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.

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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-

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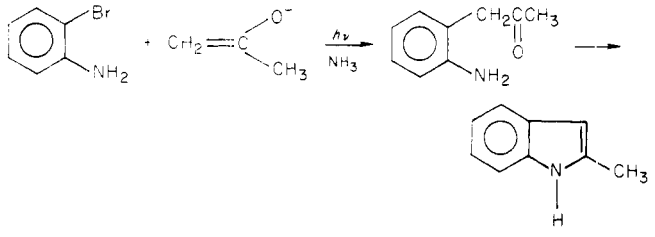
Table I. Indole Syntheses by Photostimulated Reactions of *o*-Haloanilines with Ketone Enolate Ions in Ammonia

expt no.	aniline deriv	enolate ion from	irradn time, h	% X^- release	indole deriv formed (% yield)
1	2-bromo-	acetone	2	98	2-methyl- (93)
2	2-bromo-3-methyl-	acetone	4	86	2,4-dimethyl- (80)
3	2-bromo-4-methyl-	acetone	2	98	2,5-dimethyl- (88)
4	2-bromo-5-methyl-	acetone	2	90	2,6-dimethyl- (82)
5	2-chloro-5-phenyl-	acetone	12	98	2-methyl-6-phenyl- (88)
6	2-chloro-5-methoxy-	acetone	10.5	53	2-methyl-6-methoxy- (42)
7	2-chloro-5-carboxy-	acetone	12	95	2-methyl-6-carboxy- (89)
8	2-bromo-*N*-methyl-	acetone	3	97	1,2-dimethyl- (79)
9	2-bromo-	3-methyl-2-butanone	4	97	2-isopropyl- (84[a])
10	2-bromo-	3,3-dimethyl-2-butanone	3	97	2-*tert*-butyl (94)
11	2-bromo-	cyclohexanone	4	97	1,2,3,4-tetrahydrocarbazole (14)
12	2-bromo-4-methyl-	3-pentanone	2	98	3,5-dimethyl-2-ethyl- (73)
13	2-chloro-3-aza[b]	acetone	10.5	60	4-aza-2-methyl- (45)

[a] Approximately 6 mg (ca. 0.05%) of 2,3,3-trimethylindolenine was also obtained. [b] 3-Amino-2-chloropyridine.

Scheme I. An Indole Synthesis



erality for the synthesis. It should be noted that enolate ions from various ketones can be employed and that only in the case of cyclohexanone enolate (experiment 11) is there an indication of a serious side reaction, possibly hydrogen atom abstraction from the β-carbon.[6] We call attention to the facts that 2-bromo-*N*-methylaniline with acetone enolate affords 1,2-dimethylindole in good yield (experiment 8) and that 3-amino-2-chloropyridine with acetone enolate gives 2-methyl-4-azaindole (experiment 13).

An interesting limitation lies in the fact that 2,4-dihaloanilines show very low reactivity. Thus in reactions with acetone enolate ion, 2,4-dibromoaniline released only 11% of bromide ion during 2-h irradiation under our usual reaction conditions, which involve 1 equiv of excess potassium *tert*-butoxide (*t*-BuOK) in the medium, and only 28% of bromide without excess *t*-BuOK. Likewise, 2-iodo-4-chloroaniline under the usual conditions released only 9% of iodide ion and 1% of chloride ion during 1.5 h of irradiation. We postulate that the second halogen increases the acidity of the aniline[7] sufficiently so that a large fraction of it exists as its unreactive conjugate base under our usual conditions. The fact that more bromide release occurred from 2,4-dibromoaniline in the absence of excess *t*-BuOK is consistent with this view.

We foresee wide applicability for this synthesis and for analogous transformations.

After these experiments had been completed and a draft of this communication had been written, we learned of the work of Beugelmans and Roussi,[8] who have independently discovered this principle of indole synthesis and who have reported four examples of it.

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Supplementary Material Available: Experimental procedures and evidence for assignment of product structures (5 pages). Ordering information is given on any current masthead page.

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Nitrogen Analogues of *o*-Xylylenes

Summary: The gas-phase pyrolysis of *o*-hydroxymethylanilines provides simple, one-step syntheses of acridines, acridones, and quinoline derivatives. The ease with which nitrogen analogues of *o*-xylylenes are formed during pyrolysis suggests that the methodology currently used in the synthetic applications of benzocyclobutenes can be employed with these azo-*o*-xylylenes to yield a variety of heterocycles and polycyclic amines.

Sir: The generation of benzocyclobutenes by gas-phase pyrolysis of *o*-(chloromethyl)toluenes,[1-3] and their valence tautomerization to *o*-xylylenes, has proved to be a generally useful method for syntheses of novel molecules of theoretical interest[4-8] and for syntheses of natural products.[9,10] Recently we have described the application of this method to the corresponding oxygen and sulfur analogues of the *o*-xylylenes,[11] and we now report that the extension of these methods to the nitrogen analogues provides simple, convenient syntheses for a variety of acridines, acridones, and quinolines.

An outstanding example from the literature of a nitrogen analogue of benzocyclobutene and its valence tautomerization to an *o*-xylylene analogue is the report of Burgess

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