The Synthesis of 2-Carbomethoxy-2-carbomethoxymethyl-2,3-dihydro-4(1*H*)quinazolinones

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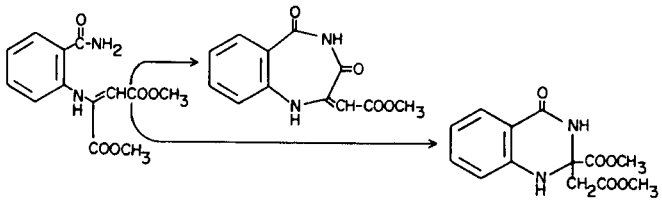
The treatment of anthranilhydrazides with dimethyl acetylenedicarboxylate resulted in enamines that cyclized to the six-membered quinazolinones instead of the seven-membered benzodiazepines.

J. Heterocyclic Chem., 14, 703 (1977).

Sir:

In earlier publications from these laboratories we have shown that the enamine prepared from anthranilamide and dimethyl acetylenedicarboxylate could experience cyclization to either seven-membered products (benzodiazepines) or to six-membered products (quinazolinones) depending on reaction conditions (1,2). Furthermore, it has been our observation (2), as well as that of many others (3), that initially formed benzodiazepines often rearranged to the more stable quinazolinones.

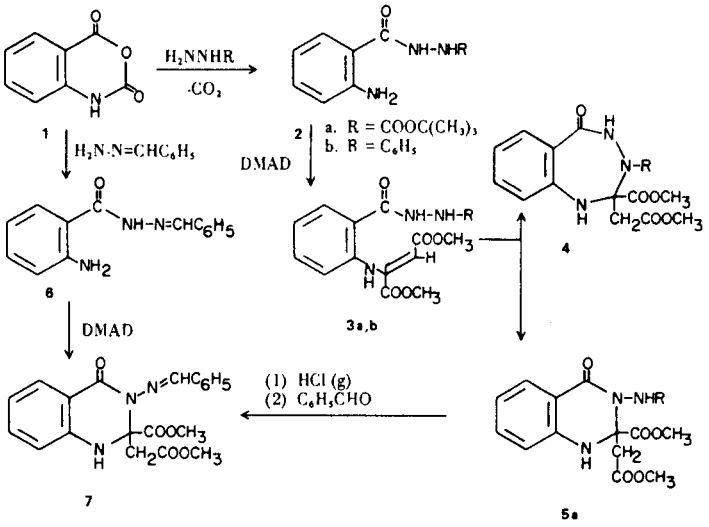


In the benzotriazepine system we have recently reported a similar unambiguous synthesis of the seven-membered compounds (4) which could be transformed by rearrangement into quinazolinone isomers (5). Earlier reports on the cyclization of *o*-aminobenzoate-hydrazine derivatives which had been claimed to produce benzotriazepines (6-8) have been corrected to show that the true products were the quinazolinones (9,10). Obviously, any reaction which can in principle, yield either a seven-membered or a six-membered product must present a structure assignment based on rigorous proof.

We wish to report preliminary results on the cyclization of the enamines, **3a-b**, prepared from anthranilhydrazides, **2a-b**, and dimethyl acetylenedicarboxylate (DMAD). The benzotriazepines, **4**, or the quinazolinones, **5**, would be equally possible products and, in light of our earlier results (1,2) are equally plausible. The quinazolinones were, in fact, the products obtained.

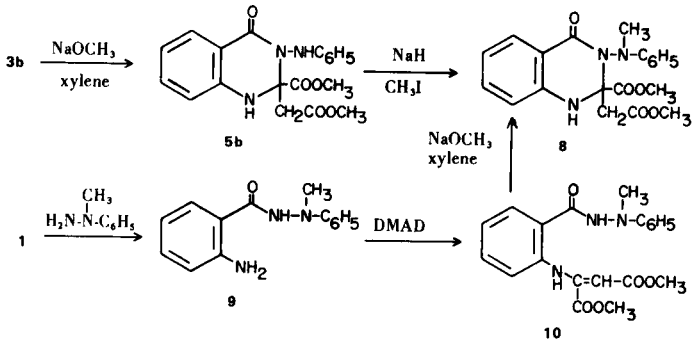
Ring-opening of isatoic anhydride **1** with either *t*-butyl carbazate (11) or phenylhydrazine (12), gave the corresponding hydrazides, **2a-b**, in 95% and 75% yields, respectively. These condensed with DMAD to the enamino-adducts, **3a-b** (54% and 76%) which were characterized as discrete geometric isomers (presumably fumarates) (2) by single vinyl proton resonances at 5.52 and 5.42 ppm δ for **3a** and **3b** (3), respectively. Adduct **3a** proved so labile that it cyclized to quinazolinone, **5a**, in 88% yield on brief warming in methanol (attempted recrystallization) while adduct **3b** converted to **5b** (92% crude yield) only under more vigorous conditions of refluxing xylene containing sodium methoxide; conditions which had previously been exploited to yield benzodiazepines from the DMAD adduct of anthranilamide (2). Proof that cyclization had indeed occurred was obtained from the absence of vinylic resonances in the pmr and from the independent syntheses (see Scheme I) (14). These syntheses established the products as quinazolinones and not benzotriazepines.

Scheme I



The hydrolysis-decarboxylation of **5a** yielded a 3-amino-quinazolinone which was trapped *in situ* with benzaldehyde to produce **7**. This same anilic product, **7**, was independently prepared from the benzylidene-anthranilhydrazide (**6**) and DMAD (34%) (see Scheme I). Affirmation that the cyclization product of **3b** was indeed **5b**, was provided by methylation and alternative synthesis of the methylated product (see Scheme II).

Scheme II



The methyl iodide/sodium hydride methylation of the assumed quinazolinone **5b** gave an *N*-methylated product, **8**, which was identical with material obtained from the cyclization of DMAD adduct of the anthranilhydrazide, **9**. This enamino-adduct, **10**, possesses only a single possible cyclization mode (see Scheme II).

The apparent advantage of this synthesis is that it utilizes readily available starting materials. The opening of a variety isatoic anhydrides with substituted semicarbazides, benzhydrazides, and hydrazines followed by treatment with DMAD and then cyclization to quinazolinones appears considerable. Work is currently in progress to show the overall scope of the route.

Acknowledgement.

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(13) Combustion and satisfactory (± 0.30 C, H, N) for **3b**, **5a-b**, **7**, **8**, and **10**. Robertson's Laboratory, 73 West End Ave., Florham Park, N.J. 07932.

(14) Pmr for **5a** (1:1 deuteriochloroform:DMSO-d_6): δ 1.43 (s, 9, CH_3), 3.22 (s, 2, CH_2), 3.60 (s, 6, OCH_3), 6.40-7.83 (m, 5, ArH and NH), and 8.36 (s, 1, NH), pmr for **5b** (DMSO-d_6): δ 3.12 (s, 2, CH_2), 3.44 (s, 3, OCH_3), 3.68 (s, 3, OCH_3), 7.35 (s, 1, NH), 7.63 (s, 1, NH), and 6.5-7.8 (m, 9, ArH), pmr for **7** (deuteriochloroform): δ 3.27 (m, 2, CH_2), 3.72 (s, 6, OCH_3), 6.32 (s, 1, NH), 6.58-8.10 (m, 9, ArH) and 9.14 (s, 1, N=CH).