379. *Some Novel Penicillin Derivatives*

By A. B. A. Jansen and T. J. Russell

Therapeutically useful derivatives of penicillin * have been sought within three classes of esters, (Ia—j), (Ik—p), and (Iq—s), derived formally from aldehydes (and a ketone), and in the acylamides (It and u).

Penicillin esters in general lack antibacterial action but several attempts [1,2] have been made to find among those capable of undergoing non-enzymic hydrolysis *in vivo* (for humans, unlike mice, lack an esterase of the necessary specificity) any that would offer therapeutic advantages such as prolongation of action by slow release of the free antibiotic, improved intestinal absorption, and penetration of tissue otherwise poorly accessible to the drug. Only one such derivative, *viz.* the diethylaminoethyl ester hydriodide (penethamate hydriodide) has found clinical application.

A group of esters that has hitherto largely escaped evaluation is that formally deriving from the hydrates of aldehydes and ketones. In this Paper three types are exemplified which can be regarded as penicillin monoesters of *gem*-diols in which the hydroxyl group is (1) etherified (Ia—j), (2) esterified (Ik—o), and (3) replaced by a nitrogen function (Iq—r). These compounds merited study for they have a mode of hydrolysis, *i.e.*, acid-catalysed alkyl-oxygen fission, not available to most of the known penicillin esters which depend for their breakdown on a nucleophilic attack on the carboxylate carbonyl group.

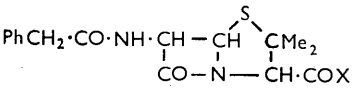
The only member of the first type so far to be described [2] is methoxymethyl benzylpenicillinate (Ia), prepared by interaction of a penicillin salt with chloromethyl methyl ether. Repeating this synthesis, we obtained the product crystalline for the first time and confirmed that it is indeed readily hydrolysed for it shows a high potency on *in vitro* assay. We prepared in addition the ethoxy- and isopropoxy-methyl esters (Ib and c) and also the diester (Id) (from dichloromethyl ether), all of which are formally derived from

* The term " penicillin " is used to embrace the penicillins generally. Individual penicillins, *e.g.*, benzyl- and phenoxymethyl-penicillin, are referred to by name.

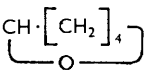
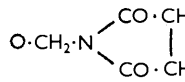
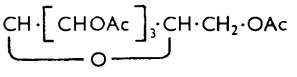
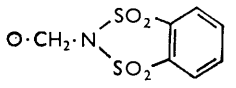
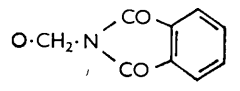
[1] E. J. Nielsen and E. K. Friederiksen, XIIth Internat. Congr. Pure and Appl. Chem., New York, 1951, Abstracts, p. 284; D. A. Johnson, *J. Amer. Chem. Soc.*, 1953, **75**, 3636; R. L. Barnden, R. M. Evans, J. C. Hamlet, B. A. Hems, A. B. A. Jansen, M. E. Trevett, and G. B. Webb, *J.*, 1953, 3733.

[2] H. F. J. McDuffie and D. E. Cooper, U.S.P. 2,650,218/1953.

formaldehyde. With other aldehydes there is the disadvantage that a new asymmetric centre is introduced usually in a sterically uncontrolled way and the resulting diastereoisomerism increases the difficulty of isolating a crystalline product. Perhaps for this reason we could only obtain the α-ethoxyethyl (Ie) and the tetrahydropyran-2-yl (If) esters as

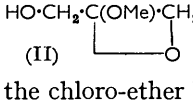


(I)

X	X
a: O·CH$_2$·OMe	m: O·CH$_2$·O$_2$C·C$_6$H$_4$Cl-*m*
b: O·CH$_2$·OEt	n: O·CH$_2$·O$_2$C·C$_6$H$_4$Cl-*p*
c: O·CH$_2$·OPr^i	o: O·CH$_2$·O$_2$CMe (with 2-ethoxynaphthyl in place of PhCH$_2$)
d: O·CH$_2$·O·CH$_2$·O$_2$C·C$_{15}$H$_{17}$N$_2$O$_2$S	p: O·CH$_2$·OH
e: O·CHMe·OEt	
f: 	q: 
g: 	r: 
h: O·C(OMe)(CH$_2$·OH)$_2$	s: 
i: O·C(OMe)(CO$_2$Et)$_2$	
j: O·C(OMe)(CO$_2$Me)$_2$	t: NMe·COPh
k: O·CH$_2$·O$_2$CMe	u: NEt·OC·CMe$_3$
l: O·CH$_2$·O$_2$CEt	

gums but the tetra-acetylglucosyl ester (Ig), obtained as the β-isomer from α-acetobromoglucose, crystallised readily.

Hemiketal esters may be expected [3] to undergo particularly ready hydrolysis so we selected for initial study two symmetrical ketones, acetone and cyclohexanone, to avoid trouble with diastereoisomers. Treatment of their enol ethers with hydrogen halides to obtain the requisite α-halogeno-ethers gave, however, very unstable products which failed to undergo the desired reaction with triethylammonium benzylpenicillinate. Analogies [4] suggested that the epoxide (II) would combine with carboxylic acids to give hemiketal esters of the desired symmetrical type, *e.g.*, (Ih), but efforts to realise this reaction with *p*-nitrobenzoic acid and phenoxymethylpenicillin (chosen for its stability as the free acid) were not fruitful. Nor could the chloro-ether be prepared by treating the epoxide with dry hydrochloric acid. Better success attended our efforts to prepare the acylals of mesoxalic esters. Ethyl and methyl methoxymalonates were brominated with *N*-bromosuccinimide to give MeO·CBr(CO$_2$Et)$_2$ and MeO·CBr(CO$_2$Me)$_2$ which, without complete purification, were treated with benzylpenicillin triethylammonium salt to give respectively (Ii) and (Ij). These esters, not unexpectedly, were relatively stable to hydrolysis owing probably to the electron attraction of the flanking alkoxycarbonyl groups.



(II)

Numerous examples of the second type of ester mentioned above, *i.e.*, α-acyloxyalkyl esters, have been prepared by interaction of a penicillin salt with α-acyloxyalkyl bromides (from the reaction of acyl bromides with aldehydes). The compounds were generally

[3] C. K. Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953, p. 334.
[4] C. L. Stevens and B. T. Gillis, *J. Amer. Chem. Soc.*, 1957, **79**, 3448.

reluctant to crystallise (and hence troublesome to obtain pure); only a few, such as (Ik—n), derived from formaldehyde did so but none derived from other aldehydes. The acetoxymethyl esters of phenoxymethyl- and 2-ethoxynaphthyl-penicillin were also prepared, but only the latter (Io) in a crystalline state.

Although such double esters would be expected to have a lower hydrolysis rate than α-alkoxyalkyl esters, readily hydrolysable entities, *e.g.*, (Ip), would result if the acyloxy-groups were split enzymically. Such a mechanism seemed to explain the relatively high serum concentrations of antibiotic observed after administration of the acetic ester (Ik), for example, to several species of mammal for acetylesterases occur widely in nature. Confirmation of the hypothesis was obtained when the same ester, though stable in buffer solution, was found to hydrolyse quite rapidly in dog and horse sera. [Simple alkyl esters of penicillin are not, of course, split in these media.]

Three samples of the third type of ester, *viz.* (Iq, r, and s) were readily prepared in good yield by interaction of triethylammonium benzylpenicillinate with *N*-bromomethyl-succinimide, *N*-bromomethylsaccharin, and *N*-bromomethylphthalimide, respectively. The hope that these esters could be disrupted by the action of amidases in a similar fashion, *mutatis mutandis*, to the α-acyloxyalkyl esters discussed above has not been realised.

Penicillin amides, like most of the esters, have little or no antibiotic activity but, as primary amides in general are hydrolysed much less readily than secondary ones (imides) it was of interest to examine some of the latter sort. A suitably mild preparative method has recently been provided by Cramer and Baer [5] which consists in the interaction of a salt of a carboxylic acid with an imidoyl chloride. Application of this reaction to benzyl-penicillin employing *N*-methylbenzimidoyl and *N*-ethylpivalimidoyl chlorides has yielded the crystalline derivatives (It) and (Iu), respectively. They showed little antibacterial activity, however, either *in vitro* or *in vivo*.

Experimental

Specific rotations were determined on 1% chloroform solutions. "Petroleum" refers to the fraction, b. p. 60—80°.

Methoxymethyl Benzylpenicillinate.—A mixture of triethylammonium benzylpenicillinate (11·6 g.), chloromethyl methyl ether (2·0 ml.) and dimethylformamide (30 ml.) was shaken for 1 hr. and then poured into water. The product, collected in chloroform, was washed with N-sodium hydrogen carbonate solution, then water, dried ($MgSO_4$), and the solvent removed under reduced pressure. The residual oil crystallised on trituration with a little isopropyl alcohol and isopropyl ether. Recrystallisation from carbon tetrachloride–petroleum gave the *ester* as needles (2·4 g.), m. p. 66—67°, $[\alpha]_D^{21}$ +158° (Found: C, 56·9; H, 5·7; N, 7·3; S, 8·4. $C_{18}H_{22}N_2O_5S$ requires C, 57·1; H, 5·7; N, 7·4; S, 8·5%).

Ethoxymethyl Benzylpenicillinate.—A mixture of triethylammonium benzylpenicillinate (1·3 g.), chloromethyl ethyl ether [6] (0·32 g.) and dimethylformamide (5 ml.) was shaken at room temperature for 1 hr. and then worked up as described above. The resulting oil after several days with isopropyl alcohol gave a crystalline solid which was collected and recrystallised from isopropyl alcohol–petroleum to yield the *ester* as needles (0·25 g.), m. p. 87·5—89·5°, $[\alpha]_D^{20}$ +186° (Found: C, 57·8; H, 6·0; N, 7·3; S, 8·1. $C_{19}H_{24}N_2O_5S$ requires C, 58·1; H, 6·2; N, 7·1; S, 8·2%).

Isopropoxymethyl Benzylpenicillinate.—A mixture of triethylammonium benzylpenicillinate (2·2 g.), chloromethyl isopropyl ether [7] (0·58 g.), and dimethylformamide (5 ml.) was shaken at room temperature for 30 min. and then worked up as above to leave a yellow oil. Trituration of this with isopropyl ether gave a solid which crystallised from isopropyl alcohol–isopropyl ether to give the *ester* as needles (0·7 g.), m. p. 94·5—95·5°, $[\alpha]_D^{20}$ +143° (Found: C, 59·0; H, 6·7; N, 6·7; S, 7·8. $C_{20}H_{26}N_2O_5S$ requires C, 59·1; H, 6·4; N, 6·9; S, 7·9%).

Di(benzylpenicillinyloxymethyl) Ether.—A mixture of triethylammonium benzylpenicillinate

[5] F. Cramer and K. Baer, *Chem. Ber.*, 1960, **93**, 1231.
[6] F. M. Litterscheid, *Annalen*, 1904, **330**, 122.
[7] H. R. Henze, V. B. Duff, W. H. J. Matthews, J. W. Melton, and E. O. Forman, *J. Amer. Chem. Soc.*, 1942, **64**, 1222.

(1·85 g.), di(chloromethyl) ether (0·49 g.), and dimethylformamide (5 ml.) was shaken at room temperature for 1 hr. The product, isolated as above, gave a solid on trituration with ethyl acetate–petroleum, which was crystallised from the same solvent to give the *diester* as needles (0·42 g.), m. p. 148—149·5°, $[\alpha]_D^{21}$ +168° (Found: C, 57·4; H, 5·5; N, 8·0; S, 9·0. $C_{34}H_{38}N_4O_9S_2$ requires C, 56·9; H, 5·3; N, 7·8; S, 8·9%).

1-*Ethoxyethyl Benzylpenicillinate.*—1-Chloroethyl ethyl ether (1·1 g.; b. p. 85—87°; prepared by passing dry hydrochloric acid into ice-cooled ethyl vinyl ether) was added to a solution of triethylammonium benzylpenicillinate (4·35 g.) in dry chloroform (20 ml.) and, after 2 hr. at room temperature, the solution was washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated under reduced pressure to give the *ester* as a gum (2·2 g.) $[\alpha]_D^{20}$ +107° (Found: N, 6·5. $C_{20}H_{26}N_2O_5S$ requires N, 6·9%).

Tetrahydropyran-2-yl Benzylpenicillinate.—2-Chlorotetrahydropyran (0·245 ml.; b. p. 42°/15 mm.; n_D^{22} 1·4655; prepared from dihydropyran and dry hydrochloric acid) in a little dry chloroform was added to an ice-cold solution of triethylammonium benzylpenicillinate (1·1 g.) in dry chloroform (5 ml.). After ½ hr. the washed and dried solution was evaporated under reduced pressure to leave the *ester* as a resin (0·82 g.), $[\alpha]_D^{20}$ +163° (Found: N, 6·7. $C_{21}H_{26}N_2O_5S$ requires N, 6·7%).

Tetra-O-acetyl-β-glucosyl Benzylpenicillinate.—A mixture of triethylammonium benzylpenicillinate (5·5 g.), acetobromoglucose (5 g.) and dimethylformamide (15 ml.) was shaken for 16 hr. at room temperature and worked up as above. The residue, which rapidly crystallised, was triturated with isopropyl alcohol to give the *ester* as prisms (4·7 g.), m. p. 197·5—199°. For analysis, a specimen recrystallised from methanol afforded needles, m. p. 198·5—199·5°, $[\alpha]_D^{20}$ +95° (Found: C, 54·2; H, 5·2; N, 4·2; S, 4·5. $C_{30}H_{37}N_2O_{13}S$ requires C, 54·05; H, 5·6; N, 4·2; S, 4·8%).

Diethyl Bromo(methoxy)malonate.—A mixture of diethyl methoxymalonate [8] (2·01 g.), freshly purified *N*-bromosuccinimide (1·88 g.), dry benzoyl peroxide (0·02 g.), and dry carbon tetrachloride (8 ml.) was refluxed for 15 hr. over a 150 w lamp. Petroleum (10 ml.) was then added and the solid filtered off. The solvent was evaporated from the filtrate under reduced pressure and the residue was distilled to give the *bromo-ester* (1·6 g.), b. p. 88—90°/0·4 mm., n_D^{21} 1·4579 (Found: Br, 28·5. $C_8H_{13}BrO_5$ requires Br, 28·7%).

Diethyl Benzylpenicillinyloxy(methoxy)malonate.—A mixture of triethylammonium benzylpenicillinate (1·1 g.), diethyl bromo(methoxy)malonate (0·7 g.), and dimethylformamide (3 ml.) was shaken for 6 hr. The product, isolated as above, was crystallised from carbon tetrachloride–petroleum to give the *penicillin ester* as prisms (0·5 g.), m. p. 147—153°. A sample crystallised for analysis from the same solvent had m. p. 153—155°, $[\alpha]_D^{20}$ +108° (Found: C, 55·1; H, 5·75; N, 5·4; S, 6·0. $C_{24}H_{30}N_2O_9S$ requires C, 55·2; H, 5·8; N, 5·4; S, 6·1%).

Dimethyl Bromo(methoxy)malonate.—Dimethyl methoxymalonate, b. p. 109—110°/16 mm., n_D^{20} 1·4230, was prepared by hydrolysing the diethyl ester with aqueous sodium hydroxide and treating the resulting acid in methanol with diazomethane. A mixture of the dimethyl ester (3·3 g.), freshly purified *N*-bromosuccinimide (3·65 g.), dry benzoyl peroxide (0·03 g.), and dry carbon tetrachloride (20 ml.) was refluxed for 15 hr. over a 150 w lamp. Petroleum (10 ml.) was added and, after removal of the precipitate, the solvent was evaporated under reduced pressure and the residue was distilled to give the bromo-ester (2·3 g.), b. p. 126—128°/16 mm., n_D^{23} 1·4630, which was used without further purification.

Dimethyl Benzylpenicillinyloxy(methoxy)malonate.—A mixture of triethylammonium benzylpenicillinate (0·9 g.), dimethyl bromomethoxymalonate (0·5 g.), and dimethylformamide (5 ml.) was shaken at room temperature for 3 hr. Isolated in the usual way, the product (1·1 g.) on trituration with isopropyl alcohol-isopropyl ether yielded a solid, crystallisation of which from a mixture of isopropyl alcohol, carbon tetrachloride, and isopropyl ether gave the *penicillin ester* as needles (0·34 g.), m. p. 104—105° (Found: C, 53·4; H, 5·2; N, 6·3; S, 6·9. $C_{22}H_{26}N_2O_9S$ requires C, 53·4; H, 5·3; N, 5·7; S, 6·6%).

Acetoxymethyl Benzylpenicillinate.—A mixture of triethylammonium benzylpenicillinate (2·6 g.), acetoxymethyl bromide [9] (4·5 ml.), and dimethylformamide (10 ml.) was shaken overnight and then poured into water. The product, after evaporation of the chloroform in which it was collected, was washed repeatedly by decantation with water and then with petroleum

[8] D. E. Ames and R. E. Bowman, *J.*, 1951, 1082.
[9] L. H. Ulich and R. Adams, *J. Amer. Chem. Soc.*, 1921, **43**, 662.

to yield the desired *ester* as a gum (2·05 g.) which crystallised from isopropyl alcohol-ethanol in prisms (1·82 g.), m. p. 104—106° after drying *in vacuo*, $[\alpha]_D^{20}$ +146° (Found: C, 56·1; H, 5·4; N, 6·8; S, 8·0. $C_{19}H_{22}N_2O_6S$ requires C, 56·15; H, 5·5; N, 6·9; S, 7·9%).

Propionyloxymethyl Benzylpenicillinate.—A mixture of bromomethyl propionate (0·31 g.; b. p. 74—76°/51 mm.; prepared by method [9] used for lower homologue), triethylammonium benzylpenicillinate (0·83 g.), and dry dimethylformamide (5 ml.) was shaken for 1 hr. at room temperature. The mixture, worked up as in the preceding experiments, gave an oil (1·0 g.) which crystallised on trituration with ethyl acetate–petroleum. Crystallisation from the same mixture gave the *ester* as needles (0·3 g.), m. p. 152—154°, $[\alpha]_D^{20}$ +186° (Found: C, 57·7; H, 5·5. $C_{20}H_{24}O_6N_2S$ requires C, 57·2; H, 5·7%).

m-*Chlorobenzoyloxymethyl Benzylpenicillinate.*—A mixture of bromomethyl *m*-chlorobenzoate (1·1 g.; b. p. 84—88°/0·2 mm.; prepared similarly to bromomethyl benzoate [9]), triethylammonium benzylpenicillinate (1·9 g.), and dry dimethylformamide (5 ml.) was treated as above to yield an oil which on trituration with isopropyl ether gave a crystalline solid (1·0 g.). Crystallisation from ethyl acetate and isopropyl ether yielded the *ester* as needles (0·64 g.), m. p. 107—108°, $[\alpha]_D^{20}$ +152° (Found: C, 57·4; H, 4·9; N, 5·35; Cl, 7·1. $C_{24}H_{23}ClN_2O_6S$ requires C, 57·5; H, 4·6; Cl, 7·0; N 5·1; S, 6·4%).

p-*Chlorobenzoyloxymethyl Benzylpenicillinate.*—A mixture of bromomethyl *p*-chlorobenzoate (0·50 g.) (prepared as described for the *m*-isomer but not purified), triethylammonium benzylpenicillinate (0·70 g.), and dry dimethylformamide (5 ml.) was treated precisely as in the preceding experiment to give after crystallisation the *ester* as needles (0·3 g.), m. p. 110—112·5°, $[\alpha]_D^{20}$ +164° (Found: C, 57·9; H, 4·7; Cl, 7·1; N, 5·4; S, 6·3%).

Acetoxymethyl 2-Ethoxynaphthylpenicillinate.—Triethylamine (1·4 ml.) was added to 2-ethoxynaphthylpenicillin [10] (4 g.) in dry dimethylformamide (20 ml.), followed by acetoxymethyl bromide (0·85 ml.). After 16 hr. the solution was poured into water and the solid collected. It was washed in chloroform solution with sodium hydrogen carbonate solution, dried ($MgSO_4$), and treated with charcoal until its colour was reduced to pale yellow. Evaporation of the solution left the *ester* as a gum (5·8 g.) which crystallised from methanol in prisms, melting unsharply between 65 and 70°, $[\alpha]_D^{20}$ +158° (Found: C, 58·1; H, 5·4; N, 6·55; S, 7·2. $C_{21}H_{22}N_2O_5S,H_2O$ requires C, 58·3; H, 5·6; N, 6·5; S, 7·4%).

Succinimidomethyl Benzylpenicillinate.—A mixture of *N*-bromomethylsuccinimide (1 g.), triethylammonium benzylpenicillinate (2·2 g.), and dimethylformamide (10 ml.) was kept at room temperature overnight and then worked up in the usual way to afford a gum which crystallised readily from methanol to give the *ester* as needles (1·28 g.), m. p. 154—155°, $[\alpha]_D^{20}$ +105° (Found: C, 56·9; H, 5·1; N, 9·3; S, 7·5. $C_{21}H_{23}N_3O_6S$ requires C, 56·6; H, 5·2; N, 9·4; S, 7·2%).

Sulphobenzimidomethyl Benzylpenicillinate.—A mixture of triethylammonium benzylpenicillinate (1·4 g.), *N*-bromomethylsaccharin (0·9 g.), and dry dimethylformamide (5 ml.) was shaken overnight at room temperature. When the mixture was poured into water the *ester* was obtained as a solid which was collected and crystallised from isopropyl alcohol to yield needles (1·0 g.), m. p. 80—85°, $[\alpha]_D^{20}$ +84° (Found: C, 54·5; H, 4·6; N, 7·9; S, 12·2. $C_{24}H_{23}N_3O_7S_2$ requires C, 54·5; H, 4·4; N, 7·9; S, 12·1%).

Phthalimidomethyl Benzylpenicillinate.—An experiment employing phthalimidomethyl bromide (1·1 g.) similar to that described for the succinimidomethyl derivative yielded the *ester* as a gum (2·3 g.), $[\alpha]_D^{20}$ +93·5°, which did not crystallise (Found: C, 60·7; H, 4·8; N, 8·3. $C_{25}H_{23}N_3O_6S$ requires C, 60·8; H, 4·7; N, 8·5%).

N-*Benzylpenicillinyl*-N-*methylbenzamide.*—*N*-Methylbenzimidoyl chloride [5] (1·1 g.) in chloroform (5 ml.) was added to a solution of triethylammonium benzylpenicillinate (3·3 g.) in chloroform (15 ml.). After 1 hr. the solution was washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated, leaving a partially crystalline residue. Crystallisation from isopropyl alcohol gave prisms (2 g.) of the N-*methylamide*, m. p. 160—163°, $[\alpha]_D^{20}$ +176° (Found: C, 64·2; H, 5·7; S, 7·4. $C_{24}H_{25}N_3O_4S$ requires C, 63·95; H, 5·6; S, 7·1%).

N-*Benzylpenicillinyl*-N-*ethylpivalamide.*—*N*-Ethyltrimethylacetimidoyl chloride (1·1 g.) in chloroform (5 ml.) was added to a solution of triethylammonium benzylpenicillinate (3·2 g.) in chloroform (10 ml.) and, after 1 hr., the solution was worked up as in the preceding experiment to give a viscous oil (3·25 g.). This was purified by dissolution in ether, filtration of the solution, evaporation of the solvent and washing of the residue with isopropyl ether before crystallisation

[10] E. G. Brain, F. P. Doyle, M. D. Mehta, D. Miller, J. H. C. Nayler, and E. R. Stove, *J.*, 1963, 495.

from isopropyl alcohol to give the N-*ethyl-imide* as prisms (1·6 g.), m. p. 77—82°, $[\alpha]_D^{25}$ +176° (Found: C, 61·8; H, 7·6; N, 8·2; S, 6·0. $C_{23}H_{31}N_3O_4S,C_3H_8O$ requires C, 61·8; H, 7·8; N, 8·3; S, 6·3%).

We thank Messrs. A. Batchelor, D. A. Jarman, and A. W. Rule for the biological results quoted herein.

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[*Received, June 10th,* 1964.]