The Pyrone Series. Part I. 2 : 6-*Diaryl*-4-*pyrones.*

By GABRA SOLIMAN and IBRAHIM EL-SAYED EL-KHOLY.

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Previous syntheses of 2 : 6-diphenylpyrone have a limited preparative value. This and five new 2 : 6-diaryl-4-pyrones have now been obtained in good yields by condensation of ethyl phenylpropiolate with the acetophenones at 0°; two of the new pyrones are accompanied by the isomeric acetylenic diketones (IV). The diarylpyrones give picrates and *N*-hydroxypyridones, and are hydrolysed with potassium hydroxide to ketones and acids, the isolation of which indicates the mode of cleavage.

2 : 6-DIPHENYL-4-PYRONE, which appears to be the only known 2 : 6-diaryl-4-pyrone, was first obtained in traces by Feist (*Ber.*, 1890, **23**, 3726) by heating dehydrobenzoylacetic acid with mineral acids, but unlike the 2 : 6-dimethyl analogue (Feist, *Annalen*, 1890, **257**, 282), it could not be obtained by decarboxylation of the 3 : 5-dicarboxylic acid. In an attempt to find a general synthesis of 2 : 6-diaryl-4-pyrones, Vorländer and Meyer's poor yield of 2 : 6-diphenylpyrone (*Ber.*, 1912, **45**, 3355) could not be improved; also di-*p*-anisylideneacetone tetrabromide failed to give 2 : 6-di-*p*-methoxyphenyl-4-pyrone (cf. Vorländer and Mumme, *Ber.*, 1903, **36**, 1475); equally, Ruhemann's synthesis of 2 : 6-diphenylpyrone (*J.*, 1908, **93**, 431), which appeared to be a suitable alternative, did not lead

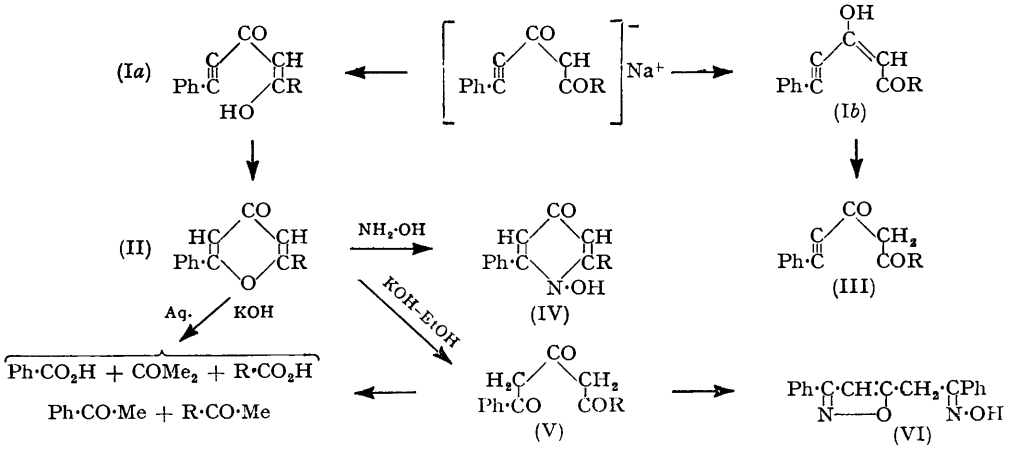
satisfactorily to this pyrone. Meanwhile, we failed to isolate the unidentified product, $C_{25}H_{20}O_3$, whose formation was attributed to the condensation of two mols. of acetophenone with one of ethyl phenylpropiolate.

In the present investigation, it has been possible to prepare 2 : 6-diphenylpyrone in about 50% yield by condensing acetophenone with ethyl phenylpropiolate at 0° in presence of sodium ethoxide in ether. Analogously, 2-phenyl-6-*p*-tolyl-4-pyrone (which could not be prepared by Ruhemann, *J.*, 1910, **97**, 457), 2-*p*-methoxyphenyl-, 2-*p*-chlorophenyl-, 2-*p*-bromophenyl-, and 2-*p*-iodophenyl-6-phenyl-4-pyrones were prepared in satisfactory yields by using substituted acetophenones. 6-Phenylindeno(3′ : 2′-2 : 3)pyrone (Ruhemann, *J.*, 1912, **101**, 1729) was also prepared in 80% yield, and gave a picrate just as the 2 : 6-diarylpyrones did. On the other hand, ethyl phenylpropiolate failed to condense with ethyl methyl ketone or propiophenone.

In each of the above cases, when the reaction mixture was mixed with water, most of the pyrone separated from the alkaline solution on standing or on saturation with carbon dioxide. Evidently, liberation of the pyrone in this manner is due to hydrolysis of a sodio-derivative of the intermediate acetylenic diketone and subsequent rearrangement of the free enol (I*a*) to (II). Otherwise, hydrolysis might lead to (I*b*) which would rearrange to the keto-form (III). The formation of such acetylenic diketones is explicable in the light of the modern interpretation of the Claisen condensation (Arndt and Eistert, *Ber.*, 1936, **69**, 2381; Hauser, *J. Amer. Chem. Soc.*, 1937, **59**, 1823; 1938, **60**, 1957).

The isomeric acetylenic diketone could not be isolated in the case of diphenylpyrone, yet variable amounts of 5-phenyl-1-*p*-tolylpent-4-yne-1 : 3-dione (III; R = *p*-C_6H_4Me) and the methoxyphenyl and bromophenyl analogues accompanied the corresponding pyrones. Those ketones are characterised by their oximes and by their solubility in cold alcoholic alkali, although they do not give a positive test with ferric chloride. Further, they were converted into the pyrones under the conditions stated on p. 1759.

Whereas the conversion of 1 : 4-pyrones into pyridones by the action of aqueous ammonia or ammonium acetate is a general reaction, 2 : 6-diaryl-4-pyrones were resistant to these reagents. 2 : 6-Diphenyl-4-pyridone, however, was prepared indirectly by the action of aqueous ammonia on dehydrobenzoylacetic acid or 2 : 6-diphenyl-4-pyrone-carboxylic acid (Petrenko-Kritschenko and Schöttle, *Ber.*, 1909, **42**, 2020; 1911, **44**, 2826, 3648). Similarly, 2 : 6-diarylpyrones did not react with aniline acetate, whereas the other 1 : 4-pyrones readily give *N*-phenylpyridones (Smirnoff, *Helv. Chim. Acta*, 1921, **4**, 599; Borsche and Peter, *Annalen*, 1927, **453**, 148).



The inertness of the carbonyl group of 1 : 4-pyrones towards carbonyl reagents is in harmony with their resonance formulæ. 2 : 6-Diphenylpyrone oxime, however, was prepared by the action of hydroxylamine on 2 : 6-diphenyl-4-thiopyrone which behaves as a true thioketone (Arndt, Nachtwey, and Scholz, *Ber.*, 1924, **57**, 1903). This yellowish

oxime, m. p. 197°, is different from a white isomer, m. p. 181°, which we have prepared by the action of hydroxylamine on 2 : 6-diphenylpyrone. Evidently, formation of the latter isomer must have involved the oxidic oxygen and would be 1-hydroxy-2 : 6-diphenylpyridone (IV; R = Ph). Other 2 : 6-diaryl-*N*-hydroxypyridones were also prepared and they appear to be analogous to some known *N*-substituted pyridones (Peratoner and Tamburello, *Gazzetta*, 1911, **41**, II, 666; Bedekar, Kaushall, and Deshapande, *J. Indian Chem. Soc.*, 1935, **12**, 465).

Unlike 1 : 4-pyrone, 2 : 6-dimethylpyrone, and 2-methyl-6-phenylpyrone which undergo ring fission to the corresponding triketones by the action of barium hydroxide, 2 : 6-diphenylpyrone was recovered unchanged. Nevertheless, Balenović and Munk (*Archiv Kemiju*, 1946, **18**, 41) prepared *s*-dibenzoylacetone by the action of potassium hydroxide in aqueous methanol: we have prepared the same trione under milder conditions. *s*-Dibenzoylacetone (V; R = Ph) gave with hydroxylamine a crystalline substance, m. p. 145°, the analysis of which is in agreement with the formula (VI) comprising an oxime group and an *iso*oxazole ring.

s-Dibenzoylacetone was readily hydrolysed with boiling aqueous potassium hydroxide to acetone, acetophenone, and benzoic acid. Apparently, acetone and benzoic acid arise from a symmetrical cleavage of the triketone, whereas cleavage between $C_{(2)}$ and $C_{(3)}$ or between $C_{(3)}$ and $C_{(4)}$ leads to acetophenone directly or through decarboxylation of benzoylacetic acid. The same hydrolysis products were also obtained from 2 : 6-diphenylpyrone, and this is evidence in favour of the formation of triketones before the degradation of the pyrones. The other 2 : 6-diarylpyrones were more resistant to the action of the alkali, but their hydrolysis products indicate that they undergo the same mode of cleavage.

Experimental

Light petroleum used had b. p. 60—80°.

2 : 6-*Diphenylpyrone*.—When ethyl phenylpropiolate and acetophenone were condensed as described by Ruhemann, the total yield of the pyrone as hydrochloride and as picrate was 12%.

Acetophenone (3·5 g., 1 mol.) and ethyl phenylpropiolate (5 g., 1 mol.) were successively added to an ice-cold suspension of sodium ethoxide (1·95 g., 1 mol.), and the the mixture was kept in the ice-chest for 2 days, then mixed with water. The ethereal solution was washed and evaporated. The reddish oil (2·5 g.) recovered gave traces of the pyrone as picrate. The alkaline solution and washings gradually became turbid and in 6—8 hr. the pyrone separated almost completely; this could be enhanced by saturation with carbon dioxide. The pyrone (50%) crystallised from benzene–light petroleum in needles, m. p. 140° (Found: C, 81·9; H, 5·0. Calc. for $C_{17}H_{12}O_2$: C, 82·2; H, 4·9%). The alkaline mother-liquor yielded 1 g. of phenylpropiolic acid.

2 : 6-*Diphenylpyrone picrate* was prepared in alcohol and crystallised from benzene in yellow needles, m. p. 183° (Found: C, 57·8; H, 3·2; N, 9·1. $C_{23}H_{15}O_9N_3$ requires C, 57·8; H, 3·2; N, 8·8%); it was hydrolysed to the pyrone when its alcoholic solution was warmed with dilute aqueous ammonia.

1-*Hydroxy*-2 : 6-*diphenylpyridone*.—This was prepared when an alcoholic solution of the pyrone (0·8 g.) was heated for 6 hr. with hydroxylamine hydrochloride (0·8 g.) and sodium acetate (0·8 g.) in water (3 ml.). The *pyridone* (50% yield), which crystallised on cooling, was washed with ether. It recrystallised from benzene–methanol in needles, m. p. 181°, depressed on admixture with 2 : 6-diphenylpyrone oxime (Arndt, Nachtwey, and Scholz, *loc. cit.*) (Found: N, 5·2. $C_{17}H_{13}O_2N$ requires N, 5·3%).

2 : 6-Diphenylpyrone was recovered unchanged after being heated with ammonium acetate in acetic acid for 10 hr. at 100°, or with aniline acetate in acetic acid for 8 hr. at 100°. When a mixture of the pyrone (0·5 g.), barium octahydrate (0·5 g.), and water (100 ml.) was boiled for 10 min., and then filtered, and the same process was repeated 5 times, 0·35 g. remained unchanged. The combined filtrates gave traces of acetophenone on distillation with steam.

s-*Dibenzoylacetone*.—This was obtained when a solution of the pyrone (1 g.) in absolute alcohol (15 ml.) and 10% alcoholic potassium hydroxide (10 ml.) was kept at room temperature for 2 days. The alcohol was then distilled under reduced pressure, the residue mixed with water and extracted with ether, and the alkaline solution acidified. The triketone (0·6 g.)

crystallised from light petroleum in yellow plates, m. p. 111° (cf. Balenovic and Munk, *loc. cit.*) (Found : C, 76·5; H, 5·3. Calc. for $C_{17}H_{14}O_3$: C, 76·7; H, 5·3%). It was also prepared by the action of alcoholic sodium ethoxide.

The iso*Oxazole Oxime* (VI).—5-(2-*Hydroxyimino*-2-*phenylethyl*)-3-*phenyl*iso*oxazole* was obtained when an alcoholic solution of *s*-dibenzoylacetone (0·2 g.) was heated for 3 hr. with hydroxylamine hydrochloride (0·2 g.) and sodium acetate (0·2 g.). It crystallised from light petroleum in prisms, m. p. 145° (Found : C, 73·3; H, 4·9; N, 10·1. $C_{17}H_{14}O_2N_2$ requires C, 73·4; H, 5·1; N, 10·1%).

s-Dibenzoylacetone (0·3 g.) was completely hydrolysed when boiled with 5% aqueous potassium hydroxide (10 ml.) for 1 hr. Its degradation products, acetone, acetophenone, and benzoic acid, were identified as described below.

Action of 20% *Aqueous Potassium Hydroxide* on 2 : 6-*Diphenyl*-4-*pyrone*.—The pyrone (1 g.) was refluxed with 20 ml. of the alkali in an all-glass apparatus for 4 hr. The mixture was then steam-distilled, the first 100 ml. and the next 400 ml. of the ketonic distillate being collected separately. Subsequently, the alkaline mixture was freed from the unchanged pyrone and resin (0·1 g.) by extraction with ether, acidified with 10% sulphuric acid, and steam-distilled until 1 l. of the acidic distillate had collected. The first ketonic distillate was freed from acetophenone by extraction with ether and treated with the vanillin reagent (Snell : "Colorimetric Methods of Analysis," Van Nostrand, New York, 1937, Vol. II, p. 96); it developed the reddish-brown colour specific for acetone.

In another identical experiment, the total ketonic distillate gave 1·4 g. of a mixed 2 : 4-dinitrophenylhydrazone, m. p. 180—190°, which were extracted with hot alcohol. The solution gave on concentration acetone 2 : 4-dinitrophenylhydrazone which crystallised from dilute alcohol in yellow needles, m. p. and mixed m. p. 124°. The insoluble residue crystallised from acetic acid in red needles, m. p. 247°, identical with acetophenone 2 : 4-dinitrophenylhydrazone.

The acidic distillate from either of the two experiments gave a negative test for acetic acid and about 0·5 g. of benzoic acid.

2-p-*Methoxyphenyl*-6-*phenyl*-4-*pyrone*.—*p*-Methoxyacetophenone (4·3 g.) and ethyl phenylpropiolate (5 g.) were condensed as for diphenylpyrone. The mixture was mixed with water, and the suspended precipitate was shaken with ether and water. The oily residue (4·3 g.) recovered from the ethereal solution gave a yellow solid (1·7 g.), m. p. 135°, on treatment with cold methanol. The alkaline solution and washings deposited a yellowish precipitate (1·8 g.), m. p. 140—145° after being washed with cold ether. The average yield of solids including the pyrone recovered as picrate was 50%. The solid products gave on fractional crystallisation from methanol, ethanol, or benzene the diketone (III; R = *p*-C_6H_4·OMe), m. p. 138°, which crystallised first, and the pyrone, m. p. 150—152°, which was recovered from the mother-liquors. The *pyrone* recrystallised from benzene in sulphur-yellow rhombs, m. p. 160—161°, which recrystallised from 5% alcoholic potassium hydroxide almost unchanged (Found : C, 77·6; H, 5·2; OMe, 11·1. $C_{18}H_{14}O_3$ requires C, 77·7; H, 5·1; OMe, 11·2%). It dissolved in hot hydrochloric acid and, on cooling, the *pyrone hydrochloride* separated in golden-yellow needles, m. p. 185° (Found : Cl, 10·5. $C_{18}H_{15}O_3Cl$ requires Cl, 11·3%). The hydrochloride was readily hydrolysed to the pyrone. The *pyrone picrate* was prepared in alcohol or benzene and crystallised from benzene in orange needles, m. p. 202° (Found : N, 8·3. $C_{24}H_{17}O_{10}N_3$ requires N, 8·3%). It gave the free pyrone with aqueous ammonia.

1-*Hydroxy*-2-p-*methoxyphenyl*-6-*phenylpyridone* was prepared as described above and crystallised from benzene in needles, m. p. 185° (Found : C, 73·5; H, 5·4; N, 4·6. $C_{18}H_{15}O_3N$ requires C, 73·7; H, 5·2; N, 4·8%).

By the action of 20% aqueous potassium hydroxide as above, about half of the 2-*p*-methoxyphenyl-6-phenyl-4-pyrone used was hydrolysed. The ketonic distillate gave a positive test for acetone and a mixed 2 : 4-dinitrophenylhydrazone, m. p. 190—200°, from which *p*-methoxyacetophenone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 207—208°, was isolated after extraction with hot alcohol and fractional crystallisation from acetic acid. The acidic distillate gave benzoic acid, but the less volatile *p*-anisic acid, m. p. 184°, was isolated from the acidic mixture by extraction with ether.

1-p-*Methoxyphenyl*-5-*phenylpent*-4-*yne*-1 : 3-*dione* (III).—The *diketone* crystallised from alcohol in yellow cubes or from benzene in yellow needles, m. p. 140°, which gave a negative test with ferric chloride (Found : C, 77·5; H, 5·2. $C_{18}H_{14}O_3$ requires C, 77·5; H, 5·1%). It was recovered unchanged after treatment with ammonium acetate or aniline acetate, and did not give a picrate. The oxime was isolated when a solution of the diketone (0·5 g.) in alcohol was heated for 4 hr. with hydroxylamine hydrochloride (0·5 g.) and sodium acetate (0·5 g.). It

crystallised from benzene–light petroleum in yellowish needles, m. p. 187° (Found : C, 73·7; H, 5·3; N, 4·8. $C_{18}H_{15}O_3N$ requires C, 73·7; H, 5·2; N, 4·8%).

The diketone readily dissolved in 5% alcoholic potassium hydroxide, and after the reddish-brown solution had been diluted with water the resinous precipitate was extracted with ether. The residue recovered from the ethereal solution gave with picric acid a reddish-orange precipitate from which the pyrone picrate, m. p. 202°, was isolated by crystallisation.

2-*Phenyl*-6-p-*tolyl*-4-*pyrone*.—Methyl *p*-tolyl ketone (3·85 g.) and ethyl phenylpropiolate (5 g.) were condensed at 0°, and the product worked up as before. The oil (3 g.) recovered from the ethereal solution gave, on cooling, a yellowish solid (0·7 g.), m. p. 129°, after being washed with ether. The alkaline solution deposited 3·4 g. of a brownish-yellow solid, m. p. 127—137°. The average yield including pyrone recovered as picrate was 57%. These solids gave on fractional crystallisation from methanol the diketone (III; R = *p*-C_6H_4Me), m. p. 133°, which crystallised first, and the pyrone, m. p. 145—147°, which was recovered from the mother-liquors.

The *pyrone* crystallised from benzene–light petroleum in yellowish needles, m. p. 150°, which recrystallised almost unchanged from 5% alcoholic potassium hydroxide (Found : C, 82·6; H, 5·4. $C_{18}H_{14}O_2$ requires C, 82·4; H, 5·4%). Its *picrate* crystallised from alcohol in yellow needles, m. p. 195° (Found : N, 8·7. $C_{24}H_{17}O_9N_3$ requires N, 8·6%).

1-*Hydroxy*-2-*phenyl*-6-p-*tolylpyridone* was prepared by the action of hydroxylamine on the pyrone in alcohol, and crystallised from benzene in needles, m. p. 184° (Found : N, 4·8. $C_{18}H_{15}O_2N$ requires N, 5·1%).

This pyrone was partly hydrolysed with 20% potassium hydroxide. The ketonic distillate gave a positive test for acetone, and a 2 : 4-dinitrophenylhydrazone which crystallised from acetic acid in red needles, m. p. 228—233°, elevated on admixture with the 2 : 4-dinitrophenylhydrazones of acetophenone or methyl *p*-tolyl ketone. In addition to benzoic acid, *p*-toluic acid, m. p. 181°, was isolated from the acidic mixture.

5-*Phenyl*-1-p-*tolylpent*-1-*yne*-1 : 3-*dione* recrystallised from benzene–light petroleum in pale yellowish prismatic needles, m. p. 133°, which gave a negative test with ferric chloride (Found : C, 82·3; H, 5·3. $C_{18}H_{14}O_2$ requires C, 82·4; H, 5·4%). Its *oxime* crystallised from benzene in needles, m. p. 190° (Found : C, 77·7; H, 5·5; N, 5·2. $C_{18}H_{15}O_2N$ requires C, 77·9; H, 5·5; N, 5·1%).

When a cold saturated solution of the diketone in alcohol or benzene was mixed with the respective solution of picric acid, the pyrone picrate gradually separated. The diketone was also converted into the pyrone when its solution in alcoholic potassium hydroxide was diluted with water.

2-p-*Chlorophenyl*-6-*phenyl*-4-*pyrone*.—This *pyrone* was prepared in 90% yield by condensation of *p*-chloroacetophenone (4·45 g.) with ethyl phenylpropiolate (5 g.). It crystallised from benzene or carbon tetrachloride in pale yellowish needles, m. p. 160° (Found : C, 71·2; H, 4·1; Cl, 12·9. $C_{17}H_{11}O_2Cl$ requires C, 72·2; H, 3·9; Cl, 12·6%). Better analyses for carbon could not be obtained irrespective of repeated crystallisation or dehydration. The *pyrone picrate* crystallised from alcohol in yellow needles, m. p. 177° (Found : N, 8·3. $C_{23}H_{14}O_9N_3Cl$ requires N, 8·3%). 1-*Hydroxy*-2-p-*chlorophenyl*-6-*phenylpyridone*, prepared as above, crystallised from benzene in needles, m. p. 188—190° (Found : N, 4·4. $C_{17}H_{12}O_2NCl$ requires N, 4·7%).

2-p-*Bromophenyl*-6-*phenyl*-4-*pyrone*.—The *bromo*-compound was prepared in 80% yield from *p*-bromoacetophenone (5·7 g.) and ethyl phenylpropiolate (5 g.) and crystallised from benzene in yellowish needles, m. p. 172° (Found : C, 62·4; H, 3·5; Br, 23·9. $C_{17}H_{11}O_2Br$ requires C, 62·4; H, 3·4; Br, 24·4%). Its *picrate* crystallised from alcohol in yellow needles, m. p. 163° (Found : N, 7·7. $C_{23}H_{14}O_9N_3Br$ requires N, 7·6%). 2-p-*Bromophenyl*-1-*hydroxy*-6-*phenyl*-4-*pyridone*, prepared as usual, crystallised from benzene in needles, m. p. 183° (Found : N, 4·2. $C_{17}H_{12}O_2NBr$ requires N, 4·1%).

During the purification of the pyrone by fractional crystallisation from alcohol, traces of 1-p-*bromophenyl*-5-*phenylpent*-4-*yne*-1 : 5-*dione* were obtained. This recrystallised from benzene in yellow needles, m. p. 190° (Found : C, 62·5; H, 3·4; Br, 24·0. $C_{17}H_{11}O_2Br$ requires C, 62·4; H, 3·4; Br, 24·4%).

2-p-*Iodophenyl*-6-*phenyl*-4-*pyrone*.—This *compound* was prepared in 75% yield by condensing *p*-iodoacetophenone (Kimura, *Ber.*, 1934, **67**, 395) with the ester at 0°, and crystallised from benzene in lemon-yellow needles, m. p. 191° (Found : C, 54·7; H, 3·2; I, 33·9. $C_{17}H_{11}O_2I$ requires C, 54·5; H, 3·0; I, 33·9%).

The halogen-containing pyrones were more resistant to the action of potassium hydroxide, and the portions hydrolysed gave positive tests for acetone and mixed 2 : 4-dinitrophenyl-

hydrazones. Together with benzoic acid, *p*-chlorobenzoic, *p*-bromobenzoic, and *p*-iodobenzoic acid respectively were also isolated.

6-*Phenylindeno*(3′ : 2′-2 : 3)*pyrone*.—This was prepared in 80% yield by condensation at 0°, and gave a *picrate* which crystallised from alcohol in yellow prisms, m. p. 217° (Found : N, 8·9. $C_{24}H_{15}O_9N_3$ requires N, 8·6%).

Attempts to condense ethyl methyl ketone or propiophenone with ethyl phenylpropiolate at 0° led to oils which did not give pyrones as hydrochlorides or picrates.

CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE,
ALEXANDRIA UNIVERSITY, MOHARRAM BEY, ALEXANDRIA. [*Received, November 18th*, 1953.]