DERIVATIVES OF *n*-HEXYL PHENYL ETHER AS ANTITUBERCULOUS COMPOUNDS

BY M. W. PARTRIDGE and H. A. TURNER

From The University, Nottingham

Received October 28, 1952

A COMPARISON of the relative antituberculous activities of *N*-phenylbenzamidine[1] and *N*-phenyl-*p*-*n*-hexyloxybenzamidine[2] (II) indicates that the *n*-hexyloxy group confers high activity on the molecule. The contribution made by the structural components of the *N*-substituted amidine group to antituberculous activity has not been investigated and appeared to be worthy of more detailed examination. For this purpose the preparation was undertaken of a series of oxygen analogues of the *N*-phenylamidine and of a number of compounds in which the *N*-phenyl group was replaced by similar cyclic structures.

p-*n*-Hexyloxybenzamidine (I), *N*-*cyclo*hexyl- (III), *N*-α-pyridyl- (IV), and *NN*-pentamethylene-*p*-*n*-hexyloxybenzamidine (VI) were prepared by Pinner's method. No homogeneous product could be isolated in attempts to prepare (VI) by the aluminium chloride method[3] but this procedure afforded the desired compound when applied to the preparation of the *N*-benzylamidine (V). 2-*p*-*n*-Hexyloxyphenylbenziminazole (VII) was readily obtained by fusion of *p*-*n*-hexyloxybenzonitrile with *o*-aminophenylammonium toluene-*p*-sulphonate at 210° C. In model experiments with benzonitrile, it was found that this reaction was just initiated at 155° C., at 180° C. it proceeded slowly and at 210° C. reaction was rapid. Notwithstanding the successful preparation of 2-benzylimidazoline by aminolysis of ethyl phenylacetimidate with 2-chloroethylammonium chloride, 2-*p*-*n*-hexyloxyphenylimidazoline (IX) could not be prepared in this manner and was accordingly made by the method of Oxley and Short.[4] The corresponding *N*-phenylimidazoline (X) was satisfactorily obtained by the general method we have described previously.[5]

ANTITUBERCULOUS ACTIVITY

The activities of the compounds tested are listed in Table I. The most noteworthy feature of these results is the structural specificity of the *N*-phenylamidine group, since the minor structural changes involved in compounds (III), (IV), (V), (VI), (VII) and (VIII) all lead to a decrease in activity. In view of the low activity of *N*-phenylbenzamidine, it is possible that the *N*-phenylamidine group acts as a haptophore. It its haptophoric properties are assumed to be a function of both its size and its physical properties, the dyschemotherapeutic effect of these relatively insignificant structural changes becomes explicable.

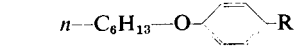
The loss of activity when the phenyl substituent in the *N*-phenylamidine group is replaced by hydrogen (I), α-pyridyl (IV), or hydroxyl (XI) or is cyclised to a benziminazole (VII) confirms previous observations with analogous derivatives of diphenyl ether.[6] From the complete loss in activity observed when an aryl substituent (compound X) is introduced

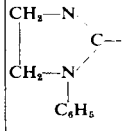
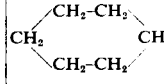
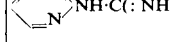
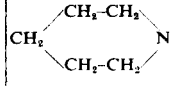
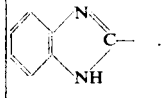
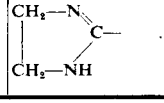
into the imidazoline (IX), it is apparent that mere arylation of a basic group *para* to the *n*-hexyloxy group is insufficient for the production of an active compound.

As was found in derivatives of diphenyl ether,[6] the oxygen isosteres, (XII), (XIII), (XIV) and (XV) of various types of amidine are devoid of

TABLE I

ANTITUBERCULOUS ACTIVITIES OF DERIVATIVES OF *n*-HEXYL PHENYL ETHER



No.	R	Activity*	No.	R	Activity*
I	$NH_2{\cdot}C(:NH)-$	10–50	X		0
II	$C_6H_5NH{\cdot}C(:NH)-$[2]	500–1000	XI	$HONH{\cdot}C(:NH)-$[8]	5
III		100	XII	$-CO{\cdot}OH$[9]	1–2
IV		10	XIII	$-CO{\cdot}OC_6H_5-$	0
V	$C_6H_5{\cdot}CH_2NH{\cdot}C(:NH)-$	50	XIV	$-CO{\cdot}NH_2$	0
VI	 ..	10	XV	$-CO{\cdot}NHC_6H_5$	0
VII		5–10	XVI	$-CO{\cdot}NHC_6H_4{\cdot}SO_2{\cdot}NH_2$ ..	0
VIII	$C_6H_5NH{\cdot}C(:NH){\cdot}NH-$[5] ..	5	XVII	$-CHO$[10]	10
IX		10–50	XVIII	$-CH:N{\cdot}NH{\cdot}CS{\cdot}NH_2$	1

* Dilution in thousands at which complete inhibition of the growth of *Mycobacterium tuberculosis* (human virulent strain) was maintained for 4 weeks in modified Long's medium (by the floating pellicle method) in the presence of 10 per cent. of serum. In the absence of serum *N*-phenylbenzamidine had an activity of 1.

activity and further evidence is thereby provided to show that molecular size is not the sole factor controlling activity. The failure of the thiosemicarbazone (XVIII) to show activity was not unexpected since combination of two biologically active groups in the same molecular normally results in the loss of activity of both. The sulphanilamide derivative (XVI) was prepared in the hope that the known affinity of such derivatives for proteins[7] may be usefully exploited; however, no activity was observed.

EXPERIMENTAL

p-n-*Hexyloxybenzamidine* (I). A solution of *p*-*n*-hexyloxybenzonitrile[2] (10·15 g.) in anhydrous ethanol (6·9 g., 3 mols.) was saturated at 0° C. with dry hydrogen chloride and kept at 0° C. Next day the solid mass was

rapidly powdered, washed with dry ether (20 ml.) and treated with anhydrous ethanolic ammonia (10 per cent.; 50 ml.). After 3 days the suspension was filtered, and the solvent was evaporated under reduced pressure. Non-basic material was removed from a solution of the residue in water by washing with ether; the base was liberated with sodium hydroxide and collected in chloroform. By acidification of the chloroform solution with an *iso*propanol solution of toluene-*p*-sulphonic acid and concentration, the toluene-*p*-sulphonate of the amidine (6·9 g., 35 per cent.) was obtained as small needles, m.pt. 187° C. Found: N, 6·8; $C_{20}H_{28}O_4N_2S$ requires N, 7·1 per cent. The picrate crystallised from ethanol as needles, m.pt. 172° C. Found: N, 15·4; $C_{19}H_{23}O_8N_5$ requires N, 15·4 per cent.

N-Cyclo*hexyl*-p-n-*hexyloxybenzamidine* (III). By interaction of *p-n*-hexyloxybenzonitrile, anhydrous ethanol and *cyclo*hexylamine (4 mols.) in the manner described for compound (I) a solution was obtained which on concentration deposited the amidinium chloride. This on recrystallisation from ethanol yielded plates, m.pt. 262° to 263° C. Yield, 82 per cent. Found: N, 8·3; $C_{19}H_{31}ON_2Cl$ requires N, 8·3 per cent. The base, prepared from the chloride, crystallised from light petroleum (b.pt. 60 to 80° C.) as plates m.pt. 77° C. Found: N, 9·4; $C_{19}H_{30}ON_2$ requires N, 9·3 per cent.

N-α-*Pyridyl*-p-n-*hexyloxybenzamidine* (IV). *p-n*-Hexyloxybenzonitrile, anhydrous ethanol and α-aminopyridine (4 mols.) were brought into reaction as described for the preparation of (I). The residue remaining after removal of the solvent was basified with ammonia and the resulting basic oil, after drying, was crystallised from light petroleum (b.pt. 60 to 80° C.). Yield 43 per cent.; m.pt. 103° C. Found: N, 14·4; $C_{18}H_{23}ON_3$ requires N, 14·15 per cent. *N*-α-Pyridyl-*p-n*-hexyloxybenzamidinium picrate crystallised as plates, m.pt. 167° C., from ethanol. Found: N, 15·9; $C_{24}H_{26}O_8N_6$ requires N, 16·0 per cent.

NN-*Pentamethylene*-p-n-*hexyloxybenzamidine* (VI). The nitrile, anhydrous ethanol and piperidine (4 mols.) were brought into reaction as described for the previous preparation. Piperidine hydrochloride which separated first on concentration of the solution was removed and the residue left after complete removal of the solvent was dissolved in water. This solution was decolorised, the base was liberated with excess of ammonia, collected in ether, dried and recovered. By reaction with an *iso*propanol solution of toluene-*p*-sulphonic acid, it afforded *NN*-pentamethylene-*p-n*-hexyloxybenzamidinium toluene-*p*-sulphonate as needles, m.pt. 156° C. Yield, 54 per cent. Found: N, 6·05; $C_{25}H_{36}O_4N_2S$ requires N, 6·1 per cent. The picrate crystallised as needles, m.pt. 106° C., from ethanol. Found: N, 13·5; $C_{24}H_{31}O_8N_5$ requires N, 13·5 per cent.

N-*Benzyl*-p-n-*hexyloxybenzamidine* (V). Finely powdered anhydrous aluminium chloride (6·7 g.) was added gradually to a mixture of *p-n*-hexyloxybenzonitrile (10·2 g., 1 mol.) and benzylamine (5·4 g., 1 mol.) and the mixture was heated at 180° C. for 20 minutes. The cooled melt was dissolved in dilute hydrochloric acid and, after charcoal treatment, the base, liberated by means of sodium hydroxide, was collected in ether,

dried and recovered. The gum so obtained slowly crystallised and was recrystallised from light petroleum (b.pt. 40 to 60° C.); yield 6·4 g. (41 per cent.); plates, m.pt. 70° C. Found: N, 8·8; $C_{20}H_{26}ON_2$ requires N, 9·0 per cent. *N*-Benzyl-*p*-*n*-hexyloxybenzamidinium toluene-*p*-sulphonate, prepared by interaction of the two components of the salt in *iso*propanol solution crystallised as plates, m.pt. 89 to 90° C. Found: N, 5·4; $C_{27}H_{34}O_4N_2S$ requires N, 5·8 per cent.

o-*Aminophenylammonium Toluene*-p-*sulphonate*. Equimolecular quantities of toluene-*p*-sulphonic acid and *o*-phenylenediamine were brought into reaction in water, the solution was evaporated and the product was crystallised from *iso*propanol as needles, m.pt. 203° C. Found: N, 10·0; $C_{13}H_{16}O_3N_2S$ requires N, 10·0 per cent.

2-*Phenylbenziminazole*. Benzonitrile (2·6 g.) and *o*-aminophenylammonium toluene-*p*-sulphonate (7 g., 1 mol.) were heated together at 210° C. for an hour; an exothermic reaction occurred, and during the first 15 minutes raised the temperature of the reaction mixture 10° C. above that of the heating bath. By basification of the product, 2-phenylbenziminazole, m.pt. and mixed m.pt. 285 to 287° C. was obtained in 84 per cent. yield.

When the reaction was carried out at 180° C. the following yields were obtained after the times stated:—1 hour, 33 per cent.; 30 minutes, 29 per cent.; 15 minutes, 14 per cent. Only a trace of 2-phenylbenziminazole was obtained after heating the reactants at 155° C. for an hour.

2-p-n-*Hexyloxyphenylbenziminazole* (VII). *p*-*n*-Hexyloxybenzonitrile (10·2 g.) and *o*-aminophenylammonium toluene-*p*-sulphonate (14 g., 1 mol.) were heated together at 210° C. for 2 hours. An aqueous ethanolic solution of the product was poured into ice-cold solution of ammonia and the precipitate (13 g.; 88 per cent., m.pt. 190 to 192° C.) by recrystallisation from aqueous ethanol afforded the required benziminazole derivative as plates (8·9 g.), m.pt. 195° C. Found: N, 9·6; $C_{19}H_{22}ON_2$ requires N, 9·5 per cent. Its picrate separated as needles from ethanol and had m.pt. 193° C. Found: N, 13·2; $C_{25}H_{25}O_8N_5$ requires N, 13·3 per cent. The toluene-*p*-sulphonate crystallised from *iso*propanol as plates, m.pt. 170° C. Found: N, 5·9; $C_{26}H_{30}O_4N_2S$ requires N, 6·0 per cent.

2-*Benzylimidazoline*. Ethyl phenylacetimidate (8·15 g.) and 2-chloroethylammonium chloride (5·8 g., 1 mol.), dissolved in anhydrous ethanol (60 ml.), were kept at room temperature for 3 days. The resulting suspension was filtered and evaporated to dryness. Basic material in the residue was liberated by sodium hydroxide, collected in chloroform and recovered. Crystals which separated from the viscous oil so obtained were recrystallised from light petroleum (b.p. 60 to 80° C.) and had m.pt. 67° C., undepressed on admixture with an authentic specimen of 2-benzylimidazoline.[4] The remaining viscous oil afforded a further quantity of the imidazoline, b.pt. 122° C./1 mm., m.pt. 66° C., on distillation. Total yield 4 g. (50 per cent.). The picrate, prepared in the usual way, had m.pt. and mixed m.pt. 148 to 149° C.

2-p-n-*Hexyloxyphenylimidazoline* (IX). A mixture of *p*-*n*-hexyloxybenzonitrile (10·2 g.) and 2-aminoethylammonium toluene-*p*-sulphonate[4]

(11·6 g., 1 mol.) was heated at 210° C. for 1½ hours and crystallised from aqueous ethanol, whereby the toluene-*p*-sulphonate of the imidazoline was obtained as needles, m.pt. 220° C.; yield 11 g. (53 per cent.). The base, liberated from this salt by means of sodium hydroxide, crystallised from light petroleum (b.pt. 60° to 80° C.) as small plates, m.pt. 124° C. Found: N, 11·4; $C_{15}H_{22}ON_2$ requires N, 11·4 per cent. The picrate was obtained as needles, m.pt. 153° C. from aqueous ethanol. Found: N, 14·8; $C_{21}H_{25}O_8N_5$ requires N, 14·7 per cent.

N-(2-*Chlorethyl*)-p-n-*hexyloxybenzamide* was obtained in 62 per cent. yield from the acyl chloride[9] and 2-chloroethylamine hydrochloride under Schotten-Baumann conditions and crystallised from *iso*propanol as fine needles, m.pt. 147° C. Found: N, 4·9; $C_{15}H_{22}O_2NCl$ requires N, 4·9 per cent.

2-p-n-*Hexyloxyphenyl*-1-*phenylimidazoline* (X). *N*-(2-Chloroethyl)-*p*-*n*-hexyloxybenzamide (7·1 g.) and phosphorus pentachloride (5·2 g., 1 mol.) were boiled together in dry benzene (90 ml.) for 10 minutes. Aniline (2·3 g., 1 mol.), dissolved in dry benzene (5 ml.), was added to the cooled solution and the mixture was heated for 4 hours. The solution was then evaporated to dryness under reduced pressure; the residue was dissolved in aqueous ethanol and treated with charcoal. The basic gum precipitated on pouring this solution into ice-cold sodium hydroxide solution slowly crystallised after drying. By recrystallisation of this material from light petroleum (b.pt. 60 to 80° C.) 4·6 g. (56 per cent.) of the required imidazoline was obtained as small plates, m.pt. 126° C. Found: N, 8·5; $C_{21}H_{26}ON_2$ requires N, 8·55 per cent. 2-*p*-*n*-Hexyloxyphenyl-1-phenylimidazolinium Reineckate crystallised from aqueous acetone as red plates, m.pt. 136° C. (decomp.). Found: N, 17·3; $C_{25}H_{33}ON_8S_4Cr$ requires N, 17·5 per cent.

Phenyl-p-n-*Hexyloxybenzoate* (XIII), prepared in 74 per cent. yield by interaction of the acyl chloride[9] and phenol in the presence of sodium hydroxide, crystallised from *iso*propanol in fine needles, m.pt. 56° C. Found: C, 76·4; H, 7·4; $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·4 per cent.

p-n-*Hexyloxybenzamide* (XIV) was prepared by interaction of *p*-*n*-hexyloxybenzoyl chloride[9] and ammonia and crystallised from ethanol as cubes, m.pt 154° C. Found: N, 6·4; $C_{13}H_{19}O_2N$ requires N, 6·3 per cent.

p-n-*Hexyloxybenzanilide* (XV) was obtained by acylation of aniline in the usual way and crystallised from ethanol as plates, m.pt. 145·5° C.; yield 87 per cent. Found: N, 4·8; $C_{19}H_{23}O_2N$ requires N, 4·7 per cent.

N^4-p-n-*Hexyloxybenzoylsulphanilamide* (XVI). A solution of *p*-*n*-hexyloxybenzoyl chloride[9] (6 g.) and sulphanilamide (4·3 g., 1 mol.) in pyridine (20 ml.) was boiled for 2 hours and poured into water. The precipitate on recrystallisation from aqueous acetone afforded N^4-*p*-*n*-hexyloxybenzoylsulphanilamide as plates, m.pt. 243° C.; yield 6·8 g. (72 per cent.). Found: N, 7·4; $C_{19}H_{24}O_4N_2S$ requires N, 7·45 per cent.

When the acylation was carried out under Schotten-Baumann conditions, the yield was 46 per cent.

p-n-*Hexyloxybenzaldehydethiosemicarbazone* (XVIII) was prepared in almost quantitative yield in the usual manner from the aldehyde[10] and

thiosemicarbazide and crystallised as leaflets, m.pt. 126° C. from aqueous ethanol. Found: N, 15·1; $C_{14}H_{21}ON_3S$ requires N, 15·1 per cent.

The authors gratefully acknowledge their indebtedness to Mr. C. E. Coulthard, Dr. L. Dickinson and Miss B. Croshaw, Boots Pure Drug Co., Ltd., for the biological tests.

Summary

1. In order to investigate the relationship between structure and activity against *Mycobacterium tuberculosis*, a series of analogues of *N*-phenyl-*p*-*n*-hexyloxybenzamidine has been prepared.

2. Amongst the nitrogen analogues, high activity was retained only in *N*-*cyclo*hexyl-*p*-*n*-hexylbenzamidine; the oxygen analogues were devoid of activity.

References

1. Charlton, Maliphant, Oxley and Peak, *J. chem. Soc.*, 1951, 485.
2. Partridge, *ibid.*, 1949, 3043.
3. Oxley, Partridge and Short, *ibid.*, 1947, 1110.
4. Oxley and Short, *ibid.*, 1947, 497.
5. Partridge and Turner, *ibid.*, 1949, 1308.
6. Partridge, *J. Pharm. Pharmacol.*, 1952, **4**, 533.
7. Davis, *Science*, 1942, **95**, 78.
8. Partridge and Turner, *J. Pharm. Pharmacol.*, 1953, **5**, 103.
9. Pierce, Salsbury and Friedricksen, *J. Amer. chem. Soc.*, 1942, **64**, 1691.
10. Weygand and Gabler, *J. prakt. Chem.*, 1940, **155**, 332.