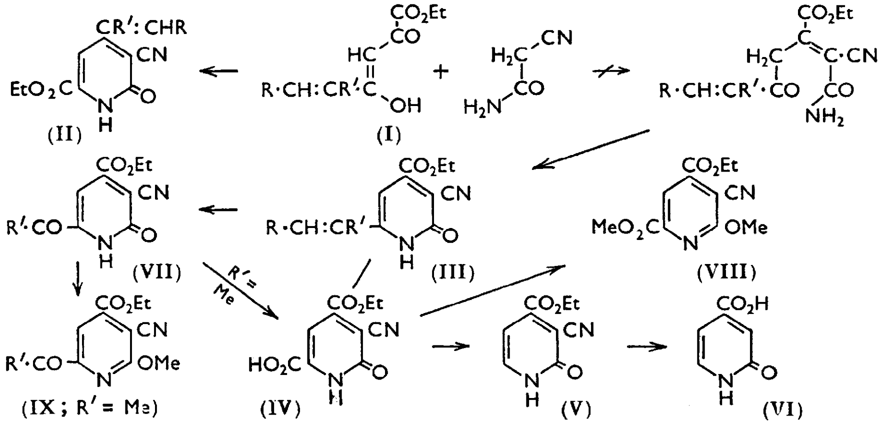
287. *Synthesis of Heterocyclic Compounds from δ-Unsaturated* 1,3-*Di-keto-esters. Part III.*[1] *Ethyl* 3-*Cyano*-6-*styryl*-2-*pyridone*-4-*carboxylates and Their Degradation Products.*

By Latif Rateb and Gabra Soliman.

Condensation of cyanoacetamide with δ-unsaturated 1,3-diketo-esters led to styryl- and (α-substituted styryl)-cyanopyridones. Ozonolysis of the pyridones (III; R′ = H) led to 4-ethoxycarbonyl-2-pyridone-6-carboxylic acid (IV) which was decarboxylated and hydrolysed to 2-pyridone-4-carboxylic acid (VI). Analogously, the pyridones (III; R′ = Me or Ph) yielded ethyl 6-acetyl- and 6-benzoyl-3-cyano-2-pyridone-4-carboxylates (VII). Diazomethane converts the compounds (IV) and (VII; R′ = Me) into 2-methoxypyridine derivatives, whereas (VI) gave methyl 2-pyridone-4-carboxylate. Some of these products have characteristic ultraviolet absorption spectra.

Thorpe's condensation[2] of cyanoacetamide with αβ-acetylenic ketones gives 3-cyano-2-pyridones[3,4] but with αβ-olefinic ketones gives piperidones or cyano-dihydro-2-pyridones depending upon the catalyst used.[5]

The products from cyanoacetamide and 1,3-dicarbonyl compounds have been the subject of controversy. Significant examples of condensation reactions illustrating the comparative reactivity of the two carbonyl groups have been set forth by Bardhan[3] and by Tracy and Elderfield,[6] who synthesised ethyl 3-cyano-6-methyl- and -6-ethyl-2-pyridone-4-carboxylate from ethyl acetyl- and propionyl-pyruvate, respectively, indicating that the carbonyl group adjacent to the electron-attracting ester group is the more reactive.



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[1] Part II, preceding paper.
[2] Thorpe *et al.*, *J.*, 1911, **99**, 422; 1913, **103**, 1586; 1919, **115**, 686.
[3] Bardhan, *J.*, 1929, 2223.
[4] Barat, *J. Indian Chem. Soc.*, 1930, **7**, 851.
[5] Barat, *J. Indian Chem. Soc.*, 1931, **8**, 699.
[6] Tracy and Elderfield, *J. Org. Chem.*, 1941, **6**, 70.

We have studied the action of cyanoacetamide on the δ-unsaturated 1,3-diketo-esters (I) in presence of piperidine. Theoretically, it is improbable that these esters should react as αβ-unsaturated carbonyl compounds to give cyano-dihydro-2-pyridones.[5] On the other hand, they are liable to react as diketomethylene systems, giving the cyanopyridones (II) or (III) or a mixture, depending on the relative reactivities of the two carbonyl groups. However, there is no experimental evidence for the existence of such a mixture since almost pure products separated from the reaction medium.

Differentiation between the two alternatives was achieved by degradation. Ozonolysis of ethyl 3-cyano-6-styryl-2-pyridone-4-carboxylate (III; R = Ph, R′ = H) led to aldehyde and 3-cyano-4-ethoxycarbonyl-2-pyridone-6-carboxylic acid (IV); this acid was decarboxylated to ethyl 3-cyano-2-pyridone-4-carboxylate (V) and the latter hydrolysed to 2-pyridone-4-carboxylic acid (VI). Although this acid melts about 30° higher (355°) than reported by Erlenmeyer *et al.*,[7] the methyl ester has the recorded melting point. This entirely excludes the alternative formula (II) which demands degradation to 2-pyridone-6-carboxylic acid,[8] m. p. 282°.

Fig. 1.

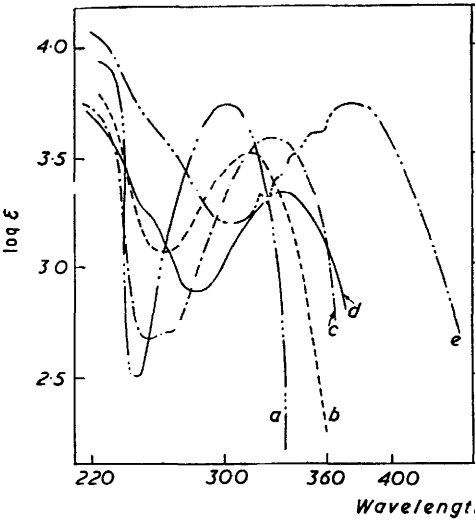

Fig. 2.

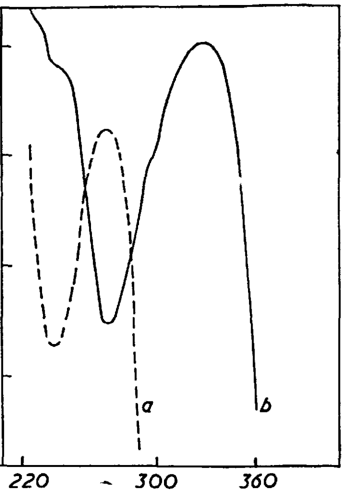

Fig. 1. *Ultraviolet spectra*: (*a*) 2-*pyridone in methanol*,[13] (*b*) 2-*pyridone*-4-*carboxylic acid* (VI), (*c*) *methyl pyridone*-4-*carboxylate*, (*d*) *ethyl* 3-*cyano*-2-*pyridone*-4-*carboxylate* (V), (*e*) 3-*cyano*-4-*ethoxycarbonyl*-2-*pyridone*-6-*carboxylic acid* (IV).

Fig. 2. *Ultraviolet spectra*: (*a*) 2-*ethoxypyridine in methanol*,[13] (*b*) *methyl* 3-*cyano*-4-*ethoxycarbonyl*-2-*methoxypyridine*-6-*carboxylate* (VIII).

Similarly, ozonolysis of analogous substituted styryl esters (III; R′ = H) led to the corresponding aldehydes and the same acid (IV). Contrary to our previous experience for the ozonolysis of ethyl 1-phenyl-5-styrylpyrazole-3-carboxylates,[9] these styrylpyridones resemble 2-vinylpyridine which undergoes ozonolysis to pyridine-2-carboxylic acid and formaldehyde.[10]

The α-substituted styryl esters (III; R′ = Me and Ph) gave on ozonolysis ethyl 6-acetyl- and 6-benzoyl-3-cyano-2-pyridone-4-carboxylate (VII; R′ = Me and Ph); the former keto-ester was readily oxidised to 3-cyano-4-ethoxycarbonyl-2-pyridone-6-carboxylic acid (IV) by the haloform reaction.

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[7] Erlenmeyer, Baumler, and Sorkin, *Helv. Chim. Acta*, 1951, **34**, 496.
[8] Fischer, Hess, and Stahlschmidt, *Ber.*, 1912, **45**, 2459.
[9] Soliman and Rateb, *J.*, 1956, 3663.
[10] Elderfield, " Heterocyclic Compounds," Vol. I, John Wiley & Sons, Inc., New York, 1950, p. 588.

Condensation of cyanoacetamide with these ethyl 2,4-diketohexenoates (I) appears to proceed by Knoevenagel's reaction in which the 2-keto-group is involved in the formation of an intermediate unsaturated amide, whereas the 4-keto-group participates in cyclisation.

However, Henecka[11] who confirmed Bardhan's work[3] regarding the structure of ethyl 3-cyano-6-methyl-2-pyridone-4-carboxylate, believes that condensation of cyanoacetamide with ethyl acetylpyruvate proceeds by Michael addition to an enolate probably formed from the 2-keto-group of the ester.

None of the synthesised esters (III) gave a characteristic colour with ferric chloride or titanium trichloride; and the prototype of this series (III; R = Ph, R′ = H) underwent neither acetylation nor methylation (with diazomethane).

On the other hand, the pyridones (IV) and (VII; R′ = Me) gave characteristic colours with these two reagents indicating the existence of keto–lactam tautomerism; and with diazomethane they readily gave methyl 3-cyano-4-ethoxycarbonyl-2-methoxypyridine-6-carboxylate (VIII) and ethyl 6-acetyl-3-cyano-2-methoxypyridine-4-carboxylate (IX), respectively.

Erlenmeyer *et al.*[7] described 2-pyridone-4-carboxylic acid as a 2-hydroxypyridine derivative. Yet, this acid (VI) in our hands did not give specific colour reactions with ferric chloride or titanium trichloride, or afford methyl 2-methoxypyridine-4-carboxylate[12] by the action of diazomethane In accordance with the fact that 2-hydroxypyridine exists in the 2-pyridone form in neutral media and that 2-methoxypyridines are formed whenever 2-pyridones undergo methylation by diazomethane,[13] the compounds (IV), (V), (VI), and its methyl ester, (VIII), and (IX) can be assigned the annexed formulæ. Moreover, the pyridone and the pyridine structures of most of these compounds have been confirmed by the determination of their ultraviolet absorption spectra in absolute ethanol (see Figures; Unicam spectrophotometer).

Comparison of curves *b* and *c* with *a* for 2-pyridone (Fig. 1) indicates that the shift towards longer wavelengths is attributable to the carbonyl and the methoxycarbonyl groups, whereas the presence of the cyano-group in (IV) and (V) appears to account for the additional shift accompanied by lowering of intensity. An analogous bathochromic shift is also perceptible in curve *b* for the 2-methoxypyridine (VIII) (Fig. 2) when compared with that of 2-ethoxypyridine.[13]

EXPERIMENTAL

Microanalyses were by Herrn Alfred Bernhardt, Mulheim, Ruhr, W. Germany. Light petroleum used had b. p. 50—70°.

Ethyl 3-*Cyano*-6-*styryl*-2-*pyridone*-4-*carboxylate* (III; R = Ph, R′ = H).—Piperidine (1 ml.) was added to a solution of ethyl 2,4-dioxo-6-phenylhex-5-enoate[9] (5 g., 1 mol.) and cyanoacetamide (3·4 g., 2 mol.) in absolute ethanol (80 ml.) at ~60°. The yellow mixture which became deep red, was kept at room temperature for 4 hr.; the *pyridone* (3·5 g.) separated completely. It crystallised from glacial acetic acid in orange diamond-shaped plates, m. p. 278° (Found: 69·3; H, 4·7; N, 10·0. $C_{17}H_{14}O_3N_2$ requires C, 69·4; H, 4·8; N, 9·5%), soluble in aqueous sodium hydroxide to a yellow fluorescent solution, but not giving a characteristic colour with ferric chloride or 5% titanium trichloride. It was unchanged on being heated with acetic anhydride or acetyl chloride, or treated with ethereal diazomethane.

The *styrylpyridones* listed in the Table were prepared analogously. They did not give characteristic colours with ferric chloride or titanium trichloride. All were orange or yellow.

Ethyl 3-*Cyano*-6-(2-2′-*furylvinyl*)-2-*pyridone*-4-*carboxylate*.—This *pyridone* was prepared by condensation of ethyl 2,4-dioxo-6-2′-furylhex-5-enoate[9] (2 g.) with cyanoacetamide (1 g.) in ethanol containing 5 drops of piperidine. It crystallised from glacial acetic acid in brownish-orange aggregate plates (1·5 g.), m. p. 309° (Found: C, 63·3; H, 4·2; N, 9·8. $C_{15}H_{12}O_4N_2$ requires C, 63·4; H, 4·25; N, 9·9%).

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[11] Henecka, *Chem. Ber.*, 1949, **82**, 36.

[12] Isler, Gutman, Straub, Fust, Bohni, and Studer, *Helv. Chim. Acta*, 1955, **38**, 1033.

[13] Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley & Sons, Inc., New York, 1950, pp. 435, 534.

Ethyl 3-*Cyano*-6-(α-*phenylstyryl*)-2-*pyridone*-4-*carboxylate*.—This was prepared when piperidine (10 drops) was added to a warm solution of ethyl 2,4-dioxo-5,6-diphenylhex-5-enoate (1 g., 1 mol.) and cyanoacetamide (0·6 g., 2 mol.) in absolute ethanol (20 ml.). The solution gradually deposited deep-red crystals (0·9 g.), m. p. 210° (Found: C, 73·2; H, 6·4; N, 9·0; OEt, 10·0. $C_{23}H_{18}O_3N_2,C_5H_{11}N$ requires C, 73·8; H, 6·4; N, 9·2; OEt, 9·9%). This pyridone–piperidine *solvate* crystallised from ethanol in a solvent-free *form* (yellow needles), m. p. 274°, having a faint fluorescence and free from piperidine (Found: C, 74·7; H, 5·0; N, 7·5; OEt, 11·7. $C_{23}H_{18}O_3N_2$ requires C, 74·6; H, 4·9; N, 7·6; OEt, 12·2%). When the ethanolic mother-liquor was distilled with steam, the distillate gave a positive colour test for piperidine.[14]

Ethyl 3-*cyano*-6-*styryl*-2-*pyridone*-4-*carboxylates* (III).

R	R′	M. p.	Solvent for crystn.[e]	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
p-MeO·C_6H_4	H	280°	G	66·8	4·9	8·5	$C_{18}H_{16}O_4N_2$	66·7	5·0	8·6
o-MeO·C_6H_4	H	256 [b]	G	67·0	4·9	8·7	$C_{18}H_{16}O_4N_2$	66·7	5·0	8·6
3,4-CH_2O_2:C_6H_3 ...	H	325 [a, c]	P	64·1	4·3	8·4	$C_{18}H_{14}O_5N_2$	63·9	4·2	8·3
3,4-$(MeO)_2C_6H_3$ ...	H	297 [c]	P	64·1	5·2	8·0	$C_{19}H_{18}O_5N_2$	64·4	5·1	7·9
p-NMe_2·C_6H_4	H	323 [a, c]	D	67·3	5·9	12·5	$C_{19}H_{19}O_3N_3$	67·6	5·7	12·5
Ph	Me	219 [c]	E	70·05	5·2	9·2	$C_{18}H_{16}O_3N_2$	70·1	5·2	9·1
p-MeO·C_6H_4	Me	262 [d]	G	67·3	5·4	8·4	$C_{19}H_{18}O_4N_2$	67·4	5·4	8·3
o-MeO·C_6H_4	Me	202 [d]	E	67·7	5·3	8·5	$C_{19}H_{18}O_4N_2$	67·4	5·4	8·3
3,4-CH_2O_2:C_6H_3 ...	Me	284 [c]	G	64·7	4·7	8·0	$C_{19}H_{16}O_5N_2$	64·8	4·6	7·95
3,4-$(MeO)_2C_6H_3$ ...	Me	215 [b]	G	65·0	5·5	7·7	$C_{20}H_{20}O_5N_2$	65·2	5·5	7·6

[a] Block. [b] Rods. [c] Plates. [d] Needles. [e] G = glacial acetic acid; P = pyridine; D = dioxan; E = ethanol.

Ethyl 3-*Cyano*-6-(α-*phenyl*-4-*methoxystyryl*)-2-*pyridone*-4-*carboxylate*.—This *ester* was prepared in 40% yield from ethyl 2,4-dioxo-6-*p*-methoxyphenyl-5-phenylhex-5-enoate as for the previous pyridone and separated in deep red plates, m. p. 260° (Found: C, 71·3; H, 6·1; N, 9·2. $C_{24}H_{20}O_4N_2,C_5H_{11}N$ requires C, 71·7; H, 6·4; N, 8·7%). It crystallised from ethanol in solvent-free *form* as yellowish-orange needles, m. p. 290° (Found: C, 72·4; H, 5·0; N, 7·3. $C_{24}H_{20}O_4N_2$ requires C, 72·0; H, 5·0; N, 7·0%). The mother-liquor gave a positive test for piperidine.[14]

Degradation.—3-*Cyano*-4-*ethoxycarbonyl*-2-*pyridone*-6-*carboxylic acid* (IV). Ozonised oxygen was bubbled through an ice-cold suspension of ethyl 3-cyano-6-styryl-2-pyridone-4-carboxylate (III) (4 g.) in chloroform. After removal of the solvent under reduced pressure, the ozonide was decomposed with water and distilled in steam until benzaldehyde ceased to pass over. On cooling of the residual brownish solution, 3-cyano-4-ethoxycarbonyl-2-pyridone-6-carboxylic acid (2·8 g.) separated (m. p. 242°). It crystallised from boiling water in yellowish-orange plates, m. p. 247° (decomp.), which gave a red colour with ferric chloride and an initial blue colour with 5% titanium trichloride (Found: C, 47·2; H, 4·1; N, 10·9. $C_{10}H_8O_5N_2,H_2O$ requires C, 47·25; H, 4·0; N, 11·0%). Water of crystallisation could not be completely removed from this acid even at 140° in a high vacuum.

Ozonolysis of ethyl 3-cyano-6-4′-methoxystyryl-, -6-2′-methoxystyryl-, and -6-(3,4-methylenedioxystyryl)-2-pyridone-4-carboxylate afforded this acid with *p*-anisic acid, *p*-anisaldehyde, *o*-anisaldehyde, and piperonaldehyde, respectively.

3-Cyano-4-ethoxycarbonyl-2-pyridone-6-carboxylic acid was also obtained when powdered potassium permanganate (1·1 g.) was gradually stirred into a suspension of ethyl 3-cyano-6-styryl-2-pyridone-4-carboxylate (2 g.) in acetone. After being kept at room temperature for 1 hr., the brown precipitate was separated and digested with warm water, and the filtrate was acidified. The acid (0·9 g.), m. p. 237°, thus obtained crystallised from water in yellowish-orange plates, m. p. and mixed m. p. 247°.

Methyl 3-*Cyano*-4-*ethoxycarbonyl*-2-*methoxypyridine*-6-*carboxylate* (VIII).—This *ether* was readily formed by the action of ethereal diazomethane on 3-cyano-4-ethoxycarbonyl-2-pyridone-6-carboxylic acid. It crystallised from light petroleum in rods, m. p. 96°, having a faint-blue

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[14] Feigl, " Spot Tests," Vol. II, Organic Applications, Elsevier, 1954, p. 189.

fluorescence (Found: C, 54·9; H, 4·8; N, 10·5; OMe, 22·5. $C_{12}H_{12}O_5N_2$ requires C, 54·55; H, 4·6; N, 10·6; OMe_2, 23·5%).

Ethyl 3-*Cyano*-2-*pyridone*-4-*carboxylate* (V).—An intimate mixture of 3-cyano-4-ethoxycarbonyl-2-pyridone-6-carboxylic acid (0·5 g.) and freshly precipitated copper powder (0·5 g.) was heated at 230°/0·1—0·3 mm. The decarboxylation product obtained as a yellow sticky sublimate (0·2 g.) was dissolved in chloroform, shaken with sodium hydrogen carbonate solution, washed, and dried. After removal of the solvent, ethyl 3-cyano-2-pyridone-4-carboxylate was recovered as a yellow solid, m. p. 156°, which was freed from an insoluble greenish-yellow impurity by being dissolved in benzene. On concentration of the solution, the pure *ester* was recovered and crystallised from benzene in yellow needles, m. p. 162° (Found: C, 56·3; H, 4·1; N, 14·7. $C_9H_8O_3N_2$ requires C, 56·2; H, 4·2; N, 14·6%). It did not give characteristic colours with ferric chloride or titanium trichloride.

2-*Pyridone*-4-*carboxylic Acid* (VI).—Ethyl 3-cyano-2-pyridone-4-carboxylate (0·5 g.) was refluxed with concentrated hydrochloric acid (10 ml.) for 10 hr. When most of the acidic solution was evaporated and the residue diluted with water, the pyridone acid separated in needles, m. p. 260°. It crystallised from boiling water in needles, m. p. 355° (block) (Found: C, 51·65; H, 3·8; N, 10·0. Calc. for $C_6H_5O_3N$: C, 51·8; H, 3·7; N, 10·1%). Its methyl ester (prepared by diazomethane) crystallised from boiling water in needles, m. p. 211° (Found: C, 54·8; H, 4·8; N, 9·3; OMe, 20·4. Calc. for $C_7H_7O_3N$: C, 55·0; H, 4·6; N, 9·15; OMe, 20·3%).

Ethyl 6-*Acetyl*-3-*cyano*-2-*pyridone*-4-*carboxylate* (VII; R′ = Me).—A suspension of ethyl 3-cyano-6-(α-methylstyryl)-2-pyridone-4-carboxylate (III) (2 g.) in dry chloroform was ozonised until a clear solution was obtained. After removal of the solvent, the ozonide was decomposed and distilled with steam until benzaldehyde ceased to pass over. Cooling the residual solution gave *ethyl* 6-*acetyl*-3-*cyano*-2-*pyridone*-4-*carboxylate* (1·3 g.) as a yellow solid, m. p. 160°. It crystallised from methanol in lemon-yellow needles, m. p. 172°, which gave a red colour with ferric chloride and a pale-brown colour with 5% titanium trichloride (Found: C, 56·2; H, 4·2; N, 12·0. $C_{11}H_{10}O_4N_2$ requires C, 56·4; H, 4·3; N, 12·0%). Its *oxime* crystallised from ethanol in yellow needles, m. p. 276° (decomp.) (Found: N, 16·6. $C_{11}H_{11}O_4N_3$ requires N, 16·9%).

The same keto-ester was obtained by ozonolysis of ethyl 3-cyano-6-(4-methoxy-α-methylstyryl)- and -6-(2-methoxy-α-methylstyryl)-2-pyridone-4-carboxylate.

Oxidation of the Ketone (VII; R′ = Me).—The ketone (0·1 g.) in methanol (15 ml.) was treated with potassium iodide (0·3 g.) in a minimum of water and 10 ml. of 2N-sodium hypochlorite. The mixture was kept at room temperature for 5 min. and the iodoform separated. On acidification of the solution, the acid (IV) separated and crystallised from water in yellowish-orange plates, m. p. and mixed m. p. 247°. It yielded a methyl ester, m. p. and mixed m. p. 96°.

Ethyl 6-*Acetyl*-3-*cyano*-2-*methoxypyridine*-4-*carboxylate* (IX; R′ = Me).—This *ether* was prepared when the foregoing keto-pyridone was kept with ethereal diazomethane for 3 hr. The product crystallised from light petroleum in yellowish-white needles, m. p. 56° (Found: C, 58·0; H, 4·8; N, 11·3; OMe, 12·7. $C_{12}H_{12}O_4N_2$ requires C, 58·1; H, 4·9; N, 11·3; OMe, 12·5%).

Ethyl 6-*Benzoyl*-3-*cyano*-2-*pyridone*-4-*carboxylate* (VII; R′ = Ph).—This keto-ester was prepared when a suspension of ethyl 3-cyano-6-(α-phenylstyryl)-2-pyridone-4-carboxylate (1 g.) in chloroform was ozonised. The *keto-pyridone* (0·6 g.) left after distillation of benzaldehyde with steam crystallised from methanol in yellow plates, m. p. 204°, which gave a pale-brown colour with titanium trichloride and a negative ferric chloride test (Found: C, 65·0; H, 3·9; N, 9·45. $C_{16}H_{12}O_4N_2$ requires C, 64·9; H, 4·1; N, 9·5%).

The same keto-ester was obtained by ozonolysis of ethyl 3-cyano-6-(4-methoxy-α-phenylstyryl)-2-pyridone-4-carboxylate.

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