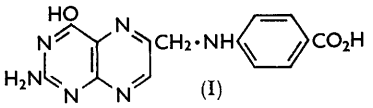
904. *Polyazanaphthalenes. Part IX.*[1] *The Synthesis of Some Folic Acid Antagonists.*

By H. N. Rydon and K. Undheim.

The synthesis of some folic acid antagonists based on the quinoline, isoquinoline, and naphthalene ring systems is described.

This is the last of a series of papers describing work which had as its main objective the synthesis of biologically antagonistic analogues of pteroic acid (I) with one or more of the ring hetero-atoms omitted. The present paper deals with the synthesis of such compounds containing the quinoline, isoquinoline, and naphthalene ring systems; analogues based on quinoxaline,[1,2] quinazoline,[3] and 1,3,5-triazanaphthalene[3,4] have been described by us earlier.



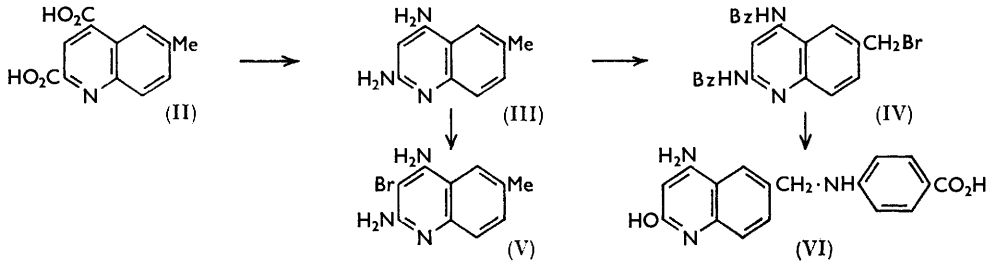
(I)

In the quinoline series, the pteroic acid analogue (VI) was synthesised from 6-methylquinoline-2,4-dicarboxylic acid (II) as shown. The route (II—VI) was chosen, rather than the alternative through 2,4-dichloro-6-methylquinoline, in view of the reported difficulty of displacing both chlorine atoms in 2,4-dichloroquinoline with nucleophilic reagents.[5] The required dicarboxylic acid (II) was readily obtained from 5-methylisatin by the Pfitzinger reaction [6] with pyruvic acid and was converted, through the acid chloride, into the diamide which, following Renshaw and Friedmann,[7] we subjected to the Hofmann reaction, obtaining the required 2,4-diamine (III) in satisfactory yield.

Treatment of this diamine (III) with *N*-bromosuccinimide in carbon tetrachloride gave a monobromo-derivative in good yield. The reactions of this product, however, showed that

[1] Part VIII, preceding paper.
[2] Leese and Rydon, *J.*, 1955, 303.
[3] Oakes, Rydon, and Undheim, *J.*, 1962, 4689
[4] Oakes and Rydon, *J.*, 1956, 4433.
[5] Buchmann and Hamilton, *J. Amer. Chem. Soc.*, 1942, **64**, 1357.
[6] Pfitzinger, *J. prakt. Chem.*, 1886, **33**, 100; Elderfield, "Heterocyclic Compounds," Wiley, New York, 1952, Vol. IV, p. 47.
[7] Renshaw and Friedman, *J. Amer. Chem. Soc.*, 1939, **61**, 3320.

it was not the required 6-bromomethyl derivative, but a nuclear bromination product; it is assigned the structure 2,4-diamino-3-bromo-6-methylquinoline (V) on the basis of the established 3-bromination of 6-methylquinoline,[8] 2-amino-4-hydroxyquinoline,[9] and 2,4-dihydroxyquinoline.[9,10] In view of this result, we turned our attention to the side-chain bromination of the dibenzoyl derivative of (III). This with *N*-bromosuccinimide in chloroform gave only the hydrobromide, produced by the action of hydrogen bromide



resulting from preferential bromination of the solvent,[11] and unsatisfactory results were obtained by the action of 1,3-dibromo-5,5-dimethylhydantoin in chloroform or tetrachloroethylene. The required bromomethyl compound (IV) was eventually obtained by bromination of the dibenzoyl derivative of the amine (III) with *N*-bromosuccinimide or 1,3-dibromo-5,5-dimethylhydantoin in carbon tetrachloride; the dibenzoyl derivative is only sparingly soluble in this solvent and this no doubt accounts for our inability to obtain the bromomethyl compound (IV) completely free from unchanged starting material or more highly brominated products.

The crude bromomethyl compound (IV) was finally condensed with ethyl *p*-aminobenzoate and the product treated, first, with sodium ethoxide, to remove the benzoyl groups, and then with aqueous-ethanolic sodium hydroxide, to saponify the ester. During this process one of the amino-groups was lost and the product is formulated as *p*-(4-amino-2-hydroxy-6-quinolylmethyl)aminobenzoic acid (VI); the postulated preferential replacement of the 2-amino-group is based on simple quantum-mechanical treatment [12] and on analogy with other nucleophilic displacement reactions of 2,4-disubstituted quinolines.[5,13]

The obvious starting material for the synthesis of the only isoquinoline analogue derivable from pteroic acid (I) by the replacement of ring-nitrogen atoms by methine groups is 1,3-diamino-7-methylisoquinoline (XI), but before embarking on the synthesis of this compound it seemed desirable to explore methods for the preparation of the more accessible, but hitherto unknown, 1,3-diaminoisoquinoline (VII; R = R′ = NH_2). Although this compound could be obtained by direct amination of isoquinoline with sodamide in boiling dimethylaniline,[14] the yield was very poor and the method unsuitable for large-scale working.

1,3-Dichloroisoquinoline (VII; R = R′ = Cl) is readily available, by the action of phosphorus oxychloride on homophthalimide,[15] but previous workers [16] found difficulty in replacing the 3-chlorine atom by reaction with nucleophiles. This relative unreactivity

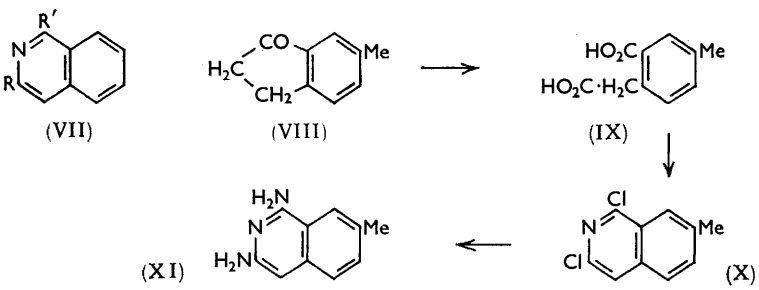
[8] Howitz and Philipp, *Annalen*, 1912, **396**, 23.
[9] Hardman and Partridge, *J.*, 1955, 510.
[10] Meyer and Heimann, *Compt. rend.*, 1936, **203**, 264.
[11] Orazi, Mercere, Corral, and Meseri, *Anales Asoc. quím. argentina*, 1952, **40**, 91.
[12] Oakes and Rydon, *J.*, 1958, 204.
[13] Friedländer and Weinberg, *Ber.*, 1882, **15**, 2679; Curd, Raison, and Rose, *J.*, 1947, 899.
[14] Cf. Bergstrom, *J. Amer. Chem. Soc.*, 1931, **53**, 3027; Ostromislensky, *ibid.*, 1934, **56**, 1713.
[15] Gabriel, *Ber.*, 1886, **19**, 2354.
[16] Haworth and Robinson, *J.*, 1948, 777.

is to be expected on theoretical grounds, approximate quantum-mechanical treatment [4,12,17] leading to the following results (symbolism of Oakes and Rydon [4]):

Nucleophilic substitution of	$\Delta U - \Delta U_0$		$\Delta U_{1Cl} - \Delta U_{3Cl}$
1-Cl	$0{\cdot}36\delta^N + 0{\cdot}24\delta^{Cl}$	}	$0{\cdot}23\delta^N + 0{\cdot}16\delta^{Cl} + \delta'$
3-Cl	$0{\cdot}13\delta^N + 0{\cdot}08\delta^{Cl}$		

Since δ is negative, nucleophilic replacement of the 1-chlorine atom should be much easier than that of the 3-chlorine atom. Nevertheless, since the method for the preparation of 1,3-dichloroisoquinoline is readily adaptable for the preparation of its 7-methyl homologue, we investigated the matter further.

Passage of ammonia through a boiling solution of 1,3-dichloroisoquinoline in phenol, a procedure [18] which had proved effective in the quinazoline series,[3] resulted in the replacement of only one chlorine atom; the product was shown to be 3-chloro-1-phenoxyisoquinoline (VII; R = Cl, R′ = OPh) by hydrogenation, over Raney nickel in ethanolic sodium ethoxide,[19] to 1-phenoxyisoquinoline (VII; R = H, R′ = OPh), identical with material obtained by the action of phenol on 1-chloroisoquinoline. Treatment of 1,3-dichloroisoquinoline with methanolic ammonia at 180° likewise gave only 1-amino-3-chloroisoquinoline (VIII; R = Cl, R′ = NH_2), converted, by treatment with nitrous acid, into the known 3-chloro-1-hydroxyisoquinoline (VII; R = Cl, R′ = OH).[15] 1,3-Diaminoisoquinoline (VII; R = R′ = NH_2) was finally obtained, in very satisfactory yield, by heating the dichloro-compound at 140° with aqueous ammonia containing copper sulphate as catalyst.[20]



(VII) (VIII) (IX) (X) (XI)

On the basis of this exploratory work, the required 1,3-diamino-7-methylisoquinoline (XI) was synthesised from 6-methylindan-1-one (VIII) as illustrated. The indanone had been prepared from β-*p*-tolylpropionic acid by direct cyclisation with sulphuric acid [21] or by treatment of the acid chloride with aluminium chloride; [22] we found it most convenient to cyclise the acid directly with polyphosphoric acid. Direct oxidation of the indanone proved unsuccessful, but treatment of the 2-hydroxyimino-derivative, prepared by the procedure of Mercer and Robertson,[23] with phosphorus pentachloride, followed by sodium hydroxide,[24] gave 4-methylhomophthalic acid (IX) in good yield. Treatment of the derived imide with phosphorus oxychloride yielded 1,3-dichloro-7-methylisoquinoline (X) which was converted into the required diamine (XI) by the method already outlined for the preparation of its lower homologue. In view of the very slight biological activity of the diamine (XI), the investigation was not pursued further in the isoquinoline series.

[17] Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 283; *Nature*, 1950, **166**, 139; Chapman, *Chem. Soc. Special Publ.* No. 3, 1955, p. 155; Chapman and Russell-Hill, *J.*, 1956, 1563.
[18] Backeberg and Marais, *J.*, 1942, 381.
[19] Cf. Osborn, Schofield, and Short, *J.*, 1956, 4191.
[20] Cf. Maier-Bode, *Ber.*, 1936, **69**, 1534.
[21] Miller and Rohde, *Ber.*, 1890, **23**, 1887.
[22] Buu-Hoï, Hoán, and Xuong, *J.*, 1951, 3499.
[23] Mercer and Robertson, *J.*, 1936, 288.
[24] Perkin and Robinson, *J.*, 1907, **91**, 1073.

The simplest possible analogue of pteroic acid (I) containing methine groups in place of ring-nitrogen atoms is *p*-(2-naphthylmethylamino)benzoic acid; this was prepared directly by condensing 2-bromomethylnaphthalene and *p*-aminobenzoic acid and also indirectly through the ethyl ester.

Experimental

Conventions used in reporting chromatographic results are as in Part VII.[3]

6-Methylquinoline-2,4-dicarboxylic Acid (II) *and its Derivatives.*—Pyruvic acid (3·5 ml.) was added dropwise, with stirring, to 5-methylisatin [25] (4·0 g.) in 33% potassium hydroxide solution (40 ml.) at 40—50°. After refluxing overnight, the solution was cooled and acidified. The grey precipitate was collected, washed with water, and recrystallised from acetic acid (charcoal), affording the *acid* (4·0 g., 69%) as needles, m. p. 242° (Found: C, 62·5; H, 4·0; N, 5·6. $C_{12}H_9NO_4$ requires C, 62·3; H, 3·9; N, 6·1%).

This acid (2·0 g.) was refluxed overnight with thionyl chloride (20 g.). The excess of thionyl chloride was removed under reduced pressure and the residue treated with anhydrous methanol (50 ml.), saturated with ammonia; ammonia was passed through the mixture for 30 min. Next day, the precipitate was collected by filtration and washed with aqueous sodium hydrogen carbonate and water; the resulting *diamide* (1·85 g., 93%) crystallised from water in needles, m. p. 295° (Found: C, 62·6; H, 4·7; N, 18·2. $C_{12}H_{11}N_3O_2$ requires C, 62·9; H, 4·8; N, 18·3%). In another experiment, the crude acid chloride was refluxed for 45 min. with anhydrous methanol (25 ml.). After treatment with charcoal, the cooled solution deposited the *dimethyl ester* (1·3 g., 58%), needles (from ethanol), m. p. 157° (Found: C, 65·1; H, 5·1; N, 5·3. $C_{14}H_{13}NO_4$ requires C, 64·9; H, 5·1; N, 5·4%).

2,4-Diamino-6-methylquinoline (III).—The finely powdered diamide (32 g.) was added slowly, with stirring, at 0° to a solution of potassium hypobromite (from bromine, 48 g., and potassium hydroxide, 100 g., in water, 1400 ml.). The mixture was stirred at room temperature for a further 15 min., then warmed slowly to 85° and kept there for 75 min. The brown precipitate was filtered off from the hot solution and recrystallised from water (charcoal), giving needles, m. p. 213° (2·0 g.). The original filtrate deposited a second crop of needles (10·2 g.), and a third crop (1·9 g.) was obtained by concentrating the mother-liquors. The *diamine* (14·1 g., 58%) crystallised from water in needles, m. p. 213°, R_{FPy} 0·64, R_{FAc} 0·72 (Found: C, 68·9; H, 6·4; N, 24·0. $C_{10}H_{11}N_3$ requires C, 69·3; H, 6·4; N, 24·3%). Potentiometric titration of a 0·05M-solution in 5% aqueous ethanol at 20° with N-hydrochloric acid showed the base to have pK_{a1} 9·45 and pK_{a2} *ca.* 2·5.

2,4-Diamino-3-bromo-6-methylquinoline (V).—The above diamine (2·0 g.) and *N*-bromosuccinimide (2·0 g.) were refluxed in carbon tetrachloride (30 ml.) for 24 hr. in the presence of benzoyl peroxide (0·26 g.) under irradiation with an ultraviolet lamp. The solution was evaporated to dryness under reduced pressure and the residue treated with cold N-sodium hydroxide (45 ml.). The insoluble material was collected, washed with water, dissolved in 0·5N-hydrochloric acid (500 ml.), and treated with charcoal. Addition of aqueous ammonia (*d* 0·880) precipitated the *bromo-compound* (2·3 g., 79%), which crystallised from aqueous ethanol in needles, m. p. 246°, R_{FHy} 0·86, R_{FAc} 0·70 (Found: N, 16·7; Br, 31·7. $C_{10}H_{10}BrN_3$ requires N, 16·7; Br, 31·7%); addition of saturated aqueous potassium iodide to a solution at pH 5·5 precipitated the *hydriodide*, m. p. 245° (from water) (Found: C, 31·9; H, 3·2; N, 11·2. $C_{10}H_{10}BrN_3$,HI requires C, 31·6; H, 2·7; N, 11·1%). The bromo-compound was unchanged in refluxing anhydrous pyridine or with hexamethylenetetramine in refluxing chloroform.

Acyl Derivatives of 2,4-Diamino-3-bromo-6-methylquinoline.—(*a*) The bromo-compound (500 mg.) was refluxed for 2½ hr. with acetic anhydride (10 ml.). The mixture was poured on ice and kept overnight at 0°. The solid product (580 mg.) was dissolved in acetic acid, treated with charcoal, and re-precipitated with ammonia. Repeated recrystallisation from aqueous ethanol gave the 4(or 2)-*acetyl derivative*, m. p. 204° (Found: C, 49·0; H, 4·7; N, 13·7. $C_{12}H_{12}BrN_3O$ requires C, 49·0; H, 4·1; N, 14·3%).

(*b*) Benzoyl chloride (0·45 ml.) was added to a stirred refluxing solution of the bromo-compound (500 mg.) and triethylamine (2 ml.) in anhydrous dioxan (25 ml.). After 30 min., triethylamine hydrochloride was removed and the filtrate evaporated under reduced pressure. The residue was washed with ether and crystallised from ethanol (charcoal), affording the

[25] Marvel and Hiers, *Org. Synth.*, Coll. Vol. I, 2nd Edition, p. 330.

4(or 2)-*benzoyl derivative* (390 mg., 56%), which recrystallised from toluene in plates, m. p. 232° (Found: 11·5; Br, 22·8. $C_{17}H_{14}BrN_3O$ requires N, 11·8; Br, 22·4%).

(*c*) Experiment (*b*) was repeated but with twice as much benzoyl chloride. The crude product was extracted with warm 6N-sulphuric acid, to remove unbenzoylated material, and recrystallised from ethanol, yielding the *dibenzoyl derivative* (290 mg., 31%) as needles, m. p. 259° (Found: C, 63·0; H, 4·3; N, 9·3. $C_{24}H_{18}BrN_3O_2$ requires C, 62·6; H, 3·9; N, 9·1%).

Acyl Derivatives of 2,4-*Diamino*-6-*methylquinoline*.—(*a*) The diamine (200 mg.) and anhydrous sodium acetate (200 mg.) were refluxed in acetic anhydride (5 ml.) for 2½ hr. The product was poured into ice–water (8 ml.) and kept at 0° for 2 days. The *diacetyl derivative* (100 mg; 34%) which separated was recrystallised from water as needles, m. p. 200° (Found: C, 65·7; H, 6·1. $C_{14}H_{15}N_3O_2$ requires C, 65·4; H, 5·9%).

(*b*) Benzoyl chloride (5 ml.) was added dropwise, with stirring, to a solution of the diamine (3·0 g.) and triethylamine (12 ml.) in anhydrous dioxan (90 ml.). After stirring and refluxing for 45 min., the product was cooled and filtered and the filtrate evaporated under reduced pressure. The residue was triturated with ether (20 ml.), and the resulting pale brown solid crystallised from ethanol (charcoal). The *dibenzoyl derivative monohydrate* (4·42 g., 67%) was obtained in needles, m. p. 245° (Found: C, 72·2; H, 5·7; N, 10·4. $C_{24}H_{19}N_3O_2,H_2O$ requires C, 72·2; H, 5·3; N, 10·5%); drying at 100° *in vacuo* gave the very hygroscopic anhydrous *compound* (Found: C, 75·7; H, 5·2. $C_{24}H_{19}N_3O_2$ requires C, 75·6; H, 5·0%).

Bromination of 2,4-*Dibenzamido*-6-*methylquinoline*.—(*a*) The above dibenzoyl derivative (400 mg.) in boiling chloroform (15 ml.) was treated with bromine (0·05 ml.) in chloroform (5 ml.) during 25 min. under irradiation with a 500-w tungsten-filament lamp. After 3 hr. the precipitate (250 mg., 52%) was collected and recrystallised from acetic acid, yielding the *hydrobromide*, m. p. 315° (decomp.), of the dibenzoyl derivative (Found: N, 8·4; Br, 18·6. $C_{24}H_{20}BrN_3O_2$ requires N, 9·1; Br, 17·3%), from which the parent base, m. p. and mixed m. p. 245°, was regenerated by the action of ethanolic sodium ethoxide.

(*b*) The dibenzamido-compound (320 mg.), *N*-bromosuccinimide (150 mg.), and benzoyl peroxide (20 mg.) were refluxed in carbon tetrachloride (20 ml.) for 48 hr., the mixture being irradiated with a 500-w tungsten-filament lamp. The mixture was evaporated under reduced pressure and the residue twice extracted with cold water (10 ml.). Precipitation of the insoluble material from acetic acid with water gave 2,4-*dibenzamido*-6-*bromomethylquinoline* (220 mg., 57%) which, after recrystallisation from benzene–light petroleum (b. p. 60—80°), had m. p. 225° (Found: C, 62·7; H, 4·0; Br, 15·9. $C_{24}H_{18}BrN_3O_2$ requires C, 62·7; H, 3·9; Br, 17·4%).

p-(4-*Amino*-2-*hydroxy*-6-*quinolylmethylamino*)*benzoic acid* (VI).—2,4-Dibenzamido-6-methylquinoline (1·15 g.) and 1,3-dibromo-5,5-dimethylhydantoin (360 mg.) were allowed to react in the usual manner in carbon tetrachloride (150 ml.) in the presence of benzoyl peroxide. The crude product (890 mg.), isolated by filtration and washed with ether, was fused on the water-bath for 20 hr. with ethyl *p*-aminobenzoate (2·0 g.). The solidified melt was triturated with ether (4 × 10 ml.), and the resulting hygroscopic yellow powder (720 mg.) refluxed for 4 hr. with ethanolic sodium ethoxide (from sodium, 87 mg., and ethanol, 20 ml.); water (6 ml.) was then added and refluxing continued for a further 2½ hr. Next day, the solution was neutralised with 2N-hydrochloric acid and evaporated to dryness under reduced pressure. The residue was dissolved in N-sodium hydroxide (40 ml.), filtered from a dark impurity, and treated with charcoal. Adjustment of the pH to 6 with hydrochloric acid precipitated the *acid* (200 mg., 31%) which, recrystallised from ethanol, had m. p. 265° (decomp.) (Found: C, 59·6; H, 5·0; N, 12·0. $C_{17}H_{15}N_3O_3,2H_2O$ requires C, 59·1; H, 5·6; N, 12·2%).

1,3-*Diaminoisoquinoline* (VII; R = R′ = NH_2).—(*a*) 1,3-Dichloroisoquinoline [15] (1·0 g.), suspended in aqueous ammonia (*d* 0·880; 20 ml.) containing hydrated cupric sulphate (0·15 g.), was heated in a sealed tube for 30 hr. at 138—140°. The *diamine* (0·51 g., 60%) separated on cooling and recrystallised from ethanol as yellow needles, m. p. 226° (Found: C, 68·2; H, 5·8; N, 25·9. $C_9H_9N_3$ requires C, 67·9; H, 5·7; N, 26·4%).

(*b*) Freshly prepared sodamide (from sodium, 12 g., and ferric nitrate, 0·5 g., in liquid ammonia, 250 ml.) was dissolved in dimethylaniline (150 ml.). Redistilled isoquinoline (17 g.) was added and the mixture stirred and refluxed for 7½ hr. Carbon dioxide was passed through the cooled dark product for 4 hr. and the mixture treated with water and filtered. Sublimation of the charred solid at 160—165°/0·001 mm. gave the diamine (1·98 g., 9%), which crystallised from ethanol in bright yellow needles, m. p. and mixed m. p. 226°.

Other Reactions of 1,3-*Dichloroisoquinoline.*—(*a*) Ammonia was passed for 9 hr. through a boiling solution of the dichloro-compound (1·0 g.) in phenol (15 g.). The mixture was cooled to 60°, added to an excess of 2N-sodium hydroxide and kept at room temperature for 4 hr. Crystallisation of the precipitated solid from ethanol gave 3-*chloro*-1-*phenoxyisoquinoline* (1·16 g., 90%) as needles, m. p. 87° (Found: C, 71·1; H, 4·3. $C_{15}H_{10}ClNO$ requires C, 70·5; H, 4·0%); the same product was obtained in 78% yield in an experiment in which the ammonia was omitted. This compound (500 mg.) was hydrogenated over Raney nickel in ethanolic sodium ethoxide (from sodium, 500 mg., and ethanol, 50 ml.) at 1 atm. and room temperature for 3 hr.; working-up in the usual manner gave 1-phenoxyisoquinoline (330 mg., 76%), prisms [from light petroleum (b. p. 60—80°)], m. p. and mixed m. p. 69°, having an infrared absorption spectrum identical with that of an authentic specimen (see below).

(*b*) The dichloro-compound (1·0 g.) was heated in a sealed tube at 180° for 14 hr. with ethanol (15 ml.) saturated with ammonia at room temperature. The cooled product was filtered and the filtrate evaporated to dryness under reduced pressure. Recrystallisation of the residue fom aqueous ethanol (charcoal) gave 1-*amino*-3-*chloroisoquinoline* (0·60 g., 66%) as needles, m. p. 153° (Found: C, 60·5; H, 4·2; N, 15·8; Cl, 20·0. $C_9H_7ClN_2$ requires C, 60·5; H, 4·0; N, 15·7; Cl, 19·8%). This compound (300 mg.) was dissolved in warm 20% w/w sulphuric acid (25 g.). The solution was rapidly cooled to 0° and treated dropwise, with stirring, with sodium nitrite (2·0 g.) in water (12 ml.). After 1 hr. at room temperature and 1 hr. at 100°, the mixture was cooled, and the precipitate dissolved in dilute aqueous ammonia. Acidification with acetic acid precipitated 3-chloro-1-hydroxyisoquinoline (200 mg., 66%) which, recrystallised from aqueous ethanol, had m. p. 218—220° (lit.,[15] m. p. 218—220°; m. p. of 1-chloro-3-hydroxyisoquinoline, 195—197°) (Found: N, 8·3. Calc. for C_9H_6ClNO: N, 7·8%).

1-*Phenoxyisoquinoline.*—1-Chloroisoquinoline [26] (2·0 g.) was refluxed with phenol (15 g.) for 8 hr. Working-up in the usual manner gave the *phenoxy-compound* (2·43 g., 90%) which crystallised from light petroleum (b. p. 60—80°) in prisms, m. p. 69° (Found: C, 81·7; H, 5·3; N, 6·3. $C_{15}H_{11}NO$ requires C, 81·4; H, 5·0; N, 6·3%).

6-*Methylindan*-1-*one* (VIII).—β-*p*-Tolylpropionic acid [27] (4·0 g., m. p. 115°) was added gradually, with stirring, to freshly prepared polyphosphoric acid [28] (from phosphorus pentoxide, 23 g., and syrupy phosphoric acid, 10 ml.) at 100°. After 24 hr. at 100°, the mixture was poured on ice, and the precipitate collected, dried, and distilled; the ketone (2·7 g., 76%), b. p. 82°/0·6 mm., when recrystallised from light petroleum (b. p. 100—120°), had m. p. 63° (lit.,[21] m. p. 63°).

2-*Hydroxyimino*-6-*methylindan*-1-*one.*—Concentrated hydrochloric acid (4 ml.) was added to a stirred solution of 6-methylindan-1-one (12·6 g.) and pentyl nitrite (30 ml.) in ethanol (90 ml.) at 40—50° (cooling). After a further 20 min. at this temperature, the mixture was cooled and the semi-solid product drained at the pump. The resulting *hydroxyimino-derivative* (12·5 g., 83%), recrystallised from ethanol, had m. p. 226° (decomp.) (Found: C, 69·1; H, 5·4; N, 7·4. $C_{10}H_9NO_2$ requires C, 68·6; H, 5·2; N, 8·0%).

4-*Methylhomophthalic Acid* (IX).—Phosphorus pentachloride was added in portions to a suspension of the above hydroxyimino-compound (11·1 g.) in anhydrous ether (250 ml.) until dissolution was complete. The solution was poured into water (200 ml.), and the ether allowed to evaporate. The product was neutralised with 40% aqueous sodium hydroxide (50 ml.), basified with hot 60% aqueous sodium hydroxide (80 ml.), and refluxed overnight. The dark solution was nearly neutralised with concentrated hydrochloric acid, boiled with charcoal, filtered, and acidified. The white precipitate was extracted with 2N-sodium carbonate; acidification of the filtered extract precipitated the *acid* (10·0 g., 81%), which crystallised from water in flakes, m. p. 205° (Found: C, 61·9; H, 5·2. $C_{10}H_{10}O_4$ requires C, 61·9; H, 5·2%).

4-*Methylhomophthalimide.*—The acid (5·0 g.) was dissolved in aqueous ammonia (*d* 0·880; 6 ml.). The solution was evaporated and the solid residue heated over a free flame until fusion was complete and no more ammonia was evolved. Crystallisation of the product from acetic acid (charcoal) gave the *imide* (4·3 g., 95%), m. p. 240° (Found: C, 68·6; H, 5·3; N, 7·9. $C_{10}H_9NO_2$ requires C, 68·6; H, 5·2; N, 8·0%).

1,3-*Dichloro*-7-*methylisoquinoline* (X).—The imide (8·0 g.) and phosphorus oxychloride

[26] Gabriel and Colman, *Ber.*, 1900, **33**, 980.
[27] Dippy and Page, *J.*, 1938, 357.
[28] Badger and Sasse, *J.*, 1957, 4.

(24 g.) were heated in a sealed tube at 160° for 4 hr. The cooled mixture was poured into ethanol (75 ml.) and the cold solution basified with 2N-sodium hydroxide. Recrystallisation of the precipitate from aqueous ethanol (charcoal) gave the *dichloro-compound* (4·65 g., 48%) as needles, m. p. 117° (Found: Cl, 33·6. $C_{10}H_7Cl_2N$ requires Cl, 33·5%).

1,3-*Diamino-7-methylisoquinoline* (XI).—The dichloro-compound (1·5 g.) was heated in a sealed tube at 145° for 48 hr. with aqueous ammonia (*d* 0·880; 20 ml.) and hydrated cupric sulphate (0·29 g.). The brown crystals which separated on cooling recrystallised from ethanol (charcoal), affording the *diamine* (0·52 g., 43%) as yellow needles, m. p. 239° (decomp.) (Found: C, 70·2; H, 6·8; N, 23·5. $C_{10}H_{11}N_3$ requires C, 69·3; H, 6·4; N, 24·3%).

Ethyl p-(2-*Naphthylmethylamino*)*benzoate*.—2-Bromomethylnaphthalene [29] (2·21 g.) was fused with ethyl *p*-aminobenzoate (4·1 g.) on the water-bath for 1 hr. The cooled product was twice triturated with ether (30 ml.) and washed free from bromide ions with water, yielding the *ester* (1·55 g., 51%), which crystallised from a small volume of ethanol in needles, m. p. 133° (decomp.) (Found: N, 4·5. $C_{20}H_{19}NO_2$ requires N, 4·6%).

p-(2-*Naphthylmethylamino*)*benzoic Acid* (XII).—(*a*) The ester was refluxed for 4 hr. with 8% alcoholic potassium hydroxide (30 ml.). Next day, water (30 ml.) was added and then concentrated hydrochloric acid until the solution was just acid to Congo Red. The precipitated *acid* (0·83 g., 91%), recrystallised from benzene or ethanol, had m. p. 204° (decomp.) (Found: N, 5·1. $C_{18}H_{15}NO_2$ requires N, 5·1%).

(*b*) 2-Bromomethylnaphthalene (2·21 g.), *p*-aminobenzoic acid (2·0 g.), and anhydrous potassium carbonate (0·69 g.) were heated in refluxing anhydrous ethanol (25 ml.) for 6 hr. Addition of water (50 ml.) precipitated the *acid* (2·43 g., 87%) which, after several recrystallisations from ethanol, had m. p. and mixed m. p. 200° (decomp.).

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[29] Buu-Hoï, *Annalen*, 1944, **556**, 1.