The above white solid was dissolved in 100 ml. of absolute ethanol to which 6 drops of concentrated hydrochloric acid was added and refluxed for 2 hr. to give a green solution. After removing the solvent and acid *in vacuo*, a green, oily solid remained. The β-sitosteryl digitonide (1.71 g.) was prepared from this solid. β-Sitosterol recovered from the digitonide was chromatographed on 20 g. of silica gel. The early benzene fractions yielded an oil and from subsequent benzene fractions 0.21 g. of a white solid was obtained. Recrystallizing from ethanol yielded 0.18 g. of a white crystalline solid, m.p. 133–137°. After two further recrystallizations from acetone, β-sitosterol was obtained having m.p. 139–140°, $[\alpha]^{24}D$ −30° (*c* 0.252) [lit. m.p. 136.5–137.5°, $[\alpha]^{26}D$ −37° ($CHCl_3$)[15]; m.p. 139.5–140°, $[\alpha]^{26}D$ −31.8° ($CHCl_3$)[2a]; m.p. 139–140°, $[\alpha]^{26}D$ −33° ($CHCl_3$)[2b]].

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The Reaction between 4-Nitroquinoline 1-Oxide and Diethyl Sodiomalonate. An Unexpected Nucleophilic Substitution[1]

HENRY J. RICHTER AND NORMAN E. RUSTAD[2]

Department of Chemistry, University of Colorado, Boulder, Colorado

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The treatment of 4-nitroquinoline 1-oxide with diethyl sodiomalonate formed diethyl sodio(4-nitro-3-quinolyl)malonate 1-oxide. This sodium salt was used as an intermediate in the synthesis of other quinolyl-substituted malonates.

It has been shown that the nitro group in 4-nitroquinoline 1-oxide (I) may be displaced by a nucleophile. Reagents such as sodium ethoxide[3] and acetyl chloride[3] will displace the nitro group to form 4-ethoxyquinoline 1-oxide and 4-chloroquinoline 1-oxide, respectively. It has also been reported that attempts to replace the nitro group in I with various carbon-containing anions gave starting material or resinous products of unknown structure.[4]

It was anticipated that the carbanion of diethyl sodiomalonate might react with I to form a quinoline derivative in which the malonate residue displaced the nitro group. This could lead to a simplified synthesis of the desired quinoline-4-acetic acid 1-oxide, which has been prepared from I in six steps by Naito and Dohmori.[5]

When I was treated with diethyl sodiomalonate, a hydrated maroon salt II, analysis of which indicated an empirical formula $C_{16}H_{17}N_2NaO_8$, separated from the reaction mixture. The treatment of II with concentrated sulfuric acid or acidification of an aqueous solution with 10% hydrochloric acid produced a yellow compound (III) having a n.m.r. spectrum which showed four different hydrogens,[6] a triplet at τ 8.7 and a quadruplet at 5.7 ($CH_3CH_2OC(=O)$), a singlet at 5.0 [$HCAr(COOEt)_2$], and several peaks between 1.3 and 3.0 (aromatic) in an area ratio of 6:4:1:5, respectively. Since both II and III indicated a nitro group (1525 and 1320 cm.$^{-1}$) in their infrared spectra and the n.m.r. spectrum of III indicated five aromatic hydrogens, the nitro group was not displaced as anticipated but substitution is indicated. The infrared spectrum of III indicated two ester groups (1740 and 1720 cm.$^{-1}$), whereas the spectrum of II had a broad single carbonyl band at 1670 cm. $^{-1}$. This may be due to delocalization of the negative charge of the carbanion of the sodium salt through the two ester carbonyls. The spectrum of II also had a broad band at 3400 cm.$^{-1}$ which is interpreted as due to water of hydration.

When I is treated with phosphorus trichloride it is converted into 4-chloroquinoline.[7] Under similar conditions compound III gave diethyl (4-chloro-3-quinolyl)-malonate (V). The n.m.r. spectrum of V was very similar to that of III. The aromatic portion showed

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(2) Taken from a portion of the dissertation submitted to the Graduate School of the University of Colorado in partial fulfillment of the requirements for the Ph.D. degree, 1964.

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(4) I. Nakayoma, *J. Pharm. Soc. Japan*, **71**, 1391 (1951).

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(6) G. V. D. Tiers, "Characteristic Nuclear Magnetic Resonance 'Shielding' Values (Spectra Positions) for Hydrogen in Organic Structures," Central Research Department, Minnesota Mining and Manufacturing Co., St. Paul, Minn., March, 1958.

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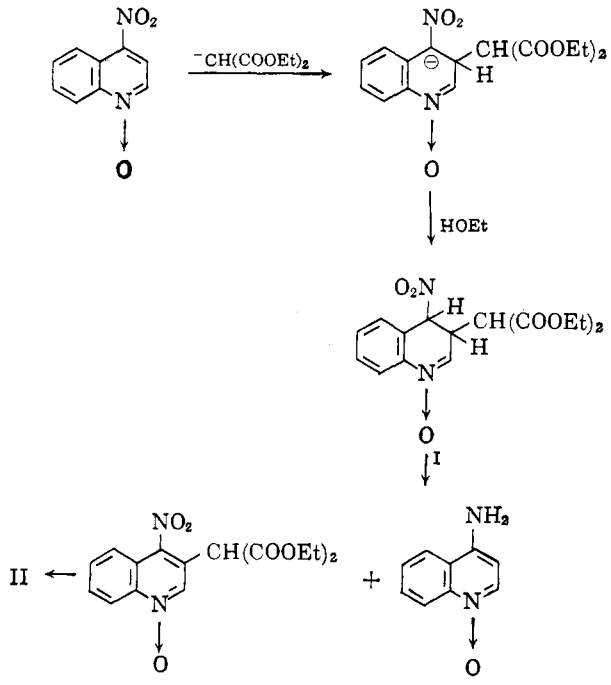
peaks between τ 1.1 and 2.5 with an area equivalent to five protons.[8a]

The hydrogen in the 2-position of pyridine and quinoline derivatives appears between τ 1.0 and 1.5.[8b] This hydrogen in 6-methoxyquinoline appears at τ 1.3 and is a doublet being split by the adjacent 3-hydrogen. The spectrum of V showed a singlet at τ 1.1. Since there is a singlet, not a doublet as in 6-methoxyquinoline, the 3-position of V must be substituted, preventing proton splitting.

Catalytic reduction of the nitro group in diethyl (4-nitro-3-quinolyl)malonate 1-oxide (III) produced a yellow solid VI. This did not melt without charring and was unreactive toward acetyl chloride. Treatment of VI with phosphorus trichloride removed the N-oxide and formed another yellow solid VII which behaved similarly but was more soluble. An infrared spectrum of VII showed a strong ammonium ion absorption at 1410 cm.$^{-1}$ and three N–H bands between 3000 and 3400 cm.$^{-1}$. Since there was a single broad carbonyl absorption at 1670 cm.$^{-1}$ as for II, a zwitterion VII is proposed.

To prevent this zwitterion formation, the acidic hydrogen on the malonate residue was methylated with methyl iodide to produce IV. This was reduced catalytically to form a yellow crystalline compound, VIII. The infrared spectrum of VIII did not show a distinct N–H absorption but did show two separate carbonyl bands at 1760 and 1715 cm.$^{-1}$. The elementary analysis corresponded to an empirical formula, $C_{15}H_{14}N_2O_4$, indicating that C_2H_5OH was lost. Treatment of VIII with phosphorus trichloride removed the N-oxide forming a compound, IX, with carbonyl absorption similar to VIII. A n.m.r. spectrum showed a singlet at τ 8.2 (tertiary methyl group) and a triplet at 8.8 (CH_3CH_2-OC=O). The areas of these peaks were equal, indicating only one carbethoxy group. Formation of the lactam, 4-methyl-4-carbethoxy-5-oxopyrrolino-[2,3-*c*]-quinoline 1-oxide (VIII), is consistent with the n.m.r. data and confirms that nucleophilic substitution occurred in the 3-position.

4-Aminoquinoline 1-oxide hydrochloride, identified by melting point, infrared spectrum, and melting point of a mixture with an authentic sample[3] prepared by reducing 4-nitroquinoline 1-oxide, was isolated from the original reaction mixture. The low yield of II (30–36%) with respect to I may indicate that the original nitro compound is serving a dual purpose. It is proposed that a 3,4-dihydroquinoline is formed first and then oxidized by the 4-nitroquinoline 1-oxide to the quinoline similar to the action of nitrobenzene in the Skraup reaction. A possible reaction path for the formation of II may be as shown (col. 2, top).



Experimental[9]

Diethyl Sodio(4-nitro-3-quinolyl)malonate 1-Oxide Monohydrate (II).—To a mixture of 4 g. (0.021 mole) of 4-nitroquinoline 1-oxide and 6.72 g. (0.042 mole) of diethyl malonate in 25 ml. of absolute ethanol, there was added with stirring, over a 15-min. period, a solution of 0.96 g. (0.042 g.-atom) of sodium in 25 ml. of absolute ethanol. A dark color developed. After stirring for 12 hr., the mixture was filtered to give 2.85 g. (36%) of a maroon salt. This product was recrystallized from 95% ethanol and obtained as maroon crystals which charred when heated to 300°.

Anal. Calcd. for $C_{15}H_{15}N_2NaO_8 \cdot H_2O$: C, 49.49; H, 4.41; N, 7.21. Found: C, 49.65; H, 4.31; N, 7.29.

When a twofold excess of 4-nitroquinoline 1-oxide (I) was treated with diethyl sodiomalonate, 25% of I was recovered and a 62% yield (with respect to diethyl malonate) of the sodium salt II was obtained. This per cent yield of II was twice that obtained when an excess of diethyl sodiomalonate was used. When nitrobenzene was added to the reaction mixture, the yield of II was unaffected.

The filtrate from above was evaporated to dryness and washed several times with 10% hydrochloric acid. The acid solution was filtered, neutralized with 10% sodium hydroxide, and extracted with benzene. The benzene solution was dried over anhydrous sodium sulfate, filtered, and treated with gaseous hydrogen chloride. Evaporation of the solution gave a small amount of salt which was recrystallized from an ethanol–chloroform mixture. This salt proved to be 4-aminoquinoline 1-oxide hydrochloride, when it was compared with an authentic sample (m.p. 275° dec.) prepared from 4-nitroquinoline 1-oxide.[3]

Diethyl (4-Nitro-3-quinolyl)malonate 1-Oxide (III).—The salt II (2.45 g.) was dissolved in 3 ml. of concentrated sulfuric acid. After 15 min. the solution was poured onto crushed ice and the yellow precipitate which formed was collected on a filter and crystallized from an acetone–water mixture. There was obtained 2.00 g. (91%) of yellow plates, m.p. 101–102°, which turned orange on standing.

Anal. Calcd. for $C_{16}H_{16}N_2O_7$: C, 55.18; H, 4.63; N, 8.03. Found: C, 55.10; H, 4.89; N, 7.89.

The derivative III was also obtained when the salt II was dissolved in water and the filtered solution was acidified with 10% hydrochloric acid.

Diethyl Methyl(4-nitro-3-quinolyl)malonate 1-Oxide (IV).—A mixture of 2.00 g. of I and 20 ml. of methyl iodide in 50 ml. of absolute ethanol was refluxed for 24 hr. An oil, which solidified on cooling, sepated when the solution was concentrated to a small volume and diluted with water. The yellow solid was separate and crystallized from an acetone–water solution giving 2.00 g. (95%) of yellow crystals, m.p. 94–95°, which turned orange on standing.

Anal. Calcd. for $C_{17}H_{18}N_2O_7$: C, 56.35; H, 5.01; N, 7.73. Found: C, 56.19; H, 5.14; N, 7.56.

Diethyl (4-Chloro-3-quinolyl)malonate (V).—A solution of 1.65 g. of II and 10 ml. phosphorus trichloride in 100 ml. of chloroform was refluxed 12 hr., cooled, and poured into water. The chloroform layer was separated and the aqueous layer was extracted

(8) "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962: (a) spectrum 249; (b) spectra 96, 154, 155, 159 and 249.

(9) All melting points were taken in capillary tubes and are uncorrected. The infrared spectra were recorded by a Beckman Model IR-5 infrared spectrophotometer. The n.m.r. spectra were run on a Varian A-60 with acetonitrile as the solvent.

with chloroform. The combined chloroform fractions were dried over anhydrous sodium sulfate and then evaporated to dryness. The oil obtained was crystallized from an acetone–water mixture producing 0.50 g. (33%) of white cubic crystals, m.p. 67–68°.

Anal. Calcd. for $C_{16}H_{16}ClNO_4$: C, 59.72; H, 5.01; N, 4.35. Found: C, 59.66; H, 5.17; N, 4.29.

Diethyl (4-Amino-3-quinolyl)malonate (VII).—A mixture of 2.10 g. of III and 200 mg. of 10% palladium on charcoal in 250 ml. of chloroform was reduced with 40 p.s.i. of hydrogen. To the reduced mixture 10 ml. of phosphorus trichloride was added, and the mixture was refluxed 3 hr., cooled, and evaporated to dryness. The residue was dissolved in ethanol, and the solution was filtered to remove the catalyst. A yellow solid separated from the filtrate on standing. When recrystallized from ethanol, yellow needles (0.45 g. 25%), which charred when heated to 300°, were formed.

Anal. Calcd. for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 5.00; N, 9.27. Found: C, 63.83; H, 5.96; N, 9.36.

4-Methyl-4-carbethoxy-5-oxopyrrolino[2,3-*c*]quinoline 1-Oxide (VIII).—A mixture of 0.90 g. of IV and 200 mg. of 10% palladium on charcoal in 100 ml. of absolute ethanol was reduced with 40 p.s.i. of hydrogen. The reduced mixture was filtered and the solution deposited 0.35 g. (50%) of a yellow solid on standing. When crystallized from ethanol, yellow needles were formed, m.p. 214°.

Anal. Calcd. for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93, N, 9.78. Found: C, 62.78; H, 5.18; N, 9.97.

4-Methyl-4-carbethoxy-5-oxopyrrolino[2,3-*c*]quinoline (IX).—A solution comprising 0.40 g. of VIII, 5. ml. of phosphorus trichloride, and 50 ml. of chloroform was refluxed for 30 min. The solvent was evaporated, leaving an oil which was diluted with water and made basic with 10% sodium hydroxide. The white precipitate (0.20 g. 53%) which formed was removed by filtration and crystallized from an acetone–water mixture, m.p. 229–230°.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.47; H, 5.37; N, 10.52.

Small Charged Rings. V. Expansion of the Aziridinium Ring by Reaction with Ketones[1-4]

NELSON J. LEONARD, JOSEPH V. PAUKSTELIS, AND LEONARD E. BRADY

Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois

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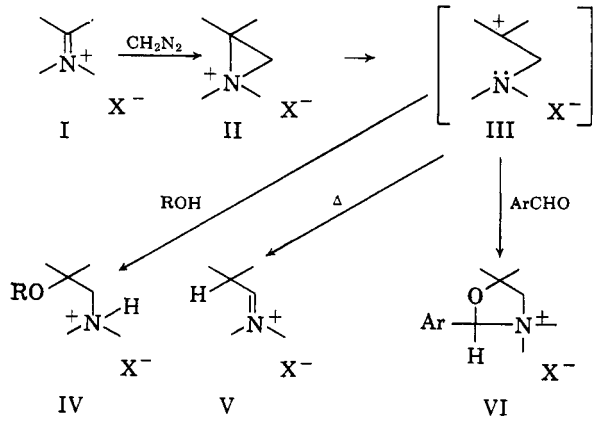
An aziridinium salt (VII) has been shown to react with cyclic, acyclic, and aryl ketones to give oxazolidinium salts (IX and XII–XVII). The structures of the products were established by analogy to the products of aziridinium salts and aromatic aldehydes[1,3,4] and by nuclear magnetic resonance spectroscopy including comparison with model compounds. The further generality of the cyclic addition with inclusion of the ketone carbonyl group was established by varying the aziridinium compound as well as the ketone (XVIII–XXII). The over-all result of the reaction may be represented as ③⁺ + 2 → ⑤⁺, descriptive of a broad type in which a charged, three-membered cycle is increased in size to a charged, five-membered cycle.

The facile synthesis of stable aziridinium salts (II, generalized formula, X = ClO_4 or BF_4)[5,6] from ternary iminium salts (I)[7] and diazomethane has fostered a continuing study of the chemistry of small charged rings, and some reactions involving the opening of the aziridinium ring accompanied by ring expansion have been previously described.[1,3,4,8] Solvolysis (→ IV)[5,6,8] and thermal rearrangement (→ V)[3,9] of substituted aziridinium perchlorates and fluoborates (II) appear to proceed with development of a carbonium ion, the more stable (III) of two possibilities resulting from aziridinium ring opening. The same intermediate would account for the ring expansion brought about by heating II in the presence of a weak nucleophile such as an aldehyde carbonyl (→ VI).[1] The analogous reaction of aziridinium salts with ketones has now been found to proceed smoothly to give oxazolidinium salts.[10]



The model aziridinium salt, 1,1,2,2-tetramethylaziridinium perchlorate (VII), prepared from N-isopropylidenedimethylaminium perchlorate[7] (or N, N-dimethylisopropylideneiminium perchlorate) and diazomethane, was used because of its simplicity, ready availability, and the ease with which its ketone reaction products could be identified by n.m.r. spectroscopy. The aziridinium salt VII was characterized by correct analysis for $C_6H_{14}ClNO_4$, solvolysis with alcohols,[8] infrared spectrum (absence of absorption maxima corresponding to C=N⁺ or N⁺—H), and n.m.r. spectrum. The n.m.r. spectrum in methylene chloride, with tetramethylsilane as the internal standard (τ 10.0),[11] exhibited signals, all singlets, at τ 8.28

(1) For the preceding article in this series, see N. J. Leonard, E. F. Kiefer, and L. E. Brady, *J. Org. Chem.*, **28**, 2850 (1963).

(2) This investigation was supported by a research grant (USPHS-RG 5829, currently GM-05829-06) from the National Institutes of Health, U. S. Public Health Service, to whom we are pleased to acknowledge our thanks.

(3) Presented in part at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, Abstracts, p. 30M, and at the XIXth International Congress of Pure and Applied Chemistry, London, England, July, 1963, Abstracts, A5-6, p. 207.

(4) N. J. Leonard, E. F. Kiefer, L. E. Brady, and J. V. Paukstelis, *Angew. Chem.*, **75**, 1031 (1963).

(5) N. J. Leonard and K. Jann, *J. Am. Chem. Soc.*, **84**, 4806 (1962).

(6) N. J. Leonard and K. Jann, *ibid.*, **82**, 6418 (1960).

(7) N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, **28**, 3021 (1963).

(8) N. J. Leonard, K. Jann, J. V. Paukstelis, and C. K. Steinhardt, *ibid.*, **28**, 1499 (1963).

(9) Abstracts, 17th National Organic Chemistry Symposium of the American Chemical Society, Bloomington, Ind., June, 1961, pp. 1–10.

(10) In point of fact, the first reaction of a ketone with an aziridinium salt was not guided by analogy[1] but was recognized independently by one of us (J. V. P.) in attempting to carry out quite another reaction of an aziridinium salt using acetone as the solvent.

(11) G. V. D. Tiers, "Tables of τ-Values for a Variety of Organic Compounds," Minnesota Mining and Manufacturing Co., St. Paul, Minn., 1958; G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).