

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

**The N-Methylformanilide Synthesis of Aldehydes**

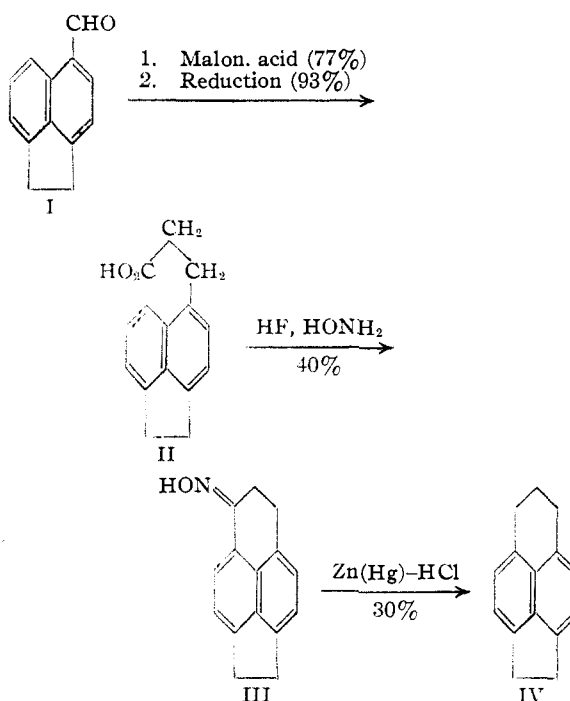
BY LOUIS F. FIESER AND J. ELMORE JONES

Vilsmeier and Haack<sup>1</sup> discovered that secondary and tertiary aromatic amines can be converted into aldehyde derivatives by the action of N-methylformanilide and phosphorus oxychloride, a reaction reminiscent of the Bischler-Napieralski synthesis of isoquinolines. In a series of patents, Kalischer, Scheyer and Keller<sup>2</sup> reported that the reaction is applicable to certain phenol ethers and aromatic hydrocarbons, and these claims were verified by Wood and Bost<sup>3</sup> to the extent of noting that  $\beta$ -naphthol ethyl ether and anthracene can be formylated by the method described, and detailed procedures for conducting these reactions have subsequently been published.<sup>4</sup>

Following the observations of Vollmann, *et al.*,<sup>5</sup> that pyrene-3-aldehyde can be obtained in excellent yield by the methylformanilide method, the reaction was applied in this Laboratory to a few carcinogenic and related hydrocarbons. With the use of *o*-dichlorobenzene as the solvent,<sup>5</sup> 3,4-benzpyrene was found to react<sup>6</sup> with the same degree of readiness as pyrene<sup>5</sup> and anthracene<sup>4,7</sup> and to afford the 5-aldehyde in 90% yield; 1,2-benzanthracene was converted into the 10-derivative somewhat less smoothly<sup>7</sup> (64%), and 1,2,5,6-dibenzanthracene failed to react.<sup>7</sup> In exploring other cases, we have found the reaction to be less generally applicable to aromatic hydrocarbons than claimed in the patents.<sup>2</sup> No trace of aldehyde could be obtained from hydrindene,  $\alpha$ -methyl-naphthalene, phenanthrene, or chrysene in condensations conducted at temperatures from 20 to 150°, and the solid hydrocarbons were recovered in good yield. 9-Methylanthracene reacted satisfactorily without added solvent, since it melts at the reaction temperature, and gave the 10-aldehyde. Acenaphthene and perinaphthene possess adequate nuclear reactivity but are

highly sensitive to the action of phosphorus oxychloride and yielded only tars when condensed at 95 and 25°, respectively.

In the condensation with acenaphthene a satisfactory conversion was accomplished by controlling the temperature to 25° and allowing a reaction period of six days. The product was purified effectively if slowly by steam distillation and obtained in 85% yield. It melted at 105–107° and was identified as 3-acenaphthaldehyde (I) by oxidation to the corresponding acid.<sup>8</sup> Hinkel, Ayling and Beynon<sup>9</sup> obtained a lower melting product (87°) by the Gattermann synthesis, but the constants for the oxime and semicarbazone are comparable. 3-Acenaphthaldehyde was converted to the corresponding alcohol by hydrogenation in the presence of Adams catalyst and ferrous chloride, and it yielded 3-methylacenaphthene when heated in an autoclave with hydrazine hydrate at 200°, according to Vollmann, *et al.*<sup>5</sup> The aldehyde was also utilized for the synthesis of the tetracyclic hydrocarbon IV.



Condensation with malonic acid and reduction

(1) Vilsmeier and Haack, *Ber.*, **60**, 119 (1927).(2) Kalischer, Scheyer and Keller (I. G. Farbenind. A.-G.), German Patents 514,415 (1930) and 519,444 (1931); French Patent 648,069 (1928); U. S. Patent 1,807,893 (1931) [*Chem. Zentr.*, **100**, I, 2528 (1929); **102**, II, 3394 (1931)].(3) Wood and Bost, *This Journal*, **59**, 1721 (1937).(4) Wood and Bost (2-ethoxy-1-naphthaldehyde), Fieser, Hartwell and J. E. Jones (9-anthraldehyde), "Organic Syntheses," **20**, 11 (1940).(5) Vollmann, Becker, Corell and Streeck, *Ann.*, **531**, 1 (1937).(6) Fieser and Hershberg, *This Journal*, **60**, 2542 (1938).(7) Fieser and Hartwell, *ibid.*, **60**, 2555 (1938).(8) Fieser and Hershberg, *ibid.*, **62**, 49 (1940).(9) Hinkel, Ayling and Beynon, *J. Chem. Soc.*, 339 (1936).

either catalytically or with sodium amalgam afforded the propionic acid II, and cyclization with hydrogen fluoride gave a tarry product from which the ketone was best isolated in the form of the oxime (III). Under the conditions of the Clemmensen reaction the oxime suffered hydrolysis and the ketone was reduced. The point of ring closure was established by oxidation of the ketone to the known naphthalene-1,4,5,8-tetracarboxylic acid. The hydrocarbon obtained as the end-product of the synthesis (m. p. 121.4–122°) can thus be assigned the structure of 3,4-aceperinaphthane (IV).

3-Methylacenaphthene and 3-methylpyrene were found to react smoothly with N-methylformanilide, but no satisfactory methods were found for separating the resulting mixtures of isomers.

### Experimental Part<sup>10</sup>

**9-Methyl-10-anthraldehyde.**—A mixture of 9-methylanthracene<sup>7</sup> (m. p. 77.9–78.4°), 2.7 g. of N-methylformanilide,<sup>11</sup> and 2.7 g. of phosphorus oxychloride was heated with stirring on the steam-bath under protection from moisture for forty-five minutes, during which time the hydrocarbon dissolved. The cooled mixture was treated with 5.6 g. of crystalline sodium acetate in 50 cc. of water and stirred for a few minutes to decompose the excess oxychloride and any intermediate complex. The collected solid product on crystallization from acetic acid gave 1.84 g. (84%) of orange needles; m. p. 170–171.4°. After three recrystallizations from benzene–ligroin the substance melted at 171.9–172.6°.

*Anal.* Calcd. for C<sub>16</sub>H<sub>12</sub>O: C, 87.25; H, 5.49. Found: C, 87.34; H, 5.61.

Oxidation of the aldehyde with chromic oxide in acetic acid gave anthraquinone (mixed m. p.) in 86% yield.

The oxime was obtained from the aldehyde with aqueous hydroxylamine hydrochloride and alkali, with enough ethanol to effect solution; after heating at the boiling point for ten minutes, the oxime separated in deep yellow plates; m. p. 210°, dec.; (94% yield).

*Anal.* Calcd. for C<sub>16</sub>H<sub>18</sub>ON: C, 81.68; H, 5.57. Found: C, 81.52; H, 5.60.

The hydrazone was prepared by adding 0.5 g. of hydrazine hydrate to a solution of 0.5 g. of the aldehyde in 70 cc. of hot alcohol, boiling the solution for ten minutes, and adding water to saturation; on cooling 0.37 g. (69%) of orange needles separated; m. p. 175.1–175.8°. A mixture with the aldehyde showed a 10°-depression. The hydrazone is stable in the solid state but decomposes on attempted crystallization.

*Anal.* Calcd. for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>: C, 82.02; H, 6.02. Found: C, 82.26; H, 6.29.

A mixture of 0.25 g. of the hydrazone with a solution of 0.05 g. of sodium in 16 cc. of absolute ethanol was shaken in a sealed tube until uniform and heated at 200–210° for

twenty-four hours. The product was collected after dilution with water and neutralization with acetic acid and crystallized from ethanol, giving 0.17 g. (74%) of light yellow plates, m. p. 183–183.7°; the picrate formed dark red needles, m. p. 175.6–176.3°. The constants agree with those reported for 9,10-dimethylanthracene (m. p. 180–181°)<sup>12</sup> and its picrate (m. p. 175–176°).<sup>13</sup>

**3-Acenaphthaldehyde (I).**—A mixture of 43 g. of acenaphthene, 90 cc. of N-methylformanilide, 60 cc. of phosphorus oxychloride, and 50 cc. of *o*-dichlorobenzene was shaken thoroughly to effect solution and allowed to stand at room temperature for six days, during which time the solution turned deep red and hydrogen chloride was evolved slowly. For hydrolysis, 150 g. of crystalline sodium acetate in 150 cc. of water was added slowly to prevent violent reaction, and the mixture was subjected to efficient steam distillation. The solvent was removed in about one-half hour, and the product then distilled very slowly. Filtration of the large volume of cooled distillate afforded 40.2 g. (85%) of the aldehyde; m. p. 105–107°. The best sample, purified by repeated crystallization from dilute acetic acid and sublimation at 110° (2 mm.), formed pale greenish needles; m. p. 107.4–108°.

*Anal.* Calcd. for C<sub>13</sub>H<sub>10</sub>O: C, 85.69; H, 5.53. Found: C, 85.95; H, 5.50.

A sample of the oxime melted at 126.8–127.9°, and the semicarbazone melted at 247.8–248.8°; Hinkel, *et al.*,<sup>9</sup> recorded the constants 126.5° and 234°. For oxidation, 0.3 g. of the aldehyde in 5 cc. of dioxane was treated slowly with 8 cc. of 30% hydrogen peroxide, followed by 10% sodium hydroxide. The mixture was heated on the steam-bath for ten minutes, filtered from a trace of unreacted aldehyde (0.04 g.), and acidified. Crystallization of the voluminous precipitate from acetic acid yielded 0.22 g. (78%) of acenaphthene-3-carboxylic acid; m. p. 219–221° (no depression with an authentic sample).<sup>8</sup>

**3-Hydroxymethylacenaphthene.**—Hydrogenation of 1.16 g. of 3-acenaphthaldehyde in 100 cc. of absolute ethanol in the presence of 25 mg. of Adams catalyst and 10 mg. of ferrous chloride proceeded to completion in one hour, and in this time a quantity of the alcohol had crystallized in colorless needles. This was dissolved by warming, and the solution was filtered and evaporated and the product crystallized from benzene, yielding 0.86 g. (73%) of needles; m. p. 153.4–154.2°. The best sample melted at 153.8–154.8°.

*Anal.* Calcd. for C<sub>13</sub>H<sub>12</sub>O: C, 84.75; H, 6.57. Found: C, 84.52; H, 6.66.

**3-Methylacenaphthene.**—A mixture of 18 g. of the aldehyde and 55 g. of hydrazine hydrate was heated in an autoclave under a nitrogen pressure of 2250 lb. at 200–210° for eight hours. The well washed reaction product on sublimation at atmospheric pressure at 100° yielded 10.4 g. (63%) of colorless blades; m. p. 95.6–95.9°. The hydrocarbon crystallized from ethanol in long, colorless needles of the same melting point (20°-depression with acenaphthene). Considerable azine was formed in the reaction and was left as a residue in the sublimation.

(10) All melting points are corrected.

(11) Fieser and Jones, "Org. Synth.," **20**, 66 (1940).

(12) Gibson and Johnson, *J. Chem. Soc.*, 753 (1931); Bachmann and Chemerda, *J. Org. Chem.*, **4**, 583 (1939).

(13) Barnett and Matthews, *Ber.*, **59**, 1437 (1926).

*Anal.* Calcd. for  $C_{13}H_{12}$ : C, 92.82; H, 7.18. Found: C, 92.57; H, 7.38.

The **picrate** crystallized from alcohol in bright red needles; m. p. 163°, dec.

*Anal.* Calcd. for  $C_{19}H_{15}O_7N_3$ : C, 57.42; H, 3.81. Found: C, 57.59; H, 3.82.

**3-Acenaphthalacetic Acid.**—A mixture of 40.2 g. of the aldehyde, 42 g. of malonic acid, and 30 cc. of pyridine was heated on the steam-bath for eight hours and the solid product which separated was collected after cooling and dissolved in 200 cc. of 10% sodium carbonate solution by heating. The filtered solution was acidified and the pale yellow precipitate was washed thoroughly and dried for six hours at 50° (20 mm.). This material had no distinct melting point and appeared to be the **dihydrate**; yield 47.8 g. (83%).

*Anal.* Calcd. for  $C_{15}H_{12}O_2 \cdot 2H_2O$ : neut. equiv., 260. Found: 256.

Crystallization from ethanol (Norit) yielded 38.4 g. (77%) of pale yellow needles of the anhydrous acid; m. p. 250°, dec. On further purification the substance melted at 251.3–251.8° with gas evolution.

*Anal.* Calcd. for  $C_{15}H_{12}O_2$ : C, 80.33; H, 5.39; neut. equiv., 224. Found: C, 80.43; H, 5.51; neut. equiv., 219.

The acid seemed to undergo some decarboxylation on melting, but attempts to isolate a pure reaction product after vacuum distillation or treatment with copper bronze were unsuccessful.

The **methyl ester**, prepared with diazomethane, distilled at 204° at 6 mm. and crystallized from ligroin in large yellow cubes; m. p. 104.4–105.4°. A second modification was obtained by rapid cooling of the melted ester; this melted at 73–74°, solidified and remelted at the higher temperature.

*Anal.* Calcd. for  $C_{16}H_{14}O_2$ : C, 80.65; H, 5.92. Found: C, 80.34; H, 5.99.

**$\beta$ -3-Acenaphthylpropionic Acid (II).**—A solution of 22.4 g. of the unsaturated acid in 200 cc. of 0.5 *N* sodium hydroxide was shaken with 450 g. of 2% sodium amalgam for three hours and the filtered solution was acidified. Crystallization of the precipitated material from benzene gave 21.0 g. (93%) of colorless needles, m. p. 188–190°, and repeated recrystallization raised the melting point to 191.7–192°.

*Anal.* Calcd. for  $C_{15}H_{14}O_2$ : C, 79.62; H, 6.24. Found: C, 79.44; H, 6.46.

The **methyl ester**, prepared by hydrogenation of the unsaturated ester in ethanol (Adams catalyst) formed colorless needles from methanol; m. p. 50.7–51.7°.

*Anal.* Calcd. for  $C_{16}H_{16}O_2$ : C, 79.97; H, 6.71. Found: C, 79.92; H, 6.94.

**3,4-Aceperinaphthanone-7.**—A solution of 5 g. of the saturated acid in 50 g. of liquid hydrogen fluoride was poured onto ice after twenty minutes. The tarry, yellow-green product which separated solidified after about three hours and was washed thoroughly and dried at 50° (20 mm.) for three hours. Extraction with ligroin from a residual green tar and clarification with Norit gave 2.5 g. (54%) of clusters of yellow plates; m. p. 92–97°. Further

purification was best accomplished through the oxime (III), which was prepared by treating a solution of the crude ketone in ethanol with the filtrate from a mixture of 13 g. of hydroxylamine hydrochloride and 14 g. of sodium carbonate which had been ground with 50 cc. of ethanol. After standing for several hours the mixture was heated to boiling, the separated solid was brought into solution with more solvent, and the solution was clarified with Norit and allowed to cool. Repeated crystallizations of the material which separated afforded 1.9 g. (40%) of colorless needles, m. p. 245–246°, dec., with darkening at 225° (even in an evacuated capillary).

*Anal.* Calcd. for  $C_{15}H_{12}ON$ : C, 80.69; H, 5.87. Found: C, 80.93; H, 5.98.

Steam distillation of a mixture of the oxime and dilute sulfuric acid yielded in the distillate 1.36 g. of the ketone (77% from the oxime, 31% from the acid). The substance crystallized from ligroin in clusters of yellow plates; m. p. 102.6–103.4°. The ketone darkened on exposure to sunlight.

*Anal.* Calcd. for  $C_{15}H_{12}O$ : C, 86.51; H, 5.80. Found: C, 86.59; H, 5.79.

The **semicarbazone** separated from a boiling solution of the components in ethanol in the form of microcrystals which turned green when introduced into a bath at 260° and melted at 268° (evacuated capillary). The substance was very sparingly soluble in the usual solvents.

*Anal.* Calcd. for  $C_{16}H_{14}ON_3$ : C, 72.43; H, 5.70. Found: C, 72.54; H, 5.86.

**Oxidation of the ketone** was accomplished by gradually adding 10 g. of chromic oxide in 20 cc. of 50% acetic acid to 1.5 g. of the ketone in 10 cc. of acetic acid. After the initial reaction had subsided the solution was refluxed for one hour and poured into water. The mixture was boiled to coagulate the dark brown solid, and this crude product was then dissolved in 20 cc. of 10% sodium hydroxide and refluxed with 3 g. of potassium permanganate for three hours. The mixture was poured into 100 cc. of water containing 20 cc. of concentrated sulfuric acid, sodium bisulfite was added until the manganese dioxide was dissolved, and the solution was evaporated to a volume of 75 cc. The gray product which separated was sublimed at 320° (3 mm.) and yielded 0.15 g. (7.7%) of **naphthalene-1,4,5,8-tetracarboxylic dianhydride**.<sup>14</sup> This was identified by the formation of the diimide and its sodium salt, by the characteristic solubility in sulfuric acid and precipitation with water, and by the analysis.

*Anal.* Calcd. for  $C_{14}H_4O_6$ : C, 62.70; H, 1.50. Found: C, 62.94; H, 1.72.

**3,4-Aceperinaphthane (IV).**—A mixture of 0.75 g. of the oxime, 12 cc. of 6 *N* hydrochloric acid, 6 cc. of acetic acid, 12 cc. of toluene, and 4 g. of amalgamated zinc was refluxed vigorously for six hours, after which another charge of zinc and acid was added and refluxing continued for thirty-six hours longer. The aqueous layer was extracted with ether, combined with the toluene layer, and evaporated to dryness. The residue was a greenish tar from which the hydrocarbon was obtained by sublimation at 135° (8 mm.) in the form of colorless needles. Two crystallizations from

(14) Bamberger and Philip, *Ann.*, **240**, 147 (1887); Freund and Fleischer, *ibid.*, **399**, 182 (1913).

ligroin afforded 0.2 g. (30%) of material melting at 121.4–122°.

*Anal.* Calcd. for  $C_{15}H_{14}$ : C, 92.75; H, 7.26. Found: C, 92.72; H, 7.24.

Attempts to prepare a pure picrate were unsuccessful, the best sample sintering at 121° and melting over the range 127–130°. The trinitrobenzene derivative crystallized from ethanol in orange needles; m. p. 147–148°.

*Anal.* Calcd. for  $C_{21}H_{17}O_6N_3$ : C, 61.91; H, 4.21. Found: C, 61.98; H, 4.50.

**Other Trials.**—3-Methylacenaphthene (10 g.) was condensed with N-methylformanilide under the conditions used in the reaction with acenaphthene. Steam distillation gave 8.0 g. (68%) of a mixture of aldehydes, m. p. 67–100°, but no satisfactory method of separation was found. 3-Methylpyrene<sup>5</sup> (9 g.) was submitted to the reaction in *o*-dichlorobenzene solution at the steam-bath temperature, and the reaction mixture when processed through the bisulfite addition product yielded 7.5 g. (73%) of a mixture of aldehydes, m. p. 98–108°, but this again proved intract-

able. The semicarbazone mixture did not seem favorable for fractionation and the regeneration proceeded poorly. Extensive fractionation of the aldehyde mixture from alcohol and from benzene-ligroin afforded only a small amount of possibly homogeneous orange needles; m. p. 138–140°.

*Anal.* Calcd. for  $C_{17}H_{10}O$ : C, 88.50; H, 4.99. Found: C, 88.60; H, 4.95.

### Summary

The reaction of aromatic hydrocarbons with N-methylformanilide to give aldehydes is limited to substances having a particularly reactive nuclear position and not too sensitive to be destroyed by the condensing agent (phosphorus oxychloride). Acenaphthene has been formylated by this method and the product utilized for the synthesis of 3,4-aceperinaphthane.

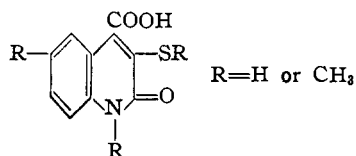
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CAMBRIDGE, MASSACHUSETTS RECEIVED APRIL 1, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

## The Synthesis from Rhodanine-oxindoles of Keto and Mercapto Derivatives of Cinchoninic Acid<sup>1</sup>

BY RUFUS VERNON JONES<sup>2</sup> AND HENRY R. HENZE

Although the preparation of derivatives of keto-cinchoninic acids has been studied to a considerable extent, little attention has been directed to the synthesis of mercapto derivatives of the type



In fact, only two examples of this type have been reported, namely, the unsubstituted keto-mercapto acid and its 1-methyl derivative, prepared, respectively, by the alkaline hydrolysis of the appropriate rhodanine-( $\Delta^{5,3'}$ )-oxindole.<sup>3</sup>

We have resynthesized these two rhodanine-oxindoles and, in addition, have prepared the 5-methyl and the 1,5-dimethyloxindole analogs, by condensation of rhodanic acid and appropriate derivatives of isatin, in order to study their conversion into keto and mercapto derivatives of

cinchoninic acid. A comparison of behavior upon hydrolysis of rhodanine-( $\Delta^{5,3'}$ )-oxindole and its 5-methyl homolog was of special interest since it had been shown<sup>4</sup> that the closely related hydantoin-(5,3')-oxindole and its 5'-methyl homolog had formed markedly different products on alkaline hydrolysis, in that the former yielded 1,2-dihydro-2-ketocinchoninic acid and the latter 5-methyloxindole.

In the present investigation, rhodanine-( $\Delta^{5,3'}$ )-oxindole and three methyl derivatives were hydrolyzed by alkali to form derivatives of 1,2-dihydro-2-keto-3-mercaptocinchoninic acid. The behavior of these compounds toward further hydrolysis, methylation and reduction was studied. It was found that rhodanine-( $\Delta^{5,3'}$ )-oxindole and its 5'-methyl homolog by treatment with one molecular proportion of potassium hydroxide are converted into mono-potassium salts of the type (A) which can be hydrolyzed to regenerate the oxindoles but cannot be methylated. With an excess of alkali, rhodanine-( $\Delta^{5,3'}$ )-oxindole was converted into the dipotassium salt of 1,2-dihydro-2-keto-3-mercaptocinchoninic acid, and the three methyl derivatives formed analogous dipo-

(1) Presented before the Division of Organic Chemistry at the 99th meeting of the American Chemical Society at Cincinnati, Ohio, April 9–11, 1940.

(2) From the Ph.D. dissertation of R. V. Jones, June, 1937. Present address of R. V. J., East Texas State Teachers College, Commerce, Texas.

(3) (a) Gränacher and Mahal, *Helv. Chim. Acta*, **6**, 467 (1923); (b) Gränacher and Kouniniotis, *ibid.*, **11**, 1241 (1928).

(4) Henze and Blair, *THIS JOURNAL*, **55**, 4624 (1933).