CHEMOTHERAPY OF BACTERIAL INFECTIONS

Part VI. Synthesis of N^1-substituted Sulphanilamides: Poly- and Hetero-cyclic Derivatives

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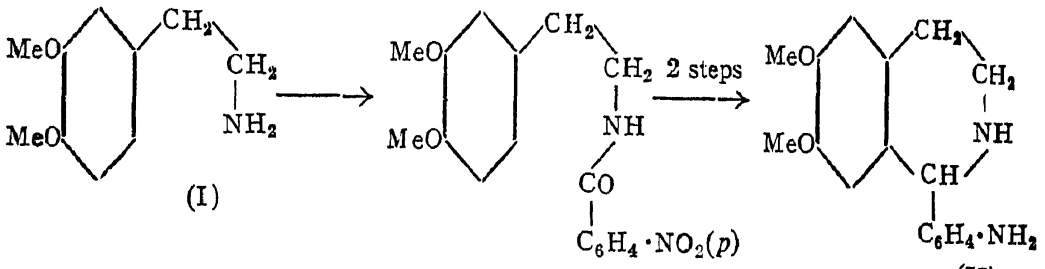
The studies on the therapeutic properties of various types of sulphanilamide derivatives in some experimental bacterial infections have convinced us that compounds with a higher degree or greater range of therapeutic activity than sulphanilamide should be searched for amongst its derivatives with cyclic, particularly heterocyclic, substituents at the sulphonamide radical. Since it is difficult at present to anticipate precisely the ring compound that will lead to the desired goal, systematic work has been undertaken to synthesise the above class of compounds with all feasible ring structures, so that we may not miss any with outstanding effects. In continuation of the work previously reported,[1] in this paper is described the synthesis of N^1-sulphanilamido derivatives of diphenylether, dibenzofuran, carbazole, acridine, chrysene, coumarin, tetrahydroisoquinoline and phenanthridine. In this preliminary study, only typical representatives of each ring system have been synthesised and if any of them show promise, further elaboration in that group will be made. The types of ring systems selected are such that they are either present in compounds showing significant pharmacological activity or expected to fill up the gaps in the data necessary to correlate chemical constitution with chemotherapeutic action.

All the compounds excepting 68 and 69 listed in the table were prepared by the customary method of condensing *para* acetaminobenzenesulphochloride with the corresponding cyclic amine and hydrolysing the resulting acetyl derivative to the free sulphanilamide derivative. The starting amines in most of the cases were prepared by methods recorded in the literature. In the experimental part, details are given in the case of those starting materials which are new or where better methods have been worked out. Thus, 4-aminodiphenylether[2] has been prepared by the hydrolysis of the N-acetyl derivative, in turn obtained by the Beckmann rearrangement of 4-phenoxyacetophenoneoxime.[3] A little known method[4] has been employed

for the preparation of dibenzofuran. 1-(*para* Amino-)phenyl-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxyisoquinoline (II) has been synthesised for the first time from 3 : 4-dimethoxyphenylethylamine (I) by the classical Bischler-Napieralsky reaction[5] through the obvious steps.



Amino sulphonamide derivatives of pyridine,[6] quinoline,[7] naphthalene,[9] and diphenyl[8] have been reported with no information on their therapeutic activity, excepting in the case of the naphthalene derivatives. Such compounds are of additional interest in ascertaining the implications of the Fildes-Woods theory [10, 11] of the mechanism of action of the sulphonamides.

No.	Name of Compound	Melting point °C.	Molecular formula	Percentage of Nitrogen	
				Found	Required
59	2-N¹-Sulphanilamidodiphenyether ..	149	$C_{18}H_{16}N_2O_3S$	7·9	8·2
	2-N¹-Acetsulphanilamidodiphenyether	162	$C_{20}H_{18}N_3O_4S$	7 6	7·3
60	4-N¹-Sulphanilamidodiphenyether ..	177–8	$C_{18}H_{16}N_2O_3S$	8·3	8·2
	4-N¹-Acetsulphanilamidodiphenylether	183	$C_{20}H_{18}N_3O_4S$	7·1	7·3
61	3-N¹-Sulphanilamidophenanthrene ..	213–5	$C_{20}H_{16}N_2O_2S$	7·8	8·1
	3-N¹-Acetsulphanilamidophenanthrene	244–5	$C_{22}H_{18}N_2O_3S$	6·9	7·1
62	6-N¹-Sulphanilamidochrysene ..	265	$C_{24}H_{18}N_2O_2S$	6·8	7·0
68	2-N¹-Sulphanilamidodibenzofuran[a] ..	242–3	$C_{18}H_{14}N_2O_3S$	..	..
64	3-N¹-Sulphanilamidocarbazole[b] ..	251 (dec.)	$C_{18}H_{15}N_3O_2S$	..	..
65	9-N¹-Sulphanilamidocarbazole ..	224 (dec.)	$C_{18}H_{15}N_2O_3S$	11·9	12·5
	9-N¹-Acetsulphanilamidocarbazole	202–3 (dec.)	$C_{20}H_{17}N_3O_3S$	10·5	11·1
66	6-N¹-Sulphanilamidocoumarin ..	189–90	$C_{15}H_{12}N_2O_4S$	8·7	8·9
67	9-N¹-Sulphanilamidoacridine dihydrochloride ..	..	$C_{19}H_{17}N_3O_2SCl_2$	9·6	10·0
	9-N¹-Acetsulphanilamidoacridine ..	273–5 (dec.)	$C_{21}H_{17}N_3O_3S$	10·5	10·8
70	1-(*p*-Sulphanilamido-) phenyl-1 : 2 : 3 : 4-tetra hydro-6:7-dimethoxyisoquinoline	162 (sint.) 159	$C_{23}H_{25}N_3O_4S$	9·4	9·6
71	9-(*m*-Sulphanilamido-) phenylphenanthridine	251–3 (dec.) (sint. 246)	$C_{25}H_{19}N_3O_2S$	9·4	9·9
68	2-Aminodiphenyl-(5?)-sulphonamide ..	186	$C_{12}H_{12}N_2O_2S$	10·6	11·0
69	4-Aminonaphthalenesulphonamide ..	250–1 (dec.)	$C_{10}H_{10}N_2O_2S$	12·0	12·6

(*a*) Described by Novelli[12] and given the m.p. 242–4° C.

(*b*) Described by Novelli[13] and given the m.p. 256–7° C.

(*c*) Described by Goldyrev and Postovskii[9] and given the m.p. 212° C.

Synthesis of some compounds of this type were therefore undertaken. 2-Acetaminodiphenyl on treatment with chlorosulphonic acid furnished a sulphochloride; this on treatment with ammonia followed by hydrolysis, yielded a product which by analogy has been described provisionally to be 2-amino-5-sulphonamidodiphenyl (compound 68). Under the conditions employed for the preparation of *para*-acetaminobenzenesulphochloride from acetanilide, the chlorosulphonation of 2-acetaminopyridine, 2-acetaminothiazole and 8-acetaminoquinoline were tried with no success, the starting products being recovered unchanged in all cases.

The compounds reported here are being tested in this Institute in experimental plague, β-hemolytic streptococcal and pneumococcal (type I) infections in mice and the results will be reported in due course.

Experimental

Synthesis of the Sulphanilamide derivatives (all compounds except 68 *and* 69).—The synthesis of these compounds being according to the well standardised methods, the details are omitted. The acetyl derivatives were obtained by condensing crystallised acetsulphanilylchloride with the corresponding amines in pyridine medium. Hydrolysis of the acetyl derivatives was carried out by means of 10% sodium hydroxide except in the cases of compounds 66, 67 and 70, where about 4-N-hydrochloric acid was used. The yields of the final products, except in the case of compound 70, were all good.

4-*Acetamidodiphenylether.*—A solution of *para* phenoxyacetophenone oxime (19·4 g.) in glacial acetic acid (130 c.c.) and acetic anhydride (100 c.c.) was saturated at 0° C. with dry hydrogen chloride by passing in a slow stream for 8 hrs. with occasional shaking, allowed to stand overnight and the separated acetyl derivative (15 g.) filtered; m.p. 130° C. (literature,[2] m.p. 127° C.).

4-*Aminodiphenylether hydrochloride.*—A mixture of the above amide (15 g.) and dil. hydrochloric acid (6 N, 200 c.c.) was boiled for 2 hrs. and the separated base hydrochloride filtered and washed with a little acetone; m.p. 225–27° C. (decomp.); (literature,[2] m.p. 222° C.).

Dibenzofuran.—A mixture of 2 : 2′-dihydroxydiphenyl (30 g.) and freshly fused zinc chloride (110 g.) were heated together at 230–50° during 4 hrs. and poured, while still warm, into dil. hydrochloric acid. The solid (m.p. 81–83° C., 25·2 g.) was filtered and thoroughly washed with dil. sodium hydroxide. A single distillation of this solid over sodium gave the pure dibenzofuran which crystallised from alcohol in colourless plates or needles; m.p. 83–84°; yield, 22 g.

(para *Nitro*)-*benzoylhomoveratrylamide.*—The amide which was prepared in good yield by the condensation of homoveratylamine and *para* nitrobenzoylchloride, separated from alcohol in faintly yellowish plates; m.p. 149°. (Found: N, 7·9; $C_{17}H_{18}O_5N_2$ requires N, 8·1%.)

1-(para *Nitro*)-*phenyl*-3 : 4-*dihydro*-6 : 7-*dimethoxyisoquinoline.*—A mixture of the above amide (crude, m.p. 143–45°, 8·7 g.) and phosphorous oxychloride (18 c.c.) was gently refluxed on sand-bath for 1½ hrs., cooled, decomposed with ice and worked up for a basic product. The dihydroisoquinoline derivative (crude, 7·8 g., m.p. 155–56°) separated from alcohol in silky needles; m.p. 158–9° C. (Found: N, 8·6; $C_{17}H_{16}O_4N_2$ requires N, 9·0%.)

1-(para *Amino*)-*phenyl*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxyisoquinoline.*—The crude forementioned nitro product (6 g.), zinc dust (50 g.) and dil. sulphuric acid (500 c.c., 1 : 3) were heated on the boiling water-bath for 3 hrs. The mixture was filtered hot, and the residue thoroughly washed with hot water. The crude tetrahydro derivative (5·1 g., m.p. 150–52°) was obtained on basifying the solution. It separated from water in colourless needles; m.p. 151–53°. (Found: N, 9·4; $C_{17}H_{20}N_2O_2$ requires N, 9·9%.)

2-*Amino*-5 (?)-*sulphonamidodiphenyl.*—The crude sulphochloride prepared by treating 2-acetamidodiphenyl (11·5 g.) with chlorosulphonic acid (18 c.c.) and working up as usual, was added to liquor ammonia (175 c.c.) and ice (50 g.) with good stirring. After standing for about half an hour, it was filtered, the filtrate acidified and allowed to stand overnight. The crude acetyl derivative so obtained (4·2 g.), m.p. 195–98°, was hydrolysed by boiling with sodium hydroxide (2·5 N, 60 c.c.) for about an hour. The free amine obtained on neutralisation of the solution, crystallised from dil. alcohol in colourless plates; m.p. 185° after sintering at 183°; yield, 2·25 g.

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Summary

With the object of studying the antibacterial effect of sulphanilamide derivatives with cyclic substituents at the sulphonamide radical, typical N^1-sulphanilamido derivatives of diphenylether, phenanthrene, chrysene, dibenzofuran, carbazole, coumarin, acridine, tetrahydroquinoline and phenanthridine have been synthesised and are reported. Aminosulphonamide derivatives of naphthalene and diphenyl are also described.

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