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

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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).

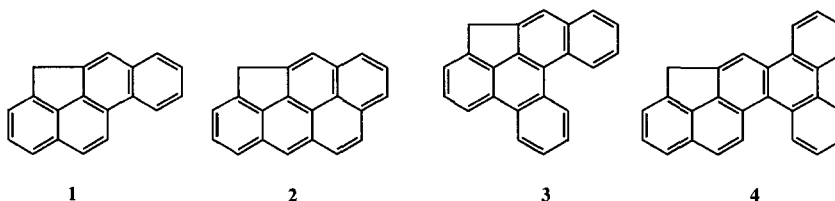
SYNTHESIS OF 4H-CYCLOPENTA[def]CHRYSENE AND OTHER METHYLENE-BRIDGED POLYCYCLIC HYDROCARBONS

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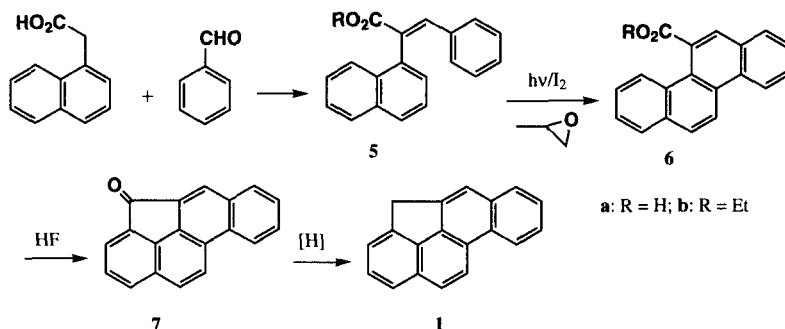
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Methylene-bridged polycyclic aromatic hydrocarbons (PAHs) are widespread environmental contaminants formed in the incomplete combustion of fossil fuels.¹⁻³ Some bridged PAHs, notably 4H-cyclopenta[def]chrysene and 4H-benz[def]cyclopenta[mno]chrysene (**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 DNA⁷ in addition to the diol epoxide pathway established for the parent PAHs without a bridge.⁸



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 8H-benzo[g]cyclopenta[mno]chrysene (**3**) and 4H-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 4H-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 8H-benzo[g]cyclopenta[mno]chrysene (**3**) and 6H-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

¹H 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 ¹H 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 Et₃N (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 MgSO₄ 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 C₁₉H₁₄O₂: 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 C₂₃H₁₆O₂ *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 C₂₇H₁₈O₂ *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. H₂SO₄ 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 C₂₁H₁₈O₂: 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 C₂₅H₂₀O₂ *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 C₂₉H₂₂O₂ *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 I₂ (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 Na₂S₂O₃, dried over MgSO₄, 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°; 1H 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°; 1H 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 1H NMR spectrum matched that of a sample prepared by an alternate route.¹⁶

8H-Benzo[g]cyclopenta[mno]chrysene-8-one (80%), mp. 216-217°; 1H 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

4H-Benzo[f]cyclopenta[pqr]picene-4-one (62%) mp. 277-278°; 1H 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 1H NMR spectrum matched that of an authentic sample.

8H-Benzo[g]cyclopenta[mno]chrysene (3) (55%) mp. 156-157°; ^1H 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 $\text{C}_{23}\text{H}_{14}$ m/e 290.10955, obsd, 290.10970.

Anal. Calcd for $\text{C}_{23}\text{H}_{14}$: C, 95.14; H, 4.86. Found: C, 94.85; H, 4.79

4H-Benzo[f]cyclopenta[pqr]picene (4) (47%) mp. 175-176°; ^1H 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 $\text{C}_{27}\text{H}_{16}$ m/e 340.12520, obsd, 340.12310.

Anal. Calcd for $\text{C}_{27}\text{H}_{16}$: C, 95.26; H, 4.74. Found: C, 95.15; H, 4.79

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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

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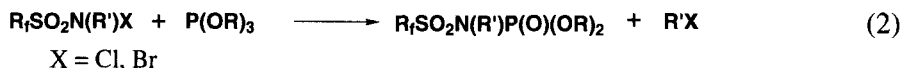
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Phosphoramides have received much attention due to their biological properties;¹ for example, sulfonyl phosphoramides are important pesticides.² It is well known that the introduction of a fluorine atom or fluorine-containing group into organic molecules 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 ($\text{R}_f\text{SO}_2\text{N}(\text{R})\text{P}(\text{O})(\text{OR}')_2$) by two different methods. The first involved the reaction of perfluoroalkanesulfonyl azides with triethyl phosphite, to give $\text{R}_f\text{SO}_2\text{N}=\text{P}(\text{OEt})_3$ which readily rearranges to $\text{R}_f\text{SO}_2\text{N}(\text{Et})\text{P}(\text{O})(\text{OEt})_2$, albeit in a yield of only about



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.



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).