

Preparation of 3-Isopropyl-7-methyl-dibenz(ah)anthracene from Retene

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Starting from 3-reteneacetic acid, 3-isopropyl-7-methyldibenz(ah)-anthracene has been prepared by application of the Pschorr ring closure reaction.

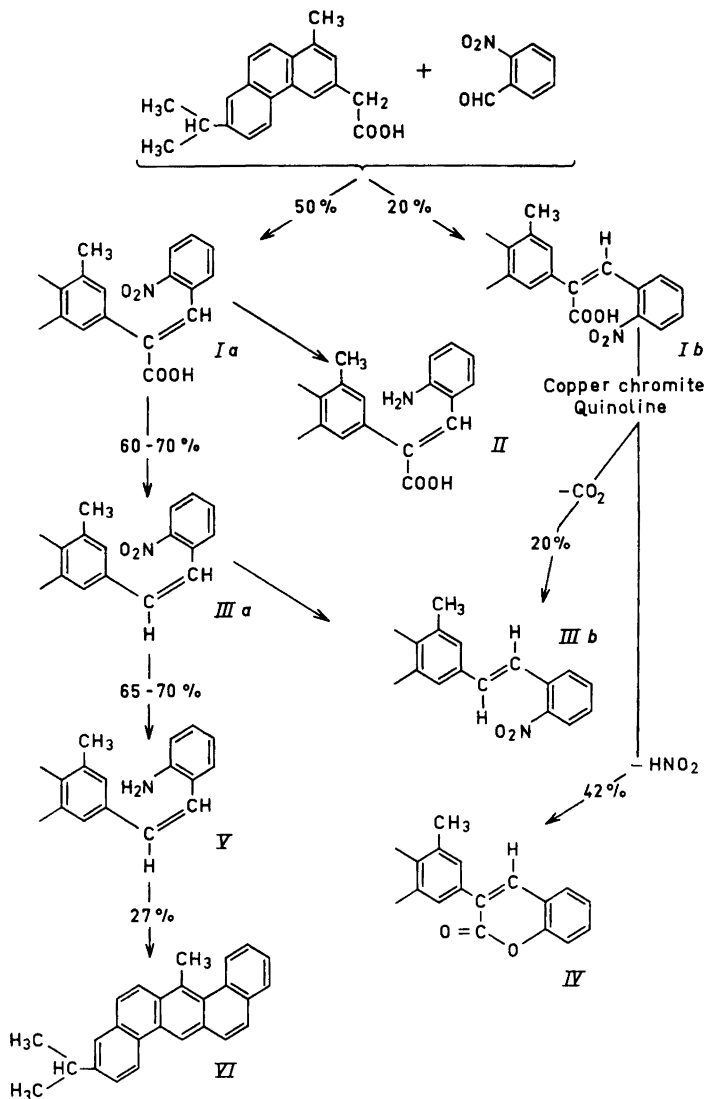
3-Isopropyl-7-methyl-benz(a)anthracene was first synthesized from retene¹ and later from dihydroretene² as starting material.

According to a report, cited by Newman and Joshel³, 3-isopropyl-7-methyl-benz(a)anthracene has given no tumors when injected into mice, thus the high carcinogenic potency of 7-methyl-benz(a)anthracene is destroyed by the introduction of an isopropyl group into the 3-position.

It seemed of interest to prepare for comparison 3-isopropyl-7-methyl-dibenz(ah)anthracene, since 7-methyl-dibenz(ah)anthracene shows marked carcinogenic activity⁴.

Several preparative methods are available for preparation of the dibenz(ah)-anthracene ring system. The most direct synthetic approach in this case, however, seemed to apply the Pschorr⁵ ring closure reaction on suitable 3-substituted retene derivatives.

The intermediate *o*-nitro- α -(3-retenyl)cinnamic acid (Ia) was prepared⁶ previously in 40–45 % yield by condensation of 3-reteneacetic acid with *o*-nitrobenzaldehyde. To increase the yield a slight modification was introduced in isolating the acid Ia. Instead of extracting the reaction product from the Perkin reaction with sodium carbonate, the product was extracted with warm benzene, in which the acid Ia was only slightly soluble. The acid Ia was pure after recrystallization from glacial acetic acid. The yield was about 50 %. Extraction of the benzene filtrate from purification of Ia and subsequent acidification gave a mixture of the acids Ia and Ib. These were separated by partial esterification with methanol. From the acid fraction the acid Ib was isolated. Fractional recrystallization of the esterified fraction gave the methyl-ester of Ib. The infrared spectra of the acids Ia and Ib are nearly identical. Other experimental facts suggest that the acid Ia has the *trans* configuration with respect to the carboxyl and *o*-nitrophenyl group and that Ib is the *cis*-



isomer. The acid Ib with the lower melting point and greater solubility is much more slowly esterified with methanol-sulphuric acid than Ia, as a result of steric hindrance from the *o*-nitrophenyl group.

The U.V. spectrum of the methylester of Ia shows two maxima, a high intensity band at 258 m μ and a maximum of lower intensity at 302 m μ . For the methylester of Ib, the 290–400 m μ range is displaced towards longer wavelengths and higher intensities, in accordance with the more elongated chromophoric system of Ib.

The usual procedure in the Pschorr reaction involves reduction of the substituted nitrocinnamic acid to the corresponding aminocinnamic acid. This reaction, however, did not appear applicable in this case, since reduction of the nitro group in Ia met with difficulties. The conventional reduction with ferrous sulphate and ammonia gave only low yields of *o*-amino-*a*-(3-retenyl)cinnamic acid (II), possibly owing to the slight solubilities of the ammonium salts of the acids Ia and II.

The carboxyl group in the substituted aminocinnamic acid is not essential to the ring closure. Ruggli and Staub⁷ have shown, that phenanthrene can be prepared in good yield by the copper catalyzed decomposition of the diazoniumsalt of *cis*-*o*-aminostilbene. The function of the carboxyl group is merely to direct the aryl nuclei into the necessary *cis*-position during the Perkin reaction. This method was used as *cis*-*o*-nitro-stilbene derivatives generally are obtained in good yields by decarboxylation of the corresponding cinnamic acid derivatives.

The decarboxylation of Ia in quinoline was previously carried out on a minor scale⁶ with anhydrous copper sulphate as catalyst. 3-(*o*-Nitrostyryl)-retene was isolated. Repetition of this reaction on a larger scale, using copper chromite as catalyst, gave the same substance in 60–70 % yield. In some experiments, however, rearrangement to the geometrical isomer occurs to some extent, especially when the temperature during decarboxylation is too high or the time of heating too long. In this case lower melting material was isolated and chromatography gave two substances, of which the weakest adsorbed was identical to the main product.

The U.V. and infrared spectra show that the main product from decarboxylation of Ia is *cis*-3-(*o*-nitrostyryl)-retene(IIIa), whereas the by-product is the *trans*-isomer(IIIb). The U.V. spectrum of IIIa has a maximum at 316 m μ . This maximum is shifted 11 m μ in going to the *trans*-isomer(IIIb). At the same time, the extinction coefficient is increased 1.5 times due to the more extended conjugated system of IIIb. The infrared spectrum of IIIb has a strong band at 957 cm⁻¹. This band is absent in the *cis*-isomer IIIa. The 957 cm⁻¹ band is characteristic of the —CH=CH— *trans* structure, usually giving rise to a medium to strong band in the 990–965 cm⁻¹ range.

The configuration of Ib is identical to that of IIIb, since IIIb is formed by decarboxylation of Ib in quinoline with copper chromite as catalyst. The yield of *trans*-3-(*o*-nitrostyryl)-retene(IIIb) was low. The main product was an almost white, slightly soluble compound. In solution it showed strong fluorescence in ultraviolet light. The substance contained no nitrogen and formed an orange complex with 2,4,7-trinitro-fluorenone. Analysis indicates that the substance contained two oxygen atoms. With alkali, the substance showed the characteristics of aromatic lactones. Accordingly, the substance appears to be 3-(3'-retenyl)-coumarin(IV).

The structure of IV is consistent with the infrared spectrum of the substance. There is no absorption in the 2 500—2 700 cm⁻¹ region characteristic of a strongly hydrogen-bonded OH-group. The spectrum shows C=O absorption at 1 705—1 725 cm⁻¹. The position of this C=O band corresponds to that found in coumarin and some of its derivatives. In addition, the infrared spec-

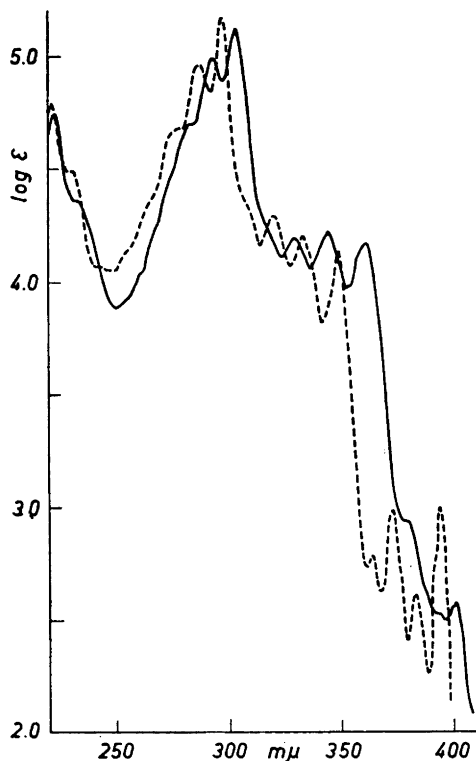


Fig. 1. Ultraviolet absorption spectra of 3-isopropyl-7-methyl-dibenz(ah)anthracene (—) and dibenz(ah)anthracene (-----). Solvent: 96 % ethanol.

trum shows a strong band at 1105 cm^{-1} , frequently observed with O-ring compounds.

Thus 3-(3'-retenyl)-coumarin(IV) is formed from Ib by elimination of nitrous acid by interaction between nitro and carboxyl groups. The reaction gives further support for the configuration of the acid Ib.

Reduction of *cis*-3-(*o*-nitrostyryl)-retene(IIIa) with ferrous hydroxide and sodium hydrosulfite did not succeed. It has, however, previously been shown that hydrazine hydrate in combination with Raney nickel⁸ or palladium carbon⁹ is an excellent reducing agent for polycyclic nitro compounds.

The reduction of IIIa, with hydrazine hydrate as reducing agent and palladium carbon as catalyst, was investigated. *cis*-3-(*o*-Aminostyryl)-retene(V) was obtained in a yield of 65–70 % by applying the mole ratio 1:4 for nitro compound to hydrazine hydrate.

The hydrochloride of V was diazotized in a mixture of tetrahydrofuran and water containing hydrochloric or sulphuric acid. A similar procedure was used by Buchta and Kallert¹⁰ in the synthesis of chrysene and 2-methoxy-chrysene. Decomposition of the diazoniumsalt was effected by copper powder. The pure hydrocarbon was isolated by chromatography of the reaction product in 27 % yield.

Two structures are possible for the cyclization product. When ring closure takes place at the 2-position of the phenanthrene nucleus, a derivative (VI) of dibenz(ah)anthracene is obtained. On the other hand, a derivative of dibenzo(cg)phenanthrene is formed, when ring closure occurs at the 4-position. Although steric hindrance makes ring closure to the 4-position less likely, a ring closure of this type has been demonstrated in the double Pschorr reaction of *a,a'*-bis-(*o*-amino-benzylidene)-*p*-benzenedi-acetic acid¹¹. In this reaction dibenzo(cg)phenanthrene was formed together with dibenz(ah)anthracene.

Conclusive evidence for the structure of the cyclization product is provided by the U.V. spectrum, which shows close resemblance with that of dibenz(ah)-anthracene. The spectrum of the cyclization product deviates considerably from the U.V. spectrum of dibenzo(cg)phenanthrene¹². The U.V. spectrum of VI and that of dibenz(ah)anthracene, Fig. 1, show that the two hydrocarbons have identical band structures both for the β and for the *p*-absorption. On the other hand the structure of the α -absorption bands is somewhat blurred in VI. The same difference in the structure of the α -absorption bands is found in the U.V. spectra of benz(a)anthracene¹³ and 3-isopropyl-7-methyl-benz(a)-anthracene¹⁴. The carcinogenic properties of VI have not yet been investigated.

EXPERIMENTAL

The melting points, which are uncorrected, are determined on an electric heated copper bloc with Anschütz thermometers. Microanalyses were performed by Mr. P. Hansen at the Chemical Laboratory of the University of Copenhagen. The ultraviolet spectra were determined on a Beckman spectrophotometer model DU. The infrared spectra were recorded with a Perkin Elmer model 21 instrument with a sodium chloride prism, using KBr discs.

trans-o-Nitro-a-(3-retenyl)cinnamic acid (Ia). A mixture of 3-reteneacetic acid (14.6 g, 0.05 mole), *o*-nitrobenzaldehyde (7.55 g, 0.05 mole), acetic anhydride (30 ml) and triethylamine (7.0 ml, 0.05 mole) was heated for 20 h at 105–110°. The excess acetic anhydride was decomposed by careful addition of water (20 ml) and heating for 45 min; the reaction mixture was then poured into 5 % hydrochloric acid (300 ml). The yellow product was filtered off, washed with water and then digested with warm benzene (75 ml) filtered and this treatment repeated twice with 50 and 60 ml benzene, respectively. After drying, the product (11.2 g) was recrystallized from glacial acetic acid (135 ml) to give 10.6 g (49.8 %) of the nitrocinnamic acid, m.p. 258.5–261.5°. U.V. absorption (in 96 % ethanol): λ_{\max} 257.5 m μ (log ϵ 4.76); 303 m μ (log ϵ 4.13). I.R. maxima (cm⁻¹): 1 343 and 1 522 (NO₂), 1 685 (C=O in CO₂H), broad absorption at 2 600 (CO₂H). Methyl *trans-o*-nitro-*a*-(3-retenyl)cinnamate, was prepared by esterification of Ia with methanol-sulphuric acid; yellow crystals from *n*-propanol, m.p. 187–189°. (Found: C 76.3; H 6.14; N 3.22. Calc. for C₂₈H₂₅NO₄(439.5): C 76.5; H 5.73; N 3.19). U.V. absorption (in 96 % ethanol): λ_{\max} 257.5 m μ (log ϵ 4.77); 302 m μ (log ϵ 4.13). U.V. absorption (in cyclohexane): λ_{\max} 258.5 m μ (log ϵ 4.77); 302 m μ (log ϵ 4.14).

cis-o-Nitro-a-(3-retenyl)cinnamic acid (Ib). The combined benzene filtrates from purification of Ia were extracted with potassium hydroxide solution, and the alkaline solution acidified. After drying, the precipitate (7.4 g) was esterified with methanol (70 ml) and concentrated sulphuric acid (0.8 ml). The mixture was refluxed for 6.5 h and the main part of methanol distilled *in vacuo*; the dark coloured residue was dissolved in ether-benzene and the solution extracted several times with sodium carbonate solution; the alkaline solution was boiled to expel dissolved ether-benzene and then filtered. The filtrate was acidified and a yellow precipitate separated. After drying, the product (4.3 g) was recrystallized from glacial acetic acid (20 ml) (charcoal), giving 3.7 g of the pure acid Ib, m.p. 207–209°. (Found: Equiv.wt. 418; C 76.1; H 5.21; N 3.25. Calc. for C₂₇H₂₃NO₄ (425.5): C 76.2; H 5.45; N 3.29). I.R. maxima (cm⁻¹): 1 340 and 1 520 (NO₂), 1 688 (C=O in CO₂H), broad absorption at 2 600 (CO₂H).

Methyl cis-o-nitro-a-(3-retenyl)cinnamate. The remaining benzene-ether solution of the esterified fraction was dried and the solvent evaporated; the dark residue (2.5 g) was dissolved in *n*-propanol-benzene, the solution treated with charcoal and filtered; yellow crystals separated with m.p. 120–140°. Two further recrystallizations from *n*-propanol gave the pure methyl ester (0.5 g), yellow needles with m.p. 140–142°, identical with a specimen prepared by direct esterification of the pure *cis-o*-nitro-*a*-(3-retenyl)-cinnamic acid. (Found: C 76.6; H 5.96; N 3.10. Calc. for $C_{20}H_{26}NO_4$ (439.5): C 76.5; H 5.73; N 3.19). U.V. absorption (in cyclohexane): λ_{\max} 264 $m\mu$ (log ϵ 4.73); 307 $m\mu$ (log ϵ 4.22). I.R. maxima (cm^{-1}): 1 340 and 1 520 (NO_2), 1 718 (C=O in ester).

trans-o-Amino-a-(3-retenyl)cinnamic acid (II). A solution of *trans-o*-nitro-*a*-(3-retenyl)cinnamic acid (Ia) (0.4 g) in concentrated ammonia (0.5 ml, 12 N) and water (25 ml) was added to a warm suspension of ferrous sulphate hydrate (3.3 g), water (125 ml) and concentrated ammonia (4 ml, 12 N). The mixture was boiled with frequent stirring for 1 hour, during which time additional water (400 ml) and concentrated ammonia (20 ml) were gradually added. To the mixture was added charcoal and the suspension filtered hot with suction; the precipitate was washed several times with dilute ammonia solution and the filtrate acidified with acetic acid. The greyish precipitate (0.1 g) had m.p. 255–257°, which was depressed on admixture with Ia; recrystallization from glacial acetic acid gave a nearly white substance with m.p. 269.5–271.5° (decomp.). (Found: N 3.56. Calc. $C_{17}H_{16}NO_3$ (395.5): N 3.54).

*cis-3-(o-Nitrostyryl)-retene** (IIIa). A mixture of Ia (3.5 g) copper-chromium oxide catalyst (1 g) and quinoline (30 ml) was heated at 215–220° for 18 min. To the mixture was added benzene. The catalyst was removed after cooling by filtration and washed with benzene. The dark coloured benzene filtrate was washed several times with dilute hydrochloric acid followed by sodium carbonate solution and then dried. After evaporation of the solvent the strongly coloured crystalline residue was dissolved in hot *n*-propanol (130 ml), the solution treated with charcoal and filtered. Yellow crystals separated on cooling; the yield was 2.1 g (67 %) m.p. 175–179°. Recrystallization from glacial acetic acid (65–70 ml) gave 1.85 g, m.p. 178–179.4°. U.V. absorption (in 96 % ethanol): λ_{\max} 266 $m\mu$ (log ϵ 4.67); 316 $m\mu$ (log ϵ 4.22). I.R. maxima (cm^{-1}): 1 337 and 1 517 (NO_2), no *trans* -CH=CH- absorption.

trans-3-(o-Nitrostyryl)-retene (IIIb). A mixture of Ia (3.4 g), copper-chromium oxide catalyst (1 g) and quinoline (25 ml) was heated at 228–235° for 30 min. The reaction mixture was worked up as described above. The benzene solution of the decarboxylation product was evaporated to dryness. Recrystallization of the crystalline residue from *n*-propanol gave yellow crystals (2.07 g), melting in the range 157–167°. Fractional crystallization of this material from glacial acetic acid gave *cis*-3-(*o*-nitrostyryl)-retene 1 g (32.8 %) m.p. 176.5–179.2°.

From the mother liquor was obtained 0.67 g impure 3-(*o*-nitrostyryl)-retene, melting in the range 146–160°; 0.3 g of this material was dissolved in benzene (6 ml) and the solution poured on to a column of alumina (20 × 2 cm). The chromatogram was developed with a mixture (3:2) of light petroleum and benzene. The development was continued until all yellow material had passed into the filtrate.

cis-3-(o-Nitrostyryl)-retene (63 mg) was isolated from the first eluate fractions, m.p. 176–177.7° one recrystallization from glacial acetic acid raised the m.p. to 177.5–179.2°.

The succeeding fractions contained a mixture of *cis* and *trans*-3-(*o*-nitrostyryl)-retene (185 mg) m.p. 152–172°.

Pure *trans*-3-(*o*-nitrostyryl)-retene (IIIb) was isolated from the last eluate fractions, yellow crystals from *n*-propanol (36 mg) m.p. 174–175.5°. The m.p. was depressed on admixture with the *cis*-isomer (IIIa). (Found: C 81.5; H 5.96; N 3.65. Calc. for $C_{26}H_{28}NO_2$ (381.5): C 81.9; H 6.08; N 3.67). U.V. absorption (in 96 % ethanol): λ_{\max} 254 $m\mu$ (log ϵ 4.65); 270 $m\mu$ (log ϵ 4.63); 327 $m\mu$ (log ϵ 4.39). I.R. maxima (cm^{-1}): 957 (*trans*-CH=CH-), 1 335 and 1 515 (NO_2).

Decarboxylation of cis-o-nitro-a-(3-retenyl)cinnamic acid (Ib). A mixture of Ib (1.0 g), copper-chromium oxide catalyst (0.3 g) and quinoline (15 ml) was heated at 225–230° for 12 min. Reddish brown fumes were observed in the condenser at the end of the reaction time. Quinoline was removed as described above for decarboxylation of Ia. On concentrating the benzene solution of the reaction product, a crystalline precipitate separated; filtration and washing with benzene gave almost white crystals of 3-(3'-retenyl)coumarin (IV) (0.25 g) m.p. 203–205.5°. Recrystallization from glacial acetic acid raised the m.p.

to 204.5–206°. (Found: C 85.3; H 5.95. Calc. for $C_{27}H_{22}O_3$ (378.5): C 85.7; H 5.86). I.R. maxima (cm^{-1}): 1 105 (C—O—C), 1 705–1 725 two peaks (C=O), no absorption at 2 500–2 700 (CO_2H). IV could be dissolved in alcoholic potassium hydroxide solution, but during back-titration with hydrochloric acid the lactone ring was closed and practically no uptake of base was found. A fraction of IV was converted to the trinitrofluorenone complex, which crystallized from benzene in red orange crystals, m.p. 186.5–188.5°. (Found: C 68.85; H 3.98; N 6.00. Calc. for $C_{40}H_{27}N_3O_9$ (693.6): C 69.3; H 3.93; N 6.06).

The mother liquor from the isolation of IV was evaporated *in vacuo*, and the crystalline residue treated with warm *n*-propanol. After cooling the product was filtered and washed with *n*-propanol. The yellowish crystalline product (0.5 g) was dissolved in benzene (20 ml) and adsorbed on a column (20 × 2 cm) of alumina. On development with a mixture (3:2) of light petroleum and benzene, a yellow zone passed rather quickly down the column. The development was continued until nearly all yellow material had passed into the filtrate. Pure *trans*-3-(*o*-nitrostyryl)-retene (IIIb) was isolated from the filtrate. The yield was 182 mg (20%), m.p. 173.5–175.5°. (Found: C 81.7; H 6.12; N 3.78. Calc. for $C_{26}H_{23}NO_2$ (381.5): C 81.9; H 6.08; N 3.67). This substance is identical with the substance prepared by rearrangement of *cis*-3-(*o*-nitrostyryl)-retene, as shown by mixed melting point determination, and by similarity both in I.R. and in U.V. spectra.

The solid column showed strong fluorescence in ultraviolet light and was fractionally eluted with hot benzene-ethanol; 130 mg of 3-(3'-retenyl)-coumarin m.p. 204–206.5° were isolated from the eluates.

cis-3-(*o*-Aminostyryl)-retene (V). A mixture of *cis*-3-(*o*-nitrostyryl)-retene (IIIa) (0.85 g, 0.0022 mole), 5% palladiumcharcoal (0.2 g), 100% hydrazine hydrate (0.445 ml, 0.0088 mole) and alcohol (25 ml) was heated under reflux on a water bath for 45 min. The catalyst was removed by filtration, and washed with warm alcohol; from the resulting greenish fluorescent filtrate nearly colourless crystals of V separated, 0.5 g, m.p. 119.7–120.7°. A further crop of material was obtained by concentrating the mother liquor; recrystallization of this material from alcohol gave 0.042 g, m.p. 119.8–120.8°. The total yield was 70%. (Found: C 88.8; H 7.27; N 4.09. Calc. for $C_{26}H_{25}N$ (351.5): C 88.9; H 7.17; N 3.99).

A fraction of V was converted to the picrate, yellow crystals from alcohol, m.p. 200–201° (decomp.). (Found: N 9.58. Calc. for $C_{22}H_{20}N_4O_7$ (580.6): N 9.65).

3-Isopropyl-7-methyl-dibenz(*ah*)anthracene (VI). The hydrochloride of V (0.4 g) (prepared by saturating an ether solution of the amine (V) with hydrogen chloride at low temperature) was dissolved in a mixture of tetrahydrofuran (6 ml) and water (2 ml). To the clear solution was added concentrated sulphuric acid (0.1 ml). The solution was cooled in an ice-salt-bath and diazotized at 0 to –5° by adding a 4% aqueous solution of sodium nitrite (0.138 g) during 5–10 min. To the red mixture was added copper powder (0.4 g), and evolution of nitrogen began at once. After 20 min at 0° and 2.25 h at room temperature copper powder was removed by filtration and washed with warm benzene. The filtrate was washed with hydrochloric acid (6 N), dilute potassium hydrogen carbonate solution and dried; the solvent was evaporated and the red brown residue taken up in benzene (5–6 ml). The benzene solution was poured on to a column of alumina (15 × 2 cm) and the chromatogram developed by a mixture (3:2) of light petroleum and benzene. When the column was examined in ultraviolet light during the chromatographic procedure, a blue fluorescent band was observed, moving quickly down the column. The development was continued until the blue fluorescent zone had passed into the filtrate. The pure hydrocarbon was isolated by evaporation of the solvent from the colourless filtrate and recrystallization of the crystalline residue from *n*-propanol-benzene. The yield of VI was 94 mg (27.4%), m.p. 201–203°. (Found: C 92.8; H 6.54. Calc. for $C_{26}H_{22}$ (334.4): C 93.4; H 6.63). U.V. spectrum, Fig. 1.

The orange 1,3,5-trinitrobenzene complex of VI is rather unstable and dissociates in boiling alcohol with formation of the free hydrocarbon. The best material from benzene-hexane had m.p. 180–182° and was composed of one mole hydrocarbon to two mole trinitrobenzene. (Found: C 59.6; H 3.86; N 10.96. Calc. for $C_{38}H_{28}N_6O_{12}$ (760.7): C 60.0; H 3.71; N 11.05).

The 2,4,7-trinitrofluorenone complex of VI, composed of one mole hydrocarbon to one of 2,4,7-trinitrofluorenone, was more stable than the trinitrobenzene complex and was obtained as dark red crystals from benzene, m.p. 212–214°. (Found: C 72.0; H 4.23; N 6.25. Calc. for $C_{35}H_{27}N_3O_7$ (649.6): C 72.1; H 4.19; N 6.47).

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