

CONDENSATION OF ISATIN WITH DIKETONES

GJ. STEFANOVIĆ, M. PAVIČIĆ-WOSS, LJ. LORENC* and M. LJ. MIHAILOVIĆ
 Institute of Chemistry, Faculty of Sciences, University of Belgrade, Yugoslavia

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Abstract—The condensation of isatin with enolisable acyclic and alicyclic 1:3-diketones has been investigated and the structures of the acylated cinchoninic acids obtained have been determined. The condensation of acetylacetone with potassium isatate is also described. Condensations of isatin with 1:3-cyclohexadiones in neutral or acid media has been shown to give products different from those in alkaline condensation.

SEVERAL acyclic 1:3-diketones with a methylene group between two carbonyl groups undergo the Pfitzinger reaction^{1,2,3} with isatin or isatic acid to yield the corresponding



2-substituted-3-acylcinchoninic acids (a) $R = R' = \text{Me}$; (b) $R = \text{Me}$, $R' = \text{Et}$; (c) $R = \text{Me}$; $R' = \text{Ph}$; (d) $R = R' = \text{Ph}$.

Acetylacetone and isatin yield 2-methyl-3-acetyl-cinchoninic acid (Ia) the structure of which was established by (i) oxidation to 2-methyl-3:4-quinolinedicarboxylic acid,⁴ (ii) decarboxylation to 3-acetylquinaldine,⁵ (iii) heating with KOH to give quinaldine. The best yields of (Ia) (73%, 80%) were respectively obtained by carrying out the condensation in presence of KOH or by heating with anhydrous potassium isatate in absence of a solvent. Strong alkali hydrolysed acetylacetone to acetone which condensed with potassium isatate to give 2-methylcinchoninic acid.

2-Methyl-3-propionylcinchoninic acid (Ib) is obtained by condensing propionylacetone with anhydrous potassium isatate in absence of solvent. Only a resinous product is formed in strongly alkaline solution. The position of the Me group in (Ib) was determined by converting the acid into quinaldine. Anhydrous potassium isatate and benzoylacetone condense to give 2-methyl-3-benzoylcinchoninic acid (Ic), the structure of which was proved by decarboxylation to 3-benzoylquinaldine,⁶ and degradation to quinaldine and benzoic acid. Under strongly alkaline conditions benzoylacetone gives acetophenone⁷ which condenses with potassium isatate giving

* Lj. Lorenc, PhD. dissertation.

¹ W. C. Sumpter, *Chem. Rev.* **34**, 393-434 (1944).

² W. Steinkopf and H. J. von Petersdorff, *Liebigs Ann.* **543**, 119 (1940) N.P. Buu-Hoi and R. Royer, *Bull. Soc. Chim. Fr.* 820 (1947); N.P. Buu-Hoi and R. Royer, *Rec. Trav. Chim.* **67**, 175 (1948); J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.* 393 (1955).

³ E. Noelting and A. Herzbaum, *Ber.* **44**, 2585 (1911).

⁴ V. M. Micović, *Bull. Soc. Chim. Fr.* **6**, 1156 (1939).

⁵ J. Eliasberg and P. Friedländer, *Ber.* **25**, 1752 (1892); O. Stark, *Ibid.* **40**, 3425 (1907).

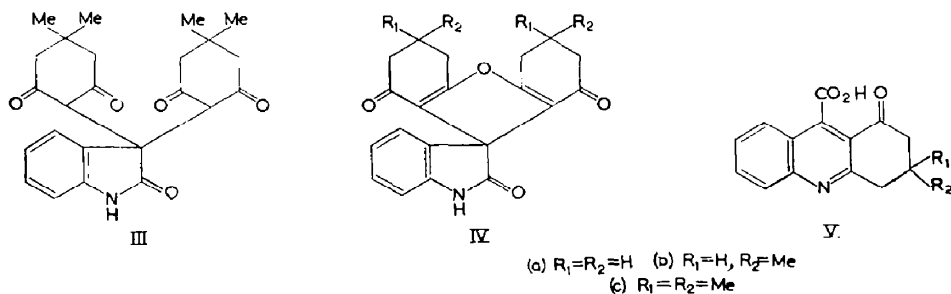
⁶ O. Stark, *Ber.* **42**, 715 (1909).

⁷ E. Fischer and C. Bülow, *Ber.* **18**, 2132 (1885); L. Claisen and O. Lowman, *Ber.* **21**, 1152 (1888); R. Connor and H. Adkins, *J. Amer. Chem. Soc.* **54**, 3420 (1932).

2-phenylcinchoninic acid. Dibenzoylmethane and anhydrous potassium isatate react to give 2-phenyl-3-benzoylcinchoninic acid (Id) (63%), and conversion of the acid to 2-phenyl-3-benzoylquinoline⁸ and subsequently to 2-phenylquinoline established the structure of the acid.

Potassium isatate reacts with 1:4-diketones e.g. acetylacetone giving 2-methyl-3-acetylcinchoninic acid (II) which on treatment with KOH gives 2:3-dimethylquinoline.

Vorländer *et al.*⁸ have shown that 1:3-cyclohexanediones react with isatin in glacial acetic acid giving the corresponding substituted octahydroxanthenes (IV). It has now been found that 1:3-cyclohexanedione and 5-methyl-1:3-cyclohexanedione react under various conditions to give the corresponding octahydroxanthenes, (IVa and b) and 5:5-dimethyl-1:3-cyclohexanedione (methone) reacts with isatin in ethanol or in absence of solvent yielding the alkali soluble 3:3-bis[5':5'-dimethyl-1':3'-dioxo-2'-cyclohexyl]oxindole (III)*, which is also readily obtained when isatin and methone are refluxed in aqueous ethanol containing KOH. In glacial acetic acid methone and isatin yield *spiro*[octahydro-3:3:6:6-tetramethyl-1:8-dioxoxanthene-9:3'-oxindole] (IVc). The cyclisation of (III) to (IVc) takes place readily in boiling glacial acetic acid. Condensation of anhydrous potassium isatate with one mole of 5-methyl- or 5:5-dimethyl-1:3-cyclohexanedione takes a different course. In addition to (IVb) and (IVc) and (III), 3-substituted-1:2:3:4-tetrahydro-1-oxo-9-acridinecarboxylic acids (Vb) and (Vc) are obtained. The structure (V) is proposed for the acridinecarboxylic acids on the assumption that isatic acid reacts with the methylene group situated between the two keto groups of the 1:3-cyclohexanedione in analogy with the reaction of open chain 1:3-diketones with isatic acid.



In the condensation of 1:3- and 1:4-diketones with isatic acid under various conditions, the only procedure which gives satisfactory yields of 2:3-substituted cinchoninic acids (I, II, V) consists in heating the diketones with anhydrous potassium isatate in absence of solvent. Condensations in aqueous KOH (the usual conditions for Pfitzinger reaction) gives lower yields and frequently causes decomposition of the diketones with the formation of resinous by-products.

* An enolisable product similar to (III) was prepared by Fischer and Cirulis.⁹

⁸ D. Vorländer, C. Ihle, H. Volkholz, M. P. Neumann, G. von Brasche and W. Zeh, *Z. Anal. Chem.* **77**, 241 (1929).

⁹ W. M. Fischer and A. Cirulis, *Liebigs Ann.* **514**, 261 (1934).

EXPERIMENTAL

Melting points are not corrected.

2-Methyl-3-acetylcinchoninic acid (Ia)

Acetylacetone (18 g, 6 moles) in ethanol (20 ml) was added to isatin (4.4 g, 1 mole) in aqueous potassium hydroxide (11.3 g, 15%, 1 mole), and the mixture heated for 6 hr. After evaporation of ethanol, the aqueous solution was extracted with ether and acidified with dilute HCl. The crude product (5 g, 72.7%), m.p. 189°, was crystallised from ethanol to give the pure acid (Ia) m.p. 198° (Found: C, 68.07; H, 4.98; N, 6.43. $C_{13}H_{11}O_3N$ requires: C, 68.11; H, 4.84; N, 6.11%).

(b) A mixture of dry potassium isatate* (2 g, 1 mole) and acetylacetone (5 g, 5 moles) was refluxed (3 hr) and on cooling, the solid product was washed twice with ether, dissolved in water (25 ml), and the solution acidified with dilute HCl. The precipitate was filtered (1.83 g, 79.9%) and crystallised from ethanol to give the pure acid, (Ia) m.p. 195–196°. It did not depress the melting point of a sample prepared according to (a).

Methyl 2-methyl-3-acetylcinchoninate. The acid (Ia, 4 g) was converted, in the usual manner, by means of diazomethane to the *methyl ester* m.p. 55–56° (from ethanol). (Found: C, 64.03; H, 5.74; N, 5.43; $C_{14}H_{13}O_3NH_2$ requires: C, 64.35; H, 5.79; N, 5.36%). For analysis, the ester was dried under reduced pressure (20 mm) in the absence of drying agents. In the presence of phosphorus pentoxide or potassium hydroxide, the compound lost water of crystallisation and liquefied.

2-Methyl-3:4-quinoline dicarboxylic acid. A solution of sodium hypochlorite (344 g) (prepared by introducing 69 g of chlorine into 275 g of 20% aqueous sodium hydroxide, at 0°) was added to (Ia) (13 g, 1 mole) dissolved in 20% aqueous sodium hydroxide (11.4 g, 1 mole). After the vigorous reaction had subsided, the mixture was heated (steam-bath) for 30 min, chloroform was evaporated and the cooled solution treated with solid sodium hydrogen sulphite and the acid (13 g, 100%) precipitated with dilute HCl, and identified as the *dimethyl ester*, m.p. 61–62° (from petroleum ether), which was prepared according to Micović⁴, *picrate*, m.p. 156°. Both compounds gave no depression of m.p. with the corresponding authentic samples.

3-Acetylquinaldine. The acid (Ia, 1.15 g) was slowly heated, under reduced pressure (15 mm), to 200°, when decarboxylation took place. On raising the temperature to 240°, an oil distilled which, on cooling, gradually solidified. After crystallisation from petroleum ether it melted at 74–75°⁵ (Found: C, 77.82; H, 6.05; N, 7.70; Calc. for $C_{13}H_{11}ON$ C, 77.81; H, 5.99; N, 7.56%).

Quinaldine. The acid (Ia, 1 g) and powdered potassium hydroxide (2.5 g) and a few drops of water were heated with a free flame. The oil, which distilled with water, was dissolved in dilute HCl and converted into the yellow chloroplatinate of quinaldine, m.p. 226° (from water).

2-Methylcinchoninic acid

Freshly prepared acetylacetone (15 g, 3 moles) was dissolved in ethanol (30 ml) and added to isatin (7.3 g, 1 mole) in aqueous potassium hydroxide (56 g, 1 mole). After heating 8 hr (steam-bath), the mixture was treated as described above to give *2-methylcinchoninic acid* (6.8 g, 72.67%) m.p. 241° (from ethanol), did not depress the m.p. of an authentic sample, prepared from isatin and acetone.^{10,11} (Found: C, 70.30; H, 4.87. Calc. for $C_{11}H_9O_2N$: C, 70.58; H, 4.85%).

2-Methyl-3-propionylcinchoninic acid (Ib)

A mixture of dry potassium isatate (2 g, 1 mole) and propionylacetone (6 g, 5.35 moles) was slowly heated to 150°. After the mixture had ceased reacting (about 20 min), the temp was maintained for 1 hr at 100° (prolonged heating at 150° gave resinous products). The cooled mixture was treated with water (50 ml) and the unreacted diketone extracted with ether. On acidifying the aqueous solution with dilute HCl the crude acid (Ib, 1.6 g, 66.7%) separated as an oil which solidified. It crystallised from aqueous ethanol m.p. 132° (Found: C, 68.9; H, 5.36; N, 5.82. $C_{14}H_{13}O_3N$ requires: C, 69.13; H, 5.38; N, 5.76%).

Quinaldine. This degradation product was obtained from (Ib) and identified.

* This salt was prepared from isatin and an equivalent amount of 20% aqueous potassium hydroxide, at temperatures below 40°. Using an excess of alkali, at higher temp, other products are formed (to be published).

¹⁰ W. Pfitzinger, *J. Prakt. Chem.* **33**, 100 (1886).

¹¹ W. Pfitzinger, *J. Prakt. Chem.* **38**, 583 (1888); **56**, 283 (1897).

2-Methyl-3-benzoylcinchoninic acid (Ic)

A mixture of dry potassium isatate (4.1 g, 1 mole) and benzoylacetone (16 g, 4 moles) was heated at 120° (10 hr). On cooling, the product was treated with water (50 ml) and excess benzoylacetone removed with ether. The aqueous solution was acidified with dilute HCl and the filtered precipitate was extracted with 3% aqueous sodium hydrogen carbonate to separate the acid from unreacted isatin. Treatment of the bicarbonate solution with dilute HCl gave 2.4 g (41.8%) of (Ic). After crystallisation from ethanol-pyridine (8 : 2) it melted at 280° (Found: C, 74.30; H, 4.76; N, 4.66. $C_{18}H_{13}O_3N$ requires: C, 74.21; H, 4.49; N, 4.81%).

The condensation in water-ethanol solution in the presence of 1 mole of potassium hydroxide, as described above gave much lower yields of (Ic), namely, 7.5–26% for the crude product and depended upon the duration of heating (8–60 hr).

Methyl 2-methyl-3-benzoylcinchoninate. Treatment of the acid (Ic) with ethereal diazomethane, gave the corresponding *methyl ester* m.p. 119–120° (from ethanol) (Found: C, 74.97; H, 5.22; N, 4.47. $C_{18}H_{15}O_3N$ requires: C, 74.74; H, 4.95; N, 4.59%).

3-Benzoylquinaldine. The acid (Ic, 1.5 g) was slowly heated, under reduced pressure (5 mm), to 290–300°, when decarboxylation took place. On raising the temp to 310–320° *3-benzoylquinaldine* distilled which solidified on cooling. After crystallisation from ligroin, it melted at 61–62° (Found: C, 82.50; H, 5.28; N, 5.79. Calc. for $C_{17}H_{13}ON$: C, 82.56; H, 5.30; N, 5.67%). *3-Benzoylquinaldine oxime*, m.p. 229–231° (from ethanol).⁶

Quinaldine. This was obtained from (Ic) and benzoic acid in the residue from the distillation was identified.

2-Phenylcinchoninic acid (Cinchophen)

To a solution of isatin (4.9 g, 1 mole) in aqueous potassium hydroxide (37 g, 20%) benzoylacetone (5.35 g, 1 mole) in ethanol (30 ml) was added, and the mixture heated (steam-bath, 8 hr). Working up as described above gave cinchophen (5.5 g, 66.9%) m.p. 208–209° (from aqueous ethanol). The acid was identified by comparison with an authentic specimen prepared from isatin and acetophenone and by degradation to 2-p-enylquinoline m.p. 83–84°, chloroplatinate m.p. 209°.

2-Phenyl-3-benzoylcinchoninic acid (Id)

A mixture of dry potassium isatate (4.1 g, 1 mole) and dibenzoylmethane (18 g, 4 moles) was heated (10 hr) at 140–150°. The condensation product was treated as described above to give crude (Id) (4.5 g, 63.2%). After several crystallisations from ethanol the m.p. was raised to 257° (Found: C, 77.98; H, 4.34; N, 4.01. $C_{23}H_{15}O_3N$ requires: C, 78.17; H, 4.28; N, 3.96%).

Methyl 2-phenyl-3-benzoylcinchoninate. This was prepared from (Id) and ethereal diazomethane and after crystallisation from ethanol melted at 159° (Found: C, 78.92; H, 4.67; N, 4.17. $C_{24}H_{17}O_3N$ requires: C, 78.46; H, 4.66; N, 3.81%).

2-Phenyl-3-benzoylquinoline. The acid (Id, 2 g) was slowly heated, under reduced pressure (5 mm), to a few degrees above its melting point (257–265°). After decarboxylation, the temp was raised to 290°. The base distilled and solidified on cooling, and on crystallisation from methanol, *2-phenyl-3-benzoylquinoline* melted at 133–135° (Found: C, 85.25; H, 4.79; N, 4.54. $C_{22}H_{16}ON$ requires: C, 85.41; H, 4.89; N, 4.53%).

2-Phenylquinoline. This base was prepared from (Id) and potassium hydroxide as described for quinaldine. Recrystallised from dilute ethanol it melted at 83°.¹²

2-Methyl-3-acetonilcinchoninic acid (II)

A mixture of dry potassium isatate (2 g, 1 mole) and acetonilacetone (10.26 g, 9 moles) was heated for 2 hr at 160–180°. The unreacted diketone was removed by distillation under reduced pressure, and the residue was treated with water (100 ml). The insoluble resinous material was filtered and the filtrate acidified with dilute HCl and the precipitate (0.8 g, 32.9%) washed with ice-cold ethanol and crystallised from boiling water. *2-Methyl-3-acetonilcinchoninic acid* melted at 280–281° (Found: C, 69.70; H, 4.75; N, 5.62. $C_{14}H_{13}O_3N$ requires: C, 69.13; H, 5.38; N, 5.76%).

Attempts to condense isatin with acetonilacetone in aqueous potassium hydroxide failed. Only resinous material was obtained, which could not be purified.

¹² O. Doebner and W. von Miller, *Ber.* 16, 1664 (1883).

2:3-Dimethylquinoline. (II, 0.5 g) and powdered potassium hydroxide (0.1 g) were treated as described for quinaldine. 2:3-Dimethylquinoline was crystallised from ether, m.p. 68°. ¹² Picrate, m.p. 227–229° (from ethanol). ¹¹

Spiro[octahydro-1:8-dioxoxanthene-9:3'-oxindole] (IVa)

(a) A solution of isatin (0.74 g, 1 mole) and 1:3-cyclohexanedione (1.12 g, 2 moles) in 75% aqueous ethanol (30 ml) was refluxed for 6 hr. Half of the ethanol was removed by distillation, and the crude product (1.3 g, 77.6%), which separated on cooling, was filtered and crystallised from ethanol, m.p. 339°, and was insoluble in cold alkali. (Found: C, 71.46; H, 5.25; N, 4.19. Calc. for C₂₀H₁₇O₄N: C, 71.63; H, 5.11; N, 4.18%.)

(b) The same quantities of reactants, but in the absence of solvent, were heated for 2 hr at 110–115°. On cooling, the mixture of solid products was triturated with cold ethanol (30 ml) and the undissolved material (1.5 g, 89.5%) was crystallised from ethanol, m.p. 339°. (Found: C, 71.39; H, 5.30; N, 3.94. Calc. for C₂₀H₁₇O₄N: C, 71.63; H, 5.11; N, 4.18%.)

(c) A solution of isatin and cyclohexanedione (same quantities as above) in glacial acetic acid (30 ml) was refluxed for 4 hr, cooled and poured into water (50 ml). The crude precipitate (0.65 g, 37.5%) was crystallised from ethanol, m.p. 339°.

Spiro[octahydro-3:6-dimethyl-1:8-dioxoxanthene-9:3'-oxindole] (IVb)

(a) Isatin (0.74 g, 1 mole) and 5-methyl-1:3-cyclohexanedione (1.26 g, 2 moles) were treated as described above to yield (1 g, 55.1%) of crude (IVb) which crystallised from ethanol and melted at 300–301° and was insoluble in alkalis. (Found: C, 72.73; H, 5.82; N, 4.10. C₂₂H₂₁O₄N requires: C, 72.72; H, 5.82; N, 3.86%.)

(b) The same quantities of reactants, but in the absence of solvent, were heated for 2 hr at 130°. On cooling, the mixture was triturated with cold ethanol (30 ml) and the undissolved material (1.20 g, 66.1%) was crystallised from ethanol, m.p. 300°. (Found: C, 72.55; H, 5.71; N, 3.88. C₂₂H₂₁O₄N requires: C, 72.72; H, 5.82; N, 3.86%.)

(c) The same quantities of reactants were dissolved in glacial acetic acid (30 ml) and treated as described above. Crystallisation of the crude precipitate (1.2 g, 66.1%) from ethanol 300°.

1:2:3:4-Tetrahydro-3-methyl-1-oxo-9-acridinecarboxylic acid (Va)

A mixture of dry potassium isatate (8 g, 1 mole) and 5-methyl-1:3-cyclohexanedione (5 g, 1 mole) was heated for 30 min at 130–140°. On cooling, the red solid was treated with water (50 ml), the insoluble portion was filtered and extracted with 6% aqueous sodium carbonate. The combined filtrates were acidified with HCl, the precipitate was filtered and triturated with ice-cold ethanol. Insoluble tetrahydro-3-methyl-1-oxo-9-acridinecarboxylic acid was filtered (1.5 g, 15.7%) and crystallised from a large volume of boiling ethanol, m.p. 258–259°. Equivalent 257.6 (calc. 255.26). (Found: C, 70.33; H, 5.20; N, 5.70. C₁₃H₁₃O₃N requires: C, 70.58; H, 5.13; N, 5.49%.)

The product, insoluble in water and sodium carbonate solution (1.7 g, 23.6%, based on the cyclohexanedione), was crystallised from ethanol and gave *spiro[octahydro-3:6-dimethyl-1:8-dioxoxanthene-9:3'-oxindole]* (IVb), m.p. 300°. It did not depress the m.p. of an authentic sample prepared as described above. (Found: C, 72.53; H, 5.74; N, 4.17. C₂₂H₂₁O₄N requires: C, 72.72; H, 5.82; N, 3.86%.)

3:3-Bis[5':5'-dimethyl-1'3'-dioxo-2'-cyclohexyl]oxindole (III)

(a) A solution of isatin (0.74 g, 1 mole) and methone (1.44 g, 1 mole) in ethanol (30 ml) was refluxed for 6 hr. A colourless product, m.p. 235–239°, crystallised upon cooling (1.3 g, 63.5%). Crystallisation from ethanol raised the m.p. to 249–250°. The compound was soluble in alkalis. (Found: C, 70.26; H, 6.62; N, 3.83. C₂₄H₂₂O₆N requires: C, 70.39; H, 6.65; N, 3.42%.)

(b) The same quantities of reactants, but in the absence of solvent, were heated for 2 hr at 140°. On cooling, the mixture was treated with cold ethanol (30 ml) and the undissolved material (1.4 g, 68.4%) was crystallised from ethanol, m.p. 249°. The m.p. was not depressed by admixture of a sample of (III) prepared above.

Spiro[octahydro-3:3:6:6-tetramethyl-1:8-dioxoxanthene-9:3'-oxindole] (IVc)

A solution of (IIIc, 1.36 g) glacial acetic acid (20 ml) was refluxed for 6 hr. On cooling, the solution was poured into water (45 ml) and the precipitate (1.2 g, 92.3%) was crystallised from ethanol. The compound melted at 294° (283–285°)⁸ and did not depress the m.p. of a sample prepared (m.p. 294°) from methone and isatin, in glacial acetic acid. (Found: C, 73.60; H, 6.21; N, 3.68. Calc. for C₂₄H₂₅O₄N: C, 73.63; H, 6.43; N, 3.58%).

1:2:3:4-Tetrahydro-3:3-dimethyl-1-oxo-9-acridinecarboxylic acid (Vc)

A mixture of potassium isatate (20.3 g 1 mole) and methone (14.4 g, 1 mole) was heated for 30 min at 135–140°. On cooling, the red solid was treated with water (100 ml), the insoluble portion was filtered and extracted with cold 10% aqueous sodium hydroxide. The combined filtrates were acidified with HCl, the precipitate was filtered and triturated with ice-cold ethanol in order to eliminate the red solid. The remaining colourless *tetrahydroacridine carboxylic acid* was filtered (7 g, 26%) and crystallised from a large volume of boiling ethanol, m.p. 292°. Equivalent 265.4; calc. 269.29. (Found: C, 71.27; H, 5.58; N, 5.20. C₁₆H₁₅O₃N requires: C, 71.36; H, 5.61; N, 5.20%).

The ethanolic extract was evaporated to dryness, the residue treated with 6% aqueous sodium carbonate and the insoluble part (3.8 g, 18.6%, based on methone) was filtered. After crystallisation from ethanol it melted at 249° and was soluble in alkalis. By mixed m.p. determination it was identified as (III).

The product insoluble in water and sodium hydroxide (7 g, 35.9%, based on methone) was crystallised from 50% aqueous ethanol to give (IVc), m.p. 294°. (Found: C, 73.76; H, 6.75; N, 3.50. C₂₄H₂₅O₄N requires: C, 73.63; H, 6.43; N, 3.50%).