trans-**Tolane Dibromide** (1.3520 g., 0.00400 mole) in 125 ml. of DMF was added to a solution of 50 ml. of DMF, 125 ml. of H_2O, and 50 ml. of 0.690 *M* Cr^{+2} (0.0345 mole). Upon mixing the reactants, much of the dibromide came out of solution and the solution remained heterogeneous during the reaction. After 3 days, 0.00820 mole of Cr^{+2} had been consumed. The reaction mixture was diluted with 350 ml. of H_2O and filtered. The crystals were washed with H_2O and dried and the filtrate was extracted with ether. The ether extract was washed with H_2O to remove DMF, dried over anhydrous Na_2SO_4, and evaporated. The combined crystals provided 0.7063 g. (0.00397 mole, 97%) of tolane, m.p. 59–59.5°, m.m.p. 59–59.5° (lit.[27] 60°). The infrared spectrum was identical with that of a known sample.

meso-**Stilbene dibromide** (1.360 g., 0.00400 mole) in 125 ml. of DMF was added to a solution of 50 ml. of DMF, 125 ml. of H_2O, and 50 ml. of 0.701 *M* Cr^{+2} (0.0351 mole). Upon mixing the reactants, much of the dibromide came out of solution and the solution remained heterogeneous during the reaction. After 3 days, 0.0080 mole of Cr^{+2} had been consumed. Dilution of the reaction mixture with H_2O, filtration, and ether extraction provided 0.7270 g. (0.00404 mole) of *trans*-stilbene, m.p. 123–124°, m.m.p. 123–124° (lit.[28] 124°). The infrared spectrum was identical with that of a known sample. No *cis*-stilbene was isolated.

meso-α,β-**Dibromosuccinic acid** (4.1414 g., 0.0150 mole) in 200 ml. of H_2O was treated with 100 ml. of 0.311 *M* Cr^{+2} (0.0311 mole). The reaction was quite rapid. After standing overnight, 0.0308 mole of Cr^{+2} had been consumed. The reaction mixture was basified with solid KOH and the $Cr(OH)_3$ precipitate was filtered off, dissolved in a minimal amount of concentrated H_2SO_4, and extracted with ethyl acetate. The reaction mixture was acidified and extracted with ethyl acetate. The combined extracts provided 1.65 g. (0.0142 mole) of fumaric acid, m.p. 280–282° (sealed tube). The infrared spectrum was identical with a known sample. No maleic acid was found. Under these reaction conditions maleic acid was not isomerized.

Hexachloroethane (2.3700 g., 0.0100 mole) in 100 ml. of DMF was added to a solution of 50 ml. of DMF, 50 ml. of H_2O, and 100 ml. of 0.690 *M* Cr^{+2} (0.0690 mole). The homogeneous reaction mixture turned green (Cr^{+3}) immediately. After 24 hr., 0.0210 mole of Cr^{+2} had been consumed. The reaction mixture was diluted with H_2O and extracted with ether. The ether extract was dried, concentrated, and analyzed by gas chromatography (DC-710 column). The product was identified as tetrachloroethylene by its retention time and its infrared spectrum. Quantitative recovery was not effected.

The following compounds were scanned[1] for reactivity with Cr^{+2} and were found to be inert: 1,2-dichloroethane, 1,2-dibromoethylene, *o*-dibromobenzene, and *o*-diiodobenzene.

Acknowledgment.—The authors are indebted to the National Science Foundation for support (G19145, GP2698) of this work. We wish to thank Drs. D. J. Pettit and R. D. Clark for generous supplies of pure *cis*- and *trans*-epoxybutane.

(27) W. McVicker, J. Marsh, and A. Stewart, *J. Chem. Soc.*, **127**, 1000 (1925).

(28) C. D. Nenitzescu, *Ber.*, **62**, 2672 (1929).

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO., PEARL RIVER, NEW YORK]

A Novel Pyrrolo[1,2-*a*]indole Rearrangement

BY WILLIAM A. REMERS

RECEIVED JULY 1, 1964

Treatment of 1-keto-1H-pyrrolo[1,2-*a*]indoles I and VII with oxalyl chloride afforded products II and IX, respectively, in which the 1H-pyrrolo[1,2-*a*]indole system had rearranged to a 9H-pyrrolo[1,2-*a*]indole system, the 1-keto group was replaced by a 1-chloro group, and 3-oxalyl substituents were introduced. The nature of this rearrangement is discussed and further transformations of the products are described.

In the course of a study[1] concerned with the introduction of a potential hydroxymethyl substituent at the 9-position of the 1-ketopyrroloindole system (I), we investigated the reaction of this system with oxalyl chloride. The reaction of 3-unsubstituted indoles with this reagent is a common method for functionalization of the 3-position[2] and, since oxalyl chloride is a strong electrophile, its reaction with the partially deactivated I was considered feasible.[2] However, treatment of I with this reagent did not proceed in the anticipated manner, and instead a novel rearrangement occurred. This rearrangement and subsequent substitution into the rearrangement product are the subject of the present paper.

When ketone I[3] was treated with 1 mole of oxalyl chloride in methylene chloride at 5°,[2] little reaction occurred and impure starting material was recovered. However, treatment of I with 2 moles of oxalyl chloride gave a good conversion of I to a noncrystalline substance which on treatment with methanol afforded yellow compound II, $C_{21}H_{16}NO_4Cl$, the chlorine of which was not reactive to silver nitrate. Infrared and n.m.r. indicated the presence of a methoxalyl group and the absence of the 1-keto function in this substance. Reduction of II with sodium borohydride gave a white compound IV, $C_{21}H_{18}NO_4Cl$, in which the ketonic carbonyl of the oxalyl group had apparently been reduced. The ultraviolet absorption spectrum of IV had a single maximum at 271 mμ, which position was lower than that of any indole we had hitherto encountered. We therefore considered the strong possibility that II and IV were not 1H-2,3-dihydropyrroloindoles (indole chromophores) but were the result of rearrangement to a different system. A fairly close match to the ultraviolet absorption spectrum of IV was provided by that of 9H-pyrroloindole V (N-phenylpyrrole chromophore, λ_{max} 265 mμ) reported by Laschtuvka and Huisgen.[4]

In order to obtain further evidence for the supposition that II and IV were members of the 9H-pyrroloindole series substituted with a methoxalyl and a reduced methoxalyl group, respectively, 7-benzyloxy-9H-pyrroloindole (VI)[5] was treated with oxalyl chloride in methylene chloride, followed by the addition of methanol. This treatment afforded yellow methoxalyl derivative VIII, which showed an ultra-

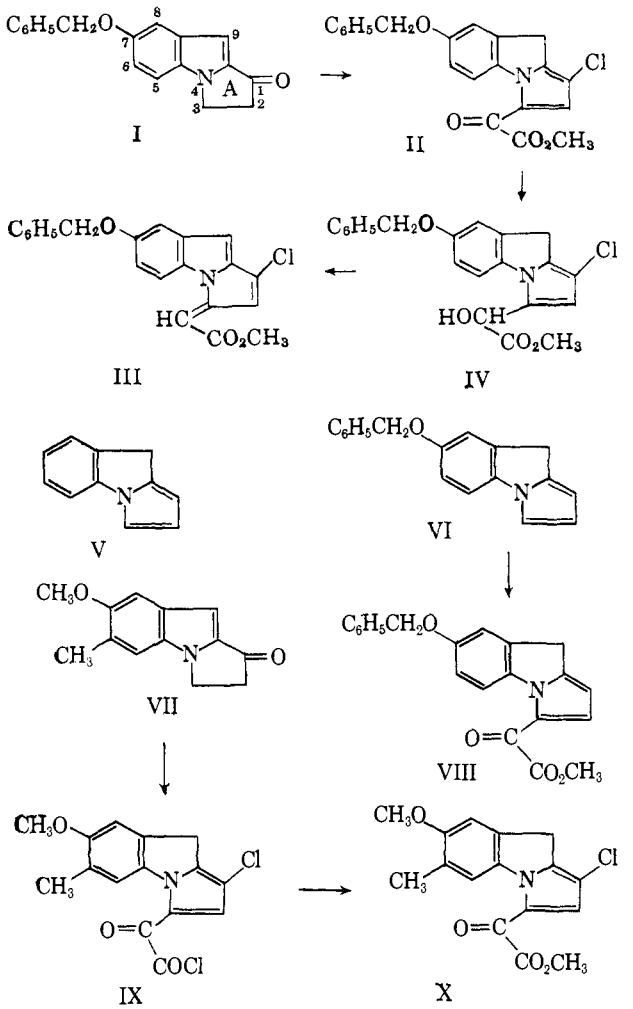
(1) W. A. Remers, R. H. Roth, and M. J. Weiss, *J. Am. Chem. Soc.*, **86**, 4612 (1964).

(2) M. E. Speeter and W. C. Anthony, *ibid.*, **76**, 6208 (1954). In this paper the 3-oxalylation of a 2-phenylindole was reported; however, 3-oxalylation of an indole-2-carboxylate was unsuccessful.

(3) G. R. Allen, Jr., and M. J. Weiss, publication forthcoming.

(4) E. Laschtuvka and R. Huisgen, *Ber.*, **93**, 81 (1960). These authors proposed the name "fluorazene" for the 9H-pyrroloindole system.

(5) Kindly furnished by Dr. G. R. Allen, Jr.



violet absorption spectrum (Fig. 1) nearly identical with the highly characteristic spectrum of II (Fig. 1). Furthermore, reduction of VIII with sodium borohydride gave a product (not isolated) that had an ultraviolet absorption spectrum with λ_{max} 268 mμ, which closely resembled the spectrum of V.

The n.m.r. spectra of these compounds shed further light on their structures, providing the basis for the assignment of specific positions to the substituents. The spectrum of VIII is nearly identical with that of its precursor VI, with the following important differences: (1) the three-proton singlet of the methyl ester is present at 6.03 τ; (2) the doublet ($J_{5,6}$ = 9 c.p.s.) of the C-5 proton is further downfield (3.09 to 1.40 τ); (3) the doubled doublet ($J_{1,2}$ = 4 c.p.s., $J_{2,3}$ = 4 c.p.s.) of the C-2 proton in VI, observed at 3.68 τ, in VIII is a doublet ($J_{1,2}$ = 4 c.p.s.) at 2.52 τ; (4) the doubled doublet ($J_{1,3}$ = 1 c.p.s., $J_{2,3}$ = 4 c.p.s.) of the C-3 proton in VI is absent in the spectrum of VIII; (5) the doubled doublet ($J_{1,2}$ = 4 c.p.s., $J_{1,3}$ = 1 c.p.s.) of the C-1 proton in VI occurs as a doublet ($J_{1,2}$ = 4 c.p.s.) in VIII and is shifted slightly from 3.96 to 3.75 τ. The above assignment of the protons at C-1 and C-2 in VIII is supported by a consideration of their coupling constants—since each is split into a doublet with J = 4 c.p.s., they must be on adjacent A-ring positions, either C-1 + C-2 or C-2 + C-3. Evidence for the C-1, C-2 positions is provided by the deshielding effects caused by introduction of the methoxalyl group. Thus, the C-5 proton and one ring-A proton are strongly

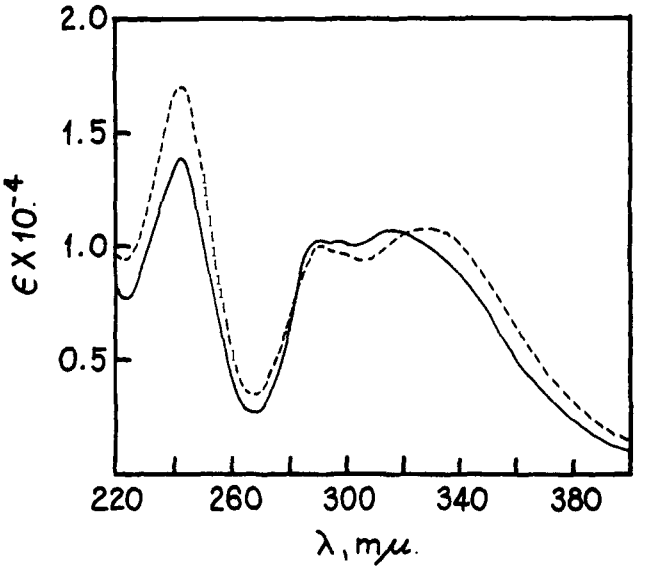


Fig. 1.—Ultraviolet absorption spectra in methanol: ———, methyl 7-benzyloxy-9H-pyrrolo[1,2-a]indole-3-oxalate (VIII); – – – –, methyl 7-benzyloxy-1-chloro-9H-pyrrolo[1,2-a]indole-3-oxalate (II).

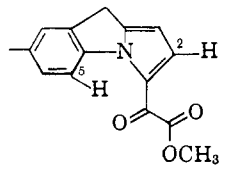
deshielded by this group while the other ring-A proton is little affected; therefore this group must be located at the 3-position and hence structure VIII is confirmed. A more detailed analysis of this effect is presented below.

It was now possible to interpret the n.m.r. spectrum of the rearrangement product, which in addition to the methoxalyl group had a chlorine atom present. On the following basis it was shown to have structure II. Substitution of a chlorine atom for either the C-1 or C-2 proton of VIII would not be expected to cause a significant shift in the location of the remaining ring-A proton in the n.m.r. spectrum.[6] The spectrum of chloro-substituted compound II is in agreement with this prediction. It shows no C-1 proton resonance, indicating the location of chlorine at this position, and the C-2 proton shows a singlet at 2.60 τ, nearly the same position as in VIII. All other peaks, including the low-field C-5 proton doublet of VIII, are essentially unchanged in the spectrum of II.

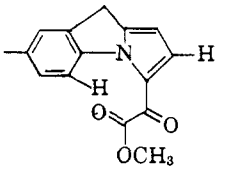
We now return to a detailed consideration of the influence of the 3-methoxalyl group on the n.m.r. spectra of II and VIII. Conjugation of the oxalyl ketonic carbonyl with the ring-A pyrrole system requires coplanarity. The most energetically favorable conformation of the ester carbonyl group is that in which its strong dipole–dipole interaction with the ketonic carbonyl group is reduced to a minimum; *i.e.*, when the two carbonyls are in an antiparallel relationship.[7] An accommodation of these two factors leads to two favored conformations of the methoxalyl group, indicated by A and B. However, the unfavorable steric crowding (Dreiding models) of the C-5 proton with the ester carbonyl eliminates structure B as a low-energy conformational possibility; therefore structure A is the most favored conformation.

(6) The chlorine substituent has little effect on the chemical shift of the protons of aromatic rings. See L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 63.

(7) (a) V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953); (b) C. A. Coulson, *Trans. Faraday Soc.*, **42**, 106 (1946).



A



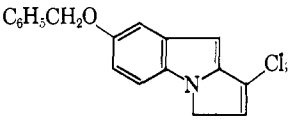
B

In conformation A the ketonic carbonyl is in proximity to the C-5 proton and is at an angle at which it should exert a strong deshielding effect on this proton.[8,9] Furthermore, the ester carbonyl is in proximity to the C-2 proton and is also at an angle at which it should strongly deshield this proton. The deshielding effects just described might not completely account for the considerable shifts of the C-5 and C-2 protons ($\Delta\tau$ = 1.69 and 1.16, respectively) that result from introduction of the methoxalyl group at C-3. Perhaps an inductive deshielding is superimposed on this diamagnetic anisotropic deshielding. In either case, a test of this explanation is provided by the changes in n.m.r. spectrum that result when the methoxalyl ketonic carbonyl is reduced with sodium borohydride. Thus, the reduction product IV, obtained from the 1-chloro-3-methoxalyl-9H-pyrroloindole (II), has an n.m.r. spectrum in which the C-5 proton doublet has returned upfield to 2.48 τ and the C-2 proton is at 3.78 τ, slightly higher than in VI. That the C-5 proton does not return to the position (3.09 τ) it had in VI might be attributed to some net deshielding effect from the methyl α-hydroxyacetate side chain (which probably rotates in contrast to the fixed conformation of the methoxalyl chain). All of the other protons of IV are in essentially the same positions they had in the spectrum of II. In addition, the new hydroxylic proton is at 6.83 τ and the proton on the carbon atom bearing the hydroxyl group is at 4.47 τ.

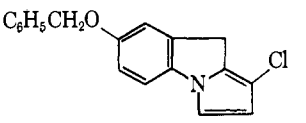
In the preceding two oxalylation examples it was not possible to isolate in crystalline form the acid chlorides present prior to the methanol treatment. However, when the methoxymethyl ketone VII[10] was treated with 2 moles of oxalyl chloride, orange needles of acid chloride IX crystallized from the solution. Treatment with methanol readily converted IX to the corresponding methyl ester X.

The reaction of oxalyl chloride with ketones is not without precedent. Deghenghi and Gaudry reported[11] the conversion of Δ^4-3-keto steroids to the corresponding 3-chloro-3,5-dienes with this reagent; however, they noted no oxalylation product. The present case is more complicated since the conversion of the ketone to the chloro-ene is accompanied by rearrangement of the 1H-pyrroloindole system to the 9H-pyrroloindole (N-phenylpyrrole) system, which moreover is subject to oxalylation. Substitution of the oxalyl group at C-3 suggests that the indicated rearrangement occurs prior to substitution and that this substitution is merely a subsequent reaction of the 9H-pyrroloindole rearrangment product. Although careful rate studies were not made, it was noted that qualitatively VI reacted with oxalyl chloride at a higher rate than did compound I. This observation lends plausibility to the concept of rearrangement prior to substitution. Molecular orbital calculations[12] indicate that the delocalization energy of the 9H-pyrroloindole (N-phenylpyrrole) system (as in V) is greater by *ca.* 4 kcal./mole than the corresponding 3H-pyrroloindole (2-vinylindole) system. Assuming that the angle-strain energy of the two systems is nearly equal, there would appear to be driving force for the indicated rearrangement independent of the effect of oxalylation.

We sought evidence of unrearranged or rearranged intermediates, such as C and D, that might have been present in the conversion of I to II, but found none either in the ultraviolet absorption spectra of samples withdrawn at various intervals (a smooth transition from the spectrum of starting material to that of II was observed) or in careful analysis of the mixture of starting material and II obtained when the partially reacted mixture was quenched with sodium acetate in methanol.



C

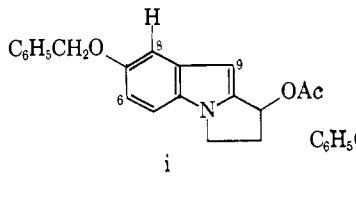


D

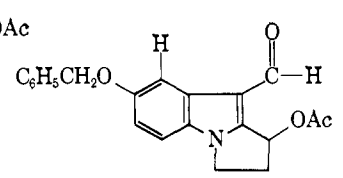
An interesting, but unresolved, facet of this study is worth noting. When ketones I or VII were treated

(8) The relationship of carbonyl group and C-5 proton is similar to the *s-cis* conformation of α,β-unsubstituted carbonyl compounds that have strongly deshielded *cis*-β-protons. See ref. 6, pp. 122–124. See also D. H. Williams, N. S. Bhacca, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 2810 (1963).

(9) Another example of deshielding in the benzenoid ring by a carbonyl substituent in an adjacent ring of a pyrroloindole is provided by compounds i and ii (ref. 1). The doublet ($J_{6,8}$ = 2 c.p.s.) of the proton at C-8 is shifted to 1.95 τ by 9-formylation from its position at 2.80 τ in the 9-unsubstituted compound i.



i

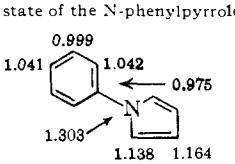


ii

(10) G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *J. Am. Chem. Soc.*, **86**, 3877 (1964).

(11) R. Deghenghi and R. Gaudry, *Can. J. Chem.*, **40**, 818 (1962).

(12) These calculations were made by Dr. A. S. Kende of this laboratory, using a value for nitrogen, $\alpha_N = \alpha_O + 0.50\beta$, that Boekelheide[13] found to fit best for the related cycl[3.2.2]azine system. The conjugation energy of the N-phenylpyrrole system is 15.498β and that of the vinylindole system is 15.280β. Dr. Kende has also calculated the following electron distribution for the ground state of the N-phenylpyrrole system.



It is evident that in this system the α- and β-pyrrole positions are nearly equally electronegative in the ground state. However, the transition state for electrophilic substitution should be more highly stabilized at the α-position (long conjugation) than at the β-position (crossed conjugation). In fact, Dr. Kende's calculation of the conjugation energies for the pyrrolenine cation intermediates, using the parameters $\alpha_N = \alpha_C + 2\beta$ and $\beta_{CN} = \beta_{CC}$, indicates that α-substitution should be favored by 0.264β. This expectation is in agreement with the generally recognized[14] preference for substitution at the pyrrole α-position.

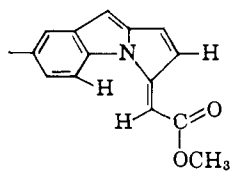
(13) R. J. Windgassen, Jr., W. H. Saunders, Jr., and V. Boekelheide, *J. Am. Chem. Soc.*, **81**, 1459 (1959).

(14) (a) A. Albert, "Heterocyclic Chemistry," The Athlone Press, University of London, London, 1959, p. 155; (b) A. H. Corwin in "Heterocyclic Compounds," Vol. 1, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, p. 300; (c) A. R. Katritzky and J. M. Lagowski, "Heterocyclic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1960, p. 162.

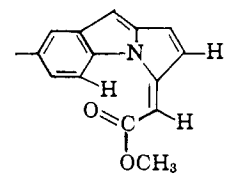
with 1 molar equiv. of oxalyl chloride, essentially no reaction occurred and starting ketones were recovered in almost quantitative yield. With 2 molar equiv., a high yield of oxalylated rearrangement product was obtained. With intermediate amounts of oxalyl chloride and ketone I the formation of low to moderate yields of oxalylated rearrangement product was indicated (spectroscopic evidence). An attractive speculation is that 1 mole of oxalyl chloride complexes reversibly with 1 mole of ketones I or VII, necessitating additional oxalyl chloride to promote reaction. However, it was not possible to demonstrate the existence of such a complex by ultraviolet absorption spectra or by quenching a mixture of 1 mole of ketone and 1 mole of oxalyl chloride in methanolic sodium acetate.

Finally, we note the facile dehydration of 9H-pyrroloindole-α-hydroxyacetate IV to the interesting highly conjugated pyrroloindole III. The former compound was prone to decomposition on recrystallization or even on contact of its solutions with drying agents. In one case a methylene chloride solution of IV was dehydrated by magnesium sulfate at room temperature. The product of this dehydration, after purification, consisted of golden needles that melted with decomposition at 140° and gave good analyses for $C_{21}H_{16}NO_3Cl$. The relatively long wave length ultraviolet absorption maximum (407 mμ) suggested a highly conjugated system, while infrared absorption maxima at 5.9 and 6.2 μ indicated that the methyl ester group was conjugated with at least one double bond. These data lead to structure III as most reasonable for the dehydration product of IV. This structure is supported by the n.m.r. spectrum which has the usual pattern of benzyl group and ring-C aromatic protons (C-5 not strongly deshielded) and, in addition, three low-field protons at 2.63, 3.65, and 4.12 τ. These three are evidently the vinyl protons at C-2, C-9, and that on the exocyclic double bond.

The absorption at 4.12 τ is reasonably expected[15] to be caused by the proton on the exocyclic double bond and the absorption at 3.65 τ is most probably attributed to the C-9 proton.[16] The vinyl proton that absorbs at 2.63 τ must therefore be at C-2. This low value is evidently due to strong deshielding by the ester carbonyl, which should be in proximity to the C-2 proton at an angle at which deshielding results, since of the two possible configurations about the exocyclic double bond only the configuration (E) having this arrangement would be free from serious steric compression (as between the ester carbonyl and C-5 proton in F).



E



F

(15) The α-proton of $(CH_3)_2C{=}CHCO_2CH_3$ absorbs at 4.38 τ (ref. 6, p. 61).

(16) Many 1H-pyrrolo[1,2-a]indoles have the C-9 proton absorption at the normal β-indole position of *ca.* 3.65–3.87 τ. See L. A. Cohen, J. W. Daly, H. Kny, and B. Witkop [*J. Am. Chem. Soc.*, **82**, 2185 (1960)] for a discussion of the indole n.m.r. spectra.

This situation closely parallels the deshielding of the C-2 proton in A, and its absorption at 2.63 τ is not far from that (2.52 τ) observed in A.

Experimental

General.—**Melting points** are corrected. **Ultraviolet spectra** were determined in methanol (unless otherwise specified) using a Cary recording spectrophotometer. **Infrared spectra** were determined in potassium bromide disks on a Perkin–Elmer spectrophotometer (Model 21). **Nuclear magnetic resonance** spectra were determined in deuteriochloroform on a Varian A-60 spectrometer with tetramethylsilane as an internal standard. **Solutions** were dried over anhydrous magnesium sulfate and concentrated under aspirator pressure on a rotary evaporator.

Methyl 7-Benzyloxy-1-chloro-9H-pyrrolo[1,2-a]indole-3-oxalate (II).—To an ice-cooled solution of 1.10 g. (4 mmoles) of 7-benzyloxy-2,3-dihydro-1-oxo-1H-pyrrolo[1,2-a]indole (I) in 50 ml. of methylene chloride was added a solution of 1.02 g. (8 mmoles) of oxalyl chloride in 8 ml. of methylene chloride.[2] Hydrogen chloride was slowly evolved. After 18 hr. the mixture was concentrated under reduced pressure. The residual tar could not be crystallized; however, treatment with methanol converted it to a yellow crystalline substance. Recrystallization of this substance from methanol with charcoal decolorization afforded 0.83 g. (54%) of methyl 7-benzyloxy-1-chloro-9H-pyrrolo[1,2-a]indole-3-carboxylate (II) as yellow needles, m.p. 135–136°; λ_{max} 5.75 (ester carbonyl), 6.05 (oxalyl keto group), no 1-ketone at 5.85 μ; ultraviolet spectrum in Fig. 1; n.m.r.: 6.35 (two protons, C-9 methylene), 6.05 (three protons, methoxyl), 4.95 (two protons, benzylic methylene), 3.10 (doubled doublet, $J_{5,6}$ = 9 c.p.s., $J_{6,8}$ = 2 c.p.s., C-6 proton), 3.00 (doublet $J_{6,8}$ = 2 c.p.s., C-8 proton), 2.60 (C-2 proton), 2.55 (five protons, phenyl), 1.50 (doublet, $J_{5,6}$ = 9 c.p.s., C-5 proton) τ; negative silver nitrate test.

Anal. Calcd. for $C_{21}H_{16}ClNO_4$ (381.80): C, 66.06; H, 4.23; Cl, 9.25; N, 3.67. Found: C, 66.12; H, 4.23; Cl, 9.45; N, 3.80.

When an ice-cooled solution of 1.10 g. (4 mmoles) of 7-benzyloxy-2,3-dihydro-1-oxo-1H-pyrrolo[1,2-a]indole (I) in 50 ml. of methylene chloride was treated with 0.56 g. (4 mmoles) of oxalyl chloride and the mixture was kept at 5° for 2 days, treated with methanol, and concentrated, 1.02 g. of a pale yellow solid that had an infrared absorption spectrum identical with that of starting material was obtained.

A mixture of 1.10 g. (4 mmoles) of 7-benzyloxy-2,3-dihydro-1-oxo-1H-pyrrolo[1,2-a]indole (I) and 0.38 g. (6 mmoles) of oxalyl chloride in 50 ml. of methylene chloride at 5° was examined in an ultraviolet spectrophotometer at intervals after 2000-fold dilution with methylene chloride. After 2 days the chromophore of starting material had decreased an estimated 30% and after 3 days it appeared that a mixture of *ca.* 55% starting material and 45% of the oxalylated rearrangement product was present.

Methyl 7-Benzyloxy-1-chloro-9H-pyrrolo[1,2-a]indole-3-(α-hydroxyacetate) (IV).—A suspension of 295 mg. (0.80 mmole) of methyl 7-benzyloxy-1-chloro-9H-pyrrolo[1,2-a]indole-3-oxalate (II) in 30 ml. of methanol was treated with 60 mg. (1.6 mmoles) of sodium borohydride. After 10 min. the mixture was concentrated under reduced pressure and the residue was treated with water and methylene chloride. The organic layer was washed with sodium bicarbonate solution, dried, and concentrated as *n*-hexane was added. Cooling this concentrate afforded 110 mg. of white crystals, m.p. 108–112°. Recrystallization from methanol gave 70 mg. (24%) of methyl 7-benzyloxy-1-chloro-9H-pyrrolo[1,2-a]indole-3-(α-hydroxyacetate) (IV), m.p. 139°; λ_{max} 2.85, 5.75 μ; 271 (ε 15,000) mμ; n.m.r.: 6.83 (OH), 6.22 (two protons, C-9 methylene), 6.13 (three protons, methyl ester), 4.88 (two protons, benzylic methylene), 4.47 (-CHOH-), 3.78 (C-2 proton), 3.05 (doubled doublet, $J_{5,6}$ = 9 c.p.s., $J_{6,8}$ = 2 c.p.s., C-6 proton), 2.88 (doublet, $J_{6,8}$ = 2 c.p.s. C-8 proton), 2.50 (five protons, phenyl), 2.48 (doublet, $J_{5,6}$ = 9 c.p.s., C-5 proton) τ.

Anal. Calcd. for $C_{21}H_{18}ClNO_4$ (383.82): C, 65.70; H, 4.73; Cl, 9.24; N, 3.65. Found: C, 65.94; H, 4.56; Cl, 10.96; N, 3.62.

Methyl 7-Benzyloxy-1-chloropyrrolo[1,2-a]indole-3-methylenecarboxylate (III).—When a solution of methyl 7-benzyloxy-1-chloro-9H-pyrrolo[1,2-a]indole-3-(α-hydroxyacetate) (IV) in methylene chloride (prepared from 3.82 g. of methyl 7-benzyloxy-1-chloro-9H-pyrrolo[1,2-a]indole-3-oxalate (II) by the procedure

described above) was dried over magnesium sulfate for 16 hr. at room temperature, the solution turned black. It was filtered and concentrated under reduced pressure and the dark residue was purified by chromatography on Florisil[17] with benzene as eluent. Concentration of the golden eluate afforded 236 mg. of golden yellow plates. Recrystallization from methanol gave 195 mg. (5%) of methyl 7-benzyloxy-1-chloropyrrolo[1,2-*a*]indole-3-methylenecarboxylate (III) as golden needles, m.p. 146°; λ_{max} 5.9, 6.2 μ; 261 (ϵ 12,000), 280 (ϵ 11,000), 407 (ϵ 23,000) mμ; n.m.r.: 6.23 (three protons, methyl ester), 4.93 (two protons, benzylic), 4.12 (proton on exocyclic double bond), 3.65 (C-9 proton), 2.63 (C-2 proton), 3.05 (doubled doublet, $J_{5,6}$ = 9 c.p.s., $J_{6,8}$ = 2 c.p.s., C-6 proton), 2.88 (doublet, $J_{6,8}$ = 2 c.p.s., C-8 proton), 2.75 (doublet, $J_{5,6}$ = 9 c.p.s., C-5 proton), 2.60 (five protons, phenyl) τ.

Anal. Calcd. for $C_{21}H_{16}ClNO_3$ (365.80): C, 68.93; H, 4.41; Cl, 9.69; N, 3.83. Found: C, 69.15; H, 4.68; Cl, 10.17; N, 3.38.

Methyl 7-Benzyloxy-9H-pyrrolo[1,2-*a*]indole-3-oxalate (VIII).—An ice-cooled solution of 520 mg. (2 mmoles) of 7-benzyloxy-9H-pyrrolo[1,2-*a*]indole (VI)[5] in 10 ml. of methylene chloride was treated with 254 mg. (2 mmoles) of oxalyl chloride. After 2 hr. the mixture was concentrated under reduced pressure and the residue was treated with methanol and solid sodium bicarbonate. This mixture was boiled and filtered, then cooled. Tan prisms, m.p. 83–85°, crystallized from the filtrate. Recrystallization from methanol afforded 283 mg. (41%) of methyl 7-benzyloxy-9H-pyrrolo[1,2-*a*]indole-3-oxalate (VIII) as yellow needles, m.p. 83–85°; λ_{max} 5.75 (ester carbonyl), 6.05 (oxalyl keto group); ultraviolet spectrum in Fig. 1; n.m.r.: 6.18 (two protons, C-9 methylene), 6.03 (three protons, methoxyl), 4.95 (two protons, benzylic methylene), 3.78 (doublet, $J_{1,2}$ = 4 c.p.s., C-1 proton), 3.08 (doubled doublet, $J_{5,6}$ = 9 c.p.s., $J_{6,8}$ = 2 c.p.s., C-6 proton), 3.03 (doublet, $J_{6,8}$ = 2 c.p.s., C-8 proton), 2.60 (five protons, phenyl), 2.53 (doublet, J = 4 c.p.s., C-2 proton), 1.40 (doublet, J = 9 c.p.s., C-5 proton) τ.

Anal. Calcd. for $C_{21}H_{17}NO_4$ (347.35): C, 72.61; H, 4.93; N, 4.03. Found: C, 72.56; H, 5.04; N, 3.72.

1-Chloro-3-chlorooxalyl-7-methoxy-6-methyl-9H-pyrrolo[1,2-*a*]indole (IX).—To an ice-cooled solution of 1.08 g. (5 mmoles) of 2,3-dihydro-7-methoxy-6-methyl-1-oxo-1H-pyrrolo[1,2-*a*]indole (VII)[10] in 75 ml. of methylene chloride was added a solution of 1.27 g. (10 mmoles) of oxalyl chloride in 10 ml. of methylene chloride. After 20 min. the orange needles that separated were collected, washed with cold methylene chloride, and dried. This procedure gave 0.45 g. of 1-chloro-3-chlorooxalyl-7-methoxy-6-methyl-9H-pyrrolo[1,2-*a*]indole (IX), m.p. 154–160°. Work-up of the mother liquor and wash gave 0.58 g. of orange needles, m.p. 142–145°. After two recrystallizations from methylene chloride, orange needles, m.p. 164–167°, were obtained; λ_{max} 5.65 (acid chloride carbonyl), 6.03 (oxalyl keto group) μ, no 1-keto group; $\lambda_{max}^{CHCl_3}$ 247 (ϵ 13,000), 305 (ϵ 10,000), 330 (ϵ 10,000) mμ; positive test with alcoholic silver nitrate; n.m.r.: 7.72 (three protons, 6-methyl), 6.36 (two protons, C-9 methylene), 6.15 (three protons, O-methyl), 3.07 (C-8 proton), 2.70 (C-2 proton), 1.60 (C-5 proton) τ.

Anal. Calcd. for $C_{15}H_{11}Cl_2NO_3$ (324.15): C, 55.58; H, 3.42; Cl, 21.88; N, 4.32. Found: C, 55.85; H, 3.57; Cl, 22.01; N, 4.48.

When a mixture of 86 mg. (0.4 mmole) of 2,3-dihydro-7-methoxy-6-methyl-1-oxo-1H-pyrrolo[1,2-*a*]indole (VII) and 51 mg. (0.4 mmole) of oxalyl chloride in 5 ml. of ether was kept at 25° for 20 hr., then concentrated under reduced pressure, the tan solid residue (80 mg.) had an infrared absorption spectrum identical with that of starting material.

Methyl 1-Chloro-7-methoxy-6-methyl-9H-pyrrolo[1,2-*a*]indole-3-oxalate (X).—A sample of 1-chloro-3-chlorooxalyl-7-methoxy-6-methyl-9H-pyrrolo[1,2-*a*]indole (IX) was dissolved in warm methanol. The yellow solid that crystallized from the solution was methyl 1-chloro-7-methoxy-6-methyl-9H-pyrrolo[1,2-*a*]indole-3-oxalate (X), m.p. 148°; λ_{max} 5.77 (ester carbonyl), 6.05 (oxalyl keto group) μ; 247 (ϵ 13,000), 305 (ϵ 10,000), 330 (ϵ 10,000,) mμ; n.m.r.: 7.77 (three protons, 6-methyl), 6.24 (two protons, C-9 methylene), 6.18 (three protons, C-7 methoxyl), 6.04 (three protons, methyl ester), 3.13 (C-8 proton), 2.68 (C-2 proton), 1.57 (C-5 proton) τ.

Anal. Calcd. for $C_{16}H_{14}ClNO_4$: C, 60.09; H, 4.41; Cl, 11.09; N, 4.38; mol. wt., 319.74. Found: C, 60.18; H, 4.61; Cl, 11.07; N, 4.88; mol. wt., 329.

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(17) Florisil is the trademark of the Floridin Co. for a magnesia–silica gel adsorbent.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO., PEARL RIVER, NEW YORK]

The Mitomycin Antibiotics. Synthetic Studies. IV.[1] Introduction of the 9-Hydroxymethyl Group into the 1-Ketopyrrolo[1,2-*a*]indole System

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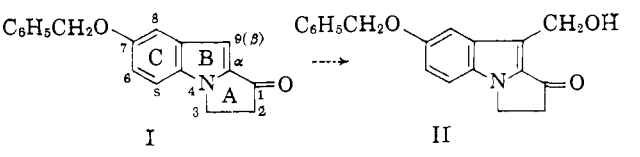
The development of a method for preparing 9-hydroxymethylpyrrolo[1,2-*a*]indoles (*e.g.*, II) bearing a group such as a carbonyl in ring A was important to the synthesis of mitomycin analogs. It was not possible to prepare such compounds by Dieckmann cyclizations with 1-cyanoethyl-2-carbethoxyindoles having potential hydroxymethyl groups at the 3-position. However, by formylation at C-9 (directly in poor yield or in higher yield *via* ketone reduction, acetylation, 9-formylation, deacetylation, and oxidation) of a precyclized 1-ketopyrrolo[1,2-*a*]indole (I), followed by preferential reduction of the 9-formyl group with diborane, a useful method for preparing compounds such as II was obtained. The 1-keto group of II effectively stabilized the potentially labile 9-hydroxymethyl group.

As part of a comprehensive program for the synthesis of analogs of the mitomycin antibiotics[2] it was necessary to develop a useful method for the introduction of the 9-hydroxymethyl substituent into a pyrrolo[1,2-*a*]indole having at the 1-position a functional group (*e.g.*, carbonyl) suitable for subsequent elaborations in ring A of the aziridine and other groups.[3]



I II

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