# THE PSCHORR SYNTHESIS

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*Received October 19, 1955*

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## I. INTRODUCTION

Pschorr's name has been associated with a single cyclization reaction (35) as well as with a synthesis which includes this reaction as the third in a series of four steps (22). For the purposes of this survey the complete synthesis, that is the four reactions described in Pschorr's first publication on this subject (60), will be used.

The first of these reactions was a Perkin condensation between the sodium salt of phenylacetic acid and *o*-nitrobenzaldehyde; *o*-nitro-$\alpha$-phenylcinnamic acid (I) was formed. The nitro group was then reduced using an ammoniacal solution of ferrous sulfate, and the amino acid (II) produced was diazotized. On shaking the diazonium salt of II with dilute sulfuric acid and copper powder

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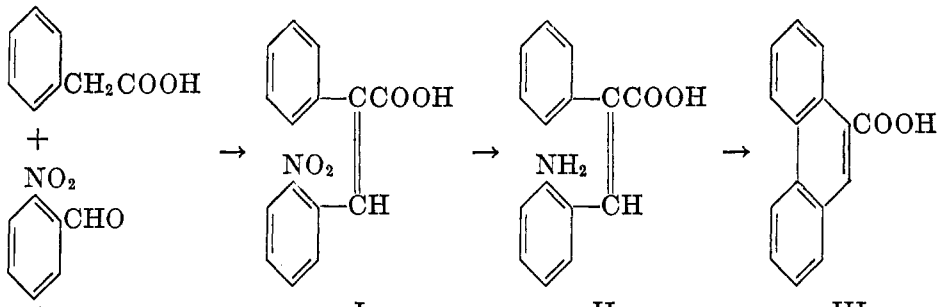
(25) nitrogen was eliminated and ring closure led to the formation of 9-phenanthrenecarboxylic acid (III). When heated, this acid lost carbon dioxide and formed phenanthrene. In subsequent work this synthesis has been broadened to include the preparation of polycyclic aromatic systems other than phenan-




I — *o*-Nitro-α-phenylcinnamic acid

II — *o*-Amino-α-phenylcinnamic acid

III — α-Phenanthrenecarboxylic acid

threne. Although this series of reactions has been known since 1896 (60), the extant summaries of its use have been brief and consequently of limited utility.

For the present survey, an effort has been made to include every recorded attempt to apply this synthesis to the preparation of polycyclic aromatic derivatives. The literature has been surveyed through 1954. Several instances have been cited in which a heterocyclic compound was the expected product, but it is not the intention of this discussion to consider all such known cases. Some were not included because they did not involve all four steps of the Pschorr synthesis; others were omitted because their utility appeared insignificant.

Prior to 1896 no methods existed for the preparation of phenanthrene derivatives, although phenanthrene itself had been prepared by the extreme conditions of hot-tube reactions (5, 21, 28, 29) or the equally ambiguous reaction of benzyl bromide with sodium (41). It was near this time that the work which was initiated in 1803 and centered around morphine had reached a point requiring an unambiguous synthesis of phenanthrene. Pschorr's method fulfilled this requirement and holds a position of significance in the elucidation of the structure of morphine. Since that time it has found continued application in other determinations of structure and, because of its unique characteristics, has proved to be the method of choice for the preparation of certain phenanthrene derivatives and other polycyclic hydrocarbons of interest in the cancer problem.

Some idea of the versatility of the Pschorr synthesis and the extent of its use can be seen from table 1. Following this table, each of the reactions—Perkin reaction, reduction, cyclization, and decarboxylation—will be discussed in detail as it pertains to the Pschorr synthesis.

## II. THE PERKIN REACTION

The results obtained from the Perkin reaction are dependent to some extent on the catalyst used, on the nature of the starting aldehyde and acetic acid derivative, and on the reaction time and temperature.

TABLE 1

*Phenanthrene derivatives*

| Starting Materials | | Reaction Yields | | | | Phenanthrene Derivative Obtained | References |
|---|---|---|---|---|---|---|---|
| Phenylacetic acid derivative | Benzaldehyde derivative | Perkin reaction | Reduction | Cyclization | Decarboxylation | | |
| Unsubstituted | 2-$NO_2$ | 50 | 77 | 93 | 64 | | (34, 60) |
| 2-$NO_2$ | 2-$NO_2$ | 72 | 70 | ?* | ? | 9-COOH | (70, 90) |
| Oxindole | Unsubstituted | ? | ? | ? | ? | 9,10-dihydro, 9-COOH | (104) |
| 2-$CH_3$ | 2-$NO_2$ | 80 | 70 | 60–70 | 70 | 1-$CH_3$ | (65) |
| 3-$CH_3$ | 2-$NO_2$ | 67 | 80 | ? | —* | 2-$CH_3$, 9-COOH<br>4-$CH_3$, 9-COOH | (53) |
| 2-$NO_2$ | 3-$CH_3$ | 29–43 | 27 | ? | ? | 2-$CH_3$<br>4-$CH_3$ | (53) |
| Unsubstituted | 2-$NO_2$, 5-$CH_3$ | 58 | 60 | 75 | 0–34 | 2-$CH_3$ | (53) |
| 4-$CH_3$ | 2-$NO_2$ | 55 | 90 | 20–70 | 35 | 3-$CH_3$ | (71) |
| Unsubstituted | 2-$NO_2$, 3-$CH_3$ | 53 | 78 | 75 | Trace | 4-$CH_3$ | (53) |
| 2-$NO_2$, 5-$CH_3$ | Unsubstituted | 20 | 69 | 3 | — | 7-$CH_3$, 9-COOH | (53) |
| Oxindole | Acetophenone | 45 | ? | ? | ? | 9-$CH_3$ | (105) |
| 4-$C_2H_5$ | 2-$NO_2$ | 47 | 85 | 40–80 | 60 | 3-$C_2H_5$ | (9) |
| 3-$C_2H_5$ | 2-$NO_2$ | 64 | 76 | Most<br>Least | ?<br>? | 5-$C_2H_5$<br>7-$C_2H_5$ | (54) |
| 2-$NO_2$ | 2-$C_2H_5$ | 20 | — | — | — | 8-$C_2H_5$ | (54) |
| 2-$C_2H_5$ | 2-$NO_2$ | 52 | 73 | Failed | — | 8-$C_2H_5$ | (54) |
| 2,4-$(CH_3)_2$ | 2-$NO_2$ | 72 | 75 | 87 | 82 | 1,3-$(CH_3)_2$ | (2, 9) |
| 2,5-$(CH_3)_2$ | 2-$NO_2$ | 75 | 74 | 85 | 90 | 1,4-$(CH_3)_2$ | (2) |
| 4-$CH_3$ | 2-$NO_2$, 3-$CH_3$ | 65 | 84 | 71 | 63 | 3,5-$(CH_3)_2$ | (48) |
| 3-$C_2H_5$ | 2-$NO_2$, 3-$CH_3$ | 57 | 85 | 30 | 50 | 2-$C_2H_5$, 5-$CH_3$ | (48) |
| 4-$C_2H_5$ | 2-$NO_2$, 3-$CH_3$ | 50 | 77 | 58 | 42 | 3-$C_2H_5$, 5-$CH_3$ | (48) |
| 2-$CH_3$, 4-$CH(CH_3)_2$ | 2-$NO_2$ | 46 | 65 | 61 | 21 | 1-$CH_3$, 3-$CH(CH_3)_2$ | (106) |
| 2-$CH_3$, 5-$CH(CH_3)_2$ | 2-$NO_2$ | 56 | 68 | 67 | 63 | 1-$CH_3$, 4-$CH(CH_3)_2$ | (9) |
| 2,3,4,5-$(CH_3)_4$ | 2-$NO_2$ | 46 | 81 | 29 | 64 | 1,2,3,4-$(CH_3)_4$ | (33) |
| Unsubstituted | 2-$NO_2$, 5-OH | 30 | 90 | 55 | — | 2-OH, 9-COOH | (73) |
| Unsubstituted | 2-$NO_2$, 3-OH | 25 | ? | Failed | — | — | (73) |
| 2-$CH_2OC_6H_5$ | 2-$NO_2$ | ? | ? | 50 | — | 8-$CH_2OC_6H_5$, 9-COOH | (12) |
| 2-$OCH_3$, 3-$CH_3$ | 2-$NO_2$ | 40–66 | 60 | ? | Smoothly | 1-$OCH_3$, 2-$CH_3$ | (37) |
| 2-$CH_3$, 4-$OCH_3$ | 2-$NO_2$ | 27 | ? | ? | ? | 3-$OCH_3$, 1-$CH_3$ | (39) |
| 2-$CH_3$, 5-$OCH_3$ | 2-$NO_2$ | 51 | 79 | ? | ? | 4-$OCH_3$, 1-$CH_3$ | (36) |
| 2-$NO_2$ | 2-$CH_3$, 4-$OCH_3$ | Failed | — | — | — | — | (36) |
| 2-$CH_3$ | 2-$NO_2$, 3-$OCH_3$ | 56 | ? | 43 | ? | 5-$OCH_3$, 1-$CH_3$ | (38) |
| 4-$CH_3$ | 2-$NO_2$, 3,4-$(OCH_3)_2$ | 50 | 100 | 80 | 40–45 | 3,4-$(OCH_3)_2$, 6-$CH_3$ | (72) |
| 2-$CH_3$ | 2-$NO_2$, 3,4-$(OCH_3)_2$ | 40–45 | 85 | 90 | 75 | 3,4-$(OCH_3)_2$, 8-$CH_3$ | (79) |
| 2,5-$(CH_3)_2$ | 2-$NO_2$, 3,4-$(OCH_3)_2$ | 67 | 61–67 | 50 | ? | 1,4-$(CH_3)_2$, 5,6-$(OCH_3)_2$ | (16) |
| 2,5-$(CH_3)_2$ | 2-$NO_2$, 4,5-$(OCH_3)_2$ | 50–55 | 76 | 83 | 45 | 1,4-$(CH_3)_2$, 6,7-$(OCH_3)_2$ | (15) |
| 2,5-$(CH_3)_2$ | 2-$NO_2$, 3-$OCOCH_3$, 4-$OCH_3$ | 50 | 80 | 47 | 42 | 1,4-$(CH_3)_2$, 5-$OCH_3$, 6-OH | (16) |
| 3-$C_2H_5$, 6-$OCH_3$ | 2-$NO_2$, 3,4-$(OCH_3)_2$ | ? | 100 | 35 | ? | 3,4,8-$(OCH_3)_3$, 5-$C_2H_5$ | (30) |
| Unsubstituted | 2-$NO_2$, 3-$OCOCH_3$, 4-$OCH_3$ | 70 | 75 | 50–60 | ? | 3-$OCH_3$, 4-OH | (84) |
| 4-$OCH_3$ | 2-$NO_2$, 3-OH, 4-$OCH_3$ | 60 | 60–70 | 70 | — | 3,6-$(OCH_3)_2$, 4-OH, 9-COOH | (76) |
| Unsubstituted | 2-$NO_2$, 3-$OCH_3$, 4-$OCOCH_3$ | ? | ? | ? | 1.6% overall yield | 3-$OCOCH_3$, 4-$OCH_3$ | (78) |

TABLE 1–*Continued*

| Starting Materials | | Reaction Yields | | | | Phenanthrene Derivative Obtained | References |
|---|---|---|---|---|---|---|---|
| Phenylacetic acid derivative | Benzaldehyde derivative | Perkin reaction | Reduction | Cyclization | Decarboxylation | | |
| 2-$OCH_3$ | 2-$NO_2$, 3-$OCH_3$, 4-$OCOCH_3$ | 60 | 70–75 | 20–25 | 40–50 | 1,5-$(OCH_3)_2$, 6-$OCOCH_3$ | (61) |
| 2-$OCH_3$ | 2-$NO_2$ | 70 | 70–75 | 55 | ? | 1-$OCH_3$ | (85) |
| Unsubstituted | 2-$NO_2$, 5-$OCH_3$ | 30 | 80 | 80 | 70 | 2-$OCH_3$ | (75) |
| 4-$OCH_3$ | 2-$NO_2$ | 50 | 70–80 | 50 | Poor | 3-$OCH_3$ | (85) |
| Oxindole | 4-$OCH_3$ | ? | ? | ? | — | 3-$OCH_3$, 9,10-dihydro, 9-COOH | (104) |
| Unsubstituted | 2-$NO_2$, 3-$OCH_3$ | 70 | 75–80 | ? | ? | 4-$OCH_3$ | (66) |
| 2,3-$(OCH_3)_2$ | 2-$NO_2$ | 60 | 75 | 60 | 50 | 2,3-$(OCH_3)_2$ | (82) |
| Unsubstituted | 2-$NO_2$, 4,5-$(OCH_3)_2$ | 85 | 65 | 50–60 | 40–45 | 2,3-$(OCH_3)_2$ | (63) |
| Unsubstituted | 2-$NO_2$, 3,4-$(OCH_3)_2$ | 70 | 70 | 70–80 | ? | 3,4-$(OCH_3)_2$ | (78) |
| 3-$OCH_3$ | 2-$NO_2$, 5-$OCH_3$ | 46 | 100 | 63 (56 / 44) | 68 / 57 | 2,5-$(OCH_3)_2$ / 2,7-$(OCH_3)_2$ | (89) |
| 3-$OCH_3$ | 2-$NO_2$, 3,4-$(OCH_3)_2$ | 80–90 | ? | Most / Least | — | 3,4,5-$(OCH_3)_3$, 9-COOH / 3,4,7-$(OCH_3)_3$, 9-COOH | (87) |
| 4-$OCH_3$ | 2-$NO_2$, 3,4-$(OCH_3)_2$ | 45 | 60 | 70 | 40–50 | 3,4,6-$(OCH_3)_3$ | (77) |
| 2-$OCH_3$ | 2-$NO_2$, 3,4-$(OCH_3)_2$ | 75 | 85 | ? | ? | 3,4,8-$(OCH_3)_3$ | (64) |
| 2,3-$(OCH_3)_2$ | 2-$NO_2$, 3,4-$(OCH_3)_2$ | ? | ? | ? | ? | 1,2,5,6-$(OCH_3)_4$ | (46) |
| 4-$OCH_3$ | 2-$NO_2$, 3,4,5-$(OCH_3)_3$ | 47 | 86 | 51 | — | 2,3,4,6-$(OCH_3)_4$, 9-COOH | (14, 95) |
| 3,4,5-$(OCH_3)_3$ | 2-$NO_2$, 5-$OCH_3$ | 84 | 87 | 63 | 86 | 2,3,4,7-$(OCH_3)_4$ | (6, 88) |
| 3,4-$(OCH_3)_2$ | 2-$NO_2$, 3,4-$(OCH_3)_2$ | 48 | 86 | 6% / 13% | — / 24 | 3,4,5,6-$(OCH_3)_4$, 9-COOH / 3,4,6,7-$(OCH_3)_4$ | (27, 47) |
| 3-$OCH_3$ | 2-$NO_2$, 3,4,5-$(OCH_3)_3$ | ? | ? | Equal / ? / Equal | — | 2,3,4,5-$(OCH_3)_4$, 9-COOH / 2,3,4,7-$(OCH_3)_4$, 9-COOH | (14) |
| 2,5-$(OCH_3)_2$ | 2-$NO_2$, 3,4-$(OCH_3)_2$ | 73 | 66 | 50 | ? | 3,4,5,8-$(OCH_3)_4$ | (31) |
| 2,4-$(OCH_3)_2$ | 2-$NO_2$, 3,4-$(OCH_3)_2$ | 40 | 70 | 30 | ? | 3,4,6,8-$(OCH_3)_4$ | (66) |
| 4-$OC_2H_5$ | 2-$NO_2$ | 40 | ? | ? | ? | 3-$OC_2H_5$ | (103) |
| 2-$OC_2H_5$ | 2-$NO_2$, 3,4-$(OCH_3)_2$ | 50–55 | ? | 80 | ? | 8-$OC_2H_5$, 3,4-$(OCH_3)_2$ | (86) |
| 3-$OC_2H_5$, 4-$OCH_3$ | 2-$NO_2$, 3-$OCH_3$, 4-$OC_2H_5$ | 49 | 88 | ? / 50 | ? / 85 | 3,5-$(OC_2H_5)_2$, 4,6-$(OCH_3)_2$ / 3,7-$(OC_2H_5)_2$, 4,6-$(OCH_3)_2$ | (97) |
| 4-$OC_2H_5$, 3-$OCH_3$ | 2-$NO_2$, 3-$OC_2H_5$, 4-$OCH_3$ | 45 | 84 | 16 / 46 | ? / ? | 3,5-$(OCH_3)_2$, 4,6-$(OC_2H_5)_2$ / 3,7-$(OCH_3)_2$, 4,6-$(OC_2H_5)_2$ | (97) |
| 3-$OC_2H_5$, 4-$OCH_3$ | 2-$NO_2$, 3-$OC_2H_5$, 4-$OCH_3$ | 52 | 83 | ? | ? | 4,7-$(OC_2H_5)_2$, 3,6-$(OCH_3)_2$ / 4,7-$(OC_2H_5)_2$, 3,6-$(OCH_3)_2$ | (97) |
| 4-$OC_2H_5$, 3-$OCH_3$ | 2-$NO_2$, 3,4-$(OCH_3)_2$ | 50 | 88 | 13 / 35 | ? | 3,4,5-$(OCH_3)_3$, 6-$OC_2H_5$ / 3,4,7-$(OCH_3)_3$, 6-$OC_2H_5$ | (97) |
| 3-$OC_2H_5$, 4-$OCH_3$ | 2-$NO_2$, 3,4-$(OCH_3)_2$ | 57 | 92 | 9 / 35 | ? / 81 | 5-$OC_2H_5$, 3,4,6-$(OCH_3)_3$ / 7-$OC_2H_5$, 3,4,6-$(OCH_3)_3$ | (97) |
| Unsubstituted | 2-$NO_2$, 4,5-$OCH_2O$ | 54 | 62 | ? | 45–50 | 2,3-$OCH_2O$ | (57) |
| Oxindole | 3,4-$OCH_2O$ | | | | 20% overall yield | 3,4-$OCH_2O$, 9-COOH | (104) |

TABLE 1—*Concluded*

| Starting Materials | | Reaction Yields | | | | Phenanthrene Derivative Obtained | References |
|---|---|---|---|---|---|---|---|
| Phenylacetic acid derivative | Benzaldehyde derivative | Perkin reaction | Reduction | Cyclization | Decarboxylation | | |
| 2-Br, 4,5-$OCH_2O$ | 2-$NO_2$, 3-$OCH_3$ | ? | ? | 57 | — | 4-$OCH_3$, 5,6-$OCH_2O$, 8-Br, 9-COOH | (26) |
| 3,4-$OCH_2O$ | 2-$NO_2$, 3-$OCH_3$ | 53 | ? | ? | ? | 4-$OCH_3$, 6,7-$OCH_2O$ | (26) |
| 2,5-$(CH_3)_2$ | 2-$NO_2$, 4,5-$OCH_2O$ | 97 | 70 | 79 | 80 | 1,4-$(CH_3)_2$, 6,7-$OCH_2O$ | (1) |
| 4-Cl | 2-$NO_2$, 4,5-$(OCH_3)_2$ | 54 | ? | 37 | — | 2,3-$(OCH_3)_2$, 6-Cl, 9-COOH | (50) |
| 3-Br, 6-$CH_3$ | 2-$NO_2$, 3-$CH_3$ | 67 | 85 | Failed | | 4,5-$(CH_3)_2$ | (48) |
| Unsubstituted | 2-$NO_2$, 3,4-$(OCH_3)_2$, 6-Br | 30 | 98 | 72–82 | Poor | 1-Br, 3,4-$(OCH_3)_2$ | (96) |
| 5-Br, 3,4-$(OCH_3)_2$ | 2-$NO_2$ | 80 | 83 | 60–65 | — | 1-Br, 3,4-$(OCH_3)_2$, 10-COOH | (62) |
| Unsubstituted | 2-$NO_2$, 3,4-$(OCH_3)_2$, 5-Br | 65 | 99 | 95 | Poor | 2-Br, 3,4-$(OCH_3)_2$ | (96) |
| 2-Br | 2-$NO_2$, 3,4-$(OCH_3)_2$ | 60–65 | 90 | 60 | Failed | 8-Br, 3,4-$(OCH_3)_2$, 9-COOH | (69) |
| 3-$OCH_3$, 6-Br | 2-$NO_2$, 3,4-$(OCH_3)_2$ | 60 | 75 | 35–50 | — | 8-Br, 3,4,5-$(OCH_3)_3$, 9-COOH | (68, 93) |
| 2-$OCH_3$, 5-Br | 2-$NO_2$, 3,4-$(OCH_3)_2$ | 75 | 80 | ? | — | 5-Br, 3,4,8-$(OCH_3)_3$, 9-COOH | (45) |
| 3,4-$(OCH_3)_2$, 6-Br | 2-$NO_2$, 3,4-$(OCH_3)_2$ | 45 | 85 | 27 | Failed | 8-Br, 3,4,5,6-$(OCH_3)_4$, 9-COOH | (27, 47) |
| 4-$OCH_3$, 3,5-$Cl_2$ | 2-$NO_2$ | 45 | 79 | 61 | 61 | 2,4-$Cl_2$, 3-$OCH_3$ | (10) |
| Unsubstituted | 2-$NO_2$, 5-Cl | 71 | 91 | 68 | — | 2-Cl, 9-COOH | (94) |
| 4-Cl | 2-$NO_2$ | 45–50 | 99 | 28–50 | ? | 3-Cl | (58) |
| 2-$NO_2$ | 4-Cl | 25 | 69 | 22 | — | 3-Cl, 9-COOH | (52) |
| 3,4-$Cl_2$ | 2-$NO_2$ | 41 | 87 | 75 | — | 2,3-$Cl_2$, 10-COOH<br>3,4-$Cl_2$, 10-COOH | (51) |
| 3-Br | 2-$NO_2$ | 45 | ? | ? | Failed | 2-Br, 9-COOH | (8) |
| 4-Br | 2-$NO_2$ | 70 | ? | ? | ? | 3-Br | (74) |
| 2-Br | 2-$NO_2$ | 65 | ? | 50–60 | — | 8-Br, 9-COOH | (83) |
| 4-Br | 2-$NO_2$, 4-Br | 52 | 87 | 88 | ? | 3,6-$Br_2$ | (4) |
| 2-$NO_2$ | 2-$NO_2$ | ? | 58 | 24–57 | 51 | 1-$NO_2$ | (35) |
| 4-CN | 2-$NO_2$ | 21 | 56 | 58 | — | 3-CN, 10-COOH | (35) |
| 2-COOH | 2-$NO_2$, 3,4-$(OCH_3)_2$ | 55–60 | 95 | 75 | — | 8,9-$(COOH)_2$, 3,4-$(OCH_3)_2$ | (81) |
| 4-COOH | 2-$NO_2$ | ? | 73 | 48 | — | 3,10-$(COOH)_2$ | (35) |
| 2-COOH | 2-$NO_2$ | 25–30 | 80 | 40–45 | — | 8,9-$(COOH)_2$ | (80) |
| 2-$NO_2$ | 2-$NO_2$ | 50 | 70 | 75 | — | 8-$NH_2$, 9-COOH | (35, 70) |
| 2-$NO_2$ | 2-$NO_2$ | ? | ? | ? | — | 8-$NH_2$, 10-OH, 9,10-dihydro, 9-COOH | (44) |

* ? = yield not given; — = reaction not carried out.

### *A. Catalyst and time effects*

In every case found, acetic anhydride was the acid anhydride used. In some cases a small amount of anhydrous zinc chloride (8, 9, 35, 52, 53, 54, 60) or stannous chloride (26) was added, but the beneficial effect of these "catalysts" is dubious. For instances in which one or the other of these metal chlorides has been used, the average yield was approximately 10 per cent lower than the aver-

age yield for this step of the Pschorr synthesis. In cases where comparisons on a single reaction were made, the addition of zinc chloride was found to be coincident with lower yield and impure product (3, 9).

It is generally accepted that the Perkin reaction proceeds through the anhydride (13), and that for interaction to take place the anhydride of the arylacetic acid, a benzaldehyde, and a base must either be present among the reactants or else must be formed by interaction of the starting materials. In almost every case where the Perkin reaction has been employed in the Pschorr synthesis, the necessary components are formed by interaction of the starting materials. Generally the sodium or potassium salt of the arylacetic acid, a benzaldehyde, and acetic anhydride are used as starting materials. Sodium or potassium acetate has been used in conjunction with the free acid, the aldehyde, and acetic anhydride (94); in two cases where triethylamine was used as the base, a good yield was obtained (7, 40, 88).

A comparison of the results obtained where sodium acetate or a sodium arylacetate is used instead of the analogous potassium salt shows that only an insignificant difference between the two sets of yields is observed. However, in certain cases where parallel experiments using each salt have been run (53, 56), better yields were reported for reactions which involved the potassium salt of the appropriate acid. Also, it appears from the data in table 1, as well as from general information concerning the Perkin reaction (24, 42), that a shorter reaction time is required when the potassium salt is used.

### *B. Functional group effect*

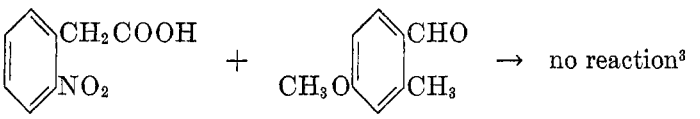
Where the Perkin reaction is part of the Pschorr synthesis, it is usually necessary to have a nitro group located ortho either to the acid side chain of the arylacetic acid derivative or to the aldehyde group of the benzaldehyde derivative. For reactions where the nitro group occupies an ortho position in the arylacetic acid, the yields are usually 10 to 20 per cent lower than the average yield for this step (3, 35, 53, 54), and where a comparison of yields for the two possible locations of the nitro group has been made (36, 53), the results are decidedly in favor of the use of the *o*-nitrobenzaldehyde derivative.[2]

Considering the benzaldehyde derivative only, this result would have been expected, since it is essentially paralleled in other condensation reactions involving the carbonyl group. Strong electron-attracting groups in any position appear to increase the reaction rate and yield (42), while the effect of electron-donating groups, at least for the cases included in the Pschorr synthesis, is not so readily generalized. Location of a hydroxyl group in the 3- or 5-position of 2-nitrobenzaldehyde leads to lower yields (73), while the effect of locating a

[2] This appears as an anomaly, inasmuch as the presence of one or more nitro groups on the ring in toluene makes the methyl group more reactive in base-catalyzed reactions with benzaldehyde. Evidently for the case under consideration, the electron density at the methylene carbon of the arylacetic acid is diminished by a nitro group to such a degree that compound formation resulting from reaction with the carbonium ion formed by benzaldehyde, or its derivatives, is slowed or stopped.

hydroxyl, methoxyl, or methyl group in one of the other positions cannot be discerned from these reaction yields.

It is apparently the summation of the effects of the various groups on the two major components of the Perkin reaction which is important. The best results are coincident with the presence of electron-donating groups on the arylacetic acid and electron-attracting groups on the benzaldehyde, while the poorest possible result is seen when this relationship is exactly reversed. When an attempt was made to condense *o*-nitrophenylacetic acid (IV) with 4-methoxy-2-methylbenzaldehyde (V), *none* of the expected *p*-methoxy-$\alpha$-(*o*-nitrophenyl)cinnamic acid could be isolated from the reaction mixture (36).




IV V

*C. By-products*

The average of the yields for the Perkin reaction reported in table 1 is 54 per cent. It can also be seen from table 1 that lower yields are sometimes associated with the formation of 5 to 10 per cent of the cinnamic acid arising from the interaction of the aldehyde with the acetyl group of the anhydride rather than with the arylacetyl moiety (3, 22, 26, 32, 33, 37, 96). This secondary reaction is found to become increasingly important as the reaction temperature is increased (3, 82) but does not seem to be related to the nature of the base used or to the presence of metallic chlorides.

*D. Miscellaneous*

The optimum reaction time is dependent on the reactants and can be best chosen by analogy. Among the reactions catalogued here, the reaction time is reported to vary from 50 min. to 90 hr.

The Perkin reaction between 2-nitrophenylacetic acid and 2-nitrobenzaldehyde is of particular interest. Under conditions which are not clearly outlined, the intermediate aldol has been isolated (44). However, in cases where these same components were used (35, 70, 90), normal condensation occurred and the expected cinnamic acid derivative was the product.

A variety of arylacetic acid and benzaldehyde derivatives has been used in the Perkin condensation, and the various functional groups are, for the most part, unaffected. The expected product has been obtained when alkyl, nitro, methoxy, ethoxy, methylenedioxy, bromine, chlorine, nitrile, and carboxylic acid groups have been present in one or both of the starting materials. If a hydroxyl group

[3] It appears improbable that the failure of this reaction could be attributed to steric effects of the methyl group, inasmuch as many such reactions have incorporated *o*-nitrobenzaldehyde or its derivatives (see table 1). For one reaction, even 6-bromo-3,4-dimethoxy-2-nitrobenzaldehyde was used as a reactant; a 30 per cent yield of the Perkin product was obtained (94).

was present (16, 61, 72, 76, 78, 84), it was sometimes acylated, and when a benzyl ether was among the reactants, debenzylation could not be avoided (89).

### III. REDUCTION

The second step in the Pschorr synthesis is reduction of the *o*-nitro-$\alpha$-arylcinnamic acid to the corresponding amino compound. Because of the presence of the double bond in cinnamic acid, some method of reduction which does not affect double bonds must be employed. The method which has found widest use for this purpose utilizes an ammoniacal solution of ferrous sulfate. The reducing action of ferrous sulfate is selective and the double bond remains unchanged.

#### *A. Methods*

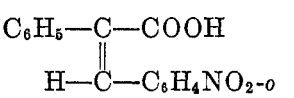
Other methods for a similar selective reduction are available, but their utilization in this particular reaction has been limited. Two instances of the use of sodium sulfide as such a reducing agent are extant (19, 100), but in parallel experiments one of them (19) was found to be considerably inferior to ferrous sulfate. The use of an ammoniacal solution of hydrogen sulfide is also recorded (35), and here again the yield of the unsaturated amino acid is very much lower than the average yield for this step.

The Adams catalyst and hydrogen, as a selective reducing agent for the system under consideration, was found by direct comparison to give yields 23 per cent lower than ammoniacal ferrous sulfate (23). Of the catalytic methods reported for this selective reduction, that involving the use of Raney nickel (90) appears best.

In general the yields for this reaction vary; for some reactions no yield is recorded, while for others an almost quantitative yield is reported. The average of all the reported yields for this selective reduction is 77 per cent.

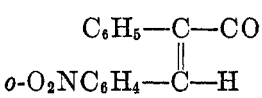
#### *B. Isomerism in this system*

With both the *o*-nitro- and the *o*-aminocinnamic acids, *cis–trans* isomerism is possible. The compound is said to be the *cis* form if the $\alpha$-carboxyl and the $\beta$-aryl groups are on the same side of the double bond (Va) and the *trans* form if these same groups are on opposite sides of the double bond (Vb). Ordinarily the *trans* form of the nitro acid is the more stable form, and in at least one case (31)



**Va**

(*cis*)



**Vb**

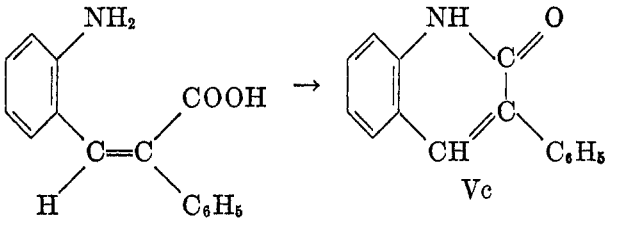
(*trans*)

the *trans* form was converted to the *cis* form by irradiating the sodium salt with ultraviolet light. The reverse conversion sometimes occurs spontaneously.

Although several cases are reported wherein two different isomers were isolated (8, 14, 30, 31, 53, 57, 63, 65, 74, 77, 85), it is not entirely definite that *cis–trans* isomerism was involved in every such case. Ordinarily the isomers are

distinguished by their color difference as one is usually white and the other yellow; it is also sometimes possible to distinguish between them by melting-point determination. It has been established for one case that polymorphism, and not *cis–trans* isomerism, was responsible for the observed differences in color and melting point (31). The unimolecular compound was bright yellow and lower melting, while the dimorphic one was almost colorless and had the higher melting point. The two forms were interconvertible by methods having little in common with those for interconverting *cis–trans* isomers.

In the same study (31), as well as in others (91), a relatively simple method for distinguishing between the *cis* and *trans* isomers of *o*-amino-$\alpha$-arylcinnamic acids was employed. If the aminocinnamic acid has a *trans* configuration, it can be cyclized to a phenanthrene derivative, while if it has a *cis* configuration, it yields the corresponding carbostyril derivative (Vc). Accordingly, the differences in color and melting point of the *o*-nitro- and *o*-amino-$\alpha$-arylcinnamic acids can be accounted for on two different bases: true *cis–trans* isomerism may exist or di- or polymorphic compounds may be present.




Vc

### *C. Stability of products*

Several investigators (2, 9, 39, 40, 78, 89) have found that the amino acids obtained on reducing 2-nitro-$\alpha$-arylcinnamic acids are unstable in air. These compounds sometimes turn dark on standing and often fail to give a correct analysis. It would appear that similar difficulties were also encountered by other workers, inasmuch as yields of the amino acid were not given in some cases and in others the isolation of the amino acid was not reported. There is no apparent simple correlation between this instability and structure, but it may be said that instability and the presence of several alkyl groups seem to be coincident.

## IV. CYCLIZATION

The cyclization step in the Pschorr synthesis leads to the formation of a six-membered ring through a diazo coupling reaction of an *o*-amino-$\alpha$-arylcinnamic acid. In the simplest case, the diazonium salt of *o*-amino-$\alpha$-phenylcinnamic acid (II) loses nitrogen and forms 9-phenanthrenecarboxylic acid.

The possibility of *cis–trans* isomerism for a compound such as II has already been mentioned, and it should be pointed out further that in order for cyclization to occur, the two aryl groups of the $\alpha$-arylcinnamic acid must be on the same side of the double bond; i.e., the cinnamic acid must have the *trans* configuration. It is fortunate, for the sake of this synthesis, that the *trans* configuration of most *o*-amino-$\alpha$-arylcinnamic acids is the favored one.

There is some indication that the *trans* form of these cinnamic acid derivatives arises during the condensation reaction because the carboxyl group is present. The product is forced into the *trans* form as a result of the mutual repulsion of the electronegative nitro and carboxylic acid groups (90, 91, 92). It has been suggested that the carboxyl group is also effective in, if not responsible for, stabilizing the *trans* form of the cinnamic acid derivative, and consequently that it promotes the formation of 9-phenanthrenecarboxylic acid rather than some other product such as a carbostyril derivative (98). Phenanthrene can be prepared from *cis*-aminostilbene (structurally analogous with *trans*-*o*-amino-$\alpha$-phenylcinnamic acid) (91, 98), but the *cis* modification is less stable than its isomer (98).

### *A. Yields*

It is difficult to determine an average yield for the cyclization step in the Pschorr synthesis because, in many cases, only physical properties for the product are recorded and no yield is given. Assuming that in such cases the yield was not above 10 per cent, the average yield for this step is approximately 45 per cent. On the basis of this assumption, it is possible to determine the effect of various factors on the cyclization reaction.

### *B. Solvent effect*

For the cyclization step in the formation of the phenanthrene derivatives listed in table 1, one of four solvents has been used—water, methanol, ethanol, or dioxane. Water has been used in most cases, while the other solvents were used when the diazonium salts were relatively insoluble or when an alkyl nitrite was used in diazotizing the amino group. No studies have been found in which the effects of the above solvents were compared for a single cyclization reaction, and it is difficult, if not impossible, to isolate a solvent effect for the above solvents from the recorded data.

### *C. Diazotizing agents*

Two different kinds of reagents, alkyl nitrites and sodium or potassium nitrite, have been used in conjunction with hydrochloric or sulfuric acid to initiate the diazo coupling reaction. Amyl nitrite (1, 2, 4, 9, 35, 48, 57, 62, 64, 69, 71, 72, 78, 83), isoamyl nitrite (15, 16, 17, 23, 48, 51, 88), and butyl nitrite (96) are the only alkyl nitrites reportedly used in the reaction under consideration.

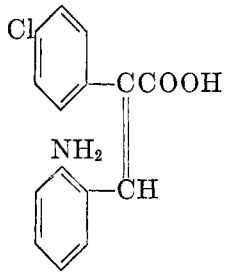
In cases where comparison between an alkyl nitrite and an inorganic nitrite has been made, the yield of cyclized product has been 33 to 50 per cent higher if the alkyl nitrite was used (9, 35, 57, 71, 85). In other cases where no direct comparison has been made, the average yield, using an alkyl nitrite, is 24 per cent above the average yield for this step in the Pschorr synthesis. No distinction between results can be found where potassium nitrite was used instead of sodium nitrite.

### *D. Decomposition of the diazonium salt*

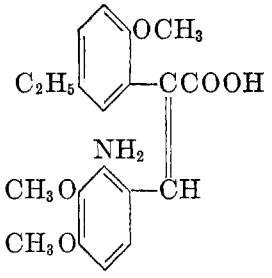
The literature contains several examples of exceptionally stable diazonium salts of *o*-amino-$\alpha$-arylcinnamic acids (14, 58, 75, 76, 84, 95). Sometimes the

sulfate or chloride may be safely isolated, and decomposition temperatures for these salts as high as 100°C. are not uncommon. In many cases the salts are insoluble in the reaction medium and are consequently slow to react. Various factors have been found which cause more of the desired coupling reaction to take place.

In Pschorr's original synthesis (60) the diazonium salt was decomposed in dilute sulfuric acid in the presence of Gatterman copper powder (25). Later the use of copper was eliminated and the reaction mixture was heated (53, 62, 80). In spite of its recorded effectiveness, the usefulness of copper cannot be predicted. With *o*-amino-$\alpha$-(*p*-chlorophenyl)cinnamic acid (VI), comparative stud-



VI



VII

ies indicated that the use of copper was advantageous (50), while with 2-amino-3,4-dimethoxy-$\alpha$-(3-ethyl-6-methoxyphenyl)cinnamic acid (VII), similar studies showed that cyclization took place in better yield if copper was not present (30).

In some cases a decomposition temperature of 50°C. was reported as desirable (86, 97). In others, temperatures of 50°C. and above were used, but results were erratic (6, 10, 23, 52, 53, 54, 88). In a number of examples, elevated temperatures were used in conjunction with an alkaline medium and in the absence of copper powder. Other examples have been reported in which the diazonium salt was stable in boiling acid solution or its decomposition under such conditions was relatively slow. However, when these salts were decomposed in solutions made basic with sodium or potassium carbonate (6, 23, 33, 38, 71, 79, 89) or with sodium hydroxide (10, 38, 39, 74, 84), the decomposition was rapid.

Another reagent used to facilitate decomposition of the diazonium salt and cyclization to a phenanthrene is sodium hypophosphite ($NaH_2PO_2$) (15, 16, 17, 23, 48, 51, 88, 92). In aqueous reaction medium, considerable phenol formation rather than cyclization was found (4, 15, 23), and in all of the reported examples of the successful utilization of this reagent, dioxane or ethanol served as reaction solvent.

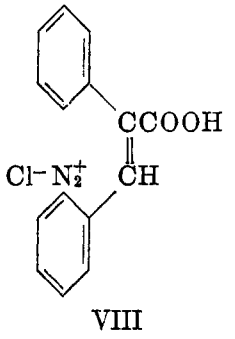
Using as the representative reaction the first one reported by Pschorr, that is, II to III (60), a survey of cyclization conditions was made (34). The results of this series of reactions appear in table 2.

For the reaction under consideration (II to III) Pschorr's original method was best. Evidence in table 2 indicates that other conditions sometimes give better results except when the product is 9-phenanthrenecarboxylic acid. Consequently,

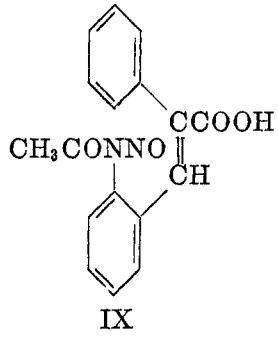
TABLE 2

*Summary of cyclization conditions*

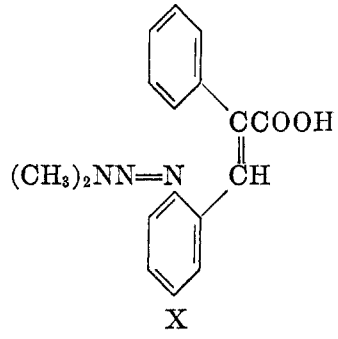
| Starting Material | Solvent | Diazotizing Agent | Decomposition Agent | Temperature | Yield |
|---|---|---|---|---|---|
| | | | | °C. | *per cent* |
| o-Amino-α-phenylcinnamic acid (II) | $H_2O$ | $NaNO_2$, HCl | Copper bronze | 100 | 40 |
| | $H_2O$ | $NaNO_2$, $H_2SO_4$ | Gatterman copper | 100 | 93 |
| | $H_2O$ | $NaNO_2$, HCl | NaOH | Room temperature | 75 |
| | $H_2O$ | $NaNO_2$, HCl | Sodium acetate | Room temperature | 56 |
| 1-o-(2-Carboxy-2-phenyl-vinyl)phenyldiazonium chloride (VIII) | Acetone | — | Gatterman copper | Room temperature | 81 |
| | Cyclohexane | — | Gatterman copper | Room temperature | No reaction |
| o-Nitrosoacetamido-α-phenyl-cinnamic acid (IX) | Benzene | — | — | 50–60 | 43 |
| | Ether | — | — | Refluxing | 37 |
| 1-o-(2-Carboxy-2-phenyl-vinyl)phenyl-3,3-dimethyl-triazine (X) | Benzene | — | HCl | Refluxing | 58 |




VIII




IX




X

in order to determine the most desirable condition for a given reaction, it is necessary to refer to analogous reactions.

### *E. Interfering reactions*

Phenol formation, or hydroxylation, is the main interfering reaction in the cyclization of o-amino-α-arylcinnamic acids. This reaction replaces cyclization, particularly if the final product is to be a polycyclic compound with more than three fused rings (17, 18, 19, 32) or if the product is to be a phenanthrene derivative with groups which sterically hinder cyclization (15, 33, 48, 54, 67). Hydroxylation sometimes occurs if a strong electronegative group is attached to the α-phenyl group of an o-amino-α-phenylcinnamic acid (35). In one case cyclization to a furan ring was attempted; the hydroxy compound was the only isolable product (3).

Phenol formation has been considerably reduced, or entirely avoided in some instances, by diazotizing the amine in ethanolic hydrogen chloride solution with

amyl nitrite and then decomposing the diazonium salt in the presence of copper powder (35). Even better results were reported when the amine sulfate in dioxane was treated with isoamyl nitrite and sodium hypophosphite (15, 17).

Other reactions which have been found to accompany cyclization, but which occur only in special situations, are cleavage of an acetoxyl (61, 78, 84) or benzoxyl (89) group. The basic or acidic conditions of cyclization make hydrolysis of such groups almost inevitable.

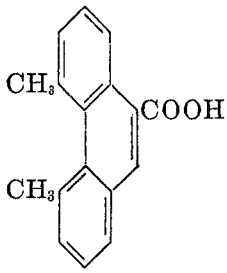
### *F. Functional group effect*

Of the recorded reactions carried out with derivatives of *o*-amino-$\alpha$-phenylcinnamic acid, only a few examples are extant in which the $\alpha$-phenyl nucleus contains an electron-attracting group (35, 80, 81). The groups were nitrile, nitro, and carboxyl, and the yields for these cyclization reactions varied from 45 to 75 per cent. Cyclization in good yield, 57–88 per cent, has also been achieved with *o*-amino-$\alpha$-phenylcinnamic acids containing chlorine or bromine atoms in the 2-, 3-, or 4-positions of the $\alpha$-phenyl ring (4, 10, 26, 51, 58, 62, 83). In a few cases (50, 68, 93) the yield of chloro- or bromophenanthrene was slightly lower, but the cyclization conditions chosen were probably not the most favorable. In almost all of the examples found, the cyclization appears to have proceeded with equal ease irrespective of the position of the deactivating substituent in the $\alpha$-phenyl nucleus (i.e., ortho, meta, or para to the position at which ring closure takes place).

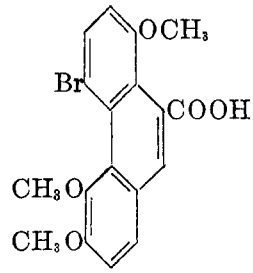
The lack of dependence of the cyclization reaction on the position of the substituent groups in the $\alpha$-phenyl nucleus is also evident where ring activators, such as alkyl, alkoxyl, and amino groups, are present. In table 1 appear many examples in which the $\alpha$-phenyl nucleus is substituted in various positions by electron-donating groups. Whether substitution was ortho, meta, or para to the point of cyclization seemed to make no great difference in the yield, except where steric hindrance was encountered.

### *G. Steric factors*

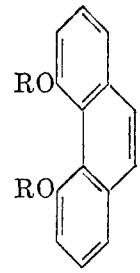
The 4- and 5-positions of the phenanthrene nucleus are relatively close together and, as a result, it becomes difficult or even impossible in some cases to prepare, by the Pschorr method, derivatives substituted in both of these positions. For instance, 4,5-dimethylphenanthrene-9-carboxylic acid (XI) could not be prepared by this method even after a number of attempts (48). In each such




XI




XII

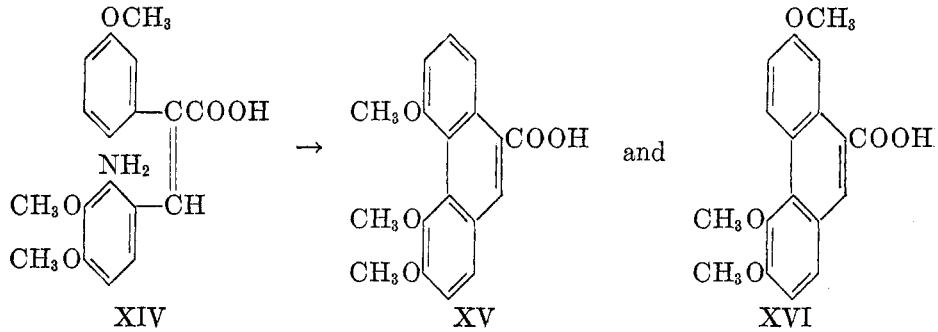



XIII

case hydroxylation or reduction occurred instead. In another case, the product was expected to be 5-bromo-3,4,8-trimethoxyphenanthrene-9-carboxylic acid (XII), but it must have been obtained in very poor yield since its weight was not given (45).

An interesting pseudo-anomaly arises relative to group interference at the 4- and 5-positions of phenanthrene. 4,5-Dialkoxy derivatives (XIII) can be prepared with no more than the usual difficulty (14, 26, 31, 47, 68, 87, 93, 97), in spite of the fact that an alkoxyl group is larger than a methyl group. There is less interference between alkoxyl groups because the oxygen–carbon bond angle is such as to separate these groups (59).

If the substituent or substituents in the α-phenyl nucleus of *o*-amino-α-phenylcinnamic acid derivatives are unsymmetrically located, cyclization can lead to two different products. For example, cyclization of 2-amino-3,4-dimethoxy-α-(3-methoxyphenyl)cinnamic acid (XIV) led to both the 3,4,5- (XV) and the 3,4,7-trimethoxyphenanthrene-9-carboxylic acids (XVI) (68).




In a second reaction series, XV was obtained uncontaminated by XVI when one of the two possible sites for cyclization was blocked with a bromine atom. After cyclization the halogen was removed by alkaline reduction to give the desired product (XV).

The cyclization step in the Pschorr synthesis has led to isomers in several different cases (14, 18, 19, 53, 54, 87, 89, 97, 101), and in some of these cases a larger yield of the product with functional groups in the 4- and 5-positions was obtained (54, 87, 89, 101). This appears as an anomaly, inasmuch as groups in these two positions would be expected to mutually interfere and thereby to curtail formation of such a compound.

### V. DECARBOXYLATION

In many cases where the Pschorr synthesis has been employed, the decarboxylated compound was desired. The difficulty encountered in effecting the loss of carbon dioxide, especially in the earlier attempts, is evident from the number of cases in which no yield is reported. Seventy-eight examples of attempted decarboxylation were found; the yield was given for only thirty-eight reactions. No representative average yield can be given; however, the yield was more than 40 per cent in thirty cases.

### *A. Methods*

The earlier methods of decarboxylating 9(or 10)-phenanthrenecarboxylic acid were, in the majority of instances, not the most effective. The Pschorr synthesis, as a result, appears less desirable than it really is, since more dependable methods for effecting decarboxylation are now known. Most of the methods employed in the Pschorr synthesis prior to 1914 have been summarized (53). Of these methods, the one which was most successful involved a dry distillation of the phenanthrenecarboxylic acid under reduced pressure. This method was used extensively by Pschorr as well as by others (2, 19, 48, 53, 57, 58, 60, 63, 65, 66, 69, 71, 72, 74, 75, 77, 78, 79, 82, 85, 86, 101). The effectiveness of the distillation was sometimes increased by adding copper bronze powder (16, 48); however, poor results were coincident with distillation of the calcium salt of the acid (53, 85, 100). Probably the poorest results were realized when the acid was heated in a sealed tube with glacial acetic acid. Of all the instances for which this method was employed (26, 30, 31, 53, 61, 64, 67, 78), the yield is given for only one reaction (61).

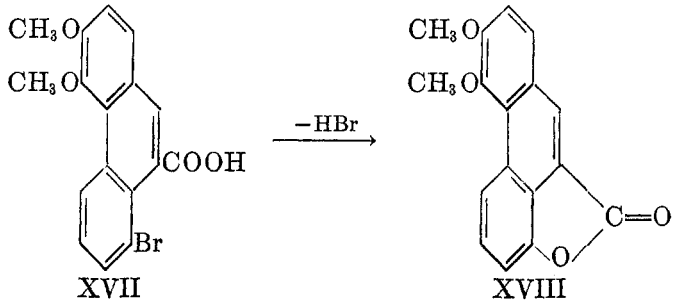
In recent years quinoline or quinaldine has been used as the solvent in these decarboxylation reactions, and copper, or one of its salts, added as catalyst. The catalysts used with quinoline were copper or copper bronze (2, 32, 33, 35, 36, 37, 38, 39, 96, 97), basic copper carbonate (48), copper chromite (4), and copper sulfate (88). With quinaldine the catalysts have been copper (1), copper bronze (10), or basic copper carbonate (1, 15, 16, 17). The reaction time varied from 10 min. (10, 97) to 6 hr. (1).

It is difficult to distinguish between results where quinoline or quinaldine was used with a catalyst. There is one case, however, in which decarboxylation in the presence of quinaldine and basic copper carbonate was unsuccessful (16); also, dubious results were obtained when quinoline and copper chromite were used (4).

### *B. Structural effects*

It is difficult to make a statement to which exception cannot be found concerning the relation between the structure of a 9(or 10)-phenanthrenecarboxylic acid and the ease with which the acid undergoes decarboxylation. It appears that such acids with alkyl groups substituted in the 1-, 2-, 3-, or 4-positions tend to undergo decarboxylation easily (9, 33, 53, 65), and that with rare exceptions (75, 79, 88, 97) difficulty is encountered where these acids are substituted with alkoxyl groups at almost any position (16, 26, 30, 31, 36, 37, 39, 64, 66, 67, 78, 84, 85, 86, 97, 103). Decarboxylation of chloro or bromo derivatives is usually attended by poor yields (4, 8, 47, 58, 69, 79), except in a recent case where quinoline and copper bronze were used (10).

Some of the difficulty in decarboxylating halophenanthrenecarboxylic acids can be explained in terms of well-defined reactions. In attempts to decarboxylate 8-bromo-3,4-dimethoxyphenanthrene-9-carboxylic acid (XVII), hydrogen bromide split out and the lactone (XVIII) was formed (69; *cf.* 67).



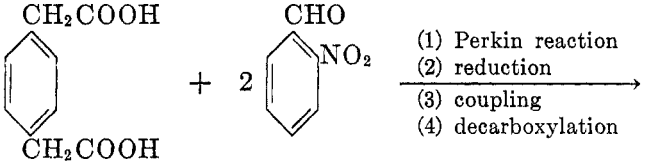

XVII XVIII

When 1-bromo-3,4-dimethoxyphenanthrene-9-carboxylic acid was subjected to decarboxylation conditions, the only isolable product was identified as methyl 1-bromo-3,4-dimethoxyphenanthrene-9-carboxylate. It was suggested that esterification of part of the original acid was made possible by demethylation of another portion of it (96). Other instances where esterification occurred during attempted decarboxylation are known (6, 68).

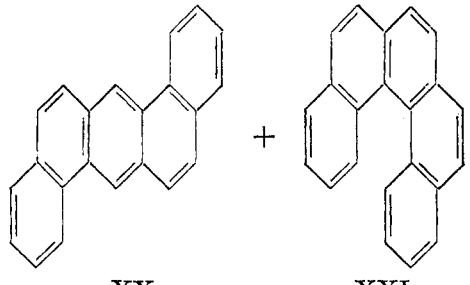
## VI. FORMATION OF RING SYSTEMS OTHER THAN PHENANTHRENE BY THE PSCHORR SYNTHESIS

### *A. The use of benzenediacetic acids*

The same four steps of the Pschorr synthesis, already outlined for the formation of phenanthrene derivatives, may also lead to the formation of polynuclear systems other than phenanthrene (see table 3). For instance, if 1,4-benzenediacetic acid (XIX), instead of phenylacetic acid, is allowed to react with two equivalents of *o*-nitrobenzaldehyde and the product is subsequently reduced, coupled, and decarboxylated, a mixture of 1,2,5,6-dibenzanthracene (XX) and 3,4,5,6-dibenzophenanthrene (XXI) is obtained (101). Reactions with derivatives of 1,4-benzenediacetic acid have also been effected (1, 17).




XIX
1,4-Benzenediacetic acid




XX
1,2,5,6-Dibenzanthracene

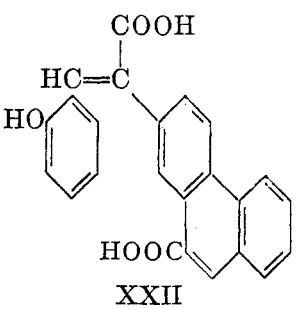
XXI
3,4,5,6-Dibenzophenanthrene

TABLE 3

*Formation of ring systems other than that of phenanthrene by the Pschorr synthesis*

| Starting Materials | | Reaction yields | | | | Products | References |
|---|---|---|---|---|---|---|---|
| | | Perkin reaction | Reduction | Cyclization | Decarboxylation | | |
| β-Naphthylacetic acid | 2-Nitrobenzaldehyde | 70 | 62 | 56 | ? | 3,4-Benzophenanthrene<br>1,2-Benzanthracene | (18, 55, 102) |
| 9-Phenanthrylacetic acid | 2-Nitrobenzaldehyde | 44 | 51 | 47 | 68 | 1,2,3,4-Dibenzophenanthrene | (32) |
| 1,2-Benzenediacetic acid | 2-Nitrobenzaldehyde | ? | ? | ? | ? | 1,2,7,8-Dibenzophenanthrene (picene) | (100) |
| 1,3-Benzenediacetic acid | 2-Nitrobenzaldehyde | ? | 67 | 14 | 11 | 1,2,7,8-Dibenzanthracene (other possible isomer not formed) | (19) |
| 1,4-Benzenediacetic acid | 2-Nitrobenzaldehyde | 24 | 86 | 93 (total) | 5.6<br>? | 1,2,5,6-Dibenzanthracene<br>3,4,5,6-Dibenzophenanthrene | (101) |
| 1,4-Benzenediacetic acid | 5-Methoxy-2-nitrobenzaldehyde | 51 | 95 | 11<br>8 | 75<br>69 | 2′,7′-Dimethoxy-3,4,5,6-dibenzanthracene<br>3′,7′-Dimethoxy-1,2,5,6-dibenzanthracene | (40) |
| 1,4-Benzenediacetic acid | 5-Hydroxy-2-nitrobenzaldehyde | 24 | 66 | Failed | — | 2′,7′-Dihydroxy-3,4,5,6-dibenzanthracene | (40) |
| 1,4-Dimethyl-2,5-benzenediacetic acid | 2-Nitrobenzaldehyde | 60 | 63 | 19 | 62 | 9,10-Dimethyl-1,2,5,6-dibenzanthracene | (1) |
| 1,4-Dimethyl-2,5-benzenediacetic acid | 4,5-Dimethoxy-2-nitrobenzaldehyde | 85 | 50–60 | 90 | 25–30 | 9,10-Dimethyl-2′,3′,6′,7′-tetramethoxy-1,2,5,6-dibenzanthracene | (17) |
| 1,4-Dimethyl-2,5-benzenediacetic acid | 4,5-Methylenedioxy-2-nitrobenzaldehyde | 64 | 70 | 23 | 72 | 9,10-Dimethyl-2′,3′,6′,7′-bismethylenedioxy-1,2,5,6-dibenzanthracene | (1) |
| 1-Acenaphthylacetic acid | 2-Nitrobenzaldehyde | 59 | 76 | ?<br>Overall 8.1 | ? | 7-Cholanthrenecarboxylic acid | (23) |
| 2-Furanacetic acid | 2-Nitrobenzaldehyde | 23 | 78 | Failed | | 1,2-Naphthofuran-3-carboxylic acid | (3) |

Still other polycyclic aromatic compounds have been prepared from 1,2-benzenediacetic acid (100) and from 1,3-benzenediacetic acid (19). In the latter case, a

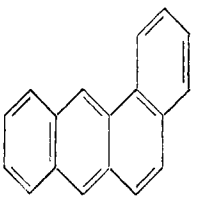



XXII

large part of the diamino compound failed to undergo cyclization at either of the possible positions, and some α-salicylal-10-carboxy-2-phenanthrylacetic acid (XXII) was isolated.

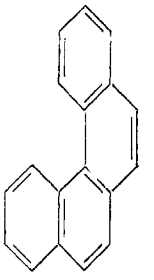
*B. The use of naphthyl-, phenanthryl-, and acenaphthylacetic acid derivatives*

β-Naphthylacetic acid (18, 55, 102), as well as 9-phenanthrylacetic acid (32), has been utilized in the Pschorr synthesis. From the naphthalene derivative both 1,2-benzanthracene (XXIII) and 3,4-benzophenanthrene (XXIV) were obtained, while from the phenanthrene derivative only 1,2,3,4-dibenzophe-



XXIII

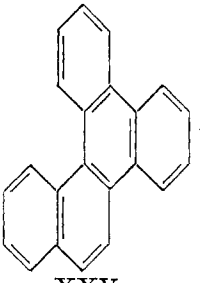
1,2-Benzanthracene



XXIV

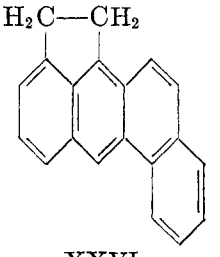
3,4-Benzophenanthrene

nanthrene (XXV) was isolated. Cholanthrene (XXVI) is the product of the Pschorr synthesis when the starting material is 1-acenaphthylacetic acid (23).



XXV

1,2,3,4-Dibenzophenanthrene




XXVI

Cholanthrene

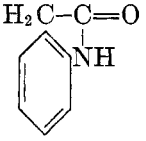
The effort to prepare heterocyclic compounds by the Pschorr synthesis has not been entirely rewarding. The condensation product of furanacetic acid and *o*-nitrobenzaldehyde failed to undergo cyclization to the expected 1,2-naphthofuran-3-carboxylic acid (3). Most other efforts to prepare heterocyclic compounds have included none or only a part of the Pschorr synthesis.

## VII. VARIATIONS OF THE PSCHORR SYNTHESIS

Starting materials slightly different from those in Pschorr's original synthesis have been used with varying degrees of success. Oxindole (XXIX), the lactam of *o*-aminophenylacetic acid, has been used to replace phenylacetic acid (104). With this material ketones as well as aldehydes may be used, *o*-nitrobenzalde-

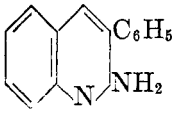
hyde or one of its derivatives is not required, and it is possible to prepare a 9- or 10-alkylphenanthrene derivative by condensing a ketone rather than an aldehyde with the oxindole (105).

It is also possible to replace the phenylacetic acid with phenylacetonitrile. In one instance, however, when reaction with the nitrile was carried out, the reaction series was interrupted at the reduction stage by the formation of $\alpha$-amino-$\beta$-phenylquinoline (XXX) (85).




XXIX

Oxindole




XXX

$\alpha$-Amino-$\beta$-phenylquinoline

## VIII. APPLICATIONS AND LIMITATIONS OF THE PSCHORR SYNTHESIS

The Pschorr synthesis, as can be gathered from the preceding discussion, has found extensive use. It was first applied in the proof of the structure of certain degradation products of morphine. Its main use, as in its first use, has been for proofs of structure. Since phenanthrene syntheses, except aromatic cyclodehydration, recently introduced by Bradsher (11), require drastic conditions such as dehydrogenation or give ambiguous results, the Pschorr synthesis has found continuous use. The conditions sometimes necessary to effect dehydrogenation in other syntheses have been known to cause elimination or rearrangement of alkyl groups (2, 43), but only limited difficulty has been reported as a result of the conditions necessary to decarboxylate substituted phenanthrene-9(or 10)-carboxylic acids obtained from the Pschorr synthesis.

There are certain very definite limitations to the Pschorr synthesis. Some of the limitations arise as a result of side reactions: reduction and/or hydroxylation may replace coupling, and where the $\alpha$-phenyl nucleus of the cinnamic acid derivative is unsymmetrically substituted, two isomeric coupling products are possible.

The main limitations to the Pschorr synthesis are difficulties in obtaining starting materials and in decarboxylating the phenanthrene derivative. *o*-Nitrobenzaldehyde is expensive and can be obtained only in poor yields (99), while substituted *o*-nitrobenzaldehydes are sometimes even more difficult to obtain. Likewise, problems connected with the preparation of substituted phenylacetic acid derivatives are sometimes the determining factors in the usefulness of the Pschorr synthesis.

## IX. SUMMARY

The Pschorr synthesis has been defined in terms of four separate reactions: condensation, reduction, coupling, and decarboxylation. Tables showing the application of this reaction series to the synthesis of phenanthrene and some of its derivatives, as well as to other polycyclic aromatic systems, are given. A

brief discussion of each of these four reactions as they pertain to the Pschorr synthesis is also presented.

The author is happy to acknowledge his indebtedness to Dr. Charles K. Bradsher for his encouragement and editorial assistance and to Dr. Frances Brown for her help in arranging the first draft of the review.

## X. REFERENCES

(1) AKIN, R. B., AND BOGERT, M. T.: J. Am. Chem. Soc. **59**, 1564 (1937).
(2) AKIN, R. B., STAMATOFF, G. S., AND BOGERT, M. T.: J. Am. Chem. Soc. **59**, 1268 (1937).
(3) AMSTUTZ, E. D., AND SPITZMILLER, E. R.: J. Am. Chem. Soc. **65**, 369 (1943).
(4) BARBER, H. J., AND STICKINGS, C. E.: J. Chem. Soc. **1945**, 167.
(5) BARBIER, M. P.: Ann. chim. [5] **7**, 479 (1876).
(6) BARTON, N., COOK, J. W., AND LOUDON, J. D.: J. Chem. Soc. **1945**, 176.
(7) BAUKUMIN, M., AND PECCERILLO, D.: Gazz. chim. ital. **65**, 1145 (1935).
(8) BERGER, H.: J. prakt. Chem. **133**, 331 (1932).
(9) BOGERT, M. G., AND STAMATOFF, G. S.: Rec. trav. chim. **52**, 584 (1933).
(10) BRADSHER, C. K., AND LEAKE, P. H.: Unpublished work.
(11) BRADSHER, C. K., AND SCHNEIDER, A. K.: J. Am. Chem. Soc. **60**, 2960 (1930).
(12) BRAUN, J. VON, AND ZOBEL, F.: Ber. **56**, 2142 (1923).
(13) BRESLOW, D. S., AND HAUSER, C. R.: J. Am. Chem. Soc. **61**, 786 (1939).
(14) BUCHANAN, G. L., COOK, J. W., AND LOUDON, J. D.: J. Chem. Soc. **1944**, 325.
(15) CASSADAY, J. T., AND BOGERT, M. T.: J. Am. Chem. Soc. **61**, 2461 (1939).
(16) CASSADAY, J. T., AND BOGERT, M. T.: J. Am. Chem. Soc. **61**, 3055 (1939).
(17) CASSADAY, J. T., AND BOGERT, M. T.: J. Am. Chem. Soc. **61**, 3058 (1939).
(18) COOK, J. W.: J. Chem. Soc. **1931**, 2524.
(19) COOK, J. W.: J. Chem. Soc. **1932**, 1472.
(20) COOK, J. W.: J. Chem. Soc. **1933**, 1592.
(21) FERKO, P.: Ber. **7**, 48 (1874).
(22) FIESER, L. F.: *The Chemistry of Natural Products Related to Phenanthrene*, pp. 28–31, 32–33, 39, 40–41, 70, 96–98. Reinhold Publishing Corporation, New York (1936).
(23) FIESER, L. F., AND KILMER, G. W.: J. Am. Chem. Soc. **62**, 1354 (1940).
(24) FUSON, R. C.: *Advanced Organic Chemistry*, p. 446. John Wiley and Sons, Inc., New York (1950).
(25) GATTERMANN, L.: Ber. **23**, 1219 (1890).
(26) GIRARDET, A.: Helv. Chim. Acta **14**, 513 (1931).
(27) GOTO, K., AND SUDZUKI, H.: Bull. Chem. Soc. Japan **4**, 163 (1929).
(28) GRAEBE, C.: Ann. **167**, 156 (1873).
(29) GRAEBE, C.: Ber. **7**, 48 (1874).
(30) GULLAND, J. M., AND VIRDEN, C. J.: J. Chem. Soc. **1928**, 921.
(31) GULLAND, J. M., AND VIRDEN, C. J.: J. Chem. Soc. **1928**, 1478.
(32) HEWETT, C. L.: J. Chem. Soc. **1938**, 193.
(33) HEWETT, C. L., AND MARTIN, R. H.: J. Chem. Soc. **1940**, 1396.
(34) HEY, D. H., AND OSBOND, J. M.: J. Chem. Soc. **1949**, 3164.
(35) HEY, D. H., AND OSBOND, J. M.: J. Chem. Soc. **1949**, 3172.
(36) HIGGINBOTTOM, A., HILL, P., AND SHORT, W. F.: J. Chem. Soc. **1937**, 263.
(37) HILL, P., AND SHORT, W. F.: J. Chem. Soc. **1937**, 260.
(38) HILL, P., SHORT, W. F., AND STROMBERG, H.: J. Chem. Soc. **1937**, 937.
(39) HILL, P., SHORT, W. F., STROMBERG, H., AND WILES, A. E.: J. Chem. Soc. **1937**, 510.
(40) HORNING, L. S.: J. Am. Chem. Soc. **74**, 4572 (1952).
(41) JACKSON, C. L., AND WHITE, J. F.: J. Am. Chem. Soc. **2**, 380 (1880).

(42) JOHNSON, J. R.: *Organic Reactions*, Vol. I, p. 210. John Wiley and Sons, Inc., New York (1942).
(43) JONES, W. E., AND RAMAGE, C. R.: J. Chem. Soc. **1938**, 1853.
(44) KISHI, N.: J. Pharm. Soc. Japan **532**, 475 (1926); Chem. Abstracts **21**, 2259 (1927).
(45) KNORR, L., AND HÖRLEIN, H.: Ber. **42**, 3497 (1909).
(46) KONDO, H., NAKAMURA, T., FUJII, M., AND KATO, T.: Ann. Rept. ITSUU Lab. (Japan) **1**, 1–4 (1950); Chem. Abstracts **47**, 5950 (1953).
(47) KONDO, H., AND OCHIAI, E.: J. Pharm. Soc. Japan **539**, 17–24 (1927); Chem. Abstracts **22**, 4521 (1928).
(48) LEWIS, E. E., AND ELDERFIELD, R. C.: J. Org. Chem. **5**, 290 (1940).
(49) LOCK, F. AND BEYER, E.: Ber. **72**, 1064 (1939).
(50) MAY, E. L.: J. Am. Chem. Soc. **69**, 717 (1947).
(51) MAY, E. L., AND MOSETTIG, E.: J. Org. Chem. **11**, 631 (1946).
(52) MAY, E. L., AND MOSETTIG, E.: J. Org. Chem. **11**, 435 (1946).
(53) MAYER, F., AND BALLE, G.: Ann. **403**, 167 (1914).
(54) MAYER, F., AND ENGLISH, F. A.: Ann. **417**, 60 (1918).
(55) MAYER, F., AND OPPENHEIMER, T.: Ber. **51**, 510 (1918).
(56) MEYER, H., AND BEER, R.: Monatsh. **34**, 649 (1913).
(57) MOSETTIG, E., AND BURGER, A.: J. Am. Chem. Soc. **52**, 2988 (1930).
(58) NYLEN, P.: Ber. **53**, 158 (1920).
(59) PAULING, L.: *The Nature of the Chemical Bond*, p. 78. Cornell University Press, Ithaca, New York (1948).
(60) PSCHORR, R.: Ber. **29**, 496 (1896).
(61) PSCHORR, R.: Ber. **33**, 176 (1900).
(62) PSCHORR, R.: Ann. **391**, 23 (1912).
(63) PSCHORR, R., AND BUCKOW, W.: Ber. **33**, 1829 (1900).
(64) PSCHORR, R., AND BUSCH, H.: Ber. **40**, 2001 (1907).
(65) PSCHORR, R., AND HOFMAN, R.: Ber. **39**, 3110 (1906).
(66) PSCHORR, R., AND JAECKEL, B.: Ber. **33**, 1826 (1900).
(67) PSCHORR, R., AND KNOFFLER, G.: Ann. **382**, 50 (1911).
(68) PSCHORR, R., AND KOCH, W.: Ann. **391**, 51 (1912).
(69) PSCHORR, R., AND POPOVICI, J.: Ber. **39**, 3118 (1906).
(70) PSCHORR, R., AND POPOVICI, J.: Ber. **39**, 3120 (1906).
(71) PSCHORR, R., AND QUADE, F.: Ber. **39**, 3112 (1906).
(72) PSCHORR, R., AND QUADE, F.: Ber. **39**, 3113 (1906).
(73) PSCHORR, R., AND QUADE, F.: Ber. **39**, 3122 (1906).
(74) PSCHORR, R., AND SCHÜTZ, M.: Ber. **39**, 3117 (1906).
(75) PSCHORR, R., AND SEYDEL, C.: Ber. **34**, 3999 (1901).
(76) PSCHORR, R., SEYDEL, C., AND STÖHRER, W.: Ber. **35**, 4408 (1902).
(77) PSCHORR, R., SEYDEL, C., AND STÖHRER, W.: Ber. **35**, 4400 (1902).
(78) PSCHORR, R., AND SUMULEANU, C.: Ber. **33**, 1810 (1900).
(79) PSCHORR, R., AND TAPPEN, H.: Ber. **39**, 3108 (1906).
(80) PSCHORR, R., AND TAPPEN, H.: Ber. **39**, 3115 (1906).
(81) PSCHORR, R., AND TAPPEN, H.: Ber. **39**, 3116 (1906).
(82) PSCHORR, R., AND TREIDEL, O.: Ann. **391**, 38 (1912).
(83) PSCHORR, R., AND TREIDEL, O.: Ann. **391**, 47 (1912).
(84) PSCHORR, R., AND VOGTHERR, H.: Ber. **35**, 4412 (1902).
(85) PSCHORR, R., WOLFES, O., AND BUCKOW, W.: Ber. **33**, 162 (1900).
(86) PSCHORR, R., AND ZEIDLER, F.: Ann. **373**, 75 (1910).
(87) PSCHORR, R., ZEIDLER, F., AND DICKHAUSER, F.: Ann. **391**, 40 (1912).
(88) RAPOPORT, H., WILLIAMS, A. R., AND CISNEY, M. E.: J. Am. Chem. Soc. **73**, 1414 (1951).
(89) RAPSON, W. S., AND ROBINSON, R.: J. Chem. Soc. **1935**, 1533.

(90) RUGGLI, P., AND DINGER, A.: Helv. Chim. Acta **24,** 173 (1941).
(91) RUGGLI, P., AND STAUB, A.: Helv. Chim. Acta **19,** 1288 (1936).
(92) RUGGLI, P., AND STAUB, A.: Helv. Chim. Acta **20,** 37 (1937).
(93) SCHLITTLER, E., AND MÜLLER, J.: Helv. Chim. Acta **31,** 1119 (1948).
(94) SCHOFIELD, K., AND SWAIN, T.: J. Chem. Soc. **1949,** 2393.
(95) SHARP, T. M.: J. Chem. Soc. **1936,** 1234.
(96) SMALL, L., AND TURNBULL, S. G.: J. Am. Chem. Soc. **59,** 1541 (1937).
(97) SPÄTH, E., AND THARRER, K.: Ber. **66,** 583 (1933).
(98) TAYLOR, T. W. J., AND HOBSON, P. M.: J. Chem. Soc. **1936,** 181.
(99) TSANG, S. M., WOOD, E. H., AND JOHNSON, J. R.: Org. Syn. **24,** 75 (1944).
(100) WALDMANN, H., PITSCHAK, G., AND HINDENBURG, K. G.: Ann. **527,** 183 (1937).
(101) WEITZENBOCK, R., AND KLINGER, A.: Monatsh. **39,** 315 (1918).
(102) WEITZENBOCK, R., AND LIEB, H.: Monatsh. **33,** 564 (1912).
(103) WERNER, A., AND SCHERER, A.: Ann. **322,** 148 (1902).
(104) WINDAUS, A., AND EICKEL, W.: Ber. **57,** 1871 (1924).
(105) WINDAUS, A., JENSEN, H., AND SCHRAMME, A.: Ber. **57, 1875 (1924).**
(106) WOLF, G.: J. Am. Chem. Soc. **75,** 2673 (1953).