Proton nmr ($CDCl_3$) δ 5.13 (s, 2 H, CH_2ONO_2), 4.75 (d, J_{HF} = 17.0 Hz, 2 H, $FCCH_2$–), and 4.48 (s, 2 H, CH_2); fluorine nmr ϕ 109.4 (poorly resolved triplet).

Acknowledgment.—The author wishes to thank Dr. K. Baum for useful discussion.

Registry No.—1, 40695-29-5; 2, 40695-30-8; (2-fluoro-2,2-dinitroethoxy)acetaldehyde, 40696-31-9; 1-(2-fluoro-2,2-dinitroethoxy)-2,3-propanediol, 40696-32-0; periodic acid, 10450-60-9; (2-fluoro-2,2-dinitroethoxy)acetaldoxime, 40696-33-1; hydroxylamine hydrochloride, 5470-11-1; sodium acetate, 127-09-3; bis(2-fluoro-2,2-dinitroethyl) ether, 30290-64-3; 2-chloro-2,2-dinitroethyl 2-fluoro-2,2-dinitroethyl ether, 40696-35-3; methyl vinyl ketone, 78-94-4; 3-(2-fluoro-2,2-dinitroethoxy)-2,2-dinitropropanol, 40696-36-4; bis[3-(2-fluoro-2,2-dinitroethoxy)-2,2-dinitropropyl] formal, 40696-37-5; s-trioxane, 110-88-3; 1,3-bis(2-fluoro-2,2-dinitroethoxy)-2-propanol, 35323-16-1; 2-fluoro-2,2-dinitroethanol, 17003-75-7; 2-fluoro-2,2-dinitroethyl glycidyl ether, 40696-32-0; 1,3-bis(2-fluoro-2,2-dinitroethoxy)acetone, 40696-41-1; 1,3-bis(2-fluoro-2,2-dinitroethoxy)acetone oxime, 40696-42-2; 2-fluoro-2,2-dinitroethyl propargyl ether, 40696-43-3; 2-fluoro-2,2-dinitroethyl-2,3-dibromoallyl ether, 40696-44-4; bromine, 7726-95-6; (2-fluoro-2,2-dinitroethoxy)acetone, 25172-32-1; 1-chloro-3-(2-fluoro-2,2-dinitroethoxy)-2-propanol, 40696-46-6; 1-bromo-3-(2-fluoro-2,2-dinitroethoxy)-2-propanol, 40696-47-7; hydrobromic acid, 10035-10-6; 1-iodo-3-(2-fluoro-2,2-dinitroethoxy)-2-propanol, 40696-48-8; hydriodic acid, 10034-85-2; 1-(2-fluoro-2,2-dinitroethoxy)-3-nitrato-2-propanol, 40696-49-9; nitric acid, 7697-37-2; 3-(2-fluoro-2,2-dinitroethoxy)-2-hydroxy-1-propyl pivalate, 40696-50-2; 3-(2-fluoro-2,2-dinitroethoxy)-1,2-propanediol, 40696-32-0; pyridine, 110-86-1; 1-chloro-3-(2-fluoro-2,2-dinitroethoxy)acetone, 40696-52-4; 3-(2-fluoro-2,2-dinitroethoxy)-2-oxo-1-propyl pivalate, 40696-53-5; 1-(2-fluoro-2,2-dinitroethoxy)-3-nitratoacetone, 40696-54-6.

Synthesis of α-Monosubstituted Indoles

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The preparation of α-monosubstituted indoles by (a) the Madelung reaction, (b) *o*-nitrobenzyl ketone reduction, and (c) *o*,β-dinitrostyrene reduction was explored. The Madelung reaction is limited to use on those toluidides which do not have double bonds or active hydrogens present. Toluidides having tertiary benzylamine groups can be used. *o*-Nitrobenzyl ketone preparations were attempted by the arylation of β-keto esters with *o*-fluoronitrobenzene. This reaction is limited to α-unsubstituted acetoacetic esters. The dinitrostyrene route appears to be useful when the appropriate primary nitro compound is available for condensation with *o*-nitrobenzaldehyde.

Of the many reported syntheses of indole alkaloids, most have used reaction sequences involving either the formation of the disubstituted indole by means of a Fisher indole synthesis or the preparation of an appropriate β-substituted indole followed by a ring closure into the α position of the indole ring.[2] It was thought, however, that it would be advantageous in some cases to first prepare an α-monosubstituted indole and then utilize the higher reactivity of the β position[3] to facilitate the subsequent ring closure.[4] This approach would also avoid the formation of intermediate 3,3-disubstituted 3*H*-indoles, which could rearrange to give a mixture of products.[5]

While a number of methods have been reported for the exclusive preparation of α-substituted indoles,[6] with the exception of the triethylphosphite reduction of *o*-nitrostyrenes[7] and the pyrolysis of *o*-azidostyrenes,[8] little is known about their generality and scope. Thus, the following methods for the preparation of α-monosubstituted indoles were investigated: (1) the Madelung reaction;[9a] (2) *o*-nitrobenzyl ketone reductions;[9b] (3) *o*,β-dinitrostyrene reductions.[9c]

The Madelung reaction,[9a] which involves the heating of an *o*-toluidide with a strong base, has been used successfully for the preparation of a number of α-alkyl-substituted indoles,[10] as well as indoles having alkyl groups on the 5 or 7 positions.[9a] It appears that nitro-[11] or halogen- substituted[12] indoles cannot be prepared by this method. This procedure has been used for the synthesis of 2-(*N*,*N*-dimethylaminomethyl)indole (**1**).[13] In a study of this reaction[13b] it was found that reasonably good yields of **1** were obtained if sodium amide was used as the base but that the use of other bases gave much poorer results. However, in this[13b] and subsequent work[14] utilizing

(1) (a) NSF Graduate Traineeship recipient, summer, 1971; (b) NSF Graduate Traineeship recipient, summer, 1970.

(2) For some examples see (a) R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, N. Y., 1970, pp 251–269; (b) J. E. Saxton in "The Alkaloids," Vol. VII, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1960, Chapter 10.

(3) R. L. Hinman and E. B. Whipple, *J. Amer. Chem. Soc.*, **84**, 2534 (1962); R. L. Hinman and C. P. Baumann, *J. Org. Chem.*, **29**, 2437 (1964).

(4) See, for example, (a) R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, and K. Schenker, *J. Amer. Chem. Soc.*, **76**, 4749 (1954); *Tetrahedron*, **19**, 247 (1963); (b) H. P. Husson, C. Thal, P. Potier, and E. Wenkert, *Chem. Commun.*, 480 (1970); (c) G. Grethe, H. L. Lee, and M. R. Uskokovic, *Syn. Commun.*, **2**, 55 (1972); (d) R. L. Augustine and S. F. Wanat, *ibid.*, **2**, 63 (1972).

(5) A. H. Jackson and A. E. Smith, *Tetrahedron*, **24**, 403 (1968).

(6) (a) Reference 2a, Chapter 3; (b) V. F. Martynov and G. Ol'man, *Zh. Obshch. Khim.*, **25**, 1561 (1955); *Chem. Abstr.*, **50**, 4909 (1956); (c) M. Panunzio, N. Tangari, and A. U. Ronchi, *Chem. Commun.*, 415 (1972); (d) C. D. Jones and T. Saurez, *J. Org. Chem.*, **37**, 3622 (1972); (e) C. D. Jones, *ibid.*, **37**, 3624 (1972); (f) P. G. Gassman and T. J. Van Bergen, *J. Amer. Chem. Soc.*, **95**, 590 (1973).

(7) R. J. Sundberg, *J. Org. Chem.*, **30**, 3604 (1965); **33**, 487 (1968).

(8) R. J. Sundberg, H. F. Russell, W. V. Ligon, Jr., and Long-Su Lin, *J. Org. Chem.*, **37**, 719 (1972).

(9) Reference 2a: (a) p 189; (b) p 176; (c) p 182.

(10) (a) C. F. H. Allen and J. Van Allan, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 597; (b) A. Verley, *Bull. Soc. Chim. Fr.*, **35**, 1039 (1924); **37**, 189 (1925); (c) C. Cardini, F. Piozzi, and G. Casnati, *Gazz. Chim. Ital.*, **85**, 263 (1955); (d) T. Lesiak, *Rocz. Chem.*, **36**, 1097 (1962); *Chem. Abstr.*, **58**, 5615 (1964); (e) F. Piozzi and M. R. Langella, *Gazz. Chim. Ital.*, **93**, 1382 (1963); (f) G. Gasnati, M. R. Langella, F. Piozzi, A. Ricca, and A. Umani-Ronchi, *ibid.*, **94**, 1221 (1964); (g) E. Walton, C. H. Stammer, R. F. Nutt, S. R. Jenkins, and F. W. Holly, *J. Med. Chem.*, **8**, 204 (1965).

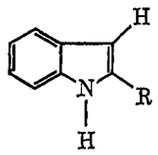
(11) W. E. Noland, L. R. Smith, and K. R. Rush, *J. Org. Chem.*, **30**, 3457 (1965), footnote 15.

(12) W. E. Noland and C. Reich, *J. Org. Chem.*, **32**, 828 (1967).

(13) (a) E. Euler and H. Erdtman, *Justus Liebigs Ann. Chem.*, **520**, 1 (1935); (b) E. C. Kornfeld, *J. Org. Chem.*, **16**, 806 (1951); (c) F. Yoneda, T. Miyamae, and Y. Nitta, *Chem. Pharm. Bull.*, **15**, 8 (1967).

(14) (a) H. R. Snyder and P. L. Cook, *J. Amer. Chem. Soc.*, **78**, 969 (1956); (b) W. Schindler, *Helv. Chim. Acta*, **40**, 1130 (1957).

1 as a synthetic intermediate the method of choice for its preparation was through ethyl indole-2-carboxylate (2).



1, R = $CH_2N(CH_3)_2$
2, R = CO_2Et

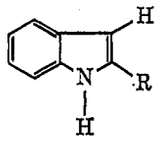
In this present work it has also been found that the nature of the base used has a marked influence on the outcome of the reaction. In contrast to the previous report,[13b] however, it was found that the use of potassium *tert*-butoxide gave, by far, the best yields of indoles, especially in those reactions involving toluidides having a nitrogen-containing acyl group. The use of other bases, such as sodium methoxide, sodium ethoxide, sodium amide, lithium amide, or *n*-butyllithium, resulted in either very low yields of cyclized material or extensive decomposition of the product. It is necessary, though, that care be taken to avoid the complete sublimiation of the potassium *tert*-butoxide before cyclization occurred completely. The best results were obtained when the toluidide was refluxed in benzene or *tert*-butyl alcohol for a short time with 4–8 equiv of the base. After removal of the solvent the residue was then placed in a bath preheated to about 270° and the temperature was raised until the residue melted and frothing was observed. The temperature was held at this level until the frothing subsided and the reaction mixture was analyzed for the presence of toluidide by tlc. If toluidide was present, the mixture was cooled and redissolved, additional base was added, and the procedure was repeated.

The optimum temperature for cyclization is determined by the nature of the substituent present on the toluidide. If the reaction temperature is too high extensive decomposition can take place. While the best temperature for a given reaction can be found by trial and error, it is generally true that temperatures 5–10° above the melting point of the toluidide salt give satisfactory results in most cases. The superiority of potassium *tert*-butoxide over the sodium- and lithium-containing bases is probably a result of the lower melting points of the potassium toluidide salts as compared to the sodium and lithium analogs. The indoles prepared here by this method and the optimum reaction temperatures are listed in Table I.

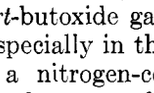
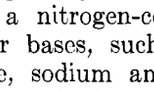
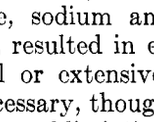
As mentioned above, this reaction is quite useful for the preparation of α-alkyl-substituted indoles; even the previously unknown α-cyclopropylindole (**3c**) is obtained in good yield by this procedure. However, if the toluidide contains double bonds (**4c** and **4o**,[15] Table II) or active hydrogens (**4e**), extensive decomposition is observed even at the lowest possible reaction temperature. In agreement with previous work[13] it was found that tertiary amines are stable under these reaction conditions, as shown by the preparation of **3d** and **3g**. However, in neither of these compounds is there available a potential secondary amine which could be utilized in further reactions. The common amine blocking groups such as the amide or the urethane proved to be ineffective, since they are readily cleaved under the reaction conditions and the resulting secondary amine is decomposed on further heating. Tertiary benzylamines are, however, stable and the *N*-benzylpiperidylindoles **3e** and **3f** are obtained in good yields. Secondary amines are potentially available by hydrogenolysis of these benzylamines.[16] The isoquinoline toluidide **4p** did not show any sign of reaction at temperatures below 340°. At higher temperatures a reaction occurred but the product was a nonindolic material which contained no methoxy group as indicated by pmr spectroscopy.

The toluidides used in this reaction are generally prepared by the reaction of *o*-toluidine with an acid chloride or anhydride. They can also be prepared by the reaction of the toluidine anion with an ester (Bourdroux reaction).[17] It has been found that anion generation using alkyllithium reagents rather than Grignard reagents gives much better yields of the toluidide. Some toluidides were also prepared using the modified

TABLE I
α-MONOSUBSTITUTED INDOLES



3

	R	Method of preparation[a]	Reaction temp,[b] °C	Yield, %	Mp, °C
a	CH_3	A	300	86	60–61[c]
		B		96	58–59
		C		42[i]	59-60
b	C_6H_5	A	325	60	186–187[d]
c		A	300	75	58–59[e]
d		A	340	92	137–139[c]
e		A	300	72	112–114[e]
f		A	300	81	195–196[e,g]
g		A	300	66	154–156[h]
h	CH_2CH_3	C		55[i]	40–41[j]
i	$CH_2C_6H_5$	C		43[i]	81–83[k]

[a] A = Madelung reaction, B = nitro ketone reduction, C = dinitrostyrene reduction. [b] For Madelung reaction. [c] Lit. mp 56–57° (ref 10a). [d] Lit. mp 186–188° [R. L. Shriner, W. C. Ashley, and E. Welch, *Org. Syn.*, **22**, 98 (1942)]. [e] All new compounds gave C, H, and N analyses within ±0.3% of theoretical values. [f] Mixture of cis and trans isomers. [g] Melting point of the maleate salt. [h] Lit. mp 155–156° (ref 7b). [i] Overall yield from *o*-nitrobenzaldehyde. [j] Lit. mp 43° [A. Verley and J. Deduwe, *Bull. Soc. Chim. Fr.*, **37**, 190 (1925)]. [k] Lit. mp 86° [P. L. Julian and J. Pikl, *J. Amer. Chem. Soc.*, **55**, 2105 (1933)].

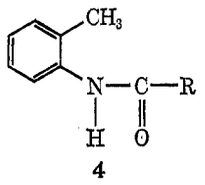
(15) Similar results in the attempted cyclization of **4o** using lithium amide have also been observed: M. R. Uskokovic, private communication.

(16) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, New York, N. Y., 1965, Chapter 6.

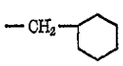
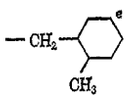
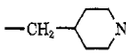
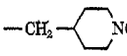
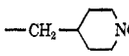
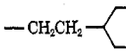
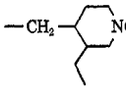
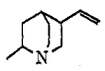
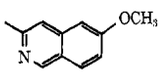
(17) F. Bourdoux, *C. R. Acad. Sci., Ser. C*, **138**, 1427 (1904); **140**, 1108 (1905); **142**, 401 (1906).

TABLE II

o-TOLUIDIDES



4

	R	Method of preparation[a]	Yield, %	Mp, °C
a	CH_3	A	75	110–112[b]
b	C_6H_5	A	90	143–145[c]
c		A	93	154–156[d]
d		A	96	129–131[d]
e	$CH_2C_6H_5$	B	80	161–162[d]
f		C	74	146–148[d]
g		C	81	136–140[d]
h		B	85	63–66[d]
i		C	73	139–140[d]
j		C	83	147–149[d]
k		C	74	143–144[f]
l		C[g]	60	128–129
m		B	79	103–105[d]
n		B	79	113–115[d]
o		B	40	*h*
p		g	75	124–125[d]

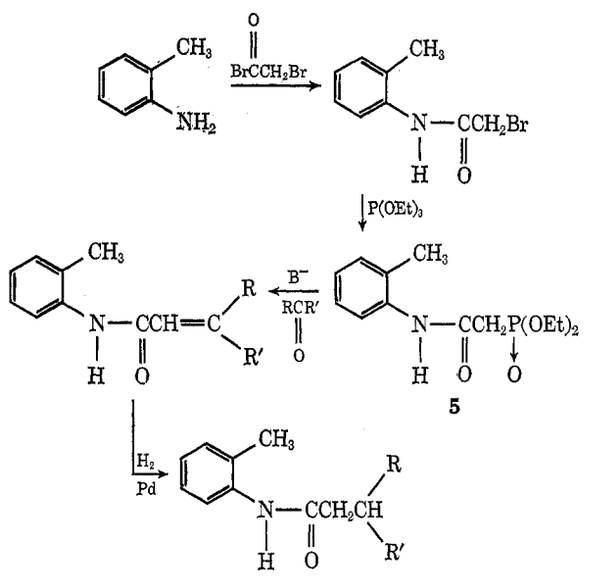
[a] A = from acid chloride or anhydride, B = Bourdroux reaction, C = modified Wittig reaction. [b] Lit. mp 110–111° (ref 10a). [c] Lit. mp 145–146° [P. Jacobson and L. Huber, *Chem. Ber.*, **41**, 660 (1908)]. [d] All new compounds gave C, H, and N analyses within ±0.3% of the theoretical values. [e] Mixture of cis and trans isomers. [f] Characterized by conversion to **4e**. [g] Modified procedure; details are given in the Experimental Section. [h] Material used without further characterization.

Wittig reaction shown in Scheme I. The toluidides prepared in this work are listed in Table II.

***o*-Nitrobenzyl Ketone Reduction.**[9b] —One of the more common reductive indole ring closure procedures is the Reissert sequence,[18] involving the condensation of *o*-nitrotoluene with ethyl oxalate followed by reduction to give ethyl indole-2-carboxylate (**2**). This compound

(18) F. T. Tyson, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 479.

SCHEME I



is the intermediate commonly used in the preparation of **1**,[13b] indole-2-acetic acid,[19] isotryptophane,[13b,14a,20] and other α-substituted indoles.[14b,21] While this procedure has been used for the preparation of a number of 4-, 5-, 6-, or 7-substituted indoles,[9b] its utility has not been extended to the direct preparation of indoles having an α substituent other than an ester. A number of attempts have been made to condense *o*-nitrotoluene with esters other than oxalates[22] but in no instance was the desired nitro ketone obtained.

The problem in the general utility of this reductive procedure lies mainly in the availability of the required nitro ketones. A partial solution to this problem has been attained with the reported condensations of *o*-nitrophenylacetyl chloride with enamines,[23] malonates,[24] and β-keto esters.[25] The preparation of oxindoles by nucleophilic substitution of malonic acid ester anions on *o*-chloronitrobenzene followed by hydrogenation has been reported.[26] By a similar reaction sequence 4-aza-3-cyanooxindole is prepared from 2-chloro-3-nitropyridine and ethyl cyanoacetate.[27] No mention could be found in the literature of the use of this type of reaction sequence to prepare *o*-nitrobenzyl ketones and of their subsequent reduction of α-substituted indoles.

The reaction between *o*-fluoronitrobenzene (**6a**) and the anion of ethyl acetoacetate occurred readily in hexamethylphosphoric triamide (HMPT) at room temperature. The product aryl β-keto ester **8** (Scheme II) was hydrolyzed and decarboxylated to give the nitro ketone **9**, which was hydrogenated to 2-methyl-

(19) W. Schindler, *Helv. Chim. Acta*, **41**, 1441 (1958).

(20) S. Swaminathan and S. Sulochana, *J. Org. Chem.*, **23**, 90 (1958).

(21) (a) J. R. Johnson, R. B. Hasbrouk, J. D. Dutcher, and W. F. Bruce, *J. Amer. Chem. Soc.*, **67**, 423 (1945); (b) W. J. Brehm, *ibid.*, **71**, 3541 (1949); (c) J. Harley-Mason and E. H. Parvi, *J. Chem. Soc.*, 2565 (1963).

(22) I. C. Pattison, Ph.D. Dissertation, Seton Hall University, South Orange, N. J., 1972.

(23) P. Rosenmund and W. H. Hoase, *Chem. Ber.*, **99**, 2504 (1966).

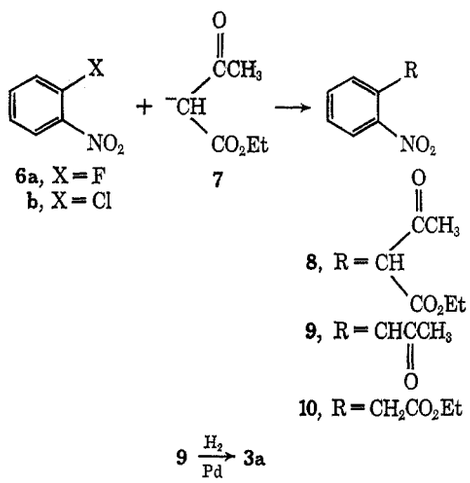
(24) J. R. Piper and F. J. Stevens, *J. Heterocycl. Chem.*, **3**, 95 (1966).

(25) R. Giuliano and M. L. Stein, *Ann. Chim. (Rome)*, **48**, 1284 (1958); *Chem. Abstr.*, **53**, 14084 (1959).

(26) C. A. Grob and O. Weissbach, *Helv. Chim. Acta*, **44**, 422 (1961).

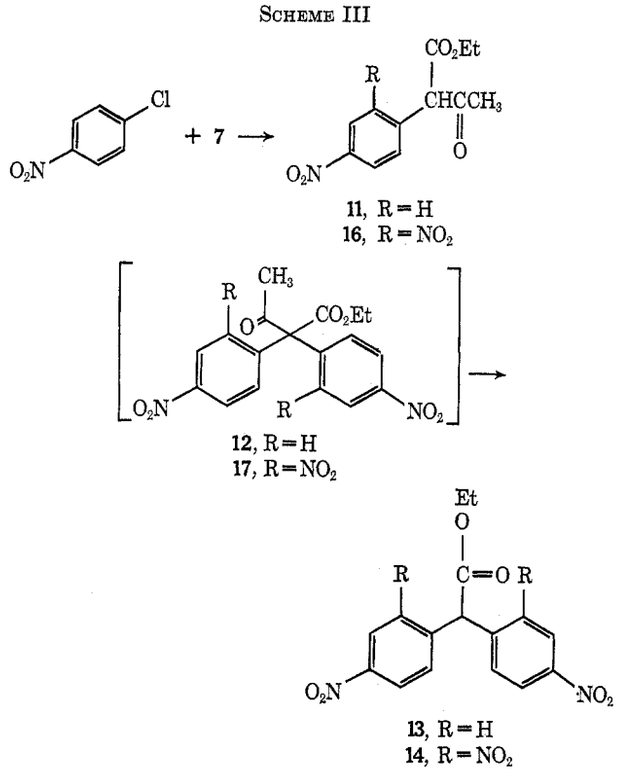
(27) N. Finch, M. M. Robison, and M. P. Valerico, *J. Org. Chem.*, **37**, 51 (1972).

SCHEME II



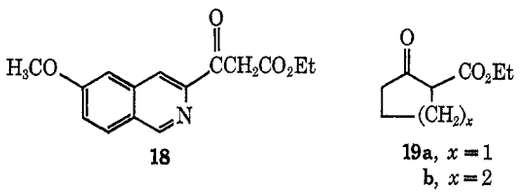
indole (**3a**) in 70% overall yield. As expected, the corresponding reaction on *o*-chloronitrobenzene (**6b**) took place only at the elevated temperatures, with **8** being formed in 65% yield after 4 hr at 110°. After 16 hr at this temperature a quantitative yield of ethyl-*o*-nitrophenylacetate (**10**) was formed. Since it was felt that this deacylation could have been assisted by the nitro group,[28] the reactions were repeated using *p*-chloronitrobenzene (Scheme III). As with the ortho

SCHEME III



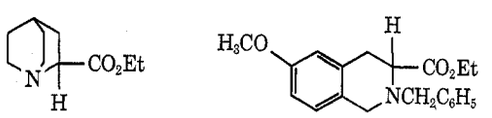
isomer the normal product, **11**, was obtained in 65% yield after 4 hr at 110°. After 20 hr at this temperature the diarylacetic ester, **13**, was formed in nearly quantitative yield. Borsche[29] has reported the formation of a small amount of the corresponding dinitro compound **14** from reaction of 2,4-dinitrochlorobenzene (**15**) with ethyl acetoacetate. He has shown that **14** could be generated by the reaction of **15** with **16** and has suggested that the diaryl β-keto ester **17** thus formed was deacylated by reaction with the solvent. None of the analogous diarylacetic ester was detected in the *o*-chloronitrobenzene reactions discussed above.

The utility of our approach as a general synthesis of α-substituted indoles was shown to be quite limited when it was found that neither the isoquinoline β-keto ester **18** nor the cycloalkanone carboxylic esters **19a** and **19b** would react with **6a** under a variety of



reaction conditions. Condensation of these β-keto esters with 2,4-dinitrochlorobenzene could be effected but the resulting products resisted all attempts at hydrolysis and decarboxylation.

In conjunction with this phase of the work several attempts were made to prepare β-keto esters from the quinuclidine and tetrahydroisoquinoline esters **20** and **21** by means of mixed Claisen condensations with both



ethyl and *tert*-butyl acetate. In contrast to a previous report of a successful condensation of **20** with ethyl acetate,[30] only starting amino esters were recovered from our attempts. In order to ascertain the reason for this failure one of the basic reaction mixtures was worked up using deuterioacetic acid, When the recovered amino ester **20** was analyzed by pmr spectroscopy, it was found that the C_2 proton was completely replaced by deuterium. It appears that in these amino esters the α proton is quite acidic and that under the basic reaction conditions relatively facile anion formation at this carbon precludes any condensation.

o,β-Dinitrostyrene Reductions.[9c]—The condensation *o*-nitrobenzaldehyde (**22**) with nitromethane to give the dinitrostyrene **23** (Scheme IV) has been well documented.[31] Reduction of **23** gives indole **24**.[9c,32] While this procedure has been used for the preparation of a number of 4-, 5-, 6-, and 7-substituted indoles[9c] and 2-methylindoles,[33] it does not appear to have been used for the preparation of any other α- or β-substituted indoles.

The primary nitroalkanes **25** required for the extension of this procedure are available by several

(28) J. D. Loudon and G. Tennant, *Quart. Rev., Chem. Soc.*, **18**, 389 (1964).

(29) W. Borsche, *Chem. Ber.*, **42**, 601 (1909).

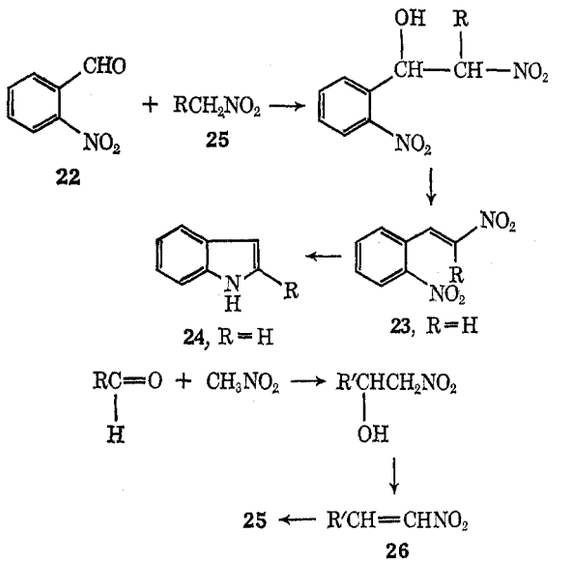
(30) L. N. Yakhontov and M. V. Rubstov, *Zh. Obshch. Khim.*, **27**, 72 (1957); *Chem. Abstr.*, **51**, 12085 (1957).

(31) L. F. Fieser and W. H. Dandt, *J. Amer. Chem. Soc.*, **68**, 2248 (1946).

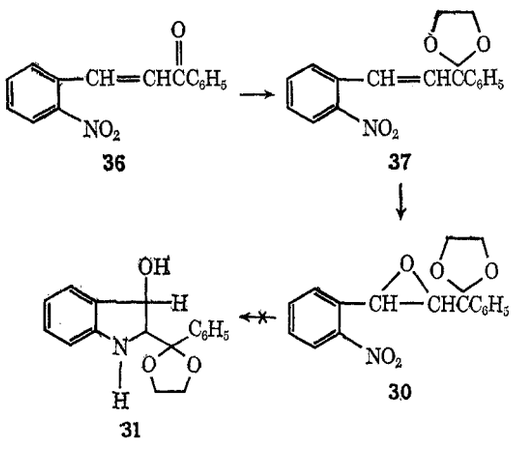
(32) T. van der Lee, *Recl. Trav. Chim. Pays-Bas*, **44**, 1089 (1925).

(33) (a) H. Burton and J. A. Duffield, *J. Chem. Soc.*, 78 (1949); (b) R. J. S. Beer, K. Clarke, H. F. Davenport, and A. Robertson, *ibid.*, 2029 (1951); (c) R. H. Heacock, O. Hutzinger, B. D. Scott, J. W. Daly, and B. Witkop, *J. Amer. Chem. Soc.*, **85**, 1825 (1963).

SCHEME IV

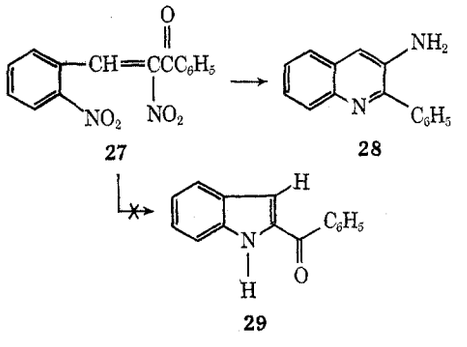


SCHEME V



routes.[34] The method used here involved the condensation of the appropriate aldehyde with nitromethane followed by dehydration of the intermediate alcohol to give the nitro olefin **26**. The double bond in **26** was reduced either with sodium borohydride[35] or by catalytic hydrogenation over $(Ph_3P)_3RhCl$,[36] the latter procedure being effective for aliphatic as well as aromatic nitro olefins. Finally, condensations of these nitroalkanes with **22** occurred readily with sodium acetate in acetic acid. By use of this procedure 2-alkylindoles have been prepared in fairly good overall yields (see Table I).

As an extension of this work, the benzoyldinitrostyrene **27** was hydrogenated to determine whether an indole, **29**, or a quinoline, **28**, would be formed. On



work-up of the reaction mixture only 3-amino-2-phenylquinoline (**28**) was found. All attempts to block the keto group in **27** by ketalization led to either the recovery of starting material or the addition of the alcohol across the double bond.

We also felt that reducing an *o*-nitrostyrene oxide after dehydrating the anticipated hydroxyindoline intermediate, **31**, could lead to the formation of indoles (Scheme V). The ketal epoxide **30** was prepared as shown in Scheme V and hydrogenated under a variety of conditions. In most instances the product mixture was composed of a large number of compounds, none of which gave the characteristic indole test reactions or showed the characteristic β-indole proton resonance in the pmr spectra,[33c] even after acid treatment to attempt dehydration. When palladium on charcoal was used as the catalyst a reasonably pure sample of a single product was obtained. This material still showed the presence of the dioxolane ring by pmr spectroscopy but was found to be polymeric by mass spectral analysis. No further work was done on this material.

Experimental Section[37]

o-Toluidide Formation (Table II). A. From Acid Chlorides.—A dioxane solution of *o*-toluidine was added to a suspension of 1 equiv of sodium hydride in hexane. After gas evolution subsided a dioxane solution of 1 equiv of the acid chloride (or anhydride) was added and the mixture was refluxed for 2–3 hr. The reaction mixture was poured into water and extracted with ether. The extracts were washed with a 2% aqueous sodium carbonate solution, 3 *N* HCl, and water, after which they were dried and evaporated. The solid toluidides were recrystallized from aqueous ethanol or benzene–pentane and were characterized by the presence of infrared absorption bands at 3450–3350 (NH) and 1680–1690 cm^{-1} (C=O) as well as by a three-proton singlet in the nmr spectrum at δ 2.1–2.2 ($ArCH_3$).

B. From Esters.—To 50–75 ml of hexane containing 0.05 mol of *n*-butyllithium was added, slowly and with stirring under nitrogen, 5.4 g (0.05 mol) of freshly distilled *o*-toluidine in 25 ml of ether. After gas evolution ceased, 0.025 mol of the ester in 25 ml of ether was added and the solution was refluxed for 1–2 hr and then poured over ice water. If a solid formed it was filtered and recrystallized from aqueous ethanol or benzene–pentane. If not, the reaction mixture was extracted with ether. The extracts were washed with water, dried, and evaporated. The excess *o*-toluidine could conveniently be removed by heating at 60° (0.2 mm) overnight.

C. From Ketones. *N*-(Diethylphosphonoacetyl)-*o*-toluidine (5).—To 500 ml of ether containing 54 g of *o*-toluidine and 55 g of triethylamine was added a solution of 125 g of bromoacetyl bromide in 200 ml of ether. After stirring for 1 hr the precipitate was removed and the ether was evaporated from the filtrate under reduced pressure. The residue was treated with 300 ml of pentane and the crystalline *N*-(bromoacetyl)-*o*-toluidine, separated by filtration, was used directly in the following step.

This toluidide (57 g) was added to 83 g of triethyl phosphite and the mixture was heated rapidly to 120°, at which temperature a violent reaction began. When the initial reaction subsided, the mixture was heated further to 150° under reduced pressure until

(34) G. B. Bachman and R. J. Maleski, *J. Org. Chem.*, **37**, 2810 (1972), and references cited therein.

(35) I. Baxter and G. A. Swan, *J. Chem. Soc.*, 468 (1968).

(36) R. E. Harmon, J. L. Parsons, D. W. Cooke, S. K. Gupta, and J. Schoolenberg, *J. Org. Chem.*, **34**, 3684 (1969).

(37) Proton nmr spectra were determined on a Varian A-60A spectrometer. Ir spectra were determined on a Beckman IR-10. Melting points and boiling points are uncorrected. Tlc determinations were performed on Eastman #6060 silica gel thin layer chromatogram sheets using chloroform as the developing solvent.

gas evolution ceased. The cooled residue was dissolved in 400 ml of ether and the resulting solution was poured slowly into 2 l. of petroleum ether (bp 30–60°). The precipitated **5** (32 g, 45%) had mp 76–78° (recrystallization from ether–petroleum ether raised the melting point to 77–78°); ir ($CHCl_3$) 3400, 1684 cm^{-1}; nmr ($CDCl_3$) δ 1.17 (t, 6, $-OCH_2CH_3$), 2.14 (s, 3, $ArCH_3$), 3.00 (d, 2, J = 21 Hz, $PCH_2C{=}O$), 4.06 (m, 4, $-OCH_2CH_3$), and 9.05 (s, 1, NH). *Anal.* Calcd for $C_{13}H_{20}NO_4P$: C, 54.73; H, 7.07; N, 4.41. Found: C, 54.79; H, 7.15; N, 4.90.

A solution of 2.85 g (0.01 mol) of **5** and 1.1 g (0.02 mol) of sodium methoxide in 10 ml of DMF was stirred for 5 min, after which time 0.01 mol of the ketone was added and the slurry was thoroughly mixed. After standing at room temperature for 96 hr the slurry was poured into 50 ml of water and the resulting mixture was extracted with ether. The extracts were dried and evaporated. The residue was dissolved in 100 ml of ethanol and hydrogenated over 50 mg of 5% Pd/C at room temperature and 35 psig. Filtration and evaporation give the toluidide, which was purified by recrystallization from aqueous ethanol or benzene–pentane.

***N*-(1-Benzyl-4-piperidylpropionyl)-*o*-toluidine (41).**—Crude *N*-(4-pyridylpropionyl)-*o*-toluidine (2.15 g, 0.009 mol), prepared from 1.1 g (0.01 mol) of 4-pyridinecarboxaldehyde by method C, was dissolved in 15 ml of ethanol and then treated with 1.4 g (0.11 mol) of benzyl chloride. The solvent was removed by heating on a steam bath and the residue was taken up in a mixture of 30 ml of ethanol and 9 ml of acetic acid. This solution was hydrogenated over 0.5 g of platinum oxide at 35 psig. After 3 equiv of hydrogen was absorbed (about 2 hr) the reaction mixture was filtered and the filtrate was evaporated. The residue was slurried with ether and treated with 15 ml of cold 30% aqueous NaOH. The ether layer was dried and evaporated and the residue was recrystallized from aqueous acetone to give 2 g (60%) of the piperidyl toluidide, **41**, mp 128–129°. *Anal.* Calcd for $C_{22}H_{28}N_2O$: C, 78.53; H, 8.39; N, 8.33. Found: C, 78.46; H, 8.56; N, 8.04.

6-Methoxy-3-isoquinolinecarboxo-*o*-toluidide (4p), prepared from 6-methoxy-3-isoquinolinecarboxylic acid[38] by the procedure of Klosa,[39] had mp 124–125°; ir (Nujol) 3320, 1680, 1625, and 1590 cm^{-1}; nmr ($CDCl_3$) δ 2.37 (s, 3, $ArCH_3$), 3.83 (s, 3, $-OCH_3$), 8.43 (s, 1, isoquinoline C_4 H), 8.87 (s, 1, isoquinoline C_1 H), and 10.13 (s, 1, NH). *Anal.* Calcd for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.59. Found: C, 74.21; H, 5.58; N, 9.38.

***N*-Benzyl-3-ethyl-4-piperidone (32).**—To a mixture of 30 g (0.27 mol) of potassium *tert*-butoxide, 200 ml of freshly distilled *tert*-butyl alcohol, and 48.3 g (0.31 mol) of ethyl iodide was added all at once 58 g (0.22 mol) of ethyl *N*-benzyl-4-oxo-3-piperidinecarboxylate[40] followed by refluxing, with stirring, for 45 min. The solvent was evaporated under reduced pressure and the residue was taken up in water and extracted with ether. The extracts were dried and evaporated to give 61 g (95% crude yield) of a red oil, nmr ($CDCl_3$) δ 0.85 (t, 3, CCH_2CH_3) 1.20 (t, 3, OCH_2CH_3), 3.57 (s, 2, NCH_2Ph), and 4.01 (q, 2, OCH_2CH_3). This oil was refluxed for 16 hr with 800 ml of 6 *N* HCl. The solution was evaporated nearly to dryness under reduced pressure, the residue was dissolved in 200 ml of water, and the solution was made basic with solid sodium bicarbonate. The mixture was extracted with ether and the extracts were washed with water, dried, and evaporated to give an oil which on distillation gave 22.3 g (49%) of **32**: bp 138–139° (1 mm); nmr ($CDCl_3$) δ 0.85 (t, 3, $-CH_2CH_3$), and 3.57 (s, 2, NCH_2Ph). *Anal.* Calcd for $C_{14}H_{19}NO$: C, 77.39; H 8.79; N, 6.45. Found: C, 77.08: H, 8.74; N, 6.41.

Ethyl-*N*-benzyl-3-ethyl-4-piperidyl Acetate (33).—A solution of 50 g (0.22 mol) of triethyl phosphonoacetate in 20 ml of dry benzene was added dropwise with stirring to a suspension of 5.3 g (0.22 mol) of sodium hydride in 300 ml of dry benzene with the temperature of the reaction mixture kept below 40°. After the addition was completed the clear solution was stirred for an additional 15 min, after which time a solution of 46 g (0.21 mol) of **32** in 20 ml of benzene was added dropwise over a period of 1.5 hr. After the addition was finished the reaction mixture was stirred for an additional 1.5 hr and then poured into water. The benzene layer was separated and the aqueous phase was extracted with ether. The combined organic solutions were washed with water, dried, and evaporated to give 45 g of an orange oil which was dissolved in 300 ml of acetic acid and hydrogenated over 1 g of platinum oxide at room temperature and 50 psig. After 1 equiv of hydrogen had been adsorbed the catalyst was removed and the solution was evaporated. The residue was dissolved in water, made basic with sodium bicarbonate, and extracted with ether. The extracts were washed with water, dried, and evaporated to give an oil which was distilled to give 21.3 g (35%) of **33**: bp 142–145° (0.3 mm); nmr ($CDCl_3$) δ 0.84 (t, 3, $-CH_2CH_3$), 1.20 (t, 3, $-CH_2CH_3$), 3.46 (2 peaks, 2, NCH_2Ph), and 4.10 (q, 2, $-OCH_2CH_3$). *Anal.* Calcd for $C_{18}H_{27}NO_2$: C, 74.69; H, 9.40; N, 4.84. Found: C, 74.82; H, 9.54; N, 4.97.

Madelung Reaction.—Under a slow nitrogen stream a mixture of 0.5–1.0 g of the *o*-toluidide and 4–8 equiv of potassium *tert*-butoxide was refluxed in 10–20 ml of dry *tert*-butyl alcohol for 30 min. The alcohol was then removed by increasing the nitrogen flow and removing the condenser. When most of the solvent had evaporated the reaction flask was transferred to a Woods metal bath which had been preheated to 200–250°. The temperature was slowly raised until the solid mixture melted with frothing (275–350°) and was held at this level until the reaction was complete. Small samples were withdrawn on a glass rod, quenched in water, and extracted with ether and the extracts were spotted on tlc sheets and developed with chloroform. Detection with iodine vapor followed by spraying with Ehrlich's reagent[41] allowed the reaction to be followed until the starting material (yellow spot) was gone and the indole (pink-violet spot) was at a maximum or until decomposition began. If the presence of starting material persisted, the mixture was cooled, more potassium *tert*-butoxide and *tert*-butyl alcohol were added, and the procedure was repeated. The reaction mixture was then cooled, quenched with water, and extracted with ether. The extracts were washed with water, dried, and evaporated to give the indole, which was readily recrystallized from aqueous ethanol and easily characterized by the β-proton peak in the nmr at δ 6.1–6.2.[33c] A list of compounds prepared in this way, their physical properties, and the optimum reaction temperatures is given in Table I.

When this reaction was attempted on the *N*-carboethoxypiperidyl toluidide **4k**, or any material containing a double bond such as the toluidides **4c** and **4o**, intractable nonindolic product mixtures were obtained. When the reaction on **4k** was run at 260° for 5 min a toluidide was obtained which was readily converted by reductive amination with formaldehyde to the *N*-methylpiperidyl toluidide, **4i**. Madelung reaction on the methoxyisoquinoline toluidide, **4p**, did not take place until the reaction temperature was raised above 340°. The product mixture obtained for this reaction showed no β-indole proton absorption or methoxy methyl absorption in the nmr spectrum.

Ethyl 3-(6-Methoxy-3-isoquinolyl)-3-oxopropionate (18).—To a refluxing solution of 25.5 g (0.11 mol) of ethyl 6-methoxyisoquinoline-3-carboxylate[38] and 13.9 g (0.12 mol) of potassium *tert*-butoxide in 100 ml of toluene was added 10.99 (0.12 mol) of ethyl acetate over a 90-min period. The reaction mixture was refluxed for an additional 15 min, cooled, and filtered. The residue was washed with ether, slurried with water, and neutralized to pH 7 with 1 *N* HCl. The product was extracted into methylene chloride and the extracts were dried and evaporated. Recrystallization of the residue from ether–petroleum ether gave 8.3 g (37%) of the β-keto ester **18**: mp 81–82°; ir (Nujol) 1740 and 1690 cm^{-1}; nmr ($CDCl_3$) δ 1.22 (t, 3, OCH_2CH_3), 3.87 (s, 3, $-OCH_3$), 4.17 (q, 2, OCH_2CH_3), and 4.22 (s, 2, CCH_2CO). *Anal.* Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.17; H, 5.50; N, 5.30.

Deuterium Exchange on Ethyl Quinuclidine-2-carboxylate (20).[4d]—A mixture of 90 mg of **20**, 500 mg of potassium *tert*-butoxide, and 10 ml of dry benzene was heated at reflux for several hours. The solvent was removed under vacuum and the residue was treated with 0.5 ml of deuterioacetic acid. The resulting solution was neutralized with saturated sodium bicarbonate solution and extracted with ether. The extracts were dried and evaporated. The nmr spectrum of the recovered ester showed no peaks between δ 3.0 and 4.0, in which region the C-2 proton of the starting material absorbed. The rest of the spectrum was essentially the same as that of the starting amino ester.

2-Methylindole from *o*-Fluoronitrobenzene.—To a solution of 1.3 g (0.01 mol) of ethyl acetoacetate in 10 ml of HMPT under nitrogen was added 1.1 g (0.01 mol) of potassium *tert*-butoxide. After 5–10 min all of the base had dissolved and 0.7 g (0.005 mol) of *o*-fluoronitrobenzene was added slowly, giving a dark red solu-

(38) G. A. Swan, *J. Chem. Soc.*, 1534 (1950).

(39) J. Klosa, *J. Prakt. Chem.*, **19**, 45 (1962).

(40) J. R. Thayer and S. M. McElvain, *J. Amer. Chem. Soc.*, **49**, 2862 (1927).

(41) H. W. van Urk, *Pharm. Weekbl.*, **66**, 473 (1929); F. G. Otten, *ibid.*, **74**, 510 (1937).

tion almost immediately. The solution was stirred at 60–70° for 1 hr and then poured into a mixture of 25 ml of 3 *N* HCl and 100 g of ice. This mixture was extracted with ether and the extracts were washed with water, dried, and evaporated. Hydrolysis and decarboxylation were effected by refluxing the residue in 3 *N* HCl. The acid mixture was extracted with ether and the extracts were washed with water, dried, and evaporated to give 0.66 g (74%) of crude nitro ketone. Catalytic hydrogenation of this material over 5% palladium on charcoal in glacial acetic acid at room temperature and 40 psig gave 0.46 g (71% overall) of 2-methylindole, mp 58–59° (Table I). The use of *o*-chloronitrobenzene gave 2-methylindole in only 48% yield. Replacing the ethyl acetoacetate with *tert*-butyl acetoacetate and utilizing benzene and *p*-toluenesulfonic acid for the hydrolysis and decarboxylation gave slightly better yields of indole.

Prolonged Reaction of Ethyl Acetoacetate with *o*-Chloronitrobenzene.—A solution of 26 g (0.2 mol) of ethyl acetoacetate in 50 ml of HMPT was added to a slurry of 7.2 g (0.3 mol) of sodium hydride in 25 ml of HMPT. This mixture was heated to 40° and 31.6 g (0.2 mol) of *o*-chloronitrobenzene was added. The mixture was then heated at 110–120° overnight, cooled, and poured over a mixture of ice and 100 ml of 3 *N* HCl. This suspension was extracted with benzene and the extracts were washed with water, dried, and evaporated, giving a nearly quantitative yield of ethyl *o*-nitrophenylacetate, mp 65–67° (lit.[42] mp 69°), mmp 67–68.5°.

***p*-Nitrophenylacetone.**—A solution of 6.5 g (0.05 mol) of ethyl acetoacetate in 25 ml of HMPT was slowly added to a suspension of 1.8 g (0.07 mol) of sodium hydride in 10 ml of HMPT under a steady nitrogen stream. After gas evolution subsided, 7.5 g (0.05 mol) of *p*-chloronitrobenzene was added and the reaction mixture was heated to 110–120° for 4 hr. The cooled reaction mixture was poured onto ice 3 *N* HCl and extracted with benzene. The extracts were washed with water, dried, and evaporated to give 7.9 g (72%) of crude β-keto ester, which was hydrolyzed and decarboxylated by refluxing with 3 *N* HCl. Extraction with ether gave 3.4 g (53%) of the ketone as an oil: ir (film) 1718 cm^{-1}; nmr ($CDCl_3$) δ 2.22 (s, 3, $OCCH_3$) and 3.85 (s, 2, $ArCH_2CO$). The 2,4-dinitrophenylhydrazone was recrystallized from aqueous ethanol, mp 180–181°. *Anal.* Calcd for $C_{15}H_{13}N_5O_6$: C, 50.14; H, 3.65. Found: C, 50.09; H, 3.62.

Ethyl Bis(*p*-nitrophenyl)acetate (13).—The procedure described above was repeated, only the reaction mixture was heated for 20 hr. On work-up 7.4 g (47%) of the ester **13** was obtained, which after crystallization from aqueous ethanol had mp 128–130°; ir ($CHCl_3$) 1737 (C=O), 1350, and 1522 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 1.25 (t, 3, OCH_2CH_3), 4.25 (q, 2, OCH_2CH_3), and 5.17 (s, 1, $OCCHAr_2$). *Anal.* Calcd for $C_{16}H_{14}N_2O_6$: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.24; H, 4.35; N, 8.35.

Ethyl 1-(2,4-Dinitrophenyl)-2-oxocyclopentanecarboxylate (34).—To 11.2 g (0.1 mol) of potassium *tert*-butoxide in 100 ml of HMPT was added 15.6 g (0.1 mol) of ethyl 2-oxocyclopentanecarboxylate. After a few minutes 20.3 g (0.1 mol) of 2,4-dinitrochlorobenzene was added slowly keeping the temperature between 20 and 25°. After the addition was complete the reaction mixture was poured onto ice and the resulting suspension was extracted with ether. The ether extracts were washed with water, dried, and evaporated, giving 16 g (50%) of crude **34**, mp 118–120°. Recrystallization from carbon tetrachloride gave 9.7 g (30%) of pure **34** as bright yellow crystals: mp 119–121°; ir (Nujol) 1755 (ester C=O), 1720 (ketone C=O), and 1500 cm^{-1} (NO_2). *Anal.* Calcd for $C_{14}H_{14}N_2O_7$: C, 52.17; H, 4.38; N, 8.69. Found: C, 52.11; H, 4.28; N, 8.43. Only starting materials were obtained on reaction of ethyl 2-oxocyclopentanecarboxylate with *o*-chloronitrobenzene, *o*-fluoronitrobenzene, or 2,4-dichloronitrobenzene. A similar reaction pattern was observed with ethyl 2-oxocyclohexanecarboxylate and the isoquinoline β-keto ester **18**.

Attempted Hydrolysis of 34.—A 2-g sample of **34** was refluxed overnight in equal parts of acetic acid and concentrated HCl. The solvent was then evaporated and the residue was taken up in ether, washed with water, dried, and evaporated. The infrared spectrum of the residue was identical with that of starting material. The use of 70% sulfuric acid or 20% HCl gave the same results. Ethyl 1-(2,4-dinitrophenyl)-2-oxocyclohexanecarboxylate exhibited similar unreactivity toward these hydrolysis conditions. Hydrolysis of the 2,4-dinitrophenylated β-keto ester **18**, using either 20% HCl or 70% sulfuric acid, gave only 6-methoxyisoquinoline-2-carboxylic acid and recovered starting material.

2-Methylindole from the *o*,β-Dinitrostyrene.—To 25 ml of a 10% anhydrous ammonium acetate solution in glacial acetic acid was added 5 g (0.03 mol) of *o*-nitrobenzaldehyde (**22**) and 10 ml of nitroethane. The resulting mixture was refluxed under nitrogen for 3 hr. After cooling, the reaction mixture was poured into water and extracted with chloroform. The extracts were washed with 10% sodium bicarbonate solution and saturated sodium bisulfite solution, dried, and evaporated to give 4.2 g (63%) of the crude dinitrostyrene **23** (R = Me) as a red oil: ir ($CHCl_3$) 1520 and 1330 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 2.6 (s, 3, $-CH_3$) and 8.1 (s, 1, C=CH). The crude dinitrostyrene was dissolved in a mixture of 10 ml of ethanol, 12 ml of acetic acid, and 80 ml of ethyl acetate and hydrogenated over 1 g of 5% palladium on charcoal at room temperature and 60 psig. After hydrogen uptake ceased the catalyst was removed by filtration and the solution was washed with three 100-ml portions of saturated sodium bicarbonate solution. The organic phase was dried and evaporated to give 1.2 g (42%) of 2-methylindole, mp 59–60° (Table I). 2-Benzylindole (**3i**) was prepared in a similar manner using 2-phenylnitroethane[34] in the condensation with *o*-nitrobenzaldehyde.

2-Ethylindole (3h).—A mixture of 5 g (0.03 mol) of **22** and 0.6 g of anhydrous ammonium acetate was dissolved in 20 ml of 1-nitropropane and the solution was refluxed under nitrogen for 4 hr. After cooling, the reaction mixture was poured onto water and extracted with chloroform. The extracts were washed with saturated sodium bisulfite solution, dried, and evaporated. The residue was chromatographed on silica gel. Elution with 3:1 benzene–hexane gave 4.6 g (66%) of the dinitrostyrene **23** (R = Et) as a light yellow oil: ir ($CHCl_3$) 1515 and 1335 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 1.12 (t, 3, CH_2CH_3), 2.25 (q, 2, $-CH_2CH_3$), and 8.15 (s, 1, C=CH). Hydrogenation under the conditions described above for the preparation of 2-methylindole gave 1.70 g (55%) of 2-ethylindole (**3h**): mp 40–41° (Table I); ir ($CHCl_3$) 3430 cm^{-1}; nmr ($CDCl_3$) δ 1.10 (t, 3, CH_2CH_3), 2.25 (q, 2, $-CH_2CH_3$), and 6.05 (s, 1, β H).

2-Cyclohexylnitroethane.—To a solution of 11 g (0.1 mol) of 1,2,5,6-tetrahydrobenzaldehyde and 6 g (0.1 mol) of nitromethane in 100 ml of methanol was added a solution of 4 g of sodium hydroxide in 20 ml of water over a period of 20 min with cooling and rapid stirring. After 1 hr the reaction mixture was filtered and the residue was washed with cold methanol. The solid was then dissolved in 20 ml of cold water, acidified with 3 *N* HCl, and extracted with chloroform. The extracts were dried and evaporated to give 8.5 g (50%) of crude 2-(3-cyclohexen-1-yl)-2-hydroxynitroethane as a light yellow oil: ir ($CHCl_3$) 3400 (OH), 1550, and 1370 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 4.0–4.6 (m, 3, CHOH and CH_2NO_2) and 5.6 (s, 2, vinyl).

This crude product was stirred overnight with 30 ml of acetyl chloride at room temperature. The solution was evaporated and the residue was treated with petroleum ether to give 10.7 g of the 1-(3-cyclohexen-1-yl)-2-nitroethyl acetate: ir ($CHCl_3$) 1740 (C=O), 1545, and 1370 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 4.5 (d, 2, CH_2NO_2), 5.1–5.5 (m, 1, CHOAc), and 5.6 (s, 2, vinyl). This acetate was dissolved in 100 ml of benzene, 2 g of anhydrous sodium acetate was added, and the mixture was refluxed for 2 hr. The cooled reaction mixture was filtered and evaporated to give 4 g of crude 2-(3-cyclohexen-1-yl)-1-nitroethene: ir ($CHCl_3$) 1540 and 1355 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 5.55 (s, 2, vinyl) and 6.8–7.3 (m, 2, nitrovinyl).

Hydrogenation of this material by the procedure of Harmon[36] gave the crude nitroethane, which on chromatography over neutral alumina with hexane as the eluent gave 3.1 g (20% overall yield) of the product was a light yellow oil: bp 79–80° (1–2 mm); ir ($CHCl_3$) 1530 and 1340 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 4.35 (t, 2, $CH_2CH_2NO_2$). *Anal.* Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.90; H, 9.34; N, 8.90.

ω-Nitroacetophenone (35).—To a solution of 1.13 g (0.16 mol) of sodium ethoxide in 100 ml of absolute ethanol was added simultaneously with cooling and stirring 18 g (0.16 mol) of benzaldehyde and 15 g (0.25 mol) of nitromethane. After being stirred at room temperature overnight the reaction mixture was filtered. The residue was dissolved in a mixture of 75 ml of cold water and 11 g of glacial acetic acid and extracted with ether. The extracts were dried and evaporated to give the crude nitro alcohol, which was dissolved in 60 ml of acetic acid and oxidized with 125 ml of Jones reagent[43] for 1 hr at 10–20°. After the addi-

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tion of an excess of sodium bisulfite the mixture was extracted with chloroform and the extracts were washed with water, dried, and evaporated to give 14.2 g (52%) of **35** as a while solid: mp 105–106° (lit.[44] mp 105°); ir ($CHCl_3$) 1710 (C=O), 1570, and 1330 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 5.85 (s, 2, $-COCH_2NO_2$).

α,2-Dinitrochalcone (27).—To a solution of 0.3 g of β-alanine in 6 ml of acetic acid and 60 ml of benzene was added 3.3 g (0.02 mol) of the nitroacetophenone and 3.3 g (0.022 mol) of *o*-nitrobenzaldehyde. The reaction mixture was refluxed through a Dean–Stark trap for 10 hr, cooled, and washed with water and saturated sodium bisulfite solution. The benzene solution was dried and evaporated to give 3.1 g (62%) of **27** which on recrystallization from benzene–hexane had mp 90–92°; ir ($CHCl_3$) 1680 (C=O), 1530, and 1345 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 8.6 (s, 1, nitrovinyl). *Anal.* Calcd for $C_{15}H_{10}N_2O_5$: C, 60.41; H, 3.38; N, 9.39. Found: C, 60.13; H, 3.49; N, 9.34.

Hydrogenation of 27.—A solution of 1 g (0.003 mol) of **27** in a mixture of 2.5 ml of absolute ethanol, 3 ml of acetic acid, and 20 ml of ethyl acetate was hydrogenated over 0.2 g of 5% palladium on carbon at room temperature and 50 psig. After 6 equiv of hydrogen had been absorbed (about 20 min) the catalyst was removed by filtration and the filtrate was washed with a saturated aqueous sodium bicarbonate solution, dried, and evaporated to give 0.9 g of a dark oil which was shown by tlc to be a complex mixture of products. Column chromatography over silica gel using ether as the eluent gave as the only identifiable species 0.2 g of 3-amino-2-phenylquinoline, mp 116–118° (lit.[45] mp 115–116°). No indolic material could be detected.

2-Nitrochalcone (36).—A solution of 4.8 g (0.35 mol) of acetophenone, 6 g (0.04 mol) of *o*-nitrobenazldehyde, and 2 g of ammonium acetate in 20 ml of acetic acid was refluxed under nitrogen for 3 hr. Upon cooling, the light yellow crystals which formed were filtered, washed with cold water, and recrystallized from aqueous ethanol to give 6.5 g (64%) of **36**: mp 117–119° (lit.[46] mp 117–121°); ir ($CHCl_3$) 1675 (C=O), 1540, and 1355 cm^{-1} (NO_2).

2-Nitrochalcone Ethylene Ketal (37).—Following the established[47] procedure, **36** was converted to the ethylene ketal in 81% yield. Recrystallization from 95% ethanol gave **37** as white crystals: mp 73–75°; ir ($CHCl_3$) 1540 and 1355 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 4.0 (m, 4, dioxolane) and 6.15 and 7.15 (d, 2, vinyl). *Anal.* Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.47; H, 5.01; N, 4.72.

2,3-Epoxy-3-(*o*-nitrophenyl)propiophenone Ethylene Ketal (30).—To a solution of 0.75 g (0.0025 mol) of **37** in 20 ml of methylene chloride was added a solution of 1 g (0.006 mol) of *m*-chloroperbenzoic acid in 20 ml of methylene chloride and the resulting solution was stirred at room temperature for 72 hr. The reaction mixture was then washed with a 10% aqueous sodium hydroxide solution, dried, and evaporated to give 0.55 g (57%) of an oil which slowly crystallized: mp 73–76°; ir ($CHCl_3$) 1535 and 1355 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 3.2 (d, 1, C_2H), 3.8–4.4 (m, 4, dioxolane), and 4.6 (d, 1, C_3H). *Anal.* Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 65.45; H, 4.75; N, 4.33.

Hydrogenation of 30.—A solution of 1.5 g (0.005 mol) of **30** in 90 ml of ethyl acetate was hydrogenated over 0.5 g of 5% palladium on carbon at room temperature and 40 psig. After 24 hr 3 equiv of hydrogen was absorbed. The catalyst was removed and the solution was evaporated to give 1.4 g of a glassy yellow solid which was shown by mass spectrometry to be a polymer having a monomer unit with a molecular weight of 281–285.

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Registry No.—**3a,** 95-20-5; **3b,** 948-65-2; **3c,** 40748-44-5; **3d,** 40748-45-6; **3e,** 40748-46-7; *cis*-**3f** maleate, 40762-74-1; *trans*-**3f** maleate, 40762-75-2; **3g,** 15224-31-4; **3h,** 3484-18-2; **3i,** 3377-72-8; **4a,** 120-66-1; **4b,** 584-70-3; **4c,** 40748-51-4; **4d,** 15924-70-6; **4e,** 40748-53-6; **4f,** 40748-54-7; *cis*-**4g,** 40762-76-3; *trans*-**4g,** 40762-77-4; **4h,** 1752-87-0; **4i,** 40748-56-9; **4j,** 40748-57-0; **4k,** 40748-58-1; **4l,** 40748-59-2; *cis*-**4m,** 40762-78-5; *trans*-**4m,** 40762-79-6; **4n,** 26801-38-7; **4o,** 40790-99-6; **4p,** 40748-61-6; **5,** 40748-62-7; **9,** 1969-72-8; **13,** 40748-64-9; **18,** 40748-65-0; **20,** 39926-11-9; **22,** 552-89-6; **23** (R = Me), 18982-46-2; **23** (R = Et), 40748-68-3; **27,** 40748-69-4; **30,** 40748-70-7; **32,** 40748-71-8; **33,** 40748-72-9; **34,** 40791-00-2; **35,** 614-21-1; **36,** 7473-93-0; **37,** 40748-75-2; *o*-toluidine, 95-53-4; *N*-(bromoacetyl)-*o*-toluidine, 5332-69-4; triethylphosphite, 122-52-1; *N*-(4-pyridylpropionyl)-*o*-toluidine, 40748-77-4; 4-pyridinecarboxaldehyde, 872-85-5; ethyl *N*-benzyl-4-oxo-3-piperidinecarboxylate, 41276-30-6; ethyl 6-methoxyisoquinoline-3-carboxylate, 40748-79-6; *o*-fluoronitrobenzene, 1493-27-2; ethyl acetoacetate, 141-97-9; *o*-chloronitrobenzene, 88-73-3; *p*-nitrophenylacetone, 5332-96-7; *p*-nitrophenylacetone dinitrophenylhydrazone, 40748-81-0; ethyl 2-oxocyclopentanecarboxylate, 611-10-9; 2,4-dinitrochlorobenzene, 97-00-7; *o*-β-dinitrostyrene, 3156-39-6; 1-nitropropane, 108-03-2; 2-cyclohexylnitroethane, 40748-84-3; 1,2,5,6-tetrahydrobenzaldehyde, 100-50-5; nitromethane, 75-52-5; 2-(3-cyclohexen-1-yl)-2-hydroxynitroethane, 40748-85-4; 1-(3-cyclohexen-1-yl)-2-nitroethyl acetate, 40748-86-5; 2-(3-cyclohexen-1-yl)-1-nitroethene, 40748-87-6; benzaldehyde, 100-52-7; nitroethane, 79-24-3.

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