Tetracyclines. VI. Some New Aspects in the Chemistry of Oxazolones and Their Sulfur Analogs

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Abstract: Several 4-alkylidene-3-oxazalin-5-ones ("unsaturated azlactones") and some sulfur analogs react with dimethyl 3-oxoglutarate in the presence of base to form derivatives of 6-aminocyclohexane-1,3-dione. Some examples and applications of this reaction are described.

The chemistry of oxazolones has riveted the attention of organic chemists since the initial detection of a member of this class of compounds in 1883.[1] A very extensive reinvestigation of these compounds was undertaken during the joint British–American development of penicillin chemistry.[2] However, despite these efforts, a clean and simple reaction remained undetected until recently.[3] This reaction can be illustrated by the following example.

If equimolar amounts of the well-known 2-phenyl-4-benzylidene-3-oxazolin-5-one (**1**) and the sodium or potassium salt of dimethyl 3-oxoglutarate (**2**) are reacted at room temperature in a nonprotic solvent such as tetrahydrofuran, the aminodihydroresorcinol derivative **3** is formed in high yield.[4]

The structure of **3** follows unequivocally from its elemental composition and from a comparison of its ultraviolet and infrared absorption spectra with the corresponding spectra of compound **5**, whose structure is well established.[5]

As can be seen from Table I, the characteristic ultraviolet spectra of **3** and **5** in alkaline and acidic media are very similar, and their infrared spectra differ only in areas where such differences are to be expected, due to the benzamido group in **3**. In order to provide further evidence for the structure of **3**, this compound was saponified and decarboxylated to **4** whose ultraviolet spectra were then compared with the corresponding spectra of 5-phenylcyclohexane-1,3-dione (**6**). As Table I indicates, this spectral comparison again proves the presence of the dihydroresorcinol chromophore.

Table I. Ultraviolet Spectra

Compd	In 0.01 *N* methanol–NaOH λ_{max}, mμ	ϵ	In 0.01 *N* methanol–HCl λ_{max}, mμ	ϵ
3	277	20,500	257	16,100
5	276	18,300	254–255	13,500
4	284	28,300	255	21,700
6	283	27,800	255	22,200

Infrared Spectra in $CHCl_3$ (10% solution) after Complete Equilibration

	λ_{max}, μ						
3	2.95	3.37	3.44	5.78	5.94	6.00	6.33
5	...	3.38	3.45	5.77	...	6.00	6.35

The mechanism of the reaction leading to **3** has not been investigated. It was our belief, however, that **2** would undergo a Michael addition to i[6] and that the Michael adduct would then form **3** by closing to the dihydroresorcinol ring, with simultaneous, irreversible opening of the oxazolone ring.[6]

i

(1) J. Plöchl, *Ber.*, **16**, 2815 (1883); E. Erlenmeyer, *ibid.*, **33**, 2036 (1900); *Ann.*, **337**, 265 (1904).

(2) H. T. Clarke, J. R. Johnson, and R. Robinson, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949.

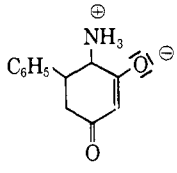
(3) Preliminary communications: H. Muxfeldt, Lecture at the 8th National Medicinal Chemistry Symposium, Boulder, Colo., June 20, 1962; IUPAC Symposium, Kyoto, Japan, 1964, Abstracts, p 162; *Antimicrobial Agents Chemotherapy*, 977 (1965); H. Muxfeldt and G. Hardtmann, *Ann.*, **669**, 113 (1963).

(4) The formulas of enolizable compounds in this article do not represent magnitude and direction of enolization nor configuration at equilibratable asymmetric centers.

(5) H. Muxfeldt, G. Grethe, and K. Uhlig, *Ber.*, **96**, 2943 (1963).

(6) i can be isolated if **1** is treated with **2** in the presence of catalytic amounts of triethylamine and it can also be converted into **3** with potassium *t*-butoxide (see Experimental Section).

The generality and preparative usefulness of the reaction have been examined. First, the preparation of **7** or its hydrochloride, by saponification of the amide function in **3** or **4**, was tried. However, due to the relatively labile β-diketone moieties in these compounds, all attempts to prepare **7** by acid- or base-catalyzed saponification proved fruitless. It was possible, however, to prepare **8** by treatment of **3** with Meerwein's reagent,[7] and subsequent aqueous work-up of the reaction mixture without isolation of the intermediate imino ether **9**. The structure of **8** and its corresponding hydrochloride follow from the elemental composition and the nmr spectrum. In addition, **8** shows ultraviolet spectra in acidic and alkaline solution similar to those of **3**. However, the most characteristic feature is that in neutral solution **8** shows an ultraviolet spectrum identical with that in alkaline solution. This indicates that the free base **8** exists in neutral solution as a betaine, as shown in formula **8**.



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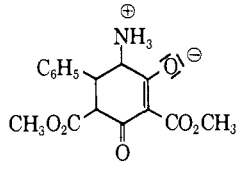

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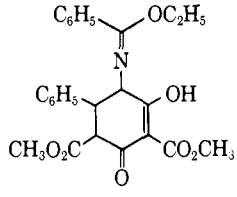
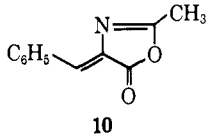


9

Although free amines were available by this procedure, we were still interested in making aminodihydroresorcinols by direct acid hydrolysis of the corresponding amide. Therefore oxazolone **10**[8] was condensed with dimethyl 3-oxoglutarate (**2**). The aminodihydroresorcinol derivative **11** was formed and could be well characterized by its elemental composition and its ultraviolet spectra in alkaline and acidic solutions. Unlike **3**, the hydrolysis of the amide function in **11** could be accomplished easily. Heating of **11** in a mixture of hydrochloric and acetic acids led directly to the hydrochloride of **7** which was characterized by its analytical and spectral data. In acidic or alkaline solution the spectra of **7** were very similar to those of **6**, whereas in neutral solution the spectrum was again identical with that in alkaline solution, indicating the presence of the betaine structure, as shown in formula **7**.



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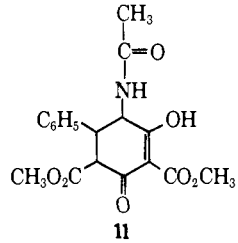
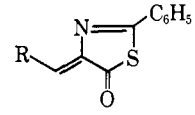
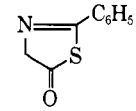


11

As a further model system, the condensation of 2-phenyl-4-benzylidene-3-thiazolin-5-one (**12a**) with dimethyl 3-oxoglutarate (**2**) was investigated. **12a** is known from the literature[9] but its structure has not been proven unequivocally. Furthermore, the method of preparing it is probably not a general one for the preparation of 2-phenyl-4-alkylidene-3-thiazolin-5-ones. Therefore 2-phenyl-3-thiazolin-5-one (**13**) was made for the purpose of condensing it with aldehydes to make compounds of the general structure **12** available.



12, R = alkyl or aryl
12a, R = C_6H_5

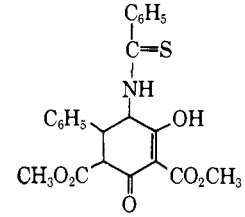


13

The preparation of **13** was very easy; treatment of thiobenzoylglycine[10] with phosphorus tribromide in dioxane led to a rapid precipitation of the hydrobromide of **13**. This hydrobromide could then be converted into **13** by treatment with sodium acetate. Compound **13** proved to be a colorless, crystalline, very labile compound which could be purified to analytical purity only by sublimation *in vacuo*. Within a few days even a pure sample decomposed into a red oil. However, **13** was stable enough to be well characterized and to be condensed with several selected aldehydes in tetrahydrofuran with triethylamine as a catalyst and magnesium sulfate as a water-binding reagent. The instability of **13** required that it be reacted immediately after its preparation. Therefore the following alternate preparation is recommended. Thiobenzoylglycine is treated with 1 equiv of cyclohexylcarbodiimide, and, after removal of the dicyclohexylurea, the solution contains crude **13** which can be used for condensation with aldehydes without further purification.

By condensing either crude or pure **13** with benzaldehyde, **12a** is formed in high yield. The melting point of **12a** compares well with that reported in the literature[9] and its structure follows clearly from its analytical and very characteristic infrared and ultraviolet spectra.

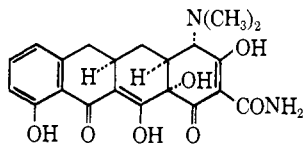
Condensation of **12a** with dimethyl 3-oxoglutarate (**2**) leads cleanly to the aminodihydroresorcinol derivative **15**. This compound shows the same ultraviolet spectra in acidic and basic solution as **5** when allowance is made for the additional thiobenzamide chromophore in **15**.



15

We now felt we could start to apply the oxazolone reaction to the synthesis of several natural products. In this article we will discuss some experiments preliminary to the now completed total synthesis of 6-deoxy-6-demethyltetracycline (**16**).[11,12]

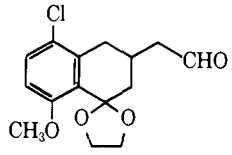
(7) H. Meerwein, G. Hinz, P. Hofman, E. Kroning, and E. Pfeil, *J. Prakt. Chem.*, [2] **147**, 257 (1937).
(8) R. M. Herbst and D. Shemin, *Org. Syn.*, **19**, 11 (1943).
(9) H. Behringer and H. W. Stein, *Ber.*, **82**, 209 (1949).
(10) An improved procedure for its preparation is described in the Experimental Section.



16

Our purpose was to condense the aldehyde **17**[11,13] with compounds of type **18**.

This article describes first a series of reactions which resulted from the condensation of **17** with **18b**, and then the condensation of **17** with **18c** and subsequent reactions.[14]



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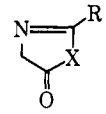
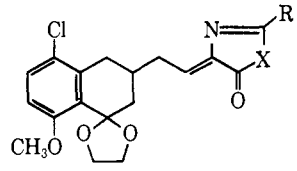


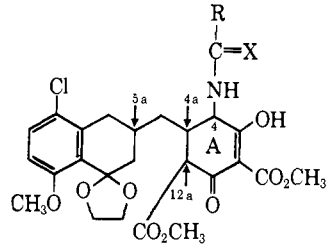
18a, X = O; R = C_6H_5
b, X = S; R = C_6H_5
c, X = O; R = CH_3

Condensation of the aldehyde **17** and the thiazolone **18b** was accomplished easily. Crystalline **19b** was obtained in 65% yield.[15] Analytical and spectral data are in complete agreement with structure **19a**.



19a, R = C_6H_5; X = S
b, R = CH_3; X = O

Condensation of **19a** with dimethyl 3-oxoglutarate in tetrahydrofuran with potassium *t*-butoxide as base proceeded smoothly in the desired manner. Crystalline **20a** was isolated in reasonable yield. Its structure could be proved by elemental analysis and ultraviolet spectra which, in acidic and basic solutions, again very much resembled the corresponding spectra of **3** and **5**.

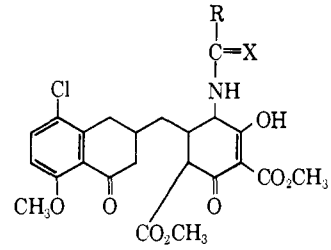


20a, R = C_6H_5; X = S
b, R = CH_3; X = O

One disadvantage of this preliminary approach to the use of the oxazolone reaction for a synthesis of 6-deoxy-6-demethyltetracycline (**16**) was that at C_{4a} a new asymmetric center was formed with no stereochemical control whatsoever.

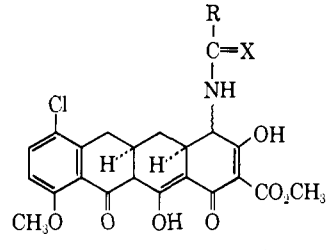
Attempts to separate the two C_{4a} epimers of **20a** were fruitless, not only because the mixture was tautomeric, but because the two asymmetric centers at C_4 and C_{12a} equilibrate with great ease.[16] However, from former experience[16] we assumed that only the isomer with *syn*-positioned hydrogens at C_{4a} and C_{5a}, in a conformation as drawn in formula **20a**, would undergo cyclization in a later step. We therefore had good reason to believe that a separation would be accomplished much more easily after the cyclization step, *i.e.*, separation of cyclized from noncyclized material.

When **20a** was deketalized with acetone–1 *N* hydrochloric acid (2:1), at room temperature, crystalline **21a** precipitated from the reaction mixture in 39% yield. This compound was characterized by its elemental composition and ultraviolet spectra.



21a, R = C_6H_5; X = S
b, R = CH_3; X = O

Cyclization of **21a** with sodium hydride in N,N-dimethylformamide gave **22a** in low yield. This compound could be isolated in crystalline form after chromatography. The elemental analysis was in complete agreement with strucutre **22a**. The visible and ultraviolet spectrum in 0.1 *N* sodium borate solution showed an absorption curve very characteristic of 12a-deoxytetracyclines, with its longest wavelength absorption maximum at 455 mμ.[16] However, attempts to desulfurize the thiobenzoyl group in **22a** with Raney nickel were unsuccessful.



22a, R = C_6H_5; X = S
b, R = CH_3; X = O

Therefore we tried to prepare **22b** in order to remove the N-acetyl group (and probably the carbomethoxy group also) by acid hydrolysis. This required condensation of aldehyde **17** with the oxazolone **18c**. It was known, however, that **18c** is a very labile compound which has never been prepared in pure form.[17] Furthermore, no condensation product of an aliphatic aldehyde had been prepared with **18c**, as far as was known. We were able to show that it was possible to condense **17** with **18c**, and then trap the labile condensa-

(11) H. Muxfeldt and W. Rogalski, *J. Am. Chem. Soc.*, **87**, 933 (1965).

(12) Before we completed our synthesis of 6-deoxy-6-demethyltetracycline (**16**), a synthesis using a different approach was accomplished by L. H. Conover, K. Butler, J. D. Johnston, J. J. Korst, and R. B. Woodward, *ibid.*, **84**, 3222 (1962).

(13) H. Muxfeldt, E. Jacobs, and K. Uhlig, *Ber.*, **95**, 2901 (1962).

(14) The condensation of **17** with **18a** and following reactions will be the subject of another paper.

(15) The configuration of the newly formed double bond in **19a** is unknown.

(16) H. Muxfeldt, W. Rogalski, and K. Striegler, *Ber.*, **95**, 2581 (1962).

(17) H. E. Carter, *Org. Reactions*, **3**, 198 (1946).

tion product **19b** with dimethyl 3-oxoglutarate, by formation of **20b**. This series of reactions was accomplished in the following way. The aldehyde **17** and N-acetylglycine were treated with dicyclohexylcarbodiimide and a catalytic amount of triethylamine. Dimethyl 3-oxoglutarate and potassium *t*-butoxide were then added, and a crystalline potassium salt of **20b** was isolated. Compound **20b** was deketalized to **21b** which was cyclized with sodium hydride to tetracyclic **22b** in 7.5% yield.

It was at this time that another version of the oxazolone reaction leading to a total synthesis of 6-deoxy-6-demethyltetracycline (**16**) was detected.[11] Since this variation of the oxazolone reaction led to a tetracyclic intermediate in 82% yield, no further attempts to improve the yield of **22b** were made and the approach described in this article was discontinued.

Experimental Section[18]

2,4-Dicarbomethoxy-4-phenyl-5-benzamidocyclohexane-1,3-dione (3). Potassium *t*-butoxide (14.8 g) was added gradually to a stirred solution of 2-phenyl-4-benzylidene-3-oxazolin-5-one (**1**) (30 g) and dimethyl 3-oxoglutarate (**2**) (25.2 g), in freshly prepared analytical grade tetrahydrofuran (450 ml). Shortly after this, the mixture became cloudy and within 10 min thickened to such an extent that it could no longer be stirred. The mixture was left overnight and then dissolved in 1 l. of water. The clear, yellowish solution was acidified with dilute HCl and extracted thrice with chloroform. The combined extracts were washed with water and dried over sodium sulfate, and the solvent was evaporated *in vacuo*. The oily residue was triturated with small amounts of methanol and ether was added. The mixture was left in a freezer for 10 hr and the crystals (43.9 g) were collected. A second fraction (4.1 g) was isolated from the mother liquors, total yield 48 g (94%) of a stereoisomeric and tautomeric mixture of **1**. This mixture was analyzed without further purification; melting range 121–217°.

Anal. Calcd for $C_{23}H_{21}NO_7$: C, 65.24; H, 5.00; N, 3.31; mol wt, 423.4. Found: C, 65.34; H, 5.18; N, 3.23.

The ultraviolet spectrum showed $\lambda_{max}^{0.01\,N\,methanol-NaOH}$ 277 mμ (ε 20,500); $\lambda_{max}^{0.01\,N\,methanol-HCl}$ 257 mμ (ε 16,100).

5-Phenyl-6-benzamidocyclohexane-1,3-dione (4). A suspension of **3** (10 g) in a 5% solution of barium hydroxide in water was heated on a steam bath for 5 hr with stirring. The mixture was then acidified with 10% HCl and heated for 1 hr on a steam bath. After the solution had cooled, it was filtered, and the filter residue was dissolved in 5% NaOH. The clear solution was acidified with 10% HCl and immediately extracted with chloroform. The chloroform extract was quickly washed with water, dried over sodium sulfate, and filtered. In a short time **4** began to crystallize. After the crystals were collected, two further fractions were obtained by concentrating the mother liquors; yield 6.3 g (89%), mp 133–135°.

Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.23; H, 5.57; N, 4.56; mol wt, 307.3. Found: C, 74.14; H, 5.60; N, 4.56.

The ultraviolet spectrum showed $\lambda_{max}^{0.01\,N\,methanol-NaOH}$ 284 mμ (ε 28,300); $\lambda_{max}^{0.01\,N\,methanol-HCl}$ 255 mμ (ε 21,700).

Hydrochloride of 5-Phenyl-6-aminocyclohexane-1,3-dione (7). A solution of **11** (12 g) in acetic acid (420 ml) and concentrated HCl (280 ml) was heated on a steam bath for 2 hr. The solvents were removed *in vacuo*, and the solid residue was dissolved in water. The almost clear solution was washed thrice with chloroform, and the water layer was evaporated *in vacuo*. The foamy residue was triturated with small amounts of methanol and ether was added. After a few hours 1.4 g (18%) of the hydrochloride of **7** was collected. The mother liquors contained more hydrochloride of **7** and an enol acetate of **7** ($\lambda_{max}^{0.01\,N\,methanol-NaOH}$ of this mixture 284 and 252 mμ). The residue of the mother liquors was therefore dissolved in 40 ml of 10% HCl and the solution was heated on a steam bath for 2 hr and then evaporated. The residue was treated as described above and a second fraction (1.7 g) of the hydrochloride of **7** was obtained; total yield 3.1 g (39%). An analytical sample was obtained from methanol-ether, mp 220° dec.

Anal. Calcd for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; N, 5.84; Cl, 14.79; mol wt, 239.7. Found: C, 59.93; H, 5.95; N, 5.88; Cl, 15.02.

The ultraviolet spectrum showed $\lambda_{max}^{0.01\,N\,methanol-NaOH}$ 282 mμ (ε 23,900); $\lambda_{max}^{0.01\,N\,methanol-HCl}$ 256 mμ (ε 16,000).

2,4-Dicarbomethoxy-5-phenyl-6-aminocyclohexane-1,3-dione (8). Triethyloxonium fluoroborate[7] (11.6 g) was added under nitrogen to a stirred suspension of **3** (16.1 g) in dry methylene chloride (60 ml). After stirring for 10 hr, a clear solution was observed. This was diluted with methylene chloride (200 ml) and then poured into an ice-cold solution of potassium bicarbonate (6.1 g) in water (200 ml). The mixture was shaken vigorously for 1 min, and the organic layer was separated, washed with ice-cold water, dried over sodium sulfate, and evaporated *in vacuo*. The oily residue (15.1 g) was triturated with small amounts of methanol, and ether was added. Crystalline **8** (1.88 g) was collected. The mother liquor was evaporated and a second fraction of **8** (5.51 g) was isolated from tetrahydrofuran and dioxane (1:1); total yield 7.39 g (61% of **8**). A sample, recrystallized from methanol turned brown above 260° when heated, and melted at 328–330° dec.

Anal. Calcd for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39; mol wt, 319.3. Found: C, 60.26; H, 5.45; N, 4.25.

The ultraviolet spectrum showed $\lambda_{max}^{0.01\,N\,methanol-NaOH}$ 274 mμ (ε 18,300); $\lambda_{max}^{methanol}$ 274 mμ (ε 18,300); $\lambda_{max}^{0.01\,N\,methanol-HCl}$ 255 mμ (ε 13,700). The mother liquors of this material were dissolved in chloroform and the solution was extracted twice with 2 *N* HCl. The combined extracts were evaporated *in vacuo* at 40°, and the oily residue was crystallized from methanol–ether, yield 0.76 g (5.6%) of hydrochloride of **8**, decomposition above 203°.

Anal. Calcd for $C_{16}H_{18}ClNO_6$: C, 54.01; H, 5.10; N, 3.94; Cl, 9.97; mol wt, 355.8. Found: C, 53.87; H, 5.17; N, 4.02; Cl, 9.89.

The ultraviolet spectrum showed $\lambda_{max}^{0.01\,N\,methanol-NaOH}$ 276 mμ (ε 18,100); $\lambda_{max}^{methanol}$ 255 mμ (ε 13,800); $\lambda_{max}^{0.01\,N\,methanol-HCl}$ 255 mμ (ε 13,900). The chloroform layer from the above was evaporated and the residue crystallized from methanol–ether, yield 1.8 g (11%) of starting material (**3**), melting range 175–193°.

Anal. Calcd for $C_{23}H_{21}NO_7$: C, 65.24; H, 5.00; N, 3.31; mol wt, 423.4. Found: C, 65.21; H, 5.18; N, 3.29.

The ultraviolet spectrum showed $\lambda_{max}^{0.01\,N\,methanol-NaOH}$ 273 mμ (ε 22,400).

2,4-Dicarbomethoxy-5-phenyl-6-acetamidocyclohexane-1,3-dione (11). Potassium *t*-butoxide (4.03 g) was added gradually with stirring to a mixture of tetrahydrofuran (80 ml, analytical grade), dimethyl 3-oxoglutarate (**2**) (6.94 g), and **10** (6.2 g). The mixture was kept at room temperature for 12 hr with stirring and then was diluted with water (500 ml). The almost clear solution was washed with ether, acidified with dilute HCl, and extracted thrice with chloroform. The combined extracts were washed with water, dried over sodium sulfate, and evaporated. The oily residue was triturated with small amounts of methanol, and ether was added. After a few hours the crystalline precipitate was collected, yield 7.25 g (61%), melting range 124–169°.

Anal. Calcd for $C_{18}H_{19}NO_7$: C, 59.83; H, 5.30; N, 3.88; mol wt, 361.4. Found: C, 59.46; H, 5.24; N, 3.89.

The ultraviolet spectrum showed $\lambda_{max}^{0.01\,N\,methanol-NaOH}$ 277 mμ (ε 19,500); $\lambda_{max}^{0.01\,N\,methanol-HCl}$ 257 mμ (ε 14,100).

2-Phenyl-3-thiazolin-5-one (13). Thiobenzoylglycine (5 g) was dissolved in freshly distilled dioxane (50 ml), and PBr_3 (5 ml) was added to the solution dropwise with stirring. The hydrobromide of **13** precipitated immediately and was filtered off after 10 min. During the entire procedure the filter residue was kept under dry ether. This residue was then suspended in ether (200 ml) and the suspension was washed with 2 *N* sodium acetate until everything was in solution, and then with water. Benzene (30 ml) was added to the ether solution which was then dried over sodium sulfate and evaporated. The solid crystalline residue of **13** (4.2 g) was purified by sublimation at 55° (0.3 mm), mp 79–81° dec.

Anal. Calcd for C_9H_7NOS: C, 60.99; H, 3.98; N, 7.90; mol wt, 177.2. Found: C, 60.98; H, 4.05; N, 7.61.

The ultraviolet spectrum showed $\lambda\lambda_{max}^{methanol}$ 240 mμ (ε 11,900), 317 mμ (ε 4300), and 359 mμ (ε 3100). The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 3.34, 5.76 (broad), 6.22, 6.32, 6.72, and 6.92 μ.

2-Phenyl-4-benzylidene-3-thiazolin-5-one (12a). Procedure a. To a solution of **13** (4.2 g) in dry benzene (56 ml) and triethylamine (0.25 ml), benzaldehyde (2.38 ml) was added, followed by magnesium sulfate (2 g). This mixture was stirred for 1 hr at room temperature, filtered, and evaporated *in vacuo*. The oily, brownish red residue crystallized on addition of ether, yield 5.57 g, mp 130–132°. An analytical sample was obtained by filtration of **12a**

(18) Melting points were determined on a Kofler micro hot stage and are uncorrected.

through a short column of silica gel (benzene–chloroform–butanol, 1:1:0.02), mp 130–132°.

Anal. Calcd for $C_{16}H_{11}NOS$: C, 72.43; H, 4.18; N, 5.28; S, 12.08; mol wt, 265.3. Found: C, 71.91; H, 4.50; N, 5.40; S, 12.00.

The ultraviolet spectrum showed $\lambda\lambda_{max}^{methanol}$ 242 (10,600), 250 (10,700), 278 (16,500), 307 (8900), and 379 mμ (ε 24,800) with shoulders at 270 (16,000), 319 (8600), 363 (21,000), and 399 mμ (ε 18,000). The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 3.28, 3.32, 5.94 (broad), 6.24, 6.28, 6.37, 6.62, 6.74, and 6.91 μ.

Procedure b. Thiobenzoylglycine (2.90 g) and dicyclohexylcarbodiimide (2.36 g) were stirred in chloroform (50 ml) for 90 min at room temperature. The dicyclohexylurea which precipitated was filtered off and the chloroform evaporated at bath temperature (30°) *in vacuo*. The residue was dissolved in dry ether and the solution filtered free of any trace of dicyclohexylurea. The ether was then removed *in vacuo* and the residue condensed with benzaldehyde as described above.

2,4-Dicarbomethoxy-5-phenyl-6-thiobenzamido-cyclohexane-1,3-dione (15). Potassium *t*-butoxide (1.6 g) was added to a solution of **12a** (3.8 g) in tetrahydrofuran (55 ml, analytical grade) and dimethyl 3-oxoglutarate (**2**) (2.8 ml). The mixture was stirred for 90 min and then diluted with benzene (250 ml) and ether (250 ml). The reaction mixture was extracted thrice with water, and the combined aqueous phases were acidified with dilute HCl and then extracted thrice with chloroform. The combined chloroform extracts were washed with water, dried over sodium sulfate, and evaporated. The oily residue was triturated with ether and the crystalline solid collected after a few hours. The yield of crude **15** was 3.25 g (52%). An analytical sample was obtained by filtering a solution of **15** in chloroform through a column of silica gel, and then recrystallizing the sample from acetone–ether, melting range 153–161°.

Anal. Calcd for $C_{23}H_{21}NO_6S$: C, 62.86; H, 4.82; N, 3.19; S, 7.30; mol wt, 439.5. Found: C, 62.85; H, 4.80; N, 3.24; S, 7.37.

The ultraviolet spectrum showed $\lambda_{max}^{0.01N\,methanol-NaOH}$ 276 mμ (ε 27,800); shoulder at 250 mμ (ε 20,200); $\lambda_{max}^{0.01N\,methanol-HCl}$ 251 mμ (ε 22,800). The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 2.98, 3.30, 5.78, 5.98 (broad), 6.35, 6.65, 6.76, and 6.92 μ.

Condensation of 2-Phenyl-3-thiazolin-5-one (13) with the Aldehyde 17 to 19a. Magnesium sulfate (5 g) was added to a solution of the aldehyde **17** (6 g) and the thiazolone **13** (3.9 g) in dry benzene (100 ml) and triethylamine (0.5 ml). The mixture was stirred under nitrogen at room temperature for 60 hr and then filtered. After removal of the filtrate solvent *in vacuo*, the oily residue was dissolved in chloroform–benzene (1:1) and filtered through a column (5 × 25 cm) of Florisil. From the residue of the first fractions 5.98 g (65%) of **20a** was obtained by triturating with ether. An analytical sample was prepared by recrystallization from ether, mp 150–151°.

Anal. Calcd for $C_{24}H_{22}ClNO_4S$: C, 63.22; H, 4.86; N, 3.07; S, 7.03; mol wt, 456.0. Found: C, 63.28; H, 4.93; N, 3.00; S, 7.26.

The ultraviolet spectrum showed $\lambda\lambda_{max}^{ethanol}$ 330 mμ (ε 12,600), 278 mμ (ε 23,400); and 231 mμ (ε 16,500). The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 3.30, 5.95 (broad), 6.15, 6.35, 6.55, 6.83, and 6.95 μ.

Condensation of 19a with Dimethyl 3-Oxoglutarate (2) to 20a. Potassium *t*-butoxide (750 mg) was added to a solution of **19a** (3 g) in tetrahydrofuran (40 ml, analytical grade) and dimethyl 3-oxoglutarate (**2**) (1.35 ml), and the solution was stirred at room temperature for 15 hr. The reaction mixture was diluted with water (150 ml) and the aqueous solution washed thrice with ether–benzene (1:1) to remove nonacidic materials. The solution was then acidified with dilute HCl and extracted thrice with 100-ml portions of chloroform. The combined chloroform extracts were washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The oil which remained (4 g) partly crystallized on treatment with small amounts of acetone, yield 1.1 g (27% of **20a**), melting range 174–182°.

Anal. Calcd for $C_{31}H_{32}ClNO_9S$: C, 59.09; H, 5.12; N, 2.22; S, 5.09; mol wt, 630.1. Found: C, 58.74; H, 4.92; N, 2.46; S, 5.57.

The ultraviolet spectrum showed $\lambda\lambda_{max}^{0.01N\,methanol-NaOH}$ 276 mμ (ε 27,800) and 236 mμ (ε 22,800). The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 2.93, 3.35 (broad), 5.75, 5.95, 6.30, 6.63, 6.73, 6.85, and 6.90 μ. The oily mother liquors from this crystallization had the same ultraviolet spectrum as the crystalline material.

Deketalization of 20a to 21a. HCl (1 *N*, 60 ml) was added dropwise with stirring to a solution of crude, oily **20a** (5.5 g) in acetone (125 ml). After 10 min, **21a** began to crystallize and the crystals were collected after 15 hr, yield 1.93 g (38% of **21a**). An analytical sample was obtained from dioxane–acetone, melting range 174–193°.

Anal. Calcd for $C_{29}H_{28}ClNO_8S$: C, 59.43; H, 4.82; N, 2.39; Cl, 6.05; S, 5.47; mol wt, 586.1. Found: C, 59.37; H, 4.78; N, 2.49; Cl, 6.12; S, 5.47.

The ultraviolet spectrum showed $\lambda\lambda_{max}^{0.01N\,methanol-NaOH}$ 320 (6200), 276 (25,200), 257 (25,600), and 224 mμ (ε 31,700). The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 3.00, 3.33, 5.76, 5.96, 6.30, 6.65, 6.75, 6.85, and 6.90 μ. The rest of the material, obtained by extraction with chloroform from the mother liquor, showed almost the same ultraviolet spectrum as crystalline **21a**.

Cyclization of 21a to 22a. Crystalline **21a** (3 g) was dissolved in dimethylformamide (30 ml freshly distilled from calcium hydride). The solution was heated to 100°, and sodium hydride (1.15 g) was added. The mixture was stirred at 100° under nitrogen for 20 min, cooled in ice–water, and poured into glacial acetic acid (21 ml). The yellow, strongly green fluorescing solution was diluted with chloroform (200 ml), washed five times with 100-ml portions of water, dried over sodium sulfate, and evaporated. This material was chromatographed on silica gel (pretreated with 0.1 *N* HCl and then activated for 40 min at 140°), 3.5 × 30 cm column, with a solvent of chloroform–acetone (975:25). The first fraction eluted from this column yielded 190 mg (6.7%) of crystalline **22a**, melting range 178–190° dec (after recrystallization from acetone ether).

Anal. Calcd for $C_{28}H_{24}ClNO_7S$: C, 60.70; H, 4.37; N, 2.53; Cl, 6.40; S, 5.79; mol wt, 554.0. Found: C, 60.59; H, 4.34; N, 2.52; Cl, 6.32; S, 5.76.

The ultraviolet spectrum showed $\lambda\lambda_{max}^{MeOH-0.1M\,Na_2B_4O_7}$ after 2 hr equilibration: 455 mμ (ε 29,700) and 218 mμ (ε 28,200); $\lambda\lambda_{max}^{0.01N\,methanol-HCl}$ after 2 hr equilibration: 450 mμ (ε 15,700), 423 mμ (ε 23,800), and 244 mμ (ε 22,500). The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 2.9 (broad), 3.3 (broad), 6.15, 6.30, 6.60, and 6.85 μ.

Preparation of 20b from Aldehyde 17, N-Acetylglycine, and Dimethyl 3-Oxoglutarate. A mixture of aldehyde **17** (9 g), N-acetylglycine (3.53 g), dicyclohexylcarbodiimide (12.8 g), tetrahydrofuran (70 ml, analytical grade), triethylamine (0.30 ml), and glacial acetic acid (0.48 ml) was refluxed for 90 min and then stirred at room temperature for 2 hr. The dicyclohexylurea was filtered off and washed with tetrahydrofuran. The filtrate and tetrahydrofuran washings were combined and dimethyl 3-oxoglutarate (**2**) (5.4 ml) and potassium *t*-butoxide (4.62 g) were added. The resulting mixture was stirred at room temperature for 20 hr during which time a crystalline potassium salt of **20b** appeared. This salt was filtered off and recrystallized from methanol–ether, yield 3.2 g (19.4%), mp 250–254° dec.

Anal. Calcd for $C_{26}H_{29}ClKNO_{10}\cdot 2CH_3OH$ ($C_{28}H_{37}ClKNO_{12}$): C, 51.41; H, 5.70; N, 2.14; Cl, 5.42; mol wt, 654.2. Found: C, 51.23; H, 5.98; N, 2.28; Cl, 5.45.

The ultraviolet spectrum showed $\lambda\lambda_{max}^{0.01N\,methanol-NaOH}$ 276 mμ (ε 22,900) and 232–237 mμ (ε 13,000). The mother liquors of this reaction contained considerable amounts of **20b**, as indicated by the ultraviolet spectrum.

Deketalization of 20b to 21b. The crystalline potassium salt of **20b** (3 g) was dissolved in water (10 ml), and acetone (20 ml) was added. The mixture was acidified to pH 1 with dilute HCl, stirred for 3 hr at room temperature, diluted with water (50 ml), and extracted with chloroform. The residue of this extract was crystallized from acetone–ether, yield 2.1 g (90% **21b**), melting range 195–211°.

Anal. Calcd for $C_{24}H_{26}ClNO_9$: C, 56.75; H, 5.16; N, 2.76; Cl, 6.98; mol wt, 508.0. Found: C, 56.87; H, 5.28; N, 2.82; Cl, 7.05.

The ultraviolet spectrum showed $\lambda\lambda_{max}^{0.01N\,methanol-NaOH}$ 327 (4300), 274 (19,800), 263 (20,200), and 224 mμ (ε 24,900). Ultraviolet and infrared absorption spectra of material isolated by treating the alkali-soluble part of the mother liquors of **20b** (6 g), as described above, were very similar to the corresponding spectra of crystalline **21b**.

Cyclization of 21b to 22b. Sodium hydride (1.18 g) was added at 100° with stirring to a solution of **21b** (5 g) in toluene (40 ml) and dimethylformamide (40 ml). After 5 min toluene (5 ml) and methanol (0.05 ml) were added, and the mixture was stirred for 1 hr at 100°. The reaction mixture was cooled and poured into acetic acid (40 ml) under nitrogen. The yellow solution was diluted with water (200 ml) and extracted with chloroform. The oily residue (2.5 g) of this extract was triturated with acetone, and then ether was added until the mixture became slightly cloudy. A drop of acetone was added and the mixture was left to crystallize, yield 169 mg of **22b**. The residue of the mother liquors was chro-

matographed on silica gel (chloroform–acetone, 20:1). A broad, yellowish brown zone was collected and evaporated. The residue was crystallized from acetone–ether as described above; yield 180 mg, total yield of **22b** 349 mg, (7.5%), mp 247–252° dec with a change at about 220° from fine yellow needles to long thick yellow needles.

Anal. Calcd for $C_{23}H_{22}ClNO_8$: C, 58.05; H, 4.66; N, 2.94; Cl, 7.45; mol wt, 475.9. Found: C, 58.18; H, 4.73; N, 2.89; Cl, 7.53.

The ultraviolet spectrum showed $\lambda\lambda_{max}^{MeOH-0.1M Na_2B_4O_7}$ after 1 hr equilibration 453 (33,800), 345 (5400), 310 (6500), and 261 mμ (ε 9000);[19] $\lambda\lambda_{max}^{0.01N\ methanol-HCl}$ after 1 hr equilibration 427 (31,300), 327 (6600), and 215 mμ (ε 22,200).

Michael Adduct i. Triethylamine (2.8 ml) was added to a solution of **1** (5 g) and dimethyl 3-oxoglutarate (**2**) (4.0 ml) in dry benzene (75 ml), and the mixture was kept at room temperature for 24 hr. The reaction mixture was then washed with water and very dilute HCl until the water layer had a pH of 4. The benzene layer was dried over sodium sulfate and evaporated *in vacuo*. The yellowish, oily residue was triturated with ether and the crystalline i was collected (1.61 g, 19%), mp 135–137°; after one crystallization from ether, 137°.

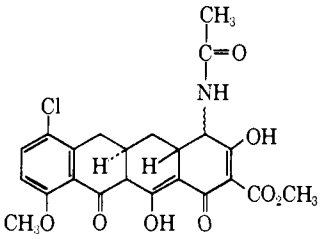
Anal. Calcd for $C_{23}H_{21}NO_7$: C, 65.24; H, 5.00; N, 3.31; mol wt, 423.4. Found: C, 65.44; H, 4.91; N, 3.11.

Spectral results were as follows: ultraviolet $\lambda_{max}^{ethanol}$ 230 mμ (ε 18,800); infrared $\lambda_{max}^{CHCl_3}$ 2.8 (broad), 3.28 (broad), 5.56, 5.75, 5.83, 6.02, 6.26, 6.32, 6.62, 6.73, and 6.93 μ; nmr, two methyl singlets at τ 6.34 and 6.21.

Transformation of i into 3. Potassium *t*-butoxide was added to a solution of i (300 mg) in tetrahydrofuran (5 ml). The mixture was stirred at room temperature for 25 hr and then worked up as described in the preparation of **3**, yield 134 mg (45% of **3**), identical in every respect with compound **3** described earlier.

Improved Method for the Preparation of Thiobenzoylglycine. Ethylthiobenzoylglycine (30 g), pyridine (60 ml) and phosphorus pentasulfide (15 g) were refluxed for 2 hr. After further addition of phosphorus pentasulfide (5 g), the mixture was refluxed for another hour. After addition of benzene (500 ml) the mixture was filtered and the filtrate washed twice with 10% aqueous NaOH (150 ml) and several times with dilute HCl. The benzene was removed *in vacuo*, and the oily residue was dissolved in ethanol (100 ml). Aqueous KOH (15%, 50 ml) was added to this solution, and the mixture was kept at room temperature for 4 days. Most of the ethanol was then removed *in vacuo* and the residue was diluted with water (100 ml), washed thrice with ether–benzene (1:1), and acidified slowly in an ice bath with 2 *N* HCl. The crystalline solid was collected and recrystallized once from hot water, mp 150–154°; $\lambda\lambda_{max}^{methanol}$ 240 mμ (ε 10,900) and 286 mμ (ε 7300).

(19) Recent findings in our laboratory by Mr. J. Philip Bays suggest that the maximum at 345 mμ may be attributable to a small amount of an isomer of structure ii.



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The Preparation and Properties of 1,2-Bis(triphenylphosphoranyl)benzocyclobutene[1,2]

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Abstract: The preparation of *trans*-1,2-bis(triphenylphosphonio)benzocyclobutene dibromide and its conversion to 1,2-bis(triphenylphosphoranyl)benzocyclobutene are described. Treatment of the dibromide salt with base followed by reaction with a benzaldehyde affords different results that depend upon the nature of the solvent. In ethanol as the major solvent, the principal products are the *cis*- and *trans*-1-benzylidenebenzocyclobutenes corresponding to the particular benzaldehyde used, together with triphenylphosphine oxide; in DMF or DMSO, the major products are the *cis,cis*- and/or *cis,trans*- and/or *trans,trans*-1,2-bisbenzylidenebenzocyclobutenes corresponding to the benzaldehydes used, as well as triphenylphosphine oxide. In both instances a number of minor products are obtained. The structure and stereochemistry of the major products are in accord with the chemical and physical data reported herein.

It has been predicted that benzocyclobutadiene (I; Y and Z = H), an 8π-electron system, should possess some cyclobutadiene character, exhibit considerable resonance energy, and have a singlet ground state.[4,5] Other considerations[6,7] suggest that the hydrocarbon will have little resonance stabilization and thus might simply act as a highly reactive olefin. Indeed, several derivatives of benzocyclobutadiene have been prepared

(1) Taken from the Ph.D. Thesis of V. J. Hruby, Cornell University, 1965. The partial support of the National Science Foundation Grant G-18902 is gratefully acknowledged.

(2) For a preliminary report of some of this work, see A. T. Blomquist and V. J. Hruby, *J. Am. Chem. Soc.*, **86**, 5041 (1964).

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