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STUDIES ON QUINOLIZONES—III

STRUCTURAL FACTORS INFLUENCING QUINOLIZONE Vs. INDOLIZINE FORMATION

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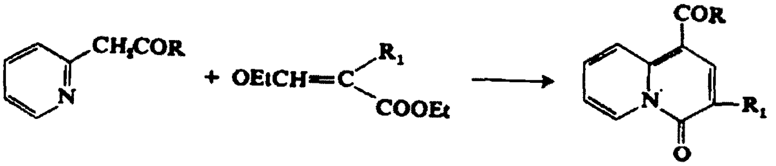
Abstract—Reaction of 6-Methyl-2-pyridylacetone, propionone and 2-phenacylpyridine with ethyl ethoxymethylene malonate yield the expected 4-quinolizone derivatives whereas reaction with β-ethoxy-α-nitroacrylic ester yields indolizine derivatives with the loss of the nitro group.

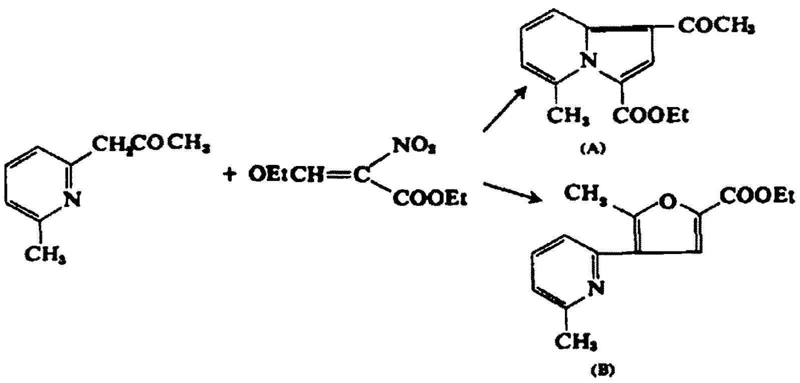
THE synthesis of a number of quinolizone derivatives was described recently[1,2] utilizing the following condensation.



(R = OEt or CH_3, R_1 = COOEt, NO_2 or $COCH_3$)

With the expectation of extending the scope of the above condensation, a similar reaction between the corresponding 2,6-lutidine derivatives and the same acrylic esters was investigated.

Although the results follow a parallel course in the instance of ethyl ethoxymethylene-malonate, a strikingly different result was obtained in the case of β-ethoxy-α-nitroacrylic ester. The latter readily lost the nitrite anion and gave a product carrying a single nitrogen atom. One might envisage two distinct paths of reaction involving the elimination of nitrite anion—leading to either an indolizine derivative (A) or a β-pyridyl furan (B) derivative.



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[1] B. S. Thyagarajan and P. V. Gopalakrishnan, *Tetrahedron* **20**, 1051 (1964).

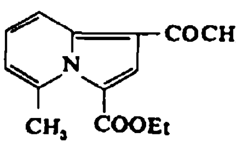
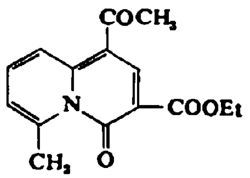
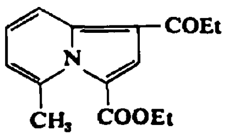
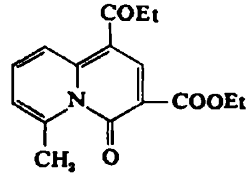
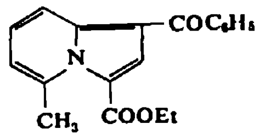
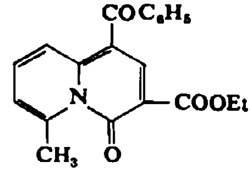
[2] B. S. Thyagarajan and P. V. Gopalakrishnan, *Tetrahedron* **21**, 945 (1965).

A decision between these two alternatives was arrived at on the basis of the following facts:

(1) Compound I formed an oxime and a greenish black 2-4-DNP derivative indicative of the presence of a carbonyl group.

(2) Oxidation with 30% hydrogen peroxide readily afforded 6-methyl-2-picolinic acid-N-oxide—a reaction characteristic of indolizine derivatives.

TABLE 1. COMPARISON OF THE UV SPECTRA OF THE PRODUCTS OBTAINED FROM 6-METHYL 2-PYRIDYLACETONE (6 METHYL-2-PYRIDYLPROPIONONE AND 6-METHYL 2-PHENACYL PYRIDINE) AND β-ETHOXY-α-NITRO ACRYLIC ESTER AND ETHYL ETHOXYMETHYLENE MALONATE

	Indolizine derivative			Quinolizone derivative		
S. No.		λ_{max}	log ϵ		λ_{max}	log ϵ
1	 IV	227 252 287 340	4·16 4·44 3·97 4·3	 II	260 353 420	3·89 3·98 4·03
2	 VI	225 252 285 338	4·2 4·45 3·92 4·25	 V	265 350 425	4·06 4·1 4·28
3	 VIII	250 288 358	4·46 3·82 4·29	 VII	258 350 430	4·21 4·11 4·26

(3) The UV absorption maxima clearly indicated an indolizine ring system* (Table 1).

(4) Added confirmation was available from the NMR spectrum: A multiplet of 4 aromatic protons at 7–9 ppm, a triplet and quadruplet of 5 protons at 1·45 and 4·4 ppm indicative of ethyl ester, two singlets accounting for 6 protons at 2·75 ppm and acetyl methyl at 2·55 ppm.

The loss of the nitrite anion in the above condensation seemed unusual and merited further study. Consequently, the following substituted lutidine derivatives

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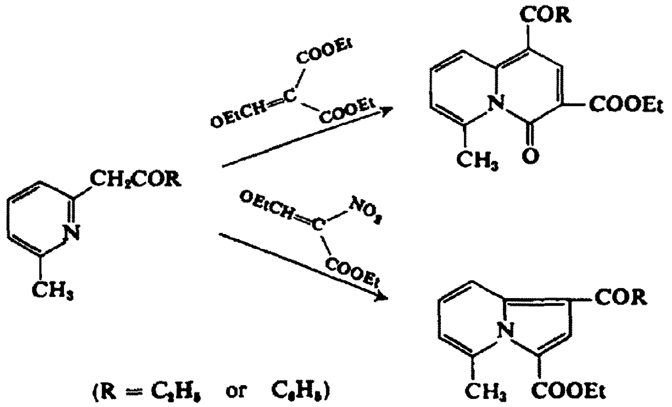
* N. J. Leonard *et al. J. Org. Chem.* **22**, 1445 (1957) have discussed the UV absorption maxima differences between indolizine and quinolizine systems.

were reacted with β-ethoxyacrylic esters leading to quinolizones or indolizines as indicated



($R = C_2H_5$ or C_6H_5)

Suggestions of possible steric hindrance by the 6-methyl group in the lutidine might easily be countered by the fact that quinolizones are formed when the leaving group is other than nitro. Besides, it has been possible to displace an ethoxide anion in preference to a nitrite anion in the condensation between ethyl-2-pyridylacetate and β-ethoxy-α-nitroacrylic ester. Similar behaviour was encountered with 2-pyridylacetone as well.[3] Therefore, probably the combination of the two factors, viz., the presence of 6-methyl group as well as a displaceable nitrite anion promote the formation of the indolizine system in preference to the quinolizone system.

The indolizine derivatives described in the present study indicate a possible application of this reaction as one more general route to indolizines.[4,5a,5b]

EXPERIMENTAL

6-Methyl-2-pyridylacetone was prepared by a procedure similar to the one used for 2-pyridylacetone.[6]

6-Methyl-2-pyridylpropionone and *6-methyl-2-phenacylpyridine* were prepared by the method of Levine *et al.*[7]

1-*Acetyl*-3-*carbethoxy*-6-*methyl*-4H-*quinolizin*-4-*one* (I). 6-Methyl-2-pyridylacetone (9 g) was mixed with ethyl ethoxymethylenemalonate (13 g) and heated at 140°–150° for 2 hr. After cooling the mixture, the solid mass was washed with ether and filtered (yield 7·0 g). It was recrystallized from benzene. m.p. 174°–175°. (Found: C, 65·76; H, 5·44; N, 5·00; $C_{15}H_{15}NO_4$ requires: C, 65·93; H, 5·45; N, 5·13%.) λ_{max}^{EtOH} 260, 353, and 420 mμ (log ε 3·89, 3·98 and 4·03); λ_{max}^{KBr} 3·4 (s), 5·8 (vs), 5·9 (vs), 6·05 (vs), 6·125 (m), 6·3 (s), 6·55 (s), 6·7 (vs), 7·05 (m), 7·125 (m), 7·25 (vs), 7·4 (m) 7·975 (vs), 8·125 (vs), 8·5 (s), 8·65 (s), 9·3 (w), 9·7 (s), 10·0 (m), 10·4 (m), 10·55 (w), 10·85 (w), 11·4 (w), 12·15 (s), 12·6 (m), 12·95 (m), and 13·35 (w). μ

NMR (in $CDCl_3$): Triplet and quadruplet of 5 protons at 1·45 and 4·4 ppm indicative of ethyl ester, singlet of 3 protons at 2·6 ppm (acetyl methyl), singlet of 3 protons at 3 ppm (ring methyl) and a multiplet of 4 aromatic protons at 7–9 ppm.

1-*Nitro*-3-*carbethoxy*-6-*methyl*-4H-*quinolizin*-4-*one* (II). To I (200 mg) was added conc. HNO_3 (2 ml). After shaking the mixture for a few sec. it was poured onto ice-pieces, the precipitated solid

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[3] B. S. Thyagarajan and P. V. Gopalakrishnan, Unpublished work.

[4] A. E. Chichibabin, *Ber. Dtsch. Chem. bew.* **60**, 1607 (1927).

[5a] V. Boekelheide and R. J. Windgassen Jr., *J. Amer. Chem. Soc.* **81**, 1456 (1959); [b] D. R. Bragg and D. G. Wibberley, *J. Chem. Soc.* 3277 (1963).

[6] J. Buchi, F. Kracher and G. Schmidt, *Helv. Chim. Acta* **45**, 729 (1962).

[7] N. N. Goldberg and R. Levine, *J. Amer. Chem. Soc.* **74**, 5217 (1952).

was filtered off and washed with ice water (wt. 120 mg). It was recrystallized from aqueous EtOH. mp. 130°–131°. (Found: C, 56·44; H, 4·27; N, 9·73; $C_{13}H_{12}N_2O_5$ requires: C, 56·52; H, 4·34; N, 10·14%). λ_{max}^{EtOH} 415 mμ (log ε 4·34); λ_{max}^{KBr} 3·34 (w), 5·71 (vs), 5·8 (m), 5·92 (m), 6·17 (s), 6·29 (s), 6·58 (vs), 6·8 (w), 6·99 (w), 7·22 (w), 7·41 (m), 7·57 (m), 7·75 (vs), 7·87 (vs), 8·2 (s), 8·44 (vs), 8·62 (m), 8·77 (w), 8·93 (s), 9·26 (m), 12·74 (m), and 13·01 (m) μ.

1-*Acetyl*-3-*carboxy*-6-*methyl*-4H-*quinolizin*-4-*one* (III). To a warm solution of I (500 mg) in EtOH (5 ml) was added 5% NaOHaq. (5 ml). After keeping the mixture overnight in a refrigerator, it was acidified and the precipitated solid filtered off and dried (wt. 150 mg). After recrystallization from EtOH, it melted with gas evolution at 194°. (Found: C, 63·61; H, 4·76; N, 5·40; $C_{13}H_{11}NO_4$ requires: C, 63·67; H, 4·50; N, 5·71%.)

Reaction of 6-methyl-2-pyridylacetone with ethyl ethoxymethylenenitroacetate to yield 1-*acetyl*-3-*carbethoxy*-5-*methyl indolizine* (IV). 6-Methyl-2-pyridylacetone (13 g) was mixed with ethyl ethoxymethylenenitroacetate (16 g) in EtOH (20 ml) containing Na (500 mg) and the mixture was kept overnight at room temp. The mixture was then poured onto ice pieces and scratched till solid began to form. The sticky solid which was obtained was dried in a vacuum desiccator and then repeatedly extracted with pet. ether decanted from the oily portion. The pet ether portion was then concentrated and cooled when white crystals formed (wt. 4 g). It was purified either by sublimation or recrystallization from pet. ether. m.p. 121°–122°. (Found: C, 68·98; H, 6·17; N, 5·5; $C_{14}H_{15}NO_3$ requires: C, 68·6; H, 6·10; N, 5·7%.) λ_{max}^{EtOH} 227, 252, 287 and 340 mμ (log ε 4·16, 4·44, 3·97, and 4·30); λ_{max}^{KBr} 3·4(s), 5·85 (vs), 6·05 (vs), 6·125 (s), 6·6 (vs), 6·7 (vs), 7·15 (m), 7·225 (m), 7·35 (s), 7·5 (vs), 8·15 (vs), 8·4 (vs), 8·65 (vs), 8·75 (s), 9·0 (w), 9·35 (w), 9·5 (vs), 10·0 (w), 10·5 (s), 11·25 (w), 11·5 (w), 12·7 (s), 13·15 (s) and 14·15 (w) μ.

The NMR (in $CDCl_3$): Triplet and quadruplet of 5 protons at 1·45 and 4·4 ppm (ethyl ester), singlet of 3 protons at 2·55 ppm (acetyl methyl), singlet of 3 protons at 2·75 ppm (ring methyl) and multiplet of 4 aromatic protons at 7–9 ppm. The *oxime* m.p. 151°–152° from EtOH gave the following analysis. (Found: C, 65·10; H, 6·6; N, 10·77; $C_{14}H_{16}N_2O_3$ requires: C, 64·60; H, 6·2; N, 10·77%.) 2-4-DNP *derivative*. m.p. 230° (dec) from a large volume of ethyl acetate gave the following analysis. (Found: C, 56·75; H, 5·0; $C_{20}H_{19}N_5O_6$ requires: C, 56·40; H, 4·5%.)

Degradation of IV *with* H_2O_2 *and* HOAc *to 6-methyl 2-picolinic acid*-N-*oxide*. Compound IV (230 mg) was treated with 30% H_2O_2 (4 ml) in acetic acid (5 ml). After keeping the mixture on the waterbath for 8 hr, it was poured onto ice water, the precipitated solid was filtered and dried (wt. 50 mg) m.p. 171°–172°. More solid (wt. 20 mg) was obtained from the mother liquor after salting, extracting with benzene and removing the benzene. After recrystallization from EtOH, it did not depress the m.p. of 6-methyl-2-picolinic acid-N-oxide obtained in one step from 6-methyl pyridine-2-aldehyde and H_2O_2 in HOAc (5 g of 6-methyl pyridine-2-aldehyde gave 3·2 g of 6-methyl-2-picolinic acid-N-oxide) and had superimposable IR spectrum with it (lit[8] m.p. 176°).

1-*Propionyl*-3-*carbethoxy*-6-*methyl*-4H-*quinolizin*-4-*one* (V). 6-Methyl-2-pyridylpropionone (2 g) was mixed with ethyl ethoxymethylenemalonate (3 g) and heated at 150°–160° for 3 hr. The mixture was then dissolved in the minimum EtOH and cooled. The solid that separated was filtered and dried. (wt. 1·7 g). It was recrystallized from benzene–pet. ether. m.p. 133°–134°. (Found: C, 67·3; H, 6·2; $C_{16}H_{17}NO_4$ requires: C, 66·9; H, 5·9%.) λ_{max}^{EtOH} 265, 350, and 425 mμ (log ε 4·06, 4·1 and 4·28); $\lambda_{max}^{CHCl_3}$ 3·35 (m), 5·775 (vs), 5·875 (s), 6·05 (vs), 6·175 (m), 6·325 (vs), 6·6 (vs), 7·325 (s), 7·675 (m), 8·0 (s), 8·425 (s) and 8·575 (s) μ.

The NMR (in $CDCl_3$): Sextet of 6 protons at 1·0–1·6 ppm ($COCH_2CH_3$ and $COOCH_2CH_3$), quadruplet of 2 protons at 4·5 ppm (OCH_2), quadruplet and singlet of 5 protons at 3·0 ppm ($COCH_2$ and ring methyl), multiplets of 4 aromatic protons at 7·0–9·0 ppm.

Reaction of 6-methyl-2-pyridylpropionone with ethyl ethoxymethylenenitroacetate to yield 3-*carbethoxy*-5-*methyl*-1-*propionyl indolizine* (VI). 6-Methyl-2-pyridylpropionone (2 g) was mixed with ethyl ethoxymethylenenitroacetate (3 g), 6 drops of piperidine were added and the mixture was kept overnight at room temp. It was then dissolved in the minimum EtOH, water was added till turbidity appeared and left aside in ice bath. The solid that separated was filtered and dried (wt. 750 mg). It was recrystallized from pet. ether. m.p. 91°–92°. (Found: C, 69·04; H, 6·76; $C_{15}H_{17}NO_3$ requires: C, 69·5; H, 6·56%.) λ_{max}^{EtOH} 225, 252, 285 and 338 mμ (log ε 4·2, 4·45, 3·92 and 4·25); $\lambda_{max}^{CHCl_3}$ 3·35 (m), 5·85 (vs), 6·10 (s), 6·175 (s), 6·65 (vs), 6·775 (m), 7·025 (m), 7·2 (m), 7·25 (m), 7·35 (m), 7·425 (s), 7·55 (m), 8·4 (vs) and 8·665 (m) μ.

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[8] W. Baker, K. M. Buggle, J. F. W. Mcomie and D. A M. Watkins, *J. Chem. Soc.* 3594 (1958).

The NMR (in $CDCl_3$): Sextet of 6 protons at 1·0–1·6 ppm ($COCH_2\underline{CH_3}$ and $COOCH_2\underline{CH_3}$), quadruplet and singlet of 5 protons at 2·85 ppm ($CO—\underline{CH_2}$ and ring methyl), quadruplet of 2 protons at 4·3 ppm ($O—\underline{CH_2}$) and 4 aromatic protons at 6·7–8·2 ppm.

1-*Benzoyl*-3-*carbethoxy*-6-*methyl*-4H-*quinolizin*-4-*one* (VII). A mixture of 6-methyl-2-phenacylpyridine (750 mg) and ethyl ethoxymethylenemalonate (1·3 g) was heated at 180°–190° for 3 hr, cooled, EtOH (5 ml) was added, and the solid that separated was filtered and dried (wt. 210 mg). mp. 175°–176° (benzene-pet. ether). (Found: C, 71·4; H, 5·19; N, 4·37; $C_{19}H_{17}NO_4$ requires: C, 71·60; H, 5·08; N, 4·18%.) λ_{max}^{EtOH} 258, 350 and 430 mμ (log ϵ 4·21, 4·11 and 4·26); λ_{max}^{KBr} 3·35 (w), 5·73 (vs), 5·95 (s), 6·15 (s), 6·21 (s), 6·31 (s), 6·37 (s), 6·58 (s), 6·78 (vs), 6·97 (m), 7·09 (m), 7·35 (m), 7·41 (m), 7·49 (s), 7·78 (s), 8·1 (s), 8·2 (s), 8·33 (vs), 8·62 (m), 8·97 (s), 9·17 (vs), 9·71 (m), 9·85 (m), 10·2 (w), 10·76 (m), 11·37 (w), 12·45 (m), 12·62 (m), 12·97 (s), 13·47 (w), 14·32 (m), 14·7 (m), and 15·42 (m) μ.

The NMR (in $CDCl_3$): Triplet and quadruplet of 5 protons at 1·35 and 4·3 ppm (ethyl ester), singlet of 3 protons at 3·1 ppm (ring methyl) and multiplet of 9 aromatic protons at 6·9–8·5 ppm.

Reaction of 6-*methyl*-2-*phenacylpyridine with ethyl ethoxymethylenenitroacetate to yield* 1-*benzoyl*-3-*carbethoxy*-5-*methyl-indolizine* (VIII). A mixture of 6-methyl-2-phenacylpyridine (2 g) and ethyl ethoxymethylenenitroacetate (3 g) was kept on the waterbath for 3 hr, dissolved in the minimum EtOH, cooled in ice and salt and scratched. The precipitated solid was filtered and dried (wt. 1·3 g). It was recrystallized from pet. ether. mp. 113°–114°. (Found: C, 74·8, H, 6·00; $C_{19}H_{17}NO_2$ requires. C, 74·3, H, 5·6%.) λ_{max}^{EtOH} 250, 288 and 358 mμ (log ϵ 4·46, 3·82 and 4·29); $\lambda_{max}^{CHCl_3}$ (2 μ to 9 μ) 3·35 (m), 5·9 (vs), 6·15 (s), 6·2 (s), 6·225 (s), 6·3 (m), 6·375 (m), 6·55 (m), 6·675 (vs), 6·75 (m), 6·95 (m) 7·05 (m), 7·2 (m), 7·25 (m), 7·35 (m), 7·45 (s), 7·525 (m), and 8·675 (m) μ.

The NMR (in $CDCl_3$): Triplet and quadruplet of 5 protons at 1·35 and 4·4 ppm (ethyl ester), singlet of 3 protons at 2·85 ppm (ring methyl) and multiplet of 9 aromatic protons at 6·8–8·2 ppm.

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