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STUDIES ON QUINOLIZONES—I

NITRATION OF 4H-QUINOLIZIN-4-ONE

B. S. THYAGARAJAN and P. V. GOPALAKRISHNAN
Department of Organic Chemistry, University of Madras, India

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Abstract—The aromaticity in 4H-quinolizin-4-one has been established by a nitration comparable to that of 2-pyridones. The position of substituents has been verified by independent synthesis, using ethyl-β-ethoxy-α-nitroacrylate. The easy displaceability of the carboxyl groups in 4H-quinolizin-4-one is also demonstrated.

THE cationoid aromaticity in 4H-quinolizin-4-one was first commented on by Boekhelheide and Lodge[1] based on its UV spectrum. Interest in the aromatic behaviour of heterocyclic amides[2] led to the investigation of the electrophilic substitution patterns in this system. Primarily the object was to determine whether the anionic charge on the oxygen activates only positions 1 and 3 (Fig. 1) towards electrophilic attack or whether it spreads evenly to positions 7 and 9 of the non-oxygenated ring.

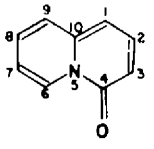


FIG. 1

Nitration of 4H-quinolizin-4-one at 0° with concentrated nitric acid results in a dinitro derivative XI. The entry of the nitro groups at positions 1 and 3 is indicated by carbonyl absorption in the infra-red. The opposing dipoles of the nitro and the carbonyl groups shift the absorption of the latter to 5·80 μ. Such a shift is well documented in the pyridone series.[3a,b]

Compound XI may also be obtained by nitration of 4H-quinolizin-4-one in glacial acetic acid with nitric acid, but the use of cupric nitrate in acetic anhydride results in a mixture of products. One of these was identified as the dinitro compound (XI). Two mononitro derivatives were also isolated but these compounds are very labile and easily undergo further nitration in the reaction medium to give XI. One of these is probably the 1-nitro-4H-quinolizin-4-one (XII), as it is clearly distinguishable from 3-nitro-4H-quinolizine-4-one (IX) on the basis of its UV and IR spectra

[1] V. Boekelheide and J. P. Lodge Jr., *J. Amer. Chem. Soc.* **73**, 3681 (1951).
[2] B. S. Thyagarajan and K. Rajagopalan, *Tetrahedron* **19**, 1483 (1963).
[3a] L. J. Bellamy, *The Infrared Spectra of Complex Molecules* p. 395. J. Wiley, New York (1958).
[3b] H. Tomisawa and T. Agatsuma, *Yakugaku Zasshi*, **82**, 25 (1962).

(Experimental). 3-Nitro-4H-quinolizin-4-one (IX), the other mononitro product was obtained by an independent synthesis, starting from ethyl-β-ethoxy-α-nitro acrylate and ethyl-2-pyridyl acetate and based on the procedure of Boekelheide and Lodge (*loc. cit.*). Hydrolysis of the resulting 1-carbethoxy-3-nitro-4H-quinolizine-4-one (III) with concentrated hydrochloric acid results in the formation of IX.

An alternative approach to the synthesis of IX is the selective hydrolysis of 1,3-dicarbethoxy-4H-quinolizine-4-one to afford the corresponding 3-carboxy derivative. Treatment of the latter with warm 1:1 nitric acid results in the facile displacement of the carboxy group by nitro group and formation of III. Further hydrolysis and decarboxylation of III yields IX. This facile replacement of carboxyl groups in the quinolizone series finds a parallel in the corresponding pyridine compounds. Berrie *et al.*[4] have observed under slightly more drastic conditions that the carboxyl groups in 3-nitro-5-carboxy-N-methyl-2-pyridone and 3-nitro-5-carboxy-2-pyridone are replaced by nitro groups. The interesting feature in the present instance is that the replacement is far more facile and proceeds under milder conditions. Application of this decarboxylative nitration resulted in an independent synthesis of XI. 1,3-Dicarbethoxy-4H-quinolizin-4-one was hydrolysed with alcoholic alkali to give the corresponding dicarboxylic acid. The latter on similar treatment with 1:1 nitric acid at water-bath temperature resulted in the facile formation of 1,3-dinitro-4H-quinolizine-4-one (XI), confirming thereby the structure assigned to the product obtained by nitration of 4H-quinolizine-4-one.

The nitration of 4H-quinolizine-4-one as well as the facile displacement of carboxyl groups demonstrates the similarity in the chemical reactivities of the pyridone and the quinolizone molecules. No evidence is available at the moment for oxygen anion activation in the non-oxygenated ring but further work is in progress investigating other electrophilic substitutions including halogenation and acylation.*

EXPERIMENTAL

Ethyl nitroacetate (I)

To ethyl α-isonitrosoacetoacetate[6] (28 g; 0·18 M) contained in a three-necked flask, fitted with a mechanical stirrer, a thermometer and a dropping funnel, a solution of sodium dichromate (40 g: 0·15 M) in 1:1·5 H_2SO_4 (62 ml) was added at room temp during 3 hr. When the temp rose above 40°, the flask was cooled to room temp. After the addition of the chromic acid solution, the mixture was poured into ice, extracted with ether (500 ml), the ether layer separated, washed with aqueous urea and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residual liquid distilled. b.p. 91°–93°/8 mm 85° 87°/5 6 mm, yield 15 g (63%).

Ethyl ethoxymethylenenitroacetate (II); (*Ethyl β-ethoxy-α-nitroacrylate*)

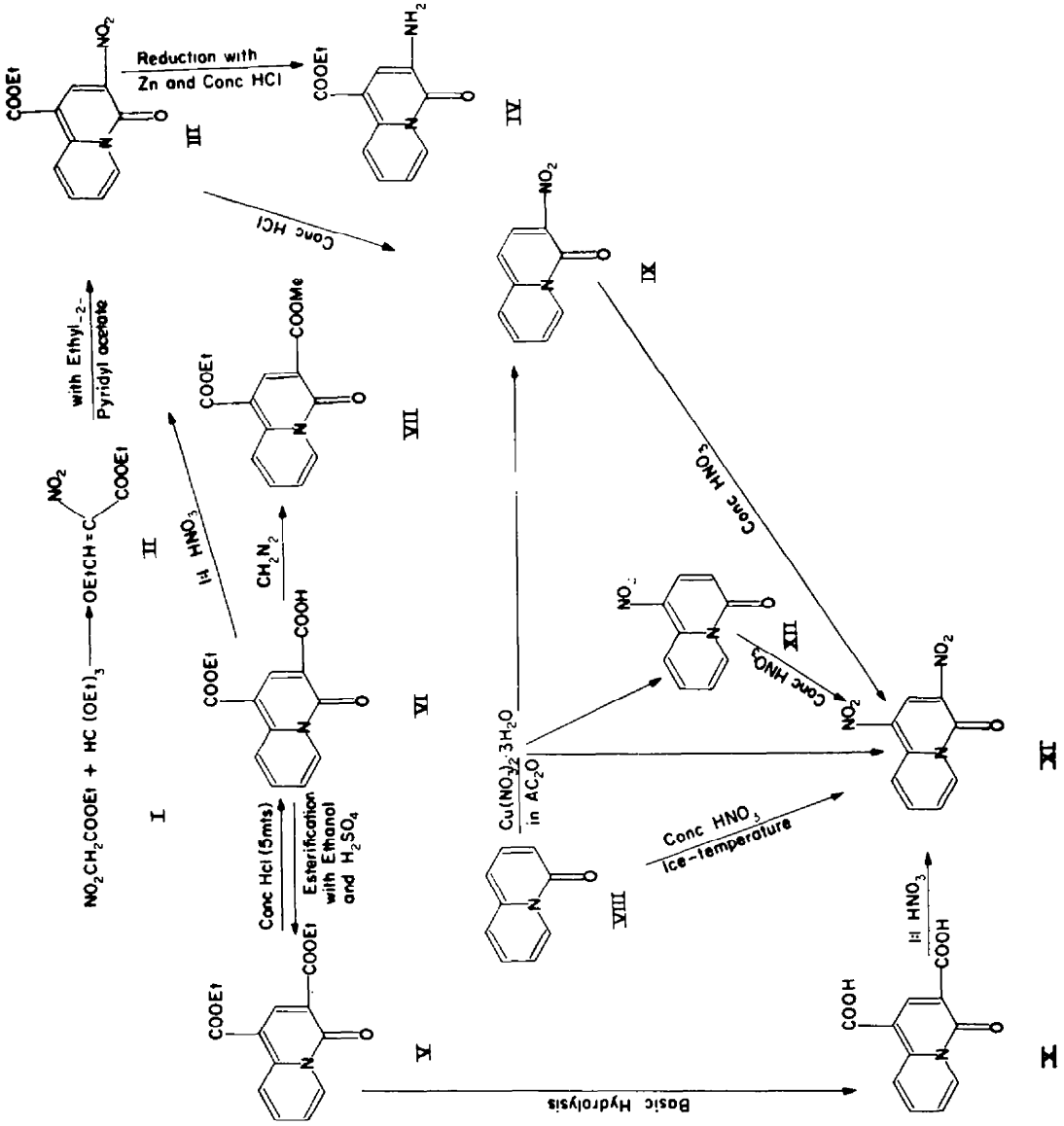
A mixture of I (9·3 g; 0·07 M), ethyl orthoformate (18·1 g; 0·123 M) and freshly distilled acetic anhydride (20·4 g; 0·199 M) was heated in a distilling flask fitted with 5 × 8/12 inch fractionating column for 1/2 hr periods at 110–120°, 120°–130° and 130°–140°. After cooling the flask, the lower

* At the time the present investigation was completed ethyl β-ethoxy-α-nitroacrylate was unknown. We have just recently noticed a report by Prystas and Gut[5] describing the use of this versatile reagent in the preparation of nitro uracils.

[4] A. H. Berrie, G. T. Newbold and F. S. Spring, *J. Chem. Soc.* 2590 (1951).

[5] M. Prystas and J. Gut, *Coll. Czech. Chem. Comm.* **28**, 2501 (1963).

[6] V. M. Rodionov, I. V. Machinskaya and V. M. Belikov, *Zh. Obsch. Khim.* **18**, 917 (1948). *Chem. Abstr.* **43**, 127 (1949).


Reduction with
Zn and Conc HCl
Conc HCl
with Ethyl-2-Pyridyl acetate
Conc HCl (5mts)
Esterification with Ethanol and H_2SO_4
Basic Hydrolysis
Conc HNO_3
Conc HNO_3
Conc HNO_3
Conc HNO_3 Ice-temperature
$Cu(NO_3)_2 \cdot 3H_2O$ in AC_2O
I
II
III
IV
V
VI
VII
VIII
IX
X
XI
XII
XIII

boiling fractions were removed (at red. press.). The distillation was then carried out at low press. and resulted in 9·2 g (70%) II, as a yellow viscous liquid. b.p. 142°–144°/2 mm, 148°–150°/3·5 mm. (Found: C, 44·96; H, 5·3. $C_7H_{11}NO_5$ requires: C, 44·44; H, 5·8%). λ_{max}^{EtOH} 380 mμ (log ε 4·52); $\lambda_{max}^{CHCl_3}$ (up to 9 μ) 3·28 (m), 5·68 (s), 6·375 (s), 7·275 (w) and 7·475 μ(s).

1-*Carbethoxy*-3-*nitro*-4H-*quinolizin*-4-*one* (III)

Method A. A mixture of ethyl 2-pyridylacetate (8 g; 0·048 M) and II (9 g; 0·048 M) was warmed to 60°. When the exothermic reaction which takes place subsided (10 min), the temp was slowly increased to and maintained at 100° for 20 min. The orange solid cake that formed, was broken into small pieces, washed several times with ice-cold pet. ether (1:2), acetone–water mixture and recrystallized from aqueous acetone, yield 6 g (45%), m.p. 205°–206°. If the reaction was carried out at a higher temp and for a longer period, tar was formed, reducing the yield of III. (Found: C, 54·66; H, 3·85, N, 11·04. $C_{12}H_{10}N_2O_5$ requires: C, 54·96; H, 3·82; N, 10·68%). λ_{max}^{EtOH} 265, 340, and 430 mμ (log ε 4·08, 4·03 and 4·3); λ_{max}^{EtOH} (with four drops of 10% NaOH solution) 265 and 380 mμ λ_{max}^{KBr} 5·8 (v.s), 5·9 (s), 6·15 (s), 6·3 (s), 6·55 (m), 6·65 (v.s), 6·95 (m), 7·2 shoulder (w), 7·3 (c), 7·5 (v.s), 7·8 (v.s), 8·0 (s), 8·25 (v.s), 8·65 (m), 9·5 (w), 9·8 (m), 10·5 (v.w), 10·9 (w), 12·6 (m), 12·85 (m) and 13·05 u (m).

Method B. (a) 1,3-*dicarbethoxy*-4H-*quinolizin*-4-*one* (V) was prepared by the method of Boekelheide and Lodge[1] with slight modifications.

A mixture of ethyl 2-pyridylacetate (10 g; 0·06 M) and ethyl ethoxymethylenemalonate (15 g; 0·07 M) was heated in a bolt-head flask attached with an air condenser at 160° for 6 hr. The flask was cooled, and the resulting solidified mass washed with ice-cold pet. ether (40°–60°), acetone–pet.-ether mixture and dried (11–12 g, 59–63%). Recrystallization from aqueous acetone or aqueous alcohol yielded V, m.p. 130°.

(b) 1-*Carbethoxy*-3-*carboxy*-4H-*quinolizin*-4-*one* (VI). Compound V (11 g, ca. 0·04 M) in conc. HCl aq. (55 ml) was heated on a water-bath, with solution of V. After 5 min, a heavy yellow precipitate began to form; the mixture was kept on the water-bath for 5 more min and cooled. The precipitate was removed, washed with water and recrystallized from ethanol (quantitative yield). m.p. 181°–185°. (Found: C, 60·2; H, 4·39; N, 5·38. $C_{13}H_{11}NO_5$ requires: C, 60; H, 4·2; N, 5·36%). λ_{max}^{EtOH} 265,, 340 and 390 mμ (log ε 4.22, 4·05 and 4·29). λ_{max}^{KBr} 2·9 (m), 5·75 (v.s), 5·825 (s), 6·1 (v.s), 6·2 (v.s) 6·3 (m), 6·6 (s), 6·75 (v.s), 6·9 (v.s), 7·1 (doublet) (w), 7·3 (s), 7·4 (s), 7·55 (s), 7·6 (s), 7·9 (s), 8·05 (v.s) 8·35 (s), 8·45 (s), 8·65 (m), 9·7 (s), 10·05 (m), 10·3 (m), 11·0 (m), 11·4 (w), 11·5 (w), 12·1 (m), 12·7 (v.s) and 13·0 μ (s).

(c) *Decarboxylative nitration of* VI *to* III. The crude VI (4 g) in 1:1 HNO_3 (80 ml) was warmed on a water-bath till brown fumes began to evolve (10 min) with a vigorous reaction. The flask was removed from the bath, shaken for some time and once again warmed on the water-bath. This operation was continued until there was a change of colour from light yellow (starting material) to bright yellow solid formed during the reaction. The flask was cooled, ice-pieces added, and the precipitate filtered, washed with ice-water and recrystallized from aqueous acetone (2 g). This material did not depress the m.p. of the compound obtained by Method A.

Reduction of III *by zinc and concentrated hydrochloric acid to* IV

To III (4 g; 0·017 M) in conc. HCl (60 ml), activated Zn powder (40 g) was added in portions, at room temp over 30 min. The solution was filtered, basified with NH_4OH aq. and the product extracted with ether till the ether layer was almost colourless. The ether layer was separated, dried, evaporated to a small volume and cooled in ice when yellow crystals separated (1·5 g) m.p. 135°–136° (benzene or hot water). (Found: C, 62·13, H, 5·13. $C_{12}H_{12}N_2O_3$ requires: C, 62·06; H, 5·17%). λ_{max}^{EtOH} 270, 300 and 380 mμ (log ε 4·17, 3·51 and 4·12). $\lambda_{max}^{CHCl_3}$ (up to 9 μ) 2·95 (w), 5·875 (m), 6·125 (s), 6·25 (m), 6·325 (m), 6·75 (m), 7·175 (m) and 7·5 μ (s). Benzoyl derivative: m.p. 181°–185° (benzene–pet. ether). (Found: C, 67·78; H, 5·20. $C_{19}H_{16}N_2O_4$ requires: C, 67·80; H, 4·80%).

3-*Nitro*-4H-*quinolizin*-4-*one* (IX)

A suspension of III (2 g; 0·008 M) in conc. HCl aq. (150 ml) was stirred mechanically and boiled under reflux for 2 hr. The mixture was cooled, filtered to remove unreacted III 230 mg) and the

filtrate neutralized in the cold (Na_2CO_3). The mixture was thoroughly extracted with chloroform (250 ml), the chloroform layer separated, dried ($MgSO_4$), and the volume reduced to 25 ml and cooled. Shining yellow crystals separated (470 mg) m.p. 216°–218°. An additional (280 mg) was obtained when pet. ether was added to the mother liquor till turbid and cooled, yield 60% based on the reacted III. Recrystallization from ethanol yielded golden yellow needles. m.p. 219°–220°. (Found: C, 56·63; H, 3·6, N, 14·4. $C_9H_6N_2O_3$ requires: C, 56·84; H, 3·16; N, 14·74%). λ_{max}^{EtOH} 265, 340 and 440 mμ (log ϵ 3·96, 3·69 and 4·34). $\lambda_{max\ (up\ to\ 9\mu)}^{KBr}$ 5·85 (shoulder), 6·125 (m), 6·3 (s), 6·75 (s), 6·9 (s), 7·5 (s) and 7·7 μ (v.s).

1-*Carbethoxy*-3-*carbomethoxy*-4H-*quinolizin*-4-*one* (VII)

Compound VI (2g; 0·008 M) was treated with 1½ fold excess diazomethane in ether (100 ml). The solution was kept overnight. After removal of the ether, VII was obtained (1·9 g; 90%) m.p. 147°–148° (benzene–pet. ether). (Found: C, 61·4, H, 4·8; N, 5·28. $C_{14}HN_{13}O_5$ requires: C, 61.1, H, 4.7, N, 5·09%). λ_{max}^{EtOH} 264, 341, and 3.93 mμ (log ϵ 4·18, 3·96 and 4·21). $\lambda_{max}^{CHCl_3}$ 5·75 (s), 5·875 (v.s), 5·976 (v.s), 6,15 (m), 6·33 (s), 6·7 (v.s), 6·95 (m), 7·1 (w), 7·33 (m), 7·42 (m), 7·55 (m), 7·725 (s), 7·95 (m), 8·2 (s), 8·7 (m), 9·0 (m), 9·5 (m), 9·75 (m), 10·1 (m), 11·25 (w), 12·8 (s), 12·9 (s), 14·2 (w), 14·5 (w) and 15·2 μ (w).

Esterification of VI *by ethanol and* H_2SO_4 *to* V

Compound VI (500 mg) was dissolved in absolute ethanol (20 ml), 6 drops conc. H_2SO_4 added and the mixture refluxed on the water-bath for 6 hr. To the cooled mixture Na_2CO_3 aq. was added till alkaline, the yellow precipitate filtered off, washed with water and dried, m.p. 122°–128°. Recrystallization from aqueous ethanol gave yellow needles, m.p. 130°, undepressed on admixture with an authentic specimen of V.

1,3-*Dicarboxy*-4H-*quinolizin*-4-*one* X

To the warm alcoholic solution (50 ml) of V (6 g, 0·026 M), 5% NaOH aq (45 ml) was added. The solution was kept in a refrigerator for 2 days. The sodium salt of the diacid which formed, was dissolved in water, filtered to remove traces of any unreacted compound, and acidified to yield XII as an amorphous yellow solid (4·5 g; 92%). Recrystallization from alcohol, gave light yellow crystals, m.p. 264°–265° (gas evolution). (Found: C, 56·46, H, 3.28. $C_{11}H_7NO_5$ requires: C, 56·65, H, 3·0%).

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

Compound X (670 mg) was heated with 1:1 HNO_3 (20 ml) on a water-bath for 30 min. The solution was cooled and poured into ice. The shining yellow crystals which formed were filtered off, washed with water, dried and crystallized from benzene, 300 mg (30%) m.p. 230° (dec). (Found: C, 46.06, 46·23, 46·5, H, 2·40, 2·47, 2·35, N, 17·99. $C_9H_5N_3O_5$ requires: C, 45·95, H, 2·13, N, 17·87%). λ_{max}^{EtOH} 255, 340, 395 and 470 mμ (log ϵ 3·89, 3·86, 3·95 and 4·28). $\lambda_{max\ (up\ to\ 9\mu)}^{KBr}$ 5·8 (shoulder), 6·175 (m), 6·3 (s), 6·5 (s), 6·65 (s), 7·0 (s), 7·25 (m), 7·53 (shoulder), 7·95 (m), 8·175 (s) and 8·65 μ (w).

4H-*Quinolizin*-4-*one* (VIII) was prepared by the method described by Boekelheide and Lodge.*

Nitration of 4H-*quinolizin*-4-*one*

(a) *With conc.* HNO_3. To conc. HNO_3 (6 ml), cooled in ice-water, VIII (1 g, 0·007 M) was added in about 10 min with evolution of oxides of nitrogen. The solution was poured into ice-water and the solid collected by suction filtration (700 mg) m.p. 228° (dec). The solid was insoluble in hot water, pet. ether and chloroform. It was soluble in large volumes of hot acetone, benzene and acetic acid. The IR spectrum in KBr was indistinguishable from that of XI.

(b) *With conc.* HNO_3 *in acetic acid.* Compound VIII (1 g, 0·007 M) was dissolved in glacial acetic acid (5 ml), and conc. HNO_3 (*d* 1·42; 5 ml) was added in drops at room temp. The solution was poured into ice-water and the solid which separated was filtered off (700 mg; 43%) m.p. 228° (dec). Purified as before, it was identical with the compound obtained above.

(c) *With cupric nitrate in acetic anhydride.* Compound VIII (2 g, 0·014 M) was added to a suspension of cupric nitrate trihydrate (3·2 g, 0·014 M) in acetic anhydride (80 ml) at room temp. After keeping the mixture for 2 hr at room temp, water was added with cooling, to decompose the

* V. Boekelheide and J. P. Lodge, Jr. (*loc. cit.*)

acetic anhydride. The precipitate was dissolved in large volumes of acetone, filtered to remove the inorganic material, concentrated to a small bulk and pet. ether added (40°–60°) yielding a brown coloured precipitate. (500 mg) m.p. 227–8° (dec), IR spectrum identical with the dinitro compound obtained by Method A.

The aqueous portion, after neutralization with solid Na_2CO_3, was extracted with benzene, (1 l.), the benzene layer separated, dried, concentrated to ca. 50 ml and cooled yielding a yellow solid (20 mg) m.p. 216°–217° with IR, UV and m.p. indistinguishable from IX.

Methanol (2 ml) was added to the viscous liquid obtained by evaporating the mother liquid completely and the greenish-yellow solid filtered, dried (50 mg) and recrystallized, m.p. 150°–152° (benzene-pet. ether). (Found: C, 57·25, H, 3·54. $C_9H_6N_2O_3$ requires: C, 56·84, H, 3·16). λ_{max}^{EtOH} 360 and 415 mμ (log ϵ 4·1 and 4·2). $\lambda_{max}^{CHCl_3}$ (up to 9 μ) 5·9 (s), 6·15 (m), 6·325 (w), 6·5 (s), 6·65 (s), 7·61 (v.s) and 7·75 μ (m). This isomer is probably XII.

1,3-*dinitro*-4H-*quinolizin*-4-*one* (XI)

(a) *From* 3-*nitro*-4H-*quinolizin*-4-*one* (IX) *and* (b) *from* XII. Treatment of IX and XII at room temp with conc. HNO_3 (*d* 1·42) and working up in the usual manner led to the formation of XI.

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