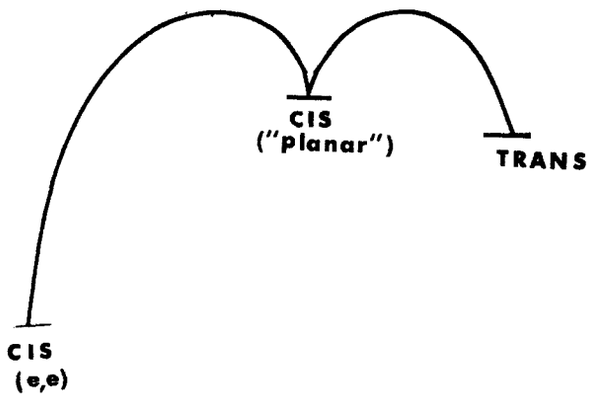

Figure 4.

cyclobutane; the former must require more energy. However, in the present case, the energetic barrier is indeed small, and will be easily overcome by the energy available for most chemical reactions. Planar conformers must therefore be taken into account in considering cyclobutane reactivity even when it is disubstituted.[22] Although this evaluation does not affect the question of conformational distinctions between isomers for certain low-energy reactions such as deamination,[23] it would predict that in other higher energy reactions such as solvolysis, which requires on the order of 20 kcal/mole of activation energy, planarization for both isomers may inhibit the appearance of behavioral disparities possible on the basis of nonplanarity for some cases.

These results allow interpretation of the cyclobutane ester equilibrium in terms of a *cis* (e,e $\rightleftharpoons$ "planar") $\rightleftharpoons$ *trans* (homo "planar") process (Figure 4) and render intelligible the compression of K_{equil} values for the 3-alkyl-substituted esters.[24] It is evident that K_{equil} measures not the thermodynamic difference between isomers differing in the extent of axial substitution, but rather a difference between conformers differing in dihedral angle. The equilibrium constant, reflecting an internal *cis* equilibrium, is thus influenced only slightly by the nature of the substituent.[24]

Experimental Section

Infrared measurements were made in a 5-cm sodium chloride gas cell using the Perkin-Elmer Model 21 double-beam recording spectrophotometer. Samples of liquid ester were inserted onto the cell floor, and the cell atmosphere was saturated with vapor by prolonged periods of moderate heating under evacuation, followed by adjustment to the desired temperature. Heating was accomplished by a transformer-controlled heating tape wound tightly around the outside of the gas cell; temperature was measured by a thermocouple held flush against the cell wall. Several measurements at each temperature were carried out after optimal equilibration was achieved.

Registry No.—Cyclobutane, 287-23-0; *cis*-methyl 3-isopropylcyclobutanecarboxylate, 14721-38-1; *trans*-methyl 3-isopropylcyclobutanecarboxylate, 14746-11-3.

Acknowledgment.—The author wishes to express his thanks to Dr. R. A. Doughty for the preparation of the esters employed in this work and to Dr. E. Brill for his assistance in obtaining the infrared spectra. The author is appreciative of the disclosure of pertinent data by Dr. G. Lampman prior to publication. This work was supported by Grant AFOSR-123-63 from the Directorate of Chemical Sciences, U. S. Air Force.

(22) Some modification of conformational conclusions reached for *cis*- and *trans*-3-isopropylcyclobutylamine on the basis of room temperature nmr measurements (I. Lillien and R. A. Doughty, *J. Am. Chem. Soc.*, **89**, 155 (1967)) may be called for by the present conclusions. It is evident that the preponderance of *cis* isomer will be diequatorial under these conditions. However, to the extent that axial carbomethoxy and amino groups resemble each other in this system, the *trans* isomer should probably be considered less puckered than had been thought likely.

(23) A quite large difference in product composition in this reaction for each isomer in ref 22 has been interpreted in terms of conformational control, with a *trans* isomer of smaller dihedral angle than the *cis* fitting quite well into the scheme presented: I. Lillien and R. A. Doughty, *Tetrahedron Letters*, 3953 (1967).

(24) The value of K_{equil} for the *cis*- and *trans*-3-*t*-butylcyclobutanecarboxylates is only slightly larger than that which we have reported[1] for the 3-isopropyl esters (Dr. G. Lampman, private communication). The unlikely alternative rationale that both groups, which differ greatly in steric effectivity, are equally able to maintain conformational homogeneity in the cyclobutane ring is untenable in the light of the present results.

Cyclization of Aniline–Acetylenedicarboxylate Adducts. An Improved Synthesis of 8-Nitro-2-carbomethoxy-4(1H)-quinolones[1]

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As a route to the synthesis of 4,8-diaminoquinolines as potential antimalarials, an attractive synthetic pathway appeared to involve 8-nitro-2-carbomethoxy-4(1H)-quinolones (IV). The traditional Conrad–Limpach–Knorr quinolone synthesis is generally unsuccessful however, for generation of the anilinocrotonates or acetoacetanilides of aromatic nitro amines,[2,3] presumably because of the reduced basicity of the amine function. In our hands, the condensation of diethyl oxaloacetate with *o*-nitroanilines has also been unsuccessful.

We have found that formation of the required anils or enamino esters (III) by the Michael condensation of *o*-nitroanilines (I) and dimethyl acetylenedicarboxylate (II) proceeds smoothly and in high yield (eq 1). Previous publications have demonstrated the generality of the reaction of (II) with *o*-aminonitriles,[4] phenones,[5] amides,[6] or esters[7] as a highly versatile heterocyclic synthesis.

Although difficulties have been reported in the saponification–decarboxylation of nitro-substituted quinoline-3-carboxylates,[8] we have encountered little difficulty with the 2-substituted carboxylates available by our method.

The cyclization of these adducts (III) to the 4(1H)-

(1) This work has supported in part by Contract No. DA-49-193-MD-3011 from the U. S. Army Medical Research and Development Command, and represents Contribution No. 255 from the Army Research Program on Malaria.

(2) S. Coffey, J. K. Thompson, and F. J. Wilson, *J. Chem. Soc.*, 856 (1936).

(3) F. Misani and M. T. Bogert, *J. Org. Chem.*, **10**, 347 (1945).

(4) N. D. Heindel, T. A. Brodof, and J. E. Kogelschatz, *J. Heterocyclic Chem.*, **3**, 222 (1966).

(5) E. C. Taylor and N. D. Heindel, *J. Org. Chem.*, **32**, 1666 (1967).

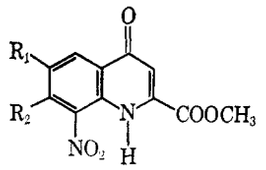
(6) N. D. Heindel and T. F. Lemke, *J. Heterocyclic Chem.*, **3**, 389 (1966).

(7) E. C. Taylor and N. D. Heindel, *J. Org. Chem.*, **32**, 3339 (1967).

(8) See R. H. Baker, G. R. Lappin, C. J. Albisetti, Jr., and B. Riegel, *J. Am. Chem. Soc.*, **68**, 1267 (1946), in which the use of the silver salts of nitroquinoline carboxylic acids is suggested.

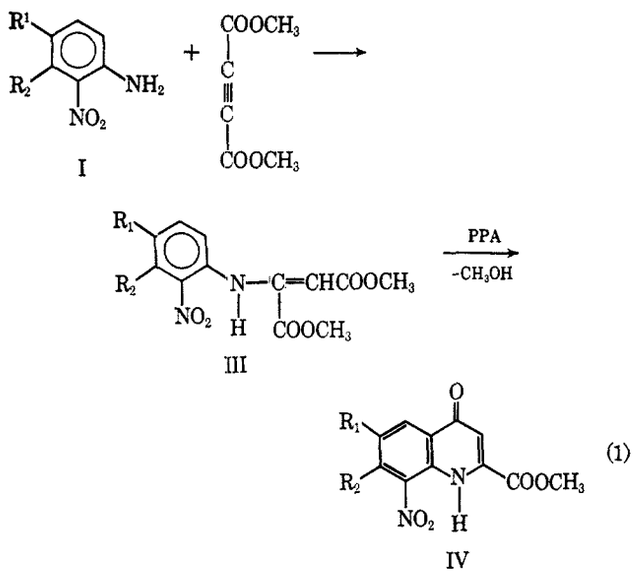
TABLE I

8-NITRO-2-CARBOMETHOXY-4(1H)-QUINOLONES



R_1	R_2	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
H	H	47	195	$C_{11}H_8N_2O_5$	53.22	3.25	11.29	53.47	3.23	11.47
OCH_3	H	25	193–195	$C_{12}H_{10}N_2O_6$	51.80	3.62	10.07	52.01	3.40	10.27
Cl	H	36	197–199	$C_{11}H_7ClN_2O_5$	46.80	2.48	9.93	46.86	2.46	10.10
CH_3	H	39	249–250	$C_{12}H_{10}N_2O_5$	54.96	3.81	10.68	54.75	4.10	10.79
CH_3	CH_3	44	168.5–169	$C_{13}H_{12}N_2O_5$	56.51	4.38	10.14	56.44	4.28	10.05

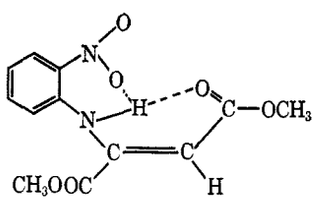
quinolones cannot be effected by refluxing in the usual Conrad–Limpach media of diphenyl ether or Nujol. Under a variety of conditions involving differing contact times and reaction temperatures, unreacted starting materials or viscous tars invariably resulted. The small amounts of product which could be obtained were difficult to free from entrained reaction solvent. On the other hand, the choice of polyphosphoric acid as a cyclization reagent gave quinolones (see Table I) which could be purified with greater facility by simply washing with water.



(1)

It is interesting to note that only when the nitro function is in the *ortho* position to the amino groups is the diphenyl ether or Nujol cyclization unsuccessful. Excellent yields of the corresponding nitroquinolones were obtained from the Michael adducts of *m*-nitro- and *p*-nitroaniline in boiling diphenyl ether.

A possible explanation for these results lies in the observation that the normal addition product of an aromatic amine and (II) is assumed to be hydrogen-bonded fumarate,[9] the proper geometry required for ring formation. In the *o*-nitroaniline adducts studied in this work there is evidence that the nitro group is involved in chelative hydrogen bonding. Strong literature precedent exists for NH···O bonding in *o*-nitroanilines.[10] The position of the N—H resonance in the nmr was remarkably constant (11.0 ± 0.1 ppm) for the five *o*-nitroaniline adducts studied.[11] This value reflects considerably more deshielded N—H proton than those in adducts without an *o*-nitro as a hydrogen-bonding acceptor. For example, the adducts of aniline, *m*-nitroaniline, and *p*-nitroaniline displayed N—H signals at 9.70, 9.74, and 9.84 ppm, respectively. These data, coupled with the results of Huisgen,[9] seem to point to a highly organized adduct which would require the disruption of considerable hydrogen bonding to attain a transition state for ring formation. It is possible



that the effect of the mildly acidic polyphosphoric acid is a necessary criterion for reorganizing the intramolecular forces which restrain the molecule in an unfavorable geometry for ring closure. The presence of a single vinyl proton resonance in the region from 5.73 to 5.90 ppm in the nmr spectra of the enamine adducts (III) can be taken as evidence for a single geometric isomer.[9,12,13]

The utilization of a propiolate ester in condensation with an *o*-nitroaniline would be expected to produce an enamino ester capable of cyclization to a 4(1H)-quinolone without the 2-carbomethoxy function.[14] We have found, however, that 4-methoxy-2-nitroaniline would not condense with methyl propiolate during 48 hr of reflux either neat or in methanol solution.

In accordance with the well-known facility of decarboxylation of 2-quinolinecarboxylic acids (compared to 3-quinolinecarboxylic acids), it is not surprising that the 8-nitro-substituted 2-quinolinecarboxylate can be saponified and decarboxylated without resorting to the silver salt method.[8] We have obtained 40–50% yields of the decarboxylated 4(1H)-quinolones by the traditional saponification–decarboxylation techniques.[15]

(9) R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966).

(10) See I. Yamaguchi and S. Brownstein, *J. Phys. Chem.*, **67**, 525 (1963) and references cited therein.

(11) All nmr spectra were run in dilute $CDCl_3$ solution against a TMS reference on a Varian A60. Dilution effects did not appear to shift the peak positions.

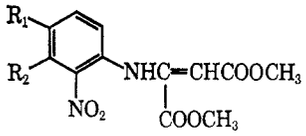
(12) J. E. Dolfini, *J. Org. Chem.*, **30**, 1298 (1965).

(13) A. N. Kurtz, W. E. Billups, R. B. Greenlee, H. F. Hamil, and W. T. Pace, *ibid.*, **30**, 3141 (1965).

(14) F. W. Gray, H. S. Mosher, F. C. Whitmore, and T. S. Oakwood, *J. Am. Chem. Soc.*, **73**, 3577 (1951).

(15) See Method 2 reported in B. Riegel, G. R. Lappin, B. H. Adelson, R. I. Jackson, C. J. Albisetti, Jr., R. M. Dodson, and R. H. Baker, *ibid.*, **68**, 1264 (1946).

TABLE II
DIMETHYL ANILINOFUMARATES



R_1	R_2	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
H	H	95	130–131	$C_{12}H_{12}NO_6$	51.43	4.32	10.00	51.60	4.35	9.79
OCH_3	H	87	138–139	$C_{13}H_{14}N_2O_7$	50.32	4.55	9.03	50.39	4.68	9.09
Cl	H	67	120.5–122	$C_{12}H_{11}ClN_2O_6$	45.80	3.53	8.90	45.65	3.66	8.89
CH_3	H	68	109–110	$C_{13}H_{14}N_2O_6$	53.06	4.79	9.52	53.06	4.93	9.48
CH_3	CH_3	72	126–127.5	$C_{14}H_{16}N_2O_6$	54.54	5.23	9.09	54.46	5.45	9.16

Experimental Section[16]

Condensation of the Aromatic Amines (I) with Dimethyl Acetylenedicarboxylate. Formation of the Michael Adducts (III).—An equimolar amount (0.02 mole) of the aniline and dimethyl acetylenedicarboxylate (II) was mixed in 100 ml of anhydrous methanol and refluxed for 24 to 48 hr. The reaction mixture was cooled in ice and the precipitated product removed by filtration. Successive crystal crops could be obtained by concentration *in vacuo* of the mother liquors. Yields and analytical results are reported in Table II. The adducts could be obtained in analytical purity by two recrystallizations from methanol.

Three adduct analogs which were not precursors of 8-nitroquinolones were prepared for comparison purposes. The adduct of aniline and (II) and its cyclization have already been described.[4,9] The adduct of *m*-nitroaniline was prepared by the above procedure in 69% yield with only 4 hr of reflux, mp 94–95°.

Anal. Calcd for $C_{12}H_{12}N_2O_6$: C, 51.43; H, 4.32; N, 10.00. Found: C, 51.52; H, 4.59; N, 9.89.

Similarly, *p*-nitroaniline was condensed with II in 78% yield after 48-hr reflux. The buff-yellow crystals, from methanol, melted at 124.5–125°.

Anal. Calcd for $C_{12}H_{12}N_2O_6$: C, 51.43; H, 4.32; N, 10.00. Found: C, 51.52; H, 4.29; N, 9.91.

Cyclization of the Michael Adducts (III) to 8-Nitro-4(1H)-Quinolones (IV).—A paste, formed from intimately mixing 2 to 4 g of the adduct (III) with 20 to 30 g of polyphosphoric acid, was heated with stirring at 140–180° for 30 min. Considerable foaming resulted, and the mixture turned progressively darker. After cooling to 100°, the viscous solution was poured into a mixture of chopped ice and water and scratched with a glass rod to induce crystallization. If allowed to stand at ice bath temperatures for 5–10 hr prior to filtration, the filterability of the product was improved. The solid, removed by vacuum filtration, was air dried and recrystallized from methanol. All of the quinolones could be obtained in analytical purity by sublimation at 0.5 mm at a temperature 20° under their melting points. Analytical data and yields are reported in Table I.

The cyclization of the adducts of (II) with *m*-nitroaniline and *p*-nitroaniline, respectively, could be carried out in diphenyl ether.

Methyl 7-nitro-4(1H)-quinolone-2-carboxylate was prepared in 74% yield by refluxing 0.30 g of dimethyl (*m*-nitroanilino)-fumarate in 4.0 g of diphenyl ether for 1 min. The crystals of the product began to precipitate in the hot reaction medium, and dilution with 50 ml of light petroleum ether (bp 30–60°) completed the precipitation. The crystals were filtered, washed well with hexane, and recrystallized from methanol (sparingly soluble). Vacuum sublimation gave analytical material, mp 268–269.5°.

Anal. Calcd for $C_{11}H_8N_2O_5$: C, 53.22; H, 3.25; N, 11.29. Found: C, 53.35; H, 3.44; N, 10.98.

The presence of the 5-nitro isomer was ruled out on the basis of the nmr spectrum.[17]

Methyl 6-nitro-4(1H)-quinolone-2-carboxylate was prepared in 85% yield from dimethyl (*p*-nitroanilino)fumarate by the method described for the 7-nitro isomer. The pale yellow solid was recrystallized from methanol–benzene (sparingly soluble) and melted at 295–297°.

Anal. Calcd for $C_{11}H_8N_2O_5$: C, 53.22; H, 3.25; N, 11.29. Found: C, 53.43; H, 3.30; N, 11.48.

Saponification–Decarboxylation of the 8-Nitroquinolones (IV).—To 300 cc of 18% by weight aqueous sodium hydroxide was added 35 g of methyl 8-nitro-4-(1H)-quinolone-2-carboxylate in small portions with vigorous stirring. The majority of the solid dissolved in 10 min, and the solution was filtered and then heated at 60° for 30 min. The carboxylic acid was precipitated by addition of cold 6 *N* HCl, filtered off, washed with 3 *N* HCl, and dried overnight in a vacuum oven. Twenty-four grams of this dried acid were pulverized to a fine powder and added with stirring to 300 ml of Nujol at 245°. After all the acid had been added, the oil was heated for 0.5 hour, cooled to room temperature, and diluted with 300 ml of petroleum ether. The black solids were removed by filtration and charged to a Soxhlet thimble. Extraction of the methanol soluble organic material and evaporation of the extracts produced 62% of the 8-nitro-4(1*H*)-quinolone, mp 200–202° (lit.[8] mp 199–200°).

By the procedure described above, methyl 6-methoxy-8-nitro-4(1*H*)-quinolone-2-carboxylate was saponified and decarboxylated to 6-methoxy-8-nitro-4(1H)-quinolone in 38% yield. The product was purified by recrystallization from methanol and sublimation *in vacuo*, mp 225–227°.

Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.54; H, 3.63; N, 12.72. Found: C, 54.54; H, 3.66; N, 12.70.

(16) Combustion analyses were performed in these laboratories by one of us (V. B. F.) or obtained from Robertson Microanalytical Laboratories, Florham Park, N. J.

(17) In trifluoroacetic acid solvent the unsplit methyl appeared at 3.82 ppm, the singlet proton on C-3 at 7.67 ppm, the singlet C-8 proton at 8.75 ppm, and an A-B quartet was centered at 8.27 ppm for the mutually coupled (J = 9 cps) C-5 and C-6 protons. The Gould–Jacobs cyclization of *m*-nitroaniline leads to the 7-nitroquinoline: C. C. Price, H. R. Snyder, O. H. Bullitt, Jr., and P. Kovacic, *J. Am. Chem. Soc.*, **69**, 374 (1947).

The Hydroboration and Subsequent Oxidation of Several Enamines[1]

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We wish to report that hydroboration of the morpholine or pyrrolidine enamine of cyclohexanone or the pyrrolidine enamine of 2-methylcyclohexanone, followed by basic hydrogen peroxide treatment, leads to the corresponding *trans*-β-aminocyclohexanols in good yield.[3]

(1) This investigation was supported in part by the U. S. Public Health Service Research Grant AI 06303 (to I. J. B.) from the National Institute of Allergy and Infectious Diseases. The initial phase was done at Columbia University in Professor Gilbert Stork's laboratory and was supported by the National Science Foundation and the National Institute of Health.

(2) To whom correspondence should be addressed at the Belfer Graduate School of Science, Yeshiva University.

(3) Preliminary results quoted by J. Szmuszkovicz, "Advances in Organic Chemistry, Methods and Results," Vol. 4, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 1.