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PYRIMIDINES

III. Dehydrogenation of 4-Phenylbenzo[h]Quinazoline Derivatives*

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Dehydrogenation of 2-hydroxy-4-phenyl-3, 4, 5, 6-tetrahydrobenzo[h]quinazoline with Pd/C, diphenyl disulfide, chloranil, and N-bromosuccinimide, was investigated. Dihydroderivatives of 2-hydroxy-4-phenylbenzo[h]quinazoline were obtained. The action of N bromosuccinimide led to dehydrogenation and bromination. Treatment of 2-hydroxy-4-phenylbenzo[h]quinazoline and its bromine derivative with phosphorus oxychloride, followed by hydrogenation, gave 4-phenylbenzo[h]quinazoline. The structures of the compounds prepared are confirmed by spectroscopic data.

In the preceding paper [1] it was shown that condensing together α-tetralone, benzaldehyde, and urea gives 2-hydroxy-4-phenyl-3, 4, 5, 6-tetrahydrobenzo[h]quinazoline I. Bromination-dehydrogenation converted the latter into 2-hydroxy-4-phenyl-5, 6-dihydrobenzo[h]quinazoline II. The present paper is concerned with dehydrogenation of I and II.

Dehydrogenation of aromatic compounds has been well studied, but little attention has been given to dehydrogenation of pyrimidines. Bromination-dehydrogenation [2, 3, 4] is the most widely applied method of dehydrogenating these compounds, and the present authors [1] used it to convert I to II. The literature contains information about sulfur dehydrogenation [5], and dehydrogenation with palladized or platinized charcoal [6, 7]. At the same time, an attempt to dehydrogenate 2-amino-5-p-chlorophenyl-4-ethyl-6-hydroxy-4, 5-dihydropyrimidine with chloranil was unsuccessful [5]. Information about dehydrogenation of quinazolines is rather scanty; and alkaline solution of potassium ferricyanide [8, 9, 10] is generally used to prepare quinazolines from their dihydro derivatives.

Attempts have now been made to effect low-temperature dehydrogenation of I and II with chloranil [11] and N-bromosuccinimide [12, 13]. Refluxing a suspension of I in xylene with two moles of chloranil gave only II, and under the conditions used, II was not further dehydrogenated.

The literature contains information regarding use of N-bromosuccinimide for brominating pyrimidine derivatives [14, 15]. It was intended to prepare 2-hydroxy-4-phenylbenzo[h]quinazoline III by bromination and dehydrobromination. However, 2 moles N-bromosuccinimide and 1 mole I followed by treatment with pyridine gave 50% II, and a derivative VII containing bromine. This derivative was also obtained by reacting II with N-bromosuccinimide. Its structure is considered below.

It proved possible to obtain III by high temperature dehydrogenation of I, and II, with diphenyl disulfide [16, 17] (diphenyl disulfide has not previously been used for dehydrogenating pyrimidines). III was also prepared from I and II by catalytic dehydrogenation with 10% Pd/C, at 300° and 280° respectively (yields 30-45%). The structure of II follows from the method of synthesis, is demonstrated by chemical reactions, and is supported by the IR and UV spectra.

To raise the yield of III from I and cut formation of thermal decomposition products, the catalytic dehydrogenation temperature was lowered to 280°. However, this gave a good yield of a compound which differed from the starting material I, as well as from II and III. Further dehydrogenation with Pd/C at 300°C converted it to III. These results suggest that the compound is most probably 2-hydroxy-4-phenyl-3, 4-dihydrobenzo[h]quinazoline IV, and consideration of the IR and UV spectra confirms this.

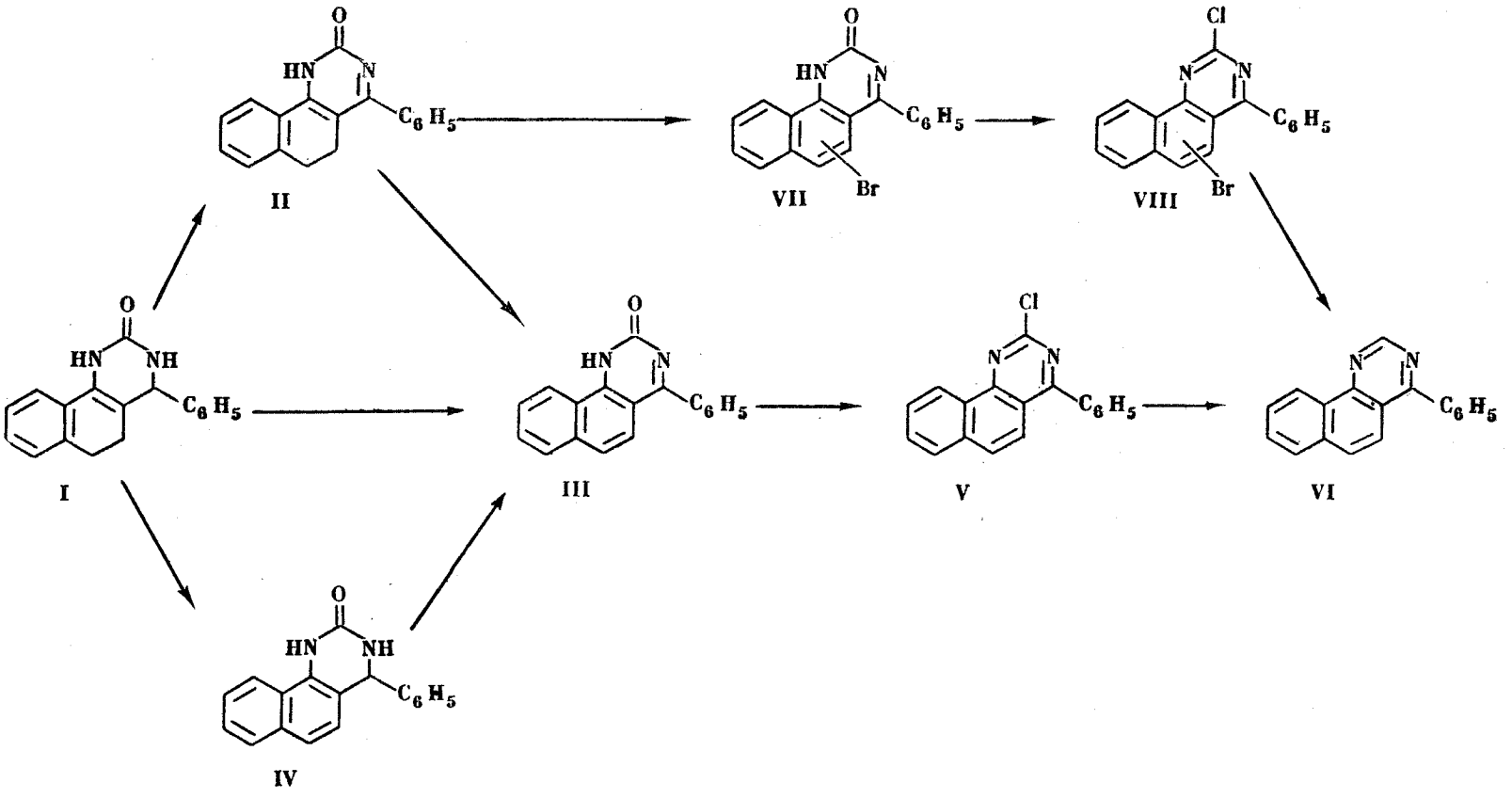
The IR spectra of I and II contain absorption bands characteristic of CH_2 group valence and deformation vibrations [18]. These bands are lacking in the IR spectra of III and IV, which have intense absorption bands in the 800-820 cm^{-1} region, characteristic of out-of-plane deformation vibrations of two adjacent hydrogen atoms in aromatic compounds [18], at 800 cm^{-1} for III, and at 808 cm^{-1} for IV (Fig. 1). The presence of these bands with compounds III and IV shows that they contain a double bond at position 5, 6.

In compounds II and III the C=O group is conjugated with the double bond, while in I and IV it is not conjugated; the results in the literature [18, 19] indicate that when C=O is conjugated with a double bond the absorption band should be shifted towards lower frequencies. It is found that for I this band is at 1700 cm^{-1}, for IV at 1690 cm^{-1}, with II it is shifted to 1650 cm^{-1}, and with III to 1655 cm^{-1} (Fig. 1).

Comparison df the UV spectra of compounds I-IV (Fig. 2) shows that with appearance of a second double bond in the pyrimidine ring (compounds II and III), the chromophoric systems change, and there appears a new absorption maxi-

*For Part II see [1].

Equations



mum in the longwave region, at 352-356 mμ for II, and at 380-386 mμ for III. These bands are somewhat less intense than those in the shortwave region, and this is in agreement with information in the literature about UV spectra of hydroxy derivatives of pyrimidine [20].

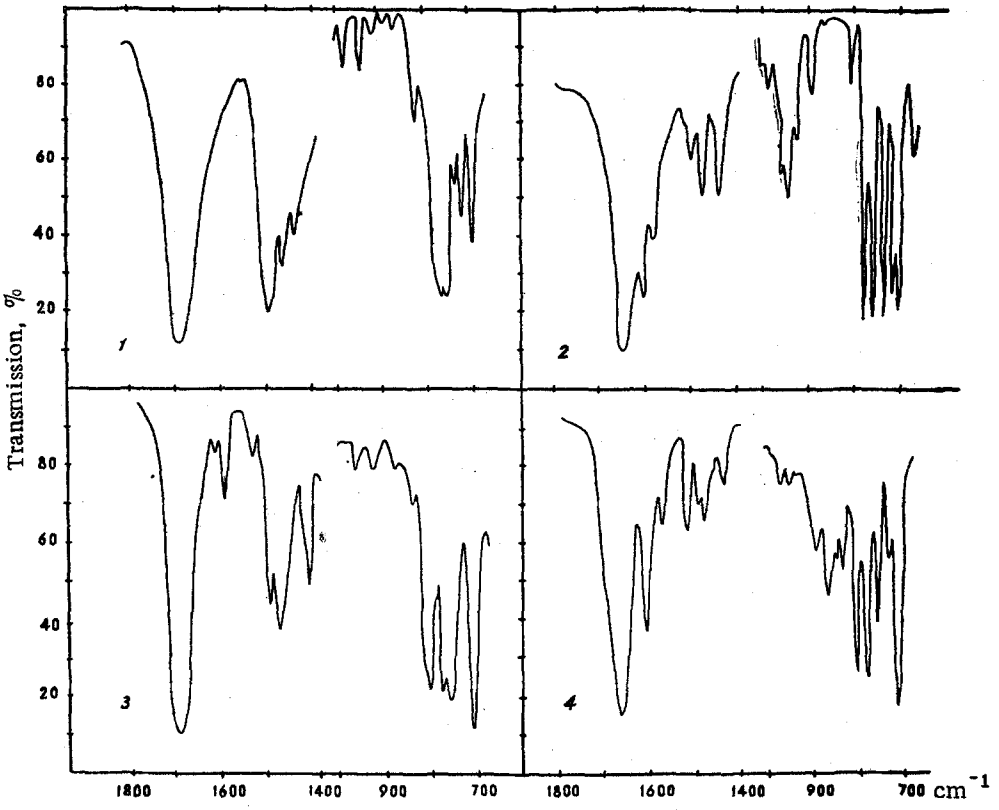


Fig. 1. IR spectra: 1) 2-Hydroxy-4-phenyl-3, 4, 5, 6-tetrahydrobenzo[h]quinazoline (I); 2) 2-hydroxy-4-phenyl-5, 6-dihydrobenzo[h]quinazoline (II); 3) 2-hydroxy-4-phenyl-3, 4-dihydrobenzo[h]quinazoline (IV); 4) 2-hydroxy-4-phenylbenzo[h]quinazoline (III).

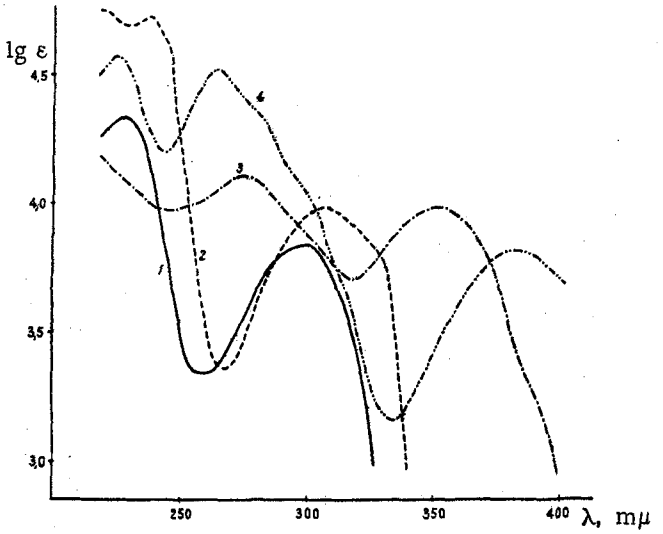


Fig. 2. UV spectra: 1) 2-Hydroxy-4-phenyl-3, 4, 5, 6-tetrahydrobenzo[h]quinazoline (I); 2) 2-hydroxy-4-phenyl-3, 4-dihydrobenzo[h]quinazoline (IV); 3) 2-hydroxy-4-phenyl-5, 6-dihydrobenzo[h]quinazoline (II); 4) 2-hydroxy-4-phenylbenzo[h]quinazoline (III).

Reaction of III with phosphorus oxychloride gave 2-chloro-4-phenylbenzo[h]quinazoline V, converted to 4-phenylbenzo[h]quinazoline (VI) by hydrogenating with Pd/C in the presence of magnesium oxide. VI was characterized as its picrate.

Frequently, reduction of chloroquinazolines results not only in loss of chlorine, but also in further hydrogenation to the corresponding dihydro derivatives [21]. Uptake of only one mole of hydrogen, as well as the agreement between

the UV absorption spectra of V and VI, which shows the presence of identical chromophoric systems (Fig. 3), confirms that hydrogenation of V leads only to splitting off of chlorine. The small hypsochromic shift in the UV spectrum of VI is connected with replacement of the chlorine by hydrogen [22].

As was mentioned above, dehydrogenation of II with N-bromosuccinimide gave a compound which contained bromine, and from which the latter was not split off by prolonged boiling with pyridine. The analysis of the compound corresponds to a formula $C_{18}H_{11}BrN_2O$. Its IR spectrum lacks a band at 800-820 cm^{-1}, showing the absence of two consecutive aromatic hydrogen atoms. At the same time, bands characteristic of CH_2 group vibrations are absent, and there are present, bands characteristic of a monosubstituted benzene. These results show that the bromine atom is not in a phenyl ring, but at position 5 (or 6) in the dehydrogenated product, so that the product obtained is 2-hydroxy-5(6)-bromo-4-phenylbenzo[h]quinazoline (VII). This was confirmed by the reaction of VII with phosphorus oxychloride, when it underwent conversion to 2-chloro-5(6)-bromo-4-phenylbenzo[h]quinazoline (VIII) the latter being dehalogenated to VI by hydrogenation with Pd/C.

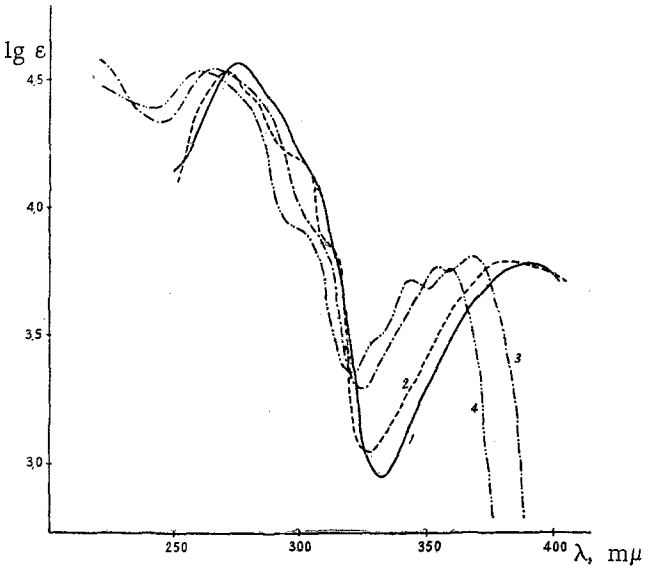


Fig. 3. UV spectra: 1) 2-Hydroxy-5(6)-bromo-4-phenylbenzo[h]quinazoline (VII); 2) 2-hydroxy-4-phenylbenzo[h]quinazoline (III); 3) 2-chloro-4-phenylbenzo[h]quinazoline (V); 4) 4-phenylbenzo[h]quinazoline (VI).

The structure of VII is confirmed by the similarity of its UV spectrum to that of III (Fig. 3), showing that these compounds have the same chromophoric system. Introduction of a bromine atom at position 5(6) in compound III gives rise to only a small bathochromic shift [of 6 mμ [22]. λ_{max} mμ (lg ε), 270 (4.53), 382-386 (3.80) for III, and 272-276 (4.56), 386-392 (3.79) for VII (in glacial acetic acid)].

Experimental

The UV spectra were measured with a SF-4 spectrophotometer, the solvent being alcohol, solution concentration 10^{-4} M.

IR spectra were recorded with a UR-10 spectrophotometer. Samples were tabletted with KBr (concentration 0.5% for the 700-100 cm^{-1} region, 0.125% for the 1400-1800 cm^{-1} region).

2-Hydroxy-4-phenyl-3, 4, 5, 6-tetrahydrobenzo[h]quinazoline (I) and 2-hydroxy-4-phenyl-5, 6-dihydrobenzo[h]-quinazoline (II) were prepared by the method of [1].

The identities of the compounds were proved by their IR spectra being the same as those of authentic specimens and the mixed mps with the latter being undepressed.

Dehydrogenation of I.

1) 2.0 g (8.1 mmole) chloranil was dissolved in 70 ml dry xylene, and 1.0 g (3.6 mmole) I (practically insoluble in xylene) added. The mixture was refluxed for 9 hr, cooled, the precipitate filtered off, and carefully washed with methanol and ether. Yield 0.85 g (85%) II, mp 255-263°. Recrystallized from methanol mp 281-283°.

2) 1.0 g (3.6 mmole) I, 1.3 g (7.3 mmole) N-bromosuccinimide, 25 ml benzoyl peroxide, and 25 ml CCl_4 were refluxed together for 1 hr 30 min. The precipitate was filtered off, washed with a small quantity of water, and with a solution of sodium acetate, suspended in 15 ml methanol, and 4 ml pyridine added. The suspension was refluxed for 20-30 min, and the reaction mixture filtered hot. Yield 0.5 g VII mp >350°.

To the filtrate was added one-third of its volume of water, and the precipitate of II formed after 24 hr filtered off. Yield 0.52 g, mp 268-273°. After recrystallizing from alcohol mp 282-284°.

3a) 1.0 g (3.6 mmole) I and 0.4 g 10% Pd/C was rapidly raised to 240°, after which the temperature was raised to 280° over a period of 20 min, and held at that temperature for 1 hr. After cooling the reaction products were extracted with hot acetic acid. The extract on cooling gave a precipitate of IV, 0.7 g (70%), mp 280-282° (from acetic acid). Found: C 78.8, 78.6; H 5.29, 5.35%. Calculated for $C_{18}H_{14}N_2O$: C 78.8; H 5.15%. UV spectrum λ_{max} mμ (lg ε): 240 (4.72, 306-308 (3.98).

3b) 1.0 g (3.6 mmole) I and 0.5 g 10% Pd/C was rapidly brought up to 260°, after which the temperature was slowly raised to 300° (reaction mixture softened), and held there for 40 min. The products were cooled (they had a strong odor of ammonia and amines) and extracted with hot acetic acid. An equal volume of methanol was added to the extract; on standing, a precipitate of III separated, 0.3 g (30%), mp 331-334° (from alcohol). Found: C 79.2, 79.3; H 4.54, 4.77; N 10.5, 10.3%. Calculated for $C_{18}H_{12}N_2O$: C 79.4; H 4.41; N 10.3%. UV spectrum λ_{max} mμ (lg ε): 228 (4.56), 266-268 (4.51), 380-386 (3.80).

4) 0.6 g (2.1 mmole) I and 1.1 g (5.0 mmole) diphenyl disulfide was heated in a sealed tube at 260° for 2 hr 30 min. The reaction products smelled very strongly and sharply of thiophenol. The contents of the tube were suspended in 15-20 ml ether, the precipitate filtered off, washed with ether, and then with methanol. Yield 0.5 g (83%) III mp 329-331°.

Dehydrogenation of 2-hydroxy-4-phenyl-5, 6-dihydrobenzo[h]quinazoline (II).

1) 1.0 g (3.6 mmole) II, 0.65 g (3.6 mmole) N bromosuccinimide, 15 mg benzoyl peroxide, and 25 ml CCl_4 were refluxed for 1 hr 30 min. The precipitate was filtered off, washed with water, and then with sodium acetate solution. Next it was suspended in 7 ml methanol, 3 ml pyridine added, and the mixture refluxed for 1 hr, after which the precipitate was filtered off. Yield of VII, mp >350° (from acetic acid). Found: C 61.2, 61.3; H 3.42, 3.29; Br 22.9, 22.5; N 7.95, 7.71%. Calculated for $C_{18}H_{11}BrN_2O$: C 61.5; H 3.16; Br 22.8; N 7.98%. UV spectrum (in glacial acetic acid) λ_{max}, mμ (lg ε): 272-276 (4.56), 386-392 (3.79).

2) 1.0 g (3.6 mmole) II and 0.2 g 10% Pd/C were maintained at 280° for 30 min. The products were extracted with acetic acid, and an equal volume of methanol added to the extract, precipitating III, 0.45 g (45%), mp 331-332° (from alcohol).

3) 1.0 g (3.6 mmole) II and 1.3 g (5.9 mmole) diphenyl disulfide were heated in a sealed tube at 260° for 3 hr 30 min. The reaction products were then suspended in 20 ml ether, and filtered. Yield 0.54 g III (55%).

Dehydrogenation of 2-hydroxy-4-phenyl-3, 4-dihydrobenzo[h]quinazoline (IV). 0.4 g (1.4 mmole) IV and 0.15 g 10% Pd/C were kept at 300° for 30 min. The reaction products were extracted with acetic acid, and an equal volume of methanol added to the extract. Yield of III 0.15 g (38%).

2-Chloro-4-phenylbenzo[h]quinazoline (V). 0.8 g (2.9 mmole) III was refluxed with 6 ml phosphorus oxychloride for 2 hr. Excess phosphorus oxychloride was distilled off under reduced pressure. The residue was dissolved in benzene, and the benzene solution washed, first with saturated sodium bicarbonate solution, then with brine. The benzene was distilled off under reduced pressure, and the residue chromatographed on alumina (activities II, III), the solvent used being benzene. The fraction fluorescing in UV light was collected. The eluate was evaporated, and the residue recrystallized from alcohol. Yield of V 0.74 g (87%), mp 173-175°. Found: C 74.3, 74.2; H 3.93, 3.92; Cl 12.0, 12.4%. Calculated for $C_{18}H_{11}ClN_2$: C 74.3; H 3.81; Cl 12.2%. UV spectrum λ_{max}, mμ (lg ε): 262-264 (4.54), 352 (3.77), 366-368 (3.81).

2-Chloro-5(6)-bromo-4-phenylbenzo[h]quinazoline (VIII) was prepared from VII by a method similar to that described above. Mp 236-237° (from benzene). Found: C 59.1, 58.9; H 2.90, 3.05; (Cl+Br) 31.2, 31.1; N 7.60, 7.81%. Calculated for $C_{18}H_{10}BrClN_2$: C 58.5; H 2.72; (Cl+Br) 31.2; N 7.58%.

4-Phenylbenzo[h]quinazoline (VI). 0.4 g (1.4 mmole) V, 0.4 g 5% Pd/C, 0.03 g (0.7 mmole) magnesium oxide, in 20 ml methanol were submitted to hydrogenation at room temperature and ordinary pressure, 6 hr being required for the uptake of about 1.4 mmole hydrogen. The catalyst was filtered off, washed with alcohol, and the filtrate evaporated. The residue was chromatographed on a thin plate, using Al_2O_3 (activity II-III), solvent, benzene. The layer with R_f 0.71-0.58 was extracted with methanol, and the solvent distilled off from the extract. Yield 0.3 g (75%) VI, mp 84.5-86° (from petroleum ether). Found: C 84.5, 84.2; H 5.01, 4.95; N 10.7, 10.9%. Calculated for $C_{18}H_{12}N_2$: C 84.3; H 4.71; N 10.9%. UV spectrum λ_{max}, mμ (lg ε): 260 (4.52), 296-298 (shoulder) (3.93), 342-344 (3.71), 358-360 (3.76).

VI picrate, mp 161-163° (from alcohol). Found: N 14.6, 14.7%. Calculated for $C_{18}H_{12}N_2 \cdot C_6H_3N_3O_7$: N 14.4%.

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22 June 1964

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