haller, *ibid.*, 1903, **136**, 788). Exclusive *O*-methylation, either with methyl sulphate and aqueous potassium hydroxide or with methyl iodide and silver oxide, of α-cyanoacetomesitylene (IV; R = H, R′ = mesityl) has been reported (Fuson, Ullyot, and Gehrt, *J. Amer. Chem. Soc.*, 1938, **60**, 1199) though *O*- and *C*-methylation occur to roughly equal extents with methyl iodide and sodium ethoxide (Fuson and Wolf, *ibid.*, 1939, **61**, 1940), while *p*-bromo-ω-cyanoacetophenone (IV; R = H, R′ = *p*-Br·C_6H_4) afforded the *O*-methyl ether with the first of these reagents and the *C*-methylated compound with the last (Fuson and Wolf, *loc. cit.*). Methyl sulphate and aqueous potassium hydroxide convert cyanodeoxybenzoin (IV; R = R′ = Ph) into stereoisomeric enol methyl ethers (Reynaud and Matti, *Compt. rend.*, 1952, **235**, 1231) but the conditions for reaction appear to be hard to define and the method lacks general usefulness (Russell and Whittaker, *J. Amer. Chem. Soc.*, 1952, **74**, 1310).

The necessity for ensuring *O*-alkylation led to the use of diazomethane for the methylation of β-keto-nitriles (IV) (Russell and Hitchings, *loc. cit.*; Chase, Thurston, and Walker, *loc. cit.*) but more satisfactory results in the case of α-formylphenylacetonitrile (IV; R = Ph,

R′ = H) were obtained on methylation with methyl iodide and potassium carbonate (Chase, Thurston, and Walker, *loc. cit.*). Reaction between β-keto-nitriles and aliphatic ortho-esters also leads to *O*-alkylation but with orthoformic ester displacement of the acyl group, R′·CO, may occur with production of an ethoxymethyleneacetonitrile (Russell and Whittaker, *loc. cit.*), and the method is not applicable to β-keto-nitriles (IV; R = H) containing a methylene group activated by two strongly negative groups (Pascual and Serratosa, *Chem. Ber.*, 1952, **85**, 686; cf. Russell and Whittaker, *loc. cit.*). We have previously reported (Chase, Thurston, and Walker, *loc. cit.*) that α-formylphenylacetonitrile (IV; R = Ph, R′ = H) and its *p*-chloro-analogue (IV; R = *p*-Cl·C_6H_4, R′ = H) may be conveniently converted into their *O-iso*butyl derivatives (III; R = Ph, R′ = H, R″ = Bu^i and R = *p*-Cl·C_6H_4, R′ = H, R″ = Bu^i) by treatment with *iso*butanol and an acid catalyst in a boiling inert solvent capable of forming a heterogeneous azeotropic mixture with water in such a manner that water is removed from the reaction mixture as it is formed. The present communication extends these observations and shows that, besides β-aldehydo-nitriles, β-keto-nitriles come within the scope of the method subject to certain reservations which will be discussed later. This general technique has been applied to dihydroresorcinols but it fails with dihydro-2-methylresorcinols (Frank and Hall, *J. Amer. Chem. Soc.*, 1950, **72**, 1645; Meek, Turnbull, and Wilson, *J.*, 1953, 811), and it is applicable to hydroxymethylene-ketones (Seifert and Schinz, *Helv. Chim. Acta*, 1951, **34**, 728). There was no *a priori* reason, however, to believe that this method would be outstandingly successful with β-keto-nitriles without interference from the cyano-group, since imidic ester salt formation could occur with inactivation of the acid catalyst, and it may be noted that β-keto-nitriles of this type (*e.g.*, IV; R = Ph, R′ = Pr^i) may actually be converted into β-keto-esters *via* the imidic esters (Wislicenus, Eichert, and Marquardt, *Annalen*, 1924, **436**, 88). With regard to the conditions of the reaction, the solvent employed should be one forming a heterogeneous azeotropic mixture with water having a boiling point lower than that of the alcohol being used; a solvent forming a ternary azeotrope with water and the alcohol may also be used provided enough alcohol is present in the reaction vessel throughout. The presence of too great an excess of the alcohol is perhaps to be avoided since acetals may be formed, as in the case of α-formylphenylacetonitrile (IV; R = Ph, R′ = H) (cf. the preparation of dimethyl β-keto-acetals and methoxymethylene ketones from hydroxymethylene-ketones; Royals and Brannock, *J. Amer. Chem. Soc.*, 1953, **75**, 2050). The acetals, *e.g.*, ββ-di*iso*butoxy-α-phenylpropionitrile, CH(OBu^i)$_2$·CHPh·CN, are, however, readily converted into enol ethers (III) on treatment with acid as described below. Either primary or secondary alcohols may be employed, although benzyl alcohol is an exception, and phenol was tried unsuccessfully. Sulphonic acids are convenient catalysts for the etherification, and "Zeo-Karb 225," a sulphonated polystyrene, is also effective, the present reaction being an addition to the growing number of types of reaction now known to be catalysed by cation-exchange resins.

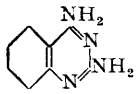
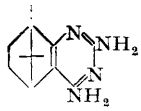
Turning now to the β-keto-nitriles it is obvious that these (IV*a*) are in tautomeric equilibrium with the enolic forms (IV*b*), and the latter are presumably the forms participating in the reaction in a similar manner to the esterification of carboxylic acids. It might be expected, therefore, that the rate of acid-catalysed etherification would be related to the degree of enolisation of any particular β-keto-nitrile modified, of course, by steric factors influencing the accessibility of the β-carbon atom and by the mobility of the tautomeric equilibrium. Evidence as to the structure of a β-keto-nitrile under the conditions of the etherification reaction is not easily obtained but it may be noted that ω-cyanoacetophenone (IV; R = H, R′ = Ph) in alcoholic solution appears to exist to the extent of ~10% as the enolic form while α-phenylacetoacetonitrile (IV; R = Ph, R′ = Me) is ~90% enolised under the same conditions as shown by bromine titration (Arndt, Loewe, and Ginkök, *Rev. Fac. Sci. Istanbul*, 1946, *A*, **11**, 147), and 2-cyano*cyclo*hexanone is similarly shown to be ~10% enolised (von Auwers, Bahr, and Frese, *Annalen*, 1925, **441**, 68). We have studied the infra-red absorption in Nujol suspension of a range of the β-keto-nitriles (IV) used in the present work and find that the results are in general accord with other available collateral data. Thus, α-formylphenylacetonitrile (IV; R = Ph, R′ = H) shows a band at 3040 cm.$^{-1}$ due to the enolic hydroxyl

group and a band at 1635 cm.$^{-1}$ due to the conjugated double bond, the latter being approximately in the same position as, and comparable in intensity with, the band at ~1640 cm.$^{-1}$ observed for αβ-unsaturated nitriles (Barnes, Liddel, and Williams, *Ind. Eng. Chem. Anal.*, 1943, **15**, 699). Likewise, α-phenylacetoacetonitrile (IV; R = Ph, R′ = Me) shows bands at 3070 and 1660 cm.$^{-1}$, α-*p*-chlorophenyl-α-propionylacetonitrile (IV; R = *p*-Cl·C_6H_4, R′ = Et) shows bands at 3050 and 1615 cm.$^{-1}$, and cyanodeoxybenzoin (IV; R = R′ = Ph) shows bands at 3090 and 1610 cm.$^{-1}$. These substances therefore exist in the solid essentially in the enolic form, and, as pointed out above, the enolic form of α-phenylacetoacetonitrile (IV; R = Ph, R′ = Me) also predominates in alcoholic solution (Arndt, Loewe, and Ginkök, *loc. cit.*), while ultra-violet light absorption also indicates predominantly the enolic structure for cyanodeoxybenzoin (Russell, *J. Amer. Chem. Soc.*, 1952, **74**, 2654). With ω-cyanoacetophenone (IV; R = H, R′ = Ph) and *p*-chloro-ω-cyanoacetophenone (IV; R = H, R′ = *p*-Cl·C_6H_4) no absorption band is found in the 3000—3500-cm.$^{-1}$ region and absorption bands ascribable to carbonyl groups linked to the benzene ring are found at 1685 and 1680 cm.$^{-1}$ respectively in Nujol (or at 1690 cm.$^{-1}$ in chloroform solution). Both in the solid and in chloroform solution therefore these substances are essentially ketonic, as has been shown also for the former in alcoholic solution (Arndt, Loewe, and Ginkök, *loc. cit.*). 3-Cyanocamphor (V) shows a band at 1735 cm.$^{-1}$ due to the alicyclic carbonyl group, and, by way of analogy, camphorcarboxylic ester is also ketonic, existing to the extent of only 0·1% in the enolic form in alcoholic solution (Henecka, *Chem. Ber.*, 1948, **81**, 204). Ethyl β-cyano-β-phenylpyruvate was also examined and found to show bands at ~3130, 2200, 1720, and 1625 cm.$^{-1}$, which are attributed to the enolic hydroxyl group, the nitrile group, the ester carbonyl group, and the conjugated double bond respectively. Throughout the series of β-keto-nitriles (IV) and enol ethers (III) studied, weak to medium intensity but well-defined sharp bands due to the nitrile group appeared at 2200—2240 cm.$^{-1}$.

No strict correlation between these structures and ease of acid-catalysed etherification was discernible. The following order of decreasing ease of reaction was, however, observed: α-formylphenylacetonitrile (IV; R = Ph, R′ = H), *p*-chloro-α-formylphenylacetonitrile (IV; R = *p*-Cl·C_6H_4, R′ = H), α-phenylacetoacetonitrile (IV; R = Ph, R′ = Me), *p*-chloro-ω-cyanoacetophenone (IV; R = H, R′ = *p*-Cl·C_6H_4), α-*p*-chlorophenyl-α-propionylacetonitrile (IV; R = *p*-Cl·C_6H_4, R′ = Et); 4 : 4′-dichlorocyanodeoxybenzoin (IV; R = R′ = *p*-Cl·C_6H_4) and cyanocamphor (V) failed to react while ethyl β-cyano-β-phenylpyruvate, CHPh(CN)·CO·CO_2Et, underwent dismutation. The failure of 4 : 4′-dichlorocyanodeoxybenzoin to react may be due to steric hindrance coupled with a clearly discernible retarding effect of *p*-chloro-substituents, but the unreactivity of cyanocamphor is less easily understandable since it reacted comparatively readily with diazomethane as, of course, did 4 : 4′-dichlorocyanodeoxybenzoin; in contrast with cyanocamphor, 2-cyano*cyclo*hexanone underwent acid-catalysed etherification with relative ease. One may conclude, therefore, that the acid-catalysed etherification reaction is shown by the enolic modifications (IV*b*) of the β-keto-nitriles (IV*a*), provided steric hindrance does not interfere, and that essentially ketonic substances will also undergo the reaction provided the mobility of the tautomeric equilibrium is adequate. That reaction does not take place through the intermediary of alkyl sulphonates was shown by recovery of α-formylphenylacetonitrile (IV; R = Ph, R′ = H) from attempted reaction with *iso*butyl toluene-*p*-sulphonate.

2 : 4-Diamino-6-methyl-5-phenylpyrimidine (I; R = Ph, R′ = Me) and pyrimethamine (II) were obtained in about 90% yield by condensation of β-*iso*butoxy-α-phenylcrotononitrile (III; R = Ph, R′ = Me, R″ = Bu^i) and 3-*iso*butoxy-2-*p*-chlorophenylpent-2-enonitrile (III; R = *p*-Cl·C_6H_4, R′ = Et, R″ = Bu^i) respectively with guanidine. β-*iso*Butoxy-β-*p*-chlorophenylacrylonitrile (III; R = H, R′ = *p*-Cl·C_6H_4, R″ = Bu^i) and αβ-bis-*p*-chlorophenyl-β-methoxyacrylonitrile (III; R = R′ = *p*-Cl·C_6H_4, R″ = Me), however, afforded 2 : 4-diamino-6-*p*-chlorophenylpyrimidine (VI) and 2 : 4-diamino-5 : 6-bis-*p*-chlorophenylpyrimidine (VII) respectively in moderate yield. By contrast, drastic conditions were necessary for the condensations of 1-*iso*butoxy-2-cyano*cyclo*hexene and 3-cyano-2-methoxycamph-2-ene with guanidine and poor yields of 2 : 4-diamino-5 : 6 : 7 : 8-

tetrahydroquinazoline (VIII) and 2 : 6-diaminocamph-2′-eno(2′ : 3′-4 : 5)pyrimidine (IX) * respectively resulted.

(VIII)   (IX)

The above substituted pyrimidines (I; R = Ph, R′ = Me), (VI), (VII), (VIII), and (IX) were kindly tested for antimalarial activity by Dr. June Thurston. Only the first of them showed activity, being active at 2 mg./20 g. mouse given intraperitoneally b.i.d. × 4 in the mouse against *P. berghei* and at 2 mg./10 g. chick given orally b.i.d. × 3½ in the chick against *P. gallinaceum* (cf. Falco, Goodwin, Hitchings, Rollo, and Russell, *Brit. J. Pharmacol.*, 1951, **6**, 187); none of the others showed observable activity against *P. berghei* in the mouse under the usual conditions of testing, and (VI) and (VII) were also inactive against *P. gallinaceum* in the chick.

Experimental

Infra-red absorption spectra were recorded between 700 and 4000 cm^{-1}; only significant absorption bands found in the 1600—4000 $cm.^{-1}$ region are reported in this communication.

β-*Ethoxy-α-phenylacrylonitrile* (III; R = Ph, R′ = H, R″ = Et).—A mixture of α-formylphenylacetonitrile (Ghosh, *J.*, 1916, **109**, 113) (14·5 g.), ethanol (6·9 g., 50% excess), and (+)-camphor-10-sulphonic acid (2·32 g.) in dry chloroform (200 c.c.) was refluxed for 42 hr., the condensate passing through an automatic separator allowing only the heavier, chloroform layer to return to the reaction vessel. The cooled solution was washed with N-sodium hydroxide and with water, and then fractionated, yielding a mixture (12·3 g.), b. p. 107—115°/0·4 mm., n_D^{17} 1·5194—1·5668, of the enol ether and the acetal. Redistillation after the addition of 1 drop of concentrated sulphuric acid gave β-*ethoxy-α-phenylacrylonitrile* as a colourless oil (10·2 g.), b. p. 116—118°/0·4 mm., n_D^{22} 1·5676, absorption bands (homogeneous) at 1620 and 2200 $cm.^{-1}$ (Found: C, 76·2; H, 6·4; N, 8·4. $C_{11}H_{11}ON$ requires C, 76·3; H, 6·4; N, 8·1%).

α-Phenyl-β-n-*propoxyacrylonitrile* (III; R = Ph, R′ = H, R″ = Pr^n).—A suspension of activated (*i.e.*, acid-treated) "Zeo-Karb 225" in a benzene solution (200 c.c.) of α-formylphenylacetonitrile (14·5 g.) containing *n*-propanol (6·6 g., 10% excess) was refluxed for 7 hr., the condensate being returned to the reaction vessel *via* a conventional Dean and Stark separator. The mixture was cooled, filtered, and washed with N-sodium hydroxide, unchanged formylphenylacetonitrile (1·05 g., 7·2%) being recovered by acidification of the alkaline washings. Fractionation of the benzene layer then afforded *α-phenyl*-β-n-*propoxyacrylonitrile* (15·4 g., 82%), b. p. 120—122°/0·4 mm., n_D^{19} 1·5598 (Found: C, 77·1; H, 6·9. $C_{12}H_{13}ON$ requires C, 77·0; H, 7·0%). In a similar experiment employing toluene-*p*-sulphonic acid (4·0 g.) in place of "Zeo-Karb 225" the same product was obtained in 88% yield after a 16-hr. period of reflux.

α-Phenyl-β-iso*propoxyacrylonitrile* (III; R = Ph, R′ = H, R″ = Pr^i).—A mixture of α-formylphenylacetonitrile (7·25 g.), *iso*propanol (3·3 g.), toluene-*p*-sulphonic acid (0·98 g.) and dry benzene (100 c.c.) was boiled under reflux in the manner described above for 5 hr. The neutral fraction was distilled and *α-phenyl*-β-iso*propoxyacrylonitrile* passed over at 123—124°/0·4 mm. as a colourless oil (8·17 g., 87%), n_D^{18} 1·5578 (Found: C, 76·7; H, 6·8; N, 7·6%).

β-iso*Butoxy-α-phenylacrylonitrile* (III; R = Ph, R′ = H, R″ = Bu^i).—(*a*) The following procedure is more convenient than that previously described (Chase, Thurston, and Walker, *loc. cit.*). A mixture of α-formylphenylacetonitrile (96 g.), *iso*butanol (58 g.), toluene-*p*-sulphonic acid (10 g.), and toluene (450 c.c.) was boiled under reflux as in the preceding experiment for 2 hr., during which the theoretical volume of water was segregated. The cooled solution was washed with N-sodium hydroxide and fractionated, β-*iso*butoxy-α-phenylacrylonitrile (114 g., 85%) passing over at 124—127°/0·4 mm., n_D^{22} 1·5475.

(*b*) A mixture of α-formylphenylacetonitrile (50 g.), *iso*butanol (60 g.), toluene-*p*-sulphonic acid (1 g.), and benzene (600 c.c.) was refluxed as above for 22 hr. The mixture, worked up as before, gave *α-cyanophenylacetaldehyde diisobutyl acetal* (56 g.), b. p. 115—118°/0·03 mm., n_D^{20} 1·4948 (Found: C, 74·4; H, 8·8. $C_{17}H_{25}O_2N$ requires C, 74·2; H, 9·2%). The acetal (122 g.)

* In the name for (IX) camphene is used systematically for a monounsaturated derivative of camphane. The naturally occurring, trivially named camphene is, of course, a derivative of *iso*camphane.—Ed.

was heated on the water-bath with toluene-*p*-sulphonic acid (10 g.) under slightly reduced pressure, *iso*butanol distilling over as it was formed. The residue, in ether, was washed with N-sodium hydroxide and water, dried, and fractionated, affording β-*iso*butoxy-α-phenylacrylonitrile (75 g.), n_D^{20} 1·5468, distilling at 116—118°/0·03 mm.

β-cyclo*Hexyloxy-α-phenylacrylonitrile* (III; R = Ph, R′ = H, R″ = C_6H_{11}).—A mixture of α-formylphenylacetonitrile (7·25 g.), *cyclo*hexanol (6·0 g.), toluene-*p*-sulphonic acid (0·9 g.), and dry toluene (100 c.c.) was boiled under reflux as above for 1 hr. The neutral fraction was distilled and β-cyclo*hexyloxy-α-phenylacrylonitrile* (10·44 g., 92%) passed over at 140—142°/0·004 mm., n_D^{18} 1·5718 (Found: C, 79·2; H, 7·4; N, 6·3. $C_{15}H_{17}ON$ requires C, 79·3; H, 7·5; N, 6·2%).

β-*Dodecyloxy-α-phenylacrylonitrile* (III; R = Ph, R′ = H, R″ = $C_{12}H_{25}$).—Similarly, α-formylphenylacetonitrile (7·25 g.), dodecanol (10·25 g.) toluene-*p*-sulphonic acid (0·9 g.), and toluene (100 c.c.), refluxed for 2 hr., afforded β-*dodecyloxy-α-phenylacrylonitrile* (15·1 g., 96%) as a pale yellow oil, b. p. 185—190°/0·002 mm., n_D^{22} 1·5206 (Found: C, 80·2; H, 9·8; N, 4·7. $C_{21}H_{31}ON$ requires C, 80·4; H, 10·0; N, 4·5%).

Enol-etherification using (a) *Internal and* (b) *External Drying Agents.*—(*a*) A mixture of α-formylphenylacetonitrile (7·25 g.), *n*-propanol (3·6 g.), toluene-*p*-sulphonic acid (0·9 g.), anhydrous calcium sulphate (41 g.), and benzene (150 c.c.) was boiled under reflux with vigorous stirring for 9 hr. The filtered solution, treated in the usual way, gave a neutral fraction which yielded, on distillation in the presence of 1 drop of concentrated sulphuric acid, α-phenyl-β-*n*-propoxyacrylonitrile (4·5 g., 48%), b. p. 120—124°/0·15 mm., n_D^{21} 1·5592.

(*b*) A mixture of α-formylphenylacetonitrile (7·25 g.), *iso*butanol (4·1 g.), toluene-*p*-sulphonic acid (0·9 g.) and dry benzene (150 c.c.) was boiled under reflux in such a way that the condensate passed over anhydrous calcium chloride (50 g.) before returning to the reaction mixture. After 6 hr. at the b. p. the mixture was worked up in the usual way, giving β-*iso*butoxy-α-phenylacrylonitrile (9·6 g., 95%), b. p. 112—114°/0·005 mm., n_D^{18} 1·5492.

Attempted Preparation of β-iso*Butoxy-α-phenylacrylonitrile using* iso*Butyl Toluene*-p-*sulphonate.*—A mixture of α-formylphenylacetonitrile (14·5 g.), *iso*butyl toluene-*p*-sulphonate (11·4 g.), prepared by the general method of Marvel and Sekera (*Org. Synth.*, **20**, 50), and benzene (100 c.c.) was boiled under reflux in the usual way, the Dean and Stark separator being used, for 3 hr. The starting materials were recovered.

β-iso*Butoxy-α-phenylcrotononitrile* (III; R = Ph, R′ = Me, R″ = Bu^i).—A mixture of α-phenylacetoacetonitrile (50 g.) (*Org. Synth.*, Coll. Vol. II, 487), *iso*butanol (50 g.), toluene-*p*-sulphonic acid (1·0 g.), and benzene was boiled under reflux for 72 hr., the Dean and Stark apparatus being used. The neutral fraction, isolated in the usual way, yielded, on distillation, β-iso*butoxy-α-phenylcrotononitrile* as an almost colourless oil (65 g., 96%), b. p. 118—120°/0·005 mm., n_D^{19} 1·5514 (Found: C, 78·1; H, 8·0; N, 6·5. $C_{14}H_{17}ON$ requires C, 78·1; H, 7·9; N, 6·5%).

3-iso*Butoxy*-2-p-*chlorophenylpent*-2-*enonitrile* (III; R = *p*-Cl·C_6H_4, R′ = Et, R″ = Bu^i).—A mixture of α-*p*-chlorophenyl-α-propionylacetonitrile (5·2 g.) (Russell and Hitchings, *loc. cit.*), *iso*butanol (2·05 g., 10% excess), toluene-*p*-sulphonic acid (0·5 g.), and toluene (100 c.c.) was boiled under reflux as above for 44 hr., during which the calculated volume of water was segregated. The neutral fraction, isolated in the usual way, gave, on distillation, 3-iso*butoxy*-2-p-*chlorophenylpent*-2-*enonitrile* (4·62 g., 70%), b. p. 140—141°/0·2 mm., n_D^{20} 1·5587, absorption bands (homogeneous) at 1600(s), 2210(m), 2850(w), and 2935(m) cm.$^{-1}$ (Found: C, 68·3; H, 6·8; N, 5·6. $C_{15}H_{18}ONCl$ requires C, 68·3; H, 6·9; N, 5·3%).

When an attempt was made to prepare the analogous *cyclo*hexyl ether, 82% of unchanged keto-nitrile was recovered after a 24-hr. period of reflux.

β-iso*Butoxy*-β-p-*chlorophenylacrylonitrile* (III; R = H, R′ = *p*-Cl·C_6H_4, R″ = Bu^i).—Bromination of *p*-chloroacetophenone in glacial acetic acid below 20° (cf. *Org. Synth.*, Coll. Vol. I, 1st Edn., p. 122) and treatment of the air-dried *p*-chlorophenacyl bromide with sodium cyanide in aqueous ethanol below 20° (cf. Long, *J. Amer. Chem. Soc.*, 1947, **69**, 990) gave *p*-chlorobenzoylacetonitrile, m. p. 125—126°, in 61% overall yield. Recrystallisation from aqueous ethanol afforded lustrous needles, m. p. 129—131°, absorption bands in Nujol suspension at 1680(s) and 2240(w), and in chloroform solution at 1690(s) and 2240(w) cm.$^{-1}$; Rabcewicz-Zubkowski and Kaflińska (*Roczn. Chem.*, 1930, **10**, 541) record m. p. 129·5—130°.

A mixture of the keto-nitrile (17·9 g.), *iso*butanol (8·9 g., 20% excess), toluene-*p*-sulphonic acid (1·9 g.), and toluene (250 c.c.) was boiled under reflux for 24 hr., the Dean and Stark apparatus being used, and then worked up in the usual way. On removal of the solvent under reduced pressure the neutral fraction largely crystallized; trituration with light petroleum yielded β-iso*butoxy*-β-p-*chlorophenylacrylonitrile*, which separated from ligroin in colourless plates

(12·9 g., 55%), m. p. 81—83°, absorption bands (Nujol suspension) at 1590 and 2200 cm.$^{-1}$ (Found: C, 66·3; H, 5·8; N, 6·0. $C_{13}H_{14}ONCl$ requires C, 66·2; H, 6·0; N, 5·9%). The combined mother-liquors were fractionated, yielding a further quantity (7·7 g., 33%) of mixed stereoisomers as a colourless oil, b. p. 129—132°/0·4 mm., n_D^{21} 1·5508—1·5558. On redistillation all fractions partly crystallised, and trituration with light petroleum gave more (1·2 g.) of the solid stereoisomer; the liquid stereoisomer was not obtained pure.

α-p-*Chlorobenzoyl*-α-p-*chlorophenylacetonitrile* (4 : 4′-*dichlorocyanodeoxybenzoin*) (IV; R = R′ = *p*-Cl·C_6H_4).—To freshly prepared alcohol-free sodium ethoxide (from 2·53 g. of sodium) was added *p*-chlorophenylacetonitrile (15·2 g.) in dry benzene (100 c.c.), followed by ethyl *p*-chlorobenzoate (20·4 g.) in dry benzene (100 c.c.). The benzene–ethanol azeotrope was slowly distilled off through a short fractionating column, the initial volume being maintained by addition of fresh benzene. When all the ethanol had been removed (3 hr.), the mixture was cooled and shaken with water (200 c.c.). The benzene layer was washed with N-sodium hydroxide (50 c.c.), and the combined aqueous solutions were washed with ether and then acidified; α-p-*chlorobenzoyl*-α-p-*chlorophenylacetonitrile*, which separated as a colourless oil (18·7 g., 65%), rapidly solidified. Recrystallisation from aqueous ethanol gave woolly needles, m. p. 135—136° (Found: C, 62·4; H, 3·2; N, 4·8. $C_{15}H_9ONCl_2$ requires C, 62·1; H, 3·1; N, 4·8%).

α-Benzoylphenylacetonitrile (cyanodeoxybenzoin), m. p. 98—99°, was obtained in an analogous manner in 80% yield.

αβ-*Bis*-p-*chlorophenyl*-β-*methoxyacrylonitrile* (III; R = R′ = *p*-Cl·C_6H_4, R″ = Me).—α-*p*-Chlorobenzoyl-α-*p*-chlorophenylacetonitrile (10 g.) was treated with diazomethane (from 10·7 g. of methylnitrosourea) in ether at 5—10°. The reaction was vigorous and the keto-nitrile rapidly dissolved. After being kept overnight at room temperature the ether and excess of diazomethane were distilled off, and the residue largely solidified. Recrystallisation from ligroin gave αβ-*bis*-p-*chlorophenyl*-β-*methoxyacrylonitrile* as long needles (6·5 g., 62%), m. p. 121—122° (Found: C, 63·6; H, 3·6; N, 4·7. $C_{16}H_{11}ONCl_2$ requires C, 63·2; H, 3·6; N, 4·6%). The stereoisomeric enol ether was not isolated in pure form from the mother-liquors.

An attempt to prepare the analogous *iso*butyl ether by the acid-catalysed azeotropic-distillation method was unsuccessful. When a mixture of the keto-nitrile (11·5 g.), *iso*butanol (3·23 g.), toluene-*p*-sulphonic acid (0·75 g.), and toluene (200 c.c.) was boiled under reflux for 16 hr. only a trace of water (0·05 c.c.) was collected and unchanged keto-nitrile (10·8 g.), m. p. 134—136°, was recovered. Cyanodeoxybenzoin was similarly recovered after a 24-hr. period of reflux.

Ethyl β-*Cyano*-α-*methoxy*-β-*phenylacrylate* (III; R = Ph, R′ = CO_2Et, R″ = Me).—Ethyl β-cyano-β-phenylpyruvate (10·85 g.) (*Org. Synth.*, Coll. Vol. II, p. 287) was treated with diazomethane (from 15·5 g. of methylnitrosourea) in ether (350 c.c.) at 10—15°. Next morning the ether and excess of diazomethane were distilled off and the residue was fractionated, yielding *ethyl* β-*cyano*-α-*methoxy*-β-*phenylacrylate* as a pale yellow oil (10·1 g.), b. p. 128°/0·4 mm., n_D^{21} 1·5509 (Found: C, 67·8; H, 5·5; N, 6·2. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·7; N, 6·1%).

An attempt to prepare the analogous *iso*butyl ether by the acid-catalysed azeotropic distillation method was unsuccessful. A mixture of ethyl β-cyano-β-phenylpyruvate (21·7 g.), *iso*butanol (8·9 g., 20% excess), toluene-*p*-sulphonic acid (1·72 g.), and toluene (150 c.c.) was boiled under reflux for 24 hr., the Dean and Stark separator being used. The neutral fraction, isolated in the usual way, gave on distillation colourless oils, (i) (2·51 g.), b. p. 84—88°/0·7 mm., and (ii) (5·23 g.), b. p. 116—123°/0·6 mm. On redistillation, fraction (i) yielded *iso*butyl phenylacetate, b. p. 65°/0·3 mm., $n_D^{19\cdot5}$ 1·4892 (Found: C, 74·8; H, 8·3. Calc. for $C_{12}H_{16}O_2$: C, 75·0; H, 8·4%), and fraction (ii) gave *iso*butyl toluene-*p*-sulphonate, b. p. 125—127°/1 mm., n_D^{22} 1·5108 (Found: C, 57·6; H, 7·1; S, 14·9. Calc. for $C_{11}H_{16}O_3S$: C, 57·9; H, 7·1; S, 14·0%).

1-iso*Butoxy*-2-*cyano*cyclo*hex*-1-*ene*.—Cyano*cyclo*hexanone was obtained in low yield by bromination of *cyclo*hexanone in the cold and treatment of the crude bromo-ketone with potassium cyanide in aqueous ethanol (cf. Meyer, *Helv. Chim. Acta*, 1933, **16**, 1291). A mixture of cyano*cyclo*hexanone (3·9 g.), *iso*butanol (2·8 g.), toluene-*p*-sulphonic acid (0·6 g.), and toluene (150 c.c.) was boiled under reflux in the manner described above for 17 hr. On distillation, the neutral fraction gave 1-iso*butoxy*-2-*cyano*cyclo*hex*-1-*ene* as a colourless oil (4·74 g., 84%), b. p. 89—90°/0·4 mm., n_D^{18} 1·4908 (Found: C, 73·8; H, 9·8; N, 8·0. $C_{11}H_{17}ON$ requires C, 73·7; H, 9·6; N, 7·8%).

3-*Cyano*-2-*methoxycamph*-2-*ene*.—Cyanocamphor (8·85 g.), prepared by Lapworth's method (*J.*, 1900, **77**, 1058), was treated with excess of diazomethane (from 15·5 g. of methylnitrosourea) in ether (250 c.c.); addition of methanol (40 c.c.) appeared to increase the rate of reaction. After 18 hours at room temperature, the solvent and excess of diazomethane were distilled off

and the residue, dissolved in ether, was washed with N-sodium hydroxide, unchanged cyanocamphor (0·52 g.) being removed. Evaporation of the ethereal solution then gave 3-cyano-2-methoxycamph-2-ene (8·94 g., 94%; m. p. 58°), crystallising from light petroleum in large colourless prisms, m. p. 62—63°, absorption bands (in $CHCl_3$) at 1620 and 2210 cm.$^{-1}$ (Found: C, 75·8; H, 9·0; N, 7·3. Calc. for $C_{12}H_{17}ON$: C, 75·4; H, 9·0; N, 7·3%). Haller and Minguin (*Compt. rend.*, 1894, **118**, 690) record m. p. 63° for this substance isolated from admixture with the *C*-methyl compound, obtained by methylation of cyanocamphor with sodium methoxide–methyl iodide.

An attempt to prepare the analogous *iso*butyl ether by the acid-catalysed azeotropic-distillation method failed. A mixture of cyanocamphor (8·85 g.), *iso*butanol (4·45 g.), toluene-*p*-sulphonic acid (7·75 g.), and benzene (200 c.c.) was refluxed for 24 hr. in the manner already described. The cooled mixture was washed with alkali in the usual way and fractionated, yielding an oil (5·3 g.), b. p. 110—130°/0·4 mm., n_D^{24} 1·4835—1·4682, which contained sulphur (? *iso*butyl toluene-*p*-sulphonate) and from which no pure material could be isolated. Acidification of the alkaline washings and crystallisation of the precipitate from aqueous ethanol gave unchanged cyanocamphor (4·8 g.; m. p. 127—128°).

2 : 4-*Diamino*-6-*methyl*-5-*phenylpyrimidine* (I; R = Ph, R′ = Me).—Guanidine nitrate (6·6 g.) and β-*iso*butoxy-α-phenylcrotononitrile (10·7 g.) were added in succession to a solution of sodium ethoxide (from 1·75 g. of sodium) in absolute ethanol (50 c.c.), and the mixture was boiled under reflux for 18 hr. The solvent was removed under reduced pressure, water (50 c.c.) was added, and pure 2 : 4-diamino-6-methyl-5-phenylpyrimidine (9·3 g., 93%), m. p. 250—252°, was obtained by washing the precipitate on the filter with water and ether until it was colourless (Found: C, 66·0; H, 6·0. Calc. for $C_{11}H_{12}N_4$: C, 66·0; H, 6·0%). Russell and Hitchings (*loc. cit.*) record m. p. 249—251° for this substance prepared from the enol methyl ether.

2 : 4-*Diamino*-5-*chlorophenyl*-6-*ethylpyrimidine* (*Pyrimethamine*) (II).—Guanidine nitrate (1·34 g.) and 3-*iso*butoxy-2-*p*-chlorophenylpent-2-enonitrile (2·64 g.) were added in succession to a solution of sodium ethoxide (from 0·25 g. of sodium) in ethanol (50 c.c.), and the mixture was boiled under reflux for 18 hr. The solvent was removed and the residue was suspended in a mixture of ether (20 c.c.) and water (20 c.c.), the solid (2·24 g., 90%), m. p. 234—236°, being collected and washed with ether and water and dried. Recrystallisation from *iso*butanol yielded 2 : 4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine as colourless flattened needles, m. p. and mixed m. p. 235—236° (Found: C, 57·7; H, 5·1. Calc. for $C_{12}H_{13}N_4Cl$: C, 57·9; H, 5·3%). Russell and Hitchings (*loc. cit.*) record m. p. 233—234°.

2 : 4-*Diamino*-6-p-*chlorophenylpyrimidine* (VI).—Guanidine hydrochloride (4·05 g.) and β-*iso*butoxy-β-*p*-chlorophenylacrylonitrile (10 g.) were added in succession to a solution of sodium ethoxide (from 0·98 g. of sodium) in ethanol (175 c.c.), and the mixture was boiled under reflux for 18 hr. The solvent was removed and the residue was distributed between ether (200 c.c.) and water (100 c.c.). Addition of 10N-hydrochloric acid to the ethereal extract precipitated 2 : 4-*diamino*-6-p-*chlorophenylpyrimidine hydrochloride* (2·9 g.) which separated from water or from methanol–ethyl acetate in colourless needles, m. p. 291—292° (Found: C, 43·4; H, 4·3; N, 20·1; Cl, 26·1. $C_{10}H_9N_4Cl,HCl,H_2O$ requires C, 43·7; H, 4·4; N, 20·4; Cl, 25·8%). The free *base* separated on addition of 2N-sodium hydroxide to a hot aqueous solution of the hydrochloride and crystallised from aqueous ethanol in colourless needles, m. p. 162—163° (Found: C, 54·2; H, 4·2; N, 25·5. $C_{10}H_9N_4Cl$ requires C, 54·4; H, 4·1; N, 25·4%).

2 : 4-*Diamino*-5 : 6-*bis*-p-*chlorophenylpyrimidine* (VII).—Guanidine hydrochloride (1·73 g.) and αβ-bis-*p*-chlorophenyl-β-methoxyacrylonitrile (5·0 g.) were added in succession to a solution of sodium ethoxide (from 0·42 g. of sodium) in absolute ethanol (50 c.c.), and the mixture was boiled under reflux for 3 hr. The solvent was removed under reduced pressure and the residue was shaken with a mixture of ether (100 c.c.) and water (100 c.c.). The 2 : 4-*diamino*-5 : 6-*bis*-p-*chlorophenylpyrimidine* (3·0 g.), which separated, was collected and washed with ether and with water. Recrystallisation from methoxyethanol gave colourless needles, m. p. 290—292°, which powdered on drying at 100° (Found: C, 58·5; H, 3·8; N, 16·9. $C_{16}H_{12}N_4Cl_2$ requires C, 58·0; H, 3·7; N, 16·9%).

Evaporation of the ethereal layer and ethereal washings gave a pale yellow solid (3·3 g.) which separated from ligroin in colourless needles, m. p. 109—110°, and proved to be αβ-*bis*-p-*chlorophenyl*-β-*ethoxyacrylonitrile* (Found: C, 64·2; H, 4·0; N, 4·1; Cl, 22·0. $C_{17}H_{13}ONCl_2$ requires C, 64·2; H, 4·1; N, 4·4; Cl, 22·3%). The m. p. was depressed on admixture with the methyl ether, m. p. 121—122°, to 97—102°.

2 : 4-*Diamino*-5 : 6 : 7 : 8-*tetrahydroquinazoline* (VIII).—(*a*) 1-*iso*Butoxy-2-cyano*cyclo*hex-1-ene was recovered unchanged after being boiled with guanidine in ethanol for 4 hr.

(*b*) Guanidine hydrochloride (3·2 g.) and 1-*iso*butoxy-2-cyano*cyclo*hex-1-ene (5·0 g.) were added in succession to a solution of sodium ethoxide (from 0·77 g. of sodium) in absolute ethanol (75 c.c.), and the mixture was heated in a stainless steel bomb tube at 160—165° (bath) for 2 hr. The cooled contents of the tube were washed out with ethanol and taken to dryness under reduced pressure. The residue was shaken with ether (25 c.c.) and water (25 c.c.), and the solid (0·30 g.) was collected. Recrystallisation from aqueous ethanol yielded pure 2 : 4-*diamino*-5 : 6 : 7 : 8-*tetrahydroquinazoline* as colourless needles, m. p. 241—243°, which became opaque on drying at 100° (Found : C, 58·2; H, 7·5. $C_8H_{12}N_4$ requires C, 58·5; H, 7·4%). Fractionation of the ethereal solution gave (apparently) unchanged enol ether (4·5 g.), n_D^{23} 1·4790.

2 : 6-*Diaminocamph*-2′-*eno*(2′ : 3′-4 : 5)*pyrimidine* (IX).—(*a*) 3-Cyano-2-methoxycamph-2-ene was recovered quantitatively after being boiled with guanidine in ethanol for 4 hr.

(*b*) Guanidine hydrochloride (2·33 g.) and 3-cyano-2-methoxycamph-2-ene (4·2 g.) were added successively to a solution of sodium ethoxide (from 0·56 g. of sodium) in absolute ethanol (75 c.c.), and the mixture was heated in the steel bomb at 160—170° (bath) for 3 hr. The mixture was worked up as before and the residue was partitioned between ether and water. Extraction of the ethereal solution with N-hydrochloric acid, basification, and extraction with ether gave 2 : 6-diaminocamph-2′-eno(2′ : 3′-4 : 5)pyrimidine as a colourless crystalline solid (0·19 g.), which separated from aqueous ethanol in colourless laths, m. p. 241—242° (Found : C, 66·1; H, 8·3. Calc. for $C_{12}H_{18}N_4$: C, 66·0; H, 8·3%). Mayer (*Ann. Sci. Univ. Jassy*, 1937, Pt. I, **23**, 279; *Chem. Zentr.*, 1937, II, 1575) records m. p. 244° for this substance prepared in very low yield from camphorcarboxylic acid.

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