The Reaction Mixture from II. The Preparation of 3-Phenyl-7,9-dioxa-3-azabicyclo[3.3.1]nonane (X).—The reaction mixture was filtered from aniline hydroiodide (0.48 g.) and steam distilled until all xylene and excess aniline was removed and only unreacted II and water distilled. The contents of the distilling flask were then made 6 *N* with sulfuric acid and heated with agitation on the steam-bath for 15 minutes. The acidic mixture was cooled and filtered. The filtrate was made basic by the addition of solid sodium hydroxide. The solid that separated was filtered and dried. It was extracted by hot ligroin and the extract evaporated and cooled to yield 0.12 g. (22%) of light yellow plates of m.p. 132–134°. The product was recrystallized again from ligroin to yield colorless plates, m.p. 134°.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82; mol. wt., 205.3. Found: C, 69.92; H, 7.36; N, 6.68; mol. wt. cryoscopic in benzene, 211.

The Reaction Mixture from III.—The reaction mixture was filtered from 0.08 g. of aniline hydroiodide (indicating some reaction) and then worked up in the same manner as the reaction mixture from II. When the aqueous acidic solution was made basic a tar (*ca.* 30 mg.) precipitated. It was extracted into hot ligroin, but could not be recrystallized from ligroin or ethanol. The tar could not be solidified at −70°.

The Preparation and Hydrolysis of 2,6-*p*-Dioxanedicarboxylic Anhydride (XI).—One and sixty-eight hundredths grams (0.00954 mole) of *cis*-2,6-*p*-dioxanedicarboxylic acid (IV) was dissolved in 50 ml. of hot acetic anhydride and the solution boiled down at atmospheric pressure to a volume of 5 ml. It was then heated at 80° under reduced pressure to remove excess acetic anhydride. Fifty ml. of hexane was added to the cooled reaction product and the resulting immiscible liquids were agitated while 15 ml. of benzene was slowly added to the mixture. The reaction product formed large crystals during this operation. The crystals were filtered off and dissolved in 25 ml. of hot benzene. The benzene solution was poured into 40 ml. of hexane and 1.14 g. (76%) of colorless crystals was precipitated. They were dried for 2 hours at 5 mm., m.p. 106°.

Anal. Calcd. for $C_6H_6O_5$: neut. equiv., 79.1; mol. wt., 158.1. Found: neut. equiv., 79; mol. wt. cryoscopic in benzene, 169.

Thirty-three hundredths gram of this anhydride was dissolved in 5 ml. of water and the solution evaporated to dryness at 105°. The acidic residue weighed 0.34 g. and melted at 179°. The mixed melting point with IV was 177–178°.

Acknowledgment.—We wish to express our thanks to the Abbott Foundation of Northwestern University for the grant of financial aid that made this work possible.

EVANSTON, ILLINOIS

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF DUKE UNIVERSITY]

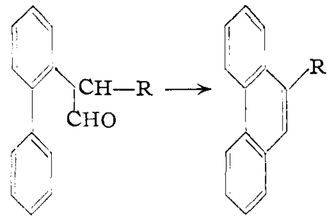
Aromatic Cyclodehydration. XXVII.[1] Cyclization of Aldehydes, Ketones and Ketonitriles

BY CHARLES K. BRADSHER AND WINSTON J. JACKSON, JR.[2]

RECEIVED OCTOBER 5, 1953

It has been shown that (2-biphenylyl)-acetaldehyde, some of its homologs and (2-biphenylyl)-acetone may be cyclized rapidly and in good yield to phenanthrene and 9-alkylphenanthrenes. Cyclization of acyl-(2-biphenylyl)-acetonitriles with hydrobromic and acetic acids affords a new route to 9-alkyl-10-phenanthronitriles and -phenanthramides.

Several years ago it was predicted that 2-biphenylyl-acetaldehyde (I, R = H) "as well as any compound converted to it under conditions of the cyclization, can be made to yield phenanthrene."[3]



I II

(R = H, CH_3, C_2H_5)

An earlier attempt to test the first part of this prediction was thwarted when the general synthesis of Darzens and Meyer[4] failed to yield the desired aldehyde.[5]

It has now been found possible to prepare the aldehyde in 46% yield by the Rosenmund reduction of 2-biphenylylacetyl chloride. In a similar manner, we have made α-(2-biphenylyl)-propionaldehyde (I, R = CH_3) and α-(2-biphenylyl)-butyraldehyde. The required α-(2-biphenylyl)-propionic acid was synthesized in a manner analogous to that described[6] for the α-(2-biphenylyl)-butyric acid. Since the acid chlorides could undergo an intramolecular Friedel and Crafts reaction, they were not purified by distillation. It appeared that little cyclization occurred under the conditions of the reduction, since only traces of phenolic material could be recovered from the reaction mixture. The chief loss in the reduction appeared to come from the further reduction of some of the aldehyde.

In boiling hydrobromic–acetic acid, the aldehydes were rapidly cyclized to the expected phenanthrene derivatives (II). The hydrocarbons crystallized in almost pure condition (melting point not more than one degree below that of a pure sample) from the cooled cyclization mixture. As an indication of the rapidity of the reaction, the biphenylylpropionaldehyde gave a 93% yield of 9-methylphenanthrene after a refluxing time of only *two minutes*.

In order to prepare 3-hydroxy-10-methylphenanthrene, α-(5-methoxy-2-biphenylyl)-propionitrile (III) was prepared from (5-methoxy-2-biphenylyl)-acetonitrile[1] by alkylation. Hydrolysis of the alkylated nitrile III with alcoholic potassium hydroxide solution yielded the acid IV. The acid was con-

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(1) For the preceding communication of this series, see THIS JOURNAL, **74**, 4880 (1952).

(2) Public Health Service Fellow of the National Cancer Institute (1950–1952).

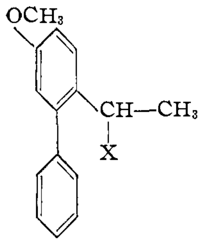
(3) C. K. Bradsher and R. W. Wert, THIS JOURNAL, **62**, 2806 (1940).

(4) G. Darzens and M. Meyer, *Compt. rend.*, **196**, 489 (1933); M. Meyer, *ibid.*, **204**, 508 (1937).

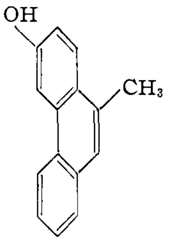
(5) S. Thomas Amore, Thesis presented in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of Arts and Sciences of Duke University, 1944.

(6) C. K. Bradsher and W. J. Jackson, Jr., THIS JOURNAL, **73**, 3235 (1951).

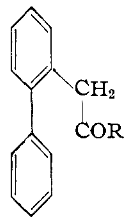
verted to the crude acid chloride which, on reduction, afforded a small yield of the aldehyde, purified only by conversion to the bisulfite derivative. The resulting aldehyde was cyclized in good yield to what is believed to be 3-hydroxy-10-methylphenanthrene (V).



III, X = CN
IV, X = COOH



V



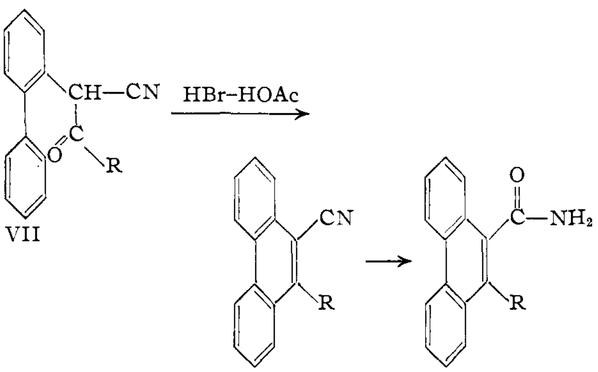
VI

Just as compounds of type I represent the simplest aldehydes which could yield phenanthrenes on cyclization, compounds of type VI represent the simplest ketones which might undergo the same type of ring-closure. Two of these, the methyl (VI, R = CH_3) and the isobutyl (VI, R = $(CH_3)_2CHCH_2$) ketones have been prepared in poor yield by the action of 2-biphenylylacetyl chloride on the respective dialkylcadmium reagents. Both of the ketones were distilled in vacuum, but neither was obtained in a state of analytical purity. When refluxed for one hour in hydrobromic–acetic acid, the methyl ketone (VI, R = CH_3) afforded 9-methylphenanthrene in 80% yield. The isobutyl ketone (VI, R = $(CH_3)_2CHCH_2$) yielded a hydrocarbon having the expected composition.

In the reaction of the biphenylylacetyl chlorides with the dialkylcadmium reagents considerable quantities of 9-phenanthrol were formed. Since this was not observed in the Rosenmund reduction despite the much higher temperature used, it suggests that cadmium chloride may have functioned as a Friedel and Crafts type catalyst in the present instance.

In another attempt to obtain 2-biphenylylacetone (VI, R = CH_3), 2-biphenylylacetic acid was treated with a large excess of methyl lithium.[7] An insoluble salt formed which even on prolonged refluxing and stirring yielded no ketone.

In earlier cyclization studies,[8] it was shown that certain ketonitriles (VII, R = aryl), on refluxing with hydrobromic–acetic acid yielded 9-arylphenanthrenes. Since the corresponding aliphatic ketonitriles are easily prepared also, by acylation of the anion from 2-biphenylylacetonitrile with suitable esters, it appeared worthwhile to determine how these behave upon refluxing with hydrobromic and acetic acids. Unlike the arylketonitriles (VII, R = aryl) the aliphatic analogs (VII, R = CH_3 or C_2H_5) undergo cyclization so rapidly[9] that there is insufficient time for hydrolysis of the nitrile group (followed by decarboxylation) to occur and the 9-alkyl-10-cyanophenanthrene (VIII) or the corresponding amide is obtained rather than the hydrocarbon.



VII VIII IX
R = CH_3, C_2H_5

Continued refluxing of the nitrile VIII in hydrobromic–acetic acid yielded first the corresponding amide and finally the hydrocarbon. Even at the end of a week of refluxing, a considerable quantity of amide remained. None of the carboxylic acid (9-alkylphenanthroic acid) was isolated. Although the new nitriles VIII are very sterically hindered, it is believed that they will form useful intermediates in some types of syntheses.

Experimental[10]

Ethyl (2-Biphenylylmethyl)-ethoxymalonate.[11]—To 0.1 mole of sodium ethoxide in 150 ml. of absolute ethanol, 20.4 g. of ethoxymalonic ester[12] was added dropwise in 50 ml. of ethanol. To this, 24.7 g. of *o*-phenylbenzyl bromide[13] dissolved in 100 ml. of ethanol was added. The solution was refluxed until it was no longer alkaline (3 hours) and precipitated sodium bromide removed by filtration. The filtrate was poured into 500 g. of ice and the resulting mixture extracted with ether. The ethereal solution was washed with saturated ammonium sulfate solution, dried (calcium sulfate) and concentrated. Upon vacuum distillation of the residue, the desired ester (84%), b.p. 202–205° (4 mm.), was obtained.

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.08; H, 7.13.

α-Ethoxy-β-(2-biphenylyl)-propionic Acid.—To a solution formed by dissolving 3 g. of sodium in 60 ml. of ethanol, 2.5 ml. of water and 22.5 g. of the ethoxy-(2-biphenylyl)-malonic ester (above) were added. The mixture was warmed on the steam-bath and shaken at frequent intervals. The resulting semi-solid mixture was cooled to 0° and the sodium salt collected. The sodium salt was placed in a separatory funnel containing 100 g. of ice, 7 ml. of concentrated hydrochloric acid and 75 ml. of ether. The mixture was shaken until all the salt dissolved. The ethereal layer was separated and the aqueous layer again extracted with ether. The combined ethereal extracts were washed, dried (Drierite) and concentrated. The residue was heated (180°) until there was no further evolution of gas, and then distilled *in vacuo*. The product was obtained in 60% yield as an oil, b.p. 201–205° (4 mm.), which solidified on standing. Recrystallized from ether–petroleum ether this gave white crystals, m.p. 100–101°.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.20; H, 6.75.

2-Biphenylylacetaldehyde (I, R = H). (a) Attempted Preparation by the General Method of Darzens and Meyer.[4]—Nine grams of α-ethoxy-β-(2-biphenylyl)-propionic acid was heated at 300° for one-half hour in the presence of a small amount of copper powder. Some ethanol distilled

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(7) *Cf.* M. S. Newman and J. R. Mangham, THIS JOURNAL, **71**, 3342 (1949); M. S. Newman and T. B. Bye, *ibid.*, **74**, 905 (1952).

(8) C. K. Bradsher and R. S. Kittila, *ibid.*, **72**, 277 (1950).

(9) It has been demonstrated (C. K. Bradsher and F. A. Vingiello, *ibid.*, **71**, 1434 (1949)) that the rate of aromatic cyclodehydration of a methyl or ethyl ketone greatly exceeds that for phenyl.

(10) Analyses by Micro-Tech Laboratories, Skokie, Illinois.

(11) We are indebted to Dr. S. T. Amore for having carried out this and the following two experiments.

(12) W. Wislicenus and M. Munzesheimer, *Ber.*, **31**, 551 (1898).

(13) J. von Braun and G. Manz, *Ann.*, **468**, 258 (1929).

during the heating period. The residue was distilled under reduced pressure yielding a small quantity of a light yellow oil, b.p. 162–165°, which gave tests with the Fuchsin-aldehyde and Tollens reagents, but proved to be almost entirely soluble in sodium bicarbonate solution. It is believed that any (2-biphenylyl)-acetaldehyde formed was destroyed under the conditions of the pyrolysis.

(b) **By the Rosenmund Reduction of 2-Biphenylylacetyl Chloride.**—The 2-biphenylylacetic acid was prepared in 83% yield essentially as was done in the preparation of the homologous α-(2-biphenylyl)-butyryl chloride.[6] The acid (25.5 g.) was refluxed with 18 ml. of thionyl chloride until gas evolution ceased. Excess thionyl chloride was removed under vacuum (water pump) at the temperature of the steam-bath and the last traces of thionyl chloride entrained by use of dry toluene and 0.5 g. of quinoline–sulfur regulator[14] and 5 g. of palladium–barium sulfate catalyst added. Reduction was carried out in the usual way.[14] When no more hydrogen chloride was evolved the catalyst was filtered off and the filtrate diluted with 100 ml. of ether. The resulting solution was stirred for 24 hours with a saturated aqueous solution of sodium bisulfite. The addition product was collected, washed with ether and decomposed by stirring for 3 hours with 250 ml. of 10% sodium carbonate solution. The aldehyde which separated was taken up in methylene chloride and the solution dried over magnesium sulfate and concentrated. Distillation of the residue gave 10.9 g. (46%) of a colorless oil boiling at 130–133° (2 mm.); n^{25}D 1.5940. The aldehyde was not obtained in a state of analytical purity, but two derivatives had the expected composition.

Anal. Calcd. for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.13; H, 6.41.

The **2,4-dinitrophenylhydrazone** of the aldehyde crystallized from ethanol as thin orange needles, m.p. 144.5–145.5°.

Anal. Calcd. for $C_{20}H_{16}O_4N_4$: C, 63.82; H, 4.29. Found: C, 63.84; H, 4.50.

The **semicarbazone** crystallized as white granular crystals from ethanol–water, m.p. 164.5–165°.

Anal. Calcd. for $C_{15}H_{15}ON_3$: C, 71.12; H, 5.97. Found: C, 71.38; H, 6.17.

α-(2-Biphenylyl)-propionitrile was prepared in a manner analogous to that used for the preparation of the homologous butyronitrile.[6] The sodio derivative from 50.4 g. of 2-biphenylylacetonitrile in 60 ml. of dry ether was alkylated by slow addition of 20 ml. of methyl iodide (exothermic reaction) and the mixture stirred at room temperature for 5 hours, during which time sodium iodide precipitated. The mixture was allowed to stand overnight, then poured on ice and acidified with hydrochloric acid. The product was taken up in ether and the ethereal solution washed with water and thiosulfate, dried over magnesium sulfate and concentrated. Fractionation of the residue under reduced pressure yielded 49.4 g. (91%) of a yellow oil boiling at 152–156° (4 mm.). The analytical sample boiled at 156° (4 mm.); n^{25}D 1.5783.

Anal. Calcd. for $C_{15}H_{13}N$: C, 86.92; H, 6.32. Found: C, 87.07; H, 6.40.

α-(2-Biphenylyl)-propionic Acid.—The nitrile above (10 g.) was refluxed for 15 hours with 75 ml. of 20% alcoholic potassium hydroxide solution. The solution was diluted with 150 ml. of water and filtered to remove a small amount of flocculent material. Acidification yielded an oil which immediately crystallized. The yellow crystalline product was collected and washed with water; yield 11 g. (100%), m.p. 114–118°. Recrystallization from ether–petroleum ether yielded 8.7 g. (80%) of colorless rectangular plates, m.p. 117.5–121.5°; analytical sample melted at 122–123°.

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.78; H, 6.39.

α-(2-Biphenylyl)-propionaldehyde (I, R = CH_3).—In a procedure similar to that employed in the preparation of 2-biphenylylacetaldehyde, 9.1 g. of α-(2-biphenylyl)-propionic acid was converted to the aldehyde *via* Rosenmund reduction of the crude acid chloride. Since the bisulfite addition compound of the aldehyde was too soapy to be easily collected, it was dissolved in water and the resulting solution washed with ether and then decomposed by the addition of solid sodium carbonate. The liberated aldehyde was taken up in ether and the ethereal solution washed, dried and concentrated. Distillation of the residue under reduced pressure gave 3.5 g. (42%) of a colorless oil, b.p. 143–145° (5 mm.); n^{25}D 1.5828. The aldehyde which solidified (m.p. 40–43°) was not obtained in a state of analytical purity although the *semicarbazone* (tiny white plates from benzene, m.p. 168–169°) had approximately the expected composition.

Anal. Calcd. for $C_{16}H_{17}ON_3$: C, 71.88; H, 6.41. Found: C, 72.21; H, 6.14.

α-(Biphenylyl)-butyraldehyde (I, R = C_2H_5).—With the same quantities of reagents as in the preparation of the homolog above, α-(2-biphenylyl)-butyric acid[6] was transformed into the acid chloride which was reduced as before. During a period of 7.5 hours, 83% of the theoretical amount of hydrogen chloride was evolved. The solid bisulfite addition compound was collected, washed with ether and decomposed with carbonate as before. The product (2.9 g., 32%) was obtained as a colorless oil, b.p. 129–132° (2 mm.); n^{25}D 1.5740.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.67; H, 7.19. Found: C, 85.81; H, 7.35.

The organic layer which had been extracted with bisulfite yielded no further bisulfite addition compound on further extraction. When the organic layer was extracted with 5% sodium hydroxide solution nothing could be precipitated from the alkaline solution by carbon dioxide, but hydrochloric acid yielded 0.9 g. (9%) of α-(2-biphenylyl)-butyric acid. The neutral non-aldehyde fraction recovered amounted to 4 g. (about 40%).

The 2,4-dinitrophenylhydrazone crystallized from ethanol as small yellow needles, m.p. 177–177.5°.

Anal. Calcd. for $C_{22}H_{20}O_4N_4$: C, 65.34; H, 4.99. Found: C, 65.51; H, 5.17.

General Cyclization Procedure.—To 1 g. of the aldehyde dissolved in 20 ml. of boiling acetic acid, 10 ml. of 48% hydrobromic acid was added and the mixture refluxed for an appropriate period (up to ten minutes). The hydrocarbon, which began immediately to separate from the refluxing solution as an oil, crystallized on cooling and was collected and washed with water.

Phenanthrene was obtained in 78% yield from 2-biphenylylacetaldehyde in 5 minutes; colorless plates from ethanol, m.p. 97.5–99° (lit.[15] 99.15°). It was identified by a mixed melting point determination.

9-Methylphenanthrene (II, R = CH_3) was obtained from α-(2-biphenylyl)-propionaldehyde in 93% yield after 2 minutes refluxing. It crystallized from ethanol as flat, colorless needles, m.p. 90.5–92° (lit.[16] 91.5–92.5°). The picrate yielded orange needles from ethanol, m.p. 154.5–156° (lit.[16] 153–154°).

9-Ethylphenanthrene (II, R = C_2H_5) was obtained from α-(2-biphenylyl)-butyraldehyde in quantitative yield after 10 minutes refluxing. It crystallized as white needles from methanol, m.p. 62–63° (lit.[17] 62.5–63°). The picrate formed orange needles from ethanol, m.p. 121–122° (lit.[17] 123–124°).

α-(5-Methoxy-2-biphenylyl)-propionitrile (III).—The sodio derivative of 2-phenyl-4-methoxybenzyl cyanide[1] (17.8 g.) was alkylated with 8 ml. of methyl iodide in a procedure similar to that used in the preparation of α-(2-biphenylyl)-propionitrile. The mixture was refluxed with stirring overnight and worked up as before. The product (15.2 g., 80%) was a viscous pale yellow oil, b.p. 162–163° (1 mm.); n^{25}D 1.5785.

Anal. Calcd. for $C_{16}H_{15}ON$: C, 80.98; H, 6.37. Found: C, 80.90; H, 6.56.

α-(5-Methoxy-2-biphenylyl)-propionic acid (IV) was prepared by hydrolysis of the above nitrile (7.7 g.) with 20% alcoholic potassium hydroxide as in the case of α-(2-biphenylyl)-propionic acid. The product crystallized from ligroin (Norite) as a yellow crystalline mass, m.p. 99–100.5°; yield 5.4 g. (65%). The analytical sample crystallized from ligroin as white prisms, m.p. 102–103°.

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(14) E. Mosettig and R. Mozingo, "Organic Reactions," Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 362.

(15) J. Feldman, P. Pantages and M. Orchin, THIS JOURNAL, **73**, 4341 (1951).

(16) C. K. Bradsher and R. W. H. Tess, *ibid.*, **61**, 2184 (1939).

(17) E. Mosettig and J. van de Kamp, *ibid.*, **55**, 3442 (1933).

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.30. Found: C, 74.98; H, 6.42.

3-Hydroxy-10-methylphenanthrene (V).—The acid above (5.4 g.) was converted to the acid chloride as was done previously and the Rosenmund reduction carried out until 78% of the theoretical quantity of hydrogen chloride was liberated. When the filtered and concentrated toluene solution was stirred for 15 hours with a saturated solution of sodium bisulfite, there was no precipitate formed. From the washed bisulfite solution, 0.5 g. (10%) of a yellow oil was obtained by treatment with sodium carbonate. This material was not purified further, but dissolved in 10 ml. of acetic acid and 5 ml. of 48% hydrobromic acid added. After the mixture had been refluxed for 3 hours, water was added and the product crystallized from the violet solution as violet feathery needles, m.p. 137–140°; yield 0.4 g. Two recrystallizations from cyclohexane (Norite) yielded white feathery needles, m.p. 141.5–142.5°. The product was soluble in dilute sodium hydroxide solution.

Anal. Calcd. for $C_{15}H_{12}O$: C, 86.51; H, 5.81. Found: C, 86.69; H, 5.85.

(2-Biphenylyl)-acetone (**VI**, **R** = $\mathbf{CH_3}$).—To a stirred Grignard reagent prepared in ether from methyl iodide and 1.2 g. of magnesium turnings, 4.9 g. of anhydrous cadmium chloride[18] was added in portions. After a few minutes the Gilman[19] test for the Grignard reagent was negative. Ether was removed on the steam-bath and the residue taken up in 20 ml. of dry benzene. To the cooled mixture a solution of (2-biphenylyl)-acetyl chloride (prepared as described earlier from 5.3 g. of 2-biphenylylacetic acid) in 20 ml. of dry benzene was added slowly. Addition of the acid chloride produced an exothermic reaction and evolution of a water-insoluble gas (methane). The mixture was refluxed for one hour with stirring and the solid complex collected on a filter and washed with benzene. Extraction of the filtrate with bicarbonate solution yielded no organic material on acidification. The solid complex was hydrolyzed with 50 ml. of water and the cadmium hydroxide suspension[20] extracted with ether.

Half of the ethereal solution was extracted with 5% potassium hydroxide solution. The alkaline solution when saturated with carbon dioxide yielded 0.5 g. of a brownish powder, m.p. 130–146°. When this was recrystallized from benzene (Norite), light brown needles, m.p. 151–153°, were obtained.[21] When the solution from which the phenolic material had been precipitated was acidified with hydrochloric acid, no further precipitate was obtained. Concentration of the ethereal solution yielded 0.5 g. of a light yellow oil, b.p. 130–132° (1 mm.). This ketone was not obtained in a state of analytical purity.

9-Methylphenanthrene from (2-Biphenylyl)-acetone.—A sample (0.4 g.) of the ketone described above was refluxed for one hour in a mixture containing 8 ml. of acetic acid and 4 ml. of 48% hydrobromic acid. Upon cooling the mixture, the product crystallized as pink needles, m.p. 87–90°; yield 0.25 g. There was no depression of melting point when it was mixed with a sample obtained by cyclization of α-(2-biphenylyl)-propionaldehyde.

1-(2-Biphenylyl)-4-methylpentanone-2 (**VI**, **R** = $\mathbf{CH_2CH(CH_3)_2}$).—This compound was prepared by treating 2-biphenylylacetyl chloride with diisobutylcadmium exactly as described for the preparation of the biphenylylacetone. The product (0.4 g., 6%) was a light yellow oil, b.p. 160–170° (2 mm.), which gave a positive carbonyl test with 2,4-dinitrophenylhydrazine reagent. The ketone was not pure and apparently contained a small quantity of (2-biphenylyl)-acetic acid. As in the case of the homolog, 9-phenanthrol was a by-product.

9-Isobutylphenanthrene from 1-(2-Biphenylyl)-4-methylpentanone-2.—The crude ketone above (0.4 g.) was cyclized in the same manner as the homolog. The product, 0.12 g. of small pink needles, melted at 94.5–96°. Recrystallized from methanol (Norite) it yielded white needles, m.p. 96–97°.

Anal. Calcd. for $C_{18}H_{18}$: C, 92.26; H, 7.74. Found: C, 92.01; H, 8.00.

(2-Biphenylyl)-acetylacetonitrile (**VII**, **R** = $\mathbf{CH_3}$).—To a stirred suspension of sodium amide in dry ether (prepared from 1.5 g. of sodium and 100 ml. of liquid ammonia as described earlier), 5.8 g. of (2-biphenylyl)-acetonitrile in 15 ml. of dry ether was added slowly. After the mixture had been refluxed with stirring for a half-hour, 60 ml. of ethyl acetate in 10 ml. of ether was added slowly. Ammonia was evolved and a white solid began to separate from solution. The mixture was refluxed and stirred for 3 hours, poured on ice, and acidified with hydrochloric acid. After the aqueous layer had been extracted with ether, the combined ethereal solutions were washed, dried (magnesium sulfate) and concentrated. Fractionation of the residue yielded 3.6 g. (51%) of an exceedingly viscous light yellow oil, b.p. 165–167° (1 mm.); $n^{25}\mathrm{D}$ 1.5956. The analytical sample boiled at 167° (1 mm.).

Anal. Calcd. for $C_{16}H_{13}ON$: C, 81.68; H, 5.57. Found: C, 81.66; H, 5.75.

9-Methyl-10-cyanophenanthrene (**VIII**, **R** = $\mathbf{CH_3}$).—The ketonitrile above (0.5 g.) was refluxed for 1.5 hours with 10 ml. of acetic acid and 5 ml. of 48% hydrobromic acid. During the refluxing, the product began to crystallize on the walls of the flask. After cooling, the product was collected and washed with water, yielding 0.26 g. (56%) of straw-colored needles, m.p. 172–175°. The analytical sample was obtained by recrystallization from ethanol as silvery white needles, m.p. 175.5–176.5°, which gave a positive test for nitrogen.

Anal. Calcd. for $C_{16}H_{11}N$: C, 88.45; H, 5.10. Found: C, 88.38; H, 4.96.

9-Methyl-10-phenanthramide (**IX**, **R** = $\mathbf{CH_3}$).—One-half gram of the ketonitrile was refluxed for 48 hours with 15 ml. of acetic acid and 5 ml. of hydrobromic acid. The solution was diluted with water and extracted with ether. The ethereal extract was washed with water, 5% potassium hydroxide solution, dried (magnesium sulfate), treated with Norite, and concentrated. Recrystallization of the residue from ethanol gave 0.1 g. (22%) of pale yellow needles, m.p. 170–174°, which gave no depression of melting point with 9-methyl-10-cyanophenanthrene.

The mother liquor was concentrated and the crude product, m.p. 155–166°, recrystallized from benzene yielding 0.12 g. (24%), m.p. 176–179°. When mixed with 9-methyl-10-cyanophenanthrene the melting point was depressed to 144–154°. The analytical sample consisted of small white needles, m.p. 180.5–181°.

Anal. Calcd. for $C_{16}H_{13}ON$: C, 81.68; H, 5.57. Found: C, 81.64; H, 5.74.

9-Methylphenanthrene from (2-Biphenylyl)-acetylacetonitrile.—The 2-(biphenylyl)-acetylacetonitrile (0.5 g.) was refluxed for one week with 15 ml. of acetic acid and 5 ml. of hydrobromic acid. When the solution was diluted with 25 ml. of water, the product slowly crystallized. This was collected and washed with water. Recrystallized from ethanol (Norite), the product was obtained as flat light yellow needles, m.p. 89.5–91°; yield 0.09 g. (22%). There was no depression of melting point when the product was mixed with 9-methylphenanthrene. Further dilution of the cyclizing medium yielded 0.08 g. (16%) of the 9-methyl-10-phenanthramide as short pink needles, m.p. 176–177.5°.

2-(Biphenylyl)-propionylacetonitrile (**VII**, **R** = $\mathbf{C_2H_5}$).—The acylation of 2-biphenylylacetonitrile (5.8 g.) was carried out as in the case of the homolog using ethyl propionate (7 ml.) as the acylating agent. During the third hour of the reflux period, the ether was slowly evaporated until only solid material remained. Ice-water and ether were added and the mixture worked up as before. Fractionation of the product gave 5.7 g. (76%) of a light yellow oil, b.p. 158–167° (1 mm.). The analytical sample distilled at 166–167° (1 mm.); $n^{25}\mathrm{D}$ 1.5800.

Anal. Calcd. for $C_{17}H_{15}ON$: C, 81.90; H, 6.06. Found: C, 82.20; H, 6.41.

9-Ethyl-10-phenanthramide (**IX**, R = $\mathbf{C_2H_5}$).—The ketonitrile above (0.5 g.), 10 ml. of acetic acid and 5 ml. of 48% hydrobromic acid were refluxed for 1.5 hours. The oil which separated did not crystallize when seeded with 9-ethylphenanthrene.[22] The acid mixture was refluxed for

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[18] J. Cason and F. S. Prout, *Org. Syntheses*, **28**, 75 (1948).

[19] L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Company, New York, N. Y., 1941, p. 408.

[20] The use of acid in the hydrolysis was avoided in order to reduce the possibility of premature cyclization.

[21] F. R. Japp and A. Findlay, *J. Chem. Soc.*, **71**, 1115 (1897), report 9-phenanthrol as light brown needles from benzene, m.p. 152–153°.

[22] It is probable that this oil contains 9-ethyl-10-phenanthronitrile;

an additional 30 hours. The oil which separated on cooling slowly crystallized when seeded with 9-ethylphenanthrene. The crude product thus obtained was recrystallized from methanol (Norite) as feathery white needles, m.p. 59–61°; yield 50 mg. (12%). This gave no depression of melting point when mixed with an authentic sample.

Dilution of the cyclizing medium yielded 300 mg. of pink material, m.p. 153–189°. Recrystallized from benzene, this yielded 120 mg. (24%) of white needles, m.p. 199–202°.

The analytical sample which gave a positive test for nitrogen, consisted of feathery white needles, m.p. 202.5–203.5°.

Anal. Calcd. for $C_{17}H_{15}ON$: C, 81.90; H, 6.06. Found: C, 81.88; H, 5.96.

9-Ethylphenanthrene from (2-Biphenylyl)-propionylacetonitrile.—When 0.5 g. of the ketonitrile was refluxed in 15 ml. of the usual cyclizing mixture for one week, an oil was obtained which crystallized on seeding with 9-ethylphenanthrene. The product was collected and washed with water; yield 0.30 g. (73%), m.p. 58–61°. This was shown to be 9-ethylphenanthrene.

The acidic mother liquor was diluted and extracted with methylene chloride. From the washed extract, a white powder was obtained by evaporation. Recrystallization yielded 100 mg. (20%) of white crystals, m.p. 203–204°. This did not depress the melting point of the 9-ethyl-10-phenanthramide described above.

DURHAM, N. C.

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, SHARP AND DOHME DIVISION, MERCK AND CO., INC.]

2-Keto-4-(*p*-methoxyphenyl)-1-methyl-3-cyclohexenecarbonitrile and Related Compounds. Analogs of Doisynolic Acid[1]

BY FREDERICK C. NOVELLO, MARCIA E. CHRISTY AND JAMES M. SPRAGUE

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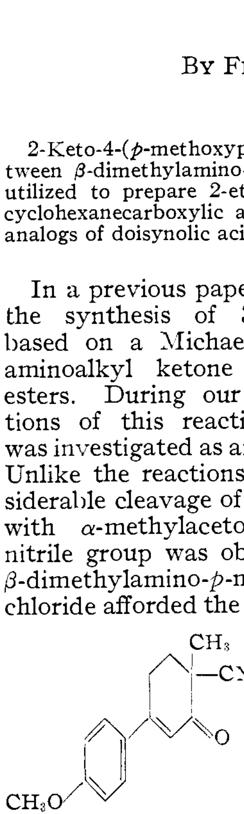
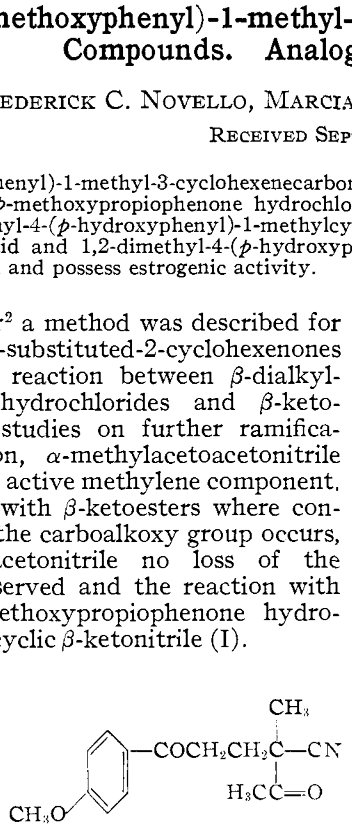
2-Keto-4-(*p*-methoxyphenyl)-1-methyl-3-cyclohexenecarbonitrile (I) was synthesized by a Michael-type condensation between β-dimethylamino-*p*-methoxypropiophenone hydrochloride and α-methylacetoacetonitrile. This intermediate was utilized to prepare 2-ethyl-4-(*p*-hydroxyphenyl)-1-methylcyclohexanecarboxylic acid, 1,2-dimethyl-4-(*p*-hydroxyphenyl)-cyclohexanecarboxylic acid and 1,2-dimethyl-4-(*p*-hydroxyphenyl)-3-cyclohexenecarboxylic acid. These compounds are analogs of doisynolic acid and possess estrogenic activity.

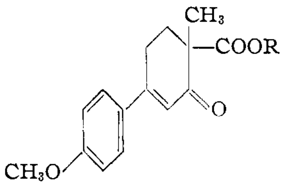
In a previous paper[2] a method was described for the synthesis of 3-substituted-2-cyclohexenones based on a Michael reaction between β-dialkylaminoalkyl ketone hydrochlorides and β-ketoesters. During our studies on further ramifications of this reaction, α-methylacetoacetonitrile was investigated as an active methylene component. Unlike the reactions with β-ketoesters where considerable cleavage of the carboalkoxy group occurs, with α-methylacetoacetonitrile no loss of the nitrile group was observed and the reaction with β-dimethylamino-*p*-methoxypropiophenone hydrochloride afforded the cyclic β-ketonitrile (I).



I



II



III, R = CH_3, C_2H_5

Formation of this compound was promoted by the use of potassium *t*-butoxide as condensing agent, which was selected for this study, since previous work[2] on the Michael reaction with β-ketoesters had demonstrated that alcoholysis was minimized under these conditions. Although cleavage of the nitrile group proved to be a negligible factor in this reaction, potassium *t*-butoxide was effective, however, in controlling the rate of the reaction to an extent that permitted isolation of the intermediate acyclic addition product II. When the condensation reaction was carried out in dioxane with potassium *t*-butoxide which contained a trace of *t*-butyl alcohol, the product was the cyclic compound I; however, when the potassium *t*-butoxide was freed completely of all traces of *t*-butyl alcohol, the product was a mixture of I and II which was separated readily by fractional crystallization. Subsequent treatment of the uncyclized product with alcoholic potassium hydroxide gave the β-ketonitrile I. As a consequence of these observations, further improvement in the synthesis of I was realized when the condensation reaction was carried out with alcoholic potassium hydroxide. Under these conditions I was obtained in 88.5% yield. Conversion of I to the carboalkoxy compounds III was accomplished by treatment with alcoholic hydrogen chloride.[3]

In the light of these observations, some conclusions about the course of the reaction may be drawn It is quite probable that the formation of I proceeds by two steps: (1) the formation of the acyclic intermediate II and (2) the aldol cyclization of II to I. Although the mechanism by which the acylic intermediate II arises from the Mannich ketone has not been investigated, two possible routes are presented: (1) by a Michael reaction involving a 1,4-addition of the active methylene component to the aryl vinyl ketone that arises by decomposition of the Mannich base[4]; (2) by a direct

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[1] Presented before the Division of Medicinal Chemistry, XIIth International Congress, New York. N. Y., Sept. 10–13, 1951.

[2] F. C. Novello. M. E. Christy and J. M. Sprague. THIS JOURNAL, **75**, 1330 (1953).

[3] V. Migrdichian, "The Chemistry of Organic Cyanogen Compounds," Reinhold Publ. Corp., New York, N. Y., 1947. p. 84.

[4] F. F. Blicke in "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 320.