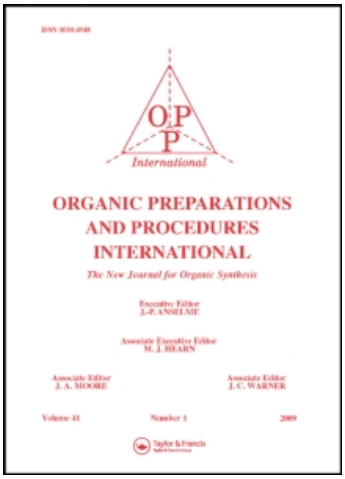


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF 4*H*-CYCLOPENTA[*def*]CHRYSENE AND OTHER METHYLENE-BRIDGED POLYCYCLIC HYDROCARBONS

Wei Dai[a]; Ronald G. Harvey[a]
[a] Ben May Institute for Cancer Research, University of Chicago, Chicago, IL

To cite this Article Dai, Wei and Harvey, Ronald G.(1997) 'SYNTHESIS OF 4*H*-CYCLOPENTA[*def*]CHRYSENE AND OTHER METHYLENE-BRIDGED POLYCYCLIC HYDROCARBONS', Organic Preparations and Procedures International, 29: 3, 347 — 352
To link to this Article: DOI: 10.1080/00304949709355210
URL: http://dx.doi.org/10.1080/00304949709355210

11. E. Pop, F. Soti, M. E. Brewster, Y. Barenholz, V. Korablyov, R. Mechoulam, V. Nadler and A. Biegon, *ibid.*, **13**, 469 (1996)

12. T. Gajda and A. Zwierzak, *Synthesis*, **1976**, 243-244.

13. E. Pop, F. Soti and M. E. Brewster, *Synth. Commun.*, **25**, 4099 (1995).

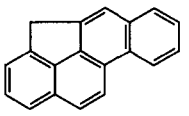
****

SYNTHESIS OF 4*H*-CYCLOPENTA[*def*]CHRYSENE AND OTHER METHYLENE-BRIDGED POLYCYCLIC HYDROCARBONS

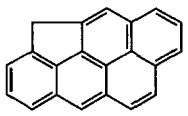
Submitted by (11/27/96) Wei Dai and Ronald G. Harvey*

Ben May Institute for Cancer Research, University of Chicago Chicago, IL 60637

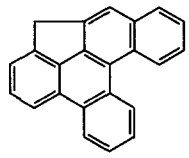
Methylene-bridged polycyclic aromatic hydrocarbons (PAHs) are widespread environmental contaminants formed in the incomplete combustion of fossil fuels.[1-3] Some bridged PAHs, notably 4*H*-cyclopenta[*def*]chrysene and 4*H*-benz[*def*]cyclopenta[*mno*]chrysene (**1** and **2**), exhibit significant activity as mutagens and carcinogens.[3-6] It has been postulated that carcinogenic PAHs of this class may undergo metabolic activation by a novel pathway that involves formation of a bridge carbocation intermediate capable of directly alkylating DNA[7] in addition to the diol epoxide pathway established for the parent PAHs without a bridge.[8]



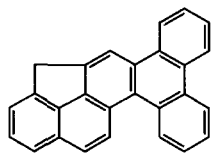
1



2

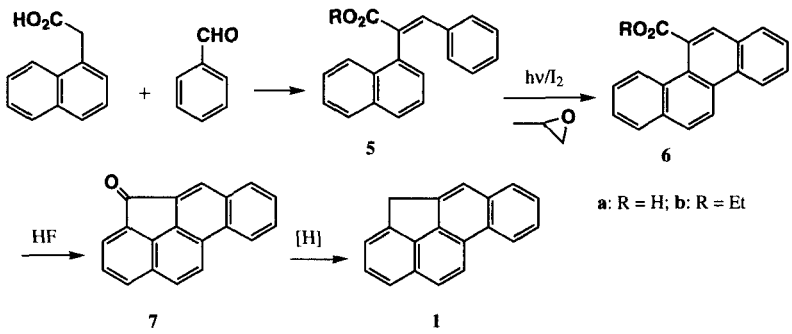


3



4

In connection with investigations of the mechanisms of carcinogenesis of bridged PAHs, we required an efficient method for the synthesis of **1** and its higher polycyclic analogs. Although several syntheses of **1** have been described,[9-12] none of these methods were entirely satisfactory because of the numbers of steps and the relatively low overall yields obtained. We now report an improved synthetic approach which provides **1** in 50% overall yield from available precursors in four steps and application of the method to the synthesis of the previously unknown polycyclic hydrocarbons 8*H*-benzo[*g*]cyclopenta[*mno*]chrysene (**3**) and 4*H*-benzo[*f*]cyclopenta[*pqr*]picene (**4**).



Scheme 1

The synthetic approach to **1** is outlined in Scheme 1. Condensation of benzaldehyde with 2-(1-naphthyl)acetic acid in the presence of acetic anhydride and Et_3N[13] furnishes 2-(1-naphthyl)-3-phenylpropenoic acid (**5a**). The reaction was carried out by the reported procedure except for an increase in reaction time from 2 to 24 hrs which increased the yield from 73% to 90%. Esterification of **5a** by heating in refluxing ethanol with a small amount of sulfuric acid yields the ester (**5b**) essentially quantitatively as a mixture of *cis* and *trans* isomers which may be used directly in the next step. The ester rather than the free acid (**5a**) is employed in order to avoid competing photocyclization to form a lactone, a process shown by Lee-Ruff *et al.*[10] to be a major pathway in the photocyclization of **5a**. Also, photoreaction is conducted with iodine as the oxidant in the absence of air and in the presence of propylene oxide to minimize competing secondary processes.[14] By the use of these modifications, the yield of the cyclized ester (**6b**) is increased from 58% to 90%. Cyclization of **6b** directly to the ketone **7** takes place on stirring its solution in CH_2Cl_2 with liquid HF. The use of a cosolvent is superior to cyclization of the free acid (**6a**) in liquid HF alone which provides **7** in lower yield (65% vs 92%).[10,15] Finally, reduction of **7** by the Wolff-Kishner method gives 4*H*-cyclopenta[*def*]chrysene in 50% overall yield from readily available precursors.

This synthetic approach was employed with appropriate modification for the synthesis of the additional novel methylene-bridged hydrocarbons 8*H*-benzo[*g*]cyclopenta[*mno*]chrysene (**3**) and 6*H*-benzo[*f*]cyclopenta[*pqr*]picene (**4**). For the synthesis of **3**, the starting compounds were 9-phenanthraldehyde and 2-(1-naphthyl)acetic acid, and those for **4** were benzaldehyde and 2-(9-phenanthryl)acetic acid, all of which are available commercially. This synthetic method appears to be relatively broad in scope and is applicable to the preparation of a wide range of methylene-bridged polycyclic aromatic compounds.

EXPERIMENTAL SECTION

^{1}H NMR spectra were obtained on the University of Chicago 300 or 500 MHz spectrometers in $CDCl_3$ with TMS as internal standard unless otherwise indicated. The full scale ^{1}H NMR spectra for all compounds for which high resolution mass spectra are reported in lieu of microanalytical data showed them to be essentially pure.

Condensation of Arylaldehydes with Arylacetic Acids.- A solution of the arylacetic acid (27 mmol) and the arylaldehyde (27 mmol) in acetic anhydride (10 mL) and Et_3N (10 mL) was stirred at 120° for 24 hrs. The solution was cooled to 0°, quenched with conc. HCl and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated to dryness. The propenoic acid products were obtained in 50-90% yield as a pale yellow solids as a mixture of *cis*- and *trans*-isomers.

2-(1-Naphthyl)-3-phenylpropenoic Acid (5a) in 90% yield from 1-naphthylacetic acid and benzaldehyde. ^1H NMR: δ 8.15 (s, 1, vinyl), 6.91-7.90 (m, 12, aryl).

Anal. Calcd for $C_{19}H_{14}O_2$: C, 83.19; H, 5.14. Found: C, 83.35; H, 4.98

2-(9-Phenanthryl)-3-phenylpropenoic Acid in 75% yield from 9-phenanthrylacetic acid and benzaldehyde. ^1H NMR: δ 8.72 (d, 1, *J* = 8.7), 8.62 (d, 1, *J* = 8.7), 8.21 (s, 1, vinyl), 6.89-7.90 (m, 12, aryl). HRMS, calcd for $C_{23}H_{16}O_2$ *m/e* 324.11502, obsd, 324.11489.

2-(1-Naphthyl)-3-(9-phenanthryl)propenoic Acid in 53% yield from 1-naphthylacetic acid and 9-phenanthraldehyde. ^1H NMR: δ 8.85 (s, 1, vinyl), 7.10-8.70 (m, 16, aryl). HRMS, calcd for $C_{27}H_{18}O_2$ *m/e* 374.13068, obsd, 374.13120.

Esterification of 2,3-Diarylpropenoic Acids.- A solution of the acid (10 mmol) in 100 mL of EtOH with 1 mL of conc. H_2SO_4 was heated at reflux for 24 hrs. Conventional workup furnished the corresponding *cis*- and *trans*-esters as oils.

Ethyl 2-(1-Naphthyl)-3-phenylpropenoate (**5b**) (99%). ^1H NMR: δ 8.05 (s, 1, vinyl), 6.89-7.90 (m, 12, aryl), 4.23 (q, 2, *J* = 7.1), 1.20 (t, 3, *J* = 7.1).

Anal. Calcd for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00. Found: C, 83.32; H, 5.88

Ethyl 2-(9-Phenanthryl)-3-phenylpropenoate (98%). ^1H NMR: δ 8.71 (d, 1, *J* = 8.3), 8.68 (d, 1, *J* = 8.4), 8.10 (s, 1, vinyl), 7.81 (d, 1, *J* = 8.1), 7.75 (d, 1, *J* = 7.8), 6.90-7.70 (m, 10), 4.25 (q, 2, *J* = 7.0), 1.20 (t, 3, *J* = 7.0). MS *m/e* 352 (M^+, 47), 239 (11), 224 (9), 202 (100), 201 (59), 189 (11), 176 (19); HRMS, calcd for $C_{25}H_{20}O_2$ *m/e* 352.14630, obsd, 352.14490.

Ethyl 2-(1-Naphthyl)-3-(9-phenanthryl)propenoate (85%).- ^1H NMR: δ 8.76 (s, 1, vinyl), 7.07-8.74 (m, 16, aryl), 4.33 (q, 2, *J* = 7.0), 1.25 (t, 3, *J* = 7.0). MS *m/e* 402 (M^+, 16), 355 (3), 329 (9), 376 (38), 247 (6), 231 (18), 203 (100), 202 (62); HRMS, calcd for $C_{29}H_{22}O_2$ *m/e* 402.16197, obsd, 402.15980.

Photocyclization of 2,3-Diarylpropenoate Esters.- Argon was bubbled through a solution (0.01 M) of the ester and I_2 (1.2 eq.) in 450 mL of benzene for 30 min. Propylene oxide (10-20 mL) was added and the solution was irradiated with a Hanovia 450 W medium pressure mercury lamp through a Pyrex filter. The reaction was followed by TLC until the starting ester was totally consumed. The solution was treated with a saturated aqueous solution of $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated under vacuum in a rotary evaporator to dryness. The crude products were triturated with ether to provide the cyclized ester products as a pale yellow solids.

5-Carboethoxychrysene (6b) (87%), mp. 148-149°; ^1H NMR: δ 8.79 (d, 1, *J* = 8.5), 8.65 (d, 1, *J* = 9.0), 8.20 (d, 1, *J* = 8.2), 8.15 (s, 1), 8.00 (d, 1, *J* = 9.0), 7.96 (d, 1, *J* = 8.0), 7.94 (d, 1, *J* = 8.0),

7.71 (d, 1, J = 7.5), 7.63 (t, 1, J = 7.5), 7.54 (m, 2), 4.57 (q, 2, J = 7.2), 1.33 (t, 3, J = 7.2); MS *m/e* 402 (M^+, 100).

Anal. Calcd for $C_{21}H_{16}O_2$: C, 83.98; H, 5.37. Found: C, 83.72; H, 5.37

9-Carboethoxybenzo[*g*]chrysene (91%), mp. 128-129°; ^{1}H NMR: δ 8.75 (d, 1, J = 8.4), 8.71 (d, 1, J = 8.1), 8.63 (d, 1, J = 8.2), 8.57 (d, 1, J = 8.1), 8.22 (s, 1), 7.98 (d, 1, J = 7.9), 7.94 (d, 1, J = 8.2), 7.51-7.67 (m, 6), 4.37 (q, 2, J = 7.3), 1.26 (t, 3, J = 7.3); MS *m/e* 350 (M^+, 100); HRMS, calcd for $C_{25}H_{18}O_2$: *m/e* 350.13068, obsd, 350.13160.

Anal. Calcd for $C_{25}H_{18}O_2$: C, 85.69; H, 5.18. Found: C, 85.75; H, 5.19

15-Carboethoxybenzo[*f*]picene (89%), mp. 177-178°; ^{1}H NMR: δ 8.90 (s, 1), 7.56-8.85 (m, 14), 4.57 (q, 2, J = 7.0), 1.40 (t, 3, J = 7.2); HRMS, *m/e* 400.14633, obsd, 400.14430.

Anal. Calcd for $C_{29}H_{20}O_2$: C, 86.98; H, 5.03. Found: C, 86.73; H, 5.22

HF-catalyzed Cyclization.- To a solution of the polycyclic ester (1 g) in CH_2Cl_2 (20 mL) in a gas tight Teflon bottle was added liquid HF (10 mL). The bottle was sealed and the resulting purple solution was stirred at room temperature for 24 hrs. The solvent was evaporated by blowing a stream of Argon over the surface of the solution in a well-ventilated hood. The solid products were triturated with a saturated aqueous solution of $NaHCO_3$ then washed with water and ether-hexane (1:9) to give the cyclized ketones as yellow solids.

Cyclopenta[*def*]chrysene-4-one (7) (92%), mp. 204-205° (lit.[16] 204-205°); the ^{1}H NMR spectrum matched that of a sample prepared by an alternate route.[16]

8*H*-Benzo[*g*]cyclopenta[*mno*]chrysene-8-one (80%), mp. 216-217°; ^{1}H NMR: δ 9.18 (d, 1, J = 8.0), 9.10 (d, 1, J = 8.5), 8.69 (d, 1, J = 7.7), 8.48 (d, 1, J = 8.0), 8.23 (s, 1), 8.08 (d, 1, J = 7.8), 7.88 (d, 1, J = 7.1), 7.56-7.78 (m, 5); MS *m/e* 304 (M^+, 100); 374 (22), 376 (16), 248 (3); HRMS, calcd for $C_{23}H_{12}O$ *m/e* 304.08882, obsd, 304.08770.

Anal. Calcd for $C_{23}H_{12}O$: C, 90.77; H, 3.97. Found: C, 90.55; H, 4.09

4*H*-Benzo[*f*]cyclopenta[*pqr*]picene-4-one (62%) mp. 277-278°; ^{1}H NMR: δ 9.13 (s, 1), 9.10 (d, 1, J = 10.0), 8.84 (d, 1, J = 9.1), 8.65-8.71 (m, 3), 7.96 (d, 1, J = 7.9), 7.91 (d, 1, J = 6.9), 7.61-7.74 (m, 5); MS *m/e* 304 (M^+, 354); HRMS, calcd for $C_{27}H_{14}O$ *m/e* 354.10446, obsd, 354.10206.

Anal. Calcd for $C_{27}H_{14}O$: C, 91.50; H, 3.98. Found: C, 91.37; H, 4.21

Wolff-Kishner Reduction. A solution of a methylene-bridged ketone (0.03 M) in diethylene glycol was prepared by heating at 120° under Argon. The solution was allowed to cool to about 100°, and anhydrous hydrazine (3 eq.) was added slowly. The reaction mixture was heated at 140° for 2 hrs after TLC showed disappearance of the starting ketone, then the solution was cooled to about 100°. A solution of aqueous 2% NaOH (3 eq.) was added and the reaction mixture was refluxed for 10 hrs, then cooled and poured into an ice cold sat. NH_4OH solution and stirred overnight. Filtration of the aqueous suspension gave the crude product which was dried and triturated with ether-hexane (1:9) to furnish the methylene-bridged hydrocarbon as a yellow solid.

Cyclopenta[*def*]chrysene (1) (70%) mp. 174-175° (lit.[8,9] 174-176°); the ^{1}H NMR spectrum matched that of an authentic sample.

8*H*-Benzo[*g*]cyclopenta[*mno*]chrysene (3) (55%) mp. 156-157°; ^{1}H NMR: δ 9.31 (d, 1, *J* = 8.2), 9.24 (d, 1, *J* = 8.2), 8.77 (d, 1, *J* = 8.0), 8.38 (m, 1), 8.09 (d, 1, *J* = 7.7), 8.06 (s, 1), 7.59-7.77 (m, 6), 4.4?? (s, 2); MS *m/e* 290 (M^+, 100); 289 (54), 287 (18), 261 (3); HRMS, calcd for $C_{23}H_{14}$ *m/e* 290.10955, obsd, 290.10970.

Anal. Calcd for $C_{23}H_{14}$: C, 95.14; H, 4.86. Found: C, 94.85; H, 4.79

4*H*-Benzo[*f*]cyclopenta[*pqr*]picene (4) (47%) mp. 175-176°; ^{1}H NMR: δ 9.11 (m, 1), 8.88 (d, 1, *J* = 7.5), 8.87 (s, 1), 8.67-8.74 (m, 4), 7.96 (d, 1, *J* = 9.1), 7.85 (d, 1), 7.64-7.71 (m, 5), 4.43 (s, 2); MS *m/e* 340 (M^+, 100); 339 (42), 328 (3), 313 (3); HRMS, calcd for $C_{27}H_{16}$ *m/e* 340.12520, obsd, 340.12310.

Anal. Calcd for $C_{27}H_{16}$: C, 95.26; H, 4.74. Found: C, 95.15; H, 4.79

Acknowledgement. This research was supported by grants from the National Institute for Environmental Health Sciences (ES 04732) and the National Cancer Institute (CA 67937).

REFERENCES

1. R. G. Harvey, *Polycyclic Aromatic Hydrocarbons*, VCH-Wiley, New York, 1997.

2. A. Gold, *Anal. Chem.*, **55**, 594 (1983).

3. G. Grimmer, *Environmental Carcinogens: Polycyclic Aromatic Hydrocarbons, Chemistry, Occurrence, Biochemistry, Carcinogenicity,* CRC Press, Boca Raton, Florida, 1983.

4. A. L. Lafleur, J. P. Longwell, J. A. Marr, P. A. Monchamp, E. F. Plummer, W. G. Thilly, P. P. Y. Mulder, B. B. Boere, J. Cornelisse and J. Lugtenburg, *Environ. Hlth. Persp.*, **101**, 146 (1993).

5. H. Glatt, R. Henschler, H. Frank, A. Seidel, C. Yang, E. Abu-shqara and R. G. Harvey, *Carcinogenesis*, **14**, 599 (1993).

6. S. Nesnow, J. Lesley, S. Curti, J. Ross, G. Nelson, R. Sangaiah and A. Gold, in *Polycyclic Aromatic Compounds: Synthesis, Properties, Analytical Measurements, Occurrence and Biological Effects,* P. Garrigues and M. Lamotte, Eds, Gordon & Breach, Yverdon, Switzerland, 1993, pp. 817-824.

7. C. Yang and R. G. Harvey, *Tetrahedron*, **48**, 3735 (1992).

8. R. G. Harvey, *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenesis*, Cambridge University Press, Cambridge, England, 1991.

9. R. G. Harvey, J. P. Pataki, C. Cortez, P. Di Raddo and C. Yang, *J. Org. Chem.*, **56**, 1210 (1991).

10. E. Lee-Ruff, H. Kruk and M. Katz, *ibid.*, **49**, 553 (1984).

11. L. F. Fieser and J. Cason, *J. Am. Chem. Soc.*, **62**, 1293 (1940).

12. D. L. Nagel, R. Kupper, K. Antonson and L. Wallcave, *J. Org. Chem.*, **42**, 3626 (1977).

13. S. Amin, S. S. Hecht, E. LaVoie, N. Hussain and D. Hoffmann, *J. Med. Chem.*, **22**, 1336 (1979).

14. Propylene oxide serves to scavenge the HI produced preventing its reduction of the primary product. L. Liu, B. Yang, T. J. Katz and M. K. Poindexter, *J. Org. Chem.* **56**, 3769 (1991).

15. The advantage of CH_2Cl_2 as a solvent for HF cyclizations of this type was previously demonstrated: W. Dai and R. G. Harvey, *ibid.*, **60**, 4905 (1995).

16. R. G. Harvey, E. Abu-Shaqara and C. Yang, *ibid.*, **57**, 6313 (1992).

****

N-PERFLUOROALKANESULFONYLPHOSPHORAMIDES

via AN IMPROVED ATHERTON-TODD REACTION

Submitted by
(07/13/96)

Shizheng Zhu*, Jie Zhang, Bin Xu and Chaoyue Qin

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
354 Fenling Lu, Shanghai 200032, P. R . CHINA

Phosphoramides have received much attention due to their biological properties;[1] for example, sulfonyl phosphoramides are important pesticides.[2] It is well known that the introduction of a fluorine atom or fluorine-containing group into organic molecules often increases their chemical or biological activities. Therefore it might be valuable to develop synthetic methods for the preparation of fluorine-containing phosphoramides and their derivatives. We recently prepared the N-perfluoroalkanesulfonylphosphoramides ($R_fSO_2N(R)P(O)(OR')_2$) by two different methods. The first involved the reaction of perfluoroalkanesulfonyl azides with triethyl phosphite, to give $R_fSO_2N{=}P(OEt)_3$ which readily rearranges to $R_fSO_2N(Et)P(O)(OEt)_2$, albeit in a yield of only about

$$R_fSO_2N_3 + P(OEt)_3 \longrightarrow R_fSO_2N{=}P(OEt)_3 \longrightarrow R_fSO_2N(Et)P(O)(OEt)_2 \quad (1)$$

40% (Eq. 1)[3] and the second method uses the Arbuzov reaction (Eq. 2).[4] This paper reports a new convenient method to prepare the title compounds.

$$R_fSO_2N(R')X + P(OR)_3 \longrightarrow R_fSO_2N(R')P(O)(OR)_2 + R'X \quad (2)$$

X = Cl, Br

The phosphorylation of perfluoroalkanesulfonylamides (**1**) was carried out with dialkyl phosphites (**2**) in carbon tetrachloride under basic reaction conditions and in the presence of a small amount of a phase-transfer catalyst, hexadecyltributylphosphonium bromide (Eq. 3).