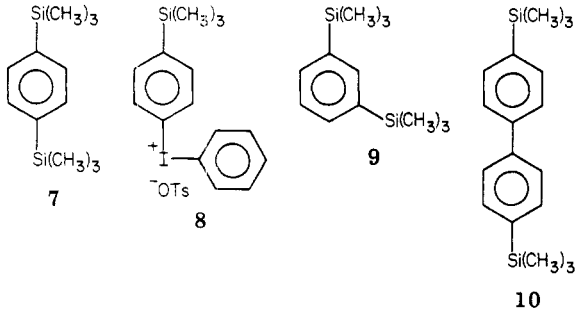
NMR spectrum of **3b** exhibits methyl singlets at δ 2.28 (OTs) and 2.57 (*o*-tolyl) and a complex, two-part aromatic pattern, the hydrogens ortho to positive iodine being sufficiently deshielded to generate a multiplet downfield from the remaining aromatic resonances. In the ^1H NMR spectrum of **3c**, the tolyl and tosylate methyl singlets exhibit the same chemical shift; a similar situation exists in the spectrum of **3d**.

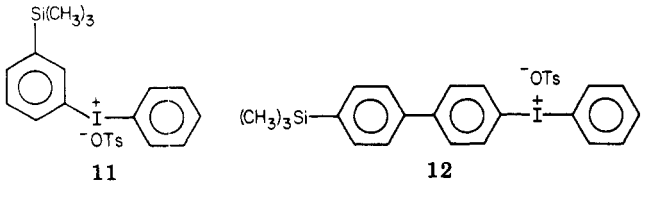
Other [hydroxy(tosyloxy)iodo]arenes behave similarly. Thus, the reaction of [hydroxy(tosyloxy)iodo]-*p*-toluene (**4a**) with (trimethylsilyl)benzene (**2a**) (CH_3CN, Δ) gave **3d** (30%) and with *o*-methyl(trimethylsilyl)benzene (**2b**) (CH_3CN, Δ) gave 2,4′-dimethyldiphenyliodonium tosylate (**5**) in 59% yield. When [hydroxy(tosyloxy)iodo]-*o*-toluene (**4b**) was allowed to react with *m*-methyl(trimethylsilyl)-benzene (**2c**), 2,3′-dimethyldiphenyliodonium tosylate (**6**) was obtained (58% yield).

Dichloromethane has also been employed successfully as a solvent in the preparation of **3d** (17%) from **4a** and **2a**, of **3c** (63%) from **1** and **2c**, and of **3a** (48%) from **1** and **2a**, although longer reaction times are required.

When *p*-bis(trimethylsilyl)benzene (**7**) was allowed to react with **1** in acetonitrile, phenyl[*p*-(trimethylsilyl)-phenyl]iodonium tosylate (**8**) was obtained in 49% yield (after recrystallization). Thus far, we have been unsuccessful in attempts to obtain a bis(iodonium) salt by replacement of the trimethylsilyl group in **8** by the action of **1**. The ^1H NMR spectrum of **8** ($CDCl_3$, Me_4Si) exhibits singlets at δ 0.23 ($SiMe_3$) and δ 2.23 (CH_3 of OTs) and a complex multiplet in the aromatic region. The four hydrogens ortho to positive iodine give rise to a multiplet distinctly downfield from the rest of the aromatic peaks. Iodonium salt **8** also has the expected elemental composition.



Similar results were obtained with *m*-bis(trimethylsilyl)benzene (**9**) and 4,4′-bis(trimethylsilyl)biphenyl (**10**). Thus, reaction of **9** with **1** in acetonitrile gave the monoiodonium tosylate **11** (24%, after recrystallization), and reaction of **10** with **1** gave the monoiodonium tosylate **12** (27%).



One of the more common methods of iodonium salt synthesis employed today involves the condensation of ArIO or $ArI(OAc)_2$ with ArH in a strong acid (H_2SO_4) medium and is therefore limited to acid-insensitive functional groups. Furthermore, there is limited control on substituent placement in the iodonium salt. For example, if the 2,3′-dimethyldiphenyliodonium ion is the synthetic target, the condensation of *o*-methyl(diacetoxyiodo)-benzene with toluene in sulfuric acid would not be of much utility. However, that cation has been specifically prepared with moderate facility via the $ArSi(CH_3)_3$ route under mild conditions. This method supplements that developed by Beringer and his co-workers in which iodonium salts were synthesized from aryllithium reagents and dichloroiodoarenes ($ArICl_2$) in ether or THF at low temperatures.[5]

We shall extend these studies to a variety trimethylsilylarenes and hydroxy tosylates with the added hope of improving yields.[6] A large number of [hydroxy(tosyloxy)iodo]arenes are available from the reactions of the corresponding iodosylarenes (ArIO) or (diacetoxyiodo)-benzenes ($PhI(OAc)_2$) with toluenesulfonic acid or by direct ligand exchange of **1** with a variety of iodoarenes (see the adjoining communication). These reactions contribute something new to the elegant methodology developed by the groups of Beringer, Willgerodt,[7] and others.

(4) Iodonium tosylates **3b–d**, **5**, **6**, **8**, **11**, and **12** were all sent out for combustion analysis and the percentages of carbon, hydrogen, and iodine determined. The experimental values (24 in all) were within 0.4% of the calculated values with two exceptions. For salts **3d** and **5**, the H and I analyses were within the 0.4% tolerance, but the best carbon analyses to date were 0.58% (**3d**) and 0.60% (**5**) from the calculated values. Repeated analyses were sometimes necessary. Melting points are uncorrected.

(5) F. M. Beringer, J. W. Dehn, Jr., and M. Winicov, *J. Am. Chem. Soc.*, **82**, 2948 (1960).

(6) Yields reported herein are rounded off to the nearest percentage point.

(7) C. Willgerodt, "Die Organischen Verbindungen mit Mehrwertigen Jod", F. Enke, Stuttgart, 1914, pp 195, 197, 198.

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Total Synthesis of Erythromycins. 6. Facile Transformation of Erythronolide A into a Tricyclic Internal Ketal

Summary: Erythronolide A (**1a**), the aglycone of erythromycin A, is unusually sensitive to acid in comparison with erythronolide B (**1b**) or the erythromycins. Upon treatment with 0.02 N perchloric acid at 23 °C it is rapidly transformed into an anhydro derivative which has been shown to possess structure **2** by single-crystal X-ray diffraction analysis.

Sir: The first total synthesis of erythronolide A (**1a**), the aglycone of the medically important antibiotic erythromycin A, was recently reported from these laboratories.[1] In the course of this work, it was discovered that the acid-catalyzed hydrolysis of the 3,5-acetonide of **1a** under conditions which effected the hydrolysis of the 3,5-acetonide of erythronolide B to erythronolide B (**1b**)[2,3] did not afford erythronolide A but instead a new compound which in contrast to **1a** is very stable to acid. Erythronolide A itself (**1a**) is transformed into the same substance

(1) Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.; Nambiar, K. P.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7131.

(2) Corey, E. J.; Nicolaou, K. C.; Melvin, L. S., Jr. *J. Am. Chem. Soc.* **1975**, *97*, 654.

(3) Corey, E. J.; Kim, S.; Yoo, S.; Nicolaou, K. C.; Melvin, L. S., Jr.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4620.

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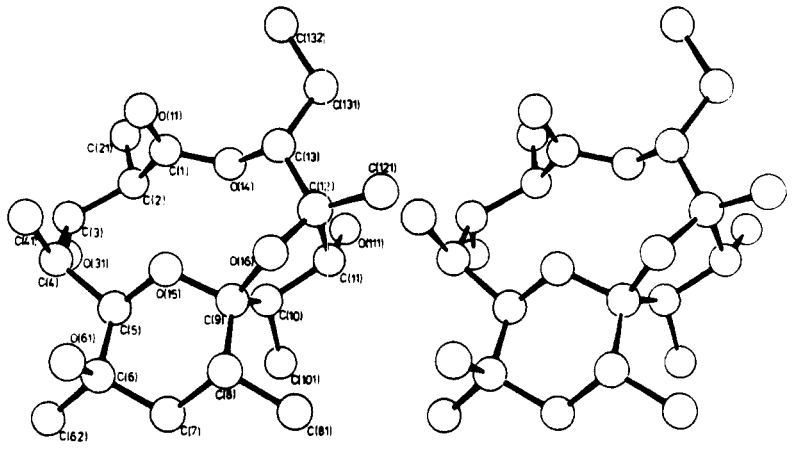
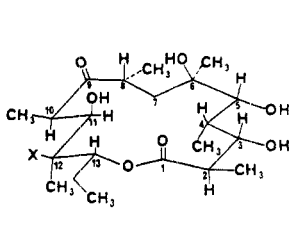


Figure 1. Stereoscopic representation of **2**.

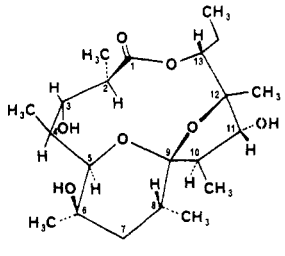
Table I. Bond Angles (deg)

O(11)-C(1)-O(14)	123.5 (4)	C(2)-C(1)-O(14)	109.0 (4)
C(2)-C(1)-O(11)	127.3 (4)	C(21)-C(2)-C(1)	107.9 (3)
C(3)-C(2)-C(1)	117.9 (3)	C(3)-C(2)-C(21)	109.7 (4)
O(31)-C(3)-C(2)	102.8 (3)	C(4)-C(3)-C(2)	119.9 (4)
C(4)-C(3)-O(31)	111.5 (3)	C(41)-C(4)-C(3)	112.9 (3)
C(5)-C(4)-C(3)	112.8 (3)	C(5)-C(4)-C(41)	116.4 (4)
O(15)-C(5)-C(4)	106.4 (3)	C(6)-C(5)-C(4)	116.7 (3)
C(6)-C(5)-O(15)	108.9 (3)	C(5)-O(15)-C(9)	118.0 (3)
O(61)-C(6)-C(5)	111.5 (3)	C(62)-C(6)-C(5)	111.9 (4)
C(62)-C(6)-O(61)	106.6 (4)	C(7)-C(6)-C(5)	106.7 (3)
C(7)-C(6)-O(61)	109.1 (3)	C(7)-C(6)-C(62)	111.0 (4)
C(8)-C(7)-C(6)	112.6 (3)	C(9)-C(8)-C(7)	110.9 (3)
C(81)-C(8)-C(9)	114.7 (4)	C(81)-C(8)-C(7)	114.7 (4)
C(10)-C(9)-O(16)	106.5 (3)	O(15)-C(9)-O(16)	103.0 (3)
O(15)-C(9)-C(10)	111.6 (3)	C(8)-C(9)-O(16)	106.5 (3)
C(10)-C(9)-C(8)	120.6 (4)	C(8)-C(9)-O(15)	107.2 (3)
C(12)-O(16)-C(9)	112.4 (3)	C(101)-C(10)-C(9)	121.4 (3)
C(11)-C(10)-C(9)	102.9 (4)	C(11)-C(10)-C(101)	111.5 (4)
O(111)-C(11)-C(10)	111.4 (4)	C(12)-C(11)-C(10)	105.5 (4)
C(12)-C(11)-O(111)	113.7 (4)	C(11)-C(12)-O(16)	100.7 (3)
C(121)-C(12)-O(16)	105.0 (4)	C(121)-C(12)-C(11)	113.1 (5)
C(13)-C(12)-O(16)	108.9 (4)	C(13)-C(12)-C(11)	117.0 (4)
C(13)-C(12)-C(121)	110.8 (4)	C(131)-C(13)-C(12)	116.1 (4)
O(14)-C(13)-C(12)	108.2 (4)	O(14)-C(13)-C(131)	108.1 (4)
C(132)-C(131)-C(13)	112.3 (5)	C(1)-O(14)-C(13)	120.3 (4)

upon mild acid treatment. For example, reaction of **1a** in 1:1 acetonitrile–0.04 N aqueous perchloric acid at 23 °C for 1 h produces the new compound in chromatographically homogeneous form [R_f 0.41 (10% CH_3OH in CH_2Cl_2, two elutions, silica gel) as compared to R_f 0.38 for **1a**] as a colorless, crystalline solid in 95% yield. Recrystallization from methanol–methyl acetate afforded colorless needles, mp 287–289 °C dec. The infrared spectrum (carbonyl absorption 1735 cm^{-1}; KBr pellet), mass spectrum (M^+ at m/e 400), and combustion analysis (C, 62.81; H, 9.29) were consistent with formation of an internal ketal involving the C-9 ketone, the hydroxyl group at C-12, and either of the hydroxyl groups at C-5 and C-6. Final structural assignment of **2** was accomplished by single-crystal X-ray diffraction studies which are summarized herein.



1a X=OH
1b X=H



2

Crystals of **2** from ethyl acetate have monoclinic symmetry, space group $P2_1$. The unit cell which has dimensions a = 9.271 (2) Å, b = 12.504 (4) Å, c = 9.667 (2) Å, and β = 106.99 (2)° contains two molecules of **2**, leading to a calculated density of 1.24 g cm^{-3}.

Data were collected on a Syntex $P2_1$ diffractometer, using graphite-monochromated Cu Kα radiation (λ 1.541 78 Å) in the θ–2θ mode in the range 3.0° ≤ 2θ ≤ 135° at scan speeds of 2–30°/min, depending on the intensity of the reflection. Lorentz and polarization factors were applied, but no absorption correction was made (μ = 6.7 cm^{-1} for Cu Kα radiation, crystal size 0.1 × 0.3 × 0.1 mm). After the data reduction 2684 independent reflections ($I \geq 2\sigma(I)$) were retained for the refinement of the structure.

Twenty-three of the nonhydrogen atoms could be located by direct methods (MULTAN 78).[4] The hydrogen atoms were found in difference maps and together with isotropic temperature factors were included in the refinement. For all other atoms anisotropic temperature factors were introduced. After several cycles the refinement converged to a final value of R = 0.059. In the last cycle of refinement the shifts divided by the standard deviation for all parameters were smaller than 0.02. The highest electron density peak that was observed in a final difference map was smaller than 0.35 e $Å^{-3}$.

(4) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *27* 368.

There are a number of noteworthy points which emerge from the X-ray identification of the internal ketal as **2**. First of all the facility with which the internal ketal **2** forms is impressive, given the known conformational stability of the 14-membered ring[5] as depicted in **1a**. It is especially interesting that the hydroxyl at C-5 participates in the ketal unit rather than that at C-6. Previous works have shown that erythromycin A upon treatment with glacial acetic acid at room temperature for 2 h produces a 6→9 enol ether which upon exposure to aqueous methanolic hydrochloric acid is transformed into an anhydro derivative presumed (but not rigorously proved) to be the internal ketal involving the hydroxyl groups at C-6 and C-12.[6,7] The much more facile (and probably thermodynamically) preferred conversion of erythronolide A to **2** rather than the isomeric 6→9,12→9-oxygen-bridged structure implies that erythromycin A analogues possessing free hydroxyl at C-5 and C-12 probably will be too acid-labile for therapeutic use by oral administration.

It is apparent that the internal ketal **2** may be a useful intermediate for the selective attachment of sugar units (or other groups) to the oxygens at C-5 and C-3. Since the former oxygen is internally protected in **2** and the latter is the most sterically accessible for the free hydroxyls in **2**, a sequence consisting of selective substitution at the C-3 hydroxyl, cleavage of the internal ketal, and attachment of another group on the C-5 hydroxyl would appear to be a likely route to erythromycin A or analogues in which the C-3 and C-5 oxygens carry substituents. With respect to the second step of this sequence we have already demonstrated that the internal ketal linkages in **2** can be cleaved by reaction with hydroxylamine which generates the oxime[1] of erythronolide A from **2**.

The molecular geometry of **2** is illustrated in Figure 1. The six-membered ring is chair-formed and the five-membered ring is nonplanar (maximum deviation from the best plane is 0.21 Å at C-12). Close intramolecular contacts of C(10) and C(101) with the substituents on the six-membered ring cause an increase in the sp^3 angles C(8)–C(9)–C(10) and C(9)–C(10)–C(101) from normal values to 120.6 and 121.4°, respectively. The lactone function in the 11-membered ring is s-trans and essentially planar, but there are a number of close contacts between substituents on this ring as well. A complete list of bond angles is shown in Table I.[8]

Supplementary Material Available: Positional parameters (Table I) and bond lengths (Table II) for **2** (2 pages). Ordering information is given on any current masthead page.

(5) See: (a) Egan, R. S.; Perun, T. J.; Martin, J. R.; Mitscher, L. A. *Tetrahedron* **1973**, *29*, 2525. (b) Perun, T. J.; Egan, R. S.; Martin, J. R. *Tetrahedron Lett.* **1969**, 4501.

(6) Wiley, P. F.; Gurzon, K.; Flynn, E. H.; Sigal, M. V., Jr.; Weaver, O.; Quarck, V. C.; Chauvette, R. R.; Monahan, M. *J. Am. Chem. Soc.* **1957**, *79*, 6062.

(7) Kurath, P.; Jones, P. H.; Egan, R. S.; Perun, T. J. *Experientia* **1971**, *27*, 362.

(8) This research was assisted financially by grants from the National Science Foundation (to W.N.L.) and the National Institutes of Health (to E.J.C.) and by a Deutsche Forschungsgemeinschaft Fellowship to D.S. and a National Science Predoctoral Fellowship to P.B.H.

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Indole Synthesis via $S_{RN}1$ Reactions

Summary: *o*-Haloanilines react with ketone enolate ions in ammonia under irradiation to form indoles in good yields.

Sir: A 1972 review[1] on the synthesis of indoles describes some 30 methods, and others have been reported since.[2] We now report a new method that is also novel in principle. It involves $S_{RN}1$ replacement of halogen[3] from an *o*-haloaniline by a ketone enolate nucleophile and subsequent cyclization.

We have found that the photostimulated reaction of acetone enolate ion with 3-bromo-*N*,*N*-dimethylaniline or 4-iodo-*N*,*N*-dimethylaniline in ammonia affords, respectively, [3- or 4-(dimethylamino)phenyl]acetone in 82% or 90% yield. Thus, halogen derivatives of aromatic tertiary amines react with ketone enolate ions much as do other aryl halides.[4] These results correct a previous impression[3,5] that a dialkylamino substituent is inimical to the participation of an aryl halide in an $S_{RN}1$ reaction.

Extending this principle, we find that *o*-bromoaniline reacts with potassium acetone enolate during irradiation for 2 h in a simple photochemical reactor to release 98% of bromide ion and form a 93% isolated yield of 2-methylindole. The reaction is believed to occur as indicated in Scheme I. It is unclear whether cyclization occurs in the original strongly basic reaction mixture or after acidification with an ammonium salt at the end of irradiation.

Furthermore, we find that reactions of acetone enolate ion with *o*-bromo- or *o*-chloroaniline bearing methyl, methoxy, phenyl, and carboxy substituents at various ring sites produce indoles with the respective substituents at sites determined by the constitution of the starting *o*-haloaniline. This method thus has an advantage over the Fischer indole synthesis and other methods which involve cyclization to either of two sites ortho to a reactive side chain and often give isomer mixtures or a preponderance of an undesired isomer. Our observations that 2-bromo-3-methylaniline is transformed into 2,4-dimethylindole in 80% yield and that 3-amino-4-chlorobenzoic acid gives 2-methylindole-6-carboxylic acid in 89% yield demonstrate that this method can lead satisfactorily to a single isomer. These and other examples are summarized in Table I.

The typical procedure was as follows: A solution of the *o*-haloaniline (0.01 mol), the potassium ketone enolate (0.03 mol), potassium *tert*-butoxide (0.01 mol), and *tert*-butyl alcohol (0.001 mol) in 100 mL of ammonia was prepared under nitrogen by adding to a solution of KNH_2 (0.04 mol) first the ketone, then *tert*-butyl alcohol, and finally the *o*-haloaniline. The flask was equipped with a solid CO_2-cooled condenser and irradiated in a Rayonet photochemical reactor equipped with lamps emitting maximally at 350 nm for times shown in Table I. Irradiation was interrupted every 20 min to remove ice from the flask exterior. At termination of irradiation, ammonium nitrate (0.03 mol) and diethyl ether (80 mL) were added, the ammonia was allowed to evaporate overnight, and the mixture was worked up conventionally.

The tabulated examples demonstrate considerable gen-

(1) R. K. Brown in "Indoles, Part One", W. J. Houlihan, Ed., Wiley-Interscience, New York, 1972, Chapter II.

(2) P. G. Gassman, T. J. van Bergen, D. P. Gilbert, and B. W. Cue, Jr., *J. Am. Chem. Soc.*, **96**, 5495 (1974); L. S. Hegedus, G. F. Allen, and E. L. Waterman, *ibid.*, **98**, 2674 (1976); M. Mori and Y. Bau, *Tetrahedron Lett.*, **1803** (1976).

(3) J. F. Bunnett, *Acc. Chem. Res.*, 11, 413 (1978).

(4) R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, **38**, 1407, 3020 (1973).

(5) J. F. Bunnett and J. E. Sundberg, *Chem. Pharm. Bull.*, **23**, 2620 (1975).

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