

A Study of Some Quinolizone Derivatives

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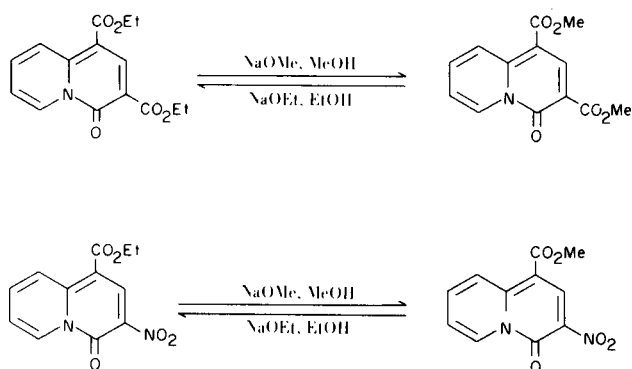
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The condensation of methyl 2-pyridylacetate and ethyl phenylpropiolate has been found to be a simple and convenient method for the preparation of 4-quinolizone derivatives. Upon hydrolysis and decarboxylation, the initial condensation product, 1-carbomethoxy-2-phenyl-4*H*-quinolizin-4-one (V) was converted to 2-phenyl-4*H*-quinolizin-4-one (VII). Nitration and bromination of these quinolizones were affected under mild conditions. Nitration of V displaced the carbomethoxy group, while bromination did not and 1,3-dinitro-4*H*-quinolizin-4-one and 1-carbomethoxy-2-phenyl-3-bromo-4*H*-quinolizin-4-one were obtained, respectively.

In the course of our study on the condensation reactions of acetylenic esters, we have reported that ethyl arylacetates reacted with ethyl phenylpropiolate to give the appropriate acetylenic β -ketoesters (1). In this work, methyl 2-pyridylacetate (I) reacted with ethyl phenylpropiolate (II) at 0° and in the presence of sodium ethoxide to give 1-carbomethoxy-2-phenyl-4*H*-quinolizin-4-one (V). The ir and nmr spectra are in agreement with the above structure (see Experimental).

The appearance of the ethyl group instead of the methyl group in the nmr spectrum of the product suggested the elimination of carbomethoxy and not carbethoxy. However, this was not the case and carbomethoxy compounds III and IV were first formed and followed by interchange to the carbethoxy compounds V and VI due to the presence of sodium ethoxide (Scheme I). Similar cases have been reported (2) for the esters of 1,3-dicarboxy-4*H*-quinolizin-4-one and 1-carbomethoxy-3-nitro-4*H*-quinolizin-4-one as outlined below:

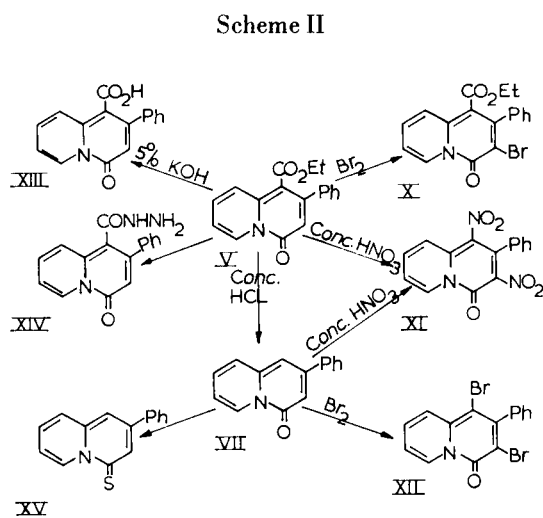
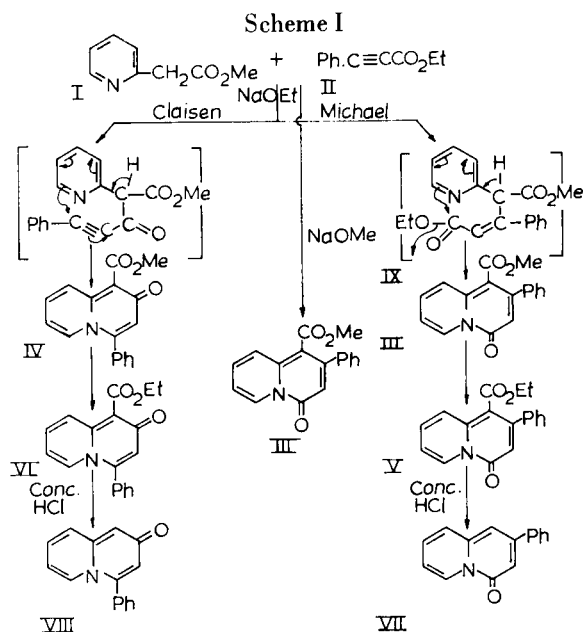


Based upon this data the condensation between I and II in the presence of sodium methoxide was repeated. The product isolated was identified as 1-carbomethoxy-2-phenyl-4*H*-quinolizin-4-one (III).

The hydrolysis of compound V in concentrated hydrochloric acid afforded 2-phenyl-4*H*-quinolizin-4-one (VII) as indicated by the nmr spectrum which did not show any signal due to ethyl group. The ir spectrum of this compound (VII) showed absorption bands at 1659 and 1630 cm^{-1} . These values are in better agreement with the absorption of 2-pyridone rather than the 4-pyridone structure (3). Katritzky and Jones reported (4) the values 1655-1665 cm^{-1} for 2-pyridones and 1575 cm^{-1} for 4-pyridones with a second strong band due to the pyridone ring C=C and C=N stretching at 1623-1640 cm^{-1} .

Accordingly, structure V and not VI favour the original condensation product which indicates that Michael addition is first involved followed by cyclisation of intermediate IX to give V through compound III (Scheme I). Treatment of 2-phenyl-4*H*-quinolizin-4-one (VII) with phosphorus pentasulfide afforded the corresponding 4-thioquinolizone (XV) as shown from the ir absorption band at 1110 cm^{-1} due to C=S (4).

Examples have been reported in the literature for the preparation of substituted 4-quinolizones which mainly includes ester substituted compounds (5). These compounds were mainly prepared by the reaction of 2-pyridylacetate or 2-pyridylacetone with ethoxymethylenemalonate or ethoxymethyleneacetate. Other methods include the condensation of acetylenedicarboxylate with some pyridine compounds where the ester substituted 4-quinolizones were obtained through multisteps reactions (6).



Regarding the formation of 2-phenyl-4H-quinolizin-4-one (VII), a white crystalline solid compound was isolated before pouring the reaction mixture into water at the end of the reaction time. This solid material was gradually converted into yellow crystalline compound which is the 2-phenyl-4H-quinolizin-4-one (VII). Most likely, the white solid compound is the hydrochloride of the quinolizone VII. A solid compound of the same nature with similar ir spectrum was obtained when dry hydrogen chloride gas was passed through the yellowish benzene solution of compound VII. The strong deliquescent character of the white solid compound is very similar to what has been reported for 4-quinolizone which was too unstable for analysis (7). Moreover, when the hydrolysis was carried

out using 5% aqueous alcoholic potassium hydroxide, the intermediate, 1-carboxy-2-phenyl-4H-quinolizin-4-one (XIII) was obtained.

Previous interest in the aromatic behaviour of heterocyclic amides led to the investigation of electrophilic substitution patterns in this system (2,8). Primarily, the object was to determine whether the anionic charge on the oxygen activates only positions 1 and 3 toward electrophilic attack or does it spread evenly to position 7 and 9 of the non-oxygenated ring. Later, Thyagarajan and Gopalakrishnan studied the nitration of unsubstituted and some substituted quinolizones and reported that the nitro groups enter into positions 1 and 3 as indicated by the carbonyl absorption in the infrared (8). The position of substituents has been varified by independent synthesis, using ethyl β -ethoxy- α -nitroacrylate.

In our case, the nitration of 1-carbethoxy-2-phenyl-4H-quinolizin-4-one (V) was best affected at room temperature using concentrated nitric acid and the product was identified as 1,3-dinitro-2-phenyl-4H-quinolizin-4-one (XI) based on analysis and ir spectrum (9,10). The same product was obtained using the same experimental conditions but starting with 2-phenyl-4H-quinolizin-4-one (VII), (Scheme II). The facile displacability of the carbethoxy group in the first case has been also demonstrated in certain carboxy and acetyl quinolizone derivatives (8).

However, the case was different with the bromination of compound V where only the monobromo derivative was obtained as 1-carbethoxy-2-phenyl-3-bromo-4H-quinolizin-4-one (X). In addition the dibromo derivative was obtained as 1,3-dibromo-2-phenyl-4H-quinolizin-4-one (XII) when 2-phenyl-4H-quinolizin-4-one (VII) was brominated under the same experimental conditions applied for compound V (Scheme II). Selective bromination of 4-quinolizone under different conditions has been reported to give mono and dibromo derivatives (2). The position of entry of the bromine atom was established by brominative decarboxylation of the corresponding carboxylic acid, comparable to the behaviour of salicylic acid or *p*-hydroxybenzoic acid.

Furthermore, when compound V was treated with hydrazine hydrate, the corresponding acid hydrazide (XIV) was obtained as inferred from the ir spectrum (11).

EXPERIMENTAL

Infrared spectra were recorded with a Beckmann IR 12 spectrophotometer, uv spectra with a Unicam SP 700 and nmr spectra with a Varian A-60D spectrometer in deuteriochloroform containing tetramethylsilane as internal standard. Microanalytical samples were analysed in West Germany by Max Plank Institute, Ruhr.

1-Carboethoxy-2-phenyl-4*H*-quinolizin-4-one (V).

A mixture of methyl 2-pyridylacetate (5.0 g.) and ethyl phenylpropiolate (5.8 g.) in dry ether (50 ml.) was added to a suspension of sodium ethoxide (0.8 g. sodium and 2 ml. absolute ethanol) in dry ether (200 ml.). The reaction mixture was left for three days at 0° with frequent shaking. The yellow crystalline solid that was formed was collected, washed with cold ether and weighed 4.4 g. More of this solid compound was also obtained by pouring the filtrate into water followed by extraction with ether. Working up the ether in the usual manner gave 4.0 g., (86.6% total) of compound V. It recrystallised from methanol as bright yellow crystals, m.p. 124-125°; ir (chloroform): 1708 (m), 1660 (vs), 1632 (s), 1560 (w), 1535 (w), 1498 (w), 1460 (vs), 1435 (s), 1283 (s) and 1246 (s) cm⁻¹; nmr (deuteriochloroform): 9.2 (t,3), 6.0 (q,2), 3.38 (s,1) and 3.2-0.6 τ (m,9); uv λ max (ethanol): 260 (ε = 31,380) and 386 nm (ε = 17,390).

Anal. Calcd. for C₁₈H₁₅NO₃: C, 73.70; H, 5.12; N, 4.78; M. Wt., 293. Found: C, 73.52; H, 5.05; N, 4.92; M. Wt., 286.

1-Carbomethoxy-2-phenyl-4*H*-quinolizin-4-one (III).

The above procedure for compound V was applied here with the exception that sodium methoxide was used instead of sodium ethoxide. There resulted 4.6 g. (50%) of yellow crystals, m.p. 132-134° (from ethanol); ir (chloroform): 1710 (s), 1665 (vs) and 1635 (s) cm⁻¹.

Anal. Calcd. for C₁₇H₁₃NO₃: C, 73.20; H, 4.66; N, 5.01; OCH₃, 11.1. Found: C, 73.53; H, 4.64; N, 5.05; OCH₃, 10.42.

2-Phenyl-4*H*-quinolizin-4-one (VII).

Compound V (2 g.) in concentrated hydrochloric acid (45 ml.) was heated under reflux at 120-130° for 15 hours and then cooled. At this stage an unstable white solid material formed, m.p. 100-130°, which may be the hydrochloride of VII, (see below). The reaction mixture was poured into water to give a yellow crystalline solid which was collected, yield 1.3 g. (85.5%). It was recrystallised from ether, m.p. 138-140°; ir (chloroform): 1659 (vs), 1630 (s), 1544 (m), 1498 (m), 1465 (vs) and 1437 (m) cm⁻¹; nmr (deuteriochloroform): 3.13 (s,2) and 3.0-0.35 τ (m,9); uv λ max (ethanol): 265 (ε = 27,625) and 405 nm (ε = 15,580).

Anal. Calcd. for C₁₅H₁₁NO: C, 81.35; H, 4.97; N, 6.33; M. Wt., 221. Found: C, 81.40; H, 5.11; N, 6.36; M. Wt. 227.

Action of Hydrogen Chloride Gas on Compound VII.

Dry hydrogen chloride gas was passed through the yellowish benzene solution of compound VII (0.1 g.) until it became colourless. Evaporation of the benzene solution under reduced pressure afforded a white solid material, m.p. 100-130°, which gradually turned to a yellow crystalline solid which was shown to be the starting material VII. This white solid material was unstable and greatly sensitive when exposed to air, thus it was difficult to analyze; ir (Nujol), 3300 (s), 3100 (s), 1648 (sh), 1620 (s) and 1568 (m) cm⁻¹.

1-Carboxy-2-phenyl-4*H*-quinolizin-4-one (XIII).

A mixture of compound V (1 g.) and 5% potassium hydroxide (10 ml.) in ethanol (10 ml.) was refluxed on a water bath for 5 hours. The reaction mixture was cooled, acidified with dilute hydrochloric acid and then cooled to 0° to give XIII (0.2 g., 22.2%) as yellow crystals, m.p. 199-200° (from ethanol); ir (Nujol), 2200-3400 (broad), 1733 (m), 1705 (m), 1646 (s) and 1620 (s) cm⁻¹; uv λ max (ethanol): 225 (ε = 30,840) and 400 nm (ε = 17,130).

Anal. Calcd. for C₁₆H₁₁NO₃: C, 72.40; H, 4.15; N, 5.28. Found: C, 72.01; H, 4.61; N, 5.43.

2-Phenyl-4*H*-quinolizin-4-thione (XV).

A mixture of 2-phenyl-4*H*-quinolizin-4-one (1.1 g.) and phosphorus pentasulfide (0.5 g.) was heated for one hour in a sublimation apparatus at 180-200°. The pressure was then reduced to 2 mm. and 2-phenyl-4*H*-quinolizin-4-thione (XV) was collected on a cold finger. After two more sublimations, there was obtained 0.5 g. (42.3%) of orange crystals, m.p. 150-151°; ir (chloroform): 1642 (s), 1600 (vs), 1579 (s), 1501 (m), 1457 (s), 1431 (s), 1370 (vs), 1310 (s), 1160 (s) and 1110 (s) cm⁻¹.

Anal. Calcd. for C₁₅H₂₂NS: C, 75.8; H, 4.64; N, 5.9; S, 13.6. Found: C, 75.38; H, 4.59; N, 6.16; S, 14.09.

3-Bromo-1-carboethoxy-2-phenyl-4*H*-quinolizin-4-one (X).

Bromine (0.5 ml.) in chloroform (10 ml.) was added slowly with stirring to a solution of compound V (1 g.) in chloroform (10 ml.). The mixture was left for three hours at room temperature, the solvent was evaporated under vacuum and the residue was triturated with ethanol whereupon shining yellow crystals were collected (0.9 g., 70%). It was recrystallised from ethanol, m.p. 209-211; ir (chloroform): 1720 (s), 1658 (vs), 1630 (s), 1558 (w), 1535 (w), 1496 (w), 1446 (m), 1426 (s), 1282 (s) and 1242 (m) cm⁻¹; nmr (deuteriochloroform): 9.2 (t,3), 6.2 (q,2) and 3.0-0.35 τ (m,9); uv λ max (ethanol): 265 (ε = 17,940) and 400 nm (ε = 17,410).

Anal. Calcd. for C₁₈H₁₄BrNO₃: C, 58.0; H, 3.76; N, 3.76. Found: C, 58.07; H, 3.84; N, 3.55.

1,3-Dibromo-2-phenyl-4*H*-quinolizin-4-one (XII).

Compound VII (0.2 g.) in chloroform (10 ml.) was treated as for compound V to give XII (0.15 g., 43.4%). It was recrystallised from ethanol, m.p. 192.5-193.5°; ir (chloroform): 1660 (vs), 1632 (s), 1550 (w), 1530 (m) and 1495 (w) cm⁻¹; uv λ max (chloroform): 265 (ε = 18,940) and 395 nm (ε = 6800).

Anal. Calcd. for C₁₅H₉Br₂NO: H, 2.37; N, 3.69. Found: H, 2.35; N, 3.64.

1,3-Dinitro-2-phenyl-4*H*-quinolizin-4-one (XI).

Concentrated nitric acid (3 ml.) was added slowly to V (1 g.). The reaction became exothermic and brown fumes evolved. The mixture was then poured onto ice. The precipitated solid was filtered and washed with ethanol to yield XI (0.8 g., 73.4%). It was recrystallised from ethanol, m.p. 213-215°; ir (chloroform): 1700 (vs), 1640 (m), 1560 (m), 1545 (s), 1500 (w), 1467 (s), 1443 (m), 1368 (m) and 1345 (s) cm⁻¹; uv λ max (chloroform): 386 nm (ε = 28,380).

Anal. Calcd. for C₁₅H₉N₃O₅: C, 57.8; H, 2.89; N, 13.5. Found: C, 57.9; H, 2.94; N, 13.31.

The above dinitro compound XI was similarly obtained from compound VII. It did not depress the m.p. of an authentic sample obtained from V and had an identical ir spectrum.

1-Carbohydrazide-2-phenyl-4*H*-quinolizin-4-one (XIV).

A solution of 1-carboethoxy-2-phenyl-4*H*-quinolizin-4-one (1.0 g.) in 1-butanol (20 ml.) was boiled under reflux for six hours with 85% hydrazine hydrate (0.5 ml.). The reaction mixture was then allowed to cool, the solvent evaporated under vacuum and the crude product was precipitated with chloroform (0.6 g., 63%). It was recrystallised from ethanol, m.p. 315-317°; ir (Nujol): 3100-3600 (broad), 1670 (vs, broad) and 1580 (m) cm⁻¹.

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.8; H, 4.66; N, 15.02.
Found: C, 68.37; H, 4.88; N, 14.55.

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REFERENCES

- (1) H. N. Al-Jallo and F. H. Al-Hajjar, *J. Chem. Soc. (C)*, 2056 (1970).
- (2) B. S. Thyagarajan and P. V. Gopalakrishnan, *Tetrahedron*, 21, 945 (1965).
- (3) A. Fozard and G. Jones, *J. Chem. Soc.*, 2760 (1964).
- (4) A. R. Katritzky and R. A. Jones, *ibid.*, 2947 (1960).
- (5) B. S. Thyagarajan in "Aromatic Quinolizines." "Advances in Heterocyclic Chemistry," Vol. 5, A. R. Katritzky (ed.) and A. J. Boulton (assistant ed.), Academic Press, New York, 1965, p. 291, and references cited therein.
- (6) R. M. Acheson in "Reactions of Acetylenecarboxylic Acids and their Esters with Nitrogen Containing Heterocyclic Compounds." "Advances in Heterocyclic Chemistry," Vol. 1, A. R. Katritzky (ed.), Academic Press, New York, 1963, p. 151, and references cited therein.
- (7) V. Boekelheide and J. P. Lodge, *J. Am. Chem. Soc.*, 73, 3681 (1951).
- (8) B. S. Thyagarajan and P. V. Gopalakrishnan, *Tetrahedron*, 20, 105 (1964).
- (9) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," p. 385, J. Wiley, New York (1958).
- (10) H. Tomisawa and T. Agatsuma, *Yakugaku Zasshi*, 82, 25 (1962).
- (11) M. Mashima, *Bull. Chem. Soc. Japan*, 35, 332 and 1862 (1962).