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Synthetic Analogs of Cortical Hormones. IV. Synthesis and Reactions of 3-Acetoxy-2-oxo-3-(2-phenanthryl)-diazopropane

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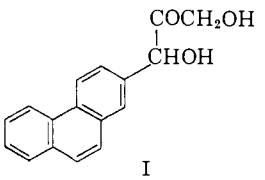
Selenium dioxide oxidation of 2- and 3-acetylphenanthrene yielded the corresponding 2- and 3-phenanthrylglyoxals which could be converted to 2- and 3-phenanthrylglycolic acids by an intramolecular Cannizzaro reaction. 2-Phenanthrylglycolic acid (IV) was acetylated and converted to the corresponding diazo ketone VII through its acid chloride. Acid hydrolysis of the diazo ketone did not give the expected hydroxy ketone I. Instead, 2-phenanthrylmethylglyoxal (IX) was shown to be a major hydrolytic product. A mechanism has been suggested for this transformation. Several approaches to the synthesis of 1-hydroxy-3-(2-phenanthryl)-2-pentanone (II) starting from α-(2-phenanthryl)-*n*-propyl bromide (XIV) proved unsuccessful.

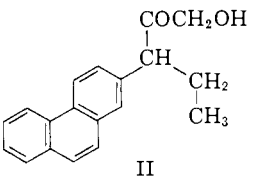
The limited accessibility of cortical steroids by synthetic procedures starting from readily available substances[2-5] or by isolation from naturally occurring sources has stimulated the search for cortical activity in simple organic compounds containing functional groups which appear to be responsible for biological activity. In general, this has amounted to the synthesis of model compounds which contain an α-ketol group that may be separated from an α,β-unsaturated carbonyl function by a suitable distance.[6-15]

Of particular interest was the observation recently made in this Laboratory that hydroxymethyl 9,10-diacetoxy-2-phenanthryl ketone compared favorably to cortisone in ability to lower the eosinophil count in adrenalectomized mice.[16]

In extending our studies to other phenanthrene derivatives in search for potential cortical steroid analogs, we have attempted to synthesize hydroxy ketones I and II.



I



II

2-Phenanthrylglyoxal (III), required for the proposed sequence, was obtained conveniently by heating 2-acetylphenanthrene with selenium dioxide in refluxing toluene for 48 hours, although the resultant product was always contaminated by trace quantities of selenium metal from which it could not be separated easily. Crystallization from non-aqueous solvents resulted in decomposition to yield, among other products, 2-phenanthroic acid.

Attempts to oxidize 2-acetylphenanthrene with selenium dioxide in refluxing aqueous ethanol failed to show any reaction. When the solvent was changed to acetic acid, the reaction product consisted mainly of 2-phenanthroic acid accompanied by small amounts of 2-phenanthrylglyoxal and the starting ketone, the composition of the mixture depending upon the reflux time.

2-Phenanthrylglyoxal formed a quinoxaline derivative, an osazone, and a methyl alcoholate and was converted to 2-phenanthrylglycolic acid (IV) *via* a benzilic acid type rearrangement. The acetyl derivative of IV was converted smoothly to its acid chloride VI by treatment with oxalyl chloride at room temperature. Use of scrupulously purified thionyl chloride for the preparation of VI caused considerable decomposition of the starting acid. Isolation of VI was rendered difficult in view of its extreme reactivity toward atmospheric moisture, but the *p*-bromoanilide of glycolic acid IV was obtained in almost quantitative yield when a freshly prepared sample of VI was treated with *p*-bromoaniline. Conventional treatment of acid chloride VI with excess diazomethane gave the crystalline diazo ketone VII in 83.5% yield.

In order to develop the synthetic procedures leading to VII, as well as to investigate the biological activity of the 3-substituted analog of I, initial experiments were conducted employing 3-acetylphenanthrene in a similar sequence. α-Acetoxy-3-phenanthrylacetyl chloride, obtained by the synthetic scheme described for the preparation of VI, did not, however, yield the corresponding diazo ketone upon treatment with diazomethane. Work on the 3-series consequently was abandoned.

Hydrolysis of VII with dilute sulfuric acid yielded a pale yellow oil which could not be made to crystallize. Treatment of the latter with phenylhydrazine gave a crystalline product, which, from its analytical data, appeared to be the osazone of either 1-(2-phenanthryl)-1,2-propanedione (VIII) or 2-phenanthrylmethylglyoxal (IX). Analogous transformations of 3-acetoxy-3-phenyl-diazo-2-propanone and 3-acetoxy-3-phenyl-1-chloro-2-pro-

(1) Abstracted from a portion of the Ph.D. dissertation of Upendra K. Pandit, June, 1958.

(2) L. H. Sarett, THIS JOURNAL, **68**, 2478 (1946).

(3) L. H. Sarett, *ibid.*, **70**, 1454 (1948).

(4) L. H. Sarett, G. E. Arth, R. M. Lukes, R. E. Beyler, G. I. Poos, W. F. Johns and J. M. Constantin, *ibid.*, **74**, 4974 (1952).

(5) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *ibid.*, **74**, 4223 (1952).

(6) W. H. Linnell, D. W. Mathieson and G. Williams, *Nature*, **167**, 237 (1951).

(7) W. Bradley and R. Robinson, *J. Chem. Soc.*, 1541 (1928).

(8) W. H. Linnell and I. M. Roushdi, *Quart. J. Pharm. Pharmocol.*, **14**, 270 (1941).

(9) P. Ruggli and K. Knecht, *Helv. Chim. Acta*, **27**, 1108 (1944).

(10) W. Logemann and P. Giraldi, *Hoppe-Seyler's Z. physiol. Chem.*, **289**, 19 (1951).

(11) M. C. Kloetzel and B. Y. Abadir, THIS JOURNAL, **77**, 3823 (1955).

(12) R. A. Khan and W. H. Linnell, *J. Pharm. and Pharmocol.*, **1**, 230 (1949).

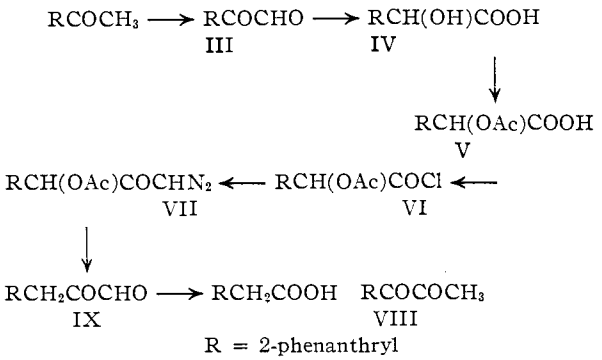
(13) W. H. Linnell and I. M. Roushdi, *Nature*, **148**, 595 (1941).

(14) G. Brownlee and W. M. Duffin, British Patent 550,262 (1942); *C. A.*, **38**, 977 (1944).

(15) J. H. Burckhalter and J. Sam, THIS JOURNAL, **74**, 187 (1952).

(16) M. C. Kloetzel and U. K. Pandit, *ibid.*, **78**, 1412 (1956).

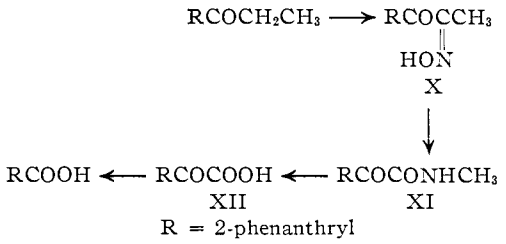
panone upon treatment with acid have been reported.[17,18]



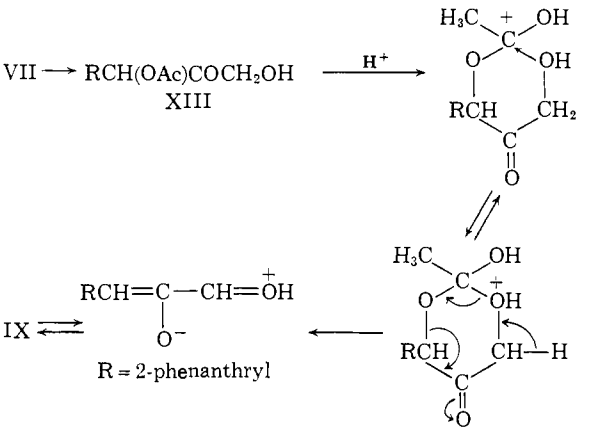
With a view to determine the structure of the hydrolytic product of VII, synthesis of VIII was undertaken so that its osazone could be compared with that of the former product. 2-Propionylphenanthrene was obtained by a Friedel–Crafts reaction of propionic anhydride with purified phenanthrene. Condensation of the ketone with butyl nitrite, in the presence of hydrogen chloride, gave monoöxime X in 70% yield. Hydrolysis of X under a variety of conditions, however, failed to give the diketone VIII. Instead, the product of acid hydrolysis was found to be N-methyl-2-phenanthroylformamide (XI). The structure of the amide was shown by its hydrolysis to 2-phenanthroylformic acid (XII), which was further decarbonylated to 2-phenanthroic acid.

The isolation of XI in 90% yield points to an almost exclusive methyl migration during the rearrangement of X. Since the Beckmann rearrangement proceeds *via* a *trans* migration,[19,20] the methyl and hydroxyl groups in X are presumed to be in the *trans* configuration.

The hydrolytic product of VII finally was shown to be 2-phenanthrylmethylglyoxal (IX), by mild oxidation of the yellow oil to 2-phenanthrylacetic acid, which was identical with an authentic sample prepared from 2-acetylphenanthrene by a Willgerodt reaction.[21]



Bradley and Eaton[17] have reported the formation of benzylglyoxal upon acid treatment of their "presumed" sample of 3-acetoxy-3-phenyldiazo-2-propanone. These workers suggest that the transformation occurs as a result of "splitting off" of the acetoxyl group followed by a rearrangement of the resulting system. The immediate evolution of nitrogen in our experiments would seem to indicate that the initial reaction is the hydrolysis of the diazomethyl group, presumably leading to the formation of the hydroxymethyl ketone XIII. A nucleophilic attack by the hydroxyl oxygen on the protonated ester carbonyl in XIII should lead to an ortho ester, which could eliminate a molecule of acetic acid at this stage to yield the keto aldehyde IX. The following mechanism is proposed for the transformation of VII to IX.



In another approach to convert VII to the cortical analog I, diazo ketone VII was smoothly converted to the corresponding chloromethyl ketone either by treatment with concentrated hydrochloric acid or by passing dry hydrogen chloride gas through an ethereal solution of the diazo ketone. However, attempts to hydrolyze the chloromethyl ketone with potassium formate and methanol or treatment with silver acetate and acetic acid in order to obtain the acetate of I proved unsuccessful.

Three routes for the synthesis of α-(2-phenanthryl)-*n*-butyric acid, an essential intermediate for the preparation of II, were investigated. Attempted preparation of the Grignard reagent from α-(2-phenanthryl)-*n*-propyl bromide (XIV), which might then be carbonated or, alternately, made to react with methoxyacetonitrile to yield the methoxy derivative of II, proved unsuccessful. When XIV was treated with magnesium metal under a variety of conditions, two products were isolated from the reaction mixture. These were a colorless solid which was infusible and a crystalline product melting at 198–200°. Analytical data indicated that both substances possessed an empirical formula $C_{17}H_{15}$. Formation of a picrate and a *sym*-trinitrobenzene derivative and determination of molecular weight indicated that the compounds were isomeric hydrocarbons of the molecular formula $C_{34}H_{30}$. Since the simplest reaction leading to the formation of such hydrocarbons would be a Wurtz-type bimolecular condensation of XIV, it is suggested that these products are the racemic and *meso* forms of 3,4-bis-(2-phenanthryl)-hexane (XV).

Since benzyl-type halides are reported to undergo easy conversion to corresponding nitriles by interaction with metal cyanides,[22] the method was applied to the preparation of α-(2-phenanthryl)-butyronitrile. Treatment of XIV with sodium

(17) W. Bradley and J. K. Eaton, *J. Chem. Soc.*, 1913 (1937).
(18) L. I. Smith and R. H. Anderson, *J. Org. Chem.*, **16**, 963 (1951).
(19) O. L. Brady and G. Bishop, *J. Chem. Soc.*, **127**, 1357 (1925).
(20) J. Meisenheimer, P. Zimmermann and U. v. Kummer, *Ann.*, **446**, 205 (1926).
(21) E. Schwenk and E. Bloch, THIS JOURNAL, **64**, 3051 (1942).
(22) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 591.

cyanide gave only an oil from which no alkali-soluble material could be isolated after hydrolysis. When XIV was treated with cuprous cyanide and pyridine a product of m.p. 101–102° was isolated. By analogy with the reported formation of 1,3-diphenyl-1-butene[23] when the analogous α-chloroethylbenzene is treated with cuprous cyanide and pyridine and in accord with the analytical data obtained for the product, structure XVI is suggested for this compound. Apparently XVI is formed by dehalogenation of bromide XIV followed by an attack of the resulting cation on a molecule of the unsaturated hydrocarbon produced by dehydrohalogenation of XIV.

In accordance with the proposed structure of XVI, a tetrabromide was obtained when the latter was treated with excess bromine. Since under conditions of bromination the addition of bromine at the 9- and 10-positions of the two phenanthryl groups is followed by dehydrohalogenation,[24] the exact location of two of the bromine atoms in the tetrabromide remains undetermined.

$$CH_3CH_2CHRCHRCH_2CH_3 \xleftarrow{} \underset{XIV}{RCHBrCH_2CH_3} \longrightarrow \underset{XVI}{CH_3CH_2CHRC(CH_3)=CHR}$$

R = 2-phenanthryl

We were unable to condense 2-propionylphenanthrene with α-halo esters, in an attempt to prepare the required glycidic ester which could be hydrolyzed and rearranged to α-(2-phenanthryl)-*n*-butyraldehyde. The reaction of 2-propionylphenanthrene with either ethyl α-chloroacetate or ethyl α-bromoacetate in the presence of condensing agents such as sodium ethoxide, sodium amide or lithium amide gave in each case reaction mixtures from which the starting ketone could be recovered almost quantitatively.

Experimental[25]

2-Phenanthrylglyoxal (III) (a).—Selenium dioxide (2.2 g.) was added to a solution of 2-acetylphenanthrene (4.4 g.) in acetic acid (100 ml.) and the mixture was heated to reflux for 24 hours. The hot reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting oil, dissolved in benzene and allowed to stand overnight, afforded 1.5 g. of a yellow product, m.p. 138–142°.

Concentration of the filtrate gave a semi-solid material which after trituration with petroleum ether (b.p. 63–69°) gave a colorless product, m.p. 200–220°. Several crystallizations from benzene gave colorless 2-phenanthroic acid, m.p. 258–260°. Mixed m.p. with an authentic sample of 2-phenanthroic acid showed no depression. The identity of the acid was further confirmed by conversion to its methyl ester, m.p. 95–96° (Mosettig[26] reports methyl 2-phenanthroate, m.p. 96–96.5°).

The product, m.p. 138–142°, was shown to be 2-phenanthrylglyoxal (III) by conversion to its quinoxaline derivative, which crystallized from ethanol in yellow needles, m.p. 202°.

Anal. Calcd. for $C_{22}H_{14}N_2$: N, 9.14. Found: N, 8.94.

(23) G. L. Goerner and W. G. Hines, THIS JOURNAL, **70**, 3511 (1948).

(24) C. C. Price, *Chem. Revs.*, **29**, 37 (1941).

(25) Microanalyses are by Mr. W. J. Schenck, formerly of this University, Mr. C. W. Beazley, Micro-Tech Laboratories, Skokie, Ill., and Dr. A. Elek, Elek Micro-Analytical Laboratory, Los Angeles, Calif. Melting points are uncorrected.

(26) E. Mosettig, THIS JOURNAL, **52**, 3704 (1930).

(b).—To a warm solution of 2-acetylphenanthrene (15 g.) in toluene (500 ml.) was added selenium dioxide (15 g.) and the mixture was heated to reflux for 48 hours. Metallic selenium was removed by filtering the hot solution and the filtrate was concentrated under reduced pressure. The residual semi-solid was triturated with dry benzene whereupon 6 g. of a colorless product, m.p. 148–150°, crystallized. On allowing the benzene filtrate to stand for several days, 7 g. more of the colorless glyoxal (III), m.p. 140–145°, was obtained. Recrystallization from benzene, toluene or dioxane caused decomposition of the glyoxal, *e.g.*, when the product, m.p. 140–145°, was dissolved in dioxane and the solution cooled, a solid, m.p. 258–260°, separated out. The latter product was shown to be 2-phenanthroic acid from its mixed m.p. with an authentic sample of the same acid, and conversion to its methyl ester, m.p. 94–96°. Recrystallization from methanol gave the **methyl alcoholate of 2-phenanthrylglyoxal**, m.p. 86° dec.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.83; H, 5.79.

The osazone of 2-phenanthrylglyoxal crystallized from ethanol in yellow cubes, m.p. 209–210° dec.

Anal. Calcd. for $C_{28}H_{22}N_4$: C, 81.14; H, 5.35; N, 13.51. Found: C, 81.15; H, 5.41; N, 13.55.

3-Acetylphenanthrene was oxidized similarly to **3-phenanthrylglyoxal**, m.p. 125–134°, in 66% yield. The quinoxaline derivative of 3-phenanthrylglyoxal was obtained from 95% ethanol in bright yellow needles, m.p. 183–184°.

Anal. Calcd. for $C_{22}H_{14}N_2$: C, 86.21; H, 4.61. Found: C, 85.89; H, 4.47.

3-Phenanthrylglyoxalosazone was obtained as a yellow solid, m.p. 175–177°.

Anal. Calcd. for $C_{28}H_{22}N_5$: C, 81.14; H, 5.35; N, 13.51. Found: C, 80.83; H, 5.52; N, 13.60.

2-Phenanthrylglycolic Acid (IV).—2-Phenanthrylglyoxal (10 g.) was added with mechanical stirring to a solution of sodium hydroxide (20 g.) in ethanol (95%, 300 ml.) and water (200 ml.). The mixture was heated to reflux for 3 hours and then poured into a large volume of water. Acidification with hydrochloric acid gave a dark brown solid. The latter was extracted with ethyl ether (700 ml.) and the filtered extract was concentrated to yield 3 g. of the acid IV, m.p. 220°. When the residual material after evaporation of the ether extracts was crystallized from benzene, 4.25 g. more of IV, m.p. 218–220°, was obtained; total yield, 7.25 g. (67%).

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.17; H, 4.79. Found: C, 76.30; H, 4.77.

3-Phenanthrylglycolic acid was obtained similarly in 50% yield and melted at 141–143°.

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.17; H, 4.79. Found: C, 75.93; H, 4.78.

α-Acetoxy-2-phenanthrylacetic Acid (V).—A mixture of IV (5.8 g.), acetyl chloride (25 ml.) and a few drops of pyridine was heated to reflux for 4 hours. The reaction product was poured into ice-cold water and stirred until the oil initially formed had solidified. The solid was filtered, washed with water and dried over sodium hydroxide. Crystallization from a mixture of benzene and petroleum ether (b.p. 63–69°) gave 5.1 g. (75%) of V, m.p. 170–171°. Treatment of the filtrates with decolorizing charcoal and concentration deposited another 900 mg. of the acid, m.p. 165–167°.

Anal. Calcd. for $C_{18}H_{14}O_4$: C, 73.55; H, 4.76. Found: C, 73.21; H, 4.89.

α-Acetoxy-3-phenanthrylacetic acid, m.p. 166–167°, was obtained from the corresponding hydroxy acid in 92% yield.

Anal. Calcd. for $C_{18}H_{14}O_4$: C, 73.55; H, 4.76. Found: C, 73.44; H, 5.06.

α-Acetoxy-2-phenanthrylacetyl Chloride (VI).—α-Acetoxyphenanthrylacetic acid (250 mg.) was dissolved in oxalyl chloride (3 ml.) and the solution allowed to stand at room temperature for 24 hours. The excess of the oxalyl chloride was removed under vacuum and the resulting oil was dissolved in petroleum ether (b.p. 63–69°). Upon cooling, a colorless product, m.p. 78–80°, was obtained. The latter was immediately dissolved in dry benzene and added to a benzene solution of *p*-bromoaniline. After heating the mixture to reflux for 2 hours the benzene layer was washed suc-

cessively with water, 1% hydrochloric acid, 2% sodium bicarbonate and again with water. Evaporation of the dried benzene solution gave 380 mg. (quantitative yield) of the anilide, m.p. 210–214°. Recrystallization from benzene gave the pure anilide, m.p. 213–214.5°.

Anal. Calcd. for $C_{24}H_{18}BrNO_3$: C, 64.30; H, 4.04. Found: C, 64.54; H, 4.07.

The *p*-bromoanilide of α-acetoxy-3-phenanthrylacetic acid, m.p. 202–204°, was obtained similarly in 80% yield.

Anal. Calcd. for $C_{24}H_{18}BrNO_3$: C, 64.30; H, 4.04; Br, 17.83. Found: C, 64.42; H, 4.11; Br, 17.89.

3-Acetoxy-2-oxo-3-(2-phenanthryl)-diazopropane (VII).—Acid V (1 g.) was treated with oxalyl chloride and converted to the acid chloride VI. A cold solution of VI in petroleum ether (b.p. 63–69°) was added to an ethereal solution of diazomethane, prepared from 3.5 g. of N-nitroso-N-methylurea, the mixture being maintained at 0–5° during the addition. After complete addition the mixture was stirred for a further period of 12 hours at room temperature. Removal of the solvent and crystallization from ether gave 900 mg. (83.5%) of diazo ketone VII, m.p. 125–126°.

Anal. Calcd. for $C_{19}H_{14}NO_3$: C, 71.70; H, 4.43; N, 8.80. Found: C, 71.94; H, 4.87; N, 8.65.

1-Acetoxy-1-(2-phenanthryl)-3-chloro-2-propanone.—Dry hydrogen chloride was passed for 1 hour through a solution of VII (1 g.) in ether. The mixture was allowed to stand at room temperature for a period of 12 hours and the solvent was evaporated under reduced pressure whereupon the colorless chloro ketone was obtained. Two crystallizations from petroleum ether (b.p. 63–69°) gave 850 mg. (83%) of the ketone, m.p. 126–128°. The ketone could also be obtained in similar yield when VII, dissolved in glacial acetic acid, was treated with concentrated hydrochloric acid.

Anal. Calcd. for $C_{19}H_{15}ClO_3$: C, 69.83; H, 4.63. Found: C, 69.53; H, 4.59.

Hydrolysis of Diazoketone VII.—To a solution of VII (150 mg.) was added 7 ml. of 5% sulfuric acid. After the evolution of nitrogen had subsided the mixture was heated to reflux for 2 hours. The reaction product was diluted with water, was extracted with ether and the ethereal layer was washed successively with water, sodium bicarbonate (2%) and again with water. Evaporation of the solvent left a pale yellow oil which showed no tendency to crystallize upon standing for a week at 0°. The oil was dissolved in 10 ml. of ethanol (95%) and the solution was heated to reflux with 0.5 ml. of phenylhydrazine and a few drops of acetic acid for 1.5 hours. Upon cooling and concentrating the solution the **osazone of 2-phenanthrylmethylglyoxal** was obtained. Recrystallization from ethanol gave 180 mg. of the osazone, m.p. 199–201°.

Anal. Calcd. for $C_{29}H_{24}N_4$: C, 81.30; H, 5.65. Found: C, 80.69; H, 5.77.

Oxidation of 2-Phenanthrylmethylglyoxal (IX).—Diazo ketone VII (500 mg.) was dissolved in dioxane and 15 ml. of 5% sulfuric acid was added. The oily glyoxal was isolated as previously described and added to a suspension of silver oxide (500 mg.) in a solution of sodium hydroxide (1 g.) in water (15 ml.). The mixture was heated to reflux with mechanical stirring for 2 hours. After being filtered the reaction mixture was acidified with hydrochloric acid, whereupon a colorless solid separated. Two crystallizations from a mixture of benzene and petroleum ether (b.p. 63–69°) gave 2-phenanthrylacetic acid, m.p. 183°, in 50% yield. A mixed m.p. of this sample with authentic 2-phenanthrylacetic acid showed no depression.

2- and 3-Propionylphenanthrene.—Purified phenanthrene[27] (178 g.) was added to a cold solution of 347 g. of aluminum chloride in 1780 ml. of dry nitrobenzene. To the resulting dark solution was added freshly distilled propionic anhydride (160 g.) over a period of 40 minutes while the temperature of the reaction mixture was maintained at 0–5°. After standing for 21 hours at room temperature, the reaction mixture was hydrolyzed by addition of 1500 g. of ice and 100 ml. of concentrated hydrochloric acid. The residual semi-solid which remained after steam distillation of nitrobenzene was dissolved in benzene and the benzene solution was shaken with dilute sodium bicarbonate. Solvents were distilled under reduced pressure and the mixture of ketones which boiled at 201–205° at 4.5 mm. was dissolved in a mixture of acetone (60 ml.) and ethanol (95%, 150 ml.). When the solution was cooled to 0°, 2-propionylphenanthrene crystallized. Recrystallization from absolute ethanol gave 36.1 g. (15%) of the ketone as colorless needles, m.p. 99–102°.[28]

After separation of the 2-isomer the mother liquor deposited 129.3 g. of crude 3-propionylphenanthrene, m.p. 40–51°. Several crystallizations from methanol gave 59.5 g. (25.4%) of the pure ketone, m.p. 52–54°.[29]

1-(2-Phenanthryl)-1,2-propanedione-2-oxime (X).—2-Propionylphenanthrene (2.34 g.) was dissolved in 200 ml. of ether in a flask fitted with a condenser, a mechanical stirrer, a dropping funnel and a gas inlet tube connected to a hydrogen chloride generator. Hydrogen chloride gas was introduced at a fairly rapid rate while 2 g. of freshly distilled butyl nitrite was added slowly over a period of 1 hour to the stirred solution. After 2.5 hours the addition of the gas was stopped and the reaction products were stirred for another 12 hours at room temperature. Evaporation of the solvent gave 2.32 g. of a colorless product, m.p. 189–191°. Four crystallizations from benzene gave 2 g. (76%) of pure oxime, m.p. 202–203°.

Anal. Calcd. for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.42; H, 5.08; N, 5.20.

Rearrangement of X.—A solution of X (500 mg.) in ethanol (95%, 30 ml.) and sulfuric acid (6%, 15 ml.) was heated to reflux for 20 hours. Upon working up the reaction mixture in the conventional manner, 450 mg. (90%) of XI, m.p. 135° dec., was obtained. When the melting point of XI was determined in a bath preheated at 110° and the temperature was raised slowly, the product formed upon initial decomposition melted at 256–258°. Hydrolysis of X with 2% sulfuric acid and shorter reflux time gave similar results.

Anal. Calcd. for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.31. Found: C, 77.44; H, 4.94; N, 5.22.

Hydrolysis of N-Methyl-2-phenanthroylformamide (XI).—A solution of XI (120 mg.) in 10 ml. of 10% sodium hydroxide was heated to reflux for 7 hours. An amine-like odor was detected during the reaction. The reaction mixture was boiled with charcoal, filtered and acidified to give **2-phenanthroylformic acid (XII)**. After crystallization from benzene, 20 mg. of the pure acid, m.p. 224° dec., was isolated.

Anal. Calcd. for $C_{16}H_{10}O_3$: C, 76.39; H, 4.03. Found: C, 76.41; H, 4.10.

Fifty mg. of the product (m.p. 224° dec.) was heated in an oil-bath at 245° for 20 minutes, and the resulting melt was dissolved in benzene, boiled with charcoal and filtered. The filtrate, upon cooling, gave colorless 2-phenanthroic acid, m.p. 257–260°, which showed no mixed m.p. depression when compared with an authentic sample of the same acid.

Reaction of α-(2-Phenanthryl)-*n*-propyl Bromide (XIV)[30] with Magnesium.—Following the general procedure described by Hauser,[31] a solution of XIV (6.7 g.) in 130 ml. of dry ether was added dropwise to a mixture of magnesium turnings (0.9 g.), XIV (150 mg.) and 20 ml. of ether. The addition of the halide was completed over a period of 90 minutes and the mixture was then heated to reflux for 3.5 hours. The colorless solid product which had separated during the reaction was filtered dissolved in hot benzene and again filtered to remove metallic magnesium. Upon cooling, the solution deposited 3 g. of **3,4-bis-(2-phenanthryl)-hexane (XV)**, infusible at 300°.

Anal. Calcd. for $C_{34}H_{30}$: C, 93.10; H, 6.89. Found: C, 92.96; H, 6.67.

The picrate of the hydrocarbon, prepared in the conventional manner, was crystallized from ethanol; m.p. 154° dec.

Anal. Calcd. for $C_{34}H_{30}(C_6H_3N_3O_7)_2$: N, 9.32. Found: N, 9.00.

(27) Y. Hirschberg and E. Bergmann, *Chemistry & Industry*, 823 (1939).

(28) B. Riegel, M. H. Gold and M. A. Kubico, THIS JOURNAL, **64**, 2221 (1942).

(29) W. E. Bachmann and W. S. Struve, *ibid.*, **58**, 1659 (1936).

(30) B. Riegel, M. H. Gold and M. A. Kubico, *ibid.*, **65**, 1772 (1943).

(31) W. J. Humphlett, M. J. Weiss and C. R. Hauser, *ibid.*, **70**, 4020 (1948).

The *sym*-trinitrobenzene derivative, showed m.p. 157–159°.

Anal. Calcd. for $C_{34}H_{30}(C_6H_3N_3O_6)_2$: C, 63.88; H, 4.20; N, 9.72. Found: C, 63.58; H, 4.16; N, 9.72.

Concentration of the benzene filtrates gave the lower melting form, m.p. 198–200°, of **3,4-bis-(2-phenanthryl)-hexane (XV)**.

Anal. Calcd. for $C_{34}H_{30}$: C, 93.10; H, 6.89; mol. wt., 438. Found: C, 92.80; H, 6.80; mol. wt. (Rast's method), 428.

Reaction of α-(2-Phenanthryl)-*n*-propyl Bromide with Cuprous Cyanide and Pyridine.—A mixture of XIV (1.0 g.), cuprous cyanide (600 mg.) and pyridine (5 ml.) was heated at 160° for 24 hours. The reaction mixture was poured into dilute ammonium hydroxide and an ethereal extract of the resulting organic material was washed repeatedly with ammonium hydroxide solution until the aqueous layer did not develop a blue color. After being washed with dilute hydrochloric acid and then with water, the ether solution was dried over calcium chloride. Evaporation of the solvent gave a gummy material which, after several crystallizations from ethanol, gave 250 mg. of the unsaturated hydrocarbon XVI, m.p. 101–102°.

Anal. Calcd. for $C_{34}H_{28}$: C, 93.53; H, 6.47. Found: C, 93.83; H, 6.38.

Bromination of XVI.—A solution of bromine in carbon tetrachloride was added to 200 mg. of XVI dissolved in absolute ethanol, until a pale yellow color persisted. The mixture was allowed to stand for 8 hours. Concentration of the solution gave a solid which, after three crystallizations from ethanol, gave the pure tetrabromide, m.p. 145°, yield 60 mg.

Anal. Calcd. for $C_{34}H_{26}Br_4$: C, 54.14; H, 3.47. Found: C, 54.36; H, 3.73.

COMMUNICATIONS TO THE EDITOR

BIS-3-METHYL-2-BUTYLBORANE AS A SELECTIVE REAGENT FOR THE REDUCTION OF REPRESENTATIVE FUNCTIONAL GROUPS

Sir:

Bis-3-methyl-2-butylborane is a highly selective reagent for the hydroboration of olefins and dienes.[1] We now report that this reagent exhibits remarkable selectivity in its reducing action toward representative functional groups, permitting selective reductions not otherwise feasible.

The groups listed are reduced at 0° in 0.5 *M* solution in tetrahydrofuran (products in parentheses): aldehydes and ketones (alcohols), unhindered olefins and acetylenes (organoboranes), γ-lactones (hydroxyaldehydes) and N,N-dimethylamides (aldehydes). Nitrobenzene and nitriles react only slowly under these conditions.

These groups react to evolve hydrogen, but do not undergo reduction: alcohols, phenols, carboxylic acids, amides, and sulfonic acids. No reaction occurs under these conditions with esters, acid chlorides, acid anhydrides, azobenzene, sulfones and sulfonyl chlorides.

The failure of bis-3-methyl-2-butylborane to reduce carboxylic acids is unexpected in view of the very fast reaction with diborane.[2] It makes possible both selective reductions and hydroborations in the presence of unprotected carboxylic acid groups, as illustrated by the following conversion of 10-undecenoic acid to 11-hydroxyundecanoic acid.

Undecenoic acid, 25 mmoles, was treated with a solution of 50 mmoles of bis-3-methyl-2-butylborane[1] in tetrahydrofuran at 0°. Hydrogen (24 mmoles) was rapidly evolved. After 30 minutes, the reaction mixture was treated with alkaline hydrogen peroxide and the product was recrystallized from water. There was obtained 20.6 mmoles, 82% yield, of 11-hydroxyundecanoic acid, m.p. 68–69°.[3]

(1) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **82**, 3222 (1960).

(2) H. C. Brown and B. C. Subba Rao, *ibid.*, **82**, 681 (1960).

(3) P. Chuit and J. Hausser, *Helv. Chim. Acta*, **12**, 463 (1929), report m.p. 70–70.5°.

γ-Lactones react with one mole of the reagent, even when the latter is in excess. That the product is the hydroxyaldehyde was confirmed by demonstrating the reduction of γ-butyrolactone to ω-hydroxybutyraldehyde (73% yield of 2,4-dinitrophenylhydrazone, m.p. 198–199°). A representative procedure is given.

γ-Valerolactone, 50 mmoles, was treated with 0.5 *M* reagent for about 15 hours at 25°, followed by oxidation with alkaline (*p*H 8) hydrogen peroxide at 0°. γ-Hydroxyvaleraldehyde, b.p. 60–61° at 9 mm.,[4] was isolated, 38 mmoles, 76% yield.

The reaction of the reagent with these lactones is more rapid than its reaction with typical ketones. Consequently, it should be possible to achieve the selective reduction of such lactones in the presence of ketone, carboxylic acid or ester groups.

We continue to explore the full applicability of this versatile reagent.

Acknowledgment.—This study was made possible by a grant from the American Cyanamid Company. This support is gratefully acknowledged.

(4) B. Helferich, *Ber.*, **52**, 1123 (1919), reports b.p. 63–65° at 10 mm.

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HYDROBORATION AS A CONVENIENT PROCEDURE FOR THE ASYMMETRIC SYNTHESIS OF ALCOHOLS OF HIGH OPTICAL PURITY

Sir:

We wish to report a new asymmetric synthesis which permits the conversion of olefins into optically active alcohols with optical purities in the neighborhood of 90%.

We previously observed that the hydroboration of hindered olefins proceeds rapidly to the dialkylborane stage and these compounds exhibit a remarkable selectivity for the hydroboration of olefins