4,4′-Dinitro-2,2′-diphenic Anhydride.—As described previously, methyl 2-bromo-5-nitrobenzoate (130 g) and Cu powder (40 g) were allowed to react at 200–205° for 40 min giving 46 g (51.2%) of 4,4′-dinitro-2,2′-diphenic acid dimethyl ester which was refluxed for 26 hr in a mixture of AcOH (670 ml), H_2SO_4 (400 ml), and H_2O (200 ml) giving 35.8 g (85%) of the dinitrodiphenic acid, mp 255–257° dec (lit.[8] mp 257–258°). The diphenic acid (18.4 g) was then heated in an open flask with Ac_2O (100 ml) until the temperature of the mixture reached 160°. It was cooled and the product was separated by filtration, giving 14.5 g (83.5%), mp 231–233° (C_6H_6). *Anal.* ($C_{14}H_8N_2O_7$) C, H, N.

5,7-Dichlorofluoren-2-amine.—A mixture of 2,4-dichloro-7-nitro-9-oxofluorene[6a] (7.3 g), 85% $N_2H_4 \cdot H_2O$ (40 ml), and 2,2′-oxydiethanol (400 ml) was refluxed gently for 24 hr. The solution was evaporated until its temperature reached 210°. Upon H_2O dilution there was obtained 5.7 g (91%), mp 124–125° (EtOH). *Anal.* ($C_{13}H_9Cl_2N$) C, H, N.

***N*-2-Fluorenyl-4′,4″-dichloro-2′,2″-diphenamic Acid (Ia).**—Fluoren-2-amine (1.1 g), 4,4′-dichloro-2,2′-diphenic anhydride (1.8 g), and CH_2Cl_2 (175 ml) were refluxed for 24 hr and the mixture was stripped of solvent giving 2.9 g (100%), mp 132–135° (glassy melt). *Anal.* ($C_{27}H_{17}Cl_2NO_3$) C, H, Cl, N.

***N*-2-(5,7-Dichlorofluorenyl)-4′,4″-dichloro-2′,2″-diphenamic Acid (Ib).**—Similarly, 5,7-dichlorofluoren-2-amine (2.5 g) and 4,4′-dichloro-2,2′-diphenic anhydride (2.9 g) gave 5.3 g (98%), mp 256–261° dec (C_6H_6–CH_2Cl_2–Me_2CO). *Anal.* ($C_{27}H_{15}Cl_4NO_3$) C, H, Cl, N.

***N*-2-Fluorenyl-4′,4″-dinitro-2′,2″-diphenamic Acid (Ic).**—Fluoren-2-amine (1.8 g) and 4,4′-dinitro-2,2′-diphenic anhydride (3.1 g) were treated in like manner to give 4.8 g (98%), mp 259–260° (Me_2CO). *Anal.* ($C_{27}H_{17}N_3O_7$) C, H, N.

***N*-2-Fluorenyl-4′,4″-dichloro-2′,2″-diphenimide (IIa).**—Ia (1 g), freshly fused NaOAc (0.5 g), and Ac_2O (10 ml) were mixed and heated with vigorous shaking on a steam bath for 15 min, cooled, and the Ac_2O was destroyed with H_2O giving 0.9 g (94%), mp 311–312° (Me_2CO). *Anal.* ($C_{27}H_{15}Cl_2NO_2$) C, H, Cl, N.

***N*-2-(5,7-Dichlorofluorenyl)-4′,4″-dichloro-2′,2″-diphenimide (IIb).**—Likewise, Ib (1.5 g) and fused NaOAc (0.5 g) in Ac_2O (15 ml) gave 1.4 g (100%), mp 298–299° (AcOH). *Anal.* ($C_{27}H_{13}Cl_4NO_2$) C, H, Cl, N.

***N*-2-Fluorenyl-4′,4″-dinitro-2′,2″-diphenimide (IIc).**—Heating Ic (2.5 g) with NaOAc (0.5 g) in Ac_2O (15 ml) gave 2.4 g (100%), mp 302–303° (PhMe). *Anal.* ($C_{27}H_{15}N_3O_6$) C, H, N.

Acknowledgment.—We thank Miss Alice C. Lee for determining the ir spectra.

(8) R. Kuhn and O. Albrecht, *Justus Liebigs Ann. Chem.*, **455**, 272 (1927).

Synthesis of Potential Anticancer Agents. 5,12-Naphthacenequinones

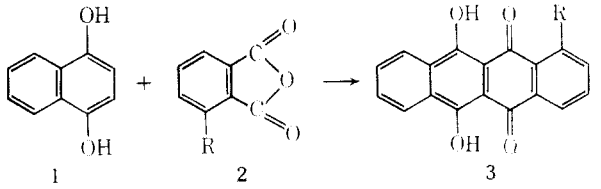
JACOB FINKELSTEIN AND JOHN A. ROMANO

Chemical Research Department, Hoffman-La Roche Inc., Nutley, New Jersey 07110

Received December 12, 1969

This report describes the syntheses and biological activities of several naphthacenequinones, an area of increasing interest.[1]

In a Friedel-Crafts type of reaction, 1,4-dihydroxynaphthalene (**1**) was allowed to react with several 3-substituted phthalic anhydrides (**2**) according to the B_2O_3 method of Weizmann and coworkers,[2] or in the presence of anhydrous $AlCl_3$, to give the compounds **3** listed in Table I.



1 2 3

a, R = NO_2
b, R = OCOCH$_3$
c, R = OH
d, R = NHCOCH$_3$
e, R = $(CH_3)_2N$
f, R = NH_2

TABLE I

INFRARED AND ULTRAVIOLET SPECTRAL DATA

No.	Derivative of 5,12-naphthacenequinone	$\nu_{C=O}$, cm^{-1}	λ_{max}, mμ (ε)
	5,12-Naphthacenequinone[a]	1680	265, 275, 293, 373, 395, 415, 440, 468 (7,400; 2,400; 1,200; 2,400; 4,500; 7,600; 9,900)
3	6,11-(OH)$_2$	1629, 1585	263, 452, 483, 515 (24,800; 5,200; 7,200; 6,800)
3c	1,6,11-(OH)$_3$	1600	265, 460, 490, 525 (54,000; 14,4000; 26,000; 26,800)
3a	1-NO$_2$-6,11-(OH)$_2$	1631, 1580	264, 487, 517 (47,900; 12,000; 8,700)
3f	1-NH$_2$-6,11-(OH)$_2$	1595	254, 374, 393, 507, 539 (50,800; 1,800; 1,900; 20,350; 21,600)
3d	1-AcNH-6,11-(OH)$_2$	1580 broad	248, 271, 468, 497, 534 (39,800; 54,200; 15,050; 26,300; 28,200)
3e	1-Me$_2$N-6,11-(OH)$_2$	1582, 1567	266, 520–530 sh, 550 (59,200; 16,000; 18,400)

[a] The authors are grateful to Dr. H. Vollmann, Bayer, A. G., Leverkusen, West Germany for an authentic sample of 5,12-naphthacenequinone, *Justus Liebigs Ann. Chem.*, **669**, 43 (1963).

For preparation of the larger amounts of **1** required, we found that the Fieser[3] method of reductive acetylation of naphthoquinone followed by hydrolysis was rather tedious. We discovered that 1,4-dihydroxynaphthalene (**1**) could be prepared easily and in good yield by hydrogenation of naphthoquinone at low pressure.

When **2** (**a**,**c**,**d**) was fused with **1** at 190° in the presence of B_2O_3, the corresponding **3** was obtained. However, when **2b** was used under similar conditions, *in situ* deacetylation took place, and the resulting 1,6,11-trihydroxynaphthacenequinone (**3c**) was obtained, identical with the product obtained from **1** and **2c**. Upon hydrolyzing 1-acetamido-6,11-dihydroxynaphthacenequinone (**3d**) in HCl, 1-amino-6,11-dihydroxynaphthacenequinone (**3f**) was obtained. Compound **3e** was prepared by the $AlCl_3$ fusion procedure of **1** with 3-dimethylaminophthalic anhydride (**2e**), which was

(1) (a) F. Arcamone, C. Franceschi, P. Orezzi, and S. Penco, *Tetrahedron Lett.*, 3349 (1968); (b) J. R. D. McCormick, J. Reichenthal, S. Johnson, and N. O. Sjolander, *J. Amer. Chem. Soc.*, **85**, 1694 (1963); (c) H. Brockmann and J. Niemeyer, *Chem. Ber.*, **101**, 2409 (1968); (d) H. Brockmann, R. Kunker, and H. Brockmann, Jr., *Justus Liebigs Ann. Chem.*, **696**, 145 (1966), and other references cited therein.

(2) C. Weizmann, L. Haskelberg, and T. Berlin, *J. Chem. Soc.*, 398 (1939).

(3) L. Fieser, *J. Amer. Chem. Soc.*, **70**, 3165 (1948).

obtained by the reductive methylation of 3-nitrophthalic acid followed by thermal dehydration.

The CO ir stretching frequencies of the naphthacenequinones are listed in Table I. There is a marked lowering as a result of the substitutions in the molecular environment. This shift is consistent with that observed in the related hydroxyquinones,[4] hydroxynaphthoquinones,[5] and hydroxyanthraquinones.[6]

The uv data listed in Table I reveal the bathochromic shift upon the introduction of the substituents adjacent to the quinoid nucleus of the naphthacenequinones. This shift is also in agreement with the reported findings for hydroxnaphthoquiones[7] and hydroxyanthraquinones.[8]

Biological Results.—The oral LD_{50} of **3c**, **d**, and **e**, as determined in mice, was >2000 mg/kg po, while **3f** had an LD_{50} of >4000 mg/kg po. Intraperitoneally the LD_{50} for **3c**, **d**, and **f** were >2000, >2000, and >1000 mg/kg, respectively. Compounds **3c**, **d**, **e**, and/or **f** showed no significant activity against *Diplococcus pneumonia* type I,[9] *Streptococcus pyogens*,[9] *Salmonella schottmuelleri*,[9] and *Candida albicans*[9] at 500–1000 mg/kg po.

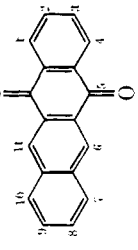
Compound **3c** exerted marked activity against the solid form of Ehrlich carcinoma[10] but was inactive against Sarcoma 180 and Ehrlich ascites.[10] Compound **3d** demonstrated a slight but definite activity against Sarcoma 180[10] and Ehrlich solid carconoma[10] but was inactive against leukemia L1201 ascites.[10] Compound **3c** was ineffective against Ehrlich ascites;[10] **3f** was appreciably active against Sarcoma 180[10] and Ehrlich solid carcinoma.[10]

Experimental Section

Melting points were determined on an electro-thermal melting point apparatus and are corrected. Ir spectra were determined in KBr on a Beckman IR-5 double beam spectrophotometer with NaCl optics. Uv spectra were determined in *i*-PrOH on a Cary spectrophotometer (Model 14M). Where analyses are indicated by the elements, results obtained were within ±0.4% of the theoretical values. Since our main objective was to obtain material for preliminary screening purposes, no attempt was made to optimize the yields. The properties of the naphthacenequinones prepared are listed in Table II.

1,4-Dihydroxynaphthalene (1).—A solution of 25 g of 1,4-naphthoquinone (Tech)[11] in 130 ml of DMF was stirred and warmed gently with charcoal for 1 hr and filtered. The filtrate was hydrogenated under 3 atm of H_2 over 0.5 g of PtO_2, and the H_2 uptake was rapid. After filtering the catalyst, the solution was evaporated to dryness *in vacuo* under N_2. The residue was triturated with H_2O, filtered, and recrystallized from boiling H_2O containing a small amount of $SnCl_2$ and HCl. Upon cooling, the product was obtained as colorless glistening needles: mp 188–190°; yield 20 g (79%). *Anal.* ($C_{10}H_8O_2$) C, H.

TABLE II
5,12-NAPHTHACENEQUINONE DERIVATIVES



5,12-Naphthacenequinones	No.	Reactant(s)	Catalyst	Yield, %	Mp, °C	Recrystn solvent	Color	Formula	Analyses
6,11-$(OH)_2$-1-NO_2	3a	1 + 2a	B_2O_3	15	348–350	$C_2H_4Cl_2$	Red	$C_{18}H_9NO_6$	C,[a] H, N[a]
1,6,11-$(OH)_3$[b]	3c	1 + 2b; 1 + 2c	B_2O_3	8.2; 11.4	298–300	$C_6H_5NO_2$ or DMF	Red	$C_{18}H_{10}O_5$	C, H
1-NHAc-6,11-$(OH)_2$	3d	1 + 2d	B_2O_3	40	232–234	DMF	Red-brown	$C_{20}H_{13}NO_5$	C, H, N
1-NH_2-6,11-$(OH)_2$	3f	3d	HCl	64	292	EtOH	Red	$C_{18}H_{11}NO_4$	C, H, N
1-Me_2N-6,11-$(OH)_2$	3e	1 + 2e	$AlCl_3$	35	196–198	DMF + H_2O	Red	$C_{20}H_{15}NO_4$	C, H, N

[a] C: calcd, 64.45; found, 63.96; N: calcd, 4.18; found, 3.70. [b] Prepared in 8% yield by H. Brockmann and W. Muller, *Chem. Ber.*, **92**, 1164 (1959) by treating **1** and **2c** with $AlCl_3$–NaCl at 200–240° for 1 hr.

(4) A. W. Johnson, J. R. Quayle, T. S. Robinson, N. Sheppard, and A. R. Todd, *J. Chem. Soc.*, 2633 (1951).
(5) M. Jasien, N. Fuson, J. Lebas, and T. M. Gregory, *J. Chem. Phys.*, **21**, 331 (1953).
(6) R. H. Howard and H. Raistrick, *Biochem. J.*, **59**, 475 (1955); M. St. C. Flett, *J. Chem. Soc.*, 1441 (1948); H. Bloom, L. H. Briggs, and B. Cleverly, *ibid.*, 178 (1959).
(7) R. A. Morton and W. T. Earlam, *ibid.*, 159 (1941).
(8) H. Birkinshaw, *Biochem. J.*, **59**, 485 (1955); A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Compounds," Pergamon Press, New York, N. Y., 1964, p 291.
(9) E. Grunberg, J. Berger, G. Beskid, R. Cleeland, H. N. Prince, and E. Titsworth, *Chemotherapia*, **12**, 272 (1967).
(10) E. Grunberg, H. N. Prince, E. Titsworth, G. Beskid, and M. D. Tendler, *ibid.*, **11**, 249 (1966).
(11) Distillation Products Industries, Eastman Organic Chemicals Department, Rochester, N. Y. 14603.

Synthesis of 5,12-Naphthacenequinones with Boric Anhydride.—Compound **1** was treated with a slight excess of **2a**,[11] **2b**,[12] **2c**,[12] and **2d**[13] in the presence of a 50% mol excess of B_2O_3 at 190° for 2 hr. The solid mass was pulverized and extracted with several portions of boiling H_2O, filtered, washed with EtOH, dried, and recrystallized. Table I lists the pertinent data for the compounds.

1-Amino-6,11-dihydroxy-5,12-naphthacenequinone (3f).—Compound **3d** (2 g) was hydrolyzed by refluxing in 20 ml of concd HCl for 2 hr. When cool, a reddish crystalline product was obtained and recrystallized.

3-Dimethylaminophthalic Acid.—A solution of 10.55 g of 3-nitrophthalic acid and 10 ml of formalin in 160 ml of EtOH was reduced under 3 atm of H_2 in the presence of 0.5 g of PtO_2 until the theoretical amount was absorbed. The filtered solution was evaporated *in vacuo*, and the solid recrystallized from EtOH as yellow crystals: mp 138–140°; yield 6.5 g (65%). *Anal.* ($C_{10}H_{11}NO_4$) C, H, N.

3-Dimethylaminophthalic Anhydride (2e).—3-Dimethylaminophthalic acid (3 g) was heated at 150–160° for 0.5 hr, cooled, and the product recrystallized from C_6H_6: mp 140–142°; yield 2.4 g (89%). *Anal.* ($C_{10}H_9NO_3$) C, H, N.

Synthesis of 6,11-Dihydroxy-1-dimethylamino-5,12-naphthacenequinone (3e).—An intimately ground mixture of 7.6 g of **2e** and 6.4 g of **1** was added portionwise during 1 hr to a molten mixture of 53.3 g of anhyd $AlCl_3$ and 11.7 g of NaCl at 150°. The temperature was then raised to 220°, and maintained for 0.5 hr. When cool, the fused mass was pulverized with a mixture of 500 ml of H_2O and 500 ml of concd HCl, and the mixture refluxed for 4 hr to decompose the complex. After cooling, an ash-free product was obtained, and recrystallized from DMF plus a small amount of H_2O. *Anal.* ($C_{25}H_{15}NO_4$) C, H, N.

Acknowledgment.—We are indebted to Dr. Al Steyermark and his staff for the microanalyses, to Dr. V. Toome for the ultraviolet spectra, and to Mr. S. Traiman for the infrared spectra and for their interesting discussions. The biological data were obtained under the direction of Dr. E. Grunberg, Director of the Department of Chemotherapy.

(12) H. Muklemann, *Pharm. Acta Helv.*, **23**, 257 (1948).
(13) C. L. Eliel, A. W. Burgstahler, D. E. Rivard, and L. Haefele, *J. Amer. Chem. Soc.*, **77**, 5092 (1955).

Reduction of 1-(4-Dimethylaminobenzylidene)indene[1a,1b]

Carl T. Bahner,[1c] David Brotherton, Thomas Harmon,

Department of Chemistry, Carson-Newman College, Jefferson City, Tennessee 37760

and B. L. Stump

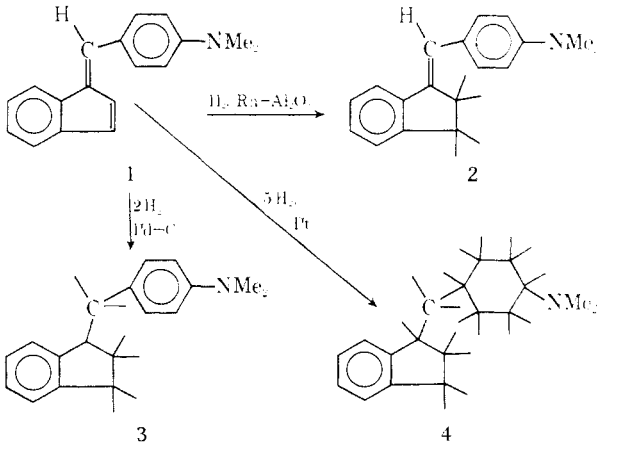
Department of Chemistry, Virginia Commonwealth University, Richmond, Virginia 23220

Received May 19, 1969

The synthesis of 1-(4-dimethylaminobenzylidene)-indene (**1**) was reported[2] recently as a result of our continuing search for compounds which have antitumor activity. Compound **1** was found to have definite effect against the Walker 256 tumor in rats, but the rats which recovered from their tumors sometimes developed mammary tumors, an effect noted particularly in female rats.[3] Further investigation revealed that tumors developed also in healthy rats treated with **1**.[4]

In an attempt to diminish or exclude the carcinogenic effect and at the same time retain the antitumor activity, various reduced derivatives were prepared by the catalytic hydrogenation of **1** (Scheme I). Based

Scheme I



on the amount of H_2 consumed in each reaction, structures **2**, **3**, and **4** represent the expected products. Analyses confirmed the postulated structures. Changes in the nmr spectra in going from **1** to **2**, **3**, and **4** are in agreement with those expected for the structures shown.

These compounds were tested against the Walker tumor by the single i.p. dose method. Compound **2** showed a slight antitumor activity, but **3** and **4** showed no antitumor effect. We conclude that the conjugated double bond system is necessary for antitumor activity in compounds of this type.

Experimental Section[5]

α-1-Indanylidene-*N*,*N*-dimethyl-*p*-toluidine (2).—Compound **1** (5.0 g, 0.02 mol) in 100 ml of EtAc was hydrogenated over 0.5 g of 5% Rh–Al_2O_3. The reaction stopped after *ca.* 1.3 mol of H_2/mol of **1** had been absorbed. The catalyst and solvent were removed and the residue was recrystallized from *i*-C_4H_{11} and MeOH. A 54% yield of a pale yellow solid, mp 123°, was recovered. *Anal.* ($C_{18}H_{19}N$) C, H.

α-1-Indanyl-*N*,*N*-dimethyl-*p*-toluidine (3).—Compound **1** (5.0 g, 0.02 mole) in 100 ml of EtAc was hydrogenated over 0.5 g of 5% Pd–C. The reaction stopped after exactly 2 mol of H_2/mol of **1** had been absorbed. The catalyst and solvent were removed and the residue was recrystallized from MeOH. An almost 100% yield of an off-white crystalline solid was obtained, mp 36.5–37.0°. *Anal.* ($C_{18}H_{21}N$) C, H.

4-(1-Indanylmethyl)-*N*,*N*-dimethylcyclohexylamine (4).—Compound **1** (20 g, 0.08 mol) in 200 ml of HOAc was hydrogenated over 0.5 g of Adams' Pt (PtO_2). The reaction stopped when

(1) (a) This investigation was supported in part by Public Health Service Research Grants CA-03717-09-10. (b) Presented before the Division of Organic Chemistry at the 29th Southeastern Regional Meeting of the American Chemical Society, Tallahassee, Florida, December, 1968. (c) To whom inquiries should be addressed.

(2) C. T. Bahner, H. Kindler, D. Brotherton, J. Spiggle, and L. Gutman, *J. Med. Chem.*, **8**, 390 (1965).

(3) R. M. Folk and M. A. Sheridan, *Proc. Amer. Ass. Cancer Res.*, **9**, 23 (1968).

(4) F. J. C. Roe, R. L. Carter, and N. A. Barron, *Nature*, **222**, 383 (1969).

(5) Melting points were determined in an oil bath and are uncorrected. Elemental analyses were carried out by Galbraith Microanalytical Laboratory, Knoxville, Tenn. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.3% of the theoretical values. Uv spectra were determined in CH_3OH on a Perkin–Elmer Model 202 spectrophotometer, ir spectra in KBr, except **4**, which was taken as a thin film on a NaCl crystal; a Perkin–Elmer Model 337 spectrophotometer was used. Reactions were carried out in a standard Parr hydrogenator which has been calibrated, so that in the pressure range 2.8–3.5 kg/cm², a H_2 pressure drop of 0.57 kg/cm² corresponded to an uptake of 0.1 mol of H_2.