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]

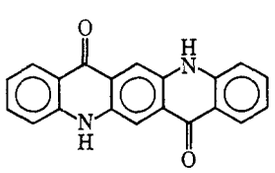
EDWARD E. JAFFE AND HOWARD MATRICK

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

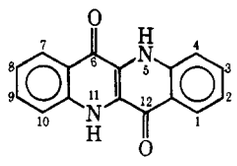
Received May 27, 1968

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-

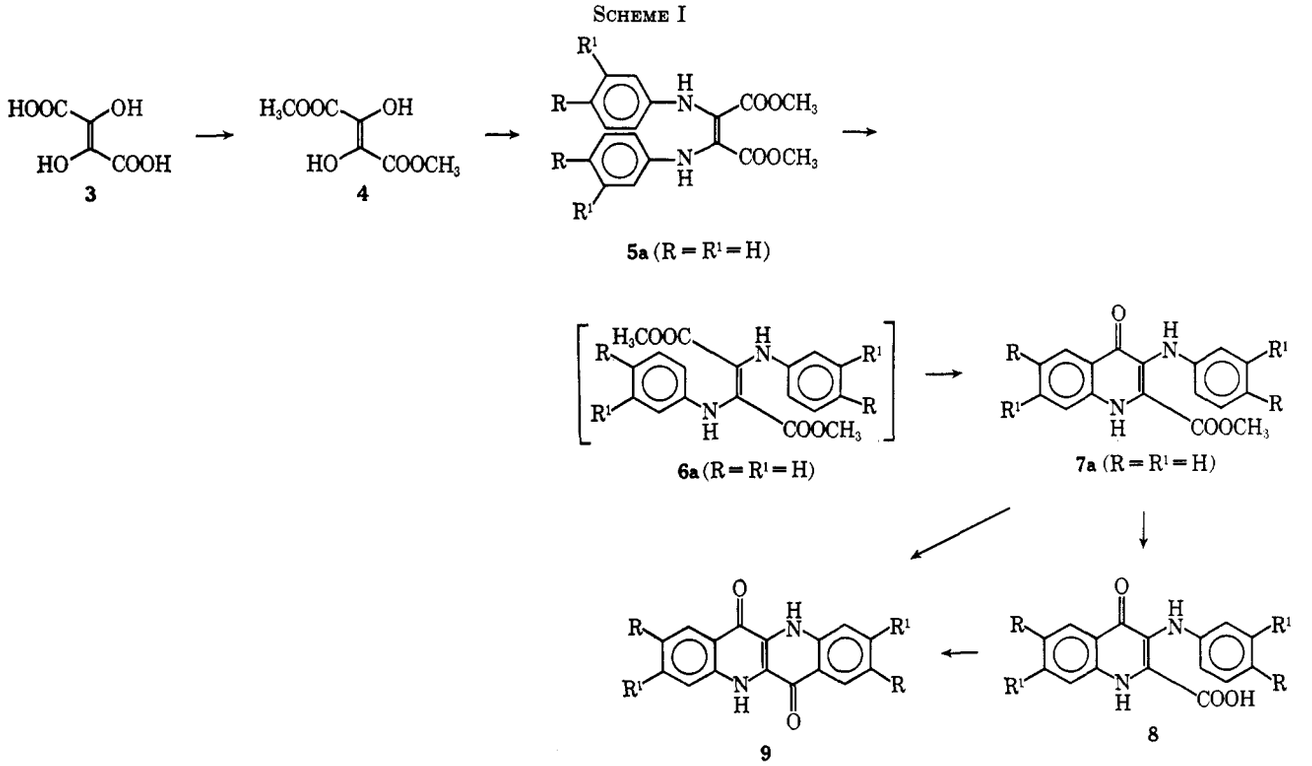
(1) Presented in part at the 3rd Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1968.

(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).

SCHEME I



pound **2**. The Ainley and Robinson synthesis started with a known but difficultly obtainable compound and gave a poor over-all yield. Subsequently, this synthesis was used for the preparation of the parent compound[5] **2**. This method is not, however, suitable for the preparation of certain substituted derivatives.

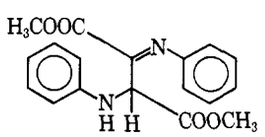
Results and Discussion

We wish to report two new and improved methods for the preparation of **2**. One of these methods gives good yields of **2** and its symmetrically substituted derivatives in relatively high purity. This synthesis is outlined in Scheme I.

Dihydroxyfumaric acid (**3**), whose structure was shown to be *trans* by Goodwin and Witkop,[6] was esterified by a modification of the usual methanol–hydrogen chloride esterification procedure. The simple modification involved conducting the reaction in the presence of anhydrous magnesium sulfate, thus more than doubling the previously reported yield of 45%.[7] The increase in yield is presumably due to removal of product water which favorably affects the esterification equilibrium. Goodwin and Witkop[6] have assigned a *trans* configuration to this ester based on infrared (ir) spectral evidence.

Dimethyl Bis(arylamino)maleates (5).—Dimethyl dihydroxyfumarate (**4**) reacts rapidly with aniline or substituted anilines under acid catalysis to give good yields of dimethyl bis(arylamino)maleates. The maleates which have been prepared in this study along with pertinent data are listed in Table I.

The dianilino compound **5a** was previously prepared by Salmony and Simonis[8] by the reaction of dimethyl dibromomaleate with aniline. The ir spectra showed the product of this reaction to be identical with the compound obtained from the reaction of aniline with **4**. Although Salmony and Simonis formulated the compound as dimethyl dianilinomaleate, they offered no evidence for the assigned structure. This compound can theoretically exist as one or more of three possible structures: **5a**, the maleate; **6a**, the fumarate; and **10**, the anilinophenylimino ester. The nmr spectrum of



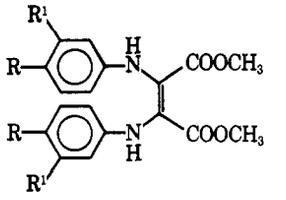
this compound shows a singlet for the ester methyl groups at δ 3.65 (6 H), an aromatic multiplet at 6.68–7.33 (10 H), and a singlet for N–H at 7.72 (2 H). The latter signal disappears upon exchange with heavy water. This evidence unequivocally excludes structure **10** from consideration.

In order to differentiate between the *cis* and *trans* structures the ir and Raman spectra of the compound were examined, and its dipole moment was determined. Between 3 and 6.5 μ the ir spectrum shows bands at 3.02, 3.08, 5.79, 5.96, 6.29, and 6.38 μ. The doublet at 3.02 and 3.08 μ is attributed to coupling of the two N–H frequencies. The doublet in the carbonyl-stretching region at 5.79 and 5.96 μ is believed to be due to the in phase and out of phase stretching vibration of the ester carbonyls. The 6.29-μ band is attributed to an aromatic double-bond vibration, and the strong 6.38-μ band is assigned to the olefinic double-bond stretching vibration as would be expected of the maleate structure. Based on the selection rules,[9] the fumarate isomer

(5) H. de Diesbach, A. Schurch, and G. Cavin, *Helv. Chim. Acta*, **31**, 716 (1948).
(6) S. Goodwin and B. Witkop, *J. Amer. Chem. Soc.*, **76**, 5599 (1954).
(7) E. F. Hartree, *ibid.*, **76**, 6244 (1953).
(8) A. Salmony and H. Simonis, *Ber.*, **38**, 2580 (1905).
(9) F. A. Miller in "Organic Chemistry," Vol. III, H. Gilman, Ed., John Wiley & Sons, Inc., New York, N. Y., pp 131, 132.

TABLE I

DIMETHYL BIS(ARYLAMINO)MALEATES

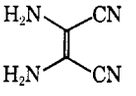


5

5	R	R¹	Mp, °C	Yield, %	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	Halogen, % Calcd	Halogen, % Found
a	H	H	196–198[a,b]	83.4	$C_{18}H_{18}N_2O_4$	66.24	66.03	5.56	5.38	8.59	8.76		
b	OCH_3	H	135–137[c]	64.9	$C_{20}H_{22}N_2O_6$	62.16	62.08	5.74	5.73	7.25	7.36		
c	CH_3	H	182–184.5[c]	73.2	$C_{20}N_{22}N_2O_4$	67.78	67.80	6.26	6.24	7.91	8.05		
d	F	H	199–200[d]	80.0	$C_{18}H_{16}F_2N_2O_4$	59.66	59.66	4.45	4.54	7.73	7.58	10.49	10.47
e	Cl	H	203–204[d]	85.1	$C_{18}H_{16}Cl_2N_2O_4$	54.70	54.71	4.08	4.03	7.09	7.03	17.94	18.18
f	H	Cl	151–154[d]	99.0	$C_{18}H_{16}Cl_2N_2O_4$	54.70	54.94	4.08	4.03	7.09	7.11	17.94	18.15
g	Cl	Cl	155–156[c]	89.0	$C_{18}H_{14}Cl_4N_2O_4$	46.58	46.82	3.04	2.94	6.04	6.23	30.56	30.68

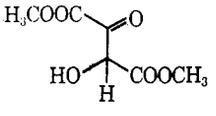
[a] Recrystallized from 1-butanol. [b] Lit.[8] mp 172°. [c] Recrystallized from petroleum ether (bp 90–120°). [d] Recrystallized from methanol.

should show little or no absorption in this region. The relatively long wavelength of this absorption is believed to be due to electronic interaction of the anilino and ester groups. It is noteworthy that the Raman spectrum shows only bands corresponding to those observed in the ir spectrum described above, thus lending support to the assignment of the maleate structure **5a** for this ester. More decisive evidence was obtained when the dipole moment of this compound was determined in dioxane and found to be 3.48 D. This evidence lends important support to the assigned *cis* structure, since the *trans* compound would be expected to have a small dipole moment or none at all. The formation of the *cis* compound is not surprising in view of the fact that the tetramer of HCN (**11**) also exists in the *cis* form. The structural assignment of **11** is conclusively supported by both dipole moment[10] and X-ray diffraction[11] data.



11

The formation of **5** from **4** can theoretically take place by either of the two following acid-catalyzed mechanisms: (a) protonation of the keto tautomer of dimethyl dihydroxyfumarate (**12**), followed by reaction with aniline, elimination of water, a second keto tautomer formation, and a repetition of the above steps; (b) acid-catalyzed addition of aniline to the double bond of **4**, followed by elimination of water, and repetition of these steps on the monoanilino compound.



12

Mechanism a is favored because dimethyl diacetoxyfumarate[6] failed to react with aniline under the acid-catalyzed conditions under which **4** reacted readily. Were mechanism b operative, the diacetoxy compound would have been expected to undergo the addition-elimination reaction. The favored mechanism a is analogous to the one proposed for the acid-catalyzed reaction of aniline and substituted anilines with benzoins.[12]

2-Methoxycarbonyl-3-arylamino-4-quinolones (7).—Since the discovery of the cyclization of alkyl β-anilinoacrylates to 4-quinolones by Conrad and Limpach[13] this reaction has been widely applied to the synthesis of 4-quinolones.[14] Assuming that **5** could isomerize to the corresponding geometric isomer **6**, the latter could be expected to undergo the Conrad–Limpach cyclization. Dimethyl bis(arylamino)maleates (**5**) were actually found to readily undergo cyclization in boiling Dowtherm A[15] to give high yields of the corresponding quinolones **7**. Although good yields can be obtained by simple boiling of Dowtherm A solutions of **5**, controlled addition of **5** to boiling Dowtherm A increased the yield of the quinolones **7**. This is believed to be due to the favoring of the monomolecular cyclization by operating at higher dilution. The quinolones **7** which have been prepared, along with pertinent data are listed in Table II.

It is well-known that 4-quinolones exist predominantly in the vinologous amide rather than the 4-hydroxyquinoline form. Nmr and ir spectra of **7a** similarly support the 4-quinolone structure for these compounds. The nmr spectrum of **7a** shows a singlet for the ester methyl group at δ 3.65 (3 H), an aromatic multiplet at 6.66–7.12 (9 H), a singlet for the anilino N–H at 7.48 (1 H), and a broad singlet for the quinolone N–H centered at 12.00 (1 H). The latter two signals disappear upon exchange with heavy water. The corresponding N–H singlet in the parent compound, 4-quinolone, was found to be centered at δ 12.06. The ir spectrum shows bands at 5.82 and 6.18 μ attributed to the ester and quinolone carbonyls, respectively. In addition, a band attributed to the anilino N–H at 2.98

(10) R. L. Webb, S. Frank, and W. C. Schneider, *J. Amer. Chem. Soc.*, **77**, 3491 (1955).

(11) B. R. Penfold and W. N. Lipscomb, *Acta Crystallogr.*, **14**, 589 (1961).

(12) E. F. Pratt and M. J. Kamlet, *J. Org. Chem.*, **28**, 1366 (1963).

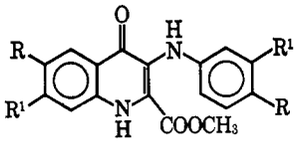
(13) M. Conrad and L. Limpach, *Ber.*, **20**, 1944 (1887); **21**, 521(1888).

(14) R. C. Elderfield in "Heterocyclic Compounds," R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1952, pp 1–343; R. H. Reitsema, *Chem. Rev.*, **43**, (1948).

(15) Dowtherm A is an azeotropic mixture of 26.5% biphenyl and 73.5% diphenyl ether.

TABLE II

2-METHOXYCARBONYL-3-ARYLAMINO-4-QUINOLONES



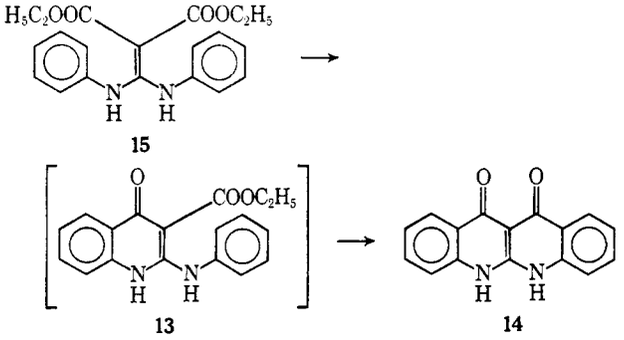
7

7	R	R¹	Mp, °C	Yield, %	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	Halogen, % Calcd	Halogen, % Found
a	H	H	201.5–203[a]	87.6	$C_{17}H_{14}N_2O_3$	69.37	69.18	4.79	4.82	9.52	9.46		
b	OCH_3	H	222–225[b]	87.0	$C_{19}H_{18}N_2O_5$	64.40	64.54	5.12	5.04	7.91	8.14		
c	CH_3	H	219–220[b]	82.6	$C_{19}H_{18}N_2O_3$	70.79	70.96	5.63	5.52	8.69	8.77		
d	F	H	223–226[a]	79.3	$C_{17}H_{12}F_2N_2O_3$	61.82	61.94	3.66	3.68	8.48	8.43	11.51	11.65
e	Cl	H	247–248.5[a]	89.4	$C_{17}H_{12}Cl_2N_2O_3$	56.21	56.33	3.33	3.37	7.71	7.88	19.52	19.56
f	H	Cl	225–226[b]	97.1[c]	$C_{17}H_{12}Cl_2N_2O_3$	56.21	55.98	3.33	3.27	7.71	7.95	19.52	19.40
g	Cl	Cl	251–253[b]	90.0[d]	$C_{17}H_{10}Cl_4N_2O_3$	47.25	47.25	2.33	2.46	6.48	6.73	32.82	32.40

[a] Recrystallized from methanol. [b] Recrystallized from acetic acid. [c] The crude product may have been a mixture of the 7-chloro and some of the 5-chloro isomer. [d] The crude product may have been a mixture of the 6,7-dichloro and some of the 5,6-dichloro isomer.

and a shoulder at 3.15 μ believed to be due to the pyridone N–H were found.

As previously stated, formation of **7** from maleates **5** requires prior isomerization to the fumarates **6**.[16] Cyclization of **6a** under conditions of the Conrad–Limpach reaction occurs in high yield to give **7a**, but there the reaction stops. All attempts to effect the cyclization of **7a** to **2** by pyrolytic means have not been successful. This is in contrast to the behavior of 2-anilino-3-ethoxycarbonyl-4-quinolone (**13**), which undergoes pyrolytic cyclization to the isomer of epindolidione, dibenzo[*b*,*g*][1,8]naphthyridine-11,12-(5,6H)-dione (**14**). In fact, pyrolysis of diethyl dianilinomethylenemalonate (**15**) proceeds directly to **14**, presumably *via* **13**.[17] An explanation of this difference in behavior is not readily apparent.

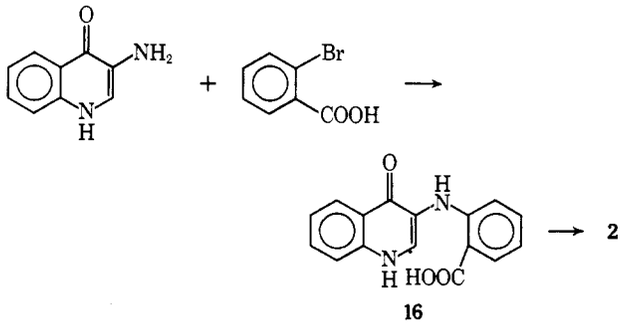


15 13 14

Epindolidiones (**9**).—Cyclization of **7** in polyphosphoric acid at 150° gave excellent yields of **9**. Although direct cyclization of **7** is the preferred method, the corresponding acids **8** can be similarly cyclized in polyphosphoric acid. The feasibility of the latter route was demonstrated in the synthesis of **2**. This route is actually preferred in the preparation of 2,8-dimethoxyepindolidione (**9**, R = OCH_3; R^1 = H) in order to take advantage of the more facile cyclization of the acid relative to the ester to avoid demethylation. A similar cyclization was effected by Ainley and Robinson[4] in boiling 60% sulfuric acid in the preparation of 2,8-dimethylepindolidione (**9**, R = CH_3; R^1 = H), although in lower yield. The cyclization of **8** (R^1 = R = H) in the preparation of **2** was carried out by de Diesbach, *et al.*,[5] with phosphorus pentoxide in nitrobenzene in undisclosed yield.

Table III gives pertinent data for epindolidione and its substituted derivatives.

Synthesis *via* 3-(2-Carboxyphenylamino)-4-quinolone.—One of the routes which were followed by Ainley and Robinson[4] in their attempt to synthesize epindolidione involved the preparation of 3-(2-carboxyphenylamino)-4-quinolone (**16**). This acid was obtained in unspecified yield from N-benzoyl-2,3-dihydro-4-quinolone and ethyl *o*-nitrosobenzoate. Many attempts by these workers to cyclize acid **16** or its acid chloride under a variety of conditions were unsuccessful. We have prepared acid **16** by a more convenient route involving the copper-catalyzed reaction of 3-amino-4-quinolone[18] with *o*-bromobenzoic acid in 69% yield. This acid was found to undergo cyclization to epindolidione in nearly quantitative yield in an aluminum chloride–sodium chloride eutectic melt at 200°. Similarly, the acid underwent cyclization in hot polyphosphoric acid, although in lower yield. The



16

failure of Ainley and Robinson to effect cyclization of **16** to **2** was due to their use of insufficiently active catalysts such as 60% sulfuric acid, zinc chloride, and stannic chloride.

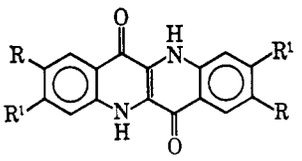
Structure and Properties of Epindolidione.—The epindolidiones range from greenish yellow to orange microcrystalline powders, which in most cases exhibit the phenomenon of polymorphism. They do not melt or decompose up to 400° and are very sparingly soluble

(16) Attempts to detect isomerization prior to cyclization by differential thermal analysis have not been successful.

(17) Subsequent to the completion of this work, this observation has been reported by R. Gompper and R. Kuntz, *Ber.*, **98**, 1391 (1965).

(18) B. B. Bachman, D. E. Welton, G. L. Jenkins, and J. E. Christian, *J. Amer. Chem. Soc.*, **69**, 365 (1947).

TABLE III
EPINDOLIDIONES[a]



9

9	R	R¹	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	Halogen, % Calcd	Halogen, % Found	λ_{max} in concd H_2SO_4, mμ
a	H	H	$C_{16}H_{10}N_2O_2$	73.27	73.55	3.84	3.89	10.68	10.96			500
b	OCH_3	H	$C_{18}H_{14}N_2O_4$	67.07	66.96	4.38	4.42	8.69	8.74			542
c	CH_3	H	$C_{18}H_{14}N_2O_2$	74.46	74.14	4.86	4.96	9.65	9.65			515
d	F	H	$C_{16}H_8F_2N_2O_2$	64.43	64.69	2.70	2.70	9.40	9.33	12.74	12.48	502
e	Cl	H	$C_{16}H_8Cl_2N_2O_2$	58.03	57.97	2.43	2.43	8.46	8.39	21.41	21.20	514
f	H	Cl[b]	$C_{16}H_8Cl_2N_2O_2$	58.03	58.10	2.43	2.41	8.46	8.70	21.41	21.30	494
g	Cl	Cl[c]	$C_{16}H_6Cl_4N_2O_2$	48.03	48.10	1.51	1.71	7.00	7.01	35.45	35.20	511

[a] Without exception, the yields of **9** were essentially quantitative. Because of the very low solubility of these compounds in organic solvents, they were purified by precipitation of their sulfates in H_2SO_4. An example of this method is given in the Experimental Section. [b] The crude product may have been a mixture of the 2,8-dichloro and some of the 1,8-dichloro isomer. [c] Experimental evidence suggests that the crude product may have been a mixture of the 2,3,8,9-tetrachloro and some of the 1,2,8,9-tetrachloro isomer.

in organic solvents. This low solubility may be attributed to strong intermolecular hydrogen bonding between the carbonyl oxygen and the N–H hydrogen atoms which are favorably situated for such bonding. Support for strong intermolecular bonding in the solid state is derived from a comparison of the visible spectra in the solid state with that of a solution in N,N-dimethylformamide. The visible absorption spectrum of epindolidione in solution is characterized by three bands increasing in intensity with increasing wavelength as shown in Table IV. The spectrum in the solid state

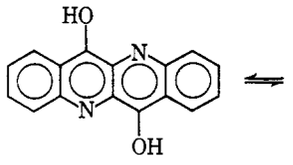
TABLE IV
VISIBLE ABSORPTION MAXIMA OF EPINDOLIDIONE

λ, mμ Solid state[a]	λ, mμ Solution in DMF	Molar extinction coefficient in DMF
494	444	20,200
462	419	13,200
429	398	5,200

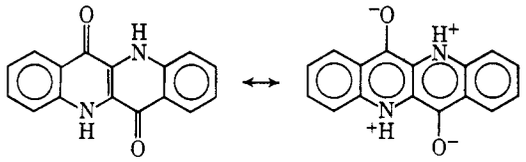
[a] Obtained from a reflectance spectrum on a dispersion of solid in an alkyd resin film.

is similar to that of the solution spectrum but shows a strong bathochromic shift which for the major absorption band is 50 mμ. A shift of this magnitude can be attributed to intermolecular hydrogen bonding in the solid state. A similar shift was shown in the case of indigo, by Weinstein and Wyman,[19] who concluded that, in the solid state, indigo is associated by means of intermolecular hydrogen bonding. Furthermore, the positions of the carbonyl and N–H stretching frequencies in the ir spectrum (see below) lend additional support to the suggestion that the epindolidiones are intermolecularly hydrogen bonded. Lüttke and Klessinger[20] came to the same conclusion based on similar findings in an ir spectral investigation of indigo and its substituted derivatives.

As shown earlier by nmr and ir spectral data, **7a** exists in the quinolone rather than the tautomeric hydroxyquinoline form. Unfortunately, the insolubility of the epindolidiones does not permit measurement of their nmr spectra. However, the ir spectra of **9** show a band at 6.10–6.28 μ attributed to the carbonyl groups and similar to that shown by **7** and 4-quinolone. In addition, the spectra of **9** show a band at 3.13–3.16 μ attributed to the N–H stretching frequencies. Based on these data it is concluded that epindolidione exists in the ketonic form **2**, not the enolic form **17**.



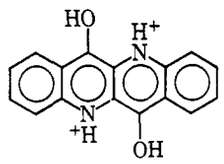
17



2 18

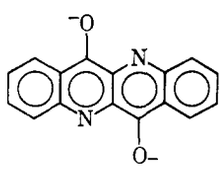
The extent of contribution of the resonance form **18** to the structures of epindolidione is difficult to assess. X-ray structural determinations of peptides and related substances has shown that the zwitterionic form contributes about 40% to the structure of the amide group.[21] Since epindolidione is a vinologous amide, the zwitterionic form **18** in which both pyridone moieties are in the charge-separated form, as well as the resonance form in which only one pyridone group is so affected, will make a significant contribution to the structure of epindolidione. It is noteworthy that the spectrum of **2** in 96% sulfuric acid is similar to that of naphthacene in N,N-dimethylformamide solution but shows a strong bathochromic shift relative to the visible spectrum of **2** in N,N-dimethylformamide. This is to be expected if the degree of aromatic character of the molecule is increased on protonation. The spec-

(19) J. Weinstein and G. M. Wyman, *J. Amer. Chem. Soc.*, **78**, 2387 (1956).
(20) W. Lüttke and M. Klessinger, *Ber.*, **97**, 2342 (1964).
(21) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, pp 281, 282.



19

trum is best interpreted on the basis of structure **19** where protonation has taken place on the oxygen rather than the nitrogen atoms. This is in agreement with the work of Katritzky and Jones[22] who have shown by an nmr study that protonation of pyridones and quinolones takes place on oxygen. Likewise, the spectrum of **2** in methanolic N-benzyltrimethylammonium hydroxide[23] shows similarity to the spectrum of the diprotonated species, although the relative peak intensities are different and the spectrum in basic solution shows a bathochromic shift. This suggests that the visible spectra in strongly basic as well as strongly acidic solutions are due to the same chromophore.[3c,24] The spectrum in methanolic N-benzyltrimethylammonium hydroxide is, therefore, indicative of an aromatic structure which is best formulated as the dianion **20**.



20

Experimental Section[25]

Dimethyl Dihydroxyfumarate (4).—To a solution of 222 g (1.5 mol) of dihydroxyfumaric acid[26] in 1.2 l. of methanol in a flask equipped with a stirrer, thermometer, a gas inlet tube, and means for external cooling, was added 300 g (2.5 mol) of anhydrous magnesium sulfate. The mixture was stirred and cooled to 0–5°, treated with a stream of anhydrous hydrogen chloride for 4.5 hr, and thereafter kept at room temperature for 3 days. The solid was collected by filtration, washed with a small amount of methanol, and reslurried in 3 l. of cold water. The product was promptly filtered and washed with cold water until free of acid and sulfate. After drying at 60° the yield of ester was 245.7 g (93.2%), mp 168–172° (lit.[6] mp 165–173°).

Dimethyl Bis(arylamino)maleates (5).—To a suspension of 17.6 g (0.10 mol) of **4** in 80 ml of methanol was added 0.22 mol of an arylamine followed by 1.0 ml (*ca.* 0.012 mol) of concentrated hydrochloric acid, and the mixture refluxed for 6 hr. Alternatively, an equivalent amount of dry arylamine hydrochloride can be used as catalyst. Upon refluxing, a clear solution formed, which became deeper in color, and eventually the product precipitated out of solution. The slurry was cooled to 5–10°; the product was separated by filtration, washed sparingly with methanol, and dried at 60°. Yields, melting points, recrystallization solvents, and elemental analyses are given in Table I.

(22) A. R. Katritzky and R. A. Y. Jones, *Proc. Chem. Soc.*, 313 (1960); A. R. Katritzky and R. A. Y. Jones, *Chem. Ind.* (London), 722 (1961).

(23) Triton B was supplied by Rohm and Haas Co.

(24) A similar relationship of two visible spectra in the anthraquinone series was suggested to be due to the same chromophore by J. Weinstein and C. Merritt, Jr., *J. Amer. Chem. Soc.*, **81**, 3759 (1959).

(25) All melting points are uncorrected. The ir spectra were determined by the Nujol mull technique on a Perkin-Elmer Model 137 or 21 recording spectrophotometer. A Varian Associates A-60 instrument was used for recording the nmr spectra in deuterated dimethyl sulfoxide, employing tetramethylsilane as an internal standard. Visible spectra were measured on a Beckman DK or DU spectrophotometer. The Raman spectrum was recorded on a Cary Model 81, laser spectrophotometer. The dipole moment was determined by Dr. H. Eatough of the Central Research Department, E. I. du Pont de Nemours and Co.

(26) J. H. H. Fenton, *J. Chem. Soc.*, **87**, 811 (1905).

2-Methoxycarbonyl-3-arylamino-4-quinolones (7).—In a 3-l. round-bottom flask, equipped with a stirrer, thermometer, heated addition funnel, and Dean–Stark tube, 400 ml of Dowtherm A was brought to reflux. To the gently refluxing solvent was added a hot (120–130°) solution of 100 g of **5** in 1 l. of Dowtherm A over a period of 0.5 hr. After completion of the addition, refluxing was continued for another 15 min. A mixture of methanol and Dowtherm A was collected in the Dean–Stark tube. The solution was cooled to room temperature, and the precipitated yellow to orange crystalline solids were separated by filtration. After thorough washing with petroleum ether (bp 60–90°) the products were dried at 60°. Yields, melting points, recrystallization solvents, and elemental analyses are given in Table II. A simplified procedure for the cyclization of **5** entails simple reflux of a solution of this ester in Dowtherm A with provision for removal of product methanol. The isolation procedure is the same, but the yields are somewhat lower.

The ester **7a** was isolated in two forms: a yellow form when the Dowtherm A solution was cooled rapidly, and a brown form when the solution was cooled slowly. Both forms showed essentially the same ir spectra and chemical reactions but had distinctive X-ray diffraction patterns. They are, therefore, believed to be different polymorphic forms of this compound.

2-Carboxy-3-anilino-4-quinolone (8, R = R¹ = H).—A mixture of 200 ml of 5% sodium hydroxide, 50 ml of ethanol, and 10 g of **7a** was refluxed for 2 hr. The solution was cooled to room temperature, filtered, and carefully acidified with 6 *N* hydrochloric acid. The resultant yellow solid was collected by filtration, washed free of acid with water, and dried at 60°. The yield was 7.5 g (78.8%). A sample was recrystallized from acetic acid. The colorless material showed mp 224–225° (lit.[5] mp 220–221°).

2-Carboxy-3-(*p*-anisidino)-6-methoxy-4-quinolone (8, R = OCH_3; R^1 = H).—A mixture of 960 ml of 10% sodium hydroxide and 49.2 g of **7** (R = OCH_3; R^1 = H) was refluxed for 2 hr. The solution was cooled to 0–5° and carefully acidified to a pH of 4 with 6 *N* hydrochloric acid. The resultant yellow solid, which turned colorless after several minutes, was collected by filtration, washed free of acid with water, and dried at 60°. The yield was 45.0 g (95.4%). A sample was recrystallized from acetic acid: mp 234–235°.

Anal. Calcd for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.74; N, 8.23. Found: C, 63.62; H, 4.64; N, 8.28.

Epindolidiones (9).—To 790 g of stirred polyphosphoric acid protected from atmospheric moisture was added 79 g of **7**, and the mixture was heated over 1 hr to 150° and then maintained at 145–150° for 2 hr. After it cooled to 40–50°, water was slowly added, maintaining the temperature at about 50°, until the vigorous hydrolysis reaction had ceased, after which an excess of water was added. The products were separated by filtration, then washed with water until free of acid, and dried at 80°. The yields were found to be essentially quantitative. The procedure does not apply to the preparation of **9** (R = OCH_3; R^1 = H). The compounds were conveniently purified by a procedure, an example of which follows.

In a flask equipped with a stirrer, drying tube, and thermometer 1380 g of 100% sulfuric acid was cooled to 8–10°. With stirring, 50 g of crude, pulverized **9** (R = Cl; R^1 = H) was added at 8–10°. The mixture was stirred at this temperature for 15–30 min or until complete solution was obtained as judged by microscopic examination. At this point water was added dropwise at a temperature not exceeding 20° until precipitation of the sulfate was nearly complete, in this case occurring at 94%. The latter value varied depending on the substituents and the concentration of **9** in the sulfuric acid. The sulfate was collected by filtration on a sintered-glass funnel and washed with sulfuric acid, the concentration of which was 5% below the concentration at which precipitation occurred, in this case 89%. The solid was transferred to 500 ml of ice–water, then heated to 90–100°, collected by filtration, and washed free of acid with hot water. After drying at 80°, the yield was 45.0 g (90% recovery).

Cyclization of 2-Carboxy-3-anilino-4-quinolone to 2.—Using a procedure analogous to that described for the cyclization of the esters **7**, a 92.6% yield of product was obtained. The ir spectrum of this material was identical with that of epindolidione obtained from the cyclization of the ester **7a**.

2,8-Dimethoxyepindolidione (9, R = OCH_3; R^1 = H).—To 100 g of stirred polyphosphoric acid protected from atmospheric moisture was added 10 g of **8** (R = OCH_3; R^1 = H), and the mixture heated over 1 hr to 100° and then maintained at 100–105° for 6 hr. The isolation procedure was analogous to that de-

scribed for the preparation of **9** from **7**. The yield was quantitative, and the purification procedure was analogous to that described for **9** (R = Cl; R^1 = H). Elemental analysis is given in Table III.

Dibenzo[*b*,*g*][1,8]naphthyridine-11,12(5,6H)-dione (14), Isomer of Epindolidione.—To 250 ml of boiling Dowtherm A was added 25 g of diethyl dianilinomethylenemalonate[27] in small portions over a period of 15 min. By the use of a Dean–Stark tube, provision was made for the removal of product ethanol. After completion of the addition, reflux was continued for 1 hr. After the mixture cooled to room temperature, the product was removed by filtration, washed with ethanol, and dried at 60°. The yield was 17.4 g (96.5%). A sample was recrystallized from acetic acid and found not to melt up to 400°.

Anal. Calcd for $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.68. Found: C, 73.30; H, 4.00; N, 10.84.

3-(2-Carboxyphenylamino)-4-quinolone (16).—A mixture of 30.4 g (0.19 mol) of 3-amino-4-quinolone, 38.0 g (0.19 mol) of *o*-bromobenzoic acid, 50.5 g (0.38 mol) of potassium carbonate, 0.5 g of spongy copper,[28] and 500 ml of amyl alcohol was refluxed for 4 hr and then steam distilled to remove the amyl alcohol. The resultant mixture was filtered hot, and the cooled filtrate was acidified with concentrated hydrochloric acid. The product was collected by filtration, then extracted with 500 ml of boiling water, filtered, washed free of acid, and dried at 80°. The yield was 34.7 g (69%). After recrystallization from methanol the melting point was 255–256° (lit.[4] mp 255°). Calcd: neut equiv, 280. Found: neut equiv, 278.

Epindolidione *via* 16. Aluminum Chloride Method I.—An intimate mixture of 70 g of aluminum chloride and **7** g of sodium chloride was heated to 130–135°. To the stirred molten mass was added 5.6 g of **16** in small portions. The mixture was heated at 200° for 3 hr, cooled to 130–135°, and cautiously poured over a mixture of 500 g of ice and 100 ml of concentrated hydrochloric acid. The slurry was heated at 95–100° for 15 min, and the yellow product was collected by filtration and washed free of acid and chloride ion with water. The wet solid was extracted with 100 ml of boiling 10% sodium carbonate, filtered, washed base free, and dried at 80°. The yield was 5.0 g (96.3%). The product showed an ir spectrum identical with that of **2** prepared *via* **5a**.

Epindolidione *via* 16. Polyphosphoric Acid Method II.—A mixture of 50 g of polyphosphoric acid and 5.0 g of **16** was heated with stirring at 200° for 6 hr. After it cooled to 40–50°, water was slowly added, maintaining the temperature at 50°, until the vigorous hydrolysis reaction had ceased, after which an excess of water was added. The mixture was heated to boiling and filtered hot. The product was washed free of acid with hot water. The wet solid was extracted with 100 ml of boiling 10% sodium carbonate, filtered, washed base free, and dried at 80°. The yield was 3.0 g (64.2%). The product showed an ir spectrum identical with that of **2** prepared *via* **5a**.

(27) W. Traube and A. Eyme, *Ber.*, **32**, 3176 (1899).

(28) R. Q. Brewster and T. Groening, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 446.

Registry No.—**2**, 17352-37-3; **5a** (Table I), 17540-23-7; **5b**, 17540-24-8; **5c**, 17540-25-9; **5d**, 17540-26-0; **5e**, 17540-27-1; **5f**, 17540-28-2; **5g**, 17540-29-3; **7a** (Table II), 16377-52-9; **7b**, 16479-61-1; **7c**, 17540-32-8; **7d**, 17540-33-9; **7e**, 16377-54-1; **7f**, 16427-99-9; **7g**, 16377-56-3; **8** (R = OCH_3; R′ = H), 16377-61-0; **9b** (Table III), 17352-38-4; **9c**, 17540-39-5; **9d**, 17341-72-9; **9e**, 17470-44-9; **9f**, 17352-60-2; **9g**, 17341-73-0; **14**, 3048-67-7.

Acknowledgment.—We are indebted to Dr. G. S. Hammond, Dr. R. C. Lord, and Dr. J. C. Sheehan for helpful comments.

Azecino[2,1-*a*]tetrahydroisoquinolines and Related Compounds. I. Reaction of 3,4-Dihydroisoquinolines with Nonenolizable β Diketones

MAXIMILIAN VON STRANDTMANN, CHESTER PUCHALSKI, AND JOHN SHAVEL, JR.

Organic Chemistry Department, Warner-Lambert Research Institute, Morris Plains, New Jersey 07950

Received December 1, 1967

3,4-Dihydroisoquinolines react with nonenolizable β diketones to give 1-(2-oxoalkyl- or -cycloalkyl)-N-acyl-1,2,3,4-tetrahydroisoquinolines (type **4** and **9**), and azecino[2,1-*a*]isoquinolines (type **3**), or other related large-ring compounds (**8**).

Recently, we have described the synthesis of benzo[*a*]quinolizines and dibenzo[*a*,*f*]quinolizines by the condensation of 3,4-dihydroisoquinolines with enolizable β diketones.[1] The present communication is concerned with the reaction of 3,4-dihydroisoquinolines with nonenolizable β diketones (Scheme I). In the course of this reaction the β diketone is cleaved, and the resulting oxoalkyl (or oxocycloalkyl) and acyl fragments alkylate and acylate the isoquinoline reactant at C-1 and N, respectively. Linear β diketones yield 1-(2-oxoalkyl)-N-acyl-1,2,3,4-tetrahydroisoquinolines (**9**, **10**), whereas β diketones of the acylcycloalkanone type give 1-(2-oxocycloalkyl)-N-acyltetrahydroisoquinolines (type **4a**, **b**) and azecino[2,1-*a*]isoquinolines (type **3**), or other related, large-ring compounds (**8**). For example, the reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline (**1**) with 2-acetyl-2-methylcyclohexanone (**2**) gave 5,6,10,11,12,13,15,15a-octahydro-2,3-dimethoxy-13-methyl-9H-azecino[2,1-*a*]-isoquinoline-8,14-dione (**3**) and two of the four possible stereoisomeric 2-acetyl-1-(3-methyl-2-oxocyclohexyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolines (**4a**, **b**). The pH dependence (the reaction is inhibited by alkali and strong acid) and the solvent dependence (rate increases with solvent polarity) are analogous to those observed in the reaction of 3,4-dihydroisoquinolines and enolizable β diketones.[1] This suggests that both reactions proceed by related mechanisms. Extension of this reaction to other dihydroisoquinolines and to 3,4-dihydro-β-carboline is summarized in Table I. The table also includes 3-phenyl-2,4-pentanedione (**10**), which in contrast to the other enolizable β diketones did not yield a benzo[*a*]quinolizine. Instead, it was cleaved analogously to nonenolizable β diketones. This may be a consequence of stabilization of the resulting anion by the phenyl group.

The structure of the large-ring compounds is based on the following evidence. The ultraviolet spectra are characteristic of the parent tetrahydroisoquinoline chromophores. The infrared spectra show bands typical of a ketone (1700–1705-cm^{-1} region) and an amide carbonyl (1620–1633-cm^{-1} region). The mono-

(1) M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., *J. Org. Chem.*, **31**, 797 (1965).