84. *New Syntheses of Heterocyclic Compounds. Part II.* 2-*Phenyl*-3 : 4 : 6 : 7-*dibenzo*-1 : 5-*naphthyridine.*

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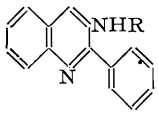
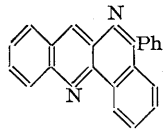
The action of various cyclising agents on the compounds (I)—(IV) has been examined. Ring closure of 3-*benzamido*-2-*phenylquinoline* (VI; R = COPh) to 2-*phenyl*-3 : 4 : 6 : 7-*dibenzo*-1 : 5-*naphthyridine* (VII) has been accomplished by means of phosphoric oxide at 270°.

The object of the present investigation was the preparation of naphthyridine compounds analogous to the trypanocidal phenanthridinium types of Browning, Morgan, Robb, and Walls (*J. Path. Bact.*, 1938, **46**, 203). The literature on the naphthyridines is limited to some thirty memoirs, and as the methods described therein

proved unsuitable for our purpose, we examined the possibility of applying Pictet and Hubert's phenanthridine synthesis (*Ber.*, 1896, **29**, 1182) to the suitably constituted pyridine and quinoline derivatives (I)—(IV) and (VI).

2- and 3-(o-*Benzamidophenyl*)*pyridine* (I and II) were prepared by benzoylation of the corresponding amino-compounds (Haworth, Heilbron, and Hey, J., 1940, 349). 2-Amino-3-phenylquinoline, obtained from *o*-nitro-α-phenylcinnamonitrile in 30% yield, furnished 2-*acetamido*-3-*phenylquinoline* (III). 2-(o-*Benzamidophenyl*)*quinoline* (IV) was prepared by benzoylation of 2-(*o*-aminophenyl)quinoline (John and Pietsch, *J. pr.*

(VI.) 

 (VII.)

Chem., 1935, **143**, 245). 3-Amino-2-phenylquinoline (VI; R = H) (*idem*, *ibid.*, 1931, **131**, 346) was conveniently prepared as follows: Benzoylation of phenacylamine hydrochloride in pyridine solution gave the *benzoyl* derivative in excellent yield. Benzoylphenacylamine condensed readily with isatin in alkaline solution to give 3-*benzamido*-2-*phenylquinoline*-4-*carboxylic acid* (V) in 90% yield, and this, heated with syrupy phosphoric acid at 210°, gave (VI; R = H) in 65% yield. The acetyl, *benzoyl*, and p-*nitrobenzoyl* derivatives were prepared.

Attempts to cyclise (I)—(IV) were not successful. The compounds were recovered unchanged after refluxing with phosphorus oxychloride (cf. Morgan and Walls, J., 1931, 2447). Anhydrous zinc chloride at 300° or syrupy phosphoric acid at 200° led to hydrolysis with regeneration of the amines, an analogous result being obtained by using phosphorus pentachloride–phosphorus oxychloride. Fusion with phosphoric oxide led to resinification. When 3-*benzamido*-2-*phenylquinoline* was heated with phosphoric oxide at 270°, however, facile ring closure occurred to give 2-*phenyl*-3 : 4 : 6 : 7-*dibenzo*-1 : 5-*naphthyridine* in 60% yield.

Experimental.

Microanalyses are by Mr. R. Maxim, University Chemical Laboratories, Cambridge.

2- and 3-(*o*-Nitrophenyl)pyridines (Haworth, Heilbron, and Hey, *loc. cit.*) were reduced in 2 vols. of concentrated hydrochloric acid with 6 parts of stannous chloride in 12 parts of concentrated hydrochloric acid, the reaction being completed by warming for 1 hour on the water-bath. 2-(o-*Aminophenyl*)*pyridine picrate*, m. p. 185—186° (decomp.) (Found: N, 16·4, 16·3. $C_{11}H_{10}N_2,C_6H_3O_7N_3$ requires N, 17·5%), and 3-(o-*aminophenyl*)*pyridine picrate*, m. p. 164° (decomp.) (Found: N, 17·4%), separated from acetone in orange needles and small yellow prisms respectively. The benzoyl derivatives were prepared by treating the amino-compounds, dissolved in pyridine, with 1·2 mols. of benzoyl chloride for 12 hours at room temperature: 2-(o-*Benzamidophenyl*)*pyridine*, needles, m. p. 117°, from absolute alcohol (Found: N, 10·5. $C_{18}H_{14}ON_2$ requires N, 10·2%) [*picrate*, yellow fibrous needles, m. p. 155° (decomp.), from acetone (Found: N, 13·9. $C_{18}H_{14}ON_2,C_6H_3O_7N_3$ requires N, 13·9%)]; 3-(o-*benzamidophenylpyridine*, squat needles, m. p. 132°, from alcohol–light petroleum (Found: N, 9·7%) [*picrate*, yellow needles, m. p. 168° (decomp.), from acetone (Found: N, 14·1%)].

2-*Amino*-3-*phenylquinoline*.—*o*-Nitro-α-phenylcinnamonitrile (Frost and Meyer, *Annalen*, 1888, **250**, 160) was obtained by adding 4 ml. of sodium ethoxide solution (10 g. of sodium in 159 ml. of alcohol) to 9·16 g. of *o*-nitrobenzaldehyde and 7·0 g. of phenylacetonitrile in 40 ml. of absolute alcohol. After 5 minutes the mixture was refluxed for 1 minute and kept for 12 hours at 0°, and the nitrile collected. Yield 90%, m. p. 129—130°. 1 G. of the nitrile, 50 ml. of spirit, 10 ml. of concentrated hydrochloric acid, and 0·6 g. of tin were refluxed until the tin had dissolved. The mixture was largely diluted with water, tin removed as sulphide, and the filtrate concentrated to small bulk and made alkaline with ammonia. 2-Amino-3-phenylquinoline was precipitated and purified by means of the picrate. Yield, 30%.

2-*Acetamido*-3-*phenylquinoline* was obtained in needles, m. p. 107—108°, from aqueous methyl alcohol (Found: N, 10·8. $C_{17}H_{14}ON_2$ requires N, 10·7%) after treatment of the amino-compound with acetic anhydride (4 vols.) for 30 minutes on the water-bath. 2-(o-*Benzamidophenyl*)*quinoline* was obtained in needles, m. p. 124°, from benzene (Found: C, 81·1; H, 5·0; N, 8·9. $C_{22}H_{16}ON_2$ requires C, 81·5; H, 4·9; N, 8·7%) after 7·6 g. of the amino-compound (John and Pietsch, *J. pr. Chem.*, 1935, **143**, 245) in 25 ml. of pyridine had been treated with 4·8 ml. of benzoyl chloride for 1 hour on the water-bath.

3-*Amino*-2-*phenylquinoline* (VI; R = H).—ω-Bromoacetophenone was prepared as follows (cf. Rather and Reed, *J. Amer. Chem. Soc.*, 1919, **41**, 77): 100 G. of acetophenone, cooled in ice, were shaken with 150 g. of glacial acetic acid and 90 g. of bromine, added in three portions. A portion (10 ml.) was removed, warmed until decolorised, and added to the main bulk; this process was repeated several times and reaction then occurred. The straw-yellow mixture was removed from the ice-bath and; after removal of hydrogen bromide in a current of air, poured on 1 kg. of ice. After crystallising, the bromoacetophenone was collected and dried on a porous plate in a vacuum. Yield, 115 g. It was converted into phenacylphthalimide in 90% yield by Goedeckmeyer's method (*Ber.*, 1888, **21**, 2685), from which phenacylamine hydrochloride was obtained essentially by Gabriel's method (*Ber.*, 1908, **41**, 1132).

12 G. of finely powdered phenacylamine hydrochloride and 21 ml. of dry pyridine were gently warmed. Immediately the suspension has assumed a red colour, 3 ml. of benzoyl chloride were added, solution effected by shaking, and the flask corked and cooled. A further 7 ml. of benzoyl chloride were added with cooling. After 12 hours at room temperature, 50 g. of ice were added with shaking and after 1 hour the precipitated *benzoylphenacylamine* was collected. It formed needles, m. p. 125—126°, from methyl alcohol (Found: C, 75·3; H, 5·7; N, 6·1. $C_{15}H_{13}O_2N$ requires C, 75·3; H, 5·4; N, 5·9%). Unless the above experimental conditions are adhered to, a fraction insoluble in methyl alcohol is obtained from which αγ-diphenylpyrazine, m. p. 193—194° (Found: C, 82·2; H, 5·4; N, 12·3. Calc. for $C_{16}H_{14}N_2$: C, 82·1; H, 6·0; N, 12·0%), and *dibenzoylphenacylamine*, silky white needles, m. p. 173—174°, from methyl alcohol (Found: C, 77·0; H, 5·2; N, 4·3. $C_{22}H_{17}ON_3$ requires C, 77·0; H, 5·0; N, 4·1%), are obtained by fractionation from acetone.

To a warm solution of isatin (7·3 g.) in absolute-alcoholic potassium hydroxide (2·8 g. in 50 ml.), a hot solution of 12 g. of benzoylphenacylamine in 50 ml. of absolute alcohol was added in three portions, with cooling to moderate the reaction. To the clear solution, 18 ml. of potassium hydroxide solution (8·8 g. in 17·5 ml. of water) were added with cooling during 2 minutes. After 3 days at room temperature the mixture was nearly neutralised with hydrochloric acid, the alcohol rapidly boiled off, and 50 ml. of water added towards the end of the heating. After acidification with hydrochloric acid

the mass became solid on stirring. 3-*Benzamido*-2-*phenylquinoline*-4-*carboxylic acid* (V) formed small, pale yellow needles, m. p. 254—255°, from methyl alcohol (Found : C, 74·5; H, 4·3; N, 7·7. $C_{23}H_{16}O_3N_2$ requires C, 75·0; H, 4·4; N, 7·6%).

5 G. of (V) and 30 ml. of syrupy phosphoric acid (*d* 1·75) were heated in an oil-bath to 170° (sublimation of benzoic acid began) and then, after 30 minutes, slowly to 210°. After 1 hour with occasional stirring the mixture was cooled, diluted with 150 ml. of water, filtered, and made alkaline with ammonia, and the sticky product collected, dissolved in N/10-hydrochloric acid (norit), reprecipitated with ammonia, and dissolved in methyl alcohol. On addition of water to the warm solution a small amount of resinous material separated. The liquid was rapidly filtered, and crystallisation induced by further addition of water. 3-Amino-2-phenylquinoline formed needles, m. p. 121—122°, from light petroleum (Found : C, 81·4; H, 5·5; N, 12·9. Calc. for $C_{15}H_{12}N_2$: C, 81·8; H, 5·5; N, 12·7%). 2 G. of the base in 10 ml. of acetic anhydride were refluxed for 30 minutes and poured on ice; from the sticky green mass, the monoacetyl derivative (VI; R = Ac), m. p. 125°, was obtained by two crystallisations from aqueous methyl alcohol (norit). 3-*Benzamido*-2-*phenylquinoline* (VI; R = COPh), silky needles, m. p. 179—180°, from methyl alcohol (Found : C, 81·2; H, 5·2; N, 8·9. $C_{22}H_{16}ON_2$ requires C, 81·5; H, 4·9; N, 8·6%), was obtained by treating 2·2 g. of the base in pyridine solution with 1·4 ml. of benzoyl chloride for 12 hours at room temperature. 3-p-*Nitrobenzamido*-2-*phenylquinoline*, pale yellow, rhombic crystals, m. p. 223°, from acetone (Found : N, 11·5. $C_{22}H_{15}O_3N_3$ requires N, 11·4%), was obtained by treating 2·2 g. of the base in 7 ml. of pyridine with 1·86 g. of *p*-nitrobenzoyl chloride for 1 hour on the water-bath and precipitating the product with dilute hydrochloric acid.

2-*Phenyl*-3 : 4 : 6 : 7-*dibenzo*-1 : 5-*naphthyridine* (VII).—An intimate mixture of 3-benzamido-2-phenylquinoline (2 g.) with excess of phosphoric oxide was heated for 2 hours at 270—280° (calcium chloride tube), and water and ice added; on stirring, a greenish-black solid separated. It was collected, extracted with ammonia–acetone (norit), and the extract concentrated until crystallisation took place. 2-*Phenyl*-3 : 4 : 6 : 7-*dibenzo*-1 : 5-*naphthyridine* formed silky needles, m. p. 197—198°, from aqueous methyl alcohol (Found : C, 86·1; H, 4·7; N, 9·3. $C_{22}H_{14}N_2$ requires C, 86·3; H. 4·7; N, 9·2%). The *monopicrate* formed yellow plates, m. p. 240—241°, from acetone (Found : N, 13·3. $C_{22}H_{14}N_2,C_6H_3O_7N_3$ requires N, 13·1%).

Attempts to cyclise the acetyl derivative (VI; R = Ac) gave a *product*, m. p. 199° (Found : C, 81·7; H, 5·2; N, 11·4%), which could not be identified. The *p*-nitrobenzoyl derivative (VI; R = $CO{\cdot}C_6H_4{\cdot}NO_2$) underwent resinification on similar treatment with phosphoric oxide.

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