dichlorostyrene[2] as the monomer pair, some variations in monomer reactivity ratios *have* been observed with different Lewis acid catalysts, although, since most of these polymerizations were heterogeneous, some of the variations may be due to surface effects.

Stannic chloride and aluminum bromide were used as catalysts for homogeneous copolymerizations carried out in *n*-hexane, nitrobenzene and nitromethane at 0°. The monomers were mixed in predetermined proportions and added to the solvent, then after cooling, the catalyst. The total concentration of monomer was 20 mole % in all cases. Polymerization times varied from 3 to 15 minutes, preliminary experiments with each system having indicated the times required for conversions to reach roughly 7%. The copolymer was precipitated by addition of methanol and purified by repeatedly dissolving in methyl ethyl ketone and precipitating by addition of methanol. The compositions of the copolymers were determined by analytical determination of their chlorine contents.

For each system studied, the monomer reactivities r_1 and r_2 (isobutylene = monomer 1; *p*-chlorostyrene = monomer 2) were calculated. The values obtained were: $r_1 = 1.01$, $r_2 = 1.02$ for copolymerization in *n*-hexane using $AlBr_3$ (0.5 mole %) as catalyst; $r_1 = 14.7$, $r_2 = 0.15$ in nitrobenzene using $AlBr_3$ (0.1 mole %); $r_1 = 22.5$, $r_2 = 0.7$ in nitromethane using $AlBr_3$ (0.5 mole %) and $r_1 = 8.6$, $r_2 = 1.2$ in nitrobenzene using $SnCl_4$ (0.3 mole %). No polymerization took place in *n*-hexane when $SnCl_4$ was used as a catalyst.

From these results it can be seen that, in the systems studied, the monomer reactivities in the non-polar solvent differ very greatly from those in the polar solvents. Although several explanations can be offered for these results, it is best to await further data. Such large variations have not been observed previously in ionic copolymerization systems in which homogeneity is retained during polymerization. Further work in this unique system is in progress.

Acknowledgment.—We gratefully acknowledge the support given by a "Grant-in-Aid" from the Shell Development Company.

(2) R. E. Florin, THIS JOURNAL, **71**, 1867 (1949); **73**, 4468 (1951).

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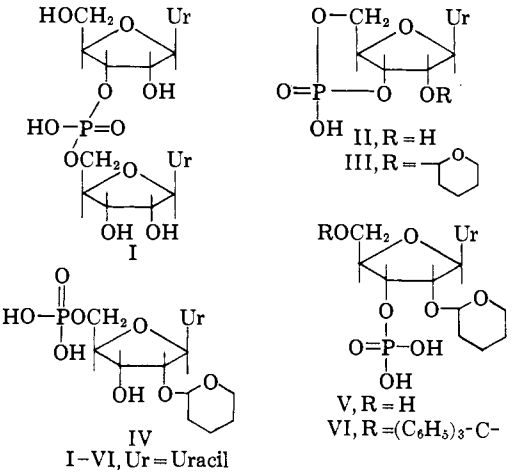
SPECIFIC SYNTHESIS OF THE C_5'–C_3' INTER-RIBONUCLEOTIDE LINKAGE: THE SYNTHESIS OF URIDYLYL-(5′ → 3′)-URIDINE[1,2]

Sir:

The problem of the synthesis of ribo-polynucleotides containing the naturally occurring (C_5'–C_3') inter-ribonucleotide linkage is seriously complicated by the presence of the 2′-hydroxyl group in ribonucleosides. Consequently, while considerable progress recently has been made in the synthesis of deoxyribo-oligonucleotides containing C_5'–C_3' internucleotide bonds,[3] no specific synthesis of corresponding compounds in the ribonucleoside series has hitherto been reported. The present communication outlines an approach which has been used successfully in the synthesis of uridylyl-(5′→3′)-uridine (I) and offers promise for the synthesis of other ribo-oligonucleotides.

Uridine-5′ phosphate was treated with dicyclohexylcarbodiimide under high dilution conditions to yield uridine-3′,5′ cyclic phosphate (II), R_f 0.29,[4] which was isolated after chromatography as the ammonium salt in 60% yield. The cyclic



phosphate (II) as the free acid was treated with dihydropyran in anhydrous dioxane to give the 2′-*O*-tetrahydropyranyl derivative (III), R_f 0.55,[4] quantitatively. Hydrolysis of III with sodium hydroxide gave a mixture of IV and V, which was treated directly in anhydrous pyridine with an excess of triphenylmethyl chloride. The resulting derivative (VI, R_f 0.68[4] isolated in 30% yield based on II) and unreacted IV, R_f 0.30[4], (10% yield from II) were separated by partition chromatography. Both IV and V, as well as VI are suitable intermediates for diester synthesis by procedures already applied in the deoxyribonucleotide field.[3a] In the present work, VI was treated with two molar equivalents of 2′,3′-di-*O*-acetyluridine[5] and dicyclohexylcarbodiimide under the standard conditions used earlier.[3a] After work-up, which included successive treatments with aqueous acetic acid to remove triphenylmethyl and tetrahydropyranyl groups, and ammonium hydroxide to remove acetyl groups, the desired uridylyl-(5′→3′)-uridine (I), R_f 0.19,[4] and uridine were found to be the only products and were readily separated. The synthetic dinucleoside phosphate was characterized in a variety of ways; it was degraded completely to uridine-3′ phosphate and uridine by a spleen diesterase preparation[6] and also by pan-

(1) For nomenclature system see ref. 3a.

(2) This work has been supported by a grant from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(3) (a) P. T. Gilham and H. G. Khorana, THIS JOURNAL, **80**, 6212 (1958); *ibid.*, **81**, in press; (b) G. M. Tener, H. G. Khorana, R. Markham and E. H. Pol, *ibid.*, **80**, 6223 (1958); (c) A. F. Turner and H. G. Khorana, *ibid.*, in press.

(4) Determined in isopropyl alcohol, ammonium hydroxide, water (7:1:2).

(5) G. W. Kenner, A. R. Todd, R. F. Webb and F. J. Weymouth, *J. Chem. Soc.*, 2288 (1954).

(6) L. A. Heppel and R. J. Hilmoe, "Methods in Enzymology," Vol. II, Academic Press, Inc., New York, N. Y., 1955, p. 565.

creatic ribonuclease. In the latter case, uridine-2′,3′ cyclic phosphate was, as expected, an intermediate in the degradation. The synthetic material was, furthermore, chromatographically and electrophoretically identical with a sample of uridylyl-(5′→3′)-uridine prepared enzymically by the general method of Heppel, Whitfeld and Markham.[7]

Further work on the synthesis of C_5'-C_3' linked ribo-oligonucleotides is in progress.

(7) L. A. Heppel, P. R. Whitfeld and R. Markham, *Biochem. J.*, **60**, 8 (1955).

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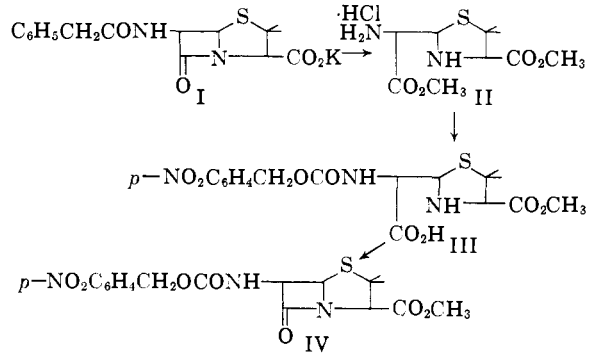
THE CHEMICAL CONVERSION OF PENICILLIN G INTO A BIOLOGICALLY ACTIVE SYNTHETIC PENICILLIN SERIES

Sir:

We wish to report the chemical removal of the phenylacetic acid side chain from penicillin G (I) to form compound II, thus opening up a promising route for the preparation of synthetic penicillins. Compound II has been converted into an intermediate (III) in a total synthetic series, thereby completing by relay a transition between a "natural" penicillin and a biologically active synthetic penicillin not directly available previously by fermentation.

Potassium benzylpenicillinate (penicillin G, potassium salt) was treated with methanol containing a catalytic amount of triethylamine to form potassium α-methyl D-α-benzylpenicilloate, which was converted directly in 22% over-all yield by reaction with methanolic hydrogen chloride to methyl D-α-4-carbomethoxy-5,5-dimethyl-α-amino-2-thiazolidineacetate hydrochloride (II), $C_{10}H_{19}ClN_2O_4S$, m.p. 174–175° dec., $\alpha^{25}D$ + 104° (C, 1.34 in methanol) [found: C, 40.28; H, 6.38; N, 9.34].

It was established that no change in configuration took place during the methanolysis by the conversion of II to the known[1] dimethyl D-α-benzylpenicilloate [m.p. 87–88°, $\alpha^{25}D$ + 82.2°] in 72% yield with phenylacetyl chloride and triethylamine. Identity with an authentic sample was established by comparison of optical rotation, melting point, mixed melting point and infrared spectra (KBr).



(1) H. T. Clarke, J. R. Johnson and R. Robinson, editors, "The Chemistry of Penicillin," Princeton University Press, Princeton, New Jersey, 1949, p. 613.

Acylation of the primary amine grouping in II was accomplished with *p*-nitrobenzyl chloroformate[2] and triethylamine to yield methyl-D-α-4-carbomethoxy-5,5-dimethyl-α-(carbo-*p*-nitrobenzyloxyamido)-thiazolidineacetate. Saponification of the α-methyl ester grouping with one equivalent of sodium hydroxide and crystallization from acetone–ether yielded D-α-4-carbomethoxy-5,5-dimethyl-α-(carbo-*p*-nitrobenzyloxyamido)-thiazolidineacetic acid (III), $C_{17}H_{21}N_3O_8S$; m.p. 138–139°, $\alpha^{27}D$ + 60.9° (C, 1.17 in methanol). [Found, C, 47.57; H, 4.98; N, 9.83.] The infrared spectrum (KBr) of this acid was identical to that of the corresponding DL-derivative prepared by total synthesis.[3] The infrared spectrum of the hydrochloride of III, m.p. 187–188°, [found, C, 44.39; H, 5.25; N, 8.84] was identical to that of the corresponding DL-hydrochloride when measured in dimethyl sulfoxide solution.

We are indebted to Bristol Laboratories of Syracuse, N. Y., for financial support and for bioassays.

(2) F. H. Carpenter and D. T. Gish, THIS JOURNAL, **74**, 3818 (1952).

(3) The DL form of this compound has been prepared in this laboratory by G. C. Stelakatos using the general procedure of J. C. Sheehan and P. A. Cruickshank (THIS JOURNAL, **78**, 3683 (1956)). DL-III has been cyclized to methyl DL-6-(carbo-*p*-nitrobenzyloxyamido)-penicillanate in 38% yield.

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THE CONFIGURATION OF MOLECULAR COMPLEXES

Sir:

Orgel and Mulliken[1] have suggested that molecular complexes may involve a variety of different relative orientations of the donor and acceptor. In order to determine the geometrical restrictions on charge-transfer interactions in molecular complexes, we synthesized and determined the spectra of a series of molecules having both the donor and acceptor groups in the same molecule and in a relatively fixed orientation with respect to each other. The donor in each case was the *p*-aminophenyl system and the acceptor, the *p*-nitrophenyl group. The compounds studied were 4-amino-4′-nitrodiphenylmethane (I), m.p. 96.9–97.5° (found for $C_{13}H_{12}O_2N_2$: C, 68.55; H, 5.21); 4-amino-4′-nitrobibenzyl (II), m.p. 136.8–137.5° (found for $C_{14}H_{14}O_2N_2$: C, 69.18; H, 5.56); 4-amino-4′-nitro-α,ω-diphenylpropane (III), m.p. 92.0–92.7°, (found for $C_{15}H_{16}O_2N_2$: C, 70.52; H, 6.40); *cis*-1-(4-aminophenyl)-2-(4-nitrophenyl)-cyclopentane (IV), m.p. 112.2–113.0° (found for $C_{17}H_{18}O_2N_2$: C, 72.25; H, 6.67); and *trans*-1-(4-aminophenyl)-2-(4-nitrophenyl)-cyclopentane (V), m.p. 76.5–77.3° (found for $C_{17}H_{18}O_2N_2$: C, 72.52; H, 6.53).

Compound I involves a 2.52 Å. separation for the 1-atoms of the ring and a 7.02 Å. separation for the 4-atoms. The aromatic rings in II and III can have an infinite variety of orientations with respect to each other because of rotation about the chain bonds. In IV the aromatic nuclei are practically

(1) L. E. Orgel and R. S. Mulliken, THIS JOURNAL, **79**, 4839 (1957).