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STUDIES ON QUINOLIZONES—IV

FORMYLATION OF 4H-QUINOLIZIN-4-ONE AND SOME SELECTIVE CATIONOID DISPLACEMENTS

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Abstract—Contrary to its resistance to acetylation, 4H-quinolizin-4-one formylates readily. The site of such formylation is established by alternative synthesis, spectral correlations and cationoid displacements. When two different functional groups are present in the quinolizone, a certain degree of selectivity in the ease of cationoid displacements is demonstrated.

THE 4H-quinolizin-4-one molecule (I) is readily amenable to nitration and bromination but is completely resistant to acetylation.[1,2] In comparison with the related 10 π electron system of indolizines, this is unusual, as indolizines undergo acetylation and formylation.[3-5] In view of this discrepancy, we investigated the formylation of 4H-quinolizin-4-one under the Vilsmeier conditions. Even with only one mole equivalent of the reagent, at room temperature, the reaction proceeded exothermally to give a mixture of formylated products II and III. When a large excess of the formylating agent was employed, only a diformyl derivative IV of I was obtained in excellent yield. From the mixture of products obtained from equivalent amounts of reagents two monoformyl quinolizones (II and III) were isolated, after purification by fractional crystallization, chromatography and vacuum sublimation. The monoformyl derivatives had nearly the same m.ps 176–177° and 174–175° respectively. The positions of formyl function in II, III and IV could be limited to the 1- and 3-positions of the quinolizone system for the following reason. All the three derivatives on treatment with warm nitric acid gave the earlier described 1,3-dinitro-quinolizone (V).[1] It has been demonstrated earlier that 1,3-dicarboxy-, 1,3-dibromo- and 1,3-diacetylquinolizones can be converted under the same conditions into V. Thus, IV must be the 1,3-disubstituted quinolizone.

Of the two monoformyl quinolizones, compound II was readily brominated to give a monobromo monoformyl quinolizone (VI). This latter derivative was identical with the product of formylation of 3-bromo-4-quinolizone (VII) reported earlier.[2] Compound VI could also be converted into V on treatment with warm nitric acid. These interconversions are illustrated in Chart I. These transformations unequivocally establish II as 1-formyl-4-quinolizone.

The obvious corollary that compound III is 3-formyl-4-quinolizone, was elegantly

[1] B. S. Thyagarajan and P. V. Gopalakrishnan, *Tetrahedron* **20**, 1051 (1964).
[2] B. S. Thyagarajan and P. V. Gopalakrishnan, *Tetrahedron* **21**, 945 (1965).
[3] E. T. Borrows, D. O. Holland and J. Kenyon, *J. Chem. Soc.* 1069 (1946).
[4] E. D. Rossiter and J. E. Saxton, *J. Chem. Soc.* 3654 (1953).
[5] D. O. Holland and J. H. C. Nayler, *J. Chem. Soc.* 1504 (1955).

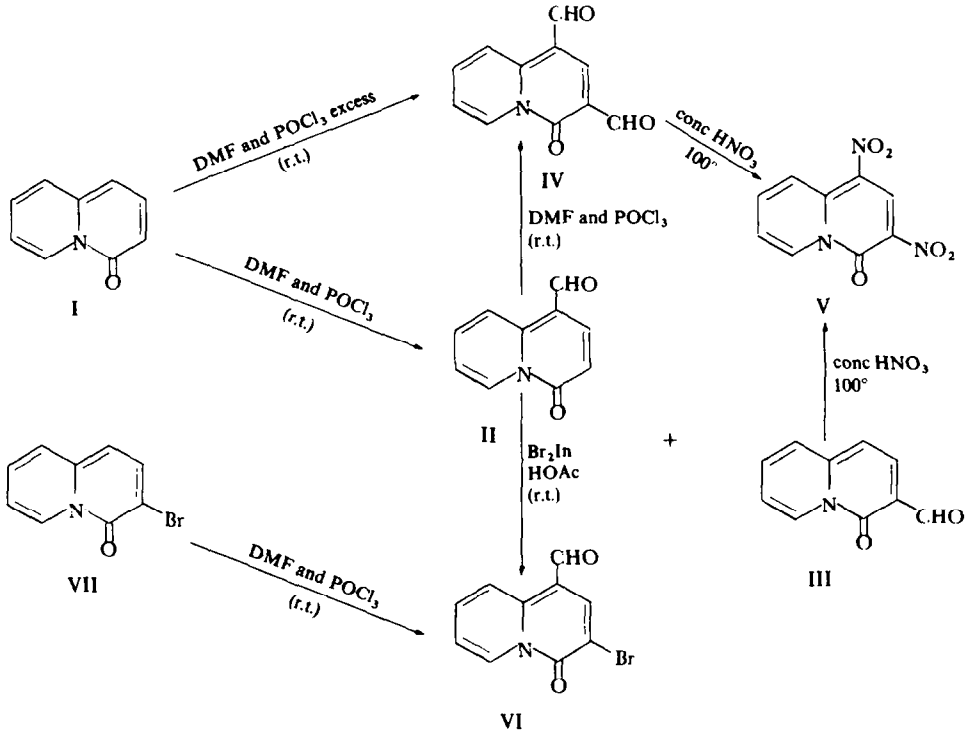


TABLE 1. UV MAXIMA IN EtOH (mμ)

				Ref.
(a)	1-Carbethoxy-4-quinolizone	255	*370*	6
	3-Carbethoxy-4-quinolizone	254	*406*	7
(b)	1-Acetyl-4-quinolizone	258, 340	288, *370*	2
	3-Acetyl-4-quinolizone	260, *420*	350	
(c)	1-Acetyl-3-bromo-4-quinolizone	263, *385*	290	2
	1-Bromo-3-acetyl-4-quinolizone	265, *440*	340	
(d)	1-Formyl-4-quinolizone (III)	260, *375*	290	
	1-Formyl-3-bromo-4-quinolizone (VI)	265, *383*	293	
	3-Formyl-4-quinolizone (IV)	265, *430*	340	

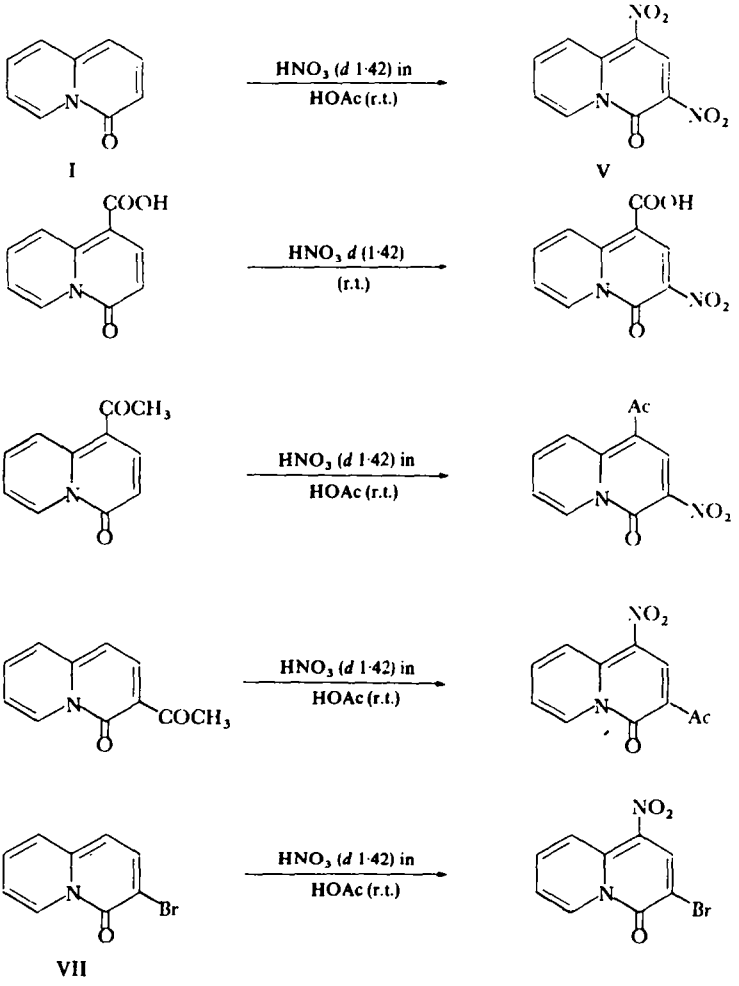
[6] V. Boekelheide and J. P. Lodge, Jr., *J. Am. Chem. Soc.* **73**, 3681 (1951).
[7] F. Bohlmann, A. Englisch, T. Politt, Hans Sander and W. Weise, *Chem. Ber.* **88**, 1831 (1955).

supported by spectral data. The data summarized in Table 1 clearly reveal that 3-acyl-4-quinolizones absorb in the UV at longer wavelengths than the corresponding 1-acyl-4-quinolizones.

Since mono and diformyl derivatives of quinolizone were obtained, this suggests that given a sufficiently reactive cation, acylation can be effected on this substrate. In parentheses, a striking difference between the acyl derivatives of quinolizones and those of indolizines deserves comment. It has been reported that diacylindolizines afford carbonyl derivatives through reaction of only one of the acyl functions. On the contrary, diacetyl and diformyl quinolizones yield dioximes.

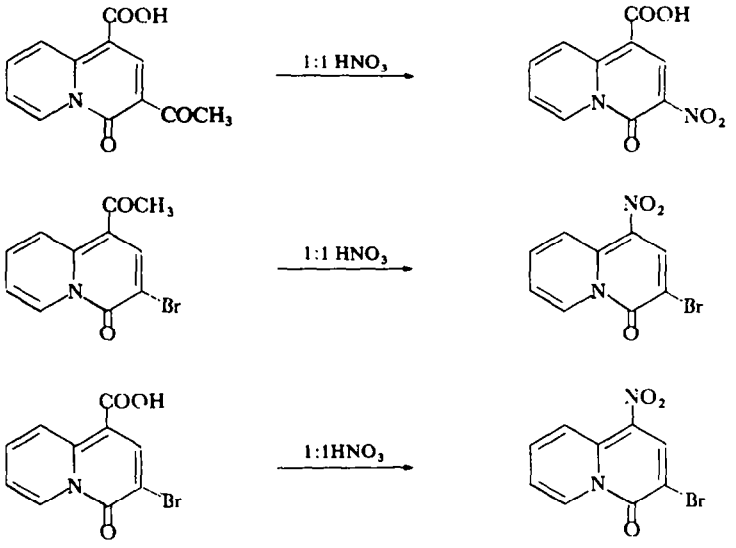
The facile displacement of carboxy, bromo and acetyl functions by the nitro group described[1,2] coupled with similar reactivity of the formyl group in the present study led us to investigate the possibility of selective displacements amongst the different substituents. The accompanying charts illustrate some of these electrophilic displacements.

Chart II shows the easy replacement of a proton in preference to other functional



groups while Chart III illustrates the selectivity observed between two different functions. The study appears to indicate the following order of reactivity in these electrophilic displacements.

$$H > COMe > COOH > Br$$



EXPERIMENTAL

Formylation of 4H-*quinolizin*-4-*one* (I) *with* DMF *and* $POCl_3$

(a) 4H-Quinolizin-4-one[6] (4 g) was dissolved in DMF (4 ml) and $POCl_3$ (4 ml) was added slowly with occasional cooling in ice-water (5 min). The viscous mixture was poured onto ice, neutralized with Na_2CO_3 and extracted with $CHCl_3$. Removal of $CHCl_3$ yielded a sticky solid (3·5 g). This was dissolved in hot benzene, the benzene layer decanted from the gummy material and pet. ether added yielding a solid (1·1 g), m.p. between 100° and 130°. Fractional crystallization from benzene yielded II and III with m.ps 150–155° (0·6 g) and 145°–150° (0·3 g) respectively. Further purification by chromatography on alumina, eluting with benzene–pet. ether and sublimation of the product *in vacuo* yielded:

Compound II, m.p. 176–177°. (Found: C, 69·36; H, 4·19; N, 7·54. $C_{10}H_7NO_2$ requires for one formyl group: C, 69·36; H, 4·06; N, 8·09.) IR spectrum (KBr): 5·9 (s), 6·13 (vs), 6·39 (vs), 6·45 (s), 6·6 (vs), 6·75 (vs), 7·0 (m), 7·09 (m), 7·2 (w), 7·35 (m), 7·8 (w), 8·0 (w), 8·33 (m), 8·44 (vs), 8·7 (s), 8·85 (m), 9·17 (m), 9·43 (s), 9·8 (w), 12·3 (m), 12·75 (m), 13·0 (s) and 13·45 (s) μ.

Compound III, m.p. 174–175°. (Found: C, 69·09; H, 3·97; N, 8·13. $C_{10}H_7NO_2$ requires for one formyl group: C, 69·36; H, 4·06; N, 8·09.) IR spectrum (KBr): 5·9 (s), 6·13 (vs), 6·39 (vs), 6·45 (s), 6·6 (vs), 6·75 (vs), 6·9 (s), 7·15 (m), 7·28 (m), 7·7 (vs), 7·85 (m), 8·65 (m) and 8·85 (m) μ.

(b) *With excess* DMF and $POCl_3$. Compound I (6·5 g) was dissolved in DMF (50 ml) and $POCl_3$ (50 ml) was added slowly with stirring during 15 min. After ½ hr, the soln was poured onto crushed ice (500 g) and scratched till solid began to form. This was filtered off, washed with water and dried (5·5 g; IV), m.p. 220–222° (dec). An analytical sample from benzene had m.p. 231–232° (dec). (Found: C, 65·48; H, 3·60. $C_{11}H_7NO_3$ requires: C, 65·67; H, 3·48%.) UV spectrum (EtOH): 273, 285, 345 and 420 mμ (log ε 3·97, 3·91, 4·10 and 4·21). IR spectrum (KBr): 6·04 (vs), 6·17 (s), 6·33 (s), 6·66 (vs), 6·94 (s), 7·41 (m), 7·52 (m), 7·9 (m), 8·0 (s), 8·16 (s), 9·35 (m), 10·85 (m), 13·0 (s) and 13·25 (s) μ. The oxime, m.p. 217–219° crystallized from EtOH. (Found: C, 57·06; H, 3·85. $C_{11}H_9N_3O_3$ requires: C, 57·14; H, 3·90%.)

2-Picolinic acid-N-*oxide from the diformyl compound IV*

Compound IV (800 mg) was treated with 30% H_2O_2 (5 ml) and kept overnight. After salting out, the

mixture was extracted with benzene, the benzene layer was dried and the solvent removed to yield a solid (250 mg). After recrystallization from EtOH, it had m.p. 161°. After one more crystallization, it was found not to depress the m.p. of 2-picolinic acid N-oxide.*

Conversion of diformyl (IV) *to* 1,3-*dinitro*-4H-*quinolizin*-4-*one* (V)

Compound IV (500 mg) was treated with HNO_3 (*d.* 1·42; 2 ml) and warmed for a few sec on the water-bath. The mixture was poured onto ice, the solid obtained was filtered off, washed with water and recrystallized from EtOH (300 mg). It did not depress the m.p. of authentic 1,3-dinitro-4H-quinolizin-4-one,[1] m.p. 230° (dec).

Conversion of monoformyl II *to diformyl* IV

Compound II (100 mg) was dissolved in DMF (1 ml) and $POCl_3$ (1 ml) was added. After shaking the mixture for a few sec, it was poured onto ice, neutralized with solid Na_2CO_3, extracted with $CHCl_3$ and the $CHCl_3$ removed yielding 80 mg of solid material. After recrystallization from $CHCl_3$–pet. ether, it did not depress the m.p. of authentic diformyl IV.

Bromination of monoformyl compound II

Compound II (350 mg) was added glacial AcOH (2 ml) containing Br_2 (0·1 ml) during 5 min. It was then poured onto ice, the solid was filtered off, washed with water and dried (380 mg; VI). After recrystallization from EtOH, it melted at 188–189°. (Found: C, 47·45; H, 2·74. $C_{10}H_6NO_2$ requires: C, 47·62; H, 2·40%.) IR spectrum (KBr/2 μ to 9 μ): 5·7 (m), 5·9 (s), 6·025 (vs), 6·1 (s), 6·35 (s), 6·78 (s), 7·35 (m), 7·55 (m), 7·75 (m) and 8·55 (s) μ.

Formylation of 3-*bromo*-4H-*quinolizin*-4-*one* VII

Compound VII (250 mg) was dissolved in DMF (1 ml) and $POCl_3$ (1 ml) was added. The mixture was shaken for a few sec and poured onto ice. The ppt was filtered off, dried (250 mg) and recrystallized from benzene–pet. ether, m.p. 188–189° (dec). This was found to have superimposable IR spectrum (KBr) with the brominated product of monoformyl 4H-quinolizin-4-one.

Conversion of formyl-bromo compound VI *to dinitro* V

Compound VI (20 mg) was treated with HNO_3 (*d.* 1·42; 1 ml) and warmed for a few sec. The mixture was poured onto ice and centrifuged. The solid was dried (10 mg) and after recrystallization from EtOH, it did not depress the m.p. of dinitro V, m.p. 230° (dec).

Conversion of monoformyl III *to dinitro* V

Monoformyl III (100 mg) was treated with HNO_3 (*d.* 1·42; 2 ml) warmed for a few sec on the water-bath, poured onto ice, the solid filtered off and dried (100 mg). After recrystallization, it was found not to depress the m.p. of dinitro compound V.

1-*Carbethoxy*-3-*formyl*-4H-*quinolizin*-4-*one*

1-Carbethoxy-4H-quinolizin-4-one[6] (1·5 g) was dissolved in DMF (3 ml) and $POCl_3$ (3 ml) was added in one lot. After a few sec, the mixture was poured onto ice, neutralized with Na_2CO_3, the solid was filtered off and washed with water. It was recrystallized from benzene–pet. ether (1·5 g), m.p. 150°. (Found: C, 63·60; H, 4·42. $C_{13}H_{11}NO_4$ requires: C, 63·67; H, 4·49%.) UV spectrum (EtOH): 270, 340 and 420 mμ (log ε 3·95, 3·66 and 3·96). IR spectrum (Nujol): 3·5 (s), 5·88 (m), 6·03 (s), 6·2 (m), 6·35 (m), 6·7 (m), 6·9 (vs), 7·325 (vs), 7·45 (m), 7·8 (m), 8·2 (s), 8·625 (m), 9·8 (m), 10·1 (m), 10·5 (m), 11·55 (w), 12·6 (m), 12·75 (m), 13·3 (w) and 14·15 (w) μ.

1-*Acetyl*-3-*bromo*-4H-*quinolizin*-4-*one*

Method A: (i) 1-Acetyl-4H-quinolizin-4-one[2] (470 mg) was suspended in glacial AcOH (5 ml) and a soln of Br_2 (0·3 ml) in glacial AcOH (3 ml) was added. After keeping the mixture for 5 min, it was poured onto ice, the solid was filtered off and dried (480 mg). It was recrystallized from EtOH, m.p. 208–209°. (Found: C, 49·75; H, 3·13. $C_{11}H_8NO_2Br$ requires: C, 49·62; H, 3·00%.) IR spectrum ($CHCl_3$): Acetyl-carbonyl and amide carbonyl (5·9 and 6·06 μ).

* O. Diels and K. Alder, *Liebigs. Ann.* **505**, 103 (1933).

(ii) Compound XI (1 g) was dissolved in DMSO (5 ml) and EtBr was added. After keeping the mixture overnight, it was heated on an oil-bath at 110–120° for 1½ hr, cooled and poured onto ice. The ppt was filtered off, washed with water and dried (1·28 g), m.p. 168–170°. Recrystallization from benzene, raised the m.p. to 179°. The IR spectrum of this in $CHCl_3$ was superimposable with the bromo-compound (m.p. 208–209°) obtained above, in spite of the dimorphic nature.

Method B. Brominative decarboxylation of 1-*acetyl*-3-*carboxy*-4H-*quinolizin*-4-*one*: The sodium salt of the acetyl-carboxy compound[2] (2·4 g) was suspended in glacial AcOH (50 ml) and liquid Br_2 (0·5 ml) was added. After refluxing the mixture for 15 min, it was cooled, poured onto ice, the solid filtered off, washed with water and dried (1·95 g). The m.p. was not sharp. Recrystallization from benzene afforded two compounds, with m.ps 179–180° (285 mg) and 208° (865 mg).

The two specimens showed identical IR spectra in $CHCl_3$.

3-*Acetyl*-1-*bromo*-4H-*quinolizin*-4-*one*

Method A 3-Acetyl-4H-quinolizin-4-one[2] (370 mg) was suspended in glacial AcOH (5 ml) and Br_2 (0·2 ml) was added. After 5 min, the mixture was poured onto ice, the ppt was filtered off, washed with water, dried (350 mg) and recrystallized from benzene–pet. ether, m.p. 155° (dec). (Found: C, 49·33; H, 3·40; N, 5·99. $C_{11}H_8NO_2Br$ requires: C, 49·62; H, 3·00; N, 5·27%.) IR spectrum ($CHCl_3$): 5·975 and 6·15 μ (carbonyls—acetyl and amide).

Method B Brominative decarboxylation of 3-*acetyl*-1-*carboxy*-4H-*quinolizin*-4-*one*: To the suspension of acetyl-carboxy compound (2·8 g) in glacial AcOH (50 ml), liquid Br_2 (1 ml) was added. The mixture was gently refluxed for 10 min, poured onto ice, the ppt was filtered off, washed with water, dried (1·6 g), and recrystallized from benzene. It had a superimposable IR spectrum with the bromo compound obtained by Method A.

1-*Acetyl*-3-*nitro*-4H-*quinolizin*-4-*one*

2-Pyridylacetone* (5 g) was mixed with ethyl ethoxymethylenenitroacetate[1] (5 g) and kept on the water bath for 1 hr. The crystalline compound (3 g) was purified by recrystallization from $CHCl_3$, m.p. 223–225°. (Found: C, 57·27; H, 3·24; N, 12·09. $C_{11}H_8N_2O_4$ requires: C, 56·90; H, 3·45; N, 12·07%.) UV spectrum (EtOH): 265, 293, 340 and 425 mμ (log ε 3·98, 3·75, 4·27 and 4·22). IR spectrum ($CHCl_3$): 5·8 (amide carbonyl), 6·03 (acetyl carbonyl), 6·325 and 7·325 μ (—NO_2).

1-*Carboxy*-4H-*quinolizin*-4-*one*

To a hot soln of 1-carbethoxy-4H-quinolizin-4-one (300 mg) in EtOH (3 ml) 5% NaOH aq (3 ml) was added. The soln was kept overnight in refrigerator, acidified, and filtered, the amorphous material was washed with EtOH, dried (220 mg) and recrystallized from EtOH, m.p. 226° (dec) (Found: C, 63·68; 63·61; H, 3·95; 4·06; N, 7·15; 7·28. $C_{10}H_7NO_3$ requires: C, 63·49; H, 3·70; N, 7·40%.) IR spectrum (KBr): 5·9 μ (acid carbonyl) and 6·025 μ (amide carbonyl).

TABLE 2

Sl. No.	Reactant	Product	% Yield
1.	1,3-Dibromo-4-quinolizone[2]	1,3-Dinitro-4-quinolizone	44
2.	1-Acetyl-3-bromo-4-quinolizone	1,3-Dinitro-4-quinolizone	Nearly quantitative
3.	3-Acetyl-1-bromo-4-quinolizone	1,3-Dinitro-4-quinolizone	Nearly quantitative
4.	1-Acetyl-3-carboxy-4-quinolizone[2]	1,3-Dinitro-4-quinolizone	Nearly quantitative
5.	3-Acetyl-1-carboxy-4-quinolizone[2]	1,3-Dinitro-4-quinolizone	Nearly quantitative
6.	3-Bromo-1-carbethoxy-4-quinolizone[2]	3-Nitro-1-carbethoxy-4-quinolizone	88

* J. Büchi, F. Kracher and G. Schmidt, *Helv. Chim. Acta* **45**, 729 (1962).

TABLE 3

Sl. No.	Reactant	Product	% Yield	Analytical values (%)					
				Found			Calc.		
				C	H	N	C	H	N
1.	1-Acetyl-4-quinolizone[2]	1-Acetyl-3-nitro-4-quinolizone[a]	40						
2.	3-Acetyl-4-quinolizone	3-Acetyl-1-nitro-4-quinolizone	64	56·98	3·90	12·52	56·90	3·45	12·07
3.	3-Acetyl-1-carboxy-4-quinolizone	1-Carboxy-3-nitro-4-quinolizone	65	51·47	2·88	12·10	51·24	2·56	11·96
4.	1-Acetyl-3-bromo	3-Bromo-1-nitro-4-quinolizone[b]	66						
5.	1-Carboxy-4-quinolizone	1-Carboxy-3-nitro-4-quinolizone[c]	60						

[a] The m.p. of this did not depress the m.p. of 1-acetyl-3-nitro-4-quinolizone synthesized.
[b] No depression in m.p. with authentic sample (*vide* Ref. 2).
[c] No depression in m.p. with the product from (3).

Electrophilic displacement by nitronium ion

General procedure. The compounds (Sl. Nos. 1 to 6—Table 2) were treated with 10-fold excess HNO_3 (*d.* 1·42), warmed for 1 to 5 min on the water-bath, cooled, poured onto crushed ice, the ppt was filtered off, washed free of acid, dried and recrystallized from EtOH. The product was found to be 1,3-dinitro-4H-quinolizin-4-one in the first 5 cases and 3-nitro-1-carbethoxy-4H-quinolizin-4-one in the last case, as is evidenced by mixed m.p. with authentic samples.[1,2]

Selective cationoid displacements

General procedure. The compound (1 g) was treated either with HNO_3 (*d.* 1·42; 3 ml) in glacial AcOH (10 ml), shaken vigorously for 1 to 5 min, and poured onto ice or warmed for a few sec with 1:1 HNO_3 (10 ml) and poured onto ice. The solids obtained were filtered off, dried and recrystallized from EtOH.

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