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A New Synthesis of Quinoline Derivatives†

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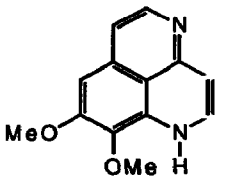
Abstract: Unsymmetrical azodicarbonyl compounds incorporating an appropriately located aryl group undergo smooth ring closure to form N-substituted dihydroquinolones or *spiro* N-substituted 2-pyrrolidone derivatives.

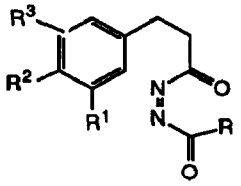
Azodicarbonyl compounds[1] are among the strongest electrophiles known. Ethyl azodicarboxylate has been shown to react with activated aromatics and other electron-rich substrates with or without acid catalysis to afford derivatives of hydrazine.[2] Recently the more reactive *bis* (2,2,2 - trichloroethyl) azodicarboxylate[3] was employed, in conjuntion with $LiClO_4$, to prepare substituted anilines. Our interest in the synthesis of aaptamine[4] (**1**), a fused pyridoquinoline alkaloid, led us to examine the chemistry of *unsymmetrical* azodicarbonyl compounds of the type **2** as possible precursors for quinolone derivatives.

The hydrazides **3**, readily obtained by hydrazinolysis of the corresponding ethyl dihydrocinnamates, on acylation with methyl chloroformate afforded the requisite starting materials, the N,N'- diacyl hydrazines **4** in excellent overall yields (> 80%). After the oxidation of **4a** with iodobenzeneditrifluoroacetate[5] (IBTA) in CH_2Cl_2 was complete (t.l.c. control), addition of BF_3 - Et_2O (1 eq) to the mixture resulted in the formation of the quinolone derivative **5a** (43%; m.p 192°-195°C). The use of silver carbonate on celite support[6] with benzene as the solvent [7] and BF_3-Et_2O as the catalyst improved the yield of the same product (61%), which on vigorous acid hydrolysis (conc. HCl, reflux) afforded the known 1-amino-3,4-dihydrocarbostyril (**6**) (97%; m.p. 139-140°C; lit [8] m.p. 143°C). Phenyl or benzyl urethanes, instead of methyl carbamates, can be profitably used without detriment to the yield in the cyclisation step. For example, the N-substituted phenyl urethane **4e** was smoothly converted into the carbostyril derivative **5e** (67%) from which the synthetically useful N-amino compound **6f** can be liberated (96%) by mild hydrolysis (10% KOH, r.t.). Deamination of **6f** either with N,N-diphenyl-N-nitroso amine[9] (benzene, reflux) or sodium nitrite in HOAc (r.t.) provided an easy access to 6,8-dimethoxy-3,4-dihydro-2-oxoquinoline (75%), identical with an authentic sample.[10] The results obtained with various other N,N'- diacyl hydrazines are collected in the Table. It shows that reactions proceed with synthetically acceptable yields in all the cases studied. It is noteworthy (entries # 2, 5, 6, 7 and 8) that in general the spirodienones **7** are the major or the exclusive products whenever the aromatic ring bears a methoxy group *para* to the alkyl side chain. These substances, themselves of potential synthetic interest, can

be converted into the quinolone derivatives. Thus the γ-lactam **7**, (entry # 5) on acid treatment[11] (0.5 M H_2SO_4-HOAc) followed by methylation (CH_2N_2) of the resulting phenol afforded the quinolone **5d** in 85% yield. The formation of the same quinolone **5b** (m.p; m.m.p.) from two regioisomeric diacyl hydrazines (entries # 1 and 2), with identical spectroscopic (^{1}H NMR, IR) and chromatographic properties proved the involvement of the spirodienone[12] **8** as the intermediate. Preferential C-C migration[13] followed by proton loss generates the quinolone **5b**.



1



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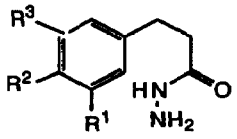

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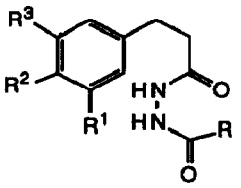

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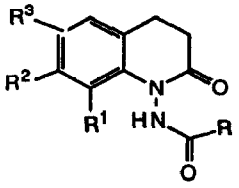

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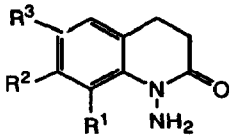

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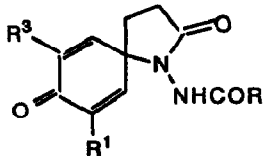

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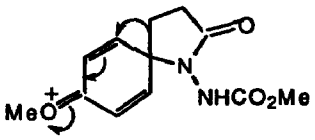

8

a: R^1= R^2=R^3=H; R=OMe
b: R^1= R^2=H; R^3=R=OMe
c: R^1=R^3=R=OMe; R^2=H
d: R^1=H; R^2=R^3=R=OMe
e: R^1=R^3=OMe; R^2=H;R=OPh
f: R^1=R^3=OMe

In conclusion it is shown that appropriately substituted diacylhydrazines are useful starting materials for the preparation of 1-carbalkoxyaminocarbostyrils and thence, via 1-amino carbostyrils, to 2-quinolones. Application of the method to the synthesis of aaptamine and other heterocylic compounds will be reported elsewhere.

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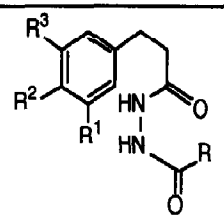
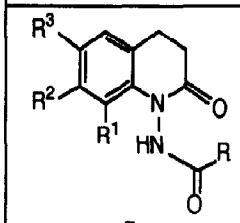
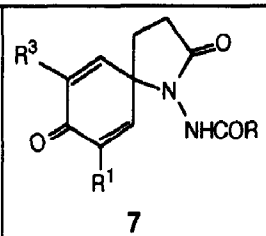
Table

#	Starting material				Oxidant[a]	Products				Yield (%)		M.p. °C[b]	
	 4					 5				 7		5	7	5	7
	R^1	R^2	R^3	R		R^1	R^2	R^3	R	R^1	R^3	R				
1	H	H	OMe	OMe	A	H	H	OMe	OMe	–			71	–	165-167 (S1)	–
2	H	OMe	H	OMe	B C	H	H	– OMe	OMe	H	H "	OMe	– 17	25 50	– 166-167 (S3)	oil "
3	OMe	H	OMe	OMe	A C	OMe	H	OMe "	OMe	–	– –		40 73	– –	178-180 (S2) "	–
4	OMe	H	OMe	OPh	A	OMe	H	OMe	OPh	–			64	–	160-165 (S1)	–
5	H	OMe	OMe	OMe	A C	H	OMe	OMe "	OMe	H	OMe "	OMe	12 54	50 14	165-166 (S3)	185-189 (S2)
6	OMe	OMe	OMe	OMe	A D	OMe	OMe	– OMe	OMe	OMe	OMe –	OMe	– 30	12 47	– 140-141 (S2)	226-228 (S3) –
7	OMe	OMe	OMe	OCH_2Ph	A	–				OMe	OMe	OCH_2Ph	–	76	–	220-235 (S1) (dec.)
8	OMe	OMe	OMe	OPh	A	–				OMe	OMe	OPh	–	75	–	235-238 (S1)

a) A: Iodobenzeneditrifluoroacetate; B: Iodobenzeneditrifluoroacetate-BF_3. Et_2O (1.0 eq); C: Ag_2CO_3-BF_3. Et_2O (0.2 eq); D: Ag_2CO_3-BF_3. Et_2O (1 eq);
b) Solvents - S1: CH_2Cl_2-*n*-hexane; S2: EtOAc; S3: EtOAc-*n*-hexane.

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