THE JOURNAL OF Organic Chemistry®

VOLUME 33, NUMBER 11

NOVEMBER 11, 1968

Cyclization of Anthranilamide–Acetylenedicarboxylate Adducts. A Facile Synthesis of 1,4-Benzodiazepine-3,5-diones[1]

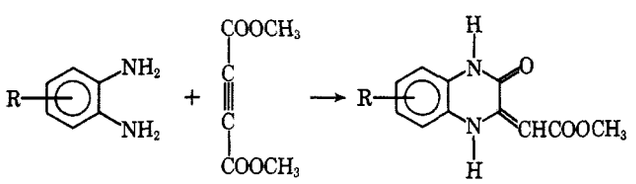
NED D. HEINDEL, VELMER B. FISH, AND THOMAS F. LEMKE

Chandler Laboratory of Chemistry, Lehigh University, Bethlehem, Pennsylvania 18015

Received February 13, 1968

Anthranilamides have been found to react with dimethyl acetylenedicarboxylate to produce fumarate Michael adducts which ring close to 2-carbomethoxymethylene-2H-1,4-benzodiazepine-3,5(1H,4H)-diones. These benzodiazepines undergo alkoxide-catalyzed rearrangement to yield mixtures of maleimides and quinazolinones. The maleimides obtained from the benzodiazepines can also be prepared by the ammonolysis of (2-carbomethoxyanilino)fumarates in a mechanistic pathway shown to involve geometric isomerism of the enamine double bond.

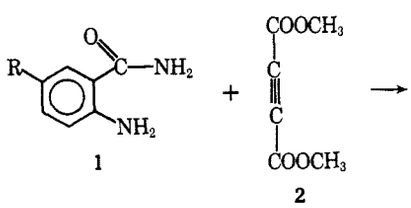
Numerous examples have appeared in the recent literature demonstrating the synthetic utility of amine–acetylenedicarboxylate adducts as convenient precursors for a variety of five-[2-4] and six-membered[4-8] heterocyclics. The facile reaction of *o*-phenylenediamines with acetylenedicarboxylate as a quinoxalone synthesis[8] has prompted us to explore the reaction of



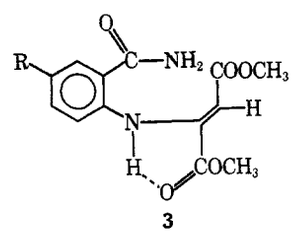
2

anthranilamides (**1**) with **2** as a potential route to benzodiazepinediones.

The reaction of anthranilamides (**1**) with dimethyl acetylenedicarboxylate (**2**) occurs spontaneously in methanol to give 71–84% yields of adducts (**3**). It is apparent that these adducts represent amine to acetylene addition, since aniline reacts under similar conditions,[9] but benzamide requires elevated temperatures and strong base catalysis.[10] Further, these



1 2



3

R = H, Cl, Br, CH_3

anthranilamide adducts (**3**) give a negative test for a free amine function and display ir spectra which lack the characteristic primary amine stretching absorptions. Primary aromatic amine adducts of **2** have been reported to exhibit exclusive fumarate geometry. The nmr criterion established by the previous workers[9,11,12] for isomeric homogeneity, namely a single vinyl proton resonance, was satisfied by all our crystalline adduct intermediates. The enamines (**3**) all possessed a single =C—H absorption in the range δ 5.42–5.67 ppm. Additional support for the transoid geometry was provided by the appearance of chelated ester bands at 1670 ± 10 cm^{-1} characteristic of analogous fumarate systems.[13,14]

Cyclization of Anthranilamide–Acetylenedicarboxylate Adducts.—When the adducts **3** were treated with

(1) Presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968. For previous papers in this series, see N. D. Heindel, I. S. Bechara, T. F. Lemke, and V. B. Fish, *J. Org. Chem.*, **32**, 4155 (1967), and references cited therein.

(2) D. S. James and P. E. Fanta, *ibid.*, **27**, 3346 (1962).

(3) G. M. Brooke and R. J. D. Rutherford, *J. Chem. Soc., C*, 1189 (1967).

(4) J. B. Hendrickson, R. Rees, and J. F. Templeton, *J. Amer. Chem. Soc.*, **86**, 107 (1964).

(5) J. W. Lown and T. C. N. Ma, *Can. J. Chem.*, **45**, 939 (1967).

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

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

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

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

(10) A. W. Johnson, "The Chemistry of the Acetylene Compounds," Vol. II, Longmans, Green and Co., New York, N. Y., 1950, p 133.

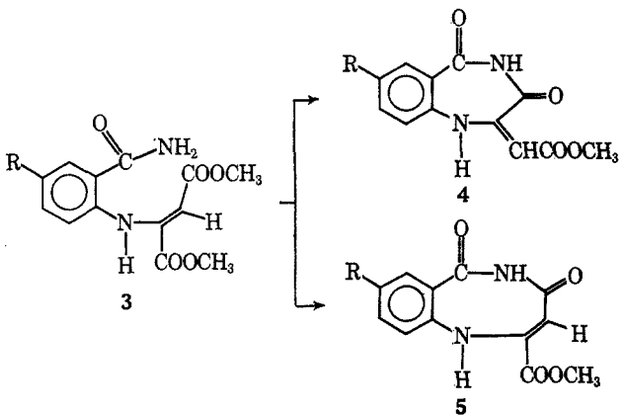
(11) J. E. Dolfini, *J. Org. Chem.*, **30**, 1298 (1965).

(12) E. Winterfeldt, *Angew. Chem. Intern. Ed. Engl.*, **6**, 423 (1967).

(13) Y. Iwanami, *Nippon Kagaku Zasshi*, **83**, 593 (1962); *Chem. Abstr.*, **59**, 5153 (1963).

(14) Y. Iwanami, S. Isoyama, and Y. Kenjo, *Bull. Chem. Soc. Jap.*, **37**, 1745 (1964); *Chem. Abstr.*, **62**, 7755 (1965).

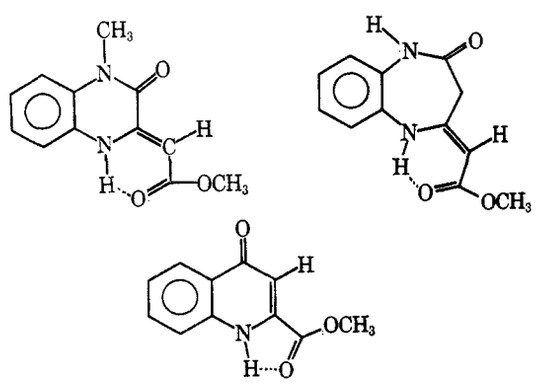
sodium methoxide in xylene at reflux for 1 hr, they yielded products whose elemental analyses indicated the loss of a single molecule of methanol. Molecular models indicate that two possible modes of cyclization exist for the adducts **3**; namely, the amide nitrogen can displace upon either of the two nonequivalent methyl esters of the fumarate portion. Displacement upon the α carbomethoxy would generate a carbomethoxymethylenebenzodiazepine (**4**), while attack upon the β ester would yield a carbomethoxybenzodiazocine (**5**).



Discrimination between alternatives **4** and **5** could not be effected by instrumental means alone, although support for structure **4** could be derived from comparison of nmr and ir data with those of model systems. Mass spectral examination was of little assistance, for the predominant high mass fragements could be rationalized with either isomeric possibility: parent at 246 amu; P − 32, loss of CH_3OH; and P − 59, loss of $\cdot CO_2CH_3$.

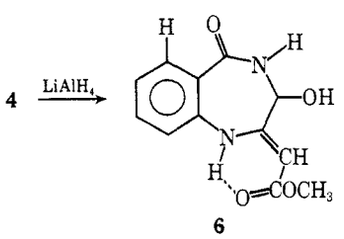
The nmr (DMSO-d_6) spectrum of the product (from **3** with R = H) could have been consistent with either isomer: singlet at δ 3.80 ppm, three protons; singlet at 5.88, one proton; aromatic multiplet at 7.0–8.2, four protons; and two broad NH singlets at 11.16 and 11.78 each integrating for a single proton.

A close analogy to the proposed benzodiazepine structure **4** is provided by the N-methylquinoxalone[15] shown below in which the vinyl resonance occurred at δ 5.82 ppm and the methyl resonance at 3.77. The ester carbonyl stretching frequencies of this model compound and those of our unknown material were likewise identical (1690 cm^{-1}) and in excellent agreement with the carbonyl assignment (1686 cm^{-1}) in a similar 2-carbomethoxymethylene-1,5-benzodiazepinone.[16] These C=O stretching frequencies are lower than the normal α,β-unsaturated esters and indicative of intramolecular chelation.[17]



Appropriate models which can be used to predict the ester C=O absorption in alternative structure **5** must reflect molecular situations in which the NH of a vinylogous amide and the carbonyl of an ester could be involved in a five-membered bonded cycle. It is of interest in this regard that 2-carbomethoxy-4(1H)-quinolones, see above, display carbonyl absorptions at 1730 ± 5 cm^{-1} which are only slightly shifted from normal ester bands.[18] In general terms it has been noted that intramolecular hydrogen bonding is most significant when a six-membered cycle is generated.[19]

The strongest support for the assignment of structure **4** to the ring-closed product is based on the results of its reduction with $LiAlH_4$. The employment of the technique of inverse addition (hydride slurry in THF added to compound in THF) yielded a product whose combustion and spectral analyses revealed it to be a hydrobenzodiazepinone (**6**). The ir spectrum displayed strong hydroxy absorption at 3395 cm^{-1}, which had been absent in the starting material. In addition, its nmr spectrum, obtained in DMSO-d_6 in order to detect splitting through the O—H bond,[20] could be rationalized only as being due to a partially reduced benzodiazepinedione.



The OH appeared as a doublet (J = 4 Hz) at δ 6.78 ppm coupled to a carbinyl proton at 5.10. This carbinyl proton was similarly coupled to an NH proton (J' = 6 Hz) at 9.00 ppm and therefore appeared as a double doublet (J = 4 Hz and J' = 6 Hz). When the spectrum was run in C_5D_5N, a solvent which accelerates hydroxyl proton exchange, the OH resonance collapsed to a singlet and the carbinyl resonance to a doublet. Upon addition of D_2O, the NH and OH signals disappeared and the carbinyl proton remained as a singlet.

The additional resonances appeared as expected in the nmr spectrum, including the vinyl singlet at δ 4.98 ppm, which had shifted to higher field as a consequence of the reduction of its flanking and deshielding carbonyl, the ester methyl at 3.85 ppm, and the chelated NH at 10.33 ppm. Further support for the fact that reduction occurred at the carbonyl in position 3 of the parent benzodiazepine and not at position 5 is obtained by examination of the signal of the aromatic proton at C-6, *i.e.*, *peri* to the carbonyl attached to the ring. This proton appears downfield at 7.83 ppm as a quartet

(15) D. D. Chapman, *J. Chem. Soc., C*, 806 (1966).

(16) E. Müller, R. Haller, and K. W. Merz, *Ann.*, **697**, 197 (1966).

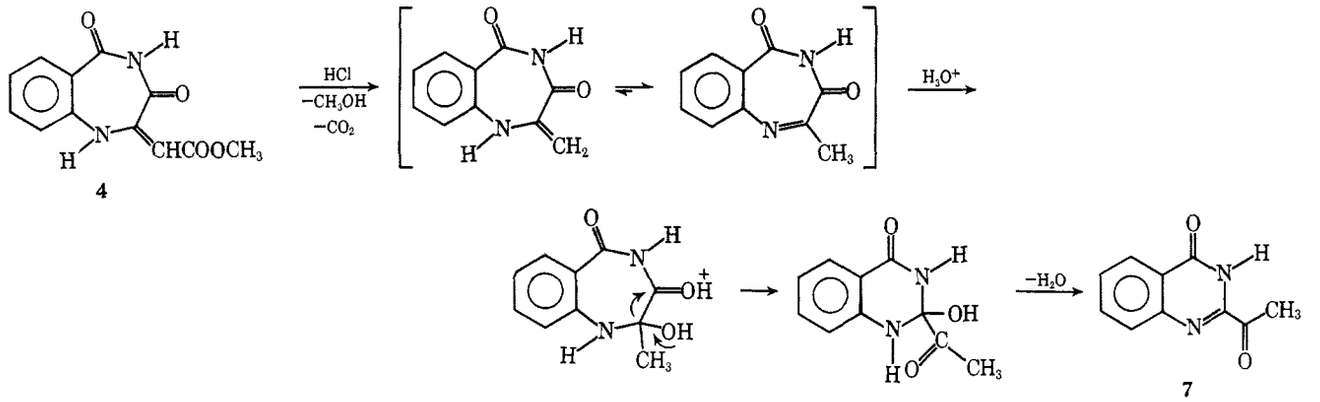
(17) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1964, pp 184, 185.

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

(19) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt-Dryden Publishers, New York, N. Y., 1959, p 30.

(20) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964).

SCHEME I



(J_o = 8 Hz, J_m = 2 Hz) coupled to its *ortho* and *meta* neighbors. Budzikiewicz and coworkers have commented in detail on this "peri-doublet" effect.[21]

The partial $LiAlH_4$ reduction of an amide carbonyl to a stable *gem*-amino alcohol is unusual but not without precedent in the literature. Hydride reduction of certain 2-oxoquinoxalines and 3-oxomorpholines has been reported to yield the carbinol amines[22] and similar precedent exists for the preparation of stable 3-hydroxy-1,4-benzodiazepines.

Ring-Contraction Reactions of the Benzodiazepines (4).—When treated with 6 *N* hydrochloric acid, the benzodiazepine (**4**, R = H) underwent a decarbomethoxylation ring contraction leading to 2-acetyl-4(3H)-quinazolinone (**7**). The acid-catalyzed contraction of diazepines has been observed on numerous occasions in a wide variety of compounds.[23] In our case, the ring contraction adds additional weight to the structure assignment of the diazepine **4** since a more plausible mechanism can be evoked for transformation of **4** into **7** than can be written for a **5** to **7** contraction. See Scheme I.

The characterization of **7** rests on nmr and ir spectral data (*vide infra*) and on the fact that a 2,4-dinitrophenylhydrazone derivative and a positive iodoform test could be obtained. Further, the uv spectrum of **7** was virtually superimposable on that of authentic 2-carboxy-4(3H)-quinazolinone[24] and also on a variety of other 4-quinazolinones reported in the literature.[25]

When treated with sodium methoxide in methanol, the 2-carbomethoxymethylene-1,4-benzodiazepine-3,5-diones (**4**) were transformed into mixtures of two heterocyclic materials by an interesting base-catalyzed rearrangement. The two products, 2-carbomethoxymethyl-2-carbomethoxy-2,3-dihydro-4(1H)-quinazolinone (**11**) and 2-carbomethoxyanilinomaleimide (**9**) can be rationalized as arising from methoxide ion attack at the two carbonyls of the imide linkage. Imides are in general known to undergo similar nucleophilic ring opening.[26] See Scheme II.

In a previous publication from our laboratories it was incorrectly reported that condensation of anthranilamides (**1**) and dimethyl acetylenedicarboxylate (**2**) in sodium methoxide–methanol gave rise to the benzodiazepinediones (**4**). The products described in that report as the seven-membered heterocycles were in reality the isomeric maleimides (**9**), the least soluble components of their respective product mixtures. The quinazolinones (**11**), the other components produced in the reaction, can be isolated in a pure state only with difficulty because of their higher solubility and tendency to crystallize with entrained traces of maleimide and starting material.

The authentic benzodiazepinediones (**4**), which can be prepared from the amide adducts (**3**) only in alcohol-free media, are very labile in the presence of alcoholic alkoxide. They are converted into the rearranged products **9** and **11** in the same ratio in which these materials are obtained from the direct combination of the acetylene diester and the anthranilamide in methanol–sodium methoxide. A plausible mechanistic possibility, therefore, is that transient formation of the benzodiazepine intervenes even in the presence of alcohol. In particular it is likely that the maleimide **9** is formed through the intermediacy of **4** because benzamide does not undergo significant methanolysis to methyl benzoate under the reaction conditions.

Geometric Isomerization of the Vinyl Linkage. Maleimide Formation.—Since it is probable that the amide adduct **3** has the fumarate arrangement for its diester side chain and since, presumably, the benzodiazepine (**4**) has a transoid geometry[27] (*i.e.*, $COOCH_3$ to C-3 carbonyl), it is apparent that formation of the maleimide has required an isomerization of the C=C double bond. Unfortunately, the proposed methyl anthranilate adduct of the half-amide–half-ester of acetylenedicarboxylic acid (**8**) could not be isolated from the reaction medium for stereochemical correlation. It is known, however, that the barrier to rotation about the enamine double bond is considerably lower[28] than that of a normal olefinic linkage; hence, such *trans–cis* isomerization is plausible. Further, we have

(21) S. C. Pakrashi, J. Bhattacharyya, L. F. Johnson, and H. Budzikiewicz, *Tetrahedron*, **19**, 1011 (1963).

(22) N. C. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, New York, N. Y., 1956, pp 600–626.

(23) See, for example, R. K. Bly, E. C. Zoll, and J. A. Moore, *J. Org. Chem.*, **29**, 2129 (1964), J. A. Moore and W. J. Theuer, *ibid.*, **30**, 1887 (1965), and L. H. Sternbach, E. Reeder, A. Stempel, and A. I. Rachlin, *ibid.*, **29**, 332 (1964), all of whom reported on the 1,4-benzodiazepine to quinazoline contraction. J. A. Barltrop, C. G. Richards, and D. M. Russell, *J. Chem. Soc.*, 1423 (1959), have studied the contraction of 1,5-benzodiazepines to quinoxalines. R. L. Williams, J. Schuller, and D. Lloyd, *J. Heterocycl. Chem.*, **5**, 147 (1968), have reported a similar conversion of 1,5-benzodiazepines into benzoimidazoles.

(24) M. T. Bogert and R. A. Gortner, *J. Amer. Chem. Soc.*, **32**, 119 (1910).

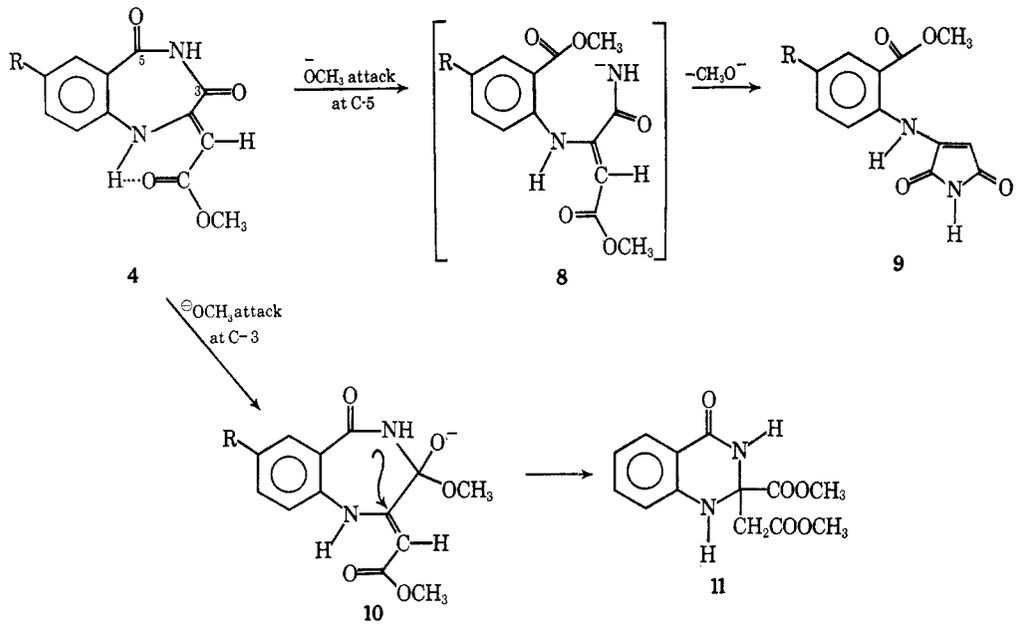
(25) See spectra 1041–1047 in L. Lang, "Absorption Spectra in the Ultraviolet and Visible Region," Vol. VI, Academic Press, New York, N. Y., 1965.

(26) C. D. Hurd, *J. Chem. Educ.*, **44**, 454 (1967).

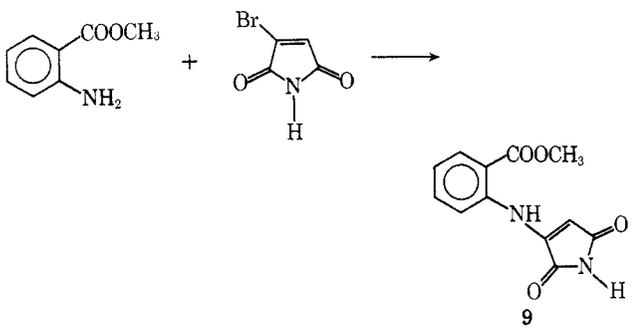
(27) This hypothesis is in accord with the chelated ester carbonyl observed in the ir spectra of **4** and is in agreement with similar observations by others; see ref 13 and 14.

(28) Y. Shvo, E. C. Taylor, and J. Bartulin, *Tetrahedron Lett.*, 3259 (1967).

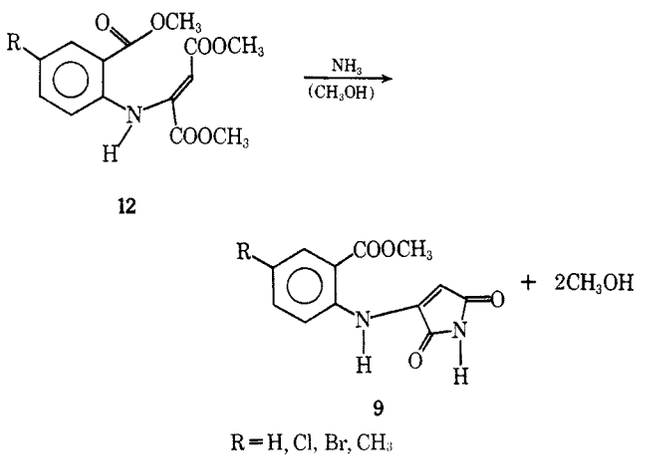
SCHEME II



demonstrated that dimethyl anilinofumarate[9] and dimethyl (2-carbomethoxyanilino)fumarate,[7] when treated with anhydrous ammonia in cold methanol, generate anilinomaleimide[29] and 2-carbomethoxyanilinomaleimide (**9**), respectively. The latter compound, **9**, was prepared in an independent synthesis by allowing methyl anthranilate to react with 3-bromomaleimide, thereby confirming its structure. The fumarate–



maleate isomerization induced by methoxide attack on **4** or by ammonolysis of the anilinofumarate clearly demonstrates the geometric lability of the enamine double bond.[30] We have ammoniated several methyl anthranilate adducts of acetylenedicarboxylate (**12**) and in all cases have obtained the maleimide products identical with those obtained by methoxide ring opening of **4**. The maleimide structure was recognized by the characteristic high-frequency imide carbonyls, 1765 and 1710 ± 15 cm^{-1}. The possibility that these materials might, in fact, be other imides (*i.e.*, benzodiazepines or benzodiazocines) linking either of the side-chain carbonyls with the carbonyl of the carboxylate on the *ortho* ring position was effectively eliminated when the ethyl ester of **9** (R = H) was ob-



tained from the treatment of the adduct of ethyl anthranilate–dimethyl acetylenedicarboxylate with ammonia.

The cyclization of the anthranilamide adduct **3** or its anionic analog (**10**) has excellent precedent in the observed ring closure of the dimethyl acetylenedicarboxylate adduct of thiosalicylamide to a 2-carbomethoxymethyl-2-carbomethoxy-1,3-benzothiazin-4-one.[31] As observed in the ring closure of the thiosalicylamide adduct, these anthranilamide adducts require trace alkoxide catalysis, presumably to enhance the nucleophilicity of the amide.

Alkylation of the benzodiazepine in the presence of excess methyl iodide occurred at the number 4 nitrogen. The site of alkylation was conveniently established when, during an attempted recrystallization of the alkylated benzodiazepine (**13**) from methanol, it was observed to take up the elements of CH_3OH. This product **14**, obtained when **13** was refluxed with methanol, was identical with the adduct formed from **2** and *o*-amino-N-methylbenzamide (**16**). See Scheme III.

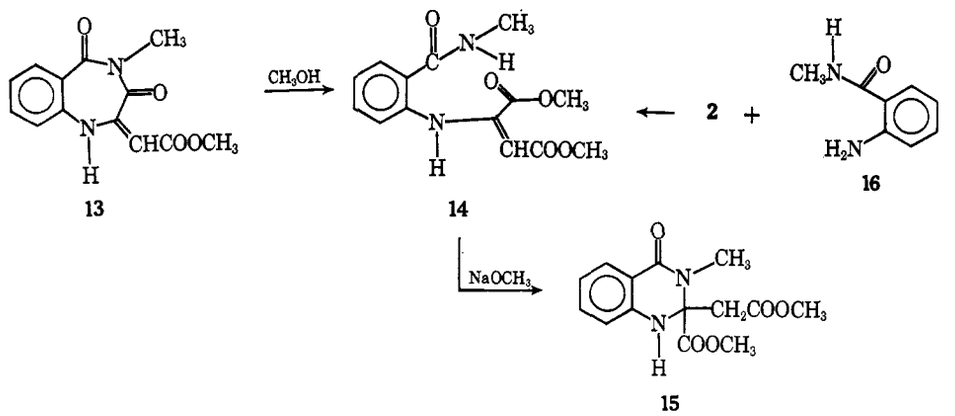
When the N-methyl amide adduct (**14**) was treated with methoxide–methanol, it gave rise to 3-methyl-

(29) S. J. Davis and C. S. Rondestvedt, Jr., *Chem. Ind.* (London), 845 (1956).

(30) J. de Wolf and L. van de Straete have shown that both dimethyl fumarate and dimethyl maleate undergo ammonolysis to their respective diamides, but the latter ester undergoes considerable isomerization to fumaramide. See *Bull. Sci. Acad. Roy. Belge*, **21**, 216 (1935).

(31) N. D. Heindel, V. B. Fish, M. F. Ryan, and A. R. Lepley, *J. Org. Chem.*, **32**, 2678 (1967).

SCHEME III



2-carbomethoxymethyl-2-carbomethoxydihydroquinazolin-4-one (**15**) but no trace of maleimide product. This result indicates that there are conceivably two pathways for transformation of amide adducts to quinazolinones: one which involves cyclization to a benzodiazepinedione which then suffers nucleophilic ring opening at both imide carbonyls to give maleimides plus quinazolinones, and the other which involves direct nucleophilic attack of the amide nitrogen upon the enamine double bond. Since **14** does not generate the corresponding diazepine **13**, even on reaction in the methoxide–xylene system, but instead yields only **15**, the presence of the N methyl apparently contributes a steric retardation to amide displacement upon the α carbomethoxy.

Structure Proof of the Quinazolinone Products.—The major products obtained upon methoxide–methanol ring opening of the benzodiazepinediones and upon direct reaction of the anthranilamide adducts in methoxide–methanol have been described herein as quinazolinone diesters (*viz.*, **11** and **15**).

The available spectral data are entirely in accord with this assignment. The ir spectra, for example, of these quinazolinone esters invariably displayed two slightly different, nonconjugated, carbonyl absorptions in the range 1715–1740 cm^{-1}. The nmr spectrum (for **11**, R = H and R = Cl) showed the two methyl singlets at δ 3.73–3.68 ppm and the unsplit methylene at 3.17–3.41 in excellent accord with the published spectrum of a similar benzothiazinone diester.[31]

Saponification of **11** (R = H) in 0.3 *M* sodium carbonate produced an unstable dicarboxylic acid which evolved CO_2 and acetic acid on attempted drying of an analytical sample. When the diacid was melted or sublimed, it was converted quantitatively into quinazolinone itself. A thermal gravimetric analysis of the diacid[32] revealed a nonconcomitant evolution of the CO_2 and acetic acid. The mass equivalents of the thermal gravimetric plateaus corresponded to the removal of a 60-amu fragment (HOAc) at 145–155° and a 44-amu species (CO_2) at 158–180°.

The mass spectra of the quinazolinone diesters displayed two competing fragmentation courses involving side-chain cleavages of methyl formate and methyl acetate moieties in excellent parallel with the thermal cleavages from the diacid. The full mass spectral data for **11** are reported in the Experimental Section, but it is of interest to note that the parent ion, *m/e* 278, undergoes fragmentation by loss of methyl acetate to a 204-amu species which loses $-COOCH_3$ to produce a quinazolinone ion, 145 amu. In a parallel pathway the parent ion evolves methyl formate to a 218-amu daughter, which in several successive cleavages fragments the methyl acetate side chain.

Encouraged by the variety of intriguing reaction pathways displayed by anthranilamide, methyl anthranilate, thiosalicylamide, and methyl thiosalicylate with acetylenedicarboxylate, we are extending these studies to salicylic acid analogs.

Experimental Section[33]

Preparation of Anthranilamides (1).—The ammonolysis procedure of Staiger and Wagner[34] for ring opening of the isatoic anhydrides was employed to obtain the anthranilamides from the 5-chloro-,[35] 5-bromo-,[36] 5-methyl-,[37] and the unsubstituted anhydrides.[35] Isatoic anhydride was treated with methyl amine by the procedure of Weddige[38] to give *o*-amino-N-methylbenzamide.

Dimethyl (2-Carboxamidoanilino)fumarate (3, R = H).—Reaction of equimolar quantities of anthranilamide and dimethyl acetylenedicarboxylate in methanol (0.1 mol/100 ml of solvent) produced a 91% yield of the crude adduct after 1 hr of reflux. Recrystallization from methanol provided yellow crystals of pure **3** (R = H): mp 153–153.5°; ir (Nujol mull) 3480 and 3370 ($CONH_2$), 3265 (chelated NH), 1718 (ester C=O), 1675 (chelated C=O), and 1658 cm^{-1} (amide C=O); nmr (DMSO-d_6) δ 11.0 (s, 1, NH), 6.8–8.0 (m, 4), 5.42 (s, 1, C=CH), 3.55 (s, 3, CO_2CH_3), and 3.68 ppm (s, 3, CO_2CH_3).

Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07. Found: C, 56.12; H, 5.11.

Dimethyl (4-Chloro-2-carboxamidoanilino)fumarate (3, R = Cl).—The reaction of 5-chloroanthranilamide with **2** as before yielded 84% crude adduct which was recrystallized twice from methanol to afford the pure adduct **3** (R = Cl): mp 156–158°; ir (Nujol mull) 3455, 3395, 3365, and 3260 (NH), 1738, 1697, 1680, and 1662 cm^{-1} (C=O); nmr ($DCCl_3$) δ 10.93 (s,

(32) We are grateful to Professor Harold C. Beachell of the University of Delaware for performing this analysis on a Du Pont Model 950 thermal gravimetric analyzer under nitrogen atmosphere.

(33) All ir spectra reported in this work were obtained on a Perkin-Elmer 257 spectrophotometer as Nujol-mulled materials. Nmr spectra are reported in parts per million (δ units) and were carried out on a Varian A-60 calibrated against internal TMS. Combustion analyses were performed by one of us (V. B. F) in these laboratories or were obtained from Dr. George I. Robertson, Microanalytical Laboratories, Florham Park, N. J. Mass spectral analyses were carried out on a Hitachi-Perkin-Elmer RMU-6E instrument equipped with a direct solids inlet system. We gratefully acknowledge the assistance of National Science Foundation Departmental Major Equipment Grants which enabled us to obtain the nmr and mass spectrometer facilities.

(34) R. P. Staiger and E. C. Wagner, *J. Org. Chem.*, **18**, 1427 (1953).

(35) These compounds were graciously provided by the Maumee Chemical Co., Toledo, Ohio.

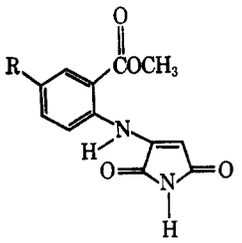
(36) R. Adams and H. R. Snyder, *J. Amer. Chem. Soc.*, **60**, 1411 (1938).

(37) W. Panaotovic, *J. Prakt. Chem.*, [2] **33**, 58 (1886).

(38) H. Weddige, *ibid.*, [2] **36**, 150 (1887).

TABLE I

(2-CARBOMETHOXYANILINO)MALEIMIDES



9

R	Method[a]	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
H	A	48	234–235.5	$C_{12}H_{10}N_2O_4$	58.53	4.08	11.38	58.81	4.16	11.17
	B	23								
Br	A	33	297	$C_{12}H_9BrN_2O_4$	44.33	2.79	8.62	44.25	2.81	8.75
	B	33								
Cl	A	21	291–292	$C_{12}H_9ClN_2O_4$	51.35	3.23	9.98	51.24	3.38	10.26
	B	33								
CH_3	A	57	264–265	$C_{13}H_{12}N_2O_4$	60.00	4.65	10.76	59.87	4.55	10.86
	B	39								
I	A	61	281–283	$C_{12}H_9IN_2O_4$	38.73	2.44	7.53	39.04	2.84	7.53

[a] Method A refers to the synthesis by ammonolysis of the adducts of 2 and methyl anthranilates. Method B refers to the products obtained by methoxide–methanol treatment of anthranilamide adducts of 2.

1, NH), 7.7–6.5 (m, 3), 6.52 (very broad, undefined, 2, NH_2), 5.63 (s, 1, C=CH), and 3.77 ppm (s, 6, OCH_3).

Anal. Calcd for $C_{13}H_{13}ClN_2O_5$: C, 49.92; H, 4.19; N, 8.96. Found: C, 49.92; H, 4.20; N, 8.73.

Dimethyl (4-Methyl-2-carboxamidoanilino)fumarate (3, R = CH_3).—By the method described above, an 84% yield of the adduct was obtained from 2 and 5-methylanthranilamide, mp 134–135°.

Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.52; H, 5.51; N, 9.59. Found: C, 57.64; H, 5.67; N, 9.43.

Dimethyl (4-Bromo-2-carboxamidoanilino)fumarate (3, R = Br).—A 71% yield, mp 162.5–164°, was obtained from 2 and 5-bromoanthranilamide.

Anal. Calcd for $C_{13}H_{13}BrN_2O_5$: C, 43.71; H, 3.67; N, 7.84. Found: C, 43.90; H, 3.78; N, 7.87.

Dimethyl (2-N-Methylcarboxamidoanilino)fumarate (14).—To a solution of 18.5 g (0.123 mol) of 2-amino-N-methylbenzamide in 250 ml of methanol was added 17.55 g (0.123 mol) of dimethyl acetylenedicarboxylate. The reaction mixture was heated on a steam bath for 0.5 hr, concentrated to 125 ml, and cooled to 0°. The precipitated material was collected by filtration. The crude product (mp 164–168°, 26.3 g, 73%) was recrystallized twice from methanol to produce yellow crystals of pure 14: mp 166–168°; ir (Nujol mull) 3340 (NH), 3165 (chelated NH), 1725 (ester C=O), and 1690 cm^{-1} (chelated C=O); nmr ($DCCl_3$) δ 10.20 (s, 1, NH), 6.7–7.7 (m, 4), 6.55 (broad undefined, s, 1, CH_3N—H), 5.57 (s, 1, C=CH), 3.83 (s, 3, CO_2CH_3), 3.80 (s, 3, CO_2CH_3), and 3.02 ppm (d, 3, J = 5 Hz, $HNCH_3$).

Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.52; H, 5.51; N, 9.58. Found: C, 57.81; H, 5.58; N, 9.88.

Dimethyl (2-Carbomethoxy-4-R-anilino)fumarates (12).—These compounds (R = H, Br, CH_3, Cl, and I) were prepared as we have described previously.[7] The 2-carbethoxy isomer, prepared by the reaction of ethyl anthranilate and 2, was a liquid: bp 195–197° (22 mm) and 162–164° (0.075 mm) [lit. bp 224° (0.1 mm)];[39] ir (thin film) 3250 (chelated NH), 1733 (methyl ester C=O), and 1686 cm^{-1} (ethyl ester C=O); nmr ($CDCl_3$) δ 11.42 (s, 1, NH), 8.2–6.6 (m, 4), 5.63 (s, 1, C=CH), 4.45 (q, 2, J = 7 Hz, OCH_2CH_3), 3.71 (s, 3, OCH_3), and 1.40 ppm (5, t, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.62; H, 5.58; N, 4.56. Found: C, 58.56; H, 5.47; N, 4.84.

(39) During the preparation of this manuscript, S. K. Khetan, J. G. Hiriyakkanavar, and M. W. George, *Tetrahedron*, **24**, 1567 (1968), reported physical data for the same compound which were not entirely in accord with what we observed. A reexamination of the reaction yielded data consistent with our original results but not entirely in agreement with the recorded boiling point and ir and nmr data.

Cyclizations of 3 in Methoxide–Xylene System. Preparation of 2-Carbomethoxymethylene-2H-1,4-benzodiazepine-3,5-(1H,4H)-dione (4, R = H).—A 2.0-g (0.072 mol) sample of dimethyl (2-carboxamidoanilino)fumarate (3) was dissolved in boiling xylene (dried over Dri-Na) and treated with a catalytic amount (less than 0.1 g) of sodium methoxide. The evolved methanol was allowed to escape from the refluxing solution. The reaction mixture was stirred and refluxed for 2 hr and then cooled to room temperature. The yellow crystals (1.35 g, 76%, mp 218–230°) that precipitated were collected by filtration and washed with hexane. A sample of these crystals was sublimed (170°, 0.1 mm) to provide the pure benzodiazepine 4 (R = H): mp 230–232°; ir (Nujol mull) 3185 (NH) and 1657 cm^{-1} (chelated ester C=O); nmr (DMSO-d_6) δ 11.78 (s, 1, NH), 11.16 (s, 1, NH), 7.0–8.2 (m, 4), 5.88 (s, 1, C=CH), and 3.80 ppm (s, 3, CO_2CH_3); mass spectrum (80 eV), m/e 246 (P).

Anal. Calcd for $C_{12}H_{10}N_2O_4$: C, 58.50; H, 4.09; N, 11.43. Found: C, 58.76; H, 4.06; N, 11.39.

Preparation of 7-Chloro-2-carbomethoxymethylene-2H-1,4-benzodiazepine-3,5-(1H,4H)-dione (4, R = Cl).—Reaction of 10.0 g (32.0 mmol) of the chloro adduct (3, R = Cl) with methoxide in xylene as above yielded 6.10 g (63%) of the crude product, which was sublimed to give the pure 4 (R = Cl): mp 233–234°; ir (Nujol mull) 3210 (chelated NH) and 1696 cm^{-1} (chelated C=O).

Anal. Calcd for $C_{12}H_9ClN_2O_4$: C, 51.35; H, 3.23; N, 9.98. Found: C, 51.63; H, 3.41; N, 9.98.

Preparation of 7-Bromo-2-carbomethoxymethylene-2H-1,4-benzodiazepine-3,5-(1H,4H)-dione (4, R = Br).—Employing the above procedure an 81% yield of this product was obtained: mp 239–240.5°; ir (Nujol mull) 3190 (chelated NH) and 1690 cm^{-1} (sh, chelated CO).

Anal. Calcd for $C_{12}H_9BrN_2O_4$: C, 44.32; H, 2.79; N, 8.62. Found: C, 44.46; H, 2.91; N, 8.68.

Preparation of 7-Methyl-2-carbomethoxymethylene-2H-1,4-benzodiazepine-3,5-(1H,4H)-dione (4, R = CH_3).—An identical method gave a 76% yield of product: mp 240–241.5°; ir (Nujol mull) 3185 (chelated NH) and 1690 cm^{-1} (chelated CO).

Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.65; N, 10.77. Found: C, 60.10; H, 4.68; N, 10.79.

Cyclizations of 3 in Methoxide–Methanol System. Reaction of 3 (R = H).—The product isolation step in the preparation of 3 (R = H) was omitted, and a trace amount of $NaOCH_3$ was added to the reaction mixture. Alternatively, the adduct 3 (R = H) can be isolated and treated under these conditions to give the same product distribution. After refluxing for 2 hr, the solution was cooled to room temperature to provide 23% crude maleimide (see Table I, method B) which was then sublimed to afford the pure 9 (R = H): mp 234–235°; ir (Nujol

mull) 3150 (NH), 1765 and 1720 (O=CNC=O), and 1690 cm^{-1} (ester C=O); nmr (DMSO-d_6) δ 10.80 (s, 1, NH), 10.68 (s, 1, NH), 7.75–7.3 (m, 4), 5.78 (s, 1, C=CH), and 3.75 ppm (s, 3, OCH_3).

Anal. Calcd for $C_{12}H_{10}N_2O_4$: C, 58.53; H, 4.08; N, 11.38. Found: C, 58.81; H, 4.16; N, 11.17.

Concentration and cooling of the mother liquor provided 71% crude light yellow crystalline quinazolinone, which was appreciably more soluble in methanol than was **9**. Careful recrystallization from methanol afforded white crystals of the pure **11** (R = H): mp 149–150°; ir (Nujol mull) 3375 and 3350 (NH), 1725 and 1715 (ester C=O), and 1675 cm^{-1} (amide C=O); nmr ($DCCl_3$) δ 8.1–6.6 (m, 4), 7.35 (s, 1, NH), 5.6 (s, 1, NH), 3.73 (s, 3, OCH_3), 3.73 (s, 3, OCH_3), and 3.17 ppm (s, 2, $-CH_2CO$); mass spectrum (80 eV), *m/e* (rel intensity) 278 (<1), 218 (100), 204 (19), 187 (22), 159 (80), 145 (31), 119 (17), 91 (24).

Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07. Found: C, 55.92; H, 5.07.

Reaction of 3 (R = Cl).—The reaction can be accomplished by adding $NaOCH_3$ to the preparation of **3** (R = Cl) before work-up or by first isolating the adduct and then treating it with methoxide. The same product distribution is obtained in either case. The more insoluble product (33% yield, see Table I) is the maleimide **9** (R = Cl): mp 291–292°; ir (Nujol mull) 3240 and 3150 (NH), 1765, 1700, and 1685 cm^{-1} (C=O); nmr (DMSO-d_6) δ 10.65 and 10.45 (s, 1, NH), 7.8–7.3 (m, 3), 5.78 (s, 1, C=CH), and 3.81 ppm (s, 3, OCH_3).

Anal. Calcd for $C_{12}H_9ClN_2O_4$: C, 51.35; H, 3.23; N, 9.98. Found: C, 51.24; H, 3.38; N, 10.26.

Concentration of the mother liquor provided 40% highly soluble chloroquinazolinone (**11**, R = Cl): mp 189–190°; ir (Nujol mull) 3330 and 3210 (NH), 1730 (ester C=O), and 1675 cm^{-1} (amide C=O); nmr ($DCCl_3$) δ 8.38 (s, 1, NH), 7.7–6.8 (m, 3), 7.55 (s, 1, NH), 3.68 (s, 6, OCH_3), and 3.41 ppm (s, 2, $-CH_2-CO$).

Anal. Calcd for $C_{13}H_{13}ClN_2O_5$: C, 49.92; H, 4.19; N, 8.96. Found: C, 50.31; H, 4.41; N, 9.21.

Reaction of 3 (R = Br and CH_3).—An identical product distribution was obtained when either the respective anthranilamide adducts (**3**) or the equimolar quantities (0.01 mol each) of the anthranilamide and **2** were dissolved in 50 ml of methanol and refluxed for 2 hr with approximately 0.10 g of sodium methoxide. The quinazolinones in these two cases could not be isolated owing to their high solubility in the methanol and their tendency to precipitate with traces of maleimide contamination. Evaporation of the methanol to one-fourth of its original volume brought about precipitation of the respective maleimides (**9**, R = Br) and (**9**, R = CH_3). These materials were sublimed to analytical purity. See Table I under method B for physical properties and yields. The mother liquors after removal of the maleimides clearly showed the NH and carbonyl absorptions characteristic of the quinazolinones. The saturated ester side chain on C-2 is clearly evident at 1725 ± 5 cm^{-1}.

Reaction of 4 (R = H).—To the refluxing solution of 3.0 g (12.2 mmol) of **4** (R = H) in 75 ml of methanol was added a trace amount of $NaOCH_3$. The solution was stirred and refluxed for a total of 2 hr, cooled to room temperature, diluted with 2 ml of H_2O, and filtered. The yellow crystals (0.61 g, 25%) obtained were shown by melting point and spectral comparisons to be the maleimide (**9**, R = H). The mother liquor was then concentrated to two-tenths of its volume, cooled, and filtered. The light yellow product (2.15 g, 63%) was identical in all respects with the quinazolinone **11** (R = H). From the resultant mother liquor was obtained 0.20 g (6%) of the open adduct **3** (R = H).

Reaction of 14.—A 3.0-g (10.0 mmol) sample of the adduct **14** in 125 ml of methanol was treated with a trace of $NaOCH_3$ (less than 0.05 g). The reaction mixture was refluxed for 22 hr, cooled, and filtered. The white crystals (2.6 g, 83%) obtained were recrystallized from cyclohexane–benzene to yield the pure 2-carbomethoxy-2-carbomethoxymethyl-2,3-dihydro-3-methyl-4-(1H)-quinazolinone (**15**): mp 116–118°; ir (Nujol mull) 3260 (NH), 1743 and 1736 cm^{-1} (ester CO); nmr ($DCCl_3$) δ 8.1–6.65 (m, 4), 6.00 (s, 1, NH), 3.80 (s, 3, OCH_3), 3.77 (s, 3, OCH_3), 3.24 (q, 2, J = 16 Hz, $-CH_2CO-$), and 3.14 ppm (s, 3, $N-CH_3$). Similar reaction in xylene solvent gave the same product. No trace of the maleimide was observed in either product mixture.

Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.52; H, 5.51; N, 9.58. Found: C, 57.65; H, 5.66; N, 9.42.

An Alternative Synthesis of the Maleimides. Ammonolysis of Dimethyl (2-Carbomethoxy-4-R-anilino)fumarates (Method A).—In a ground-glass stoppered bottle was placed 0.01 mol of the adduct of **2** and methyl 5-R-anthranilate (R = H, Cl, Br, CH_3, and I)[7] and sufficient methanol (200–300 ml) to bring the adduct into solution. The vessel was chilled to ice-bath temperatures and saturated with anhydrous ammonia. The solution was stirred in a tightly sealed bottle at room temperature for 8 hr. Some of the product precipitated directly, but isolation was facilitated by evaporation to one-tenth of the original volume. Bright yellow crystals separated and were purified by recrystallization from methanol and by sublimation at 210° (0.5 mm). Yields and analyses are summarized on Table I. Each maleimide was spectrally identical with that obtained by methoxide–methanol treatment of the amide adducts (*i.e.*, method B).

Preparation of Dimethyl 2-Anilinofumarate[9] and Its Ammonolysis to Maleimide.—To 6.3 g (67.5 mmol) of freshly distilled aniline in 30 ml of ether was added 9.58 g (67.5 mmol) of **2**. After the vigorous exothermic reaction had ceased, the reaction mixture was heated to remove the remaining solvent. Distillation of the residue gave 11.80 g (75%) of the aniline adduct: bp 105–107° (0.05–0.07 mm) [lit.[9] bp 115–118°, bath temperature (0.001 mm)].

Ammonia (anhydrous) was passed through a solution of 4.70 g (20 mmol) of the anilinofumarate in 40 ml of methanol for 2.5 hr. The solution was then stirred for an additional 18 hr. The yellow crystals that precipitated were collected by filtration, washed with 5 ml of methanol, and dried to give 1.95 g (52%) of crude product which was purified by sublimation to afford the pure maleimide, mp 211–213° (lit.[24] mp 206.5–207°).

Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.89; H, 4.56; N, 14.79.

Preparation of 3-Bromomaleimide.—A solution of 9.7 g (0.10 mol) of maleimide in 30 ml of glacial acetic acid was heated on a steam cone and subjected to the dropwise addition of 19.2 g (0.12 mol) of bromine dissolved in 25 ml of glacial acetic acid. The reaction mixture was agitated during the entire addition and was heated without agitation for 15 min following the completion of the addition. The acetic acid was evaporated under vacuum to one-tenth of the original volume, and a 5% aqueous sodium bicarbonate solution was added to achieve neutrality. The precipitated crystals were filtered off and recrystallized twice from water to produce white microneedles, mp 155–156.5°, 10.2 g (58%) (lit.[29] mp 153–154°).

Independent Synthesis of (2-Carbomethoxyanilino)maleimide (9, R = H).—Methyl anthranilate (6 ml) and 0.20 g of 3-bromomaleimide were heated at reflux for 10 min. A deep burgundy color developed in the solution. The solution was cooled to room temperature and treated with 5 ml of methanol containing 0.10 g of sodium methoxide. Chilling in an ice bath precipitated yellow crystals, which were filtered off and washed well with cold diethyl ether. The crude crystals, 0.14 g, melted at 226–229° and had an ir spectrum identical with that of the material obtained by methoxide–methanol treatment of **3** and by ammonolysis of dimethyl (2-carbomethoxyanilino)fumarate.

(2-Carbethoxyanilino)maleimide.—A 5.0-g (16.3 mmol) sample of the adduct of ethyl anthraniliate and **2** was treated with NH_3–CH_3OH as before to provide 3.70 g (87%) of the crude product, which was sublimed to afford the pure maleimide: mp 220–224°; ir (Nujol mull) 3150 (chelated NH), 1765 and 1695 (O=C—N—C=O), and 1675 cm^{-1} (ester C=O); nmr (DMSO-d_6) δ 10.88 (s, 1, NH), 8.2–7.1 (m, 4), 5.95 (s, 1, C=CH), 4.43 (q, 2, J = 7 Hz, OCH_2CH_3), and 1.40 ppm (t, 3, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 60.07; H, 4.63; N, 10.76.

Hydride Reduction of the Benzodiazepinedione (4, R = H).—To a stirred solution of 2.46 g (0.010 mol) of **4** in 350 ml of absolute tetrahydrofuran at 0° was added a slurry of 0.40 g of lithium aluminum hydride in 20 ml of absolute tetrahydrofuran over a period of 1.5 hr. The cold reaction mixture was stirred an additional 0.5 hr, treated with a saturated solution of Na_2SO_4, dried over anhydrous Na_2SO_4, and filtered. The solids were washed well with tetrahydrofuran and diethyl ether. The combined filtrates were evaporated to dryness under vacuum, and the crystalline residue was recrystallized from methanol to produce 0.90 g (36%) of pure white **6**: mp 204–206°; ir (Nujol mull) 3395 (OH), 3220 and 3130 (NH), and 1670 cm^{-1} (chelated ester C=O); nmr (DMSO-d_6) δ 10.33 (s, 1, NH), 9.00 (d, 1, J = 6

Hz, NH), 7.83 (q, 1, J_o = 8 Hz, J_m = 2 Hz, -C-6 H), 7.65–7.00 (m, 3, C-7 H, C-8 H), C-9 H), 6.78 (d, 1, J = 4 Hz, OH), 5.10 (q, 1, J = 4 Hz, J = 6 Hz, ≡C—H), 4.98 (s, 1, =C—H), and 3.85 ppm (s, 3, $COOCH_3$).

Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.21; H, 4.71; N, 11.37.

Methylation of the Benzodiazepinedione System. Preparation of 4-Methyl-2-carbomethoxymethylene-2H-1,4-benzodiazepine-3,5(1H,4H)-dione (13).—A solution of 12.30 g (0.05 mol) of **4** (R = H) in 150 ml of hot DMF (freshly distilled from P_2O_5) was added to 0.06 mol of NaH in 125 ml of dry benzene. The red-orange solution that resulted was stirred until the evolution of gases ceased (5 min) before the dropwise addition of 6.9 g (0.07 mol) of methyl iodide was initiated. The reaction mixture was then heated at 80° for 45 min, cooled to room temperature, treated with a small amount of methanol–water, and diluted with ice–water until two distinct layers appeared. The aqueous layer was separated and extracted with 150 ml of benzene. The benzene layers were combined, dried (Na_2SO_4), and concentrated. Cooling the residue produced brown-yellow crystals which were triturated with methanol and washed with hexane to afford light yellow crystals (mp 117–124, 4.70 g, 36%). Recrystallization from benzene–cyclohexane produced pure **13**: mp 126–128°; ir (Nujol mull) 1685 cm^{-1} (chelated C=O); nmr ($DCCl_3$) δ 10.93 (s, 1, NH), 6.9–8.1 (m, 4), 5.87 (s, 1, C=CH), 3.80 (s, 3, CO_2CH_3), and 3.47 ppm (s, 3, $N—CH_3$); mass spectrum (80 eV), *m/e* 260 (P).

Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 60.11; H, 4.88; N, 10.64.

Ring Opening of 13 with Methanol.—A 1-g sample of crude **13** was heated in 15 ml of methanol for 15 min. Upon cooling to 0°, the resulting solution precipitated yellow crystals which were collected and dried. By nmr ($DCCl_3$), the yellow crystals appeared to be a mixture of **13** and **14**, in the ratio of 1:2. When the spectrum of this mixture was compared with the nmr spectra of pure **13** and **14**, an exact peak for peak correspondence was obtained. In addition, the ir spectrum of the mixture could be matched peak for peak with the spectra of pure **13** and **14**. No attempt was made to separate the mixture.

Reaction of 4 (R = H) with 6 *N* HCl. Preparation of 7.—A 2.1-g (8.5 mmol) sample of **4** in 100 ml of 6 *N* aqueous hydrochloric acid was stirred and refluxed for 2 hr. After the reaction mixture cooled to room temperature, the precipitated material was collected by filtration, washed with water, and dried. The crude material (1.37 g, 86%) was recrystallized from benzene and was washed with hexane to produce pure **7**: mp 202–205°; ir (Nujol mull) 1708 (acetyl C=O), 1665 cm^{-1} (C=O); nmr (DMSO-d_6) δ 7.6–8.4 (m, 4) and 2.68 ppm (s, 3, CH_3CO–); uv max (100% EtOH) 229, 259 sh, 261 sh, and 304 mμ.

Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.88. Found: C, 63.97; H, 4.31; N, 14.80.

A positive methyl ketone test (iodoform) was obtained,[40] and a 2,4-dinitrophenylhydrazone, mp 324–326° (from ethanol), was prepared.

Anal. Calcd for $C_{16}H_{12}N_6O_5$: N, 22.81. Found: N, 22.59.

Registry No.—**3** (R = H), 17244-69-8; **3** (R = Cl), 17244-20-1; **3** (R = CH_3), 17244-21-2; **3** (R = Br), 17244-22-3; **4** (R = H), 13187-67-2; **4** (R = Cl), 13214-23-8; **4** (R = CH_3), 17244-25-6; **4** (R = Br), 17244-26-7; **6**, 17244-27-8; **7**, 17244-28-9; **7** dinitrophenylhydrazone, 17244-29-0; **9** (R = H), 17244-30-3; **9** (R = Cl), 17244-31-4; **9** (R = Br), 17244-32-5; **9** (R = CH_3), 17244-33-6; **9** (R = I), 17244-34-7; **11** (R = H), 17244-35-8; **11** (R = Cl), 17244-36-9; **12** (2-carbethoxy isomer), 17244-37-0; **13**, 17244-38-1; **14**, 17244-39-2; **15**, 17244-40-5; (2-carbethoxyanilino)maleimide, 17244-41-6; dimethyl 2-anilinofumarate maleimide, 17244-42-7.

Acknowledgment.—The authors wish to thank Dr. James Sturm of this department for his assistance in obtaining the mass spectral data. We are grateful to Drs. Thomas E. Young, Peter D. Kennewell, and Cyrus J. Ohnmacht of these laboratories for helpful discussion during the course of this work.

(40) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, John Wiley & Sons, Inc., New York, N. Y., 1967, p 137.

Synthesis of Epindolidione[1,2]

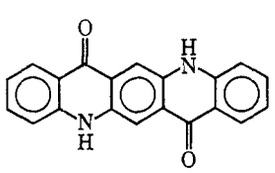
EDWARD E. JAFFE AND HOWARD MATRICK

Pigments Department, E. I. du Pont de Nemours and Company, Newark, New Jersey 07114

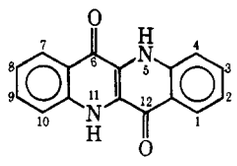
Received May 27, 1968

Two new syntheses of epindolidione (**2**) are described. The first synthesis affords **2** and some symmetrically substituted derivatives in good yield and relatively high purity. Dimethyl dihydroxyfumarate (**4**) reacts with aniline to give dimethyl dianilinomaleate (**5**). Evidence for the *cis* structure of **5** is given. The latter ester is cyclized to 2-methoxycarbonyl-3-anilino-4-quinolone (**7a**) which in turn is cyclized to **2**. The second method involves the cyclization of 3-(2-carboxyphenylamino)-4-quinolone (**16**) which is obtained by condensation of 3-amino-4-quinolone with *o*-bromobenzoic acid. Physical and spectral properties of **2** are discussed and evidence for intermolecular hydrogen bonding is presented.

The advent of quinacridone[3] (**1**) as a commercial pigment stimulated research in the synthesis of related structures. A compound of particular interest was dibenzo[*b*,*g*][1,5]naphthyridine-6,12(5,11H)-dione (**2**).



1



2

The 2,8-dimethyl derivative of **2** was first synthesized by Ainley and Robinson[4] in order to compare its properties with those of indigo, a structural isomer of **2**. These workers coined the name epindolidione for com-

(1) Presented in part at the 3rd Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1968.

(2) Included in part in U. S. Patent 3,334,102.

(3) (a) H. Liebermann, *Ann.*, **518**, 245 (1935); (b) W. S. Struve, U. S. Patent 2,821,529; *Chem. Abstr.*, **52**, 10215 (1958); U. S. Patent 2,821,530; *Chem. Abstr.*, **52**, 10216 (1958); (c) S. S. Labana and L. L. Labana, *Chem. Rev.*, **67**, 1 (1967).

(4) A. D. Ainley and R. Robinson, *J. Chem. Soc.*, 1508 (1934).