Department of Chemistry, Marshall University

Cyclization of Amine-acetylene Diester Adducts: A Modification of the Conrad-Limpach Method (1)

Ned D. Heindel, Terry A. Brodof and Jane E. Kogelschatz (2)

A projected synthesis aimed at preparing substituted members of the julolidine series required the availability of 8-cyano-4(1*H*)-quinolones as starting materials.

While such quinolones would presumably be capable of synthesis by thermal cyclization of the oxaloacetic ester adducts of the appropriate aromatic amines, (3) an improved route employing the enamine adducts of dimethyl acetylenedicarboxylate and anthranilonitriles was developed. Hendrickson has recently demonstrated that the Michael addition of amines to acetylene esters shows possibilities as a new general heterocyclic technique (4).

The enamines resulting from the reaction of anthranilonitriles and acetylenedicarboxylate were obtained in 54 to 85% yields by refluxing equimolar quantities of the reactants in methanol for 24 hours. Since enamines bearing a hydrogen *beta* to the anilino group are interesting synthetic intermediates in their own right (5), the crystalline adducts were isolated and characterized, see Table I.

The anthranilonitriles employed in this study were prepared by the Bedford-Partridge pyrolysis of isatin oximes (6). Only the 5-nitroanthranilonitrile was inert to Michael condensation with dimethyl acetylenedicarboxylate. 2,4-Dinitroaniline was also observed to be resistant and addition of basic catalysts, sodium methylate and triethylamine, was ineffective. The lack of reactivity can be attributed to the severely diminished basicity of the aromatic amine by the electron withdrawing groups on the ring.

A crystalline adduct was also obtained from *o*-anisidine, but the enamines of aniline and 2,4-dimethylaniline were viscous oils. The diethyl anilinomaleate has been previously prepared from the ethyl oxaloacetate method and its cyclization described (7).

In the case of the non-crystalline adducts of aniline and 2,4-dimethylaniline, the oil isolated by evaporation of the methanol solvent was directly utilized for cyclization.

All enamine adducts displayed a sharp -NH at approximately 3200 cm^{-1} and three carbonyl maxima at 1732 $\pm$ 10, 1680 $\pm$ 10 and 1620 $\pm$ 10 cm^{-1}. In the case of the anthranilonitrile adducts a -CN absorption at 2225 cm^{-1} was also apparent.

The cyclized quinolones possessed NH bands at 3335 to 3360 cm^{-1}, vinylogous amide carbonyls at 1630 to 1645 cm^{-1}, ester carbonyl absorption at 1725 to 1735 cm^{-1} and nitrile bands at 2230 to 2240 cm^{-1}. The NMR spectrum of the parent 8-cyano-2-carbomethoxy-4(1*H*)-quinolone, in trifluoroacetic acid with external tetramethylsilane, showed the methyl ester singlet at 4.32 ppm, and the ring protons at positions 3, 5, 6, and 7 as a complex multiplet at 8.1 to 9.3 ppm.

Cyclization of the adducts in refluxing diphenyl ether was carried out in 37 to 80% yield, see Table II. The low yield of the 8-methoxy-2-carbomethoxy-4(1*H*)-quinolone was a reflection of its higher solubility in the cyclization solvent and its resistance to petroleum ether precipitation.

EXPERIMENTAL

Combustion analyses were performed by the Crobaugh Microanalytical Laboratories, Charleston, West Virginia and by Dr. George Robertson, Florham Park, New Jersey. Proton NMR spectra were obtained on a Varian A-60 spectrometer and are reported against tetramethylsilane as an external standard. Infrared spectra were scanned as nujol mulls on a Perkin-Elmer 237 spectrometer and peak positions are reported as calibrated against the polystyrene standard.

Preparation of Anthranilonitriles.

Anthranilonitrile, 5-chloroanthranilonitrile, 5-methylanthranilonitrile, and 5-nitroanthranilonitrile were prepared as described by Bedford-Partridge (6). Application of the procedure to the pyrolysis of 5-bromoisatin oxime gave a 43% yield of 5-bromoanthranilonitrile, m.p. 92-94°, reported m.p. 96-97° (8).

The pyrolysis of 5-methoxyisatin oxime gave a 51% yield of 5-methoxyanthranilonitrile, m.p. 37-38°, reported m.p. 40° (9).

General Procedure for Preparation of Adducts (I): Dimethyl Anilinomaleates.

An equimolar (0.02 mole) solution of the aromatic amine and dimethyl acetylenedicarboxylate in 35 ml. of methanol was refluxed for 24 hours, concentrated in vacuum and the residual oil allowed to crystallize. The anilinomaleates were recrystallized from methanol to analytical purity. Results are summarized in Table I. The adducts of aniline and 2,4-dimethylaniline were non-crystallizable oils and were used directly in the cyclization procedure.

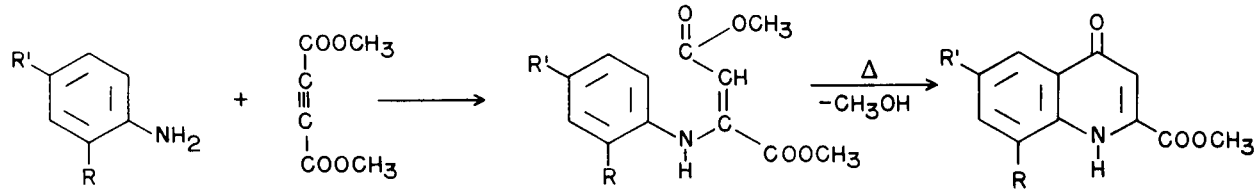
General Procedure for Preparation of 2-Carbomethoxy-4(1*H*)-Quinolones (II).

An intimate mixture of the purified adduct and ten to fifteen times its own weight of diphenyl ether was refluxed with a Bunsen flame in a small flask equipped with a condensor. The solution progressively darkened and the quinolone product began to sublime into the cooler area of the reaction vessel.

After cooling to room temperature, the product was precipitated with a five to ten fold excess of petroleum ether (30-60°). The crude product was washed thoroughly on the filter with petroleum ether, recrystallized from methanol, and sublimed in vacuum at 25° under its melting point at 0.5 mm. Hg. The results are reported in Table II.

TABLE I

Dimethyl Anilinomaleates (I)

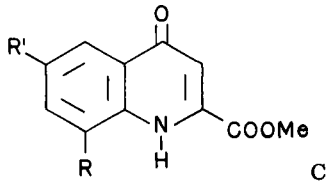


I II

R	R'	M.P. °C	Formula	% Yield	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CN	H	105-106	$C_{13}H_{12}N_2O_4$	75	59.99	4.65	10.77	60.19	4.82	10.63
CN	Cl	148.5-150	$C_{13}H_{11}ClN_2O_4$	68	52.98	3.77	9.51	53.21	3.85	9.51
CN	Br	150.5-151.5	$C_{13}H_{11}BrN_2O_4$	54	46.04	3.27	8.26	46.16	3.17	8.49
CN	CH_3	118.5-120	$C_{14}H_{14}N_2O_4$	81	61.31	5.15	10.21	61.10	5.19	9.96
CN	CH_3O	132.5-133	$C_{14}H_{14}N_2O_5$	85	57.92	4.86	9.65	57.50	4.81	9.66
OCH_3	H	72-73	$C_{13}H_{14}NO_5$	52	59.08	5.34	5.30	58.85	5.63	5.27

TABLE II

2-Carbomethoxy-4(1*H*)-quinolones (II)



R	R'	M.P. °C	Formula	% Yield	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
-CN	-H	197	$C_{12}H_8N_2O_3$	80	63.16	3.53	12.28	62.97	3.54	11.90
-CN	-Cl	254-254.5	$C_{12}H_7ClN_2O_3$	70	54.87	2.69	10.67	55.36	2.69	10.69
-CN	-Br	281	$C_{12}H_7BrN_2O_3$	53	46.93	2.28	9.12	47.34	2.52	9.45
-CN	$-CH_3$	262-263	$C_{13}H_{10}N_2O_3$	57	64.46	4.16	11.57	64.30	4.33	11.36
-CN	$-OCH_3$	228	$C_{13}H_{10}N_2O_4$	84	60.46	3.90	10.85	60.47	3.95	10.71
$-CH_3$	$-CH_3$	121-123	$C_{13}H_{13}NO_3$	63	67.52	5.67	6.06	67.32	5.49	6.44
-H	-H	223-224.5(a)	$C_{11}H_9NO_3$	66						
$-OCH_3$	-H	162-163	$C_{12}H_{11}NO_4$	37	61.80	4.75	6.01	61.43	4.81	6.09

(a) Previously prepared in indirect fashion by E. Spath, *Monatsh. Chem.*, 42, 89 (1921), reported m.p. 224°.

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(2) Undergraduate Research Participation Student.

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