value of 12.34 shows that it is more than 800,000 times as basic as any of the less N-methylated derivatives of 1,8-diaminonaphthalene.[18]

Experimental Section

Chemicals. The synthesis and properties of the *N,N*,2-trimethyl-1,3-propanediamine, *N,N*,2,2-tetramethyl-1,3-propanediamine, *N,N,N',N'*,2,2-hexamethyl-1,3-propanediamine, *cis-* and *trans*-2-(dimethylaminomethyl)cyclohexylamine, the 3-dimethylaminomethyl-2-norbornanamines, *o*-(dimethylaminomethyl)benzylamine, and *o*-bis(dimethylaminomethyl)benzene used have been described recently.[19] The other compounds were commercial products.

p*K* Determinations. The diamines and *N,N*-dimethylcyclohexylamine were titrated with standard 0.10 *M* hydrochloric acid in aqueous solution at 35.0 ± 0.5° using a Radiometer Model 26 pH meter and type G202B and K401 glass and reference electrodes. The pH values were read to 0.001 from the meter after the stirrer had been turned off. Values obtained when 0.2–0.8 and 1.2–1.8 equiv of acid had been added were used in a computer program[20] that obtained the p*K* values that minimized the sums of the squares of the deviations of the calculated from the observed pH values, of which there were usually about 25. In no case was the standard deviation as large as 0.040. The 20-, 25-, or 30-ml samples of 0.020 ± 0.005 *M* amine solutions titrated gave ionic strengths in the range 0.003–0.016 during the first half of the titration, which largely determined the value of pK_1, and 0.018–0.045 during the second half, which largely determined pK_2. The pH was taken to be $-\log a_{H^+}$ and ionic activity coefficients were calculated from the Davies equation.[6]

The p*K* for 2-*endo*-norbornanamine was determined analogously except that 0.040 *M* amine hydrochloride was titrated with 0.10 *M* sodium hydroxide.

^{1}H Nuclear Magnetic Resonance Measurements. All ^{1}H NMR measurements were made at about 37° in H_2O using a Varian A-60A spectrometer except in the case of the measurements on the methylene protons of *N,N,N',N'*-tetramethyl-1,3-propanediamine, which were made in D_2O at about 31° using a JEOL JNM-MH-100 instrument to minimize complications arising from spin–spin splitting and overlap with other peaks. All the amines were studied at a total concentration of 0.1 *M* except in the case of *o*-bis(dimethylaminomethyl)benzene, 3-*endo*-dimethylaminomethyl-2-*endo*-norbornanamine, and the methylene proton study of *N,N,N',N'*-tetramethyl-1,3-propanediamine, where concentrations of 0.04–0.05 *M* were used. In the case of the 3-*endo*-dimethylaminomethyl-2-*endo*-norbornanamine 20% methanol was added to increase the solubility of the amine. In all other cases 0.1–0.5 *M* methanol was used as an internal reference. The concentrations of the three forms of the diamines present were calculated from the concentrations of amine and hydrochloric or perchloric acid used to make up the solutions and the p*K* values at 35°. This resulted in values of f_m and f_d that were combined with the δ'_{obsd} values to calculate the values of δ_0, δ_m, and δ_d shown in Table III by the method of least squares.

Calculation of Micro p*K* Values for Primary–Tertiary Diamines. These calculations may be illustrated by the case of *trans*-2-(dimethylaminomethyl)cyclohexylamine. For pK_{TPH} we start with the p*K* of 10.27 for a cyclohexylamine (or $RCH_2CH_2NH_2$). A contribution of −0.20 is added because the primary amino group has a single β branch (not held away with a dihedral angle of 120° or more). Finally, −0.52 is added for the effect of the dimethylamino substituent three carbons away from the primary amino group. For pK_{HTP} the uncorrected value is 9.81, −0.07 is added because of the single branch β to the dimethylamino group, and −0.42 is added because of the primary amino group three carbon atoms away. The resulting pK_{TPH} and pK_{HTP} values of 9.55 and 9.32, respectively, and the experimentally determined value 10.29 for pK_1 (from Table I) give *K* values that leave K_{THP} as the only unknown in eq 5. The value 10.14 thus obtained for pK_{THP} is then used to calculate f_c, which may be seen to be equal to K_1/K_{THP}. Similarly, f_t is equal to K_1/K_{HTP} and f_p to K_1/K_{TPH}.

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9,9'-Dianthrylmethane Derivatives. Conjugate Rearrangements and Photocyclizations

Douglas E. Applequist* and Daniel J. Swart

Department of Chemistry, University of Illinois, Urbana, Illinois 61801

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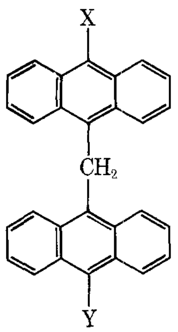
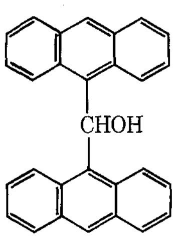
Attempted preparation of di-9-anthrylmethane and its brominated derivatives led to the discovery of incorrect structural assignments in previous work. The successful preparation of 9,9'-dianthrylmethane derivatives is reported, and the photocyclization of some of them is described.

It was earlier reported from this laboratory that 9,9'-dianthrylmethane (**1a**) had been prepared by catalytic hydrogenolysis of 9,9'-dianthrylcarbinol (**2**) using 5% palladium on carbon in ethanol.[1] The preparation has since been found unreproducible (yields of zero to 9%) and alternatives have therefore been sought. A satisfactory two-step procedure has been found, the first step being reduction of **2** with a 2:1 mixture of aluminum chloride and lithium aluminum hydride in ether to give **3a**, an isomer of **1a**, in 94% yield, and the second step being the isomerization of **3a** to



1a, X = Y = Br
b, X = H; Y = Br
c, X = Y = Br
d, X = Y = Cl



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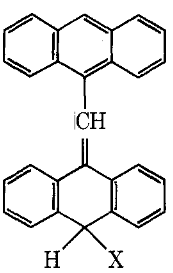


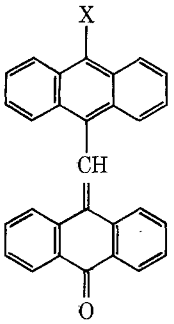
3a, X = H
b, X = OC_2H_5
c, X = Cl

1a in 94% yield with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol or potassium hydroxide in refluxing isoamyl alcohol.[2]

Unfortunately, neither **1a** nor **3a** as prepared by the present method is the same as the substance previously assigned structure **1a**. The respective melting points are 315–317°, 189–191° dec, and 382–384° dec. The infrared spectra are all distinctly different. Both **1a** and **3a** (present report) show parent mass peaks at *m/e* 368. **1a** shows an anthracene chromophore in the uv with nearly twice the intensity of that in **3a**: for **1a**, λ_{max} 339 nm (ϵ 4400), 357 (8500), 376 (15,000), and 396 (17,000); for **3b**, λ_{max} 338 nm (sh) (ϵ 2700), 357 (5500), 375 (8900), and 394 (9500). The ^1H NMR spectrum of **1a** shows two two-proton singlets, at δ 5.60 (for $-CH_2-$) and 8.04 (for the 10 and 10′ positions). The ^1H NMR spectrum of **3a** shows a two-proton singlet at δ 4.19 (for $-CH_2-$) and two one-proton singlets at δ 7.68 and 8.39 (assigned respectively to the central vinyl proton and the 10-anthryl proton). These data appear consistent only with the structures assigned.[3]

Two other examples of the facile formation of the 9-(9-anthrylmethylidene)-9,10-dihydroanthracene system were discovered during attempts to prepare **1a**. In the first, **2** reacted with zinc chloride in ethanol to give ether **3b** under conditions where triphenylcarbinol gives triphenylmethane.[4] In the second, **2** reacted with thionyl chloride and pyridine in benzene to give chloride **3c**. The structures of **3b** and **3c** are assigned primarily from the ^1H NMR spectra, which show singlets for the vinyl proton at about δ 7.7, as in **3a**, and which show appropriately downshifted methine protons α to ethoxy and chlorine at δ 5.62 and 6.13, respectively, to be compared with the methylene signal at δ 4.19 in **3a**. For comparison, the corresponding signals in fluorene, 9-methoxyfluorene, and 9-chlorofluorene are at δ 3.90, 5.59, and 5.80, respectively.[5]

Our particular reason for repeating the earlier preparation of **1a** was to reinvestigate the bromination of that hydrocarbon.[1] It had been reported that monobromo compound **1b** was easily formed, while dibromination, to form **1c**, was much slower. Since the wrong compound was brominated in that study, the result is not necessarily a surprising one. In fact, it has now been shown that **1a** is readily dibrominated with bromine in carbon tetrachloride to form **1c** in 22% yield. No **1b** was found, but a 22% yield of bromo ketone **4** was isolated, presumably arising from an air oxidation. Compound **4** was independently prepared by reaction of ketone **5** with cupric bromide in refluxing chlorobenzene, and **5** was in turn prepared by the permanganate oxidation of **3a** (39% yield, along with 53% of anthraquinone). Comparison of infrared and NMR spectra revealed that the substance assigned structure **1a** in the earlier report was probably an impure form of **4**.

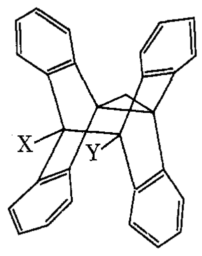


4, X = Br
5, X = H

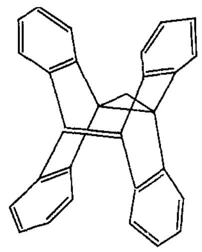
10-Bromo-9,9′-dianthrylmethane (**1b**) was not obtained by bromination of **1a**, but was independently prepared by coupling of 9-bromo-10-lithioanthracene with 9-chloromethylanthracene. Bromination of **1b** in carbon tetrachloride yielded 43% dibromide **1c** and 3% ketone **4**.

Also prepared in the present study was the dichlorodianthrylmethane **1d**, from reaction of 9-chloroanthracene with paraformaldehyde and hydrogen chloride in acetic acid (42% yield). A similar preparation of **1c** gave only a 10% yield.

Having the authentic dianthrylmethanes **1a–d**, it was next desirable to reinvestigate their photocyclization reactions, which had previously[1] been examined on the wrong compounds. It was found that **1a** and **1b** in benzene solution readily underwent photocyclization to the typical anthracene photodimer structures, **6a** and **6b**. These were colorless solids which reverted to **1a** and **1b** upon melting or refluxing in benzene. The uv spectra show only the typical *o*-xylene chromophores.[6] Substances **1c** and **1d** did not yield photoproducts, which is in accord with the fact that no dianthracene with vicinal bridgehead halogens has been reported.



6a, X = Y = H
b, X = H; Y = Br



7

Compound **6b** is of special interest as a possible precursor of the bridgehead alkene **7**. In fact, dehydrohalogenation with *tert*-butoxide, trapping of **7** with azide ion, and regeneration of **7** through the elegant procedure of Greene[7] did yield a colorless solid having the expected molecular weight (mass spectrum). It will be the subject of a future report.

Experimental Section

All melting points were determined on a Buchi melting point apparatus and are uncorrected. Infrared (ir) spectra were recorded on a Perkin-Elmer Model 521 grating Infracord or on a Beckman IR12 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on Varian T-60, A-60A, HA-100, or HR-220 instruments. Chemical shifts are expressed in parts per million (ppm) relative to tetramethylsilane used as internal standard and assigned the value δ 0 ppm. Ultraviolet (uv) spectra were recorded on a Cary 14 or Beckman DB spectrophotometer. Mass spectra were run on a Varian MAT CH-5 spectrometer. Microanalyses were performed by Mr. J. Nemeth and his associates.

All chemicals and solvents were reagent grade unless otherwise noted and were used without further purification except as noted.

10-Ethoxy-9-(9-anthrylmethylidene)-9,10-dihydroanthra-

cene (3b). A mixture of 0.78 g (0.00203 mol) of 9,9′-dianthrylcarbinol (2)[1] and 2.77 g (0.0203 mol) of zinc chloride in 15 ml (0.256 mol) of absolute ethanol was magnetically stirred and heated at reflux for 1.5 hr. The mixture was cooled and 12 ml of aqueous hydrochloric acid (1:5) was added to remove any solid zinc chloride. The organic material was extracted with diethyl ether, the extract was washed with water, dried ($MgSO_4$), and filtered, and the solvent was removed to give 0.762 g of a yellow oil. Separation on a silica gel column with 1:1 benzene–hexane gave 0.6 g (72%) of a yellow solid, mp 149–151°. Recrystallization from benzene–hexane gave 0.45 g (54%) of yellow crystals of **3b**: mp 150.5–151.5°; ir (KBr) 3050 (m), 2975 (m), 2890 (m), 1620 (w), 1480 (m), 1455 (m), 1440 (m), 1120 (m), 1070 (s), 780 (m), 760 (s), 730 cm^{-1} (s); NMR ($CDCl_3$) δ 1.34 (t, 3, J = 6 Hz, $-CH_2CH_3$), 3.61 (q, 2, J = 6 Hz, $-CH_2CH_3$), 5.62 (s, 1, 10 proton of 9,10-dihydroanthracene ring), 6.32–6.59 (m, 2, aromatic protons), 6.75–7.62 (m, 10, aromatic protons), 7.72 (s, 1, vinyl proton), 7.80–8.14 (m, 4, aromatic protons), 8.29 (s, 1, 10 proton of anthracene nucleus).

Anal. Calcd for $C_{31}H_{24}O$: C, 90.26; H, 5.86. Found: C, 90.30; H, 5.84.

10-Chloro-9-(9-anthrylmethylidene)-9,10-dihydroanthracene (3c). A solution of 2.0 g (0.0052 mol) of 9,9′-dianthrylcarbinol (2) in 100 ml of warm benzene was added dropwise over 30 min to a stirred solution of 1.66 g (0.014 mol) of thionyl chloride and 3 drops of pyridine in 25 ml of benzene. The mixture was stirred at room temperature for 2 hr and then reluxed for 40 min. The solvent and thionyl chloride were removed in vacuo from the cooled mixture to give a yellow oil. Crystallization with hexane and recrystallization from benzene–hexane gave 1.06 g (51%) of a yellow solid: mp 196–198° dec (lit.[8] mp 190–192°); ir (KBr) 3050 (m), 1620 (m), 1470 (m), 1450 (m), 1440 (m), 885 (m), 840 (m), 785 (m), 770 (s), 635 cm^{-1} (m); NMR ($CDCl_3$) δ 6.13 (s, 1, 10 proton of the 9,10-dihydroanthracene nucleus), 6.30–6.58 (m, 2, aromatic protons), 6.68–7.73 (m, 10, aromatic protons), 7.78 (s, 1, vinyl proton), 7.87–8.25 (m, 4, aromatic protons), 8.28 (s, 1, 10 proton of anthracene nucleus).

9-(9-Anthrylmethylidene)-9,10-dihydroanthracene (3a). To a magnetically stirred suspension of 0.2 g (0.0052 mol) of lithium aluminum hydride in 10 ml of dry ether was added a solution of 1.41 g (0.0106 mol) of aluminum chloride in 15 ml of dry ether. Dry ether (15 ml) was added to the flask and a Soxhlet thimble containing 1.0 g (0.0026 mol) of 9,9′-dianthrylcarbinol (2) was placed in the extraction apparatus. The stirred mixture was heated to reflux (50–54°) for 10 hr, or until the carbinol had been introduced into the reaction flask. Ethyl acetate was added dropwise to destroy excess reagent and the mixture was poured into 30 ml of 20% sulfuric acid. The mixture was filtered, the layers were separated, the water layer was washed once with ether, the ether layer was washed twice with water, dried ($MgSO_4$), and filtered, and the ether was removed in vacuo to give 0.9 g (94%) of a yellow solid, mp 183–188° dec. Two recrystallizations from ethanol–benzene gave 0.64 g (80%) of a yellow solid: mp 189–191° dec; ir (KBr) 3050 (m), 3020 (m), 2930 (w), 2850 (w), 2180 (w), 1620 (w), 1475 (m), 1455 (ms), 1440 (w), 1345 (m), 880 (ms), 845 (m), 780 (s), 730 (s), 710 cm^{-1} (m); 100-MHz NMR (CCl_4) δ 4.19 (s, 2, $-CH_2-$), 6.34–6.62 (m, 2, aromatic protons), 6.92 [doublet (J = 2 Hz) of triplets (J = 7 Hz), 1, aromatic proton)], 7.18–7.58 (m, 8, aromatic protons), 7.68 (s, 1, vinyl proton), 7.94–8.28 (m, 5, aromatic protons), 8.39 (s, 1, meso proton on anthracene nucleus); uv ($CHCl_3$) 259 nm (ϵ 84,000), 338 sh (2500), 354 (4900), 372 (7500), 391 (7900); mass spectrum (70 eV) *m/e* (rel intensity) 369 (29), 368 (100), 367 (26), 365 (13), 363 (12), 353 (12), 339 (11), 289 (13), 191 (11), 190 (10), 189 (17), 184 (13), 177 (5), 176 (11).

Anal. Calcd for $C_{29}H_{20}$: C, 94.53; H, 5.47. Found: C, 94.63; H, 5.54.

In a few runs an insoluble yellow solid which did not melt below 360° was isolated. Combustion of the material left a white solid which gave a positive test for the aluminum ion when treated with aluminon reagent.[9]

9,9′-Dianthrylmethane (1a) from Reduction of 3c. A solution of 0.91 g (0.0023 mol) of **3c** in 30 ml of dry tetrahydrofuran was added dropwise over 15 min to a magnetically stirred solution of 0.1 g (0.0029 mol) of lithium aluminum hydride in 10 ml of dry tetrahydrofuran at room temperature. The mixture was stirred and heated at reflux for 45 min, then cooled to room temperature, and wet tetrahydrofuran and ethyl acetate were added until foaming stopped. The solution was filtered and the gray precipitate was washed with tetrahydrofuran and toluene. To the filtrate was added 250 ml of toluene, the solution was dried ($MgSO_4$) and filtered and the solvents were removed in vacuo to give 0.814 g of a yellow solid. The yellow solid was partially dissolved in diethyl ether to give a greenish-yellow solution plus a bright yellow precipitate. The solid was washed with ether and benzene until the filtrate showed no color. The filtrate was evaporated to give 0.617 g (73%) of a yellow solid, mp 181–186° dec. The solid was recrystallized from ethanol–benzene to give 0.43 g (51%) of a yellow solid, mp 188–190° dec, shown by ir (KBr) and melting point comparison with an authentic sample to be the hydrocarbon **3a.**

The bright yellow precipitate isolated in the filtration (0.16 g, 19%) melted at 313–316°. The solid was recrystallized several times from benzene or tetrahydrofuran to give bright yellow needles of 9,9′-dianthrylmethane (**1a**): mp 315–317°; ir (KBr) 3050 (m), 1620 (m), 1520 (m), 1445 (w), 1340 (m), 955 (m), 880 (s), 870 (m), 735 (s), 725 (s), 530 (m), 495 cm^{-1} (m); 220-MHz NMR (CCl_4) (200 250-sec scans, computer averaged, 81°) δ 5.60 (s, 2, $-CH_2-$), 6.95 (m, 8, aromatic protons), 7.65 (d, 4, aromatic protons), 7.94 (d, 4, aromatic protons), 8.04 (s, 2, 10-protons); uv ($CHCl_3$) 254 nm sh (ϵ 84,000), 260 (92,000), 322 sh (1900), 336 (4400), 353 (8500), 372 (15,000), 394 (17,000); mass spectrum (70 eV) *m/e* (rel intensity) 369 (31), 368 (100), 367 (23), 353 (18), 352 (10), 291 (8), 290 (7), 289 (10), 191 (31), 190 (22), 189 (39), 184 (12), 177 (9), 176 (14).

Anal. Calcd for $C_{29}H_{20}$: C, 94.53; H, 5.47. Found: C, 94.30; H, 5.55.

9,9′-Dianthrylmethane (1a) from Isomerization of 3a. A mixture of 4.26 g (0.109 g-atom) of freshly cut potassium in 60 ml of dry *tert*-butyl alcohol (freshly distilled from sodium) was refluxed under nitrogen for about 4 hr until all the potassium dissolved. Addition of 0.568 g (0.00154 mol) of hydrocarbon **3a** to the refluxing solution resulted in almost immediate formation of an insoluble, highly fluorescent, yellow solid. The mixture was refluxed for 48 hr.

The mixture was cooled to room temperature and 10 ml of wet *tert*-butyl alcohol was added to the mixture, followed by 10 ml of water. The mixture was filtered through a sintered glass funnel and the precipitate was washed with water and ether several times. The precipitate was dried in vacuo to give 0.159 g (91.5%) of 9,9′-dianthrylmethane (**1a**), mp 312–316°. Recrystallization from tetrahydrofuran gave yellow needles, mp 315–317°. The ir (KBr) spectrum matched that of **1a** formed in the preceding method.

The isomerization was also successfully performed in a 10% solution of KOH in isoamyl alcohol at reflux for 1.5 hr to give a 93% yield, mp 312–314°, or 73%, mp 313–315° after recrystallization from toluene.

10-(9-Anthrylmethylidene)anthrone (5). A mixture of 0.7 g (0.0019 mol) of hydrocarbon **3a** and 8.0 g (0.0564 mol) of sodium permanganate in 150 ml of dioxane and 100 ml of water was mechanically stirred at 48–51° for 4 hr. The mixture was cooled to 25° and filtered. The solid manganese dioxide was washed several times with benzene and ether and then extracted with benzene in a Soxhlet extractor for 4 hr. The organic layers were combined and after separation the water layer was extracted with benzene, the combined organic layers were dried ($MgSO_4$) and filtered, and the solvents were removed to give a mixture of orange and yellow solids.

Ether extraction of the mixture afforded an orange solution and left a light yellow solid. The yellow solid was shown to be 0.424 g (53.2% based on 2 mol/1 mol of **3a**) of anthraquinone, mp 285–287° (lit.[10] mp 286°). The ir (KBr) spectrum matched that recorded for anthraquinone.[11]

The ether extract yielded 0.29 g (39.3%) of the ketone **5**: mp 253–255° dec; 100-MHz NMR ($CDCl_3$) δ 6.60–6.76 (m, 2), 7.05–8.41 (several complex multiplets, 15), 8.43 (s, 1, meso proton of anthracene nucleus); ir (KBr) 3050 (m), 1660 (s), 1600 (s), 1475 (m) 1460 (w), 1440 (w), 1315 (s), 1270 (m), 935 (m), 775 (s), 735 (s), 675 cm^{-1} (m); uv ($CHCl_3$) 252 nm sh (ϵ 52,000), 259 (65,000), 356 (4500), 373 (4800), 391 (5000); mass spectrum (70 eV) *m/e* (rel intensity) 383 (32), 382 (100), 381 (20), 354 (9), 353 (27), 352 (19), 351 (14), 350 (19), 191 (11), 190 (6), 177 (5), 176 (17), 175 (32), 168 (12), 32 (14), 31 (17), 28 (23).

Anal. Calcd for $C_{29}H_{18}O$; C, 91.07; H, 4.74. Found: C, 90.76; H, 4.79.

10-(10-Bromo-9-anthrylmethylidene)anthrone (4). A mixture of 0.1 g (0.00026 mol) of **5** and 0.08 g (0.00036 mol) of cupric bromide in 7 ml of chlorobenzene was magnetically stirred at reflux for 18 hr. The mixture was cooled to room temperature and filtered to give a red filtrate and gray precipitate. The solvent was removed in vacuo from the filtrate to give a dark oil.

A solution of the oil in benzene was applied to a column containing 35 g of silica gel and the mixture was eluted with benzene to give 80.7 mg of an orange-yellow solid, mp 202–206° dec. The solid was washed with carbon tetrachloride and filtered to give 37 mg (31%) of a gold solid. Recrystallization from ethanol–water gave orange crystals: mp 220–222°; ir (KBr) 3060 (w), 1660 (s), 1600 (m), 1470 (w), 1460 (w), 1435 (w), 1310 (s), 1280 (m), 1165 (w), 920 (w), 900 (w), 770 (m), 755 (m), 730 (w), 680 cm^{-1} (w); 220-MHz NMR ($CDCl_3$) δ 6.65 (m, 1.3), 7.05–7.80 (several complex multiplets, 8.0), 7.80–8.60 (several complex multiplets, 7.7); mass spectrum (70 eV) *m/e* (rel intensity) 462 (100), 460 (98.9), 434 (2.1), 433 (4.8), 432 (2.9), 431 (3.9), 383 (10.1), 382 (34.6), 381 (39.9), 380 (13.3), 354 (7.6), 353 (7.6), 352 (34.7), 351 (26.4), 350 (39.8), 349 (4.9), 348 (10.8), 191 (19.5), 190 (11.2), 176 (18.0), 175 (36.2), 168 (12.0), 162 (9.1).

Anal. Calcd for $C_{29}H_{17}BrO$: C, 75.50; H, 3.71; Br, 17.32. Found: C, 75.52; H, 3.66; Br, 17.08.

10,10′-Dibromo-9,9′-dianthrylmethane (1c). A magnetically stirred suspension of 1.96 g (0.0053 mol) of 9.9′-dianthrylmethane (**1a**) in 60 ml of carbon tetrachloride was brought to reflux. At reflux a solution of 1.75 g (0.0109 mol) of bromine in 25 ml of carbon tetrachloride was added dropwise during 30 min, after addition of one to two crystals of iodine. The mixture was stirred at reflux for 4 days and then cooled to room temperature and filtered to give a red filtrate and a yellow precipitate. The precipitate was washed with carbon tetrachloride, benzene, and finally ether. Recrystallization from toluene gave 0.60 g (22%) of fluffy, yellow crystals of **1c**: mp 295–305° (turned brown, did not melt below 400°); ir (KBr) 3070 (w), 3030 (w), 1620 (w), 1520 (w), 1440 (w), 1325 (m), 895 (s), 740 cm^{-1} (s); 220-MHz NMR (CCl_4) (250 250-sec scans, computer averaged, 88°) δ 5.75 (s, 2, $-CH_2-$), 7.12 (m, 4, aromatic protons), 7.35 (m, 4, aromatic protons), 8.06 (d, 4, aromatic protons), 8.48 (d, 4, aromatic protons); uv ($CHCl_3$) 267 nm (ϵ 62,400), 346 (2400), 366 (4500), 388 (7600), 411 (10,000); mass spectrum (70 eV) *m/e* (rel intensity) 529 (2), 528 (5.5) ($C_{29}H_{18}{}^{81}Br_2$), 527 (4), 526 ($C_{29}H_{18}{}^{79}Br^{81}Br$) (11), 525 (2), 524 (5.6) ($C_{29}H_{18}{}^{79}Br_2$), 448 (13), 447 (36.5), 446 (14), 445 (38), 367 (15.5), 366 (38), 365 (33), 364 (12), 363 (19), 289 (4), 272 (1), 271 (5), 270 (2), 269 (7), 259 (1), 258 (3.5), 257 (1), 256 (3), 190 (11), 189 (32), 178 (8), 177 (9), 176 (10), 175 (42), 174 (28), 65 (100).

Anal. Calcd for $C_{29}H_{18}{}^{79}Br_2$: mol wt, 523.9775. Found: mol wt, 523.9772 (mass spectrum). Calcd for $C_{29}H_{18}Br_2$: C, 66.19; H, 3.44; Br, 31.37. Found: C, 66.38; H, 3.36; Br, 30.36.

The solvents were removed in vacuo from the filtrate to give a yellow oil. The oil was dissolved in toluene and the solution was applied to a column of 250 g of silica gel in 1:1 toluene–hexane. Elution with 1:1 toluene–hexane yielded 0.54 g (22%) of orange crystals of bromo ketone **4**, mp 200–215° dec. The ir (KBr) spectrum matched that of an authentic sample. A second band gave 0.17 g of a yellow solid which decomposed at 228–235° to a black oil.

10,10′-Dichloro-9,9′-dianthrylmethane (1d). A suspension of 9.0 g (0.042 mol) of 9-chloroanthracene in 45 ml of glacial acetic acid plus 0.9 g (0.03 mol) of paraformaldehyde in 18 ml of glacial acetic acid (brought into solution by bubbling with hydrogen chloride gas until clear) was magnetically stirred and heated at 75–80° for 6.5 hr. The mixture was cooled to room temperature and filtered. The precipitate was washed with acetic acid, water, benzene, and ether to give 5.28 g (57.5%) of a yellow solid, mp 322–325° dec. The solid was recrystallized from toluene to give 3.81 g (41.5%) of a bright yellow solid (**1d**): mp 335–337° dec; ir (KBr) 3030 (w), 1615 (m), 1520 (w), 1440 (m), 1430 (w), 1330 (s), 1250 (w), 1020 (w), 920 (s), 745 (s), 710 cm^{-1} (m); mass spectrum (70 eV) *m/e* (rel intensity) 440 (9), 438 (42), 436 (60), 404 (16), 403 (39), 401 (100), 400 (40), 399 (12), 367 (22), 366 (41), 365 (43), 227 (13), 225 (40), 224 (12), 214 (5), 212 (15), 200 (21), 190 (23), 189 (88), 176 (27), 175 (21).

Anal. Calcd for $C_{29}H_{18}Cl_2$: C, 79.64; H, 4.15. Found: C, 79.38; H, 4.13.

10-Bromo-9,9′-dianthrylmethane (1b). A flask equipped with a rubber septum inlet, condenser, dropping funnel, argon atmosphere system, and magnetic stirrer was charged with 14.92 g (0.044 mol) of 9,10-dibromoanthracene and flushed with argon overnight. By syringe, 60 ml of dry ether was added to the flask and then 44 ml (0.044 mol) of 1.4 *M* phenyllithium was added to the stirred suspension. The mixture was stirred at room temperature for 20 min.

A solution of 9.95 g (0.044 mol) of 9-chloromethylanthracene in 185 ml of dry benzene was then added dropwise to the stirred mixture over 3.5 hr. The resulting mixture was stirred overnight and then diethyl ether and water were added. The precipitate was filtered and washed with water and ether to give an orange filtrate plus 19.40 g of a lemon-yellow, fluorescent precipitate. Dissolution of 4.0 g of the precipitate in toluene and filtration gave 0.77 g of an insoluble white solid which was soluble in water. Removal of the solvent from the filtrate gave 3.2 g (80%) of a bright, fluorescent yellow solid, mp 282–283° dec. Recrystallization from benzene or toluene gave yellow crystals of **1b**: mp 286–289° dec; ir (KBr) 3080 (w), 3040 (w), 1620 (m), 1520 (m), 1440 (m), 1425 (w), 1330 (m), 1320 (m), 1245 (w), 1150 (w), 1025 (w), 895 (s), 870 (s), 745 (s), 720 (s), 705 cm^{-1} (m); 100-MHz NMR (benzene-d_6) δ 5.52 (s, $-CH_2-$), 7.0 (large solvent peak covering part of aromatic absorptions), 7.5–8.5 (several multiplets which integrate for five protons vs. two protons for the absorption at δ 5.52); uv ($CHCl_3$) 258 nm (ϵ 83,000), 320 sh (1700), 337 sh (3800), 354 (7200), 364 sh (9300), 372 (11,200), 382 (14,000), 392 (12,000), 404 (15,500); mass spectrum (70 eV) *m/e* (rel intensity) 449 (21), 448 (65), 447 (24), 446 (64), 369 (8), 368 (37), 367 (100), 366 (16), 365 (21), 363 (14), 290 (6), 289 (12), 191 (16), 190 (14), 189 (44), 183 (18), 177 (11), 176 (26).

Anal. Calcd for $C_{29}H_{19}Br$: C, 77.86; H, 4.28. Found: 77.81; H, 4.22.

Bromination of 10-Bromo-9,9′-dianthrylmethane (1b). A suspension of 1.0 g (0.00224 mol) of 10-bromo-9,9′-dianthrylmethane (**1b**) and one crystal of iodine in 30 ml of dry carbon tetrachloride was magnetically stirred at reflux under argon. To the stirred suspension at reflux was added a solution of 0.36 g (0.00224 mol) of bromine in 15 ml of carbon tetrachloride over 45 min. The mixture was then stirred at reflux for 2 days, cooled to room temperature, and filtered. The precipitate was washed with carbon tetrachloride, 10% sodium bisulfite, acetone, and finally ether and sucked dry to give 0.64 g (54.5%) of a yellow solid which darkened at 290–295° but did not melt below 360°. The solid was recrystallized from toluene to give 0.5 g (43%) of the dibromo compound **1c**, which darkened at 280–290° and did not melt below 360°. The ir (KBr) spectrum matched the spectrum of **1c** as described above.

The solvent was removed from the filtrate to give a mixture of colored products as evidenced by thin layer chromatography on silica gel with benzene as the mobile phase. The mixture was dissolved in benzene and applied to a column containing 100 g of silica gel in benzene. Elution with benzene gave four bands which were collected.

The third component eluted proved to be 0.031 g (3%) of the ketone **4** as shown by ir (KBr) and mass spectral comparison with the known spectra.

Photocyclization of 9,9′-Dianthrylmethane (1a). A solution of 0.407 g (0.0011 mol) of 9,9′-dianthrylmethane (**1a**) in 3250 ml of benzene (all benzene for the photolysis reactions was washed with sulfuric and water and distilled from calcium hydride) was placed in a 5-l. flask fitted with a quartz immersion well designed to accomodate a 450-W Hanovia mercury lamp. The magnetically stirred solution was boiled under nitrogen and bubbled with dry nitrogen to remove oxygen. The solution was cooled to room temperature and the stirred solution was irradiated for 17 hr. The solvent was removed in vacuo to leave a pale brown solid. Addition of hexane followed by filtration left 0.261 g (63.8%) of a beige solid which turned to a yellow solid at 180–210° and melted at 308–317°. Recrystallization of the solid from benzene–hexane gave 0.156 g (38%) of a white solid (**6a**) which turned fluorescent yellow at 180–210° and melted at 311–313° (remelt 311–313°): ir (KBr) 3060 (w), 3040 (w), 3010 (w), 2920 (w), 1600 (w), 1470 (m), 1450 (s), 1245 (w), 1130 (m), 765 (s), 745 (w), 675 (m), 640 (m), 595 (m), 500 cm^{-1} (m); 220-MHz NMR ($CDCl_3$) δ 2.78 (s, 2, $-CH_2-$), 4.62 (s, 2, bridgehead protons), 6.74–7.05 (two multiplets, 16, aromatic protons); uv ($CHCl_3$) 272 nm (ϵ 3000), 281 (2000); mass spectrum (70 eV) essentially the same as that of 9,9′-dianthrylmethane (**1a**).

Anal. Calcd for $C_{29}H_{20}$: C, 94.53; H, 5.47. Found: C, 94.62; H, 5.52.

Photocyclization of 10-Bromo-9,9′-dianthrylmethane (1b). A suspension of 2.00 g of 10-bromo-9,9′-dianthrylmethane (**1b**) in 3225 ml of benzene was stirred under reflux for 10 min under argon. Benzene (150 ml) was distilled off under argon and the solution was cooled to room temperature and sealed under argon. The solution was irradiated with a 450-W Hanovia mercury lamp (Pyrex filter) for 19 hr at 40°. Removal of the solvent in vacuo left a brown solid. Addition of 300 ml of ether and filtration gave a creamy white solid which was washed with ether and cold benzene to give 1.50 g (75%) of a creamy white solid (**6b**), which turned orange at about 150°, then fluorescent yellow around 200° and melted at 270–272° dec: ir (KBr) 3070 (m), 3040 (w), 3020 (w), 1475 (m), 1460 (s), 1285 (w), 1155 (w), 1145 (w), 890 (w), 798 (m), 773 (s), 750 (m), 685 (s), 650 (s), 620 (m), 520 cm^{-1} (m); 100-MHz NMR ($CDCl_3$) δ 2.74 (s, 2, $-CH_2-$), 5.30 (s, 1, bridgehead proton), 6.60–6.95 (m, 12, aromatic protons), 6.85–7.15 (m, 2, aromatic protons), 7.65–7.88 (m, 2 aromatic protons); mass spectrum (70 eV) *m/e* (rel intensity) 449 (3.4), 448 (10), 447 (4.5), 446 (10), 369 (31), 368 (100), 376 (50), 366 (11), 365 (12), 363 (12), 353 (29), 352 (20), 351 (15), 291 (10), 290 (9), 289 (11), 191 (29), 190 (25), 189 (48), 184 (15), 183 (11), 182 (13), 175 (27), 164 (10); uv ($CHCl_3$) 271 nm (ϵ 3340), 281 (2180). Recrystallization from benzene–hexane gave an analytical sample.

Anal. Calcd for $C_{29}H_{19}Br$: C, 77.86. Found: C, 77.60; H, 4.47; Br, 17.76.

Removal of solvents from the filtrate and addition of small amounts of cold ether and benzene followed by filtration and benzene and ether washings gave an additional 0.25 g (12.5%) of product, mp 259–262° dec. The total yield of **6b** was 1.75 g (87.5%).

Registry No.—**1a**, 15080-14-5; **1b**, 15156-60-2; **1c**, 15080-12-3; **1d**, 55043-36-2; **2**, 15080-13-4; **3a**, 55043-37-3; **3b**, 55043-38-4; **3c**, 55043-39-5; **4**, 55043-40-8; **5**, 55043-41-9; **6a**, 55043-42-0; **6b**, 55043-43-1; anthraquinone, 84-65-1; 9,10-dibromoanthracene, 523-27-3; 9-chloroanthracine 716-53-0; 9-chloromethylanthracene, 24463-19-2; bromine, 7726-95-6.

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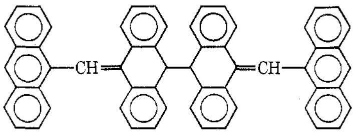
(3) The structure of the substance of mp 382–395° dec previously assigned structure **1a**[1] has been briefly reinvestigated. The observations that its infrared spectrum closely resembles that of **3a** between 1400 and 1500 cm^{-1}, that its mass spectrum shows the highest mass at *m/e* 367 instead of 368, and that its uv spectrum is essentially the same as that of **3a** with nearly the same extinction coefficients on a weight basis, suggest a dimeric structure $C_{58}H_{38}$ as follows.



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Polyphenolic Acids of *Lithospermum ruderale* Dougl. ex Lehm. (Boraginaceae). 1. Isolation and Structure Determination of Lithospermic Acid[1a]

Charles J. Kelley, J. R. Mahajan, Lucille C. Brooks, Leonard A. Neubert, W. R. Breneman,[1b–f] and Marvin Carmack*

Contribution No. 2620 from the Department of Chemistry, Indiana University, Bloomington, Indiana 47401

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A structure is proposed for lithospermic acid ($C_{27}H_{22}O_{12}$, **1a**), the major polyphenolic acid of *Lithospermum ruderale* and several other plant species of the families, Boraginaceae and Labiatae. Chromatography on Sephadex of aqueous extracts of the plant yields the dipotassium salt of **1a**, together with salts of lesser constituents which include (*R*)-3-(3,4-dihydroxyphenyl)lactic acid (**2a**), 2-(3,4-dihydroxyphenyl)-3-carboxy-4-(2-carboxy-*trans*-vinyl)-7-hydroxycoumaran (**3a**), and rosmarinic acid (**4a**). Structures were deduced from spectral studies of the salts, the free acids, and also the methylated derivatives produced by the action of diazomethane on the free acids or dimethyl sulfate on the salts.

This paper describes our isolation of lithospermic acid, $C_{27}H_{22}O_{12}$, the principal polyphenolic acid constituent of roots of the plant *Lithospermum ruderale* Dougl. ex Lehm. (Boraginaceae; common names, gromwell, puccoon) and the structure elucidation of this acid and of three closely related plant constituents.

Interest in the chemical constituents of *Lithospermum ruderale* was stimulated by the report in 1941 of Train et al.[2] that certain Indians of Nevada use the plant to make a contraceptive tea. Extracts from at least six species of the genus *Lithospermum* have been found to inactivate gonadotropins.[3] The most readily cultivated of these species, *Lithospermum officinale* L., long known in European herbal medicine,[4,5] has been shown to produce a pituitary hormone blocking effect[5] both in vitro and in vivo.

The plants *Lycopus europaeus* and *Lycopus virginicus*, although members of the family Labiatae, were reported to have antihormonal activities remarkably similar to those of *Lithospermum* species.[6]

Lithospermic acid[7] has been implicated[8,9] in the hormonal inhibitory mechanisms, presumably as the chemical precursor of the active inhibitory substances produced by oxidative processes involving air- or enzyme-catalyzed reactions. It has been recognized[9–11] as a constituent of *Lycopus europaeus, Lycopus virginicus, Lithospermum ruderale, Lithospermum officinale,* and *Symphytum officinale* (common name, comfrey). More recently, *Anchusa officinalis* and *Echium vulgare* were added to the growing number of Boraginaceae which have antigonadotropic activity in animals and also contain lithospermic acid.[12] Reviews of contraceptive plant species have been published.[13,14]

von Seemann and Grant[15] isolated fractions of *Lithospermum ruderale* as amorphous powders having antigonadotropic activity. They characterized the materials as polyphenolic acid salts, possibly flavanoids, which gave reactions characteristic of phlobatannins, and observed that the active principle(s) in the plant extract could be precipitated by acids and redissolved at pH above 5. A number of phytochemical investigations failed to identify the specific antihormonal compound(s) of *Lithospermum* species.[16]

In 1963, Johnson et al.[7] reported the isolation of a polyphenolic acid from roots of *Lithospermum ruderale* which they named lithospermic acid and assigned the structure of 2-hydroxy-2,4-bis(3,4-dihydroxyphenyl)butenoic acid, $C_{16}H_{14}O_7$. The amorphous, water-soluble acid was said to melt at 130–131° and the structure was supported by analyses for several crystalline derivatives, including a "pen-