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Synthesis of Benzyl 6-Oxopenicillanate[1] and Derivatives. I

Sir:

We wish to report the synthesis of benzyl 6-oxopenicillanate (II) and illustrate the potential of this type of substance as a source of new antibacterial agents, for example by transformation to 6β-(phenoxyacetoxy)penicillanic acid (VI)—an oxygen analog, including stereochemistry, of penicillin V.

Benzyl 6-α-hydroxypenicillanate (I) was prepared from 6-aminopenicillanic acid by the method of Hauser and Sigg.[2] Oxidation of I by diisopropylcarbodiimide in methyl sulfoxide[3] gave benzyl 6-oxopenicillanate[4] (II) which was purified by column chromatography: ir (film) 1830, 1780, 1735 cm^{-1}; nmr ($DCCl_3$) δ 7.4 (s, 5 H), 5.85 (s, 1 H), 5.3 (s, 2 H), 4.87 (s, 1 H), 1.55–1.62 (d, 6 H). The contaminant originating from diisopropylcarbodiimide was removed with difficulty. Water-soluble carbodiimides such as 1-ethyl-3-(dimethylamino)carbodiimide hydrochloride and methiodide are not promising for this oxidation. Under these conditions no benzyl 6-oxopenicillanate (II) could be isolated. Only the starting hydroxy compound I was recovered.

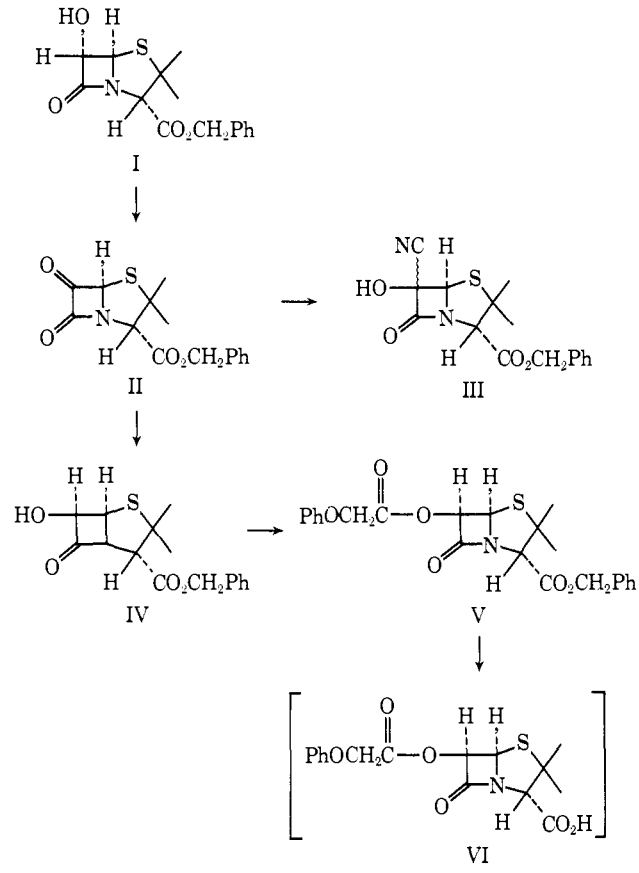
Treatment of benzyl 6-oxopenicillanate (II) with liquid hydrogen cyanide immediately gave a solid. After washing with benzene and recrystallization from methylene chloride, a colorless, crystalline cyanohydrin[4] (III) of II was obtained [mp 148–162° dec; ir (KBr) 3300, 1790, 1730 cm^{-1}; nmr (acetone-d_6) δ 7.5 (s, 5 H), 5.9 (s, 1 H), 5.35 (s, 2 H), 4.7 (s, 1 H), 3.1 (s, 1.5 H), 1.63 (s, 3 H), 1.50 (s, 3 H)].

Reduction of II by potassium borohydride in aqueous alcohol gave only one hydroxy isomer, namely, benzyl 6-β-hydroxypenicillanate (IV). The product was isolated by column chromatography and purified by recrystallization [ir (KBr) 3420, 1775, 1725 cm^{-1}]. Table I compares some of the physical properties of the 6-α- and 6-β-hydroxy isomers I and IV.

Table I. Physical Properties of I and IV

	I (lit.)[2]	IV
Mp, °C	157–160	97.5–98.5
$[\alpha]^{25}D$, deg	191 (*c* 0.53, methanol)	222 (*c* 0.87 methanol)
Nmr		
C_5	δ 5.3, d, J = 1.5 Hz	δ 5.65, d, J = 4.0 Hz
C_6	δ 4.83, m	δ 5.1–5.3, q, J = 4.0, 11.0 Hz
OH	δ 4.3, s, br	δ 3.2–3.5, d, br, J = 11.0 Hz

(1) See J. C. Sheehan, K. R. Henery-Logan, and D. A. Johnson, *J. Amer. Chem. Soc.*, **75**, 3292 (1953) for naming system.
(2) D. Hauser and H. P. Sigg, *Helv. Chim. Acta*, **50**, 1327 (1967).
(3) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **85**, 3027 (1963).
(4) All new compounds gave satisfactory analytical data.



Benzyl 6-β-hydroxypenicillanate (IV) was phenoxyacetylated to give benzyl 6-β-(phenoxyacetoxy)penicillanate[4] (V). The compound was purified by column chromatography and isolated as an oil [ir (film) 1790, 1740, 1600, 1500 cm^{-1}; nmr ($DCCl_3$) δ 7.35 (s, 5 H), 7.4–6.7 (m, 5 H), 5.8–5.6 (q, 2 H, J = 4 Hz), 5.25 (s, 2 H), 4.7 (s, 2 H), 4.55 (s, 1 H), 1.6 (s, 3 H), 1.45 (s, 3 H)].[5]

Compounds IV and VI[6] were submitted for bioassay and showed little or no bioactivity against a variety of organisms.[8]

(5) This work was assisted financially by the Sloan Basic Research Fund.
(6) Hydrogenolysis of V over 5% Pd/$BaCO_3$ in ethyl acetate for 8 hr[2] gave a pale yellow syrup containing 6-β-(phenoxyacetoxy)penicillanic acid (VI) based on spectroscopic data (ir, nmr). Attempts to remove all contaminants from this material by column chromatography were unsuccessful due to strong adsorption of the acid on the support. The acid does not readily form a crystalline *N*-ethylpiperidine salt[7] analogous to penicillin G and V.
(7) J. C. Sheehan, W. J. Mader, and D. J. Cram, *J. Amer. Chem. Soc.*, **68**, 2407 (1946).
(8) Bristol Laboratories, Division of Bristol-Myers Co., Syracuse, N. Y.

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Negatively Charged Electrophiles. Acylation of Strong Nucleophiles by Enolate Salts of β-Keto Esters

Sir:

Poly-β-carbonyl compounds are presently of interest because their reactions bear a relationship to the biosynthesis of phenolic natural products.[1] We have de-

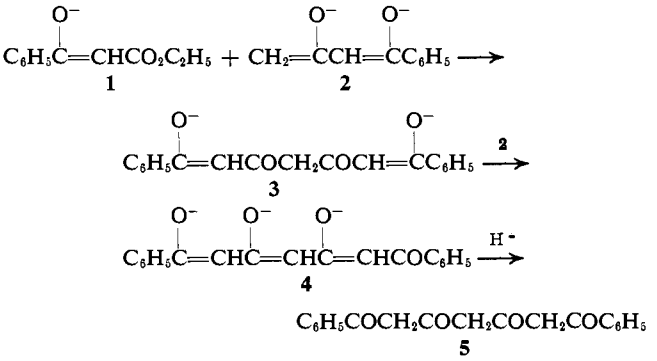
(1) For a review, see T. Money, *Chem. Rev.*, **70**, 553 (1970).

veloped methods for the preparation of some of the lower members of this series; these procedures involve terminal acylation and carboxylation of multiple anions of 2,4-di-, 2,4,6-tri-, and 2,4,6,8-tetraketones.[2-7] The highest members to be prepared thus far are a 3,5,7,9-tetraketo acid and a 1,3,5,7,9-pentaketone.[7] These procedures constitute a linear synthetic method[8] and formally require n steps to assemble a molecule containing $n + 1$ carbonyl groups. This, coupled with the fact that some of the condensation steps suffer from poor yields and difficult work-ups, restricts their practicality for preparation of higher poly-β-carbonyl compounds.

A better approach would be the introduction of two carbonyl groups at a time, thereby halving the number of synthetic steps. The use of β-keto esters (or equivalent species) as acylating agents would serve this purpose. However, the acidic α-methylene group in these compounds provides an apparent barrier to use in Claisen-type condensations, because ionization occurs under the reaction conditions. Several workers have addressed themselves to this problem, all of them masking the ketone as a ketal or enol ether in order to reduce the acidity of the methylene group.[9-12] These efforts have been successful to the extent that several protected tetracarbonyl compounds have been synthesized, but methods have not yet been found for removing the masking groups without concomitantly cyclizing the resulting tetracarbonyl compounds.

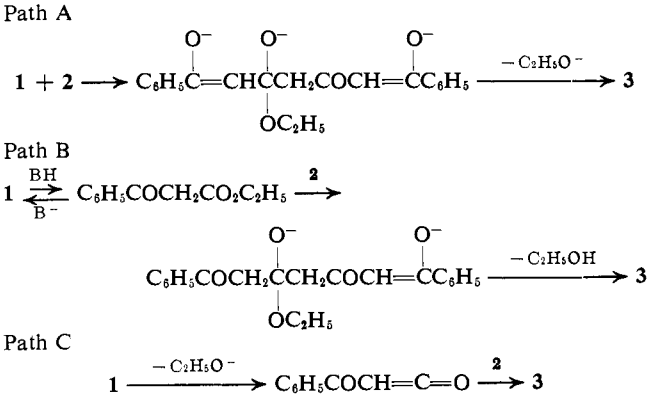
In view of these results, we sought to ascertain whether the enolate anions formed from unprotected β-keto esters would be able to serve as acylating agents if sufficiently powerful nucleophiles were employed. Previous examples of anion–anion reactions include the second ionization of diketones and the second and third ionizations of triketones by strong bases.[2-6] Most of the anion–anion reactions that have been observed are proton transfer processes rather than condensations.[13]

The sodium salt **1** of ethyl benzoylacetate was formed by treatment of the keto ester with sodium hydride in tetrahydrofuran. The solution was added to a solution of 2 equiv of dilithiobenzoylacetone (**2**) in tetrahydrofuran (prepared by treatment of the diketone with a twofold amount of lithium diisopropylamide). Two equivalents of **2** was employed to provide for the possibility that the methylene group at the 5 position of the condensation product **3** would be ionized by **2** to give trianion **4**. The faintly turbid mixture was stirred at room temperature for 48 hr, evaporated *in vacuo*, neutralized with cold, dilute hydrochloric acid, and extracted with ether. Chromatography of the crude product on silica gel (elution with ether–hexane mixtures) gave 51% of tetraketone **5**.[4]



Several mechanisms can be proposed for the acylation reaction. One is that it simply proceeds by attack of dianion **2** on the negatively charged ester **1** to give a tetrahedral intermediate which decomposes to **3** (Scheme I, path A). The electrostatic barrier to this

Scheme I



condensation process is substantial but will be reduced in tetrahydrofuran by the close association of the enolate anions with metal cations. It is noteworthy that the reaction of **2** with **1** is far slower than the reaction of **2** with uncharged esters.[2,4,7] A second mechanism is that anion **1** is unreactive and that acylation occurs *via* the minute amount of un-ionized β-keto ester in equilibrium with **1** (path B). This process can also be expected to be very slow. A third possibility is that **1** eliminates ethoxide ion to give an acylketene which acylates **2** (path C). The last process receives considerable support from studies of the hydrolysis of β-keto esters and related compounds, where kinetic data suggest the intermediacy of acylketenes.[14,15]

In attempts to find further examples of the reaction, no difficulty was experienced in the preparation of pentaketone **6**[7] (41%) by acylation of trilithio-1-phenyl-1,3,5-hexanetrione with **1**; however, treatment of lithioacetophenone with **1** failed to give a detectable amount of triketone **7**.[2] This failure with lithioacetophenone, which is a weaker nucleophile than **2** or **6**, suggests that the condensation of **1** proceeds mainly by path A, or possibly path B, rather than by path C.

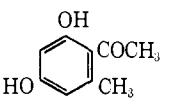
(2) T. M. Harris and C. R. Hauser, *J. Amer. Chem. Soc.*, **84**, 1750 (1962).
(3) T. M. Harris and C. M. Harris, *J. Org. Chem.*, **31**, 1032 (1966).
(4) K. G. Hampton, T. M. Harris, C. M. Harris, and C. R. Hauser, *ibid.*, **30**, 4263 (1965).
(5) T. M. Harris and R. L. Carney, *J. Amer. Chem. Soc.*, **89**, 6734 (1967).
(6) T. T. Howarth, G. P. Murphy, and T. M. Harris, *ibid.*, **91**, 517 (1969).
(7) T. M. Harris and G. P. Murphy, *ibid.*, **93**, 6708 (1971).
(8) See L. Velluz, J. Valls, and G. Nominé, *Angew. Chem., Int. Ed. Engl.*, **4**, 181 (1965).
(9) F. M. Dean, C. Stealink, and J. Tetaz, *J. Chem. Soc.*, 3386 (1958).
(10) H. Stetter and S. Vestner, *Chem. Ber.*, **97**, 169 (1964).
(11) U. Schmidt and M. Schwochau, *ibid.*, **97**, 1649 (1964); *Monatsh. Chem.*, **98**, 1492 (1967).
(12) G. Bram, *Tetrahedron Lett.*, 4069 (1967).
(13) For one example of an anion–anion condensation, see A. F. Hegarty and T. C. Bruice, *J. Amer. Chem. Soc.*, **91**, 4924 (1969).
(14) R. F. Pratt and T. C. Bruice, *ibid.*, **92**, 5956 (1970).
(15) P. S. Tobias and F. J. Kézdy, *ibid.*, **91**, 5171 (1969).

$C_6H_5COCH_2COCH_2COCH_2COCH_2COC_6H_5$
6

$C_6H_5COCH_2COCH_2COC_6H_5$
7

The utility of the β-keto ester condensation reaction for synthesis of large polycarbonyl compounds will depend upon its applicability with aliphatic keto esters, especially with acetoacetic ester. The sodium salt of methyl acetoacetate was treated with dianion **2** and with dilithioacetylacetone to give tetraketones **8**[7] and **9**, respectively, in yields of 30 and 31%. The structure of **9**, mp 38–42°, was supported by spectra and elemental analyses and by cyclization to resorcinol **10**.[10]

$CH_3COCH_2COCH_2COCH_2COR$
8, R = C_6H_5
9, R = CH_3


10

Self-condensation of methyl acetoacetate was not observed in either of these acylation reactions, indicating that proton abstraction from the 4 position of methyl sodioacetoacetate by diketone dianions is not a significant reaction under the present conditions.[16]

The reactions of enolate salts of β-keto esters with strong nucleophiles represent a generally unrecognized, if not novel, class of anionic condensation reactions. We are presently studying the use of these acylating agents for synthesis of poly-β-carbonyl compounds containing six, seven, and more carbonyl groups, as well as surveying the reactions of other negatively charged electrophiles to determine their potential usefulness in organic synthesis.

(16) See K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **28**, 1946 (1963).

(17) Career Development Awardee of the U. S. Public Health Service (GM-27103). Research support by the U. S. Public Health Service (GM-12848) is gratefully acknowledged.

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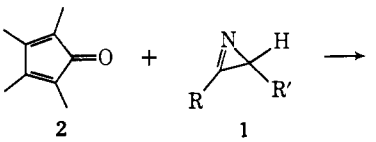
The Mechanism of Azepine Formation in the Cycloaddition of 1-Azirines to Cyclopentadienones[1]

Sir:

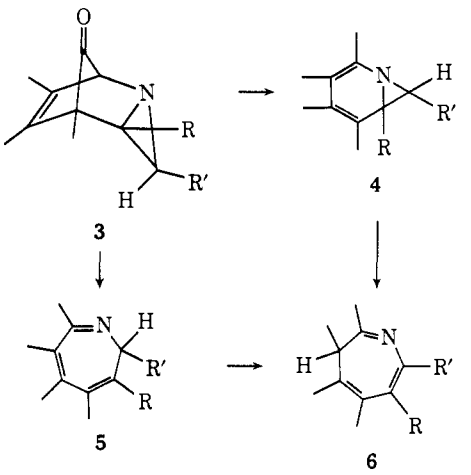
Recently we described the cycloaddition of 1-azirines **1** to cyclopentadienones **2** to give 3*H*-azepines **6**.[2] A possible mechanism for this reaction was proposed[2,3] involving first a Diels–Alder type addition to produce **3** followed by formation of an azanorcaradiene intermediate **4**, which then undergoes a 1,5-hydrogen shift.[2] An analogy to step **3** → **4** is provided by the facile loss of CO in the conversion of norbornadien-7-ones to benzenes.[4]

An equally plausible mechanism involves opening of the aziridine ring in **3** with simultaneous loss of CO. This would lead to a 2*H*-azepine **5** which can be converted into **6** by a 1,5-hydrogen shift.

(1) Cycloadditions. XI. For the previous paper in this series, see A. Hassner, M. J. Haddadin, and A. B. Levy, *Tetrahedron Lett.*, in press.
(2) D. J. Anderson and A. Hassner, *J. Amer. Chem. Soc.*, **93**, 4339 (1971).
(3) V. Nair, *J. Org. Chem.*, **37**, 802 (1972).
(4) S. Yankelevich and B. Fuchs, *Tetrahedron Lett.*, 4945 (1967), and references therein.

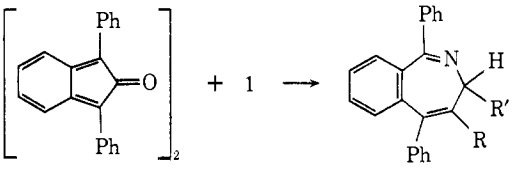

2 **1**

a, R = C_6H_5; R′ = H
b, R = C_6H_5; R′ = Me
c, R = C_6H_5; R′ = C_6H_5
d, R = Et; R′ = Et


3 **4** **5** **6**

A differentiation between these two pathways should be possible if one chooses a substrate in which participation by the double bond during the loss of CO in step **3** → **4** is energetically unfavorable. The benzocyclopentadienone[5] **7** represents such a case, in which formation of an azanorcaradiene and ultimately of a 3*H*-azepine requires disruption of benzene resonance.

Indeed, cycloaddition of azirines **1a–c** to 1,3-diphenylinden-2-one (**7**) proceeded cleanly to produce the 2*H*-azepines **8a–c**. Further heating of **8** at 260° did not


7 **8**

a, R = Ph; R′ = H
b, R = Ph; R′ = CH_3
c, R,R′ = Ph

cause isomerization to 3*H*-azepines. These results, however, do not mitigate against a 3*H*-azepine as a primary product which had isomerized to the more stable **8**.

Since the delocalization energy in the phenanthrene center ring is much lower than in benzene, we investigated the cycloaddition of phencyclone **9** with azirines **1a–d**. The reaction was carried out in refluxing toluene or xylene and gave the 2*H*-azepines **10** in 50–80% yield. The structure of azepines **8** and **10** was immediately apparent from their nmr spectra. For example, in **8b** and **10b** the azepine ring proton appeared as a quartet (J = 6.5 Hz) and the methyl group as a doublet (J = 6.5 Hz). Similarly, in **8a** and **10a** the two azepine ring protons appeared as two doublets (J = 9 and 10 Hz, respectively, for **8a** and **10a**) at 25°, indicating slow inversion of the 2*H*-azepine ring on the nmr time scale.

(5) J. M. Holland and D. W. Jones, *J. Chem. Soc. C*, 608 (1971).