Quinoline Syntheses by Reaction of Hydrazoic Acid with α,β-Disubstituted *cis*-Chalcones (1)

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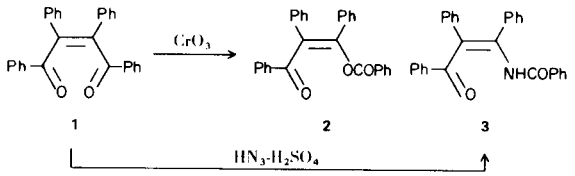
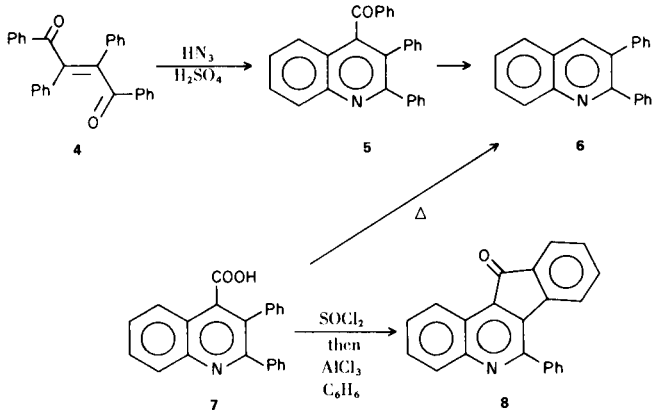
Hydrazoic-sulfuric acid mixture converted *cis*-α-phenyl-β-benzoylchalcone (*trans*-dibenzoylstilbene, **4**) into 2,3-diphenyl-4-benzoylquinoline (**5**) the structure of which was proved by debenzoylation to 2,3-diphenylquinoline. α,β-Diphenyl and *cis*-α,β-dibromochalcones similarly were converted respectively into 2,3,4-triphenylquinoline (**19**) and 2-phenyl-3,4-dibromoquinoline (**20**). The structure of **19** was shown by difference from the corresponding isoquinoline **21** (synthesized). Smith's mechanism for the analogous conversion of *o*-phenylbenzophenone into 9-phenylphenanthridine through the 9-fluorenol and the 9-hydroazide with loss of nitrogen and ring expansion, was supported by methyl label experiments using 2-(*p*-tolyl)benzophenone which gave a 53:47 mixture of 3- and 8-methyl-6-phenylphenanthridines. Applicability of the mechanism to the reactions with disubstituted *cis*-chalcones was shown by sulfuric acid conversions of two of these into indenol **22** and 2-bromo-3-phenylindenone (**24**), respectively. *trans*-Dibenzoylstilbene underwent resinification in sulfuric acid, giving the quinoline (**5**) only when hydrazoic acid was present.

This investigation stems from the study of 1,2-diaroyl mono and disubstituted ethylenes where *cis*-dicarbonyl group interactions seem to be responsible for certain of their reactions which proceed slowly or not at all with the *trans* isomers (5). For example, *cis*-dibenzoylstilbene (**1**) undergoes ready oxidative rearrangement with carbon-to-oxygen migration of the bulky vinyl moiety, giving the enol-benzoate **2**, whereas under similar conditions the *trans* isomer **4** is inert (4c, 5b). Hydrazoic-sulfuric acid mixture also brings about oxidative rearrangement of **1** but with carbon-to-nitrogen migration of the vinyl moiety, giving the enamine benzoate **3** (5b,6,7).



For comparison, *trans*-dibenzoylstilbene (**4**) was also subjected to the conditions of the Schmidt reaction because, without the proximity of the carbonyl groups, slow reaction or none at all was expected. However, reaction did occur, rapidly, giving 2,3-diphenyl-4-benzoylquinoline (**5**), the structure of which was assigned on the basis of its properties and on first but incorrect ideas concerning the mechanism (**9a** below). This reaction had seemed to take place with retention of the *trans* configuration of **4** by attack of hydrazoic acid at a carbonyl group followed by cyclization involving the sterically adjacent phenyl group, an overall and typically facile *cis*-group interaction.

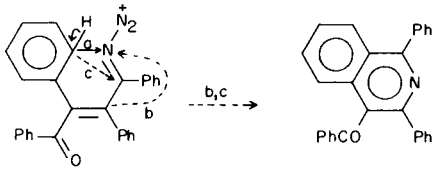


The structure of quinoline **5** was proved by base-induced hydrolytic debenzoylation to the known 2,3-diphenylquinoline (**6**) which was identified by comparison with a sample prepared by decarboxylation of 3-phenylcinchophen (**7**) (8).

Attempts to synthesize quinoline **5** from **7** were unsuccessful because of the excessive steric hindrance at the 4-carbonyl group. The methyl ester and the nitrile of **7** were unreactive toward phenyllithium. Attempted Grignard and Friedel-Crafts condensations of benzene with

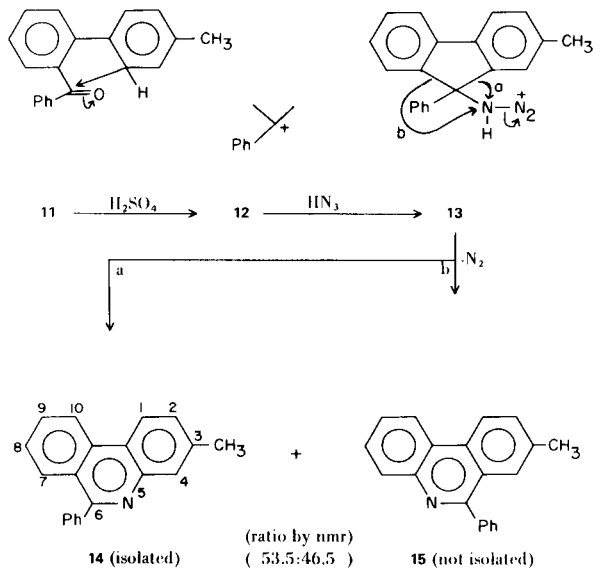
the acid chloride of **7** caused intramolecular dehydrohalogenation to a new compound for which the tetracyclic fluorenone-type structure **8** is suggested on the basis of analysis and ultraviolet and infrared spectra.

Formation of the quinoline **5** by attack of hydrazoic acid at the sterically hindered carbonyl group seemed unlikely although subsequent ring closure **9a** with the proximate phenyl group, would then be possible, facilitated by the buttressing effects of nearby groups. Carbon-to-nitrogen migrations in **9** are excluded because phenyl group migration would have given an anilide, and because migration of the vinyl moiety followed by cyclization **9bc** would have led to isoquinoline **10** rather than to **5**. A mechanism involving hydrazoic acid β-attack on the chalcone system of **4** seemed unlikely, on steric grounds, and because it would not lead directly to quinoline **5**.



9 **10** (not obtained)

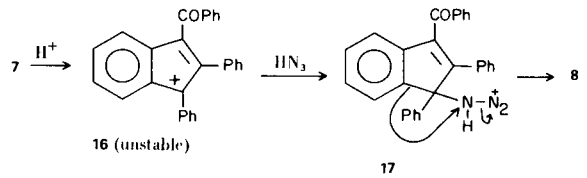
In an analogous reaction Smith (9) converted *o*-phenylbenzophenone, containing the *cis*-α,β-disubstituted chalcone system, to 6-phenylphenanthridine, first proposing a mechanism of type **9a** which requires the sterically unlikely initial attack at a carbonyl group, and which is excluded in the cases of the chalcones. He later (6) suggested a preferable mechanism which is without the steric objection and which would account both for his results and ours, namely: cyclodehydration to the 9-fluorenyl cation and the hydroazide, followed by ring expansion by migration of one arm of the fluorenyl system to nitrogen. This mechanism was put to test using the methyl labeled analog, *o*-tolylbenzophenone (**11**).



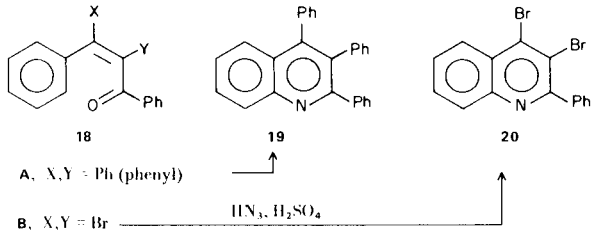
The synthesis of **11** was accomplished by a Diels-Alder condensation of butadiene and *trans*-*p*'-methylchalcone followed by sulfur dehydrogenation, a scheme successfully used in another series (10). The Schmidt reaction converted **11** into a mixture of 3- and 8-methyl-6-phenanthridines (**14** and **15**) from which pure 3-methyl isomer **14** was isolated by fractional crystallization and identified by mixture melting point and infrared comparison with a sample synthesized according to Ritchie (11). The 8-methyl isomer **15** was not isolated from the remaining constant-crystallizing mixture but its presence and concentration were shown by nmr analysis utilizing the 3-methyl peak (δ 2.56) of **14** and the second peak of the mixture at δ 2.46 which was assignable by difference to the 8-methyl group of the isomer **15**. The ratio of the isomers **14**:**15** of 53.5:46.5 was strikingly close to that reported for the hydrazoic acid conversion of 2-methyl-9-fluorenol to the mixture of the 3- and 8-methylphenanthridines (12).

Based on these results, the above Schmidt reaction is best formulated as **11** → **12** → **13** → **14** + **15**. Operation of a mechanism of type **9a** would have led to **15** only; the first Smith mechanism (of type **9bc**, disproved for **4**) would have led to isomer **14** only; competition between mechanisms seems most unlikely.

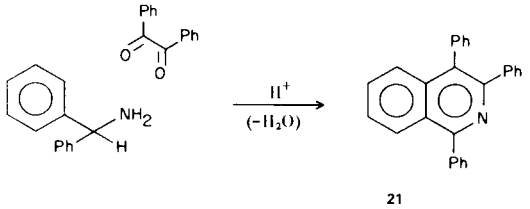
Convincing support for the assigned mechanism is the reaction of *o*-benzophenone with hydrogen bromide to give 9-bromo-9-phenylfluorene which is hydrolyzed to the fluorenol (13). In the case of the *trans*-dibenzoylstilbene **4**, concentrated sulfuric acid alone caused resinification; successful conversions to the quinoline **5** required constant presence of excess hydrazoic acid in the reaction mixture. This suggests that the indenyl cation **16** is formed first and is very reactive (it would be destabilized by the β-benzoyl group), but that it is converted through the hydroazide **17** to the quinoline **5**, rapidly, in successful competition with resinification. It is noteworthy that the bulky phenyl arm of the indenyl system of 17 migrates to nitrogen rather than the vinyl arm of the indenyl system or the phenyl group, as would be expected (cf. 6).



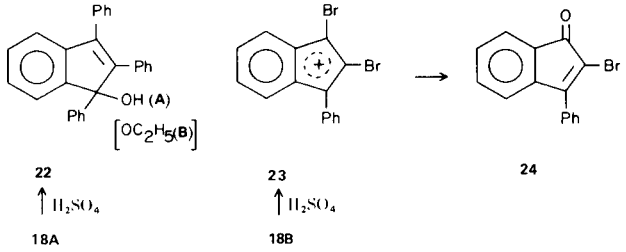
It appears that the essential requirement for a general reaction of the above type is the *cis*-α,β-disubstituted styrylketone system **18** where the *cis* configuration is persistent, where cyclization would be favored, and where an α-group (Y) would induce a hydroazide configuration favorable to migration of the vinyl moiety, with the β-group (X) offering complimentary buttressing effect. As we anticipated, Schmidt reaction conditions did indeed convert α,β-diphenylchalcone (**18A**) (14) into 2,3,4-triphenylquinoline (**19**). *cis*-α,β-Dibromochalcone (**18B**) (15) reacted similarly giving the known 3,4-dibromo-2-phenylquinoline (**20**) (16).



Attempts to prove the structure of 2,3,4-triphenylquinoline (**19**) synthetically by condensation of aniline and phenyldibenzoylmethane, failed. The isomer, 1,3,4-triphenylisoquinoline (**21**), was synthesized by condensing benzhydrylamine and benzil; it proved to be different from quinoline **19**, thereby supporting structure **19** by that difference.



That the mechanism of formation of **19** conformed to the general mechanism outlined above and involved formation of an indenyl cation analogous to, but more stable than, **16**, was shown by treatment of the *cis*-disubstituted ketones (**18A** and **18B**) with concentrated sulfuric acid alone. In the case of **18A**, water and ethanol quenches gave respectively triphenylindenol (**22A**) and its ethoxy analog (**22B**) (17) while the *cis*-dibromochalcone (**18B**) upon water quench gave 2-bromo-3-phenylindenone (**24**) (18).



The new quinoline synthesis promises to be useful although limited in applicability (19).

EXPERIMENTAL (20)

Preparation of β-Phenylchalcone (14,2b).

Pyrolysis of *cis*-1,2-dibenzoylstyrene (350°, 20 minutes, 100 mm.) gave β-phenylchalcone in 45% yield, m.p. 87-89° [lit. 92° (21)]. The Schmidt reaction, giving the anilide (7a), was repeated with identical results.

4-Benzoyl-2,3-diphenylquinoline (**5**).

A 75 ml. chloroform solution of 8 g. of *trans*-dibenzoylstilbene (**4**) (22) and 7 ml. of 1.38 *N* hydrazoic acid in chloroform (0.01 mole) was warmed to 40°. Under vigorous stirring 6 ml. of concentrated sulfuric acid was added dropwise over 30 minutes. Upon cessation of evolution of nitrogen, pouring into ice water, neutralizing with potassium hydroxide, and separation and evaporation of solvent, the residual oil was crystallized from absolute ethanol; 1.6 g. (53%); m.p. 130-132° (not hydrolyzed by hot sodium hydroxide or sulfuric acid); λ max: cm^{-1} 1655 (C=O); nm. (ε) 237.5 (46,100), shoulders at 252, 262 (41,000, 32,000).

Anal. Calcd. for $C_{28}H_{19}NO$: C, 87.25; H, 4.97; N, 3.63. Found: C, 87.07; H, 5.20; N, 4.12.

It forms an unstable hydrochloride with ether-hydrogen chloride, and a picrate from hot ethanol (m.p. 190-192°).

Action of Concentrated Sulfuric Acid-Chloroform Mixture on **4**.

Within one minute deep red color developed. Quenching in ice gave an oil which neither crystallized nor gave a crystalline product when submitted to the above Schmidt reaction conditions. Tetraphenylfuran failed to react with hydrochloric acid under the above conditions.

Debenzoylation of 4-Benzoyl-2,3-diphenylquinoline (**5**) to 2,3-Diphenylquinoline (**6**).

An intimate mixture of 2 g. of **5**, 5 g. of powdered potassium hydroxide and 1 ml. of water was heated until the water and an oil had distilled. The oil (**6**) was extracted by ether, washed with acid and then base, isolated by evaporation of solvent, and added to 20 ml. of saturated ethanolic picric acid (heated). The **6**-picrate separated and was recrystallized from ethanol [yellow, 1.4 g. (44%)]; m.p. 224-225°. Its ir spectrum was identical to that of a sample of m.p. 223-225° (20a) prepared from authentic 2,3-diphenylquinoline [m.p. 88-89°; made by decarboxylation of **7** (8)].

Anal. Calcd. for $C_{27}H_{18}N_4O_7$: C, 63.53; H, 3.55. Found: C, 63.47; H, 3.59.

3-Phenylcinchophen (**7**) (8) and its Methyl Ester, Amide and Nitrile.

The acid **7** was prepared according to Pfitzinger (8) by condensation of isatin with desoxybenzoin (73% ethanolic potassium hydroxide) (20a); λ max: cm^{-1} 1755 (C=O); nm. (ε) 236, 330 (46,000, 8,270).

The methyl ester of **7** was made from the acid chloride of **7** by methanolic sodium methoxide (reflux, 1 hour); recrystallized from methanol; 54%, m.p. 138-139°; λ max: cm^{-1} 1715 (C=O); nm. (ε) 237, 258, 332 (36,400, 25,700, 7,000). It did not react with phenyllithium in ether (toluene, reflux 3 hours).

Anal. Calcd. for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05; N, 4.13. Found: C, 81.70; H, 5.02; N, 4.58.

The amide of **7** was prepared in a new way (95%) from **7**-acid chloride and concentrated ammonium hydroxide; m.p. 276-278° (23a); ν 1670 cm^{-1} (C=O), 3170, 3310 (NH).

The nitrile (of **7** (23b)) was prepared in a new way from the **7**-amide by phosphorus pentoxide in tetrachloroethane (reflux 2 hours); m.p. 154-155°; ν 2220 cm^{-1} (C≡N); λ (ethanol) 246, 345 nm, ϵ^{-3} 31.3, 6.95; no reaction with phenylmagnesium bromide (ether, reflux 12 hours) or with phenyllithium (toluene, reflux 3 hours.).

3-Phenylcinchophen Acid Chloride.

A solution of 10 g. of **7** in 40 ml. of thionyl chloride was refluxed for 12 hours and evaporated. Benzene extraction of the residual oil, evaporation under reduced pressure and crystallizations of the residue from petroleum hexane-benzene mixture and from isooctane gave 7 g. of the acid chloride (60%); m.p. 140-142°; λ max: cm^{-1} 1780 (C=O).

Anal. Calcd. for $C_{22}H_{14}ClNO$: C, 76.85; H, 4.10. Found: C, 76.47; H, 3.91.

6-Phenyl-11-oxo-11*H*-indeno[1,2-*c*]quinoline (**8**).

To a mixture of 20 ml. of dry benzene and 0.8 g. of aluminum chloride was added dropwise a 10 ml. benzene solution of **7**-acid chloride. After stirring for one hour, hydrolysis of the red solution with ice-hydrochloric acid and crystallizations from absolute ethanol-benzene mixture and from glacial acetic acid gave orange crystals; 0.55 g. (62%), m.p. 259-261°; λ max: cm^{-1} 1730 (C=O); nm. (ε) 265 (47,000).

It was also obtained (8%) upon reaction of the acid chloride for 45 minutes with refluxing ethereal phenylmagnesium bromide (recovery of acid chloride 17%).

Anal. Calcd. for $C_{22}H_{13}NO$: C, 85.97; H, 4.26. Found: C, 85.71; H, 4.17.

Preparation of α,β-Diphenylchalcone (**18A**) (14,2b).

Pyrolysis of *cis*-dibenzoylstilbene (**1**) at 320° (20 minutes) and recrystallization from glacial acetic acid, gave **18A** in 78% yield, m.p. 152-153°; λ max: cm^{-1} 1660 (C=O).

Action of Concentrated Sulfuric Acid on α,β-Diphenylchalcone (**18A**).

While stirring, 5 ml. of concentrated sulfuric acid was added over 2 minutes to a solution of 12% of **18A** in 50 ml. of dry chloroform. The red solution after 5 minutes was quenched with ice. Evaporation of the washed and dried chloroform extracts and crystallization of the residual oil from hexane (requiring 2 days), gave 1,2,3-triphenylinden-1-ol (**22A**); m.p. 128.5-130.5° (20a) [lit. 129° (17)]. Another run with quenching in absolute ethanol gave 1-ethoxy-1,2,3-triphenylindene (**22B**); m.p. 172-173.5° (20a) [lit. 172° (17)].

2,3,4-Triphenylquinoline (**19**).

To a 75 ml. chloroform solution of 5 g. (0.12 mmoles) of **18A** and 18 ml. (15 mmoles) of 0.87 *N* hydrazoic acid in chloroform, was added dropwise with stirring (5°) 10 ml. of concentrated sulfuric acid (over 0.5 hours). After warming to room temperature, quenching in ice, and neutralization with aqueous sodium hydroxide, the chloroform solution was dried over sodium sulfate and evaporated. Recrystallization from absolute ethanol gave 1.75 g. (35%); m.p. 189-190°; λ max: nm (ε) 247, 298, 335 (47,600, 14,660, 12,480).

Anal. Calcd. for $C_{27}H_{19}N$: C, 90.72; H, 5.36; N, 3.92. Found: C, 90.68; H, 5.23; N, 4.38.

1,3,4-Triphenylisoquinoline (**21**).

A mixture of 5 g. of benzhydrylamine and 5.5 g. of benzoin was melted at 150° (10 minutes). Addition of 20 ml. of mineral oil, heating at 280° (20 minutes), cooling, and addition of 10 ml. of ether gave a solid which was crystallized from hexane; m.p. 208-209°.

Anal. Calcd. for $C_{27}H_{19}N$: C, 90.72; H, 5.36; N, 3.92. Found: C, 90.58; H, 5.89; N, 3.76.

Schmidt Reaction on *cis*-α,β-Dibromochalcone (**18B**).

To 10 ml. of chloroform, 0.5 g. (1.4 mmoles) of **18B** (15) and 1.5 ml. of 1.03 *N* hydrazoic acid in chloroform, was added dropwise with stirring, 1.5 ml. of concentrated sulfuric acid. After 2 hours, quenching in ice, neutralization, separation, and evaporation of the chloroform, gave a residue of 2-phenyl-3,4-dibromoquinoline (**20**) (0.2 g.) which was recrystallized from ethanol; 0.15 g. (30%), m.p. 148-149° (20a); identified by ir comparison with an authentic sample (16c).

Action of Concentrated Sulfuric Acid on *cis*-α,β-Dibromochalcone (**18B**).

A mixture of 4 g. of **18B** and 10 ml. of concentrated sulfuric acid in 100 ml. of chloroform at 40° was stirred for 10 minutes, quenched in ice, and neutralized. Evaporation of combined and dried chloroform extracts gave an oil which was placed on an alumina column by dry benzene and eluted with hexane-benzene mixtures; this gave small amounts of *cis* and *trans* **18B**, and then 1.5 g. of the yellow-orange 2-bromo-3-phenylinden-1-one (**24**), m.p. 111-113° [lit. 112-113° (18)]. This was identified by analysis (20a), mixture melting point and ir comparison with a sample synthesized from β,β-diphenylpropionic acid [m.p. 149-153° (18b,c)] through dehydration to 3-phenylindan-1-one [m.p. 73-76° (18d)], bromination to the dibromide [m.p. 120-123° (18a)], and pyridine dehydrobromination to **24** [m.p. 111-113° (18a)].

Synthesis of 3-Methyl-6-phenylphenanthridine **14** (11).

2-Nitro-4-methyldiphenyl (b.p.$_{1.6}$ 140-142°) (11) was reduced by treatment of a stirred mixture of 27 g. (0.127 mole), 250 ml. of 95% ethanol and palladium on charcoal (50°), with 15 ml. of hydrazine hydrate added dropwise over 30 minutes. Another 0.1 g. of catalyst was added with refluxing (1 hour). Filtration, washing with ethanol, and concentration to 50 ml. and addition of 50 ml. of hot water, gave an oil which was distilled; 23 g. (98%), b.p.$_{1.5}$ 126-128° (cf. 11). Treatment of 20 g. (0.109 mole) of the oil in 15 ml. of pyridine and 23 g. of benzoyl chloride (100°, 20 hours), followed by 75 ml. of 5% sodium bicarbonate and extraction with 100 ml. of benzene and evaporation, gave 2-benzamido-4-methyldiphenyl; 21 g. (67%), m.p. 90-92° (cf. 11). Cyclization of 2 g. (7 moles) by 4 ml. of phosphoryl chloride (reflux, 8 hours), evaporation under reduced pressure, extraction with 25 ml. of benzene, evaporation, and crystallizations from

benzene, gave 1.8 g. (96%) of **15**; m.p. 116-118° [analyzed (20a)] [picrate, m.p. 238-245° dec. (11)]. Nmr (carbon tetrachloride), δ 8.0 (m, 12H, aromatic) 2.56 (s, 3H, CH_3).

4-Benzoyl-5-(4-tolyl)-cyclohexene.

A mixture of 111 g. (0.5 mole) of 4-methylchalcone [m.p. 94-96° (cf. 24)], 120 ml. of absolute ethanol and 54 g. (0.5 mole) of butadiene, was heated in a steel reactor for 12 hours at 170°. Cooling gave 60 g. (37%); the product after recrystallization from *n*-hexane and ethanol had m.p. 83.5-85°; λ max: cm^{-1} 1678 (C=O).

Anal. Calcd. for $C_{20}H_{20}O$: C, 87.00; H, 7.24. Found: C, 86.94; H, 7.51.

2-(*p*-Tolyl)benzophenone (**11**).

A mixture of 27.6 g. (0.1 mole) of 4-benzoyl-5-(*p*-tolyl)-cyclohexene and 6.4 g. (0.2 mole) of sulfur was heated for 1 hour at 200-230° and then for 2 hours at 260°. Distillation under reduced pressure and crystallization from hexane gave 4.1 g. (15%) of **11**, m.p. 77-79°; λ max: cm^{-1} 1671 (C=O).

Anal. Calcd. for $C_{20}H_{16}O$: C, 88.20; H, 5.92. Found: C, 88.41; H, 5.97.

The Schmidt Reaction on **11**.

This was carried out on 8 g. (0.0294 mole) in 80 ml. of stirred concentrated sulfuric acid at 50° by portionwise addition of 3 g. (0.046 mole) of sodium azide over 3 hours, stirring for an additional 12 hours, quenching in ice, filtration of the precipitate, solution of the precipitate in 200 ml. of ether, extraction with 50 ml. portions of 10% hydrochloric acid, and neutralization with 10% sodium hydroxide. The resulting orange oil (3 g.) was taken up in hexane, placed on a 60 g. florisil column, and eluted with 8:92 ether-benzene mixture which gave 2.8 g. of **14-15** mixture, m.p. 100-113°. Fractional crystallizations from hexane gave 9.0 g. of pure **14**, m.p. 116-118°; identified by correct analysis (20a), spectral comparison, and mixture m.p. with authentic **14** synthesized as above (11). The 1.9 g. of material from the combined filtrates from **14** was not resolved by further crystallizations and was a constant melting mixture, m.p. 97-106°; it showed gradual rise in melting point when mixed with increments of pure **14**, and gave correct C, H analysis for $C_{20}H_{15}N$. Its nmr spectrum showed a 12 proton aromatic multiplet resembling that of **15**, and two methyl singlets, one of δ 2.56 (**14**), and the other δ 2.46 which represents the one possible structural isomer, namely, 8-methyl-6-phenylphenanthrene (**15**) (not isolated pure). From the yield of pure **14** isolated, and the amounts of the two isomers in the mixtures obtained (estimated from the intensities of the respective nmr methyl peaks) the ratio of the isomers **14**:**15** was 53.5:46.5.

Acknowledgment.

Repetitions of the Schmidt reaction on **18B** and identification of **20** were carried out by Richard E. Johnson (16c,19).

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(1) Supported in part by: (a) a contract with the Office of Ordnance Research, U. S. Army. (b) Grants 25029, 5453 and 8631 from the National Science Foundation.

(2) Fellowships: P. F. duPont (a) 1962-1963; (b) 1960-1961. (c) National Science Cooperative Fellowship 1963-1964.

(3) Present locations: (a) Union Oil Co., Research Center, Brea, California. (b) A. H. Robins Co., Richmond, Virginia.

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(20) Melting points are corrected. Instruments: Infrared: Perkin-Elmer 137 or 337, potassium bromide pellet. Ultraviolet: Perkin-Elmer 4000-A or Beckman DK-2, 5 x 10^{-5} *M* (ethanol). NMR: Varian A-60, deuteriochloroform (tetramethylsilane). (a) Known compound: analyzed correctly for C, H ± 0.4%.

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Received April 15, 1970 Charlottesville, Virginia 22901