# Isolation of Crystalline Keto–Enol Tautomers. Conversion into Indoles and Oxindoles[1]

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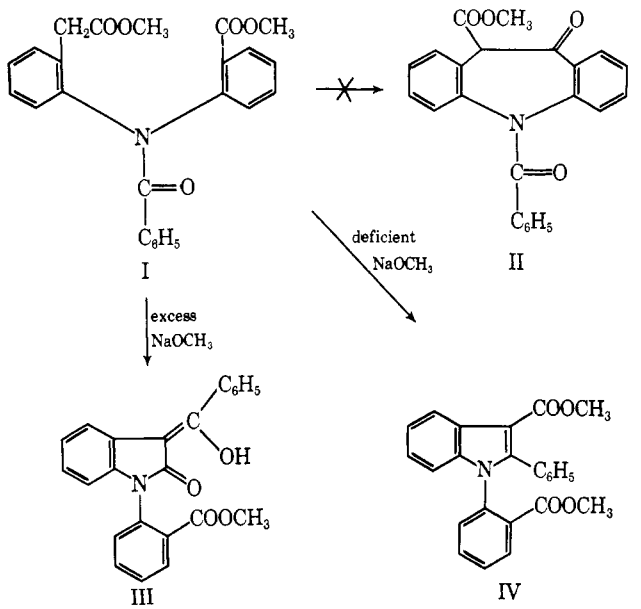
**Abstract:** Although treatment of the N-benzoyldiphenylamine diesters I and VI with excess sodium methoxide furnished oxindoles III and VII, the reaction between I and a deficient amount of sodium methoxide, followed by acidification, afforded the indole IV. When VI was treated with a deficient amount of the same base, the enol IX was obtained. This could be converted into the tautomeric keto compound X. Both keto and enol isomers were converted into oxindoles with excess base and indoles with acid. Equilibration of the tautomers was studied, the mixtures being analyzed by nmr.

Several years ago, we reported that the reaction between the diester I and a slight excess of commercial sodium methoxide in benzene failed to give the anticipated Dieckmann product II.[2] Instead, the oxindole III was obtained in good yield.[3] Recently, additional supplies of the oxindole were needed and the original procedure was repeated. Surprisingly, little or no oxindole was formed and a new compound, shown to be the indole diester IV, was isolated in 63% yield.




The correct structure of IV was suggested by elemental analyses, which indicated the loss of a mole of water, and by spectra. The ultraviolet spectrum was indicative of the indole nucleus while infrared bands at 5.79 and 5.87 $\mu$ suggested that both of the original ester groups were intact. This was confirmed by the nmr spectrum, which exhibited O-methyl singlets at $\delta$ 3.75 and 3.43, and by saponification with excess base to furnish a dibasic acid in high yield. Hydrolyzing IV with an equimolar amount of base afforded a low yield of half-ester acid identical with material previously obtained as a by-product in the synthesis of III[2] (see Experimental Section for structure).

It was not clear at first why the course of the cyclization reaction had changed. The starting diester I was shown by infrared comparison to be identical with the earlier sample. The original experimental procedure including the work-up—acidification of the cooled mixture followed by extraction with ether and crystallization from methanol—had been followed as closely as possible. Therefore, the most likely culprit appeared to be the sodium methoxide, since it had been taken from a bottle that was at least 2 years old.[4] Accordingly, a new bottle of sodium methoxide was obtained[4] and the reaction repeated. The product, obtained in 72% yield, was the oxindole III.

A determination of base content then demonstrated that the sodium methoxide, although still a free-flowing white powder, had indeed deteriorated. While the new base gave an assay of 97%, the old sodium methoxide had a base content of only 80%. Therefore, instead of using a 10% excess of base in the cyclization reaction, a 10% excess of amide I had actually been present. In order to confirm that the divergent results were due solely to the quantity of base used, the reaction was repeated with the old sodium methoxide, making sure that a large excess was actually used. As expected, the oxindole III was obtained. On the other hand, use of a deficient amount of the new base led to the indole IV in good yield.[5]

It was still not obvious why excess base should furnish oxindole and deficient base lead to indole. It seemed possible that oxindole formation was reversible, and the reaction had been forced to completion only by conversion to the oxindole's enolate anion with excess base. However, when the oxindole was treated with a deficient amount of sodium methoxide in benzene, none of the indole resulted, III being recovered in high yield. Therefore, oxindole formation seems to be irreversible. When the indole IV was subjected to the original reaction conditions, using excess sodium methoxide plus a little water (water had been evolved in forming IV), none of the oxindole resulted. The indole was recovered, along with anticipated indole acids. Therefore, as expected, indole formation also appears to be irreversible.

(1) Preliminary report: J. W. Schulenberg, *J. Amer. Chem. Soc.*, **90**, 1367 (1968).

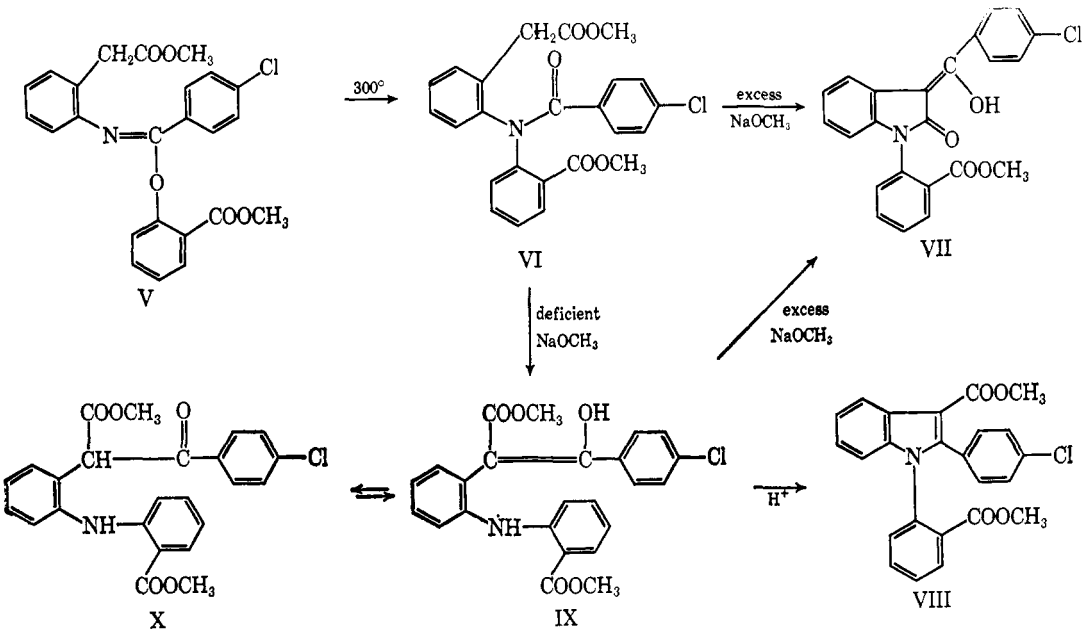
(2) J. W. Schulenberg and S. Archer, *ibid.*, **83**, 3091 (1961).

(3) Although depicted in the original paper[2] as the keto tautomer, the oxindole has been shown by nmr to exist as the enol.

(4) The sodium methoxide was supplied by Matheson Coleman and Bell.

(5) Use of a catalytic amount (0.2 mol) of sodium methoxide resulted in a 75% recovery of amide I contaminated with indole IV. Traces of III were also formed.

**Scheme I**



The clue to the mechanism of the cyclization reactions was provided by a study of the *p*-chloro analog VI (Scheme I). This was synthesized by Chapman rearrangement of the imidate V.[6] Compound V, in turn, was prepared from methyl *o*-(*p*-chlorobenzamido)-phenylacetate. This was treated with phosphorus pentachloride to give the corresponding benzimidoyl chloride. Reaction with the sodium salt of methyl salicylate then afforded V.

The reaction between VI and excess sodium methoxide provided the oxindole VII in 71% yield. This compound, identified by elemental analysis (loss of methanol in its formation) and by spectral similarity to III, exhibited a single $OCH_3$ peak at $\delta$ 3.63 while the enolic proton was found at $\delta$ 12.4.[7] Mild basic hydrolysis converted VII into the corresponding carboxylic acid which melted without decarboxylation at 242–249°. The isomeric azepinone structure analogous to II was accordingly ruled out.

As in the case of the deschloro compound, the cyclization of VI had originally been attempted with the old sodium methoxide. As a result, a deficient amount of base had been inadvertently used and the oxindole VII was not produced. In this case, however, the indole VIII was not the major product. Instead, a substance isomeric with the starting amide was obtained. This compound gave a positive test with ferric chloride and therefore appeared to be enolic. This was confirmed by the nmr spectrum which exhibited a band far downfield at $\delta$ 13.5.[7] Two sharp singlets at $\delta$ 3.80 and 3.70 indicated the presence of two carbomethoxy groups while a peak at $\delta$ 9.33 suggested a N–H linkage. The compound was therefore assigned structure IX. In a second run in which a deficient amount of "new" sodium methoxide was used, the enol IX was isolated in 54% yield.

Recrystallization of the enol from hexane was uneventful, but serendipity again intervened when the compound was recrystallized from methanol. Although the resulting crystals all appeared to be similar prisms, they fell into two distinct classes according to size. The small crystals, which comprised the major portion of the product, were starting enol IX. The larger prisms, however, were soon shown to be a new substance since they gave a negative reaction with ferric chloride. Accordingly, a portion of enol was again dissolved in boiling methanol. After refluxing for 1 hr, the mixture was seeded with the large prisms. Slow crystallization furnished the keto isomer X in 68% yield.

The structure of X was suggested by the presence of an additional carbonyl band in the infrared spectrum. The nmr curve still showed the N–H band at $\delta$ 9.38 and the $OCH_3$ singlet of the aromatic ester group at $\delta$ 3.72. However, the other $OCH_3$ singlet was now found a little further downfield at $\delta$ 3.88 while the peak due to the enolic hydrogen had been replaced by a new singlet at $\delta$ 5.75. In the ultraviolet spectrum, run in ethanol, a strong peak at 285 m$\mu$ in the more highly conjugated enol was reduced to a shoulder in X. After 3 hr at room temperature, both ethanol solutions gave essentially the same ultraviolet curve.

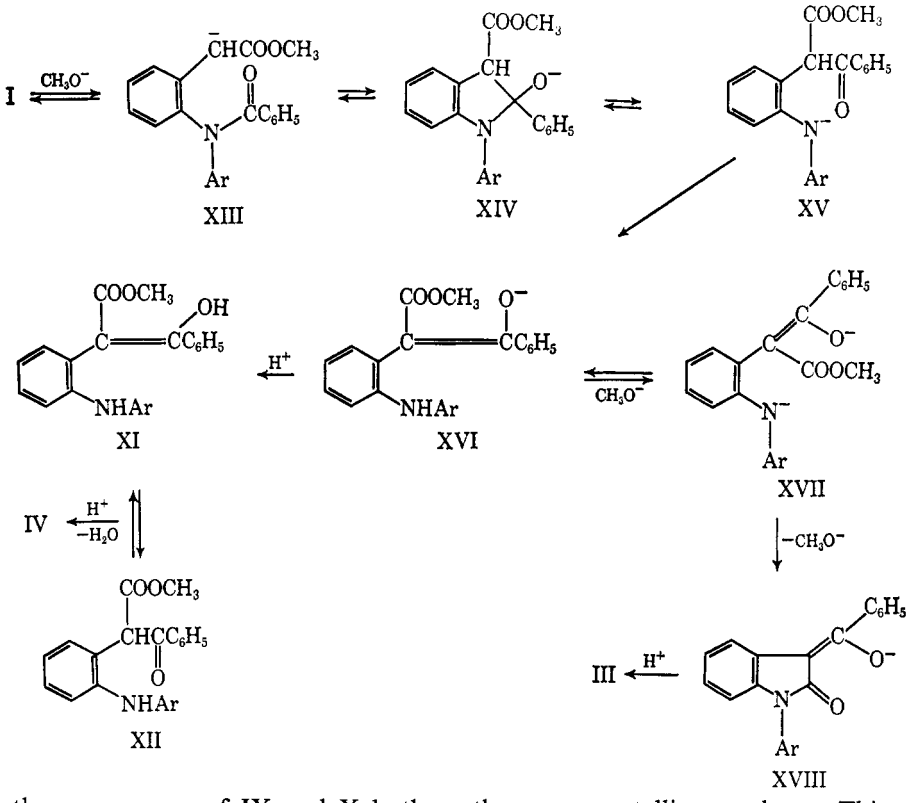
Although isolation of keto–enol tautomers has been accomplished many times in the past,[8] IX and X proved to be of interest because of their slow rate of interconversion in the absence of catalysts. Solutions of either tautomer in deuteriochloroform were essentially unchanged after 24 hr at room temperature, as shown by their nmr curves. In the solid state, the tautomers were essentially unchanged after 1 year at room temperature, as indicated by their infrared spectra. Furthermore, the enol could be recrystallized from boiling hexane to give a 90% recovery of solid shown to be at least 95% enol. On the other hand, when a drop of triethylamine was added to the deuteriochloroform solution of either tautomer and the nmr spectrum determined, both compounds produced the same curve, indicating rapid formation of the equilibrium mixture.

(6) J. W. Schulenberg and S. Archer, *Org. Reactions*, **14**, 1 (1965).

(7) The enolic proton in hydrogen-bonded enols is found far-downfield. In acetylacetone, for example, it absorbs at $\delta$ 13.58: L. W. Reeves, *Can. J. Chem.*, **35**, 1351 (1957).

(8) For example: L. Knorr, O. Rothe, and H. Averbeck, *Ber.*, **44**, 1138 (1911); L. Knorr and H. P. Kaufmann, *ibid.*, **55**, 232 (1922); R. C. Fuson, W. D. Emmons, and G. W. Parshall, *J. Amer. Chem. Soc.*, **76**, 5466 (1954).

**Scheme II**



The differences in the nmr curves of IX and X both with respect to the aliphatic ester group and the enolic hydrogen, facilitated the analysis of mixtures of the tautomers[9] and showed that the equilibrium mixture resulting from triethylamine catalysis contained about 30% enol and 70% keto.

Thermal equilibration was also studied. When solutions in methanol were refluxed for 4 hr, both tautomers gave the same mixture which contained 74% keto. On the other hand, in refluxing hexane (24 hr) the enol form predominated,[10] the equilibrium mixture containing only 45% of the keto isomer. Heating the enol for 3 hr on the steam bath without solvent furnished a mixture in which the keto compound was present to the extent of 70%. Under the same conditions, but starting with X, the product still contained 82% keto, showing that equilibration of at least one of the tautomers was incomplete. When heated at 120–125° for 4 hr complex mixtures, apparently containing VII, VIII, IX, and X, resulted from each isomer.

When a solution of the keto tautomer in deuteriochloroform was treated with one drop of trifluoroacetic acid, equilibration to the enol did not occur. Instead, the initial nmr spectrum, which suggested protonation of X on nitrogen, changed slowly, the final spectrum indicating conversion to the indole VIII. Similar treatment of the enol with trifluoroacetic acid also produced indole (peak at $\delta$ 3.45), but the reaction was slower. Again, there was no sign of tautomeric equilibration. The reaction was then repeated on a preparative scale, each tautomer giving the same crystalline product. This was identical with material isolated in 13% yield from the reaction of VI with a deficient amount of sodium methoxide, the new compound having been obtained from the mother liquors of the enol. That the product was indeed the anticipated indole VIII was shown by its spectral similarity to IV. The ultraviolet spectrum showed the typical indole peaks, the infrared curve exhibited carbonyl bands at 5.81 and 5.94 $\mu$ and the nmr spectrum had singlets at $\delta$ 3.78 and 3.45. A second by-product obtained in 4% yield from the reaction of VI and sodium methoxide was shown to be a half-ester acid of VIII.

It is well known that bromine generally reacts instantaneously with enols, but much more slowly with keto tautomers. Therefore IX and X were each subjected to dropwise addition of bromine in carbon tetrachloride. In each case, the bromine color was discharged at once. The product, obtained from each isomer, proved to be the indole VIII rather than a bromination product. Presumably, hydrobromic acid generated by initial bromination catalyzed rapid cyclization of IX and X to the indole.

Since IX and X could serve as intermediates for synthesizing VIII, it seemed likely that they could also be converted into the oxindole VII. Therefore, each isomer was treated with excess sodium methoxide in benzene. In each case, the oxindole was obtained in good yield.

The results with the *p*-chloro derivatives prompted further work with the original amide I. A benzene solution of I was treated with a deficient amount of sodium methoxide at room temperature and the reaction followed by thin layer chromatography. Within 7 min, the starting material was almost completely gone. A trace of oxindole was apparently formed, but the major component, as indicated by a more rapidly moving spot on the tlc plate, appeared (by $R_f$) to be

(9) For analyses of keto–enol mixtures by nmr, see, for example, ref 7; also S. Hünig, H. Buysch, H. Hoch, and W. Lendle, *Ber.*, **100**, 3996 (1967); G. Klose and E. Uhlemann, *Tetrahedron*, **22**, 1373 (1966).

(10) In the communication[1] keto predominance was erroneously reported.

indole IV. That this was *not* the case was soon apparent. After 1 hr, tlc analysis of the mixture showed essentially no further change. However, when additional sodium methoxide was then added, such that excess base was present, the picture changed. Within 30 min, considerable oxindole had been formed, although the less polar component was still present. However, after 2 hr the rapidly moving component was gone, conversion to oxindole being essentially complete. Since it had been shown before that the indole is not converted to oxindole by sodium methoxide in benzene, the intermediate could not have been IV. The usual work-up afforded crystalline oxindole, confirming the tlc results.

In a parallel experiment, instead of adding more base after 1 hr, the mixture was worked up more carefully than in prior runs. Only a slight excess of HCl was added to the cold mixture and the product was quickly extracted. Alternatively, acetic acid was used for the acidification. In each case, the product was a gum from which crystalline material could not be isolated (in earlier runs, crystalline indole IV was obtained at this stage). The nmr spectrum of the gum showed clearly the presence of both enol (XI, Scheme II) and keto (XII) compounds, peaks at $\delta$ 13.5 and 5.78 being prominent. In the mixture obtained after acetic acid work-up, there was about 40% keto, 25% enol, and 10% indole. No oxindole was apparent. Addition of HCl to a solution of the gum in benzene then effected ring closure, crystalline indole IV being isolated in fair yield.

The dependence of the course of the reaction on the amount of sodium methoxide used could now be explained (Scheme II). The initially formed anion XIII is converted into XIV which might be expected to pick up a proton and dehydrate. Since little or no IV is actually formed at this stage this could only be a minor pathway. However, it could account for the small amount of indole half-ester acid formed,[2] the water produced in the dehydration causing the partial hydrolysis. The major pathway must involve benzoyl transfer to give XV. In our earlier paper,[2] we suggested that XV loses methoxide ion to produce oxindole, but this cannot be an important path since very little oxindole is formed when a deficient amount of base is used.

The next step in the scheme involves proton transfer to give the stable enolate anion XVI. This anion appears to be the intermediate which the tlc results show to be formed within a few minutes. In the absence of excess base, XVI presumably remains unchanged in the mixture, its molar quantity being roughly equal to that of the sodium methoxide used. Upon acidification, the enol and keto compounds XI and XII can be obtained by rapidly removing them from contact with acid. Otherwise, rapid cyclization to the indole IV occurs. In the case of the *p*-chloro analog, acidification gives the kinetically controlled product IX. Either because of an inherently slower rate of cyclization or because of a fortuitously more rapid extraction away from the aqueous phase, the cyclization of IX to VIII occurred to a much smaller extent than did the cyclization to IV, permitting facile isolation of the *p*-chloro enol. The fact that the mixture from careful acidification of XVI contained the keto compound XII as the predominant tautomer indicates either that protonation of XVI occurs both on oxygen and on carbon, or that the initially formed product tautomerizes more rapidly than does the *p*-chloro analog.

With a deficient or an equivalent amount of base, XVI is not converted in any appreciable quantity to oxindole III. This is probably because of the stability of the enolate anion, its formation from XV (the logical intermediate for the oxindole) being essentially irreversible. Since excess base does produce oxindole, XVI must be converted into a different intermediate, undoubtedly the dianion XVII. Although the equilibrium between mono- and dianion must lie to the left, the dianion can react by a second path, intramolecular expulsion of methoxide affording the stable oxindole enolate anion XVIII. Since this is formed irreversibly, a small excess of base is sufficient to force the conversion of XVI into oxindole to completion.

## Experimental Section

**General.** Melting points were determined in capillaries and are corrected. Elemental analyses were provided by Mr. K. D. Fleischer and staff. Spectra were run under the direction of Dr. R. K. Kullnig. Ultraviolet spectra were run in 95% ethanol (Cary spectrophotometer, Model 15), infrared spectra in potassium bromide (Perkin-Elmer Model 21), and nmr spectra in 10–20% deuteriochloroform (Varian A-60; internal TMS) unless otherwise stated. Plates coated with silica gel were used for tlc; ultraviolet light revealed the position of compounds on the plates.

**Methyl 1-(*o*-Methoxycarbonylphenyl)-2-phenyl-3-indolecarboxylate (IV).** **A.** A mixture of 12.1 g (0.03 mol) of methyl N-benzoyl-N-[*o*-(methoxycarbonylmethyl)phenyl]anthranilate (I),[2] 1.8 g of "old" sodium methoxide[4] (0.026 mol assuming a base content of 80%), and 125 ml of dry benzene was used, the procedure being that previously followed for the synthesis of III.[2,11] Crystallization from methanol provided 4.8 g of IV, mp 138–143°. Concentration of the mother liquors gave a second crop, 2.5 g, mp 136–141°. The total yield was 63% based on I or 71% based on the sodium methoxide. Recrystallization of the first crop from methanol gave the colorless analytical sample, mp 140–144°.

*Anal.* Calcd for $C_{24}H_{19}NO_4$: C, 74.79; H, 4.97; N, 3.63. Found: C, 74.67; H, 4.85; N, 3.56.

Ultraviolet spectrum, $\lambda_{max}$ 235 m$\mu$ ($\epsilon$ 36,200) and 294 (19,600); ir, 5.79 and 5.87 $\mu$; nmr, singlets at $\delta$ 3.75 and 3.43. Since methyl 1,2-diphenyl-3-indolecarboxylate exhibits its singlet at $\delta$ 3.72, the downfield peak may be assigned to the ester group on the indole ring.

**B.** A mixture of 4.03 g (0.01 mol) of I, 0.43 g (0.008 mol) of "new" sodium methoxide,[4] and 50 ml of benzene was refluxed 2 hr (without distilling off solvent) to furnish 2.1 g (55% on I, 68% on base) of IV, mp 134–142°. The material was shown to be identical with the product from A by ir comparison and mixture melting point.

**C.** The mixture from 3 mmol of I after careful work-up with HCl (containing keto and enol, XI and XII; see last part of Experimental Section, A, below) was dissolved in dry benzene and treated with two drops of 2 *M* ethanolic HCl. After 16 hr at room temperature, $MgSO_4$ was added to remove water, and the solvent was then removed. The nmr spectrum of the resulting gum showed that the indole IV was now the main component.[12] The NH and keto CH bands were gone. Crystallization of the remaining gum from methanol gave 0.37 g of IV, mp 138–143°. There was no melting point depression when mixed with the indole from A, but the melting point of the oxindole III was depressed. A second crop, mp 135–141°, raised the total yield to 0.49 g (42% based on I).

**1-(*o*-Carboxyphenyl)-2-phenyl-3-indolecarboxylic Acid.** A mixture of 4.0 g (0.0104 mol) of IV, 10 g of KOH, 50 ml of methanol,

(11) Later, when the reaction was followed by tlc, it became evident that the synthesis could be carried out at room temperature without nitrogen and without distilling off solvent.

(12) I am indebted to Dr. R. K. Kullnig and Miss C. M. Martini for nmr analysis of mixtures and for spectral interpretations which were instrumental in establishing the structures of new compounds.

and 20 ml of water was stirred and refluxed for 22 hr. After dilution with water and filtration, the filtrate was acidified with HCl and the resulting solid washed with water. Recrystallization from absolute ethanol afforded 3.15 g (86%) of white solid (two crops), mp 215–218° dec (variable melting point). The uv spectrum had $\lambda_{max}$ 233 mμ (sh, ε 33,500) and 294 (17,200). The ir curve showed carbonyl bands at 5.91 and 6.04 μ, the latter peak presumably resulting from the carboxyl on the indole ring (by analogy with 1,2-diphenyl-3-indole-carboxylic acid[2]).

*Anal.* Calcd for $C_{22}H_{15}NO_4$: C, 73.94; H, 4.23; N, 3.92; neut equiv, 178.7. Found: C, 73.95; H, 4.14; N, 3.81; neut equiv, 179.4.

**Methyl 1-(*o*-Carboxyphenyl)-2-phenyl-3-indolecarboxylate.** To a solution of 770 mg (2 mmol) of IV in 40 ml of methanol was added 108 mg (2 mmol) of "new" sodium methoxide and 10 ml of water. After stirring and refluxing for 4 hr, water and aqueous salt solution were added, and the neutral material was extracted with ether to give 140 mg of unreacted diester IV. Acidification of the aqueous solution gave a solid which was recrystallized from absolute ethanol to furnish 0.17 g (23%) of white solid, mp 259–266°, identical by mixture melting point, ir, and uv with previously obtained half-ester.[2] The structure previously assigned to this compound (with the carboxyl on the indole ring), on the basis of ir evidence,[2] appears to be incorrect. The nmr spectrum ($CD_3SOCD_3$) shows the O-methyl singlet at δ 3.62. This corresponds to the singlet at δ 3.63 (in the same solvent) in methyl 1,2-diphenyl-3-indolecarboxylate,[2] showing that the ester group on the indole ring is intact in the half-ester. Since the diester IV resonates at δ 3.63 and 3.42 in $CD_3SOCD_3$, the absence of the latter peak in the half-ester confirms the removal of the $OCH_3$ group on the benzene ring by the partial saponification reaction. The apparent failure of the half-ester to decarboxylate on heating, in contrast to the usual behavior of 3-indolecarboxylic acids, is in accord with the suggested structure.

*Anal.* Calcd for $C_{23}H_{17}NO_4$: C, 74.38; H, 4.61; neut equiv, 371.4. Found: C, 74.24; H, 4.50; neut equiv, 380.7.

**Methyl *o*-[3-(α-Hydroxybenzylidene)-2-oxo-1-indolinyl]benzoate (III). A.** Using a 10% excess of the "new" sodium methoxide, and following the earlier procedure,[2] III was prepared in 72–78% yield. In one run the mixture was refluxed 2 hr without distillation of solvent to give 73% of III.[11] The filtrate from one run gave a 2% yield of indole half-ester (above). Examination of the mother liquors by tlc failed to reveal any indole diester IV. The nmr spectrum of III revealed a broad band due to the enolic proton at δ 11.7 and a singlet at δ 3.63 for the $OCH_3$ group.

**B.** A mixture of 4.03 g (0.01 mol) of I, 1.35 g (0.02 mol assuming a base content of 80%) of "old" sodium methoxide, and 50 ml of dry benzene was refluxed 2 hr to give 2.3 g (62%) of oxindole, mp 120–126°. Although less pure than other samples, the structure of the product was proven to be III by mixture melting point and infrared analysis, the latter indicating the absence of indole IV.

**Reversibility Studies. A.** The oxindole III was refluxed in benzene with 0.8 equiv of "new" sodium methoxide. The usual work-up returned starting material. Neither the recovered solid nor the mother liquors showed (by tlc) the presence of any indole IV.

**B.** The indole IV was refluxed 1 hr with 2.0 equiv of "new" sodium methoxide and 1 equiv of water in benzene. Solid was present, presumably sodium salts. The solution, analyzed by tlc ($CHCl_3$) contained IV but apparently no oxindole. Aqueous acetic acid was added and the mixture filtered to give a 40% yield of 1-(*o*-carboxyphenyl)-2-phenyl-3-indolecarboxylic acid (80% based on the water added), mp 211–214° dec. Extraction of the filtrate with ether and recrystallization from methanol gave a 40% recovery of IV, mp 142–145°.

**Methyl *o*-(*p*-Chlorobenzamido)phenylacetate.** A solution of 29.3 g (0.15 mol) of methyl *o*-nitrophenylacetate[2] in 175 ml of methanol was shaken under hydrogen with 50 mg of platinum oxide on a Parr hydrogenator, keeping the temperature below 45°. Solvent removal with minimal heating left the *o*-amino ester as an orange oil which was then dissolved in 75 ml of cold pyridine. The solution was kept below 10° and stirred during the dropwise addition of 31.7 g (0.18 mol) of *p*-chlorobenzoyl chloride over 45 min. After standing overnight at room temperature, 75 ml of acetic acid was added followed by an equal volume of water. The product, 34.6 g, induced to crystallize by scratching, could be recrystallized from aqueous methanol or from heptane, the latter solvent giving 30.5 g (67%) of tan crystals, mp 102–109°. The analytical sample, obtained as a white solid by recrystallization from isopropyl alcohol had mp 107.5–110°.

*Anal.* Calcd for $C_{16}H_{14}ClNO_3$: C, 63.26; H, 4.65; Cl, 11.67; N, 4.61. Found: C, 63.31; H, 4.76; Cl, 11.66; N, 4.95.

***o*-(Methoxycarbonyl)phenyl *p*-Chloro-N-(*o*-methoxycarbonylmethyl)phenyl Benzimidate (V).** A mixture of 81.4 g (0.27 mol) of methyl *o*-(*p*-chlorobenzamido)phenylacetate and 56.2 g of phosphorus pentachloride was briefly swirled in a 500-ml flask. Evolution of HCl began almost at once and the mixture soon became fluid, permitting a magnetic stirrer to operate. After gas evolution had subsided, the mixture was heated for 30 min at 55° to provide a clear yellow solution. The phosphorus oxychloride was then removed on the water pump (maximum temperature 60°), last traces being removed by addition and subsequent evaporation of toluene. This left ***p*-chloro-N-(*o*-methoxycarbonylmethyl)phenylbenzimidoyl chloride** as a red-brown oil which was used at once without purification.[13]

A solution of 48.6 g (0.32 mol) of methyl salicylate in 50 ml of methanol was added to 18.9 g (0.35 mol) of sodium methoxide in 300 ml of methanol. The solution was cooled in an ice-bath and the above imidoyl chloride, in 75 ml of absolute ether, was added, with stirring, over a 15-min period. After stirring at room temperature for 2.5 hr, the mixture was poured into water[14] and the resulting solid extracted into ether. Crystallization from benzene–hexane gave 83.9 g (71%) of pale yellow prisms, mp 96–99.5°. The analytical sample, obtained from an earlier run by recrystallization from isopropyl alcohol, melted at 96.5–99°. The ir spectrum had peaks at 5.84 and 6.01 μ. The methylene group absorbed at δ 3.47 in the nmr, while the methoxy singlets were found at δ 3.80 and 3.53.

*Anal.* Calcd for $C_{24}H_{20}ClNO_5$: C, 65.83; H, 4.60; Cl, 8.10; N, 3.20. Found: C, 66.18; H, 4.65; Cl, 8.07; N, 3.31.

**Methyl N-(*p*-Chlorobenzoyl)-N-[*o*-(methoxycarbonylmethyl)phenyl]anthranilate (VI).** The imidate V (83.9 g) was heated for 20 min at 280–300° (Wood's metal bath) and the product crystallized from absolute ethanol to furnish 76.5 g (91%) of tan solid, mp 104.5–110.5°. In a similar run on a smaller scale, an 85% yield of sharper melting product resulted. Recrystallization from ethanol gave an 88% recovery of solid, mp 109–111°. The infrared spectrum revealed carbonyl bands at 5.78 and 6.05 μ. The nmr curve showed the expected ratio of aliphatic–aromatic protons. However, instead of three singlets, uneven multiplets were found at δ 3.33–4.00, including two predominant peaks at δ 3.78 and 3.48. Hindered rotation, producing nonequivalence of protons within each group, is presumably the reason for the anomalous spectrum. The deschloro analog I had a similar nmr spectrum.

*Anal.* Calcd for $C_{24}H_{20}ClNO_5$: C, 65.83; H, 4.60; Cl, 8.10; N, 3.20. Found: C, 66.35; H, 4.81; Cl, 8.16; N, 3.52.

**Methyl *o*-[3-(*p*-Chloro-α-hydroxybenzylidene)-2-oxo-1-indolinyl]benzoate (VII). A.** To 43.8 g (0.1 mol) of amide VI in 250 ml of warm, dry, benzene under nitrogen was added carefully 6.5 g (0.12 mol) of "new" sodium methoxide. The mixture was then stirred and refluxed for 3 hr, solvent being distilled off in the process and replaced from time to time with fresh, dry benzene. The cloudy red mixture was then cooled, water was added dropwise, then excess dilute HCl was added. Since insoluble material was present, chloroform sufficient to effect solution was added and the aqueous phase was extracted with additional $CHCl_3$. The combined organic solutions were dried over magnesium sulfate, most of the solvent was removed, and the concentrated solution was then diluted with methanol to afford 29.0 g (71%) of yellow solid, mp 176–183°. Recrystallization from ethyl acetate furnished the analytical sample, mp 179–183°.

*Anal.* Calcd for $C_{23}H_{16}ClNO_4$: C, 68.07; H, 3.97; Cl, 8.74; N, 3.45. Found: C, 68.01; H, 3.92; Cl, 8.90; N, 3.39.

The uv spectrum had a shoulder at $\lambda_{max}$ 270 mμ (ε 13,750) and a peak at 323 (12,500). The ir curve exhibited bands at 5.80, 6.09, and 6.16 μ. The enolic nature of VII was suggested by a strongly positive $FeCl_3$ reaction and proved by the nmr spectrum which

(13) N-(*o*-Methoxycarbonylmethyl)phenylbenzimidoyl chloride (the intermediate for synthesizing the precursor of I), previously reported as an oil,[2] could be crystallized from the phosphorus oxychloride solution by addition of hexane. The product, tan needles, mp 60–67°, 80–82% yield, readily hydrolyzed in the presence of moisture. Over-all yields of imidates were not improved by the use of crystalline chloride.

(14) The mixture should be basic. In one run with the deschloro analog, the "old" sodium methoxide (80%) had been used, supposedly in 12% excess over imidoyl chloride. Accordingly, the final aqueous mixture was actually acidic. None of the desired imidate was isolated and only traces remained in the resulting oil (tlc, ether), indicating rapid hydrolysis in the acidic medium.

showed the enolic proton at δ 12.4, the multiplet due to the 12 aromatic protons at 6.55–8.33 and the methoxy singlet at 3.63.

**B.** A mixture of 876 mg (2 mmol) of enol IX (below), 162 mg (3 mmol) of sodium methoxide, and 20 ml of dry benzene was stirred and refluxed 3 hr, then worked up as above to give 590 mg (73%) of VII, mp 170–179°. Identity with the oxindole from A was proved by mixture melting point and ir comparison.

**C.** Keto X (131 mg, 0.3 mmol) was similarly treated with 32 mg (0.6 mmol) of sodium methoxide in 5 ml of benzene to give 62 mg (51%) of oxindole. Identity with the product from A was shown by melting point, mixture melting point, and ir comparison.

***o*-[3-(*p*-Chloro-α-hydroxybenzylidene)-2-oxo-1-indolinyl]benzoic Acid.** A solution of 16.2 g (0.04 mol) of oxindole ester VII, 12 g of KOH, 200 ml of dimethylformamide, and 30 ml of water was stirred 1.5 hr at 40–44°. After diluting with 600 ml of water, cooling, and filtering, the iced filtrate was acidified with HCl. The precipitated solid was washed with water, dried, and recrystallized from 900 ml of toluene to afford 9.6 g (61%) of yellow solid, mp 210–250°. Two more recrystallizations from the same solvent gave 7.9 g (50%), mp 242–249°; uv, $\lambda_{max}$ 324 mμ (ε 11,900); ir, 5.88, 5.94, 6.08, and 6.15 μ. Nmr ($CD_3SOCD_3$) did not distinguish between the keto and enol forms. No enolic proton was found as low as δ 25, nor was a singlet found near δ 6. The proton in question could be masked by the aromatic absorption or spread out downfield.

*Anal.* Calcd for $C_{22}H_{14}ClNO_4$: C, 67.44; H, 3.60; N, 3.58; neut equiv, 391.8 or 195.9. Found: C, 67.50; H, 3.78; N, 3.51; neut equiv, 203.2.

**Methyl 1-(*o*-Carboxyphenyl)-2-(*p*-chlorophenyl)-3-indolecarboxylate and Methyl 4-Chloro-β-hydroxy-α-{*o*-[*o*-(methoxycarbonyl)-anilino]phenyl}cinnamate (IX).** To a solution of 23.2 g (0.053 mol) of amide VI in 250 ml of dry benzene was added 2.86 g of "new" sodium methoxide. This would be 0.053 mol if pure, but since analysis had indicated a base content of 97%, a very slight excess of amide was actually used. The mixture was stirred for 3 hr at room temperature, then cooled in an ice bath. Water (100 ml) was added followed by excess aqueous HCl. Extracting with ether, drying, and removing most of the solvent *in vacuo* gave an oil which was diluted with hexane to furnish 0.9 g (4%) of yellow solid. Recrystallization from methanol gave the analytical sample, mp 259–275°. Spectral data showed the product to be the half-ester acid analogous to the deschloro analog previously prepared (see above). The uv curve $\lambda_{max}$ 235 mμ (ε 30,800) and 297 (ε 17,600) pointed to the indole structure. The ir spectrum had carbonyl bands at 5.86 and 5.92 μ while the nmr ($CD_3SOCD_3$) exhibited a singlet at δ 3.68 due to the ester group on the indole ring. There was no sign of a peak at δ 3.45 (see VIII below) showing that the ester group on the benzene ring had been hydrolyzed. The acid melted without decarboxylation indicating the absence of a carboxyl group on the indole ring.

*Anal.* Calcd for $C_{23}H_{16}ClNO_4$: C, 68.07; H, 3.97; N, 3.45. Found: C, 67.46; H, 4.24; N, 3.99.

The solvent was removed from the mother liquors and the residue crystallized from benzene–hexane to give only 3.8 g of enol IX. However, a larger second crop was obtained by crystallization of the gum (after solvent removal) from absolute ethanol. The total yield was 12.5 g (54%) of almost white solid. Two recrystallizations from hexane furnished the white analytical sample, prisms, mp 110–122°. The enol gave a purple color with ferric chloride.

*Anal.* Calcd for $C_{24}H_{20}ClNO_5$: C, 65.83; H, 4.60; Cl, 8.10; N, 3.20. Found: C, 65.31; H, 4.50; Cl, 8.35; N, 3.21.

Spectral and other data for the enol are included with data for the keto isomer X, below.

**Methyl α-(*p*-Chlorobenzoyl)-*o*-[(*o*-methoxycarbonyl)anilino]phenylacetate (X).** When 2 g of the enol, mp 100–118°, was recrystallized from 140 ml of methanol, 1.4 g of prisms was recovered. Most of the material was small prisms, mp 105–124°, purple color with $FeCl_3$, spectrally similar to starting enol. However, a few larger prisms, mp 93–98°, negative $FeCl_3$ reaction, were also formed. A mixture of 1.5 g of enol was then refluxed for 1 hr in 150 ml of methanol. The solution was seeded with the large prisms and then cooled for 6 days to give 1.02 g (68%) of keto, pale yellow crystals, mp 93–99°.

*Anal.* Calcd for $C_{24}H_{20}ClNO_5$: C, 65.83; H, 4.60; Cl, 8.10; N, 3.20. Found: C, 66.37; H, 4.70; Cl, 8.29; N, 3.30.

The uv spectra of the tautomers showed the expected differences due to increased conjugation in the enol. The enol had $\lambda_{max}$ 219 mμ (ε 32,700), 241 sh (18,800), 285 (19,200), and 350 (8700). The keto showed $\lambda_{max}$ 216 mμ (ε 34,900), 242 sh (17,700), 258 (18,200), 284 sh (12,900), and 347 (7800). The main difference in the uv curves was the prominent peak at 285 mμ in the enol. After standing 3 hr at room temperature both solutions (95% ethanol) gave essentially the same uv curve, which resembled more closely that of the keto isomer. The enol had ir bands at 3.04, 5.70 (weak), 5.94, and 6.08 μ while the keto compound exhibited a new strong band at 5.77, in addition to peaks at 3.05, 5.95, and a small shoulder at 6.08 μ. In $CHCl_3$ solution, a peak found at 5.75 μ in the keto, presumably due to the aliphatic ester, occurred only as a small shoulder in the enol. Peaks at 3.01 and 5.93 μ occurred in both curves, but only the enol had a band at 6.11 μ (bonded carbonyl) and broad absorption at 3.5–4.0 μ (bonded OH). The nmr spectra, previously discussed in the paper, showed no evidence for enol in the keto isomer.[12] The analytical sample of enol, however, was shown by nmr to contain traces of keto compound, confirming the ir data. The tautomers exhibited similar tlc behavior ($R_f$ 0.25 in chloroform) and mixture melting points were variable.

**Methyl 2-(*p*-Chlorophenyl)-1-(*o*-methoxycarbonylphenyl)-3-indolecarboxylate (VIII). A.** The mother liquors from the reaction between a slight excess of VI and sodium methoxide (after removal of the half-ester and the enol) were concentrated to a small volume and cooled to give 5.3 g of solid, mp 90–173°, containing keto, enol, and indole (by nmr). Recrystallization from absolute ethanol gave 2.8 g (13% yield) of indole, mp 192–198°, and another recrystallization from the same solvent gave the analytical sample, 2.5 g, mp 194–197.5°; uv, $\lambda_{max}$ 234 mμ (ε 31,900) and 295 (17,400); ir, 5.81 and 5.94 μ; nmr, δ 3.78 and 3.45. The nmr spectrum in $CD_3SOCD_3$ had singlets at δ 3.67 and 3.45, the downfield peak resulting from the indole ester group (by analogy with methyl 1,2-diphenyl-3-indolecarboxylate, δ 3.63).

*Anal.* Calcd for $C_{24}H_{18}ClNO_4$: C, 68.65; H, 4.32; Cl, 8.45; N, 3.34. Found: C, 68.55; H, 4.33; Cl, 8.63; N, 3.39.

**B.** The enol IX (300 mg, 0.68 mmol) in 5 ml of chloroform was treated with five drops of trifluoroacetic acid. After 70 hr at room temperature, the red solution was refluxed 0.5 hr. Dilution with hexane then gave 175 mg (61%) of VIII, mp 192–197°. Identity with material from A was proven by mixture melting point and ir comparison.

**C.** To 44 mg of keto (X, 0.10 mmol) in 1 ml of chloroform, was added one drop of trifluoroacetic acid. After 46 hr at room temperature, the solution was diluted with hexane to furnish 25 mg (60%) of indole, mp 197–200°.

**D.** To 438 mg (1 mmol) of enol in 10 ml of chloroform a solution of bromine in carbon tetrachloride was added dropwise until the bromine color persisted. Dilution with hexane gave 230 mg of VIII, mp 189–194°, identical with the material from A by mixture melting point and ir comparison. A second crop raised the yield to 330 mg (79%). Similar treatment of X also furnished VIII.

**Equilibration of Tautomers.**[12] **A.** The amount of enol was determined by peak height at δ 3.80, keto at δ 3.88. The results thus obtained were confirmed approximately by integration of the sharp enolic hydrogen band at δ 13.5 and the –CHCO keto peak at δ 5.75. The error appears to about ±3%. Integration of the NH peak at δ 9.35 and the $OCH_3$ band at δ ~3.71, found in both tautomers, served as a check on the total amounts of IX plus X. The presence of oxindole VII and indole VIII was detected by signals at δ 3.63 and 3.45, respectively. The enol used was material recrystallized once from hexane, mp 102–109°, shown by nmr to contain over 95% enol. The keto compound, mp 93–99°, contained no detectable enol.

**B.** A solution of enol in $CDCl_3$ at room temperature showed a slight increase in keto content after 24 hr, but after standing for 7 days the solution still contained over 90% enol. A little indole was also present. The keto isomer exhibited no perceptible change in nmr spectrum after 24 hr. When a drop of triethylamine was added to a solution of the keto isomer in $CDCl_3$ and the nmr spectrum determined at once, the keto:enol ratio was 71:29. The spectrum did not perceptibly change during the next week. Similar treatment of the enol led to a keto:enol ratio of 68:32, essentially unchanged (71:29) after 5 hr.

**C.** Addition of a drop of trifluoroacetic acid to the keto isomer in $CDCl_3$ gave quickly signals at δ 6.48, 3.80, and 3.48. The first peak could be due to protonation on nitrogen while the others are consistent with conversion to indole VIII. After standing over the weekend the solution gave a spectrum lacking the 6.48 band and showing complete conversion to indole. When the enol was treated similarly, an approximately 1:1 mixture of enol and indole resulted after 1 week at room temperature.

**D.** After refluxing 200 mg of keto tautomer in 25 ml of methanol for 4 hr, the solvent was removed *in vacuo* at below 30°. Nmr analysis of the resulting gum in $CDCl_3$ indicated a keto:enol ratio of 75:25. Similar treatment of the enol gave a 73:27 ratio.

**E.** That equilibration in hexane was slow was proved by recrystallizing 5.8 g of enol from boiling hexane and recovering 5.2 g (90%) of material containing less than 5% keto. When 200 mg of either isomer was refluxed 5.5 hr in 25 ml of hexane, the keto gave a mixture containing 51% keto while the product from the enol contained 43% keto. After refluxing for 24 hr, the keto gave a keto:enol ratio of 43:57, showing that equilibration had not been complete after 5.5 hr. The enol gave a 45:55 ratio after 24 hr. The latter mixture also contained 4% of indole while the mixture from the keto isomer contained about 12% indole.

**F.** The keto isomer was heated without solvent for 3 hr on the steam bath. The product had a keto:enol ratio of 82:18. The enol tautomer gave a 70:30 ratio, and, in addition contained about 9% of oxindole and a trace of indole. When the keto compound was heated for 4 hr at 120–125°, the complex mixture appeared to contain 36% oxindole, 34% keto, 20% indole, and 10% enol. Similarly, the enol gave a mixture containing 46% oxindole, 27% indole, 19% keto, and 8% enol. It should be noted that the presence of oxindole is based solely on the sharp signal at $\delta$ 3.63, so this assignment must be considered tentative.

**N-Benzoyl-N-(*o*-carboxymethyl)phenylanthranilic Acid.** In our earlier paper,[2] we reported that hydrolysis of I with aqueous KOH gave a compound which we believed was a half-ester N-benzoyl acid. The carbonyl band at 5.78 $\mu$ was assigned to the ester group. However, the nmr spectrum ($CD_3SOCD_3$) clearly shows that no ester group is present. The product is actually the expected dibasic acid, one of the carboxyl groups absorbing at an unusually low wavelength.

*Anal.* Calcd for $C_{22}H_{17}NO_5$: C, 70.66; H, 4.60; N, 3.75; neut equiv, 197.0. Found: C, 70.39; H, 4.57; N, 3.73; neut equiv, 187.7.

**Keto–Enol Mixture, XI and XII.** The reaction was followed by tlc using unpurified $CHCl_3$ (stabilized with ethanol) to develop the plates. The amide I gave a circular spot, $R_f$ 0.15. The oxindole III gave an elongated spot, centered at $R_f$ 0.10. The indole IV, as well as the keto–enol mixture had $R_f$ 0.40, while the indole acid remained at the origin. The $R_f$ values were not always reproducible. The mixtures were generally acidified with acetic acid before putting on the plate.

**A.** To 1.21 g (3 mmol) of amide I in 15 ml of dry benzene, was added at room temperature 151 mg (2.8 mmol) of "new" sodium methoxide. After stirring 2 min, tlc showed, in addition to starting I, a strong spot at $R_f$ 0.40. After 7 min, the solid had dissolved, and the clear light brown solution was found to contain only a trace of I. A trace of oxindole was also present but the only predominant spot was that at 0.40. The tlc picture remained the same after 1 hr. The mixture was cooled in an ice bath and 0.3 ml (3.6 mmol) of concentrated aqueous HCl was added. After brief stirring, the organic material was extracted with ether, the extracts were dried, and the solvent was removed below room temperature to give a tan gum which, by nmr, contained about 30% keto XII and 13% enol XI. The gum was converted into indole IV (first part of Experimental Section, C, above).

Use of 0.2 ml (3.5 mmol) of acetic acid for the acidification in a parallel run gave a mixture which contained 40% keto XII ($\delta$ 3.83, 3.65, 5.78), 25% enol XI ($\delta$ 3.78, 3.65, 13.5), and about 10% indole IV ($\delta$ 3.72, 3.40). The NH peak was found at $\delta$ 9.28. Other constituents of the mixture were not identified, although starting amide I must have comprised roughly 7% of the mixture. Apparently little if any oxindole was present.

**B.** In another parallel run, after 70 min at room temperature, instead of adding acid, 108 mg (2 mmol) of additional sodium methoxide was added and stirring was continued. Within 2 hr, the spot with $R_f$ 0.4 (XI plus XII) was gone, being replaced by the typical elongated oxindole spot. The usual work-up with excess HCl, afforded 0.57 g (51%) of oxindole III, mp 127–134°.

# Thermal Decompositions of N-Nitrosohydroxylamines. II. N-Acetyl-N-nitroso-O-*t*-butylhydroxylamine

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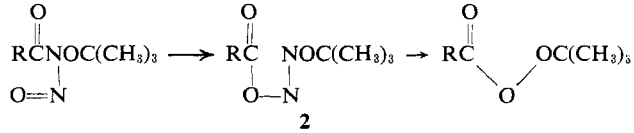
**Abstract:** The decomposition of N-acetyl-N-nitroso-O-*t*-butylhydroxylamine has been studied under conditions of varying viscosity. The products include *t*-butyl peracetate and methyl *t*-butyl ether. The yields of these products increase with increasing viscosity. Oxygen-18-labeling studies show the perester is formed with at least 92% equilibration of the carbonyl oxygen label. The amount of cage combination from the deaminative radical pair is significantly lower than that which occurs from decomposition of the corresponding *t*-butyl peracetate.

Oxy–oxy radical combination reactions have been the subject of several recent investigations.[1] Our preliminary study[2] of the decomposition of N-benzoyl-N-nitroso-O-*t*-butylhydroxylamine (**1a**) suggested that this class of compounds could serve as a convenient source of acyloxy–*t*-butoxy radical pairs under conditions where the corresponding peresters are stable. We now wish to report the results of our studies on the products of decomposition of N-acetyl-N-nitroso-O-*t*-butylhydroxylamine (**1b**) under conditions of varying viscosity.



**1a**, R = $C_6H_5$
**b**, R = $CH_3$

## Results

Solutions of the starting nitroso compound were obtained by nitrosation of N-acetyl-O-*t*-butylhydroxylamine with nitrosyl chloride and pyridine at low temperature. The infrared spectra of freshly prepared solutions obtained in this way show nitroso group absorption at 1541 $cm^{-1}$ and carbonyl absorption at 1762 $cm^{-1}$. The nmr spectra of such solutions show singlets at 1.22 and 2.75 ppm in a 3:1 intensity ratio. The visible spectra of such solutions show weak maxima at 391, 407, and 427 m$\mu$. All of these observations are in accord with expectations for a simple N-nitroso compound.[3]

(1) (a) H. Kiefer, and T. G. Traylor *J. Amer. Chem. Soc.*, **89**, 6667 (1967); (b) W. A. Pryor and K. Smith, *ibid.*, **89**, 1741 (1967); (c) J. C. Martin and J. Taylor, *ibid.*, **89**, 6904 (1967).
(2) T. Koenig and M. Deinzer, *ibid.*, **88**, 4518 (1966).