The Base-catalyzed Condensation of *o*-Nitropropiophenone*

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Treatment of *o*-nitropropiophenone with sodium acetylide in liquid ammonia at −70°C gave a yellow phenol, $C_{18}H_{18}O_3N_2$, as a major product. The permanganate oxidation of the phenol gave 2-(1-carbamoylethyl)-2-methyl-3-indolinone, which was synthesized independently. From this result and the spectral data, the structure of the phenol was postulated to be 1-(*o*-hydroxyphenyl) derivative of the above indolinone. The neutral fraction of the reaction mixture gave three new compounds: 3-(*o*-Nitrophenyl)-1-pentyn-3-ol, 2-methyl-2-(2-methyl-3-indolinon-2-yl)-3(2*H*)-benzofuranone, and 3,3a-dihydro-2-hydroxy-3,3a-dimethyl-2-(*o*-nitrophenyl)-4(2*H*)-isoxazolo[2,3-*a*]indolone. Their structures were assigned from their spectral data. A mechanism for the formation of these products as well as for the base-catalyzed condensation of *o*-nitroacetophenone is discussed.

A previous paper[1] from this laboratory reported that *o*-nitroacetophenone underwent a peculiar *o*-substituent interaction to form an orange-red product, compound A, along with *o*-nitrobenzoic acid when the ketone was treated with sodium acetylide in liquid ammonia at a temperature of −70°C. Compound A was proved to be 1,3-dihydroxy-3-methyl-2-(*o*-nitrophenacylidene)-indoline.[2] The base-catalyzed condensation of *o*-nitropropiophenone was studied in order to inquire into the mechanism of the formation of compound A. This paper deals with the elucidation of the structure of the condensation products of *o*-nitropropiophenone.

o-Nitropropiophenone was previously prepared either by the nitration of propiophenone[3] or by the reaction of *o*-nitrobenzaldehyde with diazoethane.[4] We prepared the ketone by the acylation of di-*t*-butyl methylmalonate with *o*-nitrobenzoyl chloride followed by decarboxylative hydrolysis in 57% overall yield based on *o*-nitrobenzoic acid. The purity of the ketone was confirmed both by gas-chromatography and by NMR spectroscopy.

Treatment of *o*-nitropropiophenone with sodium acetylide under the same condition as that in the condensation of *o*-nitroacetophenone[1] gave yellow crystals, $C_{18}H_{18}O_3N_2$, melting at 214°C, in a yield of 54—56%. The formation of the compound by the use of sodium amide instead of sodium acetylide indicated that the acetylide did not participate in the reaction. The yellow product will be referred to as compound C in this paper.

Compound C is a weakly acidic compound (pK_a 9.5) soluble in 2N sodium hydroxide solution; it is also soluble in concentrated hydrochloric acid. The weak acidity of compound C may be attributed to a phenolic hydroxyl. The presence of the function was not detected by the ferric chloride test, but inferred from a positive ferricyanide test[5] and from the coupling reaction with *p*-nitrobenzenediazonium salt.[6] The methylation of compound C with diazomethane gave a monomethyl ether, $C_{19}H_{20}O_3N_2$; the acetylation with acetic anhydride and pyridine at a room temperature led to a monoacetyl derivative, $C_{20}H_{20}O_4N_2$, whereas heating with acetic anhydride in the presence of sodium acetate gave a diacetyl derivative, $C_{22}H_{22}O_5N_2$.[7]

The IR spectrum of compound C shows the presence of the carbonyl group and the absence of the nitro group in the molecule. Its 3000-cm^{-1} region contains a broad band of a bonded hydroxyl group besides two sharp peaks at 3520 and 3405 cm^{-1}. The disappearance of the broad band by methylation or acetylation as well as the appearance of a new band at *ca.* 1760 cm^{-1} by acetylation allowed to assign the phenolic hydroxyl to the broad band.

The ultraviolet spectra of compound C and its derivatives reveal an absorption band at 400 nm characteristic of the pseudoindoxyl.[8] A bathochromic shift by 25 nm of the maximum of compound C by the addition of alkali suggests that the phenolic function may be associated with the pseudoindoxyl system. The carbonyl bands in the infrared spectra of these compounds are also compatible with those of pseudoindoxyls.[8a] The fact that the characteristic absorption band at 400 nm remained unchanged on diacetylation requires that the indoxyl ring be substituted at the nitrogen atom.[9]

The NMR spectrum[10] of compound C shows the presence of a tertiary methyl (singlet at 1.38 ppm), a secondary methyl (doublet at 1.42 ppm), and a methine

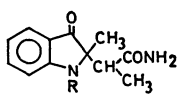
* Dedicated to Professor Munio Kotake on the celebration of the seventy-seventh anniversary of his birthday (Kiju).

1) T. Sakan, K. Kusuda, and T. Miwa, This Bulletin, **37**, 1678 (1964).
2) T. Sakan, K. Kusuda, and T. Miwa, *ibid.*, **38**, 18 (1965).
3) L. A. Elson, C. S. Gibson, and J. D. A. Johnson, *J. Chem. Soc.*, **1930**, 1128; B. L. Zenitz and W. H. Hartung, *J. Org. Chem.*, **11**, 444 (1964); J. R. Keneford and J. C. E. Simpson, *J. Chem. Soc.*, **1948**, 354.
4) C. W. Warner, E. J. Walsh, and R. F. Smith, *ibid.*, **1962**, 1232.
5) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," Interscience Publishers, New York (1957), p. 230.
6) F. Wild, "Estimation of Organic Compounds," Cambridge University Press, New York (1953), p. 96.
7) This compound is apparently an *N*-acetyl amide; the C=O absorptions at 1734 and 1696 cm^{-1} correspond to this grouping. The values, 1743—1747 and 1690—1698 cm^{-1}, are given in the literature: T. Uno and K. Machida, This Bulletin, **35**, 1226 (1962).
8) a) B. Witkop, *J. Amer. Chem. Soc.*, **72**, 614 (1950); B. Witkop and A. Ek, *ibid.*, **73**, 5664 (1951). b) J. Kerble, H. Schmid, P. Waser and P. Karrer, *Helv. Chim. Acta*, **36**, 102 (1953).
9) *N*-Acetylation of a pseudoindoxyl causes a hypsochromic shift to 340 nm[8a])
10) The NMR spectrum of this compound was measured on a Varian model A-60 instrument at the Shionogi Research Laboratory. We are indebted to Doctor Ken'ichi Takeda, the Director of the Laboratory.

(quartet at 2.88 ppm) group. The complicated bands between 6.3 and 7.7 ppm correspond to eight aromatic protons. The phenolic proton appears at 10.9 ppm, the location of a rather low-magnetic field being due to a hydrogen bonding.[11] A broad band near 6 ppm (2 protons) suggests the presence of a primary amide group, to which two sharp peaks in the 3000-cm^{-1} region of the infrared spectrum (see above) may be attributed.

The presence of the amide group was confirmed by the acid hydrolysis of compound C followed by the identification of ammonium ion by paper chromatography.[12] On the other hand, no evolution of carbon dioxide in the hydrolysis indicated that the carbamoyl group was not attached to the α-carbon atom of the indoxyl nucleus directly. Any definite organic compounds were not characterized from the hydrolysis product.

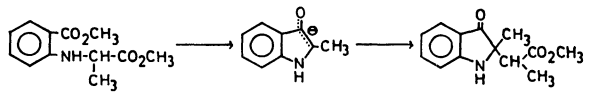
The hydrogenation of compound C either over Raney nickel under high pressure or in the presence of platinum oxide under atmospheric pressure gave a tetrahydro-compound. Tetrahydro-compound C is a phenol (pK_a 9.0), giving a positive reaction with *p*-nitrobenzenediazonium salt. This compound gave a monomethyl ether on methylation with diazomethane. The ultraviolet absorption spectra of tetrahydro-compound C and its methyl ether show no absorption band of the pseudoindoxyl system at 400 nm, but possess a new maximum at 330 nm. The spectral data of these compounds correspond to those of *N*-aryl-β-acylvinylamines (λ_{max} near 340 nm).[13] The survival of the phenolic function during the hydrogenation of the pseudoindoxyl system[8a] allowed to locate the hydroxyl group on the *N*-phenyl nucleus. From these observations structure I was postulated for compound C.



I: R=*x*-Hydroxyphenyl II: R=H

The carbon skeleton of the indoxyl nucleus was verified by the oxidative degradation of compound C. The permangenate oxidation of compound C gave a neutral compound, $C_{12}H_{14}O_2N_2$, mp 228°C. This was identified with 2-(1-carbamoylethyl)-2-methyl-3-indolinone (II), which was synthesized as follows.

Giovannini *et al.*[14] reported that the Dieckmann condensation of *N*-(*o*-ethoxycarbonylphenyl)alanine ethyl ester under atmospheric oxygen yielded 2,2'-dimethyl-[2,2'-bisindoline]-3,3'-dione (VI) instead of the expected 2-methyl-3-indolinone. In the absence of oxygen, this reaction should give the enolate anion (IV) of 2-methyl-3-indolinone, which would be alkylated with α-bromopropionate to give the ester V corresponding to the amide II. Actually, the alkylation of the Dieckmann condensation product of the dimethyl ester III[15] under the atmosphere of nitrogen occurred expectedly to give the ester V along with the *o*-alkylation product VII, the latter being not isolated but detected by the NMR spectrum of the crude product. Chromatography of the crude product gave the ester V as a crystalline state. The ester V was heated with ammonia in a sealed tube at 100°C for 8 hr to give the amide II.



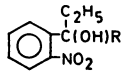
III IV V

VI VII

Although no direct proof was obtained about the position of the hydroxyl group on the *N*-phenyl nucleus, the existence of an intramolecular hydrogen bonding of the phenolic hydroxyl group inferred from the IR and NMR spectra may sufficiently allow to locate the group at the *ortho* position to the nitrogen. Hence, the structure of compound C was postulated to be 2-(1-carbamoylethyl)-1-(*o*-hydroxyphenyl)-2-methyl-3-indolinone (I, *x*=*o*).[16]

Chromatography on silicic acid of the neutral fraction of several runs of the condensation gave an oil, $C_{11}H_{11}O_3N$, and two crystalline products, $C_{18}H_{16}O_5N_2$ and $C_{18}H_{15}O_3N$, along with the unchanged ketone.

The IR spectrum of the oil revealed the presence of the hydroxyl, terminal alkyne, and nitro functions, but no carbonyl groups in it. Therefore, the oil was assumed to be 3-(*o*-nitrophenyl)-1-pentyn-3-ol (VIII), the expected product of the condensation of *o*-nitropropiophenone with sodium acetylide. The NMR spectrum of this compound is compatible with this structure. The permanganate oxidation of this compound gave a crystalline acid, $C_{10}H_{11}O_5N$, mp 154—156°C, which was assumed to be 2-hydroxy-2-(*o*-nitrophenyl)propionic acid (IX).



VIII: R=C≡CH IX: R=CO_2H

One of the crystalline products, $C_{18}H_{15}O_3N$, melting at 206—207°C, was assigned the structure of 2-methyl-2-(2-methyl-3-indolinon-2-yl)-3(2*H*)-benzofuranone (X) from its spectral data. The ultraviolet absorption spectrum of this compound showed maxima at 229, 335, and 390 nm and a shoulder at 255 nm. The absorption band at 390 nm is that characteristic of the psuedoindoxyl system and the band at 335 nm may be attri-

11) A. L. Porte, H. S. Gutowsky and I. M. Hunsberger, *J. Amer. Chem. Soc.*, **82**, 5057 (1960).

12) A. E. Steel, *Nature*, **173**, 315 (1954).

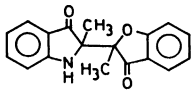
13) K. Bowden, E. A. Braude, E. R. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, **1946**, 45.

14) E. Giovannini, F. Farkas, and J. Rosales, *Helv. Chim. Acta*, **46**, 1326 (1963).

15) O. Neuenhöffer and G. Lehmann, *Chem. Ber.*, **94**, 2960 (1961).

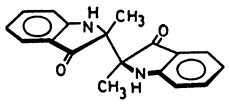
16) Attempt was made to determine the location of the hydroxyl group by the analysis of the aromatic region of the 100-MHz NMR spectrum of tetrahydro-compound C in DMSO-d_6; however, the pattern was too complicated to assign *o*-substituted benzene. The authors thank the Japan Electron Optics Laboratories for the measurement.

buted to the coumaranone system.[17] The infrared spectrum revealed the absorptions corresponding to the N–H (3400 cm^{-1}) and carbonyl (1700 cm^{-1}) groups. The existence of the two methyl groups was confirmed by two singlets (1.65 and 1.75 ppm) in the NMR spectrum.

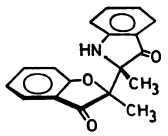


X

2,2-Dimethyl-3-indolinone shows its methyl signal at 1.32 ppm.[18] The methyl signal of the biindoxyl VI appears at 1.17 ppm, indicating a shielding effect by the keto group on the other nucleus. On the other hand, the methyl signals of the compound X is shifted extensively downfield, suggesting that the methyl groups are deshielded by the keto group on the other nucleus. These observations may be explained by postulating that the biindoxyl is a *meso* compound and the compound X is a racemoid, assuming conformations as shown in XI and XII, respectively. The conformation XII is apparently due to the compensation of the steric hindrance of two ethyl groups and of the dipole-dipole interaction between two keto groups.

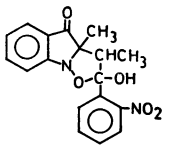


XI

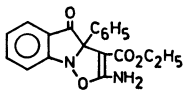


XII

Another crystalline product, $C_{18}H_{16}O_5N_2$, decomposing at 150°C, was tentatively postulated to be 3,3a-dihydro-2-hydroxy-3,3a-dimethyl-2-(*o*-nitrophenyl)-4-(2*H*)-isoxazolo[2,3-*a*]indolone (XIII) from the spectral data. Its infrared spectrum suggested the presence of the hydroxyl, carbonyl, and nitro groups. The NMR spectrum showed the existence of a tertiary methyl (1.58 ppm, singlet) and a secondary methyl (1.24 ppm, doublet) in accordance with the structure. The ultraviolet spectrum with maxima at 240, 310, and 360 nm needs some comments. 1-Hydroxy-2,2-dimethyl-3-indolinone has an absorption band at 381 nm;[19] the hypsochromic shift compared with that of 2,2-dimethyl-3-indolinone (391 nm[18]) may be due to the electrostatic attraction for the lone electron pair on the nitrogen atom exerted by the electro-negative oxygen. The *cis*-fusion of the isoxazolidine ring in the compound XIII would force the nitrogen atom to assume an sp^3-like configuration unfavorable for the unshared electron pair to conjugate with the carbonyl group, causing hence a hypsochromic shift of the absorption characteristic of the pseudoindoxyl system. This assumption is supported by the fact that the isoxazoloindolone XIV possesses an absorption band at 313 nm corresponding to the band at 310 nm of compound XIII and shows no absorption maximum over 350 nm.[20]



XIII

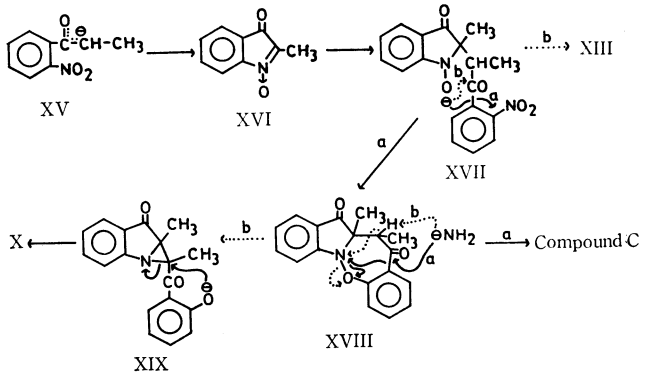


XIV

Treatment of the compound XIII with sodium amide in liquid ammonia yielded the compound X as a major product.

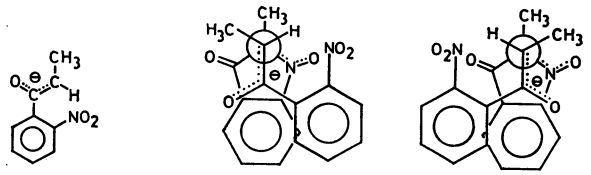
This observation and the fact that every crystalline product in this condensation was obtained as a single isomer, as inferred from the results of NMR spectroscopy, require the mechanism for the reaction to involve stereochemical consideration.

It has been pointed out[21] that the base-catalyzed condensation of *o*-nitrobenzoyl derivatives undergo cyclization to isatogens. In our case, 2-methylisatogen XVI is to be formed in the first step. Such isatogens are susceptible to nucleophilic addition at the carbon-nitrogen double bond.[22] The attack of another molecule of the enolate anion XV will produce either of the diastereoisomeric anions XVII. The attacking enolate anion should have the conformation as shown in XX because of the steric repulsion between the methyl and phenyl groups, on the one hand, and of the dipole-dipole repulsion between the carbonyl and nitro groups, on the other. The addition through the transition



XV XVI XVII XIX XVIII

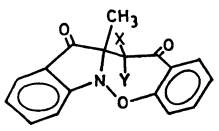
state XXI will be followed by the replacement of the nitro group by the *N*-oxide anion to form a seven-membered ring intermediate XVIII with two methyl groups in *trans*-relationship. On the other hand, the addition through the transition state XXII will cause the attack of the *N*-oxide anion on the carbonyl group rather than on the nitro group to give the compound XIII with two methyl groups in *cis* configuration.



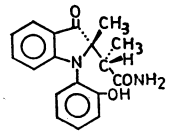
XX XXI XXII

17) P. McClockey, *J. Chem. Soc.*, **1958**, 4732.
18) R. T. Sundberg and T. Yamazaki, *J. Org. Chem.*, **32**, 290 (1967).
19) K. Nishimura and T. Miwa, unpublished work.
20) J. E. Bunney and M. Hooper. *Tetrahedron Lett.*, **1966**, 3857.
21) J. D. Loudon and G. Tennant, *Quart. Rev.*, **18**, 389 (1964).
22) D. A. Patterson and D. G. Wibberley, *J. Chem. Soc.*, **1965**, 1706.

Inspection of the framework molecular models of the intermediate XVIII proposes the conformation XXIII as the most favorite one.[23] Although the compound XIII was isolated as a by-product, the compound also may be transformed into the intermediate XVIII on prolonged exposure to sodium amide. In this case, the intermediate XVIII should have two methyl groups in *cis* relationship as shown in XXIV. The abstraction of the equatorial α-proton of the carbonyl group in XXIII will be more difficult than that of the axial α-proton in XXIV because of the stereoelectronic effect. In the former case, the attack of the amide anion to the carbonyl becomes prevailing and the reaction will proceed through the course a in XVIII to give compound C.[24] On the basis of these assumptions, compound C is expected to have two methyl groups in such a relative configuration as shown in XXV.

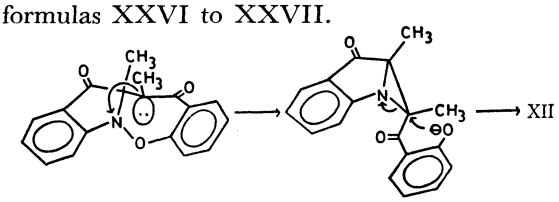


XXIII: X=H, Y=CH_3
XXIV: X=CH_3, Y=H



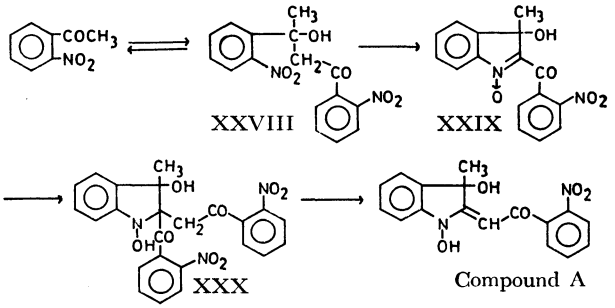
XXV

When the abstraction of the α-proton of the carbonyl group is assisted by the stereoelectronic effect, the resulting carbanion will attack on the nitrogen atom to form an aziridine intermediate XIX with liberation of a phenoxide anion,[25] which will cleave the aziridine ring to give the compound X. Since the stereochemistry of the compound X was proposed to be XII, these transformation would take a stereochemical course as shown in formulas XXVI to XXVII.



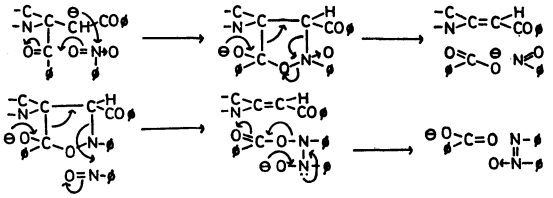
XXVI XXVII

Now, the attention is turned to the mechanism for the formation of compound A (see above). In this case, the first step of the reaction is assumed to be the aldol condensation of *o*-nitroacetophenone.[26] The product XXVIII will undergo a cyclization similar to that of *o*-nitropropiophenone to give a nitrone XXIX,[27] which will be transformed into an *N*-hydroxyindoline XXX by the addition of another mole of the enolate anion of *o*-nitroacetophenone. The oxidative deacylation of the indoline will give compound A.



XXVIII XXIX XXX Compound A

The final step needs further comment. The simple Haller-Bauer reaction[28] of XXX with base should give aliphatic carboxylic acid derivatives as observed in the case of compound C. The formation of *o*-nitrobenzoic acid in this reaction requires another type of cleavage with simultaneous oxidation. This cleavage is well interpreted by the partial structures shown in Chart 1. The participation of *o*-nitroacetophenone in this oxidation was verified by the isolation of *o,o'*-azoxyacetophenone from the neutral fraction of the reaction. This compound was identified with an authentic sample synthesized according to a procedure for the preparation of *p,p'*-azoxyacetophenone.[29]



φ=*o*-Acetyl- or *o*-nitrophenyl
Chart 1

In conclusion, it is noteworthy that no alkynol was obtained from the neutral fraction of the condensation of *o*-nitroacetophenone in contrast with the formation of the alkynol VIII in the case of *o*-nitropropiophenone.

Experimental[30]

o-Nitropropiophenone. A mixture of 66.6 g (0.289 mol) of di-*t*-butyl methylmalonate[31] and 19.0 g (0.433 mol) of

23) The possibility for the nitrogen atom to assume an sp^3-like configuration cannot be precluded; however, in this case also, the environment around the carbonyl group in the seven-membered ring is not changed so much.

24) Methoxyamine reacts with Grignard compounds to give corresponding amines. R. Brown and W. E. Jones, *J. Chem. Soc.*, **1946**, 781.

25) O. C. Dermer and G. E. Ham, "Ethyleneimine and Other Aziridines," Academic Press, New York (1969), p. 59.

26) With *o*-nitropropiophenone also, the aldol condenstion may be possible; however, the condensate corresponding to XXVIII cannot be cyclized to an isatogen and will be reversed to the original ketone in this case.

27) Both of the nitro groups have the opportunity to react with the methylene group. The triagonal carbon of the keto group might prevent the formation of a five-membered ring. Actually, 1,3-bis(*o*-nitrophenyl)-1-propanone gave 1-hydroxy-2-(*o*-nitrobenzoyl)indole rather than 2-benzylisatogen (N. Nakatsuka and T. Miwa, unpublished work).

28) K. E. Hamlin and A. W. Weston, "Organic Reactions," Vol. IX, John Wiley, New York (1957), p. 1.

29) V. M. Clark, J. B. Hobbs, and D. W. Hutchinson, *Tetrahedron*, **25**, 4241 (1949).

30) All melting points are not corrected. Unless otherwise noted, UV, IR, and NMR spectra were measured in solution in 95% ethanol, chloroform, and deuteriochloroform, and presented in λ_{max} nm (log ε), ν_{max} cm^{-1}, and δ ppm, respectively. The instruments used for the measurements are a Hitachi model EPS-2 recording spectrophotometer, a Hitachi model EPI-2 infrared spectrophotometer, and a JEOLCO model C-60 spectrometer. The authors are much indebted to Mr. Jun'ichi Goda for the elemental analyses.

31) Pure material of this ester (bp 94—95°C/7 mmHg) was prepared from the corresponding acid (mp 134—136°C) and isobutylene in *ca.* 60% yield according to a general method for the *t*-butyl ester [R. E. Strube, "Organic Syntheses," Vol. 37, p. 34 (1957)].

54.4% sodium hydride dispersed in mineral oil (washed several times with benzene) in 1500 m*l* of dry benzene was heated under reflux with stirring for 2 hr. To the mixture was added a solution of *o*-nitrobenzoyl chloride, prepared from 48.3 g (0.289 mol) of *o*-nitrobenzoic acid and 57.9 g (0.289 mol) of phosphorus pentachloride, in 60 m*l* of dry benzene at room temperature over a period of 1 hr. The mixture was refluxed for 2 hr and then left to stand overnight. The excess of sodium hydride was decomposed by the addition of *p*-toluenesulfonic acid monohydrate. The salts were removed by filtration and the solvent was distilled off completely. The residue was heated under reflux with 75 m*l* of acetic acid, 9 m*l* of concentrated sulfuric acid and 50 m*l* of water for 5 hr. After cooling, the reaction mixture was made alkaline with 20% aqueous sodium hydroxide and extracted with ether. After drying and evaporation of the solvent, the residue was distilled under reduced pressure to give 29.7 g (57.3%) of *o*-nitropropiophenone boiling at 144—145°C/8 mmHg. Gas chromatography of this sample on silicone grease showed a single peak. UV: 259 (3.70). IR: 1704 (C=O); 1531, 1348, 855 (NO_2). NMR (CCl_4): 1.17^t (3H), 2.75^q (2H), 7.35—8.25^m (4H). (Found: C, 59.68; H, 5.28; N, 7.37%).

The Condensation of o-*Nitropropiophenone by Sodium Acetylide.* A mixture of 0.77 g (0.033 mol) of sodium and 150 m*l* of liquid ammonia was saturated with acetylene. The mixture was cooled to −70°C and a solution of 9 g (0.05 mol) of *o*-nitropropiophenone in 15 m*l* of dry ether was added in one portion. A violent reaction took place and the temperature of the mixture reached −50°C. After stirring at −70°C for 1 hr, 1.5 g (0.028 mol) of ammonium chloride was added and the liquid ammonia evaporated while about 150 m*l* of ether was added. The resulting yellow crystals were filtered and washed with water. Recrystallization of the crystals from ethanol gave 2.2 g of compound C, melting at 213—214°C. The filtrate was washed successively with 5% aqueous sodium hydrogen carbonate, 2N hydrochloric acid and 2N aqueous sodium hydroxide. The neutral fraction was processed as described below. The washing with 2N aqueous sodium hydroxide was acidified with sulfuric acid and extracted with ether. The ethereal extract was dried and evaporated to give 2.1 g of compound C, melting at 206—209°C. Total yield was 55.6%. Several recrystallization from ethanol gave a pure sample melting at 214°C. UV: 232 (4.54), 260^{sh} (4.07), 281^{sh} (3.90), 400 (3.69). UV (0.5N NaOH-EtOH): 237 (4.51), 300 (3.93), 425 (3.53). IR: 3520, 3405 (NH); 3300—2800 (OH); 1687 (C=O). NMR: 1.38^s (3H), 1.42^d (3H), 2.88^q (1H), 5.57—6.13^b (2H), 6.38—7.64^m (8H), 10.90^s (1H).

Found: C, 69.93; H, 5.97; N, 9.05%; C-Methyl group[32] 0.65; mol wt (Rast), 279. Calcd for $C_{18}H_{18}O_3N_2$: C, 69.66; H, 5.85; N, 9.03%; mol wt, 310.

The above-mentioned neutral fraction from several runs were combined and treated with benzene. After removal of insoluble material by filtration, the solvent was distilled off under reduced pressure. The residue (*ca.* 30 g) was chromatographed on 200 g of silicic acid (Mallincrodt, 100 mesh AR) and eluted with methylene chloride-benzene (2.5: 1, v/v). Fractions 1 to 5 were collected in each 200 m*l*. Fraction 2 gave pure *o*-nitropropiophenone. Fraction 6 to 13 were collected in each 300 m*l*. Fraction 6 gave the alkynol VIII. High-vacuum distillation of this fraction gave a yellow oil, bp 90°C (bath temperature)/10^{-3} mmHg. IR (neat)[33]: 3580 (OH); 3310 (≡CH); 2340 (C≡C); 1540, 1360, 860 (NO_2). NMR: 1.04^t (3H), 2.12^q (2H), 2.50^s (1H), 7.05^b (1H), 7.2—7.8^m (4H).

Found: C, 64.27; H, 5.51; N, 6.69%. Calcd for $C_{11}H_{11}O_3N$: C, 64.38; H, 5.40; N, 6.83%.

Fraction 8 gave yellow crystals, which, after recrystallization from ethanol, melted to a red liquid at 206—207°C. UV: 229 (4.44), 251^{sh} (4.16), 335 (3.62), 390 (3.51). IR:[33] 3400 (NH); 1700 (C=O). NMR: 1.65^s (3H), 1.75^s (3H), 4.50^s (1H), 6.5—7.8^m (8H).

Found: C, 73.54; H, 5.21; N, 4.80%. Calcd for $C_{18}H_{15}O_3N$: C, 73.70; H, 5.15; N, 4.78%.

Fraction 13 gave faintly colored crystals, which, after two recrystallizations from benzene-hexane, decomposed at 150°C. UV: 236 (4.40), 310 (3.32), 360 (3.23). IR:[33] *ca.* 3500 (OH); 1710 (C=O); 1540, 1355, 860 (NO_2). NMR: 1.24^d (3H), 1.58^s (3H), 3.12^q (1H), 3.37^s (1H), 7.0—7.7^m (8H).

Found: C, 63.65; H, 4.90; N, 8.10%. Calcd for $C_{18}H_{16}O_5N_2$: C, 63.52; H, 4.74; N, 8.23%.

The condensation using sodium amide instead of the acetylide under the same condition gave 46.4% yield of compound C.

Methylation of Compound C. Into a solution of 1.0 g (3.2 mmol) of compound C in a mixture of each 100 m*l* of ether and methanol was added ethereal solution of diazomethane prepared from 10 g of *N*-nitrosomethylurea. After being left to stand overnight, the mixture was treated with acetic acid to decompose excess of diazomethane and the solvent evaporated under reduced pressure, giving 867 mg (87%) of pale yellow crystals, which, after recrystallization from aqueous methanol, melting at 224.5—225°C. UV: 230.5 (4.48), 281 (3.77), 393 (3.66). IR: 3510, 3402 (NH); 1684 (C=O).

Found: C, 70.42; H, 6.21; N, 8.57%. Calcd for $C_{19}H_{20}O_3N_2$: C, 70.35; H, 6.22; N, 8.64%.

Acetylation of Compound C. *a) With Acetic Anhydride and Sodium Acetate*: A mixture of 300 mg (0.97 mmol) of compound C, 9 m*l* of acetic anhydride and 90 mg of anhydrous sodium acetate was boiled under reflux for one hour. After decomposition of the excess anhydride with water, the separated crystals were filtered and dried, to give 244 mg (64%) of yellow needles, mp 195—197°C. Recrystallization from aqueous methanol gave pure sample, mp 196.5°C. UV: 231 (4.48), 386 (3.64). IR: 3380, 3245, 3200, 3140 (NH); 1758, 1734, 1696 (C=O).

Found: C, 67.03; H, 5.56; N, 7.25%. Calcd for $C_{22}H_{22}O_5N_2$: C, 66.99; H, 5.62; N, 7.10%.

b) With Acetic Anhydride and Pyridine: A solution of 75 mg (0.26 mmol) of compound C in 0.5 m*l* of pyridine was treated with 0.08 m*l* of acetic anhydride and left to stand at room temperature for 2 hr, during which almost colorless crystals separated out. After the addition of ether, the solvent was decanted; the crystals were washed with ether and recrystallized from aqueous ethanol, giving pure sample melting at 229—230°C. IR: 3550, 3410 (NH); 1765, 1690 (C=O).

Found: C, 68.06; H, 5.88; N, 7.90%. Calcd for $C_{20}H_{20}O_4N_2$: C, 68.17; H, 5.72; N, 7.95%.

Acid Hydrolysis of Compound C. A mixture of 300 mg (0.97 mmol) of compound C and 15 m*l* of 6N hydrochloric acid was refluxed under the atmosphere of nitrogen for one and a half hours. No carbon dioxide was evolved during the reaction. After filtration from a solid material which could not be led to any crystalline derivatives, the filtrate, after concentration, was chromatographed on "Toyo" No. 51 filter paper, using ethanol - concentrated hydrochloric acid - water (7: 1: 2 v/v) as solvent. Detection of spots was made accord-

32) E. J. Eisenbraun, S. M. McElvain, and B. F. Aycock, *J. Amer. Chem. Soc.*, **76**, 607 (1954).

33) IR spectra of these compounds are taken on a spectrophotometer Model IR-E of Japan Spectroscopic Co.

ing to Steel.[12] The R_f value was 0.36.

Hydrogenation of Compound C. *a) Under High Pressure*: A mixture of 200 mg of compound C, 2 m*l* of Raney nickel and 40 m*l* of ethanol was hydrogenated at a hydrogen pressure of 80 atm and 110°C for 2 hr. After filtration of the catalyst, the solvent was removed under reduced pressure to give crystals, which, after recrystallization from aqueous ethanol, melted at 243°C. UV: 285 (3.50), 330 (4.06). IR: 3500, 3395 (NH); 3300—2800 (OH); 1660 (C=O).

Found: C, 69.00; H, 7.18; N, 8.76%. Calcd for $C_{18}H_{22}O_3N_2$: C, 68.77; H, 7.05; N, 8.91%.

b) Under Atmospheric Pressure: A solution of 200 mg of compound C in 10 m*l* of glacial acetic acid was hydrogenated in the presence of 100 mg of platinum oxide until the solution had lost the yellow color. After filtration, the solvent was evaporated under reduced pressure. Trituration of the residue with aqueous alcohol caused crystallization. The crystals were identified with the above mentioned tetrahydro-compound C by IR spectroscopy.

Methylation of Tetrahydro-compound C. Methylation of the tetrahydro derivative with diazomethane under the same condition as that of compound C gave a methyl ether melting at 223—224°C. UV: 285 (3.31), 330 (4.04). IR: 3480, 3376 (NH); 1671 (C=O).

Found: C, 68.92; H, 7.51; N, 8.70%. Calcd for $C_{19}H_{24}O_3N_2$: C, 69.49; H, 7.37; N, 8.53%.

Permanganate Oxidation of Compound C. Into a stirred solution of 465 mg (1.5 mmol) of compound C in aqueous potassium hydroxide (1.0 g of potassium hydroxide in 200 m*l* of water) was added each 158 mg (1 mmol) of finely powdered potassium permanganate. On the addition of eighteen portions, the color of the permanganate remained for 2 hr. The color was discharged by the addition of 0.4 m*l* of 30% of hydrogen peroxide and manganese dioxide was filtered off. The filtrate was extracted several times with ether and the combined extracts were washed with 2N sodium hydroxide, dried and evaporated to give 32 mg of crystals, which, after recrystallization from ethanol, melted at 228°C. UV: 233 (4.40), 255^{sh} (3.80), 400 (3.60). IR: 3520, 3470, 3405, 3350 (NH); 1690^{sh}, 1676 (C=O).

Found: C, 66.12; H, 6.67; N, 12.18%.[34] Calcd for $C_{12}H_{14}O_2N_2$: C, 66.03; H, 6.47; N, 12.84%.

A little amount of this compound was heated with acetic anhydride under reflux for 4 hr. After removal of the solvent under reduced pressure, the residue showed UV maxima at 233 and 334 nm.

2-(1-Methoxycarbonylethyl)-2-methyl-3-indolinone. Into a suspension of 1.92 g (44 mmol) of 54.5% sodium hydride dispersed in mineral oil in 400 m*l* of benzene was added a solution of 9.5 g (40 mmol) of *N*-(*o*-methoxycarbonylphenyl)-alanine methyl ester[15] (bp 137—140°C/2 mmHg) in 10 m*l* of benzene under atmosphere of nitrogen. The mixture was refluxed for 6 hr, during which about 800 m*l* of hydrogen was evolved, and cooled with ice-water. Into the mixture was added 7.5 g (45 mmol) of methyl α-bromopropionate and the mixture was left to stand at room temperature for 21 hr and then refluxed for 7 hr. After addition of 0.5 m*l* of acetic acid, water and ether, the organic layer was separated, washed with 2N hydrochloric acid and 2N sodium hydroxide successively and dried over anhydrous sodium sulfate. The residue obtained by the evaporation of the solvent showed the presence of the desired ester V and the *O*-alkylated product VII[35] (*ca.* 10:8) as major products. The crude product dissolved in benzene was applied to a column of 160 g of active alumina (Wako) and eluted with 2 *l* of benzene.[36] After evaporation of the benzene, the residue (4.00 g) was chromatographed again on 100 g of alumina and eluted with benzene. The fractions were collected after a yellow band reached the bottom of the column. The first 100-m*l* fraction gave a yellow oil. Thereafter, thirteen 100-m*l* fractions gave yellow crystals, which, after recrystallization from hexane, gave 0.77 g of pure ester V, melting at 53—54°C. IR: 3460 (NH); 1722, 1693 (C=O). NMR: 0.93^d (3H), 1.30^s (3H), 2.95^q (1H), 3.72^s (3H), *ca.* 5^b (1H), 6.5—7.2^m (4H).

Found: C, 67.06; H, 6.75; N, 5.84%. Calcd for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48; N, 6.01%.

2-(1-Carbamoylethyl)-2-methyl-3-indolinone. A mixture of 0.21 g (0.9 mmol) of the above ester V and 2 m*l* of 28% aqueous ammonia was heated in a sealed tube in a boiling water bath for 10 hr. On cooling, crystals separated and they were washed with water and dried; mp 230°C (Found: C, 65.70; H, 6.35; N, 12.76%). IR spectrum was completely identical with that of the specimen obtained above by the permanganate oxidation of compound C.

Permanganate Oxidation of the Alkynol VIII. Into a solution of 1 g of the alkynol VIII contaminated by *o*-nitropropiophenone in acetone was added powdered potassium permanganate in small portions until the purple color remained. After 3 hrs' stirring at room temperature, the excess permanganate was decomposed with methanol and manganese dioxide was filtered off. The filtrate was evaporated under reduced pressure and the residue taken into ether and water. The separated aqueous solution was acidified with hydrochloric acid, extracted with ether. The evaporation of the ether solution, after drying, gave crystals, which, after recrystallization from hexane-ether, melted at 154—156°C.

Found: C, 53.36; H, 4.90; N, 6.15%. Calcd for $C_{10}H_{11}O_5N$: C, 53.33; H, 4.92; N, 6.22%.

The Reaction of Compound XI with Sodium Amide. Into a solution of sodium amide in liquid ammonia (prepared from 126 mg (5.5 mmol) of sodium and 20 m*l* of liquid ammonia) was added a solution of 213 mg (0.63 mmol) of compound XI in one portion at −70°C. The mixture was stirred for 30 min and 400 mg (7 mmol) of ammonium chloride was added. The liquid ammonia was evaporated while ether was added. Evaporation of the ether solution left 160 mg of a residue, which was chromatographed on 5 g of silicic acid and eluted with dichloromethane - benzene (2.5:1, v/v). Evaporation of the solvent gave 90 mg of crystals, which was identified with compound X by comparison of the infrared spectra.

o,o′-*Azoxyacetophenone.* *a) From the Reaction Mixture of* o-*Nitroacetophenone*: The neutral fraction of the reaction mixture of *o*-nitroacetophenone with sodium acetylide in liquid ammonia[1] was subjected to steam distillation. Essentially no distillate was obtained. The residue in the distillation flask was dissolved in ether, the solution washed with dilute sulfuric acid, and the solvent evaporated. The residue was

34) The poor result of this nitrogen analysis is apparently due to concomitant impurity; however, this substance is very difficult to purify, another sample, which was purified by repeated sublimations and recrystallizations, giving much worse results in the elemental analyses.

35) The following peaks in the NMR spectrum of the crude product are assigned to this compound: 1.58^d (3H), 2.26^s (1H), 3.69^s (3H), 4.71^q (1H), 8.6^{bs} (1H).

36) The *O*-alkylation product is slightly more polar on silicic acid than the desired ester. Prolonged contact with silicic acid seems to hydrolyze this by-product; no *O*-alkylation product was isolated after repeated chromatography on silicic acid.

distilled under a 7-mmHg pressure until the bath temperature reached 200°C to give *o*-nitroacetophenone as the distillate. The residue was dissolved in hot ethanol. After removal of a black resin which deposited immediately after cooling by decantation, the solution was treated with charcoal and left to stand overnight to separate brown crystals, which, after recrystallization from ethanol, melted at 117—119°C. IR (Nujol): 1688, 1676 (C=O); 1478 (azoxy).

Found: C, 68.24; H, 5.24; N, 9.90%. Calcd for $C_{16}H_{14}O_3N_2$: C, 68.07; H, 5.00; N, 9.92%.

b) Synthesis: This compound was prepared from *o*-nitroacetophenone following a procedure for the preparation of *p,p'*-azoxyacetophenone by Clark *et al.*[29] *o*-Nitroacetophenone ethylene ketal was obtained, after distillation (bp 98—100°C/0.05 mmHg) followed by trituration with methanol, in 65% yield, mp 67°C. IR: 1535, 1375, 860 (NO_2); 1040 (ketal). NMR (CCl_4): 1.76^s (3H), 3.4—4.1^m (A_2B_2, 4H), 7.2—7.7^m (4H). (Found: C, 57.23; H, 5.40; N, 6.49%. Calcd for $C_{10}H_{11}O_4N$: C, 57.41; H, 5.30; N, 6.70%). Refluxing the nitro ketal with alkaline zinc dust for 5 hr gave *o,o'*-azoxyacetophenone bis-ethylene ketal in 28% yield, mp 206°C. Prolonged refluxing did not improve the yield. IR: 1470 (azoxy); 1040 (ketal). (Found: C, 64.77; H, 6.07; N, 7.49%. Calcd for $C_{20}H_{22}O_5N_2$: C, 64.85; H, 5.99; N, 7.56%). The acid hydrolysis of the ketal gave *o,o'*-azoxyacetophenone in 64% yield, mp 116—118°C. The IR spectrum of this compound was completely identical with that of the specimen obtained in a).