216. *New Potential Chemotherapeutic Agents. Part II. Derivatives of 2-Aminobenzocinnoline.*

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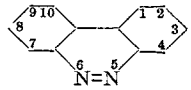
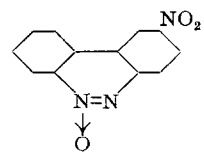
The nitration of benzocinnoline-6-oxide gives chiefly 2-*nitrobenzocinnoline*-6-*oxide* (II) and a small amount of the 3-*nitro* derivative. The positions of substitution were determined by hydrogenation of the two related *aminobenzocinnolines* to triaminodiphenyls which were cyclised by acid to known aminocarbazoles. The *amines* (III, R = $CH_2 \cdot CH_2 \cdot NEt_2$) and (III, R = $CH_2 \cdot CH_2 \cdot CH_2 \cdot NEt_2$) were obtained by hydrolysis of the alkylated 2-*p*-toluenesulphonamidobenzocinnolines.

IN addition to the synthetical work on aminoalkylquinoxalines described in Part I (this vol., p. 791), investigations were planned in certain other groups of diazines, *e.g.* the cinnolines. Difficulties arise, however, in the preparation of simple aminocinnolines owing to the inaccessibility of the parent compound, but in view of the ease with which the nucleus (I) can be synthesised—either from azobenzene (G.P. 513,206; Friedländer, **17**, 650) or from 2 : 2′-dinitrodiphenyl (Ullmann and Dieterle, *Ber.*, 1904, **37**, 24)—the amino-3 : 4-benzocinnolines appeared to be readily available, and an investigation of this group was accordingly undertaken.



(I.)



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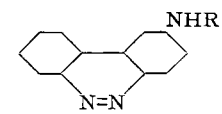

(III.)

Information regarding substitution in the benzocinnoline nucleus is scanty, and the 2-sulphonic acid and corresponding phenol are the only monosubstituted benzocinnolines hitherto prepared (G.P. 577,631; Friedländer, **20**, 462). Reference is also made (*loc. cit.*) to a disulphonic acid, and, as in the analogous case of azobenzene, mono- and di-substitution would appear to occur simultaneously. From the standpoint of those aspects of chemotherapy with which we were concerned, it was primarily the monosubstituted benzocinnolines which were of interest, and in order to avoid the possible formation of disubstitution products an alternative route to the monosubstituted benzocinnolines, starting with benzocinnoline-6-oxide, was explored. It was expected that as a result of the diminution in anionoid character of the benzene ring adjacent to the co-ordinate link, substitution would occur, as with azoxybenzene, exclusively in the other aromatic nucleus. This expectation was realised in the nitration of benzocinnoline-6-oxide, and a monoaminobenzocinnoline thus made available on reduction.

Ullmann and Dieterle (*loc. cit.*) prepared benzocinnoline-6-oxide by the reduction of 2 : 2′-dinitrodiphenyl with a large excess of sodium sulphide, but we were at first unable to duplicate the high yields claimed by these authors. This may have been due to the presence in their reagent of free alkali, since on adding sodium hydroxide, quantitative reduction was effected with little more than the theoretical amount of sulphide The nitration of benzocinnoline-6-oxide with fuming nitric acid gave a mixture of isomeric mono-nitro derivatives, the principal constituent 2-*nitrobenzocinnoline*-6-*oxide* (II), being readily purified by crystallisation from acetic acid. Evaporation of the filtrate from the first crystallisation afforded the small amount of more soluble 3-*nitrobenzocinnoline*-6-*oxide*, m. p. 226°, which is also formed.

The orientation of these two nitro compounds was established by total reduction to triaminodiphenyls followed by ring-closure with hydrochloric acid to the aminocarbazoles, all of which are known. Reduction of 2-nitrobenzocinnoline-6-oxide (II) to 2-*aminobenzocinnoline* (III, R = H) was effected with stannous chloride, and the 2-*acetamidobenzocinnoline* hydrogenated over Raney nickel to 2 : 2′-*diamino*-5-*acetamidodiphenyl*. Heating under pressure with hydrochloric acid gave an aminocarbazole, m. p. 243° (decomp.), having an acetyl derivative, m. p. 218°. Ullmann (*Annalen*, 1903, **332**, 101) records for 3-aminocarbazole, m. p. 243° (decomp.) and for 3-acetamidocarbazole, m. p. 217°. A similar series of reactions with the nitro compound, m. p. 226°, carried out without isolating the acetyltriaminodiphenyl, gave an isomeric amine, m. p. 240° (decomp.), believed to be 2-aminocarbazole, for which Blank (*Ber.*, 1891, **24**, 306) gives m. p. 238° (decomp.).

Alkylation experiments were restricted to the more available 2-aminobenzocinnoline, but this base failed to condense with β-chloroethyldiethylamine under normal conditions, *e.g.*, by prolonged heating in ethanol under pressure or in boiling amyl alcohol, with or without the addition of sodium acetate. Heating in boiling toluene with sodamide, as in Eisleb's method of diethylaminoethylation (*Ber.*, 1941, **64**, 1433) was also unsuccessful, but before extending this process to the acetyl and p-*toluenesulphonyl* derivatives, it was tried in model experiments with anilides. The aceto-β-diethylaminoethylanilide (*Chem. Centr.*, 1929, **1**, 1966) and *p*-toluenesulphon-β-diethylaminoethylanilide (Clemo and Perkin, *J.*, 1924, 1809) thus obtained were hydrolysed to β-diethylaminoaniline, from which a crystalline *monoxalate* was prepared.

β-Chloroethyldiethylamine did not react with 2-acetamidobenzocinnoline in presence of sodamide, but with the *p*-toluenesulphonamide it successfully yielded 3-p-*toluensulphon*-β-*diethylaminoethylamidobenzocinnoline*. This was later more conveniently prepared from the amide sodium salt, a method also used for the synthesis of the higher homologue, 3-p-*toluenesulphon*-γ-*diethylaminopropylamidobenzocinnoline*. Hydrolysis

of the sulphonamides with cold sulphuric acid gave the *amines* (III, R = $CH_2 \cdot CH_2 \cdot NEt_2$) and (III, R = $CH_2 \cdot CH_2 \cdot CH_2 \cdot NEt_2$) which were converted to crystalline *dihydrochlorides*.

Experimental.

Benzocinnoline 6-oxide (cf. Ullmann and Dieterle, *loc. cit.*).—Sodium sulphide nonahydrate (60 g., 1·3 mol.) and sodium hydroxide (12 g.,) were dissolved in water (100 c.c.) and slowly added to a hot solution of 2 : 2′-dinitrodiphenyl (30 g., 1 mol.) (Shaw and Turner, *J.*, 1933, 139) in alcohol (550 c.c.). When the initial vigorous reaction was over and the solution had refluxed on a steam-bath for 4 hours, the alcohol was evaporated and the residue poured into water (1 l.). When recrystallised from aqueous alcohol the benzocinnoline-6-oxide (23 g., 95%) formed long buff needles having the recorded m. p. 138°, but the crude product was sufficiently pure for nitration.

2-Nitrobenzocinnoline-6-oxide (II).—A solution of benzocinnoline-6-oxide (23 g.) in nitric acid (150 c.c., *d* 1·5) was maintained at 80—90° for 3 hours and then poured into cold water. The precipitated solid was collected, washed with water and alcohol, and then dissolved in the minimum quantity of boiling acetic acid (*ca.* 3·5 l.). *2-Nitrobenzocinnoline-6-oxide* separated on cooling in long pale yellow needles (18 g., 63·5%) which after 4 crystallisations had m. p. 269° (decomp.) (Found : 59·5; H, 3·1. $C_{12}H_7O_3N_3$ requires C, 59·7; H, 2·9%).

3-Nitrobenzocinnoline-6-oxide.—The acetic acid solution from which the 2-nitro compound had crystallised was evaporated to *ca.* 100 c.c., and the solid which separated was crystallised successively from *cyclo*hexanone, acetic acid and, finally, pyridine–ethanol. The pure *3-nitrobenzocinnoline-6-oxide* (0·7 g., 2·5%) was obtained as pale yellow prisms, m. p. 226° (decomp.) (Found : C, 60·2; H, 3·2; N, 17·3. $C_{12}H_7O_3N_3$ requires C, 59·7; H, 2·9; N, 17·4%).

2-Aminobenzocinnoline.—When 2-nitrobenzocinnoline-6-oxide (10 g., 1 mol.) was added to a solution of stannous chloride dihydrate (41 g., 1·1 mol.) in concentrated hydrochloric acid (200 c.c.) and the suspension warmed to 45°, an exothermic reaction, complete in 2 hrs., ensued. The dark orange product was collected, washed with concentrated hydrochloric acid and the *2-aminobenzocinnoline* liberated by alkali as a lemon-yellow solid, crystallising from aqueous alcohol in long needles (6 g., 75%), m. p. 243° (decomp.) (Found : C, 73·9; H, 4·6; N, 21·7. $C_{12}H_9N_3$ requires C, 73·8; H, 4·6; N, 21·6%). 2-Nitrobenzocinnoline-6-oxide, suspended in ethanol, was also reduced at 40°/70 atm. over Raney nickel in hydrogen. After one crystallisation the pure amino-compound was obtained in 80% yield. Solutions of the base in alcohol and ether exhibit an intense green fluorescence. Treatment with hydrochloric acid (15%) gave the hydrochloride, a bright orange solid soluble in water and alcohol, insoluble in the acid, and showing in dilute solutions the fluorescence characteristic of the free base. The *picrate* crystallised from alcohol in orange needles, m. p. 265° (decomp.) (Found : 50·7; H, 3·1. $C_{12}H_9N_3,C_6H_3O_7N_3$ requires C, 50·9; H, 2·8%).

By heating 2-aminobenzocinnoline (2 g.) with acetic anhydride (2 c.c.) on a steam-bath for 1 hour, a solid mass was obtained which, after trituration with water (50 c.c.), was dissolved in boiling aqueous alcohol. *2-Acetamidobenzocinnoline* (2·2 g., 91%) crystallised in thin pale yellow needles, m. p. 233° (decomp.) (Found : C, 70·5; H, 4·8. $C_{14}H_{11}ON_3$ requires C, 70·9; H, 4·6%). Its solutions do not exhibit fluorescence.

2 : 2′-Diamino-5-acetamidodiphenyl.—The 2-acetamidobenzocinnoline (2 g.) in alcohol (150 c.c.) was hydrogenated over Raney nickel at 70°/70 atm. The residue obtained on evaporation of the filtered solution did not crystallise and was dissolved in alcoholic hydrogen chloride to which dry ether was added. *2 : 2′-Diamino-5-acetamidodiphenyl dihydrochloride* (2 g. 86%) separated as colourless deliquescent needles, which darkened in air, and after 3 crystallisations from alcohol–ether had m. p. 215° (decomp.) (Found after drying at 100° : C, 53·7; H, 5·4. $C_{14}H_{15}ON_3,2HCl$ requires C, 53·5; H, 5·4%). The product had the unusual property of a negative temperature–solubility coefficient.

3-Acetamidocarbazole.—2 : 2′-Diamino-5-acetamidodiphenyl (1·5 g.) was heated in a sealed tube with hydrochloric acid (30 c.c. of 15%) at 200° for 15 hours. Ether extraction of the basified solution gave an oil which, after addition of water to its solution in acetic anhydride, yielded impure 3-acetamidocarbazole (0·5 g., 35%). Repeated crystallisation from aqueous alcohol and, finally, from toluene gave the pure compound, m. p. 218° (Found : C, 75·0; H, 5·5; N, 12·6. Calc. for $C_{14}H_{12}ON_2$: C, 75·0; H, 5·4; N, 12·5%). Hydrolysis with boiling dilute hydrochloric acid and addition of alkali gave 3-aminocarbazole (m. p. 240°).

3-Aminobenzocinnoline.—3-Nitro-benzocinnoline-6-oxide (2·5 g.) was reduced with stannous chloride and the product isolated as in the preparation of 2-aminobenzocinnoline. The product (1·5 g., 75%), after crystallisation from aqueous ethanol, gave *3-aminobenzocinnoline* as bright orange needles, m. p. 194—195° (decomp.). This isomer could not be completely dehydrated below its decomp. point (Found after drying to constant weight : C, 72·3; H, 4·6; N, 20·7. $C_{12}H_9N_3,\frac{1}{4}H_2O$ requires C, 72·2; H, 4·8; N, 21·1%). 3-Aminobenzocinnoline is characterised by a bright blue hydrochloride and dark brown picrate. Its fluorescence, though much weaker, resembles that of the 2-isomer.

When warmed at 100° for 10 minutes with excess acetic anhydride, the amine (0·5 g.) gave *3-acetamidobenzocinnoline* (0·55 g., 92%) crystallising from dilute aqueous ethanol in pale yellow needles, m. p. 171—172° (decomp.). Like the parent amine this derivative remained partly hydrated even after prolonged drying (Found : C, 69·5; H, 4·7; N, 17·4. $C_{14}H_{11}ON_3,\frac{1}{4}H_2O$ requires C, 69·6; H 4·8; N, 17·4%).

Hydrogenation of the acetamido compound (0·5 g.) in alcohol (175 c.c.) over Raney nickel at 70°/70 atm. for 1 hour gave, after evaporation of solvent, an oil which was heated under pressure with hydrochloric acid (15 c.c. of 15%) at 290° for 20 hours. Precipitation by alkali and crystallisation from aqueous alcohol and finally from toluene, gave a colourless solid, probably 2-aminocarbazole (Found : C, 79·1; H, 5·5. Calc. for $C_{12}H_{10}N_2$: C, 79·1; H, 5·5%).

Acet-(β-diethylaminoethyl)-anilide.—Powdered sodamide (1·6 g., 1·1 mol.) was slowly stirred into a mixture of β-chloroethyldiethylamine (5·5 g., 1·1 mol.), acetanilide (5 g., 1 mol.) and dry toluene (50 c.c.). When addition was complete (15 minutes) the temperature was raised during 1 hour to 100° and, after 3 hours at 100°, the mixture was refluxed for 1 hour. The filtered solution was carefully extracted with hydrochloric acid (5%) and the oil, liberated by sodium carbonate, was distilled giving acet-(β-diethylaminoethyl)-anilide (6 g., 73%) as a colourless viscous oil, b. p. 167—169°/13 mm. Its *methiodide*, formed in ethanol, crystallised from alcohol–ether in small needles, m. p. 163—164° (Found : C, 47·6; H, 6·6; N, 7·3. $C_{14}H_{22}ON_2,MeI$ requires C, 47·9; H, 6·6; N, 7·5%).

The acetyl compound (4 g.) was refluxed in concentrated hydrochloric acid (20 c.c.) for 2 hours, after which the solution was made alkaline and its ether extract distilled. The resulting β-diethylaminoethylaniline (3·5 g., 93%), b. p. 143°/13 mm., gave a *monoxalate* which separated from alcohol–ether in colourless needles, m. p. 96° (Found : C, 59·7; H, 7·9. $C_{12}H_{26}N_2,C_2H_2O_4$ requires C, 59·5; H, 7·9%).

p-Toluenesulphon-(β-diethylaminoethyl)-anilide (cf. Clemo and Perkin, *loc. cit.*).—The product obtained from *p*-toluenesulphonanilide (5 g.), β-chloroethyldiethylamine (3 g.) and sodamide (0·9 g.) in toluene (100 c.c.) under the same conditions as used for the acetyl compound gave *p*-toluenesulphon-(β-diethylaminoethyl)-anilide (6·2 g. 88%) as an oil characterised by a *picrate* crystallising from ethanol in large yellow plates, m. p. 150° (Found : C, 52·2; H, 5·2. $C_{19}H_{26}O_2N_2S,C_6H_3O_7N_3$ requires C, 52·1; H, 5·1%). Hydrolysis as described by Clemo and Perkin (*loc. cit.*) gave the alkylaniline of b. p. 146°/15 mm., in 79% yield.

2-p-Toluenesulphonamidobenzocinnoline (III, R = p-$SO_2 \cdot C_6H_4 \cdot Me$).—A mixture of 2-aminobenzocinnoline (2 g., 1 mol.), *p*-toluenesulphonyl chloride (2·2 g., 1·1 mol.) and pyridine (2 c.c., 2·5 mol.) heated at 100° for 2 hours gave, on

pouring into water, a red oil which, when solid, was crystallised from aqueous acetic acid (charcoal). The pure 2-p-*toluenesulphonamidobenzocinnoline* formed pale buff needles (3·5 g., 86%), m. p. 230° (decomp.) (Found: C, 65·7; H, 4·4. $C_{19}H_{15}O_2N_3S$ requires C, 65·4; H, 4·3%).

2-p-*Toluenesulphon-(β-diethylaminoethyl)-amidobenzocinnoline.*—The interaction of 2-*p*-toluenesulphonamidobenzocinnoline (4·5 g., 1 mol.), β-chloroethyldiethylamine (3 g., 1·7 mol.) and powdered sodamide (1 g., 2 mol.) in toluene (250 c.c.) finally at the b. p. for 7 hours, gave, by extraction of the filtered solution with hydrochloric acid (10%) and basifying, a red oil which was crystallised from aqueous ethanol. Pure 2-p-*toluenesulphon-(β-diethylaminoethyl)-amidobenzocinnoline* (3 g., 52%) was obtained in colourless needles, m. p. 122—123° (Found: C, 69·9; H, 6·3. $C_{25}H_{28}O_2N_4S$ requires C, 70·0; H, 6·2%).

Treatment of the sulphonamide (III, R = p-$SO_2{\cdot}C_6H_4{\cdot}Me$) with aqueous sodium hydroxide and crystallisation of the product from alcohol–ether gave the sodium salt (3 g.); this was refluxed in toluene with β-chloroethyldiethylamine (1·6 g., 1·5 mol.) for 15 hours and the yield of alkylated sulphonamide of m. p. 122—123° was 56%.

2-*β-Diethylaminoethylaminobenzocinnoline.*—A solution of the toluenesulphonamide (3 g.) in sulphuric acid (90%, 20 c.c.) left at 0° for 12 hours was poured into ice, basified with ammonia and extracted with chloroform. The extract was cleaned by passing through a column of alumina, and the product obtained on evaporation was dissolved in dry ether and treated with hydrogen chloride. The precipitated *dihydrochloride* gave hygroscopic orange needles (1·3 g., 50%), m. p. 224—225° (Found after drying in a high vacuum at 100°: C, 58·4; H, 6·8. $C_{18}H_{22}N_4,2HCl$ requires C, 58·9; H, 6·5%). A solution of picric acid in alcohol and the free base gave a *dipicrate* crystallising in small orange needles, m. p. 178—179° (decomp.) (Found: C, 47·6; H, 4·1; N, 18·8. $C_{18}H_{22}N_4,2C_6H_3O_7N_3$ requires C, 47·9; H, 3·7; H, 18·6%).

2-*γ-Diethylaminopropylaminobenzocinnoline.*—A mixture of sodio-2-*p*-toluenesulphonamidobenzocinnoline (6 g., 1 mol.) and γ-chloropropyldiethylamine (4 g., 1·8 mol.) (Magidson and Strukow, *Arch. Pharm.*, 1933, **271**, 569) was heated in boiling toluene (150 c.c.) for 15 hours. Extraction from the filtered solution with hydrochloric acid (10%) and basifying gave the 2-p-*toluenesulphon-(γ-diethylaminopropyl)-amidobenzocinnoline* (7 g., 56%) which crystallised from ethanol–water in pale yellow slender prisms, m. p. 108—109° (Found: C, 67·4; H, 6·5. $C_{26}H_{30}O_2N_4S$ requires C, 67·5; H, 6·5%).

Hydrolysis of the sulphonamide (5 g.) with sulphuric acid (50 c.c. of 90%) at 0° gave 2-γ-diethylaminopropylaminobenzocinnoline of which the *dihydrochloride* (2·3 g., 58%) separated from alcohol–ether in hygroscopic dark red needles, m. p. 222° (Found: 59·5; H, 7·2; N, 14·6; Cl, 18·0. $C_{19}H_{24}N_4,2HCl$ requires C, 59·8; H, 6·8; N, 14·7; Cl, 18·6%).

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