had $[\alpha]^{25}D$ +252.2° (*c* 1, water); λ_{max}^{Nujol} 5.65 (lactam carbonyl), 6.0 (amide carbonyl), 13.4, and 14.2 μ (aromatic system).

2-Biphenylylpenicillin Potassium Salt.—This compound (**1a**) had $[\alpha]^{25}D$ +253.0° (*c* 1, water); λ_{max}^{Nujol} 5.65 (lactam carbonyl), 6.0 (amide carbonyl), 13.35 and 14.2 μ (aromatic system).

Ethoxypenicillin Potassium Salt.—6-Aminopenicillanic acid was acylated with ethyl chloroformate by A and the product was isolated as its potassium salt. The penicillin was obtained in 65% yield after recrystallization from dimethylformamide–ethyl acetate and had m.p. 222–223° dec.; λ_{max}^{Nujol} 5.65 (lactam carbonyl) and 5.85 μ (carbamate carbonyl); infrared assay, 103%.

Anal. Calcd. for $C_{11}H_{15}KN_2O_5S$: C, 40.48; H, 4.63; N, 8.58. Found: C, 40.40; H, 4.60; N, 8.29.

Attempted Preparation of 2-Biphenylylpenicillin by a Mixed Anhydride Reaction.—2-Biphenylcarboxylic acid (19.8 g., 0.1 mole) as its triethylamine salt in tetrahydrofuran was treated successively with 0.1 mole each of ethyl chloroformate and the triethylamine salt of 6-aminopenicillanic acid according to a published procedure.[51] Extraction of the product from acid solution into 4-methyl-2-pentanone and precipitation of its potassium salt with potassium 2-ethylhexanoate gave 25 g. of solid, m.p. 200–220° dec., showing infrared bands at 5.65 (lactam carbonyl) and 5.85 μ (carbamate carbonyl), but lacking the bands at *ca.* 13.4 and 14.2 μ attributed to the aromatic system of 2-biphenylylpenicillin. Paper chromatography[52] showed ethoxypenicillin as the major component.

Infrared Assay of Penicillins.—Measurements were made on a 0.04 *M* solution of the penicillin salt in dimethyl sulfoxide (which could contain up to 5% water) in a cell consisting of two plates of Kodak IRTRAN® AB-1 separated by a 0.1 mm. spacer. The Infracord was adjusted so that the solution showed 95% transmittance at 5.35 μ, and the peak at *ca.* 5.65 μ was traced out. The height of the peak was measured on a scale showing absorbance and compared to that given by an equimolar solution of penicillin G to find the purity of the sample; allowance was made for the hydration of the penicillins in calculating their percentage purity. Penicillin G showed a linear relation between concentration and absorbance in the 0.02 to 0.08 *M* range.

Acknowledgment.—We wish to thank Mrs. K. H. Swered and Mr. J. J. Taggart for their contributions to the chemistry reported in this paper, and Miss M. Davis, Miss J. P. Froelich, Mrs. L. R. Gordon, Mr. W. N. King, Miss L. Phillips, Mrs. R. R. Tumilowicz, and Mr. D. S. Ziv for their microbiological work. We are indebted to Dr. G. Dudek of the Department of Chemistry, Harvard University, for the determination and interpretation of n.m.r. spectra, to Dr. W. E. Thompson for valuable discussions of the infrared spectra, to Mr. A. Post for the chromatographic work, and to Mrs. D. A. Rolston and her staff for the microanalyses.

(51) See ref. 8 for this specific reaction; ref. 7 describes the preparation of (D-α-phenoxyethyl)penicillin by a similar mixed anhydride reaction.

(52) Whatman 3MM paper, dipped in a pH 6 buffer. 0.018 *M* in citric acid and 0.064 *M* in disodium hydrogen phosphate, and dried in air; moving phase, 9 vol. of *t*-amyl alcohol and 1 vol. of 2-propanol, equilibrated with the buffer. Zones were located by spraying the paper with sodium azide and iodine, then with starch reagent. In this system, the R_f values of ethoxypenicillin and 2-biphenylylpenicillin were *ca.* 0.65 and *ca.* 0.85, respectively.

Semisynthetic Penicillins. II. Structure–Activity Studies on the 2-Biphenylyl Side Chain[1]

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A number of new penicillins were prepared in order to examine the effect of major side-chain modifications on the biological properties of 2-biphenylylpenicillin. All the new penicillins were quite active against penicillin G-susceptible staphylococci, but only those with *o*-biarylyl side chains had good activity against penicillin G-resistant staphylococci. Some of the side-chain carboxylic acids used as intermediates were synthesized for the first time or were made by new methods.

In the previous paper of this series[1] we described the preparation and *in vitro* testing of a group of substituted 2-biphenylylpenicillins. These penicillins combine high antibacterial potency with immunity to staphylococcal penicillinase; they are consequently active not only against "susceptible" staphylococci but also against the clinically important "resistant" strains. In this paper, as in the previous one, we use the term susceptible for staphylococci which are sensitive to penicillins G and V, and resistant for those which are unaffected by high levels (*e.g.*, 500–1000 γ/ml.) of these antibiotics because they produce a lactam-opening penicillinase.[2] We were interested in discovering the effect of major side-chain modifications on the biological properties of 2-biphenylylpenicillin and in elucidating the structural features responsible for its good activity against both classes of staphylococci.

The present paper reports some new semisynthetic penicillins which were prepared for this investigation. These penicillins were synthesized by condensing the appropriate side-chain carboxylic acids with 6-aminopenicillanic acid[3] using methods already described.[1] New work involved in the preparation of the side-chain acids is reported in the Experimental section; the footnotes to the tables give literature references to acids made by known procedures. Of the biological properties which were determined for the penicillins, the minimal inhibitory concentrations for two strains of staphylococci, one susceptible and the other highly resistant,[4] give the most concise indication of activity and are presented in the tables.

(1) Part I: J. R. E. Hoover, A. W. Chow, R. J. Stedman, N. M. Hall, H. S. Greenberg, M. M. Dolan, and R. J. Ferlauto, *J. Med. Chem.*, **7**, 245 (1964).

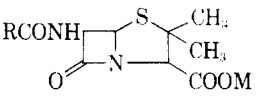
(2) See footnote 3 of ref. 1.

(3) F. R. Batchelor, F. P. Doyle, J. H. C. Nayler, and G. N. Rolinson, *Nature*, **183**, 257 (1959).

(4) See Table I, footnote *e*. The organisms used were the same as in the previous paper (ref. 1).

TABLE I

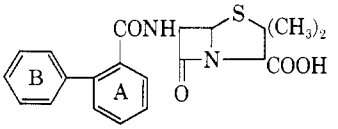
PENICILLINS



No.	R	Source of side chain acid	Penicillin cryst. from[a]	Yield,[b] %	Dec. pt., °C.[c]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Infrared assay,[d] %	Minimal inhibitory concentrations for staphylococci[e] (γ/ml.) Suscept.	Resist.
1[f]	2-Biphenylyl											0.22	0.45
2	2-Biphenylylmethyl	*g*	I–B	46	...	$C_{22}H_{21}N_2O_4SNa \cdot H_2O$	58.66	58.96	5.15	4.98	91	0.18	1000
3	3-Biphenylyl	*h*	F–D	62	180–182	$C_{21}H_{19}N_2O_4SK \cdot 1.5H_2O$	54.64	54.39	4.80	4.38	90	0.18	500
4[i]	4-Biphenylyl	*j*	C–E	45	149–151	$C_{21}H_{20}N_2O_4S$	63.62	63.59	5.08	5.31	72	1.8	500
5[i]	Phenyl	*j*	C–E	27	145–147	$C_{15}H_{16}N_2O_4S$	56.24	55.95	5.03	5.14	71	0.5	125
6	*o*-Benzylphenyl	*k*	J–G	48	164–166	$C_{22}H_{21}N_2O_4SK \cdot 1.5H_2O$	55.56	55.56	5.09	5.35	91	0.045	1000
7	*o*-Phenoxyphenyl	*l*	F–B	24	165–168	$C_{21}H_{19}N_2O_5SK \cdot H_2O$	53.83	53.34	1.52	4.29	93	0.37	250
8	*o*-Chlorophenyl	*j*	A–D	45	199–203	$C_{15}H_{14}ClN_2O_4SK \cdot H_2O$	43.84	43.99	3.92	3.96	91	0.18	1000
9	*o*-Tolyl	*j*	A–D	44	190–194	$C_{16}H_{17}N_2O_4SK \cdot H_2O$	49.21	49.35	4.90	4.77	*m*	0.18	500
10	*o*-Ethylphenyl	*n*	A–B	55	174–177	$C_{17}H_{19}N_2O_4SNa \cdot H_2O$	52.57	52.66	5.45	5.31	92	0.09	500
11	*o*-Vinylphenyl	*o*	A–B	40	166–169	$C_{17}H_{17}N_2O_4SNa \cdot H_2O$	52.84	52.71	4.96	5.02	86	0.09	500
12[p]	*o*-*t*-Butylphenyl	*p*	A–K	36	...	$C_{19}H_{24}N_2O_4S$	60.62	60.58	6.43	6.56	80	0.75	31
13	*o*-Cyclopentylphenyl	*h*	A–B	23	...	$C_{20}H_{23}N_2O_4SK \cdot 1.5H_2O$	52.96	52.87	5.78	5.60	105	0.11	250
14	*o*-Cyclohexylphenyl	*q*	A–B	35	...	$C_{21}H_{25}N_2O_4SNa \cdot 1.5H_2O$	55.86	55.79	6.25	6.29	95	0.09	7.5
15[r]	2-Phenyl-1-naphthyl	*s*	C–B	12	...	$C_{25}H_{21}N_2O_4SNa \cdot H_2O$	61.72	61.63	4.77	4.71	88	0.45	0.75
16	1-Phenyl-2-naphthyl	*s*	L	72	...	$C_{25}H_{21}N_2O_4SK \cdot 3H_2O$	57.91	57.91	5.71	5.50	99	0.75	1.5
17	*o*-(1-Naphthyl)phenyl	*t*	L	88	...	$C_{25}H_{21}N_2O_4SK \cdot H_2O$	59.74	59.99	4.61	4.51	87	0.18	0.22
18	*o*-(2-Naphthyl)phenyl	*h*	L	44	...	$C_{25}H_{21}N_2O_4SK \cdot H_2O$	59.74	59.86	4.61	4.84	75	0.75	0.15
19	4-Fluorenyl	*u*	A–B	42	210–212	$C_{23}H_{19}N_2O_4SNa \cdot 1.5H_2O$	57.76	57.11	4.85	4.65	91	0.37	15.6
20	9-Fluorenon-4-yl	*v*	A–B	46	211–214	$C_{23}H_{17}N_2O_6SK \cdot 2H_2O$	53.21	53.31	4.26	4.51	105	0.8	125

[a] Recrystallizations were carried out without heating. Solvents: A, methanol; B, ether; C, acetone; D, isopropyl ether; E, pet. ether; F, ethanol; G, ethyl acetate; H, 1-butanol; I, chloroform; J, dimethylformamide; K, water; L, not recrystallized. [b] Yields of purified products. No attempt was made to find the maximum yield for each reaction. [c] At the decomposition point, which was dependent on the rate of heating, the penicillin changed from a solid to a bubbling liquid; darkening and shrinking had usually already occurred. Where no decomposition point is reported, the same changes took place, but over a range of temperature, neither the beginning nor the end of which was well defined. [d] See ref. 1 for the method. Assays are calculated for the appropriate hydrates. [e] Measured in broth by serial twofold dilutions. End points were determined by macroscopic readings after incubation for 18 hr. at 37°. Inoculum, 10^6 organisms per ml. The susceptible staphylococcus was coagulase positive, not phage typable, MIC 0.04 γ/ml. of penicillin G, 1.8 γ/ml. of methicillin. The resistant staphylococcus was Finland 400, phage type 54, MIC > 1000 γ/ml. of penicillin G, 3.7 γ/ml. of methicillin. [f] See ref. 1. [g] J. von Braun and G. Manz, *Ann. Chem.*, **468**, 258 (1929). The acid was obtained from the nitrile by alkaline hydrolysis. [h] This paper. [i] Obtained as the crystalline free acid by extracting from the acidified reaction mixture into ethyl acetate and adding petroleum ether. [j] Ordinary commercial sources. [k] E. deB. Barnett, J. W. Cook, and I. G. Nixon, *J. Chem. Soc.*, 504 (1927). [l] H. M. Chemical Company. [m] Infrared assay not done. [n] M. Crawford and F. H. C. Stewart, *J. Chem. Soc.*, 4443 (1952). [o] W. J. Dale, L. Starr, and C. W. Strobel, *J. Org. Chem.*, **26**, 2225 (1961). [p] Prepared by method B of ref. 1. The crystalline free acid was precipitated by acidifying an aqueous solution of the sodium salt. [q] J. W. Cook and C. L. Hewett, *J. Chem. Soc.*, 62 (1936). [r] Prepared by method B of ref. 1, but with acetone substituted for chloroform as solvent. [s] R. Huisgen and H. Rist, *Ann. Chem.*, **594**, 137 (1955). [t] F. G. Baddar and F. L. Warren, *J. Chem. Soc.*, 401 (1938). [u] E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, **20**, 1396 (1955).

Table I reports a group of analogs of 2-biphenylylpenicillin (**1**) encompassing a range of structurally diverse side chains. For the sake of convenience in discussing the relationship of the new structures to the parent penicillin, the benzene rings in the side chain of the latter proximal and distal to the penicillin nucleus will be designated A and B, respectively. Compound **2** has a methylene group between the 2-biphenylyl system and the amide carbonyl, making it reminiscent



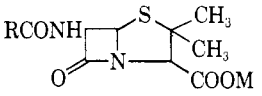
1

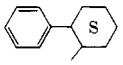
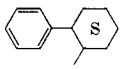
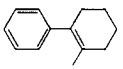
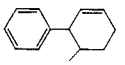
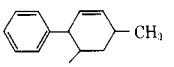
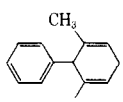
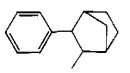
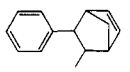
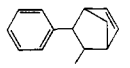
of penicillin G; **3** and **4** are isomers of the parent penicillin with ring B shifted to the *meta* and *para* positions relative to the amide carbonyl. These three analogs, like phenylpenicillin (**5**), were active against the susceptible staphylococci but not against the resistant ones. This observation established the requirement for ring A to be attached directly to the amide carbonyl and for ring B to occupy the *ortho* position on ring A. In order to find out whether other groups would produce the same effect as phenyl ring B, we prepared a variety of *ortho*-substituted phenylpenicillins. These included *o*-benzylphenylpenicillin (**6**) and *o*-phenoxyphenylpenicillin (**7**) which might also be regarded as derivatives of 2-biphenylylpenicillin with a linking atom interposed between rings A and B. Although all the compounds in this group (**6**–**14**) were effective against the susceptible organisms, none was as active as 2-biphenylylpenicillin against the resistant ones.[5] Compound **12**, with the very bulky *t*-butyl group as the *ortho* substituent, had slight activity, but the best member of the group was *o*-cyclohexylphenylpenicillin (**14**); this had about one-sixteenth of the activity of 2-biphenylylpenicillin. Apparently a nonaromatic cyclic system can, to a limited extent, duplicate the effect of a phenyl ring as the *ortho* substituent, but the failure of *o*-cyclopentylphenylpenicillin (**13**) to display any activity against the resistant organisms shows that there are very exacting structural requirements. On the other hand, the good activities of the naphthalene derivatives (**15**–**18**) against both types of staphylo-

(5) Y. G. Perron, W. F. Minor, L. B. Crast, A. Goorevitch, J. Lein, and L. C. Cheney, *J. Med. Pharm. Chem.*, **5**, 1016 (1962), reported that *o*-carboxyphenylpenicillin and some of its derivatives were somewhat active against moderately resistant staphylococci, but their data did not extend to the highly resistant organisms used in the present work.

TABLE II

PENICILLINS



No.	R[f]	Source of side chain acid	Penicillin cryst. from[a]	Yield,[b] %	Dec. pt., °C.[c]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Infrared assay,[d] %	Minimal inhibitory concentrations for staphylococci[e] (γ/ml.) Susceptible	Minimal inhibitory concentrations for staphylococci[e] (γ/ml.) Resistant
21	 (*trans*)	*g*	C–B	20	...	$C_{21}H_{25}N_2O_4SNa \cdot H_2O$	57.00	56.69	6.15	6.22	89	0.9	7.5
22	 (*cis*)	*h*	L	12	169–172	$C_{21}H_{23}N_2O_4SK \cdot 2.5H_2O$	51.94	51.88	6.23	6.41	95	0.16	15.6
23		*i*	H–D	38	...	$C_{21}H_{23}N_2O_4SK \cdot H_2O$	55.24	55.02	5.52	5.71	87	0.09	250
24	 (*cis*)	*h*	L	40	169–171	$C_{21}H_{23}N_2O_4SK \cdot 0.5H_2O$	56.35	56.26	5.40	5.42	84	0.2	5.0
25	 (all *cis*)	*j*	I–B	82	...	$C_{22}H_{25}N_2O_4SK \cdot H_2O$	56.15	55.80	5.78	5.96	100	0.75	3.7
26		*k*	G–B	72	...	$C_{22}H_{23}N_2O_4SK \cdot 1.5H_2O$	55.32	55.53	5.49	5.45	94	0.18	125
27	 (*endo*-phenyl, *exo*-carboxamido[l])	*m*	F–B	48	...	$C_{22}H_{25}N_2O_4SNa \cdot H_2O$	58.13	58.40	5.99	5.98	91	0.045	500
28	 (*endo*-phenyl, *exo*-carboxamido[l])	*n*	C–B	64	165–169	$C_{22}H_{23}N_2O_4SK \cdot 2H_2O$	54.30	54.06	5.59	5.70	107	0.125	500
29[o]	 (*exo*-phenyl, *endo*-carboxamido[l])	*n*	L	48	...	$C_{22}H_{23}N_2O_4SK \cdot 1.5H_2O$	55.32	55.59	5.49	5.90	105	0.18	125

[a–e] As in Table I. [f] The asymmetric side-chain acids were all racemic, but possibly some concentration of one form occurred in the synthesis and purification of the penicillin. It is assumed that no *cis–trans* isomerization or double bond migration took place. [g] C. D. Gutsche and W. S. Johnson, *J. Am. Chem. Soc.*, **68**, 2239 (1946). [h] K. Alder, H. Vagt, and W. Vogt, *Ann. Chem.*, **565**, 135 (1949). [i] W. L. C. Veer and P. J. A. Oud, *Rec. Trav. Chim.*, **72**, 1083 (1953). [j] K. Alder, M. Schumacher, and O. Wolff, *Ann. Chem.*, **570**, 230 (1950). [k] K. Alder, J. Haydn, K. Heimbach, and K. Neufang, *ibid.*, **586**, 110 (1954). [l] Stereochemical description based on the norborane skeleton. [m] This paper. [n] See ref. 18. [o] The triethylamine salt of the side-chain acid in acetone–dioxane was treated with isobutyl chloroformate to give the mixed anhydride, which was coupled with the triethylamine salt of 6-aminopenicillanic acid in water (*cf.* Y. G. Perron, W. F. Minor, C. T. Holdrege, W. J. Gottstein, J. C. Godfrey, L. B. Crast, R. B. Babel, and L. C. Cheney, *J. Am. Chem. Soc.*, **82**, 3934 (1960)). The acid chloride method was not tried.

cocci prove that, when the side chain is made up of two homoaryl systems in the appropriate orientation, the shape and size of each are not critical. Rather suprisingly, the fluorene derivatives (**19, 20**) were effective against the susceptible organisms but were much less active than 2-biphenylylpenicillin against the resistant ones. Since substituents in the 2′- or 6-positions of 2-biphenylylpenicillin do not have much effect on its activity,[1] it seems that the deleterious influence of the one-carbon bridge in **19** and **20** must be associated with the restriction it imposes on the rotation of the rings.

Most of the compounds of Table I retain ring A of the 2-biphenylylpenicillin side chain while ring B is modified. In the penicillins of Table II ring B is retained while A is replaced by various nonaromatic six-membered rings. As in Table I, all the penicillins were active against the susceptible staphylococci. The two isomeric 2-phenylcyclohexylpenicillins (**21, 22**) and some of the unsaturated compounds (**24, 25**) had modest activities against the resistant organisms; other unsaturated derivatives (**23, 26**) and all the bridged ring compounds (**27–30**) were inactive. Although no obvious pattern is discernible, it is clear that a nonaromatic ring A is subject to very stringent structural requirements. Moreover, the best penicillin

with ring A nonaromatic (**25**) had only one-eighth of the activity against the resistant staphylococci of 2-biphenylylpenicillin.

From these studies, and from additional work on penicillins with heterocyclic side chains,[6] we conclude that various *o*-biarylyl side chains confer good activity against both susceptible and resistant staphylococci. Many of the 2-biphenylylpenicillins are as active against both classes of staphylococci as phenylpenicillin is against the susceptible ones.[1] It seems that the phenyl ring B, when situated as an *ortho* substituent on ring A, in some way protects the penicillin from staphylococcal penicillinase, but does not impair its ability to disrupt bacterial metabolism. Good resistance to penicillinase may also be conferred by a phenyl side chain with two appropriate nonaromatic *ortho* substituents, as in methicillin[7] (2,6-dimethoxyphenylpenicillin), but the presence of the two substituents markedly interferes with the ability of the penicillin to exert its antimicrobial activity.[8] Oxacillin[9] (5-methyl-3-phenyl-4-isoxazolylpenicillin) may be considered as a penicillin of the *o*-biarylyl type[9a] and closely resembles 2-biphenylylpenicillin in its biological properties.[10] Similar activities are shown by two other new penicillins, nafcillin[11] (2-ethoxy-1-naphthylpenicillin) and quinacillin[12] (3-carboxy-2-quinoxalinylpenicillin), which have side chains consisting of an aromatic system with a single nonaromatic *ortho* substituent, but these appear to be exceptional cases. Nafcillin, indeed, may also be regarded as a special type of *ortho*-disubstituted phenylpenicillin. The high activity of quinacillin seems to depend on a rather specific combination of the appropriate aromatic system and *ortho* substituent; not much variation of either is possible without detrimental effects.[12]

Experimental[13]

3-Biphenylcarboxylic Acid.—A solution of 23.3 g. (0.1 mole) of 3-bromobiphenyl in 50 ml. of ether was added during 30 min. to a stirred ice-cooled solution of 0.2 mole of *n*-butyllithium (17% solution in hexane) in 150 ml. of ether. The reaction was carried out under dry nitrogen. Stirring and cooling were continued for 2 hr., and the mixture was then refluxed for a further hour. The resulting yellow suspension was poured slowly into a stirred slurry of a large amount of Dry Ice in ether. The excess carbon dioxide was allowed to evaporate, and the product (as lithium salt) was extracted into water. Acidification gave a solid which was recrystallized from chloroform–petroleum ether to give 4.72 g. (24%) of the crude acid, m.p. 150–152° (satisfactory for the preparation of the penicillin). For purification, an ethereal solution of the acid was treated with cyclohexylamine and the resulting solid was recrystallized first from water and then from acetone to give the colorless **cyclohexylammonium salt,** m.p. 181–184° dec.

Anal. Calcd. for $C_{13}H_{10}O_2 \cdot C_6H_{13}N$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.45; H, 7.39; N, 4.70.

Acidification of the salt gave 3-biphenylcarboxylic acid as colorless crystals (from acetone–petroleum ether), m.p. 163–165° (lit.[14] m.p. 166.5–166.8° and 160°).

o-Cyclopentylbenzoic Acid.—*o*-Chlorophenylmagnesium bromide was treated with cyclopentanone, and the product was dehydrated with formic acid, following the procedures reported for an analogous case,[15] to give a 39% yield of *o*-(1-cyclopentenyl)-chlorobenzene, b.p. 135–141° (26 mm.), $n^{25}D$ 1.5760. This material was treated with cuprous cyanide in refluxing N-methylpyrrolidone, and the resulting complex was decomposed with ferric chloride (published general procedure[16]) to give a 44% yield of *o*-(1-cyclopentenyl)benzonitrile, b.p. 113–118° (0.5 mm.), $n^{25}D$ 1.5842. The nitrile (16.9 g., 0.1 mole) was refluxed for 20 hr. with 17 g. of sodium hydroxide in 170 ml. of ethylene glycol to which 0.5 ml. of water had been added. The reaction mixture was poured into water, and *o*-(1-cyclopentenyl)benzoic acid was isolated as a crude solid by acidification and extraction into ether followed by back extraction into aqueous sodium carbonate and precipitation with acid. An ethanolic solution of the crude acid was treated with cyclohexylamine, and **cyclohexylammonium *o*-(1-cyclopentenyl)benzoate** was precipitated by adding ether. Recrystallization from ethyl acetate gave 13.6 g. (48% from the nitrile) of the colorless salt, m.p. 161–163°.

Anal. Calcd. for $C_{12}H_{12}O_2 \cdot C_6H_{13}N$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.48; H, 8.70; N, 4.83.

Acidification of an aqueous solution of the above salt precipitated a 93% yield of the free acid, m.p. 45.5–47°, which was too unstable to purify further. A solution of 2.82 g. (0.015 mole) of this acid in 100 ml. of ethyl acetate was hydrogenated at atmospheric pressure over 0.2 g. of 10% palladium-on-carbon. The theoretical quantity of hydrogen was consumed in 3 hr. Evaporation of the filtered solution and recrystallization of the residue from aqueous methanol gave 2.6 g. (91% on the hydrogenation) of colorless *o*-cyclopentylbenzoic acid, m.p. 81–82°.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.55; H, 7.43.

o-(2-Naphthyl)benzoic Acid.—A stirred mixture of 50.8 g. (0.2 mole) of 2-iodonaphthalene and 105 g. (0.4 mole) of methyl *o*-iodobenzoate in a bath at 200° was treated with 125 g. of powdered copper bronze in portions during 1.5 hr. When the addition had been completed, the bath temperature was raised to 250° for 4 hr. The reaction mixture was extracted with 1 l. of acetone, and the oily residue left on evaporation of the extract was hydrolyzed by refluxing with excess potassium hydroxide in aqueous ethanol. After concentration to remove the ethanol, the hydrolysate was washed with benzene and acidified to precipitate a crude solid which was stirred with 500 ml. of benzene at room temperature; the insoluble portion consisted mainly of diphenic acid. The benzene was evaporated and the residue was recrystallized from aqueous methanol to give 1.95 g. (3.9%) of the colorless product, m.p. 191–192.5° (lit.[17] m.p. 189–190°).

***endo*-3-Phenyl-*exo*-2-norbornanecarboxylic Acid.**—A solution of 21.4 g. (0.1 mole) of *endo*-3-phenyl-5-norbornene-*exo*-2-carboxylic acid[18] in 150 ml. of ethanol was hydrogenated at 3.5 kg./cm.^{2} over Raney nickel[19] for 3 hr. The uptake of hydrogen

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(7) (a) F. P. Doyle, K. Hardy, J. H. C. Nayler, M. J. Soulal, E. R. Stone, and H. R. J. Waddington, *J. Chem. Soc.*, 1453 (1962); (b) G. N. Rolinson, S. Stevens, F. R. Batchelor, J. C. Wood, and E. B. Chain, *Lancet*, **2**, 564 (1960).

(8) Compare the activities of methicillin (Table I, footnote *e*) and phenylpenicillin (**5**) against the susceptible staphylococci.

(9) F. P. Doyle and J. H. C. Nayler, U. S. Patent 2,996,501 (1961).

(9a) NOTE ADDED IN PROOF.—However, F. P. Doyle, J. C. Hanson, A. A. W. Long, J. H. C. Nayler, and E. R. Stove, *J. Chem. Soc.*, 5838 (1963), have recently reported that the resistance of oxacillin to penicillinase is dependent on the presence of both the phenyl and methyl groups on the isoxazole ring. The requirement for a second (albeit small) *ortho* substituent in this case is in keeping with our observation (ref. 6) that only specific types of heterocycle can replace ring A without loss of activity against the resistant staphylococci.

(10) H. Abu-Nassar, T. W. Williams, Jr., and E. M. Yow, *Am. J. Med. Sci.*, **245**, 459 (1963).

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(12) H. C. Richards, J. R. Housley, and D. F. Spooner, *Nature*, **199**, 354 (1963).

(13) Capillary melting and decomposition points were determined and are corrected. Ethanol was S.D.A. grade 2B (anhydrous); petroleum ether was the fraction b.p. 30–60°. Dilute hydrochloric acid was used for acidification. Evaporations were carried out under aspirator vacuum. Refractive indices were measured with an Abbé refractometer.

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(15) See the preparation of *o*-1-cyclohexenylchlorobenzene by W. E. Parham, C. D. Wright, and D. A. Bolon, *J. Am. Chem. Soc.*, **83**, 1751 (1961).

(16) (a) L. Friedman and H. Shechter, *J. Org. Chem.*, **26**, 2522 (1961); (b) M. S. Newman and H. Boden, *ibid.*, **26**, 2525 (1961).

(17) J. W. Cook and R. Schoental, *J. Chem. Soc.*, 288 (1945).

(18) C. S. Rondestvedt, Jr., and C. D. Ver Nooy, *J. Am. Chem. Soc.*, **77**, 4878 (1955).

was quantitative. The filtered solution was evaporated and the residue was recrystallized from aqueous methanol to give 18.7 g. (87%) of the colorless product, m.p. 140–142°.

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.68; H, 7.57.

Preparation of Penicillins.—The methods used are described in the previous paper of this series.[1] In almost all cases the chlorides of the side chain acids were coupled with 6-aminopenicillanic acid in aqueous acetone in the presence of sodium bicarbonate (method A), and the penicillins were isolated as their alkali metal salts. Departures from these procedures are reported in the footnotes to the Tables.

(19) J. Weinstock, N. Schwartz, and M. F. Kormendy, *J. Org. Chem.*, **26**, 5247 (1961), reported that *exo*-3-phenyl-5-norbornene-*endo*-2-carboxylic acid could be hydrogenated in ethanol with palladium-on-carbon. This catalyst did not hydrogenate our compound.

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New Antiviral Compounds with Considerable Activity *in Vivo*. IV. Aromatic α-Keto Aldehydes

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The antiviral activity in tissue culture, in chick embryo, and in mice of α-keto aldehyde derivatives of biphenyl, diphenylmethane, diphenylethane, stilbene, diphenyl ether, diphenyl sulfide, and diphenyl sulfone was studied. Several substances were found active in chick embryo against A-PR8 virus, in tissue culture against poliomyelitis virus, adenovirus, and vaccinia virus. All substances were active in mice against MHV3 virus and nonactive against Columbia SK virus. Some of them were also active in mice against A-PR8 virus. The biphenyl, diphenylethane, and diphenyl sulfide derivatives showed the best antiviral activity.

In previous papers the synthesis and the antiviral properties of 4-biphenylglyoxal, of 4,4′-bisbiphenylglyoxal, and of several derivatives[2–4] have been described. The glyoxal derivatives of biphenyl proved active as antiviral agents *in vivo* and also in human therapy.[5,6] It appeared interesting to synthesize additional substances formed from diglyoxals in several ring systems; some of these compounds were found to display good antibacterial activity.[7,8] Mono- and bis-α-keto aldehydes were introduced into the 4- and 4,4′-positions of diphenylmethane, diphenyl ether, diphenyl sulfide, diphenyl sulfone, diphenylethane, and of stilbene, and into the 2,2′-positions of biphenyl.

Experimental[9]

The aromatic α-keto aldehydes listed in Table I were prepared by two methods: (A) by oxidation of the corresponding aryl methyl ketones with selenium dioxide in aqueous dioxane; (B) by reaction of the corresponding α,α-dichloromethyl aryl ketones with hydrochloric acid. The keto aldehydes were isolated as hydrates or as monosodium bisulfite addition products. In a few cases the anhydrous α-keto aldehydes were obtained by vacuum distillation.

In order to confirm their structure, quinoxaline derivatives were prepared by condensation of *o*-phenylenediamine with the keto aldehydes. All the α-keto aldehydes reduced Tollen's reagent. 4-Acetyldiphenylmethane, 4-acetyldiphenylethane, 4,4-bisacetyldiphenylethane, 4,4′-bisacetylstilbene, 4-acetyldiphenyl ether, 4,4′-bisacetyldiphenyl ether, 4-acetyldiphenyl sulfide, and 4,4′-bisacetyldiphenyl sulfide were prepared by Friedel–Craft's reactions according to the literature.[10–15] 4-Acetylstilbene was prepared by the Meerwein reaction from 4-aminoacetophenone and cinnamic acid,[16] 2,2′-bisacetylbiphenyl by oxidation of 9,10-dioxo-9,10-dimethyldihydrophenanthrene,[17] and 4-acetyldiphenyl sulfoxide and 4-acetyldiphenyl sulfone by oxidation of 4-acetyldiphenyl sulfide with hydrogen peroxide.[18]

The α,α-dichloromethyl aryl ketones used for the preparation of the keto aldehydes according to method B were prepared by Friedel–Craft's reaction or by chlorination of the corresponding methyl aryl ketones.[8]

Preparation of α-Keto Aldehydes (Table I). A.—The aryl methyl ketone (0.1 mole), dissolved in 120 ml. of warm dioxane, was added to a solution of 0.15 mole of SeO_2 in 50 ml. of 30% aqueous dioxane at 50–60° (for the preparation of the bisketo aldehydes 0.3 mole of SeO_2 was used). The mixture was refluxed gently for 10 hr. The selenium which separated was filtered hot. The solution after standing for some days in the sunlight was filtered again and water was added in order to crystallize or precipitate the keto aldehyde hydrate which was filtered and recrystallized from aqueous dioxane or water. When this procedure was not convenient, the solvent was evaporated under reduced pressure and the residue was dissolved in anhydrous ethanol, filtered with charcoal, and again evaporated. The crude ethyl hemiacetal obtained was distilled under reduced pressure to prepare the anhydrous keto aldehyde.

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