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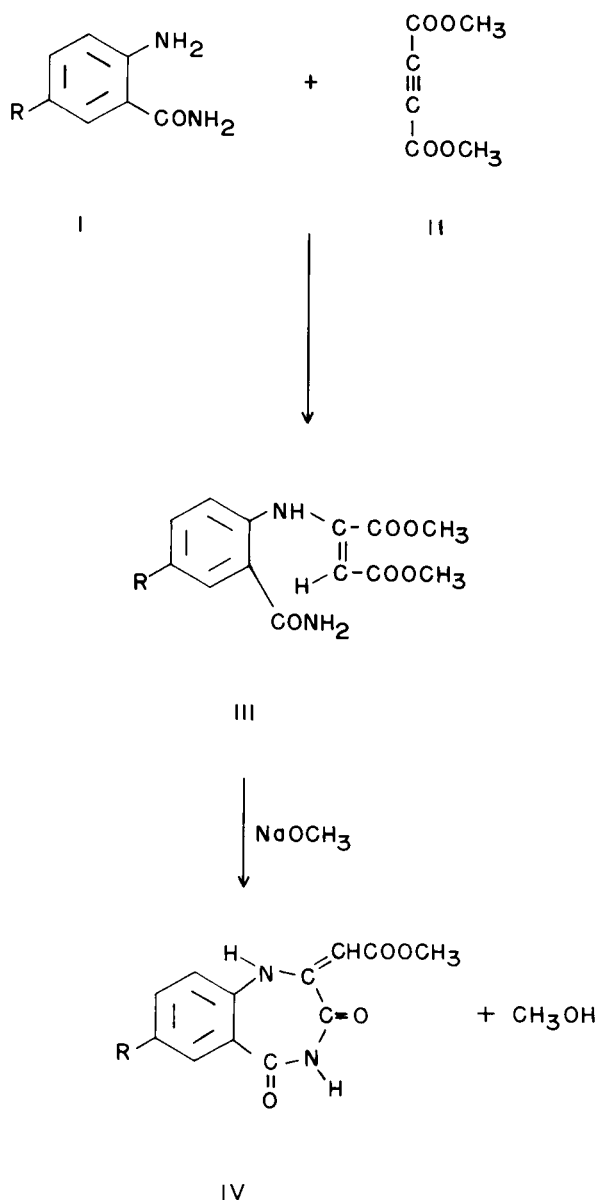
A Direct Synthesis of 1,4-Benzodiazepine-3,5-diones (I)

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Sir:

The discovery of psychophysiological activity in many members of the 1,4-benzodiazepine series has led to extensive synthetic efforts in this area (3). Most of the compounds are available only by laborious multi-step syntheses (4, 5).

We wish to report a simple direct synthesis of the title compounds which shows promise of considerable modification and utility in the preparation of potential tranquilizers and anti-anxiety agents.



When equimolar quantities of 2-amino-5-R-benzamides (I) and dimethyl acetylenedicarboxylate (II) were dissolved in methanol (0.01 mole per 100 ml.) and refluxed for 20 minutes, high yields of the corresponding Michael adducts could be prepared. Dimethyl 2-(*o*-carboxamidoanilino)butenedioate (III, R=H) was isolated in 91% yield as a pale yellow solid, m.p., 147-148°. *Anal.* Calcd. for C₁₃H₁₄N₂O₅: C, 56.11; H, 5.07. Found: C, 55.92; H, 5.07. Similarly the chloro analog, (III, R=Cl) was obtained in 84% yield, m.p. from methanol 154-155°. *Anal.* Calcd. for C₁₃H₁₃ClN₂O₅: C, 49.93; H, 4.19. Found: C, 49.92; H, 4.20.

Aromatic amines and dimethyl acetylenedicarboxylate (II) under identical conditions gave high yields of the Michael adducts (6), but benzamide was completely inert. Thus amine, not amide, addition to the acetylene function was clearly established (7).

If, instead of evaporation of solvent and product isolation after the initial reflux period, 0.10 grams of sodium methoxide were added and the solution refluxed for an additional two hours, the 1,4-benzodiazepine-3,5-diones could be isolated.

2-Carbomethoxymethylene-1,4-benzodiazepine-3,5-(1*H*,4*H*)dione (IV, R=H) was obtained in analytical purity by recrystallization from methanol and sublimation *in vacuo*, m.p. 234-235.5°, 23% yield. *Anal.* Calcd. for C₁₂H₁₀N₂O₄: C, 58.53; H, 4.09; N, 11.38. Found: C, 58.81; H, 4.16; N, 11.19. The chloro compound (IV, R=Cl) was isolated and purified similarly, m.p. 291-292°, 33% yield. *Anal.* Calcd. for C₁₂H₉ClN₂O₄: C, 51.35; H, 3.23; N, 9.98. Found: C, 51.24; H, 3.38; N, 10.26.

The observation that Michael adducts of amines to II are of predominant *cis* stereochemistry (8) when studied with molecular models of the adducts, demonstrates that cyclization to the seven-membered heterocycle is the only possible course. The proton nmr is consistent with this conclusion. For (IV, R=Cl) in D₆ dimethyl sulfoxide the ester methyl group appeared as a singlet at 3.81 ppm, the vinyl proton as a singlet at 5.78 ppm and the aromatic protons as a complex multiplet at 7.3 to 7.8 ppm.

Two broad down-field resonances at 10.45 and 10.65 ppm were assigned to the two N-H groupings in IV.

The unsubstituted product (*i.e.*, IV, R=H) displayed general central nervous system depressant activity in the Irwin mouse profile screen (9) and was relatively nontoxic (LD₅₀ 1778 mg./kg.).

Considerable modification of the products and the general synthetic method reported above are possible. Iwanami (10) has shown that similar tautomeric carbomethoxymethylene groups in quinoxalones could be saponified-decarboxylated to methyl groups. The utilization of *o*-aminobenzylamines and *o*-aminobenzylmercaptans should lead to benzodiazepinones and benzothiazepinones. Synthetic efforts in these areas are under investigation in our laboratory.

REFERENCES

- (1) Supported in part by a Sigma Xi Grant-in-Aid to N.D.H. and taken in part from the M.S. thesis of T.F.L., Marshall University, 1966.
- (2) Current address, Department of Chemistry, Lehigh University, Bethlehem, Pennsylvania.

- (3) An excellent review is provided by L. H. Sternbach, L. O. Randall, and S. R. Gustafson, in "Psychopharmacological Agents," M. Gordon, Ed., Academic Press, New York, N. Y., 1964, p. 137-224.

- (4) A. Stempel, E. Reeder, and L. H. Sternbach, *J. Org. Chem.*, **30**, 4267 (1965).

- (5) M. Uskokovic, J. Iacobelli, and W. Wenner, *ibid.*, **27**, 3606 (1962).

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

- (7) Amide additions to acetylene esters have been reported but only under drastic conditions. See A. W. Johnson, "The Chemistry of the Acetylene Compounds," Vol. II, Longmans, Green and Co., New York, N. Y., 1950, p. 133.

- (8) E. Winterfeldt and H. Preuss, *Chem. Ber.*, **99**, 450 (1966).

- (9) Testing data provided by Dr. Thomas Fitzpatrick, Assistant Director, Union Carbide Technical Center, South Charleston, W. Va.

- (10) Y. Iwanami, *Nippon Kagaku Zasshi*, **83**, 161 (1962); *Chem. Abstr.*, **59**, 3920 (1963).

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