Synthesis of New 3-(Pyridylmethylene)-, 3-(Pyridylmethyl)-, 3-(Piperidylmethyl)-, and 3-(β-Alkylaminoethyl)-2-indolinones. The Reduction of Isoindogenides, Nitro Compounds, and Pyridines in a Series of 2-Indolinones

GORDON N. WALKER, RONALD T. SMITH, AND BARBARA N. WEAVER

Research Division, CIBA Pharmaceutical Company, Division of CIBA Corporation, Summit, New Jersey

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Through improved procedures in Knoevenagel condensation and hydrogenation, a variety of new 3-(pyridylmethylene)-, 3-alkylidene-, and 3-arylidene-2-indolinones, together with nitromethane addition products, reduction products, and selectively alkylated derivatives, have been made available. This work has led to synthesis of a variety of new oxytryptamines. The physiological effects produced by these compounds indicate that some revision of earlier views in this area of pharmacological chemistry is in order.

In recent years the reported syntheses of indoles substituted at position 3 with basic groups, and especially the tryptamine side chain, have reached the proportions of a long list. Rather than to review that body of well-documented work, much of which has been inspired by consideration of structures and proposed biogeneses of various indole metabolites and alkaloids, it is the purpose of this paper to present some routes both known and novel to comparatively neglected similar 2-indolinones (oxindoles) and to indicate that certain established pharmacological considerations in indole chemistry require revision for these indolinones.

Julian's early, successful approaches to eserolines[1-3] and yohimbine-related pentacyclic indoles[4,5] demonstrated the variety of synthetic methods applicable to basic 2-indolinones, and interest in such compounds is reflected in later papers and patents[6-18] dealing further with their synthesis. In addition to the obvious possibility of further transforming 2-indolinones into indoles and indolenines, the interest of some of this work in the context of time centered around (1) a structural resemblance of 3-(2-piperidylmethyl)-indoles to skeletal fragments of lysergic acid,[9,19] (2) an imagined similarity of substituted oxytryptamines to a portion of the morphine molecule or to what is commonly thought of as the "analgetiphoric" moiety,[6,7,11,13] and (3) interest in metabolism of tryptophan[20] through corresponding 2-oxo compounds. Currently, revived interest in 2-indolinones[14-18] may be fostered by recent solutions to the structural problems presented by the alkaloids, gelsemine,[21] mitraphylline,[22] and rhyncophylline,[22] together with newly available information[5,23] about the course of earlier[4] syntheses of spiro-3,3-disubstituted basic 2-indolinones.

One of the best-known characteristics of 2-indolinone (oxindole) is its sometimes very easy condensation with carbonyl compounds to give so-called isoindogenides.[17] With aromatic aldehydes, the reaction usually is promoted by piperidine. It has supplied the starting point for a well-known variation[24] of the Pschorr synthesis[25] and might be considered potentially at least as generally applicable to the preparation of 3-alkylidene- or 3-arylidene-2-indolinones as its alternative, the reaction of isatins with active methylene compounds.[9] This is in a sense parallel to the fact that 3-alkylation of 2-indolinones[3,6-8,11-13,15] is certainly superior to the reaction of active methylene compounds with 2-indolinones bearing a displaceable 3-group. The apparent simplicity of isoindogenide formation, however, is deceptive. Experimentally it is found that 2-indolinone, albeit it has a sterically exposed and quite reactive 3-methylene group, is no exception among delocalized carbanion-forming compounds in regard to the well-known fact that such anions in general add initially with much less ease to the carbonyl group of ketones than to that of aldehydes.

It was found that attempted condensation of 2-indolinone with ketones, although more or less feasible using piperidine and temperatures higher than that sufficing for aldehydes, or by base-acetate-catalyzed modifications of the Knoevenagel method,[26] did not

(1) P. L. Julian, J. Pikl, and D. Boggess, *J. Am. Chem. Soc.*, **56**, 1797 (1934).

(2) P. L. Julian and J. Pikl, *ibid.*, **57**, 539, 563, 755 (1935).

(3) P. L. Julian and F. E. Wantz, *ibid.*, **57**, 2026 (1935).

(4) (a) P. L. Julian, A. Magnani, J. Pikl, and W. J. Karpel, *ibid.*, **70**, 174 (1948); (b) P. L. Julian and A. Magnani, *ibid.*, **71**, 3207 (1949).

(5) P. Belleau, *Chem. Ind.* (London), 229 (1955).

(6) O. Eisleb, *Ber.*, **74**, 1433 (1941).

(7) E. C. Horning and M. W. Rutenberg, *J. Am. Chem. Soc.*, **72**, 3534 (1950).

(8) E. Kretz, J. M. Müller, and E. Schlittler, *Helv. Chim. Acta*, **35**, 520 (1952).

(9) A. M. Akkermann and H. Veldstra, *Rec. trav. chim.*, **73**, 629 (1954); see also A. M. Akkermann, D. K. De Jongh, and H. Veldstra, *ibid.*, **70**, 899 (1951).

(10) R. A. Abramovitch and D. H. Hey, *J. Chem. Soc.*, 1697 (1954).

(11) G. Palazzo and V. Rosnati, *Gazz. chim. ital.*, **82**, 584 (1952); *Chem. Abstr.*, **47**, 12347 (1953).

(12) E. Wenkert, A. K. Bose, and T. L. Reid, *J. Am. Chem. Soc.*, **75**, 5511 (1953); E. Wenkert, N. K. Bhattacharyya, T. L. Reid, and T. E. Stevens, *ibid.*, **78**, 797 (1956).

(13) M. E. Speeter, U. S. Patent 2,759,935 (1956); *Chem. Abstr.*, **51**, 2050 (1957).

(14) G. Hallmann, *Ber.*, **95**, 1138 (1962).

(15) H. E. Zaugg and R. W. De Nel, *J. Am. Chem. Soc.*, **84**, 4574 (1962).

(16) G. Tacconi, *Farmaco* (Pavia), *Ed. Sci.*, **19**, 913 (1964).

(17) I. W. Elliott and P. Rivers, *J. Org. Chem.*, **29**, 2438 (1964), and references therein.

(18) C. S. Franklin and A. C. White, *J. Chem. Soc.*, 1335 (1963).

(19) H. Plieninger, M. Schach von Wittenau, and B. Kiefer, *Ber.*, **91**, 1898, 1905, 2095 (1958).

(20) P. L. Julian and H. C. Printy, *J. Am. Chem. Soc.*, **75**, 5301 (1953); P. L. Julian, H. C. Printy, R. Ketcham, and R. Donne, *ibid.*, **75**, 5305 (1953); P. L. Julian, H. C. Printy, and E. E. Dailey, *ibid.*, **78**, 3501 (1956); P. L. Julian, E. E. Dailey, H. C. Printy, H. L. Cohen, and S. Hamashige, *ibid.*, **78**, 3503 (1956).

(21) H. Conroy and J. Chakravarti, *Tetrahedron Letters*, **L4**, 6 (1959).

(22) N. Finch and W. I. Taylor, *J. Am. Chem. Soc.*, **84**, 1318, 3871 (1962).

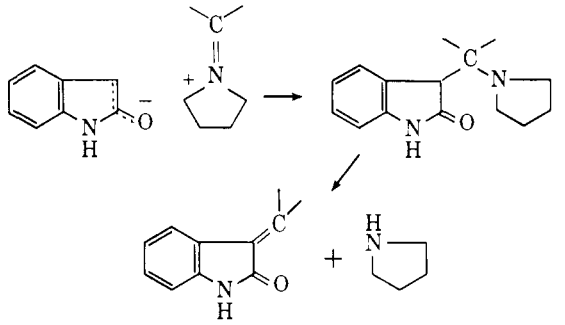
(23) Y. Pan and T. Oishi, *Chem. Pharm. Bull.* (Tokyo), **11**, 441, 446, 451 (1963).

(24) A. Windaus, H. Jensen, and A. Schramme, *Ber.*, **57**, 1875 (1924).

(25) P. H. Leake, *Chem. Rev.*, **56**, 27 (1956).

(26) A. C. Cope, *J. Am. Chem. Soc.*, **59**, 2327 (1937); A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenbergh, *ibid.*, **63**, 3452 (1941); E. A. Cragoe, C. M. Robb, and J. M. Sprague, *J. Org. Chem.*, **15**, 381 (1950); F. B. Gairaud and G. R. Lappin, *ibid.*, **18**, 1 (1953).

proceed smoothly. Such attempts in practice are superseded by a simple, effective procedure developed for the purpose, as follows. The pyrrolidine enamine of a ketone was prepared first and then allowed to react with 2-indolinone in benzene. The method in concept is similar to one found by Robertson[27] involving reaction of Schiff bases with phenylnitromethane to generate nitrostilbenes, with the difference that in the present reaction of 2-indolinones, acetic acid or other added proton source usually need not be present. We visualize the intermediacy of first a proton-transferred salt or complex (immonium indolinonate), then formation of the new carbon–carbon bond, and finally loss of pyrrolidine, to form the 3-alkylidene-2-indolinone in this reaction, which provided the means for efficient, facile synthesis of compounds VI. This reaction is so



rapid and smooth that it might even be recommended as a possible addition to the armamentarium of methods for characterizing some ketones *via* their enamines through reaction with 2-indolinone to form crystalline 3-ylidene derivatives, and through subsequent hydrogenation of these to crystalline compounds (VII). One is also inclined to believe in the intermediacy of immonium salts, formed by proton transfer from reactive methylene group to an imine or enamine, in all amine-catalyzed Knoevenagel reactions. This makes more readily understood the frequently observed sluggishness of many Knoevenagel condensations as carried out classically by simply mixing the three components without providing for removal of water, by assigning rate determination to the initial, reversible step of carbonyl + amine ⇄ [imine, carbinolamine, or enamine].

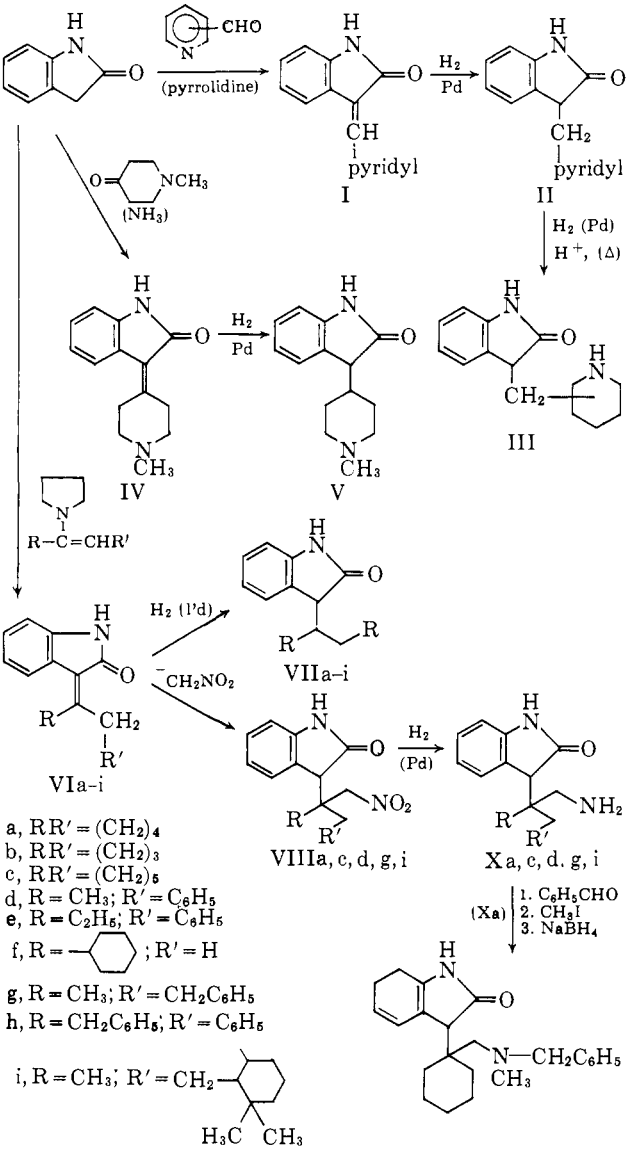
The usefulness of preformed imines[27] and enamines in the condensation of carbonyl compounds with reactive methylene group containing molecules should be listed with those uses of other types currently recognized as improvements over older processes.[28]

In a few cases, notably 4-piperidones, the ketone enamine procedure was inferior to simply using ammonia, *e.g.*, in the preparation of IV. But since pyrrolidine so effectively mediated most of the ketone condensations it was also tried in direct reactions of 2-indolinone with aldehydes (methanol solution) and found to be superior to piperidine as a promoter of

(27) D. N. Robertson, *J. Org. Chem.*, **25**, 47 (1960).

(28) G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954); G. Stork and H. K. Landesman, *ibid.*, **78**, 5128, 5129 (1956); G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963); G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.*, **28**, 1459 (1963); K. C. Brannock, R. D. Burpitt, V. W. Goodlet, and J. G. Thweatt, *ibid.*, **28**, 1462 (1963); K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *ibid.*, **29**, 801 (1964); C. F. Huebner, L. Dorfman, M. M. Robison, E. Donoghue, W. G. Pierson, and P. Strachan, *ibid.*, **28**, 3134 (1963).

CHART I

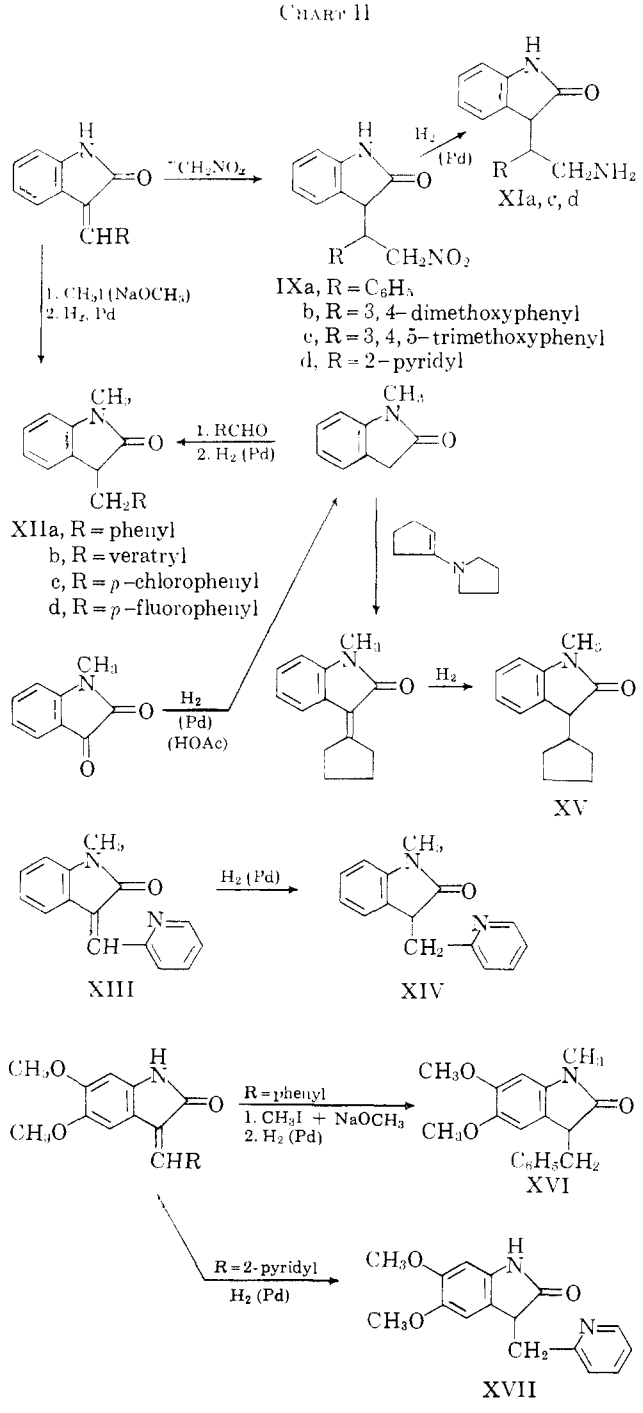


some of these, and also of the condensation of N-methyl-2-indolinone with some aldehydes and ketones. Especially interesting was its effectiveness in providing good yields of 3-picolylidene-2-indolinones (I) from 2-indolinone and the pyridine aldehydes, and a more versatile method for these than the earlier isatin–picoline reactions.[9]

Since the time (1962) when most of our work on compounds I–XV was completed, it has emerged that the double bond of isoindogenides is somewhat more reactive[17] than that of the average conjugated ester or amide. Awareness of this comes as the result of finding the double bond to be borohydride reducible,[17] and of finding as we did that its palladium-catalyzed hydrogenation, giving compounds II from I, V from IV, and VII from VI (see Chart I), is also unusually facile. We also observed that the Michael addition of the nitromethane anion,[29] giving VIII from VI, and IX from various benzylidene-2-indolinones, proceeds quite readily in some cases. The yields from the reaction VI → VIII varied widely, however, in con-

(29) See E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 179 (1959).

CHART II



pounds derived from cyclic ketones, the cyclohexylidene-2-indolinone (VIa) proceeding in good yield with sodionitromethane, the cycloheptylidene compound (VIc) poorly, and the cyclopentylidene-2-indolinone (VIb) not at all. This may be attributed to steric effects in cases (b) and (c).

The further reduction of pyridine groups in compounds II to give the corresponding piperidines III, in the presence of palladium–charcoal, has been noted briefly earlier[30] in connection with other work. The Experimental part provides the details of these examples of the classically unsuspected efficacy of palladium in promoting hydrogenation of protonated or shielded,[31] catalyst-inactivating, heterocyclic bases. Additional examples (XIII → XIV, and preparation of XVII and XVIII) now serve to illustrate further the applicability of the method (see Chart II). While at present there is no definite, comparative information upon which to base a choice between catalytic reduction and borohydride reduction[17] of the double bond in alkylidene- and arylidene-2-indolinones, it may be advisable in future extensions of these to employ borohydride where catalytic hydrogen might undesirably reduce other groups, and to resort to hydrogenation in cases where harm to base-sensitive groups is to be avoided. It is obvious that both borohydride and palladium are superior in avoiding reduction of platinum and sodium alcohol reducible moieties.

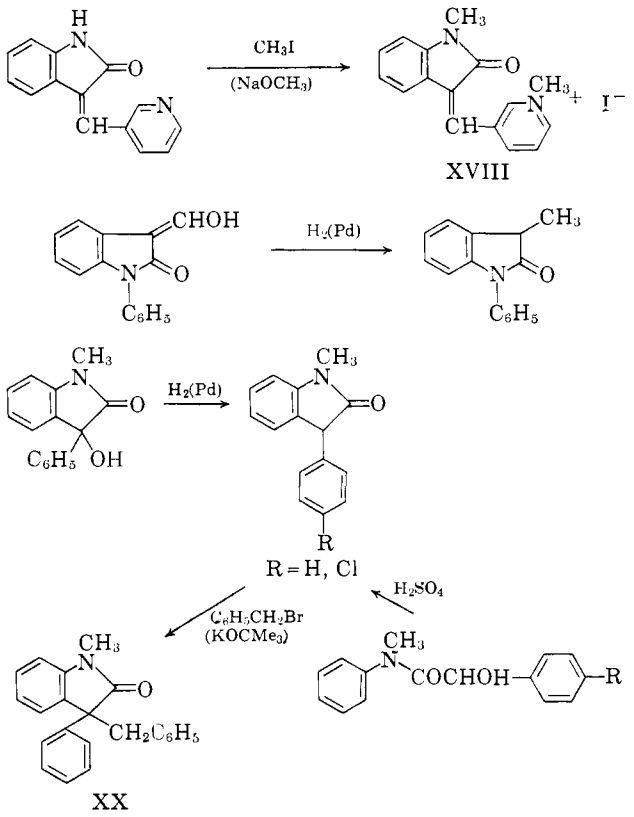
It was of interest to find as well that the nitromethyl compounds VIII and IX were hydrogenated to the respective amines, X and XI, in the presence of palladium charcoal, thus opening a route to certain rather highly substituted oxytryptamines. The yields of readily isolated, crystalline amines X in some cases, however, were rather low.

For the purpose of synthesizing other oxytryptamines having a quaternary 3-carbon atom, through standard alkylations, selected 1,3-disubstituted 2-indolinones (XII, XV, and XVI) were prepared from some of the isoindogenides. N-Methylation of 3-alkylidene- and 3-arylidene-2-indolinones is sometimes found to be incomplete under mild conditions (using sodium methoxide and methyl iodide) but avoids the otherwise difficultly circumvented 3-alkylation[32] accompanying N-alkylation of a 2-indolinone having available 3-hydrogen atom(s). It should be noted that whereas selective 1-methylation of 3-(2-pyridylmethylene)-2-indolinone to give XIII was possible, methylation under the same conditions of the corresponding 3-(3-pyridylmethylene) compound resulted also in quaternization of the pyridine ring, giving XVIII (see Chart III). Subsequent palladium hydrogenation of 1-methylisoindogenides smoothly affords 3-monosubstituted 2-indolinones. An alternative procedure, condensation of an aldehyde or a ketone enamine with N-methyl-2-indolinone, followed by reduction, can be used to the same end, and N-methyl-2-indolinone in turn may be prepared by hydrogenolysis of N-methylisatin[33] in the presence of palladium–charcoal in acetic acid, as well as by the usual Stollé method.[7,34] Similarly, 1-phenyl-3-methyl-2-indolinone is now accessible through formylation of 1-phenyl-2-indolinone[35] and hydrogenolysis[3,20,36] of the resulting 3-hydroxymethylene derivative, a now well-known sequence. An alternative to the Meisenheimer[37] or Stollé syntheses of N-alkyl-3-aryl-2-indolinones is found in proton-assisted, palladium hydrogenolysis[6] of 3-aryldioxindoles, which in

(30) G. N. Walker, *J. Org. Chem.*, **27**, 2906 (1962).
(31) See M. Freifelder, *ibid.*, **29**, 2895 (1964).

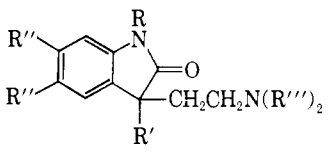
(32) Although certain mono-3-alkylations of 3-unsubstituted 2-indolinones have been carried out[12] we found that methylation of 3-phenyl-2-indolinone could not be limited to attack on nitrogen, but gave 1,3-dimethyl-3-phenyl-2-indolinone, identified by nitration to the corresponding 5-nitro compound, the same as that described by H. S. Boyd-Barrett, *J. Chem. Soc.*, 321 (1932).
(33) W. Borsche and W. Jacobs, *Ber.*, **47**, 354 (1914).
(34) (a) R. Stollé, *J. prakt. Chem.*, [2] **128**, 1 (1930); (b) see also P. L. Julian in "Heterocyclic Compounds," Vol. 3, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, Chapter 1, pp. 117, 142–146.
(35) R. Stolle, *Ber.*, **47**, 2120 (1914).
(36) G. N. Walker, *J. Am. Chem. Soc.*, **77**, 3844 (1955).
(37) J. Meisenheimer and H. Meis, *Ber.*, **57**, 289 (1924).

CHART III



turn are obtained by controlled aryl Grignard[38] or aryllithium[39] treatment of N-alkylisatins. From all these routes one can obtain 1,3-disubstituted 2-indolinones amenable to uncomplicated, final 3-alkylation,[2] *e.g.*, with benzyl (XX) and other halides.

Alkylation of the 1,3-disubstituted 2-indolinones (XII, XV, and XVI), of two 1-methyl-3-aryl(phenyl- or *p*-chlorophenyl)-2-indolinones, and of 1-phenyl-3-methyl-2-indolinone, in turn, with β-dialkyl- (usually dimethyl-) aminoethyl chlorides, unexceptionally using sodamide, was then carried out and provided 3-(β-



XIXa, R = CH_3; R′ = benzyl; R″ = H; R‴ = NEt_2
b, R = CH_3; R′ = *p*-chlorophenyl; R″ = H; R‴ = NMe_2
c, R = CH_3; R′ = *p*-chlorobenzyl; R″ = H; R‴ = NMe_2
d, R = CH_3; R′ = *p*-fluorobenzyl; R″ = H; R‴ = NMe_2
e, R = CH_3; R′ = benzyl; R″ = OCH_3; R‴ = NMe_2
f, R = CH_3; R′ = cyclopentyl; R″ = H; R‴ = NMe_2
g, R = phenyl; R′ = CH_3; R″ = H; R‴ = NMe_2
h, R = benzyl; R′ = phenyl; R″ = H; R‴ = NMe_2

dialkylaminoethyl)-2-indolinones (XIX) with a new assortment of 1- and 3-substituents. These, together with the other basic compounds I–V, X, XI, and XIV, have been subjected to general pharmacological testing.

We believe that some of the methods presented here will be useful in the future to other investigators. Using many of the intermediates prepared as described in the Experimental part of this report, we have investigated other alkylations of 1,3-disubstituted 2-indolinones, particularly those leading to derived 3-acetic and 3-propionic acids and subsequently to spiro compounds, which are to be described in another paper.

Pharmacology.—Data enabling presentation of the following summary of results obtained in this group of compounds, as well as descriptions of the test procedures employed, are contributed by Drs. Walter Barrett and Albert Renzi, as well as other members of the Macrobiology staff.

None of the compounds showed appreciable analgetic effect,[7,13] and no pronounced hypotensive,[38] antihistaminic, or isolated tissue anticholinergic[13] activity was encountered, except with XIi which lowered blood pressure somewhat in the dog. Although IV and XX at 5 mg./kg. had a central stimulant action on mice, other compounds, V–XIa and c and XV–XVII, were virtually devoid of interesting effects on blood pressure or the central nervous system and in general showed little or no toxicity as well (LD_{50} 400 mg./kg. or greater, in most cases).

In mice and rats at moderate dose levels (*ca.* 50–100 mg./kg.), all nine compounds I, II (2-, 3-, and 4-pyridyl), and III (2-, 3-, and 4-piperidyl) elicited in varying degrees a fairly pronounced central depression, characterized by lethargy and occasional catatonia, salivation, urination, etc., from which recovery later took place. These effects may be described as nonspecific, ataractic action and, pending any closer examination, are at present tentatively attributed to central inhibition of cholinesterase. Whatever the exact mechanism of action of these substances may be, they certainly seem to be quite different in their physiological effect from earlier described,[9] similarly constituted indoles.

With compounds XIX, activities such as analgesia,[6–8,13] spasmolysis,[13] lowering of blood pressure, or antagonism of acetyl choline again were absent or minimal, in contrast with what one might anticipate on the basis of earlier findings or expectations in such basic 2-indolinones. Instead antiinflammatory activity made its appearance when XIXa–i were tested in rats (granuloma pouch). Compounds XIXa–d, g, and h, at 50 mg./kg., were moderately effective in this respect; XIXe was slightly active, and XIXf rather potent. In addition, XIXa and b were moderately active as diuretics in the rat, although they also produced marked kaliuresis. Unfortunately, compounds XIX were not effective when given orally. The antiinflammatory activity of basic 2-indolinones (XIX) is interesting, not only as a corollary to recently reported,[40] superior effects of the same type found in heavily substituted indole-3-acetic acids, but also perhaps as an indication of the direction in which future pharmacological study of basic indoles and indolinones may be pursued.

Pharmacological Methods

Blood Pressure Test.—Mongrel dogs of both sexes were anesthetized with sodium pentobarbital. Blood pressure was recorded from the femoral artery and respiration from a tracheal cannula. The compounds were administered intravenously through a cannula placed in a femoral vein. The effects of varying doses of the tested compound on blood pressure, respiration, and heart rate were measured, and at the same time their possible

(38) F. J. Myers and H. G. Lindwall, *J. Am. Chem. Soc.*, **60**, 2153 (1938); R. F. Reeves and H. G. Lindwall, *ibid.*, **64**, 1086 (1942); see also ref. 34b, p. 219.

(39) J. M. Bruce, *J. Chem. Soc.*, 2366 (1959).

(40) T. Y. Chen, *et al.*, *J. Am. Chem. Soc.*, **85**, 488 (1963).

effects on injected *l*-epinephrine, *l*-norepinephrine, and amphetamine were determined.

Central Effects Tests.—The compounds were injected subcutaneously into groups of three mice, and the mice were placed in a recording jiggle cage apparatus which registered their spontaneous motor activity. For each treated group there was a placebo-treated control group of mice. This test is very sensitive for the detection of compounds which increase or decrease spontaneous motor activity.

Any compound which increased or decreased the spontaneous movement pattern of the mice was then tested in unanesthetized dogs for its effect on this species. The compounds were administered orally by capsule. Stimulation or sedation in dogs is readily seen without a recording apparatus by the practiced observer.

Isolated Tissue Tests.—Compounds were tested on the isolated ileum of the guinea pig against the spasm induced by acetylcholine or histamine, for their possible anticholinergic and antihistaminic activity.

Analgetic Test.—The mouse tail flick reaction time method was employed to detect possible analgesia effected by the compounds. The time required for mice to remove their tails from a point source of radiant heat was recorded, first during a control period and then after subcutaneous administration of a compound. Prolonged reaction time indicated analgetic activity.

Antiinflammatory Test.—Compounds were studied in rats using a modification[41] of the Selye granuloma pouch technique. Compounds were administered either orally by stomach tube, or by subcutaneous injection, for 4 days at doses averaging 50 mg./kg., to albino rats having on their backs the inflamed pouch created by introduction of 0.5 ml. of croton oil. The animals were sacrificed on the fifth day, and the pouch exudate volume was measured. Activity of compounds was determined by comparing the volume of exudate in treated animals with that observed in control groups. A compound was considered active if exudate from a treated animal was 75% or less of that of a control animal.

Diuretic Test.—Male rats of the CIBA strain, weighing 180–200 g., were fasted 18 hr. and given 5 ml. of 0.2% saline solution/100 g. of body weight, by stomach tube. Compounds to be tested were given at 50 mg./kg. at the time of fluid loading. The rats were placed in metabolism cages, and urine volumes were measured at 30-min. intervals over a period of 3 hr. and compared with control values. Total amounts of Na^+ and K^+ excreted over the 3-hr. period were determined by flame photometry.

Experimental[42]

Condensation of Oxindole with Pyridinealdehydes (I). 3-(2-Pyridylmethylene)-2-indolinone.—When a warm solution of 12.5 g. of 2-indolinone and 10.6 g. of pyridine-2-aldehyde in 30 ml. of methanol was treated with 7 ml. of pyrrolidine, an exothermic reaction occurred, and the boiling hot solution, on scratching, very soon deposited a thick mass of crystals. After cooling to room temperature, these were collected, washed with methanol, and air dried to give 19 g. (91%) of orange crystals, m.p. 204–206° dec. Recrystallization from methanol raised the melting point to 207–209° dec. (lit.[17] m.p. 205–206°), λ_{max}^{Nujol} 5.85 and 6.10–6.17 μ, λ_{max}^{EtOH} 256 and 333 mμ (ϵ 15,320 and 14,960, respectively).

3-(3-Pyridylmethylene)-2-indolinone.—Similar reaction of 12.5 g. of 2-indolinone with 10.6 g. of pyridine-3-aldehyde in 150 ml. of methanol, in the presence of 7 ml. of pyrrolidine also led to an exothermic effect. The solution, upon cooling and seeding with a sample of product previously obtained in an exploratory run, deposited crystals which were collected, washed with methanol, and air dried; yield 11.5 g. (55%) of bright yellow needles, m.p. 178–181°, raised on further recrystallization from methanol to 193.5–196°; λ_{max}^{Nujol} 5.86, 6.07, and 6.18 μ; λ_{max}^{EtOH} 256, 316, and 390 (ϵ 14,110, 11,060, and 2480, respectively).

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.94; H, 4.62; N, 12.33.

This compound was reluctant to crystallize at first, and initially was obtained in crystalline form as follows. The crude methanol solution from reaction of 52.4 g. of 2-indolinone and 43.8 g. of pyridine-3-aldehyde in the presence of 34 g. of piperidine (boiled, as a solution in 200 ml. of methanol, for 0.5 hr.) was evaporated to small volume, cooled, and treated with water and acetic acid (30 ml.). The crude oil was extracted with ethyl acetate–ether; the organic solution was washed with several portions each of 3% NaOH solution and water, and was dried ($MgSO_4$), filtered, and evaporated to small volume. Crystallization then occurred, and after 1 day the product was collected, washed with a little ethyl acetate, and air dried to give 37.6 g. (43%) of yellow crystals, m.p. *ca.* 150–160°, which, after recrystallization from methanol had m.p. 193–196°.

3-(4-Pyridylmethylene)-2-indolinone.—A warm solution of 12.5 g. of 2-indolinone and 10.6 g. of pyridine-4-aldehyde in 150 ml. of methanol was treated with 7 ml. of pyrrolidine. After the exothermic reaction, the solution was allowed to stand and cool. Scratching induced crystallization, and after the suspension had been chilled briefly in ice the product was collected, washed with methanol, and dried. The yield of yellow crystals was 10.5 g. (50%), m.p. 216–220° dec. Recrystallization from methanol gave finely divided, yellow crystals: m.p. 229–231° dec.; λ_{max}^{Nujol} 5.75–5.81 (doublet) and 6.16–6.23 μ (doublet); λ_{max}^{EtOH} 258, 312, and 395–400 mμ (ϵ 15,530, 8530, and 2020, respectively).

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.81; H, 4.61; N, 12.34.

1-Methyl-3-(2-pyridylmethylene)-2-indolinone (XIII).—To a solution of 3.0 g. of Na in 100 ml. of methanol was added 9.2 g. of 3-(2-pyridylmethylene)-2-indolinone. The deep red solution was then treated cautiously with 40 ml. of CH_3I, under a reflux condenser. When the initial, exothermic reaction subsided, the solution was boiled gently under reflux for 5.5 hr. The resulting green-orange solution was evaporated on a steam cone to *ca.* 40 ml., and after cooling was diluted with *ca.* 300 ml. of cold water. The crude, crystalline product was collected, washed with water, and air dried; yield 5.6 g. (57%), m.p. 145–149°. Recrystallization from methanol gave pure material as bright yellow needles: m.p. 154–155°; λ_{max}^{Nujol} 5.87 and 6.20 μ; λ_{max}^{EtOH} 260, 334, and 397 mμ (ϵ 16,300, 17,000, and 1770, respectively). Like its precursor, the compound was soluble in dilute HCl.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.27; H, 5.22; N, 11.89.

1-Methyl-3-(3-pyridylmethylene)-2-indolinone Methiodide (XVIII).—Addition of 3.7 g. of 3-(2-pyridylmethylene)-2-indolinone to a solution of 1.0 g. of Na in methanol (80 ml.) was followed by addition of 15 ml. of CH_3I. The initially very dark solution became light orange when refluxed and after *ca.* 1.5 hr. there occurred separation of crystalline material. The mixture was refluxed for a total of 5.5 hr.; after cooling, the product was collected. The crude material (*ca.* 2 g.), after trituration with methanol, consisted of red-orange needles, m.p. *ca.* 243–265° dec. After recrystallization from methanol there were obtained orange needles, melting partially at 253–255°, and then completely at 267–270° dec. The infrared spectrum (Nujol) had sharp peaks at 5.84, 5.94 (m), and 6.23 μ. The compound was soluble in water.

Anal. Calcd. for $C_{16}H_{15}N_2IO$: C, 50.81; H, 4.00; I, 33.5; N, 7.41. Found: C, 50.83; H, 4.10; I, 32.2; N, 7.13.

Hydrogenation of 3-(Pyridylmethylene)-2-indolinones to 3-Pyridylmethyl-2-indolinones (II). 3-(2-Pyridylmethyl)-2-indolinone.—A suspension of 10 g. of 3-(2-pyridylmethylene)-2-indolinone and 4 g. of 10% Pd–C in 250 ml. of ethyl acetate was shaken at room temperature under 3.15 kg./cm.^{2} of hydrogen for 1 hr.; a pressure drop of 0.274 kg./cm.^{2} (4-l. system), equivalent to 1.08 proportionate moles of hydrogen, took place during the first 20 min., after which there was no further uptake. Filtration of the catalyst and evaporation of the solvent left a colorless residue which soon crystallized in the presence of a little ethyl acetate. Trituration with this solvent gave 8.0 g. of product: m.p. 128–130°, raised on recrystallization from the same solvent to 130–132° (lit.[17] m.p. 130–131°); λ_{max}^{Nujol} 5.89, 6.19, and 6.25; λ_{max}^{EtOH} 250–254 mμ (ϵ 10,110) with inflection points 260 and 284 mμ (ϵ 8650 and 1390, respectively).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.99; H, 5.38; N, 12.49. Found: C, 74.80; H, 5.48; N, 12.45.

3-(3-Pyridylmethyl)-2-indolinone.—Similar hydrogenation of 11.2 g. of 3-(3-pyridylmethylene)-2-indolinone in ethyl acetate in the presence of 4 g. of 10% Pd–C required application of heat (70°) for 1.5 hr., whereupon the 4-l. system pressure dropped 0.288 kg./cm.^{2}. After evaporation of the filtered solution, the residual oil was induced to crystallize by adding some ether. There separated 7.1 g. of colorless crystals: m.p. 130–132°, raised by recrystallization from ethyl acetate to m.p. 139–141°;

(41) A. Robert and J. E. Nezamis, *Acta Endocrinol.*, **25**, 105 (1957).

(42) Melting points, requiring no appreciable correction, were obtained using a coil-heated, rapidly stirred, silicone oil bath with a previously calibrated, correctly reading 360° thermometer.

λ_{max}^{Nujol} 5.88 and 6.18 μ; λ_{max}^{EtOH} 252 mμ (ϵ 9510) with inflections at 261 and 279 mμ (ϵ 7840 and 1410, respectively).

Anal. Cald. for $C_{14}H_{12}N_2O$: C, 74.99; H, 5.38; N, 12.49. Found: C, 74.86; H, 5.45; N, 12.07.

3-(4-Pyridylmethyl)-2-indolinone.—Hydrogenation of 12.0 g. of 3-(4-pyridylmethylene)-2-indolinone in ethyl acetate in the presence of 4 g. of 10% Pd–C was run in a controlled manner at 70°, as in the preceding experiment. After a pressure drop of 0.281 kg./cm.^{2} had been observed (0.5–0.7 hr.), the shaking was continued only for 10–15 min. longer, and then discontinued. The product separated from the ethyl acetate solution on cooling; therefore, after filtration, the catalyst was leached with several portions of ethanol. The combined, filtered solutions were evaporated, and the product was triturated with ethyl acetate. There was obtained 7.0 g. of colorless crystals, m.p. 193–197° dec.; recrystallization from ethanol gave a pure sample: m.p. 199–201° dec.; λ_{max}^{Nujol} 5.83 and 6.20; λ_{max}^{EtOH} 251, 263, and 279 mμ (ϵ 9320, 6270, and 1330, respectively).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.99; H, 5.38; N, 12.49. Found: C, 75.19; H, 5.60; N, 12.29.

Both this reaction and to a lesser extent the preceding one with the β-picolylidene derivative had a tendency slowly to proceed further and give mixtures of products if let run for prolonged periods at 70°. Complete reaction of the α-picolylidene-2-indolinone to the corresponding 3-(2-piperidylmethyl)-2-indolinone, as described below, took place if the reaction was run at elevated temperature in ethyl acetate.

1-Methyl-3-(2-pyridylmethyl)-2-indolinone.—A solution of 3.5 g. of 1-methyl-3-(2-pyridylmethylene)-2-indolinone in 200 ml. of ethyl acetate was treated with 3 g. of 10% Pd–C and shaken under 3.15 kg./cm.^{2} hydrogen at 70°. The expected pressure drop occurred rapidly, and there was no further absorption during 1 hr. Evaporation of the filtered solution gave pale yellow, basic material which did not crystallize. It was converted to the corresponding **hydrochloride** by treatment of an ethereal solution with ethanolic HCl. The salt crystallized slowly, and after being washed with ether had m.p. 203–208° dec.; recrystallization from ethanol–ether raised the melting point to 215–216.5° dec.; λ_{max}^{Nujol} 5.87–5.91 and 6.21 μ, in addition to ionic bands (4.16 broad, 4.84, and 4.99 μ); λ_{max}^{EtOH} 255 mμ (ϵ 12,160) with shoulder at 262 mμ (ϵ 10,760).

Anal. Calcd. for $C_{15}H_{15}ClN_2O$: C, 65.57; H, 5.50; N, 10.20. Found: C, 65.29; H, 5.75; N, 9.99.

The crude base, prepared on a larger scale by hydrogenation of 39 g. of 1-methyl-3-(2-pyridylmethylene)-2-indolinone in ethyl acetate with 12 g. of catalyst at 60°, and isolated as usual, deposited a small amount of solids, on standing. After removal of this material by filtration, the oil was suitable for use in alkylations as described elsewhere.

Hydrogenation of 3-(Pyridylmethylene)-2-indolinones to 3-(Piperidylmethyl)-2-indolinones (III). 3-(2-Piperidylmethyl)-2-indolinone.—A suspension of 15 g. of 3-(2-pyridylmethylene)-2-indolinone and 6 g. of 10% Pd–C in *ca.* 300 ml. of ethyl acetate was shaken under 3.2 kg./cm.^{2} of hydrogen at 80° for a total of 10 hr. (periods of time extending over 2 days), when absorption (total pressure drop 1.48 kg./cm.^{2}, representing *ca.* 3.9 molar equiv.) appeared to be complete. Evaporation of the filtered solution and collection of the product with the aid of some ether afforded 11.5 g. of colorless crystals: m.p. 138–141°, raised by recrystallization from ethyl acetate to 140–142°; λ_{max}^{Nujol} 2.92, 5.99, and 6.10 μ (intense doublet); λ_{max}^{EtOH} 235 and 287 mμ (ϵ 6840 and 2410, respectively). The shift in 2-indolinone carbonyl position in the infrared spectrum evidently is due to group interaction with the sterically adjacent secondary amino group.

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 73.05; H, 7.92; N, 11.76.

The same compound also was prepared by hydrogenation of 3-(2-pyridylmethylene)-2-indolinone in acetic acid solution in the presence of Pd as described in following experiments, followed by regeneration of base from acetate using NaOH solution.

3-(3-Piperidylmethyl)-2-indolinone.—A solution of 13.2 g. of 3-(3-pyridylmethylene)-2-indolinone in 250 ml. of glacial acetic acid was treated with 6 g. of 10% Pd–C and hydrogenated at 3.15 kg./cm.^{2} initial pressure and 80°. A pressure drop of 1.37 kg./cm.^{2} was observed (4.1 molar equiv.) in 3 hr. Evaporation of the filtered solution gave an oil which crystallized in the presence of ether and acetone. By trituration with acetone there was obtained 10.4 g. of the **acetate salt** as finely divided, colorless crystals, m.p. 176–179°; recrystallization from ethanol–ether gave a sample: m.p. 177–178°; λ_{max}^{Nujol} 5.81 and 6.17 μ, in addition to bonded NH and ionic bands.

Anal. Calcd. for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 65.71; H, 7.66; N, 9.33.

Treatment of the hydroacetate with excess K_2CO_3 solution and extraction with ether gave a solution of the crude **base,** which was dried (K_2CO_3) and evaporated. From a small volume of ether there were obtained crystals: m.p. 129–132° (softening, 125°); after recrystallization from ethyl acetate, m.p. 137–138°; λ_{max}^{Nujol} 3.02, 3.27, 5.89, and 6.16 μ; λ_{max}^{EtOH} 249 and 275–279 mμ (ϵ 8410 and 1410, respectively).

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 72.56; H, 7.81; N, 11.30.

3-(4-Piperidylmethyl)-2-indolinone.—Similar hydrogenation of a solution of 15.0 g. of 3-(4-pyridylmethylene)-2-indolinone in 250 ml. of acetic acid in the presence of 5 g. of 10% Pd–C at 80° resulted in a pressure drop of 1.48 kg./cm.^{2} in the 4-l. system (*ca.* 3.9 molar equiv.) in 2 hr. Filtration and evaporation of the acetic acid gave oily material which crystallized in the presence of ether and afforded, after trituration with ether, 17.0 g. of slightly pink crystals, m.p. 210–214° dec. Recrystallization of this **acetate salt** from ethanol gave pure material: m.p. 222–225° dec. (sintering); λ_{max}^{Nujol} 5.80 and 6.07–6.16 μ (doublet) in addition to bonded NH and ionic bands; λ_{max}^{EtOH} 249 mμ (ϵ 8620) with a shoulder 280 mμ (ϵ 1430).

Anal. Calcd. for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 65.90; H, 7.75; N, 9.49.

3-(2-Pyridylmethylene)-5,6-dimethoxy-2-indolinone.—Condensation of 10 g. of 5,6-dimethoxy-2-indolinone[36] with 6.2 g. of pyridine-2-aldehyde in warm methanol (700 ml.) in the presence of 5 ml. of pyrrolidine gave, after exothermic reaction and subsequent cooling, 12.5 g. of dark red crystals: m.p. 240–244°, raised by ethyl acetate recrystallization to 243–245°; λ_{max}^{Nujol} (bonded NH), 5.90, 6.12, and 6.19 μ; λ_{max}^{MeOH} 273–278, 340, and 442 mμ (ϵ 19,370, 13,880, and 4410, respectively), with inflections 288 and 354 mμ (ϵ 16,150 and 11,490, respectively).

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.11; H, 5.10; N, 10.19.

3-(2-Pyridylmethyl)-5,6-dimethoxy-2-indolinone (XVII).—A solution of 10 g. of 3-(2-pyridylmethylene)-5,6-dimethoxy-2-indolinone in ethyl acetate absorbed H_2 very slowly when shaken in the presence of 2.5 g. of 10% Pd–C, at room temperature. After 8 hr., when uptake appeared to be complete, the solution was filtered and evaporated; discoloration was observed in the presence of air. The red-brown residue provided 9.4 g. of tan crystals when triturated with ether. Recrystallization from ethyl acetate gave slightly discolored crystals: m.p. 119–121°; λ_{max}^{Nujol} bonded NH *ca.* 3.15 (broad), 5.85, and 6.13 μ; λ_{max}^{MeOH} 2.62 mμ (ϵ 9140) and inflections 267 and 300 mμ (ϵ 8690 and 3700, respectively). The compound was slowly soluble in, and rather unstable to, acids.

Anal. Calcd. for $C_{16}H_{16}NO_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.51; H, 5.80; N, 9.77.

Attempted synthesis of the corresponding piperidylmethyl-2-indolinone by further reduction of this compound in acetic acid in the presence of Pd at 80° gave, after uptake of 3.10 molar equiv. of H_2, an unstable, rapidly discoloring base which did not crystallize and could not be converted to crystalline salts.

3-(1-Methyl-4-piperidylidene)-2-indolinone (IV).—Anhydrous NH_3 was passed to saturate a solution of 11.7 g. (0.088 mole) of 2-indolinone and 10.2 g. (0.09 mole) of 1-methyl-4-piperidone in 250 ml. of ethanol which was then boiled 2.5 hr., gradually reducing to a smaller volume. Upon treatment of the cooled, concentrated solution with water, there were obtained crystals which were collected, washed with water and with 3:1 aqueous methanol, giving 14.3 g. (72%) of product, m.p. 169–172°. Recrystallization from aqueous methanol raised the melting point to 178–180°; λ_{max}^{Nujol} 5.92 and 6.17 μ; λ_{max}^{EtOH} 254, 260, 294, and 355 mμ (ϵ 27,280, 28,330, 7830, and 1890, respectively).

Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.60; H, 7.15; N, 12.42.

3-(1-Methyl-4-piperidyl)-2-indolinone (V).—Hydrogenation of 4.1 g. of compound from the preceding experiment in the presence of 3.5 g. of 10% Pd–C, in 300 ml. of ethyl acetate, under 3.2 kg./cm.^{2} of H_2, was complete in 5 min. or less at room temperature. Filtration of the catalyst and evaporation of the solvent gave oil which crystallized on standing overnight. The base, purified by recrystallization from ether, had m.p.

131–133°; λ_{max}^{Nujol} 5.91 and 6.20 μ; λ_{max}^{EtOH} 250 and 275–278 mμ (ε 6650 and 1410, respectively).

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 73.13; H, 7.86; N, 12.01.

The corresponding **hydrochloride**, prepared by treatment of an ether solution of the base with alcoholic HCl and recrystallized from ethanol, had m.p. 311–313° dec.; λ_{max}^{Nujo} 5.88 and 6.20 μ as well as NH (*ca.* 3.15 μ) and hydrohalide (*ca.* 3.8 and 4.0 μ) bands.

Anal. Calcd. for $C_{14}H_{19}ClN_2O$: C, 63.03; H, 7.18; N, 10.50. Found: C, 63.10; H, 7.24; N, 10.67.

3-Cycloalkylidene-2-indolinones.—The procedure used in the condensation of 2-indolinone with enamines of ketones is exemplified by the preparation of 3-cyclohexylidene-2-indolinone (VIa) as follows. A solution of 10 g. (0.102 mole) of cyclohexanone and 7.9 g. (0.111 mole) of pyrrolidine in 300 ml. of benzene was refluxed under a water separator for 1 hr. The enamine solution was added to 12.9 g. (0.097 mole) of 2-indolinone, which dissolved rapidly. The solution was heated on a steam cone for 0.5 hr., and then evaporated to smaller volume to complete the crystallization of the product, which was then collected, washed with benzene, and air dried. The yield of slightly discolored, yellow crystals was 18.2 g. (88%), m.p. 168–171°, raised by further recrystallization from benzene to 199–201° (lit.[17] m.p. 192–193°); λ_{max}^{Nujol} 5.96 and 6.20 μ; λ_{max}^{EtOH} 255, 262, 294, and 349–354 mμ (ε 27,800, 32,550, 8150, and 1980, respectively).

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 79.14; H, 7.15; N, 6.73.

3-Cyclopentylidene-2-indolinone (VIb) was prepared by similar procedure using cyclopentanone and crystallized rapidly from the benzene solution, giving 84% of yellow crystals, m.p. 215–219°, raised by recrystallization from methanol to 220–221.5°; λ_{max}^{Nujol} 5.91 and 6.10–6.20 μ (doublet); λ_{max}^{EtOH} 217, 251, 255, 260, 293, and 349 mμ (ε 8870, 26,160, 26,680, 32,565, 7680, and 1850, respectively).

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.40; H, 6.81; N, 7.09.

3-Cycloheptylidene-2-indolinone (VIc) was prepared by the same procedure using cycloheptanone (17.7 g.) and 2-indolinone (20 g.), and did not crystallize immediately. From the evaporated reaction solution there was first recovered 3.8 g. of unchanged 2-indolinone. The remaining oily material was treated with 13 ml. of glacial acetic acid and warmed gently on a steam cone for a brief period, then taken up in ether. The ether solution was washed with three portions of water, dried ($MgSO_4$), and evaporated to a small volume. The crude product (7.3 g., 21%) then crystallized and was collected. Recrystallization from methanol gave yellow needles: m.p. 169–171°; λ_{max}^{Nujol} 5.95 and 6.24 μ; λ_{max}^{EtOH} 253–255, 262, 295, 304, and 352 mμ (ε 27,300, 32,810, 8100, 6490, and 1930, respectively).

Anal. Calcd. for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.41; H, 7.63; N, 6.27.

Other 3-Alkylidene-2-indolinones (VI) were prepared by the same general reaction of 2-indolinone with pyrrolidine enamines of respective starting ketones.

3-(1-Phenylethylidene)-2-indolinone (VId) was obtained using phenylacetone; yield 81% after trituration with methanol. Recrystallization from methanol gave yellow needles: m.p. 187–189°; λ_{max}^{Nujol} 5.90 and 6.13–6.18 μ (doublet); λ_{max}^{EtOH} 253, 260, 295, and 353 mμ (ε 31,460, 32,250, 8150, and 1730, respectively).

Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.80; H, 6.09; N, 5.59.

3-(1-Phenylpropylidene)-2-indolinone (VIe) was obtained from benzyl ethyl ketone; yield 65% of yellow crystals, initially m.p. 161–165° and changing to m.p. 182–185° after recrystallization from methanol; λ_{max}^{Nujol} 5.95 and 6.18 μ; λ_{max}^{EtOH} 255, 261, 294–297, and 353–360 mμ (ε 29,720, 29,420, 8200, and 1810, respectively).

Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.15; H, 6.66; N, 5.13.

After treatment with methanolic sodium methoxide–nitromethane solution and subsequent work-up involving treatment with aqueous acetic acid, this compound was recovered as a mixture of two forms. After separation of some of the higher melting form, the mother liquor (aqueous methanol) deposited a **lower melting form**, m.p. 160–162° after recrystallization from methanol. The infrared spectrum (Nujol) was very similar to, but not identical with, that of the m.p. 182–185° substance. The ultraviolet spectra (EtOH), however, were virtually the same.

Anal. Found: C, 82.14; H, 6.61; N, 5.17.

3-(1-Cyclohexylethylidene)-2-indolinone (VIf) was obtained from cyclohexyl methyl ketone, crystallized in 67% yield from methanol; a pure sample, recrystallized from the same solvent, had m.p. 210–212°; λ_{max}^{Nujol} 5.90 and 6.19 μ; λ_{max}^{EtOH} 254, 261, 293, and 349–352 mμ (ε 30,320, 35,790, 8120, and 1840, respectively).

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.68; H, 8.04; N, 5.76.

3-(α-Methylphenethylidene)-2-indolinone (VIg) was obtained from methyl phenethyl ketone in 83% yield by crystallization (3 crops) from methanol; a sample (yellow needles) recrystallized from the same solvent had m.p. 200–202°; λ_{max}^{Nujol} 5.89 and 6.14–6.19 μ (doublet); λ_{max}^{EtOH} 254, 261, 294, and 352–355 mμ (ε 29,500, 32,050, 7730, and 1710, respectively).

Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.26; H, 6.56; N, 5.25.

3-(α-Benzylphenethylidene)-2-indolinone (VIh), from dibenzyl ketone, emerged after treatment of the crude reaction solution with acetic acid, as in the cycloheptanone reaction; the yield of subsequently methanol-triturated crystals was 20%; yellow needles (from methanol), m.p. 184–186°; λ_{max}^{Nujol} 5.91 and 6.11–6.18 μ (quadruplet); λ_{max}^{EtOH} 255, 298, and 358–364 mμ (ε 28,320, 8490, and 1870, respectively).

Anal. Calcd. for $C_{24}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 84.84; H, 5.96; N, 4.19.

3-[α-(2,2,6-Trimethylcyclohexyl)ethylidene]-2-indolinone (VIi), from tetrahydroionone, was obtained in 60% yield; yellow needles from methanol, m.p. 155–157°; λ_{max}^{Nujol} 5.89 and 6.16 μ; λ_{max}^{EtOH} 251–255, 261, 293, and 350–354 mμ (ε 29,140, 35,010, 7820, and 1740, respectively).

Anal. Calcd. for $C_{20}H_{25}NO$: C, 80.98; H, 9.39; N, 4.50. Found: C, 80.86; H, 9.33; N, 4.49.

3-(α-Methylbenzylidene)-2-indolinone.—A solution of 10.9 g. (0.082 mole) of 2-indolinone, 15 g. (0.125 mole) of acetophenone, and 9 ml. of piperidine in 80 ml. of diglyme was refluxed 3.5 hr. The solvent was evaporated. Trituration of the dark residue with methanol gave 4.6 g. (24%) of orange crystals, m.p. 189–193°; further recrystallization from methanol raised the melting point to 193–197° (lit.[24] m.p. 194°).

Hydrogenation of 3-Alkylidene-2-indolinones.—In each case, the solution of *ca.* 10 g. of a given compound in 200 ml. of ethyl acetate was treated with *ca.* 3 g. of 10% Pd-charcoal, and the suspension was shaken at room temperature under 3 kg./cm.² of H_2. Usually the uptake of the calculated amount of hydrogen was complete in 5–10 min. at room temperature. A few cases, notably the cycloheptylidene derivative (VIc), were more sluggish, requiring elevated temperature (60°) for a short period for completion. Evaporation of the filtered solutions gave quantitative crude yields of colorless crystalline products, which were purified by recrystallization from methanol, ether, or ethyl acetate.

These 2-indolinones all showed ultraviolet maxima at or near 250 mμ (ε 1800–1900) as well as maxima or inflexion points *ca.* 260 mμ (ε 5000–5700) and peaks 275–280 mμ (ε 1450–1600).

The hydrogenation of VIa gave VIIa, m.p. 168–169° (lit.[17] m.p. 168–169°). Other derivatives of VII are listed in Table I.

3-Arylidene-2-indolinones and Hydrogenation to 3-Benzyl-2-indolinones.—Condensation of 2-indolinone with benzaldehyde, veratraldehyde, 3,4,5-trimethoxybenzaldehyde, and other neutral aromatic aldehydes was carried out by treatment of a methanol solution of equimolar amounts of 2-indolinone and the appropriate aldehyde in each case with the *ca.* equivalent amount of piperidine; after the solutions had been boiled 5–10 min. on a steam cone, there was copious separation of crystals. After cooling, these were collected, washed with methanol and, if necessary, purified by further recrystallization from ethyl acetate or methanol.

3-Benzylidene-2-indolinone was obtained as yellow crystals: m.p. 181–183° (lit.[43] m.p. 175–176°); λ_{max}^{Nujol} 5.85 and 6.10–6.19 μ (doublet); λ_{max}^{EtOH} 240–245, 253, and 321 mμ (ε 11,280, 12,060, and 17,940, respectively) with inflections 273 and 392 mμ (ε 8300 and 3050, respectively).

3-(3,4,5-Trimethoxybenzylidene)-2-indolinone was obtained from ethyl acetate as yellow needles, m.p. 214–217°, λ_{max}^{Nujol} 5.91 and 6.17–6.22 μ (doublet), λ_{max}^{EtOH} 253 and 354 mμ (ε 15,050 and 16,740, respectively).

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.17; H, 5.47; N, 4.43.

(43) A. Wahl and P. Bagard, *Compt. rend.*, **148**, 716 (1909).

TABLE I

VII	M.p., °C.	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	Infrared, λ_{max}, μ
b	114–116	77.58	7.51	6.96	77.36	7.59	6.95	5.91, 6.17
c	150–152	78.56	8.35	6.11	78.60	8.42	6.00	5.90, 6.17
e	109–111	81.47	7.22	5.28	81.41	7.33	5.26	5.81, 5.97, 6.17
f	165–167	78.97	8.70	5.76	79.19	8.75	5.58	5.84, 6.16
g	97–99	81.47	7.22	5.28	81.60	7.28	5.26	5.86, 6.16
h	167–169	84.37	6.47	4.28	84.12	6.65	4.19	5.86, 6.12–6.18
i	148–152	80.46	9.97	4.47	80.71	10.04	4.49	5.87, 6.15

Hydrogenation of an ethyl acetate solution of this compound (6 g.) in the presence of 10% Pd–C (1.5 g.) gave **3-(3,4,5-trimethoxybenzyl)-2-indolinone**, crystallizing from ether–ethyl acetate as colorless crystals: m.p. 120.5–125°; λ_{max}^{Nujol} 5.85, 5.99 (m), 6.15, and 6.26 μ; the ultraviolet spectrum (EtOH) had inflection points 232, 249, and 279 mμ (ϵ 11,410, 8650, and 1960, respectively).

Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.23; H, 6.29; N, 4.35.

3-(3,4-Dimethoxybenzylidene)-2-indolinone was recrystallized from ethyl acetate as bright yellow needles, m.p. 239–242°; λ_{max}^{Nujol} 5.90 and 6.16–6.30 μ; λ_{max}^{EtOH} 251 and 371 mμ (ϵ 16,070 and 17,960, respectively).

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.36; H, 5.39; N, 4.79.

3-(*p*-Fluorobenzylidene)-2-indolinone upon recrystallization from ether gave one of the isomers as yellow crystals: m.p. 194–196°; λ_{max}^{Nujol} 5.84 and 6.11–6.18 μ; λ_{max}^{CH3OH} 252, 322 mμ (ϵ 12,940 and 13,920, respectively) with inflections 224, 272, and 388 (ϵ 13,460, 8670, and 3310, respectively).

Anal. Calcd. for $C_{15}H_{10}FNO$: C, 75.30; H, 4.21; N, 5.86. Found: C, 75.10; H, 4.24; N, 5.95.

3-Benzylidene-5,6-dimethoxy-2-indolinone.—By condensation of 45 g. of 5,6-dimethoxy-2-indolinone[38] and 30 g. of benzaldehyde in *ca.* 2000 ml. of methanol, in the presence of 45 ml. of piperidine there was obtained 59.6 g. of red crystals, m.p. 210–212°, not raised on further recrystallization from methanol; λ_{max}^{Nujol} NH band and 5.93 and 6.20 μ; λ_{max}^{MeOH} 270, 325, and 414 mμ (ϵ 16,740, 12,060, and 3930, respectively).

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.60; H, 5.42; N, 4.91.

Condensation of 3-Alkylidene and 3-Arylidene-2-indolinones with Nitromethane. 3-(1-Nitromethylcyclohexyl-1)-2-indolinone (VIIIa).—To a solution of 17.7 g. (0.77 g.-atom) of Na in *ca.* 300 ml. of dry methanol was added 62 g. (1.02 moles) of nitromethane, and then 65.6 g. (0.307 mole) of 3-cyclohexylidene-2-indolinone (VIa) together with about 200 ml. of additional methanol. The suspension was heated on a steam cone and stirred, which brought about solution of the crystals and formation of an orange solution in about 5 min. The solution was then boiled 4–5 min. and allowed to stand and cool gradually for 1 hr. Addition of 60 ml. of acetic acid and then water (*ca.* 1500 ml.) caused the product to separate as a viscous gum. This crude material was conveniently separated and washed with water several times, by decantation; when then treated with some warm methanol, it crystallized. After being broken up thoroughly in methanol, the crystals were collected and washed with the same solvent. There was obtained, in three crops, a total of 75 g. (89%) of air dried, nearly colorless crystals, m.p. 153–156°. A pure sample was prepared by further recrystallization from methanol; colorless, gleaming crystals: m.p. 159–161°; λ_{max}^{Nujol} 5.87, 6.17, and 6.44 μ; λ_{max}^{EtOH} 251 and 283 mμ (ϵ 7800 and 1540, respectively).

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.61; H, 6.72; N, 10.42.

Attempts to add sodionitromethane to 3-cyclopentylylidene-2-indolinone by the same procedure, and by using a longer reaction time or stronger base (KO-*t*-Bu) catalyst, were unsuccessful. When the procedure was applied to **3-cycloheptylidene-2-indolinone** (19.5 g.), using sodionitromethane and boiling 20 min., the starting material dissolved after about 7 min. and from the deep green solution a brown solid separated later. When worked up as in the preceding experiment, adding first 15 ml. of acetic acid and then water and crystallizing the crude material by means of methanol, this reaction mixture provided 17.8 g. of crystals melting over the range 115–145°. Fractional crystallization of this mixture from methanol gave first 8.4 g. of recovered starting material, having m.p. 169–171° and identical infrared spectrum. The material remaining in the filtrate was an enriched mixture of starting material and product VIIIc, as proven by reduction to the corresponding amine, described under the next heading. However, efforts to purify VIIIc by further fractional crystallization of the mother liquors were unsuccessful, giving four additional crops of crystals, weighing a total of 7.6 g. and having melting point ranges 120–145, 118–124, 112–117, and 122–125°, all of which were mixtures and did not, after further recrystallization, provide analytically pure VIIIc.

3-(1-Methyl-1-phenyl-2-nitroethyl)-2-indolinone (VIIId) was prepared from VId (15 g.) and sodionitromethane (from 3.0 g. of Na and 9.5 ml. of nitromethane) by a similar procedure in which the mixture was boiled 13 min. and allowed to stand and cool 0.5 hr. before working up as described above. From methanol there was secured 15.7 g. (84%) of light yellow crystals, m.p. 155–163°. Recrystallization from methanol gave colorless crystals: m.p. 196–199°; λ_{max}^{Nujol} 5.89, 6.16, and 6.42 μ; λ_{max}^{EtOH} 251 and 282 mμ (ϵ 8150 and 1490) with inflection 293 mμ (ϵ 1160).

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.55; H, 5.90; N, 8.81.

Compound **VIf** failed to condense with sodionitromethane.

3-(1-Benzyl-1-methyl-2-nitroethyl)-2-indolinone (VIIIg) was obtained as an oily mixture with unchanging starting material by condensation of 30 g. of VIg with methanolic sodionitromethane reagent prepared using 5 g. of Na and 15 ml. of nitromethane. The reaction was boiled 17 min. until none of the slowly dissolving crystals of VIg remained, and after standing another 0.5 hr. was worked up as described above to give first a small amount of starting material (m.p. 194–196°) and then an oil which was extracted with ether. The ether solution was washed several times with water, dried ($MgSO_4$), and evaporated. The residual 34 g. of red-brown oil did not crystallize; that it consisted mainly of VIIIg was shown by reduction to corresponding amine Xg as described below.

3-[1-Methyl-1-nitromethyl-2-(2,2,6-trimethylcyclohexyl)-ethyl]-2-indolinone (VIIIi).—Reaction of 30 g. of VIi with sodionitromethane prepared using 5.5 g. of Na in methanol and 16.5 ml. of nitromethane, was brought about by boiling for 19 min. until the starting material dissolved and a light brown solution was obtained. The crude product, isolated after acidification with 17 ml. of glacial acetic acid and treatment with water, did not crystallize in the presence of methanol. It was extracted with ether; the ether solution was washed twice with water, dried ($MgSO_4$), and evaporated to a small volume. Partial crystallization occurred after the crude material had been allowed to stand several days in the presence of ether. Filtration eventually gave a total of 5.5 g. of crystalline product. After further recrystallization from methanol the compound had m.p. 151–152°; λ_{max}^{Nujol} 5.86, 6.16, and 6.42 μ; λ_{max}^{EtOH} 250 and 283 mμ (ϵ 7260 and 1360, respectively).

Anal. Calcd. for $C_{22}H_{32}N_2O_3$: C, 70.93; H, 8.66; N, 7.52. Found: C, 71.07; H, 8.66; N, 7.42.

The remaining material did not crystallize further but contained a diastereoisomer of the same product as shown later by reduction to corresponding amine, Xi.

3-(α-Phenyl-β-nitroethyl)-2-indolinone (IXa).—To methanolic sodium methoxide, prepared from 7.6 g. (0.33 g.-atom) of Na and 27.1 g. (0.444 mole) of nitromethane, was added 32.5 g. (0.147 mole) of 3-benzylidene-2-indolinone. Slow reaction, evidenced by a noticeable tendency for the crystals to dissolve, took place at room temperature. The mixture upon warming just to the boiling point rapidly became a bright red solution. This solution was allowed to stand and cool very gradually for 1 hr., during which time the red color faded and was replaced by a much less intense brown. After treatment with 25 ml. of acetic acid, the solution was diluted with 1700 ml. of water. The crude product which separated crystallized readily after having been

washed with water and treated with a small quantity of methanol. There was collected 28 g. (67%) of product, m.p. 120–125°. Recrystallization from methanol gave colorless crystals: m.p. 153.5–155°; λ_{max}^{Nujol} 5.86, 6.16, and 6.45 μ; λ_{max}^{EtOH} 251 and 277–283 mμ (ε 7030 and 1400, respectively).

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.11; H, 5.05; N, 10.09.

Compound **IXb**, prepared by analogous procedure, was obtained as a viscous oil.

3-(α-[(3,4,5-Trimethoxyphenyl)-β-nitroethyl]-2-indolinone (IXc).—Condensation of 49.5 g. (0.159 mole) of 3-(3,4,5-trimethoxybenzylidene)-2-indolinone with sodionitromethane, prepared from 7.2 g. (0.313 g.-atom) of Na in methanol and 24.8 g. (0.406 mole) of nitromethane, was slower than the preceding reaction and required 8 min. of boiling for dissolution of starting material. Otherwise the manipulations were the same as described in the preceding experiment; the yield of crude product (m.p. 188–193°) was 43 g. (72%). Recrystallization from methanol gave nearly colorless, pure crystals: m.p. 203–204°; λ_{max}^{Nujol} 5.83, 6.14, 6.27, and 6.42 μ; λ_{max}^{EtOH} inflections at 248 and 279 mμ (ε 7060 and 2240, respectively).

Anal. Calcd. for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41; N, 7.52. Found: C, 61.22; H, 5.60; N, 7.37.

3-[α-(2-Pyridyl)-β-nitroethyl]-2-indolinone (IXd).—A similar reaction of 21 g. (0.0945 mole) of 3-(2-pyridylmethylene)-1-indolinone with methanolic sodionitromethane prepared from 4.2 g. (0.183 g.-atom) of Na and 14.7 g. (0.24 mole) of nitromethane gave, under the conditions described for the benzylidene-2-indolinone reaction, an oily product. After extraction with ether, washing with water, drying ($MgSO_4$), and evaporation, there was obtained 29.6 g. of brown oil. After 3 days this material crystallized. Trituration with ether–methanol and recrystallization from methanol gave colorless needles: m.p. 151–153°; λ_{max}^{Nujol} 5.84, 6.16, 6.26, and 6.42 μ; λ_{max}^{EtOH} 251 mμ (ε 9240) and inflection points 259 and 283 mμ (ε 8140 and 1430, respectively).

Anal. Calcd. for $C_{15}H_{13}N_3O_3$: C, 63.59; H, 4.63; N, 14.83. Found: C, 63.25; H, 4.66; N, 14.56.

Hydrogenation of Nitro Compounds VIII and IX to Oxytryptamines (X and XI). 3-(1-Aminoethyl-1-cyclohexyl)-2-indolinone (Xa).—A mixture of 36.5 g. of VIIIa, 20 g. of 10% Pd-C, and 300 ml. of ethyl acetate was shaken under H_2 (initially 3.15 kg./cm.²). There was not appreciable uptake at room temperature, and therefore heat was applied to raise the temperature to *ca.* 75°, whereupon a pressure drop of 2.52 kg./cm.² (*ca.* 3.3 molar equiv.) took place within 1 hr. The suspension was filtered while still warm, and the catalyst was extracted with two portions of hot ethyl acetate, for the product separated from cooled ethyl acetate solutions. The combined filtrates were evaporated to small volume and the accumulated crystals were collected in several crops and washed sparingly with ethyl acetate; yield 14.7 g. (45%); m.p. of purest material 221–223°, not raised on further recrystallization from methanol (m.p. 218–221°); λ_{max}^{Nujol} 2.92, 3.00, 3.14, 3.25, 5.90, and 6.09 μ; λ_{max}^{EtOH} 238 and 291 mμ (ε 7310 and 2570, respectively).

Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.73; H, 8.25; N, 11.47. Found: C, 73.53; H, 8.25; N, 11.58.

The same amine was formed in lower yield when VIIIa was hydrogenated in acetic acid solution in the presence of Pd–C. The compound was soluble in aqueous acids. The yield of material, m.p. 217–220°, was increased to 70% by carrying out the hydrogenation in 2.5:1 ethyl acetate–ethanol, as solvent.

The **corresponding N-benzyl-N-methyl derivative** was prepared by a combination of Decker methylation[2] and reduction, as follows. The amine (3.2 g.) and 1.9 g. of benzaldehyde in 200 ml. of toluene was refluxed under a water trap for 0.5 hr., and the resulting solution was treated with excess (*ca.* 10 ml.) CH_3I and refluxed 3.5 hr. Evaporation gave a yellow glassy material which was dissolved in methanol and treated with excess (*ca.* 8 g.) $NaBH_4$ in portions. The mixture was boiled on steam cone for 15 min. to remove most of the methanol, and the cooled residue was treated with water. An oil separated, and crystallized when chilled. An ether extract of this base, after drying (K_2CO_3) and evaporating, gave a solid which melted over the range 50–105°, was solvated, and could not be recrystallized effectively. The corresponding hydrochloride was precipitated from ether and reconverted to base; this base was again extracted with ether and reconverted to the hydrochloride which, after such treatment, was sufficiently pure to recrystallize from ethanol–ether; colorless crystals, m.p. 243–246° dec. after drying *in vacuo*; λ_{max}^{Nujol} 5.90 and 6.19 μ, in addition to protonated N bands; λ_{max}^{EtOH} 254 mμ (ε 6960) with shoulder 279 mμ (ε 1480).

Anal. Calcd. for $C_{23}H_{29}ClN_2O$: C, 71.76; H, 7.59; N, 7.28. Found: C, 71.67; H, 7.39; N, 7.34.

3-[1-Aminomethyl-1-cycloheptyl)-2-indolinone (Xc). Hydrogenation of 7.6 g. of the impure, crystalline mixture containing VIIIc, obtained as described above, in 300 ml. of ethyl acetate in the presence of 4 g. of 10% Pd-C at 75° for 2 hr. gave, after filtration, a colorless solution which, after evaporation to 50 ml. and chilling, first deposited 4.4 g. of VIIc, m.p. 149.5–152°, when recrystallized from methanol (infrared spectrum the same as authentic VIIc). The filtrate after removal of this material, upon slow evaporation then yielded a small (*ca.* 0.5 g.) sample of acid-soluble Xc: m.p. 186–188° after methanol recrystallization; λ_{max}^{Nujol} 2.91, 2.98, 3.14, 3.24, 5.89, 6.08, and 6.23–6.27 μ (triplet); λ_{max}^{EtOH} 237 and 292 mμ (ε 7440 and 2680, respectively).

Anal. Calcd. for $C_{18}H_{28}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.53; H, 8.74; N, 10.76.

3-(1-Methyl-1-phenyl-2-aminoethyl)-2-indolinone (Xd). Similar hydrogenation of 9.0 g. of VIIId in the presence of 10 g. of 10% Pd–C in 300 ml. of ethyl acetate at 80° for 0.8 hr. resulted in the calculated pressure drop. After filtration, evaporation of solvent, and trituration of the residue with ethyl acetate or methanol, there was obtained 3.0 g. of acid-soluble, colorless crystals, m.p. 221–229°, raised to 239–240.5° dec. upon further recrystallization from methanol; λ_{max}^{Nujol} 2.89, 3.01, 3.14, 5.94, and 6.08 μ; λ_{max}^{EtOH} 237 and 292 mμ (ε 7220 and 2770, respectively).

Anal. Calcd. for $C_{18}H_{20}N_2O$: 77.11; H, 7.19; N, 9.99. Found: C, 77.03; H, 7.34; N, 10.00.

3-(1-Benzyl-1-methyl-2-aminoethyl)-2-indolinone (Xg). Hydrogenation of 20 g. of crude, oily VIIIg in the presence of 12 g. of 10% Pd–C in 300 ml. of ethyl acetate at 80° for 1 hr., until a correct pressure drop had been observed, resulted, after filtration and evaporation, in a yellow oil. After this material had been allowed to stand for 1 month, occasionally in the presence of ethanol and ether, there were formed some colorless crystals which, after ether trituration, amounted to 0.8 g., m.p. *ca.* 160–170°. Purification by recrystallization from ethanol gave a pure sample, presumably the higher melting diastereoisomer of Xg; m.p. 195–197°; λ_{max}^{Nujol} 2.89, 3.00, 3.13, 3.25, 5.95, and 6.08 μ; λ_{max}^{EtOH} 238 and 293 mμ (ε 7610 and 2550, respectively) with a shoulder at 268 mμ (ε 846).

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.32; H, 7.50; N, 9.30.

3-[1-Methyl-1-aminomethyl-2-(2,2,6-trimethylcyclohexyl)-ethyl]-2-indolinone (Xi).—Hydrogenation of 5.0 g. of crystalline VIIIi in the presence of 5 g. of 10% Pd–C in 300 ml. of ethyl acetate for 2 hr. afforded, after filtration and evaporation, a colorless oil, crystallizing in ethyl acetate and giving eventually 2 g. of colorless crystals; after repeated recrystallization from methanol: m.p. 184–186°; λ_{max}^{Nujol} 2.89, 2.97, 3.13, 5.96, and 6.12 μ; λ_{max}^{EtOH} 237 and 291 mμ (ε 7550 and 2720, respectively).

Anal. Calcd. for $C_{22}H_{34}N_2O$: C, 77.14; H, 10.01; N, 8.18. Found: C, 76.94; H, 10.00; N, 8.03.

Separate, similar hydrogenation of crude, oily VIIIi in the presence of 10–20% Pd-C took place for the most part at room temperature, and was completed by continuing the reaction for a brief period at 75°. The crude product, a yellow oil, crystallized partly on standing with ether–ethanol, and after ether trituration gave 3.0 g. of the same amine as obtained from the preceding experiment, but in an impure condition; m.p. 163–165° after recrystallization from methanol. This sample was resubjected to hydrogenation at 3 kg./cm.² in ethyl acetate in the presence of 3 g. of 10% Pd-C at 75° for 6 hr. Purification of the resulting material by recrystallization from ethyl acetate, gave colorless crystals, m.p. 189–191°; spectra identical with those of the sample described above.

Anal. Found: C, 77.25; H, 10.16; N, 8.00.

3-(α-Phenyl-β-aminoethyl)-2-indolinone (XIa).—A solution of 14.7 g. of nitro compound IXa in 250 ml. of ethyl acetate, containing 7 g. of 10% Pd–C, absorbed 0.973 kg./cm.² (3.3 molar equiv.) of H_2 when shaken as part of a 4-l. system under 3.15-kg./cm.² gauge pressure at 75°. The cooled suspension was filtered. The catalyst was leached with two portions of boiling ethyl acetate–ethanol, and the combined solutions were evaporated. Trituration of the pardy crystalline residue with ethyl acetate gave a total of 3.2 g. (24%) of colorless, acid-soluble crystals, m.p. 195–203°. The mother liquor turned purple on standing and did not provide any more of the crystalline product. A sample, recrystallized from ethanol, had m.p. 212.5–215°; λ_{max}^{Nujol}

2.88, 3.07, 5.91, and 6.17 μ; λ_{max}^{EtOH} 251 and 275–282 mμ (ϵ 7390 and 1370, respectively).

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.32; H, 6.55; N, 10.88.

Similar hydrogenations of IXb and IXc gave acid-soluble, gradually air-discoloring, viscous oils from which crystalline amines could not be obtained. Acetylation, or attempts to prepare corresponding hydrochlorides, did not lead to crystalline derivatives.

3-[α-(2-Pyridyl)-β-aminoethyl]-2-indolinone (XId).—Hydrogenation of 26.2 g. of IXd in ethyl acetate in the presence of 11 g. of 10% Pd–C was carried out first at room temperature, until *ca.* 2 molar equiv. had been taken up (*ca.* 2 hr.), and then at 60° until a total of 3.0 molar equiv. had been absorbed. Some green gum separated from the filtered, chilled solution. The clear, decanted solution, upon evaporation gave yellow oil, which deposited crystals when scratched in the presence of ether and a small amount of ethanol. The colorless crystals (4.0 g.) obtained by trituration with these solvents were purified by further recrystallization from ethanol–ether: m.p. 169–171°; λ_{max}^{Nujol} 2.97, 3.03, and bonded NH bands, 5.91 and doublet 6.16–6.27 μ; λ_{max}^{EtOH} 253 (ϵ 9940) and inflections 262 and 283 mμ (ϵ 8200 and 1560, respectively).

Anal. Calcd. for $C_{15}H_{15}N_3O$: C, 71.12; H, 5.97; N, 16.59. Found: C, 70.55; H, 6.21; N, 16.09.

Attempts to promote further reduction of the pyridine moiety of this compound to the corresponding piperidine, using Pd–C and warm ethyl acetate, resulted in the expected uptake of H_2, but the base obtained was not crystalline. Acetylation of the crude oil with acetic anhydride at room temperature gave, after several days, crystals, m.p. 235–237° dec. after recrystallization from ethyl acetate, which appeared to be a solvated form of the **N,N'-diacetate of the aminopiperidine**: λ_{max}^{Nujol} strong multiple NH bands, 5.78 and intense doublet 5.93–5.98 μ; λ_{max}^{EtOH} 250 mμ (ϵ 14,110) and inflection 284 mμ (ϵ 1240).

Anal. Calcd. for $C_{19}H_{25}N_3O_3 \cdot H_2O$: C, 63.14; H, 7.53; N, 11.63. Found: C, 63.06; H, 6.06; N, 12.16.

1,3-Dimethyl-3-phenyl-5-nitro-2-indolinone.—To sodium methoxide (from 1.1 g. of Na) in methanol (100 ml.) was added 2.1 g. of 3-phenyl-2-indolinone[37] and 12 ml. of CH_3I. The solution was refluxed 3 hr., evaporated to smaller volume, and the cooled residue was treated with water. The red oil, crude 1,3-dimethyl-3-phenyl-2-indolinone, was isolated by extraction with ether, washed until neutral, dried ($MgSO_4$), and evaporated; the residue did not crystallize (lit.[32] m.p. *ca.* 50°). It was dissolved in 7 ml. of glacial acetic acid and nitrated by addition of 12 ml. of concentrated HNO_3 (*d* 1.42) while cooling in ice to prevent temperature from rising above 30°. After 5 min. the mixed acid solution was poured over ice. The brown, partly crystalline, crude product was extracted with ether; the ether solution was washed with successive portions of water, dilute NaOH solution, and water, dried ($MgSO_4$), and evaporated. By recrystallization from ether there was obtained 1 g. of crystalline nitro compound, m.p. 132–138°. Purified by recrystallization from methanol, the sample had m.p. 135.5–137° (lit.[32] m.p. 138°); λ_{max}^{Nujol} 5.80, 6.19, and 6.59 μ.

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.06; H, 4.99; N, 9.74.

1-Methyl-3-benzyl-2-indolinone (XIIa). A. Methylation.—To a solution of 8.4 g. (0.365 g.-atom) of sodium in 500 ml. of methanol was added 69 g. (0.312 mole) of 3-benzylidene-2-indolinone and then, in portions, 55 ml. of CH_3I. After the initial, exothermic action had subsided, the solution was refluxed 2.4 hr., and allowed to stand 3 days. Additional methyl iodide (20 ml.) was added; the solution was refluxed 2 hr. longer, then evaporated to smaller volume, and the cooled residue was treated with water. The ether-extracted material, after washing with water, drying ($MgSO_4$), and evaporating part of the ether, deposited 9.3 g. of recovered starting material, m.p. 174–178°. The remaining crude, oily product (56 g., 76%) did not crystallize and was used in the next step.

B. Hydrogenation.—The 56 g. of greenish oil from A in 350 ml. of ethyl acetate was treated with 8 g. of 10% Pd-C, and the suspension was shaken under 3.2 kg./cm.^{2} (gauge) of hydrogen at 60° for 8 hr. when, in the 4-l. system, a 1.4-kg./cm.^{2} pressure drop had occurred. The filtered solution was still yellow, and therefore was charged with 9 g. of fresh catalyst, rehydrogenated at 3.2 kg./cm.^{2} and 60° for 2.5 hr., and again filtered. From the resulting colorless solution, upon evaporation, there was obtained 36.1 g. (64%) of colorless product, m.p. 64–68°. A pure sample, after recrystallization from ether, had m.p. 70–71°, λ_{max}^{Nujol} 5.85 and 6.16 μ, λ_{max}^{EtOH} 253 mμ (ϵ 8200) with shoulders at 263 and 281 mμ.

Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.98; H, 6.37; N, 5.79.

1-Methyl-3-(3,4-dimethoxybenzyl)-2-indolinone (XIIb). A. 1-Methyl-2-indolinone was prepared either by Stollé cyclization[34] or in larger quantities and in a less pure condition by hydrogenolysis of N-methylisatin as follows. A mixture of 21 g. of N-methylisatin and 5 g. of 10% Pd–C in 250 ml. of glacial acetic acid, shaken under 3.2 kg./cm.^{2} of H_2 at 70°, consumed *ca.* 1 molar equiv. of H_2 in 1 hr. and then, more slowly, additional gas to a total of 1.17 molar equiv. Evaporation of the filtered solution gave a thick, red oil, from which, on standing, there slowly separated 4 g. of a high-melting by-product, m.p. 197–199° (probably an isatide) which was removed by filtration. No attempt was made to further purify the remaining clarified, crude oil before using it in subsequent reactions, since N-methyl-2-indolinone is fairly soluble in water and extraction and washing procedures led to much loss of material. Distillation of the crude compound in the presence of traces of acetic acid also is inadvisable, due to decomposition.

When N-methylisatin (16.1 g.) was hydrogenated in ethyl acetate (200 ml.) and acetic acid (50 ml.) in the presence of 10% Pd–C (4 g.) at 70°, only 1.09 molar equiv. of H_2 was taken up, and from the filtered, evaporated solution there was obtained, after addition of water, extraction with ether, washing with $NaHCO_3$ solution, drying, and evaporation, 3.2 g. of crystals which, after recrystallization from ether and benzene, had m.p. 155.5–157° and proved to be N-methyldioxindole (lit.[44] m.p. 149–151°); λ_{max}^{Nujol} 3.07 (broad), 5.86–5.92, and 6.19 μ; λ_{max}^{MeOH} 210, 258, and 288 mμ (ϵ 26,700, 6120, and 1220, respectively).

Anal. Calcd. for $C_9H_9NO_2$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.48; H, 5.73; N, 8.34.

B. 1-Methyl-3-(3,4-dimethoxybenzylidene)-2-indolinone.—To 19 g. of crude N-methyl-2-indolinone and 21 g. of veratraldehyde in 200 ml. of methanol was added 8.8 g. of pyrrolidine. The green solution was boiled 15 min., reduced to smaller volume, cooled, and treated with water. The crude product was extracted with ether–ethyl acetate. The organic solution was washed with two portions of dilute HCl, then several portions of water, dried ($MgSO_4$), and evaporated. The residual oil crystallized in ether giving 11.3 g. (30%) of yellow crystals, m.p. 112–118°. Recrystallization from ether gave a pure sample: m.p. 127–129°; λ_{max}^{Nujol} 5.91 and triplet 6.21, 6.29, and 6.35 μ; λ_{max}^{MeOH} 263 and 368 mμ (ϵ 16,070 and 23,520, respectively).

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.01; H, 5.83; N, 4.65.

C.—Reduction of 11.3 g. of the veratrylidene compound from B in ethyl acetate in the presence of 3 g. of 10% Pd-C at room temperature gave, after ether treatment of crude oil, 6.0 g. (53%) of colorless crystals: m.p. 109–111°; λ_{max}^{Nujol} 5.84 and doublet 6.17–6.25 μ; λ_{max}^{MeOH} 231, 253, and 279 mμ (ϵ 12,610, 10,090, and 5360, respectively).

Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.69; H, 6.66; N, 4.70.

1-Methyl-3-(*p*-Chlorobenzyl)-2-indolinone (XIIc). A.—3-(*p*-Chlorobenzylidene-2-indolinone was prepared by condensation of 2-indolinone with *p*-chlorobenzaldehyde in methanol in the presence of piperidine (boiled 12 min.) and recrystallized from methanol; yellow-orange crystals, m.p. 196–198° (lit.[45] m.p. 184°); λ_{max}^{Nujol} 5.82 and 6.14–6.21 μ; λ_{max}^{EtOH} 254, 329, and 396 mμ (ϵ 12,730, 16,160, and 3610, respectively).

Anal. Calcd. for $C_{15}H_{10}ClNO$: C, 70.45; H, 3.94; N, 5.49. Found: C, 70.86; H, 3.97; N, 5.47.

B. N-Methylation of 39 g. of compound from A in a solution of 6 g. of Na in methanol with 50 ml. of CH_3I, as described for the 1-methyl-3-benzylidene compound, gave a crude solid mixture of product and starting material, which was fractionated and remethylated to obtain the former by the following steps: (1) several filtrations of progressively more concentrated methanol suspensions of the material removed 9.5 g. of the less soluble starting material; (2) the residue from evaporation of filtrate was refluxed 3 hr. with a solution of 6 g. of Na in 100 ml. of methanol and 50 ml. of CH_3I and, after evaporation, worked up as before to give 30.5 g. of low-melting (89–95°) material; (3) a solution of

(44) See F. K. Beilstein, "Handbuch der Organischen Chemie," Vol. 21, 1st Ed., 1935, p. 579.

(45) P. W. Neber and E. Rockner, *Ber.*, **56**, 1710 (1923).

this material in ligroin, filtered clear of remaining insoluble residue and evaporated, gave nearly pure product which, after recrystallization from ether, afforded a total of *ca.* 24 g. (58%) of yellow crystals suitable for further work. Repeated recrystallization from ether gave a pure sample: m.p. 108–110°; λ_{max}^{Nujol} 5.82 and 6.19 μ; λ_{max}^{EtOH} 256, 260–270, and 330 mμ (ϵ 11,880, 11,420, and 16,910, respectively) with shoulders at 278 and 390 mμ.

Anal. Calcd. for $C_{16}H_{12}ClNO$: C, 71.24; H, 4.49; N, 5.19. Found: C, 71.12; H, 4.54; N, 5.27.

C.—Reduction of 13.5 g. of the product from B in ethyl acetate in the presence of 4.4 g. of 10% Pd-C at room temperature led to uptake of 1.1 molar equiv. of H_2 in 7 min. and, after filtration and evaporation, gave a quantitative yield of crude crystals suitably pure for further work. A sample, recrystallized from ether, had m.p. 116–118°; λ_{max}^{Nujol} 5.87 and 6.17 μ; $\lambda_{max.}^{EtOH}$ 254 (ϵ 8210), with shoulders 222, 265, and 276 mμ.

Anal. Calcd. for $C_{16}H_{14}ClNO$: C, 70.70; H, 5.20; N, 5.16. Found: C, 71.08; H, 5.25; N, 5.09.

1-Methyl-3-(*p*-fluorobenzyl)-2-indolinone (XIId). A.—Impure 1-methyl-3-(*p*-fluorobenzylidene)-2-indolinone was prepared either by condensation of *p*-fluorobenzaldehyde with N-methyl-2-indolinone (from reduction of methylisatin) in methanol in the presence of piperidine, following the procedure described in foregoing experiments, or by methylation of 3-(*p*-fluorobenzylidene)-2-indolinone as described for 1-methyl-3-benzylidene-2-indolinone.

B. Reduction.—The crude product (m.p. *ca.* 130°) after removal of less soluble, resinous material by solution in cyclohexane, decantation, and evaporation, was hydrogenated in ethyl acetate solution in the presence of 10% Pd-C at room temperature, as usual. Filtration and evaporation gave colorless oil or low-melting solid suitable for further use. A sample was purified by crystallization from ether–ligroin; colorless crystals, melting partially at 87–90° and completely at 135°: λ_{max}^{Nujol} 5.80–5.87 (broad) and 6.18 μ: λ_{max}^{MyOH} 206 and 253 mμ (ϵ 31,910 and 8280, respectively) with inflection 281 mμ (ϵ 1500).

Anal. Calcd. for $C_{16}H_{14}FNO$: C, 75.27; H, 5.53; N, 5.49. Found: C, 75.20; H, 5.51; N, 5.54.

1-Methyl-3-benzyl-5,6-dimethoxy-2-indolinone (XVI). A. Methylation of 59.6 g. of 3-benzylidene-5,6-dimethoxy-2-indolinone in the presence of sodium methoxide (from 5 g. of Na) and 50 ml. of CH_3I, was carried out in 1 l. of toluene, by refluxing for 6 hr. and allowing to stand 3 days. The reaction mixture was distilled *in vacuo* to a smaller volume and treated with water. After filtration to remove impure crystals of starting material–product mixture, the organic layer, diluted with ether, was washed with water, dried ($MgSO_4$), and evaporated, to give crude product. The yield of orange crystals, melting *ca.* 135–140° and suitable for reduction, was 17.7 g. A completely pure sample of the 3-benzylidene-N-methyl derivative, prepared in this way, could not be obtained by recrystallization; crystals, m.p. 145–146°, obtained from methanol or other solvents always appeared to be contaminated with unmethylated material; λ_{max}^{Nujol} bonded, weak NH band as well as 5.86 and 6.18 μ. The ultraviolet curve showed strong absorption at 274, 289, 326, and 420 mμ.

Anal. Found: C, 73.87; H, 5.73; N, 5.01.

B. Hydrogenation was performed on a filtered ethyl acetate solution of 17.5 g. of product from A in the presence of 4.5 g. of 10% Pd-C for 2 hr. at 60°. Evaporation of the filtered solution gave, upon trituration with a small amount of ether, 15.5 g. of slightly pink crystals, m.p. 103–107°. Recrystallization from ether gave colorless crystals, m.p. 108–110°, λ_{max}^{Nujol} 5.84–5.95 (broad peak) and 6.19 μ, λ_{max}^{MeOH} 208 and 274 mμ (ϵ 31,950 and 6320, respectively) with inflection 297 mμ (ϵ 4670).

Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71. Found: C, 73.02; H, 6.48; N, 4.66.

1-Methyl-3-cyclopentylidene-2-indolinone.—A solution of N-Δ^1-cyclopentenylpyrrolidine was prepared as usual by refluxing a solution of 10 g. (0.119 mole) of cyclopentanone and 11 ml. (9.4 g., 0.132 mole) of pyrrolidine in benzene under a water trap. This was added to a solution of crude N-methyl-2-indolinone (from reduction of 22.7 g. of N-methylisatin) in 200 ml. of benzene, and the solution was boiled 10 min. The cooled, dark green solution was treated with dilute HCl. After addition of ether, shaking, and separating, the organic layer was washed with several portions of water, dried ($MgSO_4$), and evaporated. A solution of the dark, residual oil in a small amount of ether deposited 9.6 g. (38%) of greenish yellow crystals, m.p. 78–82°. Recrystallization from ether (Norit) raised the melting point to 83–84°: λ_{max}^{Nujol} 5.91, 6.08 (m), and 6.21 μ; λ_{max}^{MeOH} 257, 262, 294, and 350 mμ (ϵ 30,030, 35,660, 7460, and 1330, respectively).

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 79.04; H, 6.98; N, 6.55.

Hydrogenation of this compound in ethyl acetate in the presence of 10% Pd–C, as usual, resulted in the expected uptake (in 10 min.). The product, crude 1-methyl-3-cyclopentyl-2-indolinone (XV) isolated as usual, was an oil, not fully characterized but sufficiently pure for alkylation to give the corresponding 3-(β-dimethylaminoethyl) compound, characterized as the picrate, as described below.

1-Methyl-3-(*p*-chlorophenyl)-2-indolinone. A. *p*-Chloromandelate of N-Methylaniline.—A solution of 49.5 g. of *p*-chloromandelic acid in 400 ml. of acetic anhydride was refluxed 7 hr., the excess reagent was distilled *in vacuo* (steam cone), and the residual syrup finally was dried in a stream of air. The chilled, crude material was treated with 45 ml. of N-methylaniline. After initial exothermic reaction was complete, the material was heated (steam cone) overnight. The purple oil, dissolved in ether, was washed with successive portions of dilute HCl, water, $NaHCO_3$, and water, and was dried ($MgSO_4$). Evaporation of solvent left 37 g. of light brown oil, crystallizing partly on standing. The crystals (N-methylacetanilide, m.p. 100°) were removed by filtration, and the 33 g. of remaining, crude oil was used in the next step without further purification.

B. Meisenheimer Cyclization.[13]—The crude oil from A was added slowly (0.7 hr.) while stirring, to 180 ml. of concentrated H_2SO_4, while chilling in ice to prevent the temperature from rising above 10°. The solution was kept at ice temperature 3 hr. longer, then poured over ice. When hydrolysis was complete, and before the aqueous suspension warmed to room temperature, the gray solid was collected, washed with water, with dilute K_2CO_3 solution, and again with water, and air dried. The crude product (19.6 g., m.p. *ca.* 153–158°), recrystallized from ether, provided the pure product: m.p. 164–165°; λ_{max}^{Nujol} 5.89 and 6.20 μ; λ_{max}^{EtOH} 255 mμ (ϵ 8530) with inflections 220, 265, and 283 mμ.

Anal. Calcd. for $C_{15}H_{12}ClNO$: C, 69.90; H, 4.70; N, 5.44. Found: C, 69.87; H, 4.67; N, 5.47.

1-Benzyl-3-phenyl-2-indolinone. A. Crude N-Methylmandelanilide was obtained by similar treatment of 404 g. of mandelic acid with 2500 ml. of acetic anhydride and, after removal of excess reagent, reaction with 500 g. of N-benzylaniline. The material was filtered from 163 g. of a by-product which proved to be N-benzyl-α-acetoxy-α-phenylacetanilide, m.p. 118–119°, after methanol recrystallization. The remaining crude oil (440 g.) was used in the next step.

Anal. Calcd. for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 76.93; H, 6.08; N, 4.03.

B. Cyclization of the 440 g. of crude oil from A by gradual addition to 1550 ml. of concentrated H_2SO_4 at 10° or below, followed by a 3-hr. period of stirring at 0–5° and work-up as usual through ether extraction of ice-hydrolyzed mixture, washing with dilute NaOH and water, drying, and evaporating, gave crude oil from which by means of trituration with ether were obtained crystals, m.p. 115–117° (lit.[13] m.p. 113–115°), λ_{max}^{Nujol} 5.83 and 6.21 μ, λ_{max}^{EtOH} 253 mμ (ϵ 7750).

Anal. Calcd. for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68. Found: C, 84.89; H, 5.76; N, 4.72.

1-Methyl-3-phenyl-2-indolinone. A. Meisenheimer cyclization[13] of the crude product from reaction of 400 g. of mandelic acid first with acetic anhydride (2500 ml.) and then with N-methylaniline (360 ml.), with 1 l. of concentrated H_2SO_4 at 0–15°, gave 121 g. of crystals (from ether), m.p. 119–120° (lit.[13,33] 118–119°), λ_{max}^{Nujol} 5.99 and 6.22 μ, λ_{max}^{EtOH} 254 mμ (ϵ 8330).

B. Hydrogenolysis of 1.1 g. of 1-methyl-3-hydroxy-3-phenyl-2-indolinone[38] in 200 ml. of glacial acetic acid in the presence of 1.5 g. of 10% Pd-C at 65° for 5 hr. gave a crude, discolored product which, after recrystallization from ether, had m.p. 117–118°. The mixture melting point with crystals from A was 118.5–120°, and the infrared spectra of the samples were identical.

1-Phenyl-2-indolinone was prepared by simplified Stollé[35] cyclization. An intimate mixture of 65 g. of N-chloroacetyldiphenylamine and 81 g. of anhydrous $AlCl_3$ in a beaker was stirred by hand with a thermometer and heated on a hot plate to *ca.* 140° until exothermic reaction set in, releasing HCl and causing spontaneous temperature rise to 180°; after exothermic reaction ceased, the melt was heated again to 180° for a few minutes. Hydrolysis of the cooled melt with ice and HCl, and recrystallization

of the crude product from ethanol, gave a quantitative yield of product, m.p. 121–123° (lit.[35] m.p. 121°), λ_{max}^{Nujol} 5.85 and 6.19–6.23 μ (doublet), λ_{max}^{MeOH} 245 mμ (ϵ 12,750) with inflection 280 mμ (ϵ 1270).

1-Phenyl-3-hydroxymethylene-2-indolinone.—Dry sodium methoxide was prepared from 2.8 g. of Na and suspended in 500 ml. of dry ether. There was added 25 g. of N-phenyl-2-indolinone and 50 ml. of ethyl formate, and after a mildly exothermic reaction was complete the mixture was allowed to stand at room temperature, protected from moisture, for 5 hr. Addition of water, separation, and acidification of the ether-washed, aqueous layer afforded 10.0 g. of crude enol as light yellow crystals, m.p. 200–203° (giving deep blue ferric test). After recrystallization from methanol a pure sample had m.p. 202–204°; λ_{max}^{Nujol} broad bonded OH and/or NH, 5.90 and 6.16–6.25 μ (doublet); λ_{max}^{MeOH} 262 and 301 mμ (ϵ 23,940 and 10,100, respectively) with inflections 219, 294, and 328 mμ (ϵ 23,720, 9880, and 2150, respectively).

Anal. Calcd. for $C_{15}H_{11}NO_2$: C, 75.93; H, 4.67; N, 5.90. Found: C, 75.87; H, 4.75; N, 5.92.

1-Phenyl-3-methyl-2-indolinone.—A solution of 10.5 g. (0.0463 mole) of 1-phenyl-3-hydroxymethylene-2-indolinone in 250 ml. of ethyl acetate and 3 ml. of glacial acetic acid was treated with 3 g. of 10% Pd–C and shaken under 3.2 kg./cm.^{2} of H_2, first at room temperature and finally at 60°. The pressure drop (2.2 molar equiv.) indicated hydrogenolysis, and the solution was filtered and evaporated to give 10.7 g. of pale greenish yellow oil. The material could not be induced to crystallize. A clarified, evaporated, ether solution returned yellow oil which was used in subsequent alkylation, and the 3-(β-dimethylaminoethyl) derivative was characterized, as described below.

1-Methyl-3-benzyl-3-phenyl-2-indolinone (XX).—To a solution of 0.7 g. of K in 100 ml. of *t*-butyl alcohol was added 4.1 g. of 1-methyl-3-phenyl-2-indolinone and then 3.2 g. of benzyl bromide. After the initial reaction, the mixture was stirred and warmed on steam cone 0.8 hr., then evaporated to smaller volume *in vacuo* and treated with cold water. The product was extracted with ether. The organic layer was washed with several portions of water, dried ($MgSO_4$), and evaporated. The residue crystallized in ether, giving 3.3 g. of colorless crystals, m.p. 126–128°; recrystallization from the same solvent raised the melting point to 128–130°, λ_{max}^{Nujol} 5.83 and 6.18 μ, λ_{max}^{MeOH} 257 mμ (ϵ 6750) with inflection 284 mμ (ϵ 1680).

Anal. Calcd. for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.35; H, 6.20; N, 4.35.

1,3-Disubstituted 3-(β-Dialkylaminoethyl)-2-indolinones (XIX).—The general procedure for the alkylation of 1,3-disubstituted 2-indolinones with β-dialkylaminoethyl chlorides was adapted from well-known precedents and carried out as follows. A stirred solution of 0.025 mole of the 2-indolinone in 200 ml. of dry toluene was treated first with 0.05 mole of powdered $NaNH_2$, then with a dried toluene solution (*ca.* 1 g./5 ml.) of 0.05 mole of the β-dialkylaminoethyl chloride (freshly prepared from corresponding hydrochloride). The stirred suspension was warmed, under reflux, first to *ca.* 80° for a brief period until the first evolution of NH_3 was nearly complete, and finally to reflux temperature for 4–5 hr. The cooled mixture was treated with water, ether was added, and after shaking and separating, the organic layer was washed with two portions of water and extracted with two small portions of cold 18% hydrochloric acid. The aqueous, acid solution was made basic at ice temperature by gradual addition of cold, concentrated NaOH solution. The oily base which separated was extracted with ether; the ether solution was washed with two portions of water, dried (K_2CO_3), filtered, and evaporated on a steam cone. From the ether solutions of the crude products, after removal of volatile constituents, the crude hydrochlorides were prepared by addition in each case of a slight excess of 5% alcoholic HCl. The crude, oily salts were washed with dry ether by decantation and induced to crystallize in the presence of small respective amounts of ethanol, occasionally with the addition of a small amount of ether, and recrystallized from the same solvents. If the hydrochloride was too hygroscopic or did not crystallize after partial purification by reprecipitation from ethanol with ether, it was converted back to base in some cases and a sample of the latter used to prepare the picrate, which was recrystallized from ethanol. Yields of crude products appeared to be uniformly fairly good, but because of losses of material incurred in purifying crude substances the observed yields of pure samples are not significant and so are not reported.

1-Methyl-3-benzyl-3-(β-diethylaminoethyl)-2-indolinone hydrochloride (XIXa) was hygroscopic; m.p. 121–123° (with prior sintering 100°) after drying *in vacuo* at 80°; m.p. 124–127° in the hydrated form, after drying *in vacuo* at room temperature; λ_{max}^{Nujol} hydrated salt bands, 5.84 and 6.20 μ; λ_{max}^{EtOH} 255 mμ (ϵ 7100) with inflections 206 and 285 mμ (ϵ 31,000 and 1400, respectively).

Anal. Calcd. for $C_{22}H_{29}ClN_2O \cdot 0.5H_2O$: C, 69.18; H, 7.92; N, 7.34. Found: C, 69.02; H, 8.16; N, 7.23.

1-Methyl-3-(*p*-chlorophenyl)-3-(β-dimethylaminoethyl)-2-indolinone hydrochloride (XIXb) was obtained as hemihydrate, slightly greenish crystals, m.p. 187–190° dec.; too hygroscopic for useful Nujol mull; λ_{max}^{MeOH} 256 mμ (ϵ 8140) with inflection 282 mμ (ϵ 1880).

Anal. Calcd. for $C_{19}H_{22}ClN_2O \cdot 0.5H_2O$: C, 60.96; H, 6.19; N, 7.49. Found: C, 61.36, 61.16; H, 6.25; N, 7.25.

1-Methyl-3-(*p*-chlorobenzyl)-3-(β-dimethylaminoethyl)-2-indolinone (XIXc).—The crude base crystallized in hydrated form from ether; m.p. 82–86°; λ_{max}^{Nujol} 2.84, 5.85–5.89, and 6.18 μ; λ_{max}^{EtOH} 255 mμ (ϵ 7270) with inflections 266 and 281 mμ (ϵ 5290 and 1730, respectively).

Anal. Calcd. for $C_{20}H_{23}ClN_2O \cdot 0.5H_2O$: C, 68.19; H, 6.82. Found: C, 68.74; H, 6.94.

Further drying gave anhydrous material.

Anal. Calcd.: N, 8.74. Found: N, 8.57.

The corresponding **hydrochloride** was obtained as hygroscopic crystals: melting point indefinite; Nujol mull not suitable for infrared; λ_{max}^{EtOH} 256 mμ (ϵ 7770) with inflection 280 mμ (ϵ 1970).

Anal. Calcd. for $C_{20}H_{24}Cl_2N_2O \cdot 0.5H_2O$: C, 61.85; H, 6.49 N, 7.22. Found: C, 61.26; H, 6.47; N, 7.33.

The corresponding **picrate** had m.p. 227–230° dec., after recrystallization from ethanol.

1-Methyl-3-(*p*-fluorobenzyl)-3-(β-dimethylaminoethyl)-2-indolinone hydrochloride (XIXd) was obtained as monohydrate: m.p. 190–192° dec.; λ_{max}^{Nujol} 2.86, broad 3.85–4.09, 5.83, and 6.19 μ; λ_{max}^{MeOH} 207 and 255 mμ (ϵ 28,000 and 6890, respectively) with inflection 284 mμ (ϵ 1360).

Anal. Calcd. for $C_{20}H_{24}ClFN_2O \cdot H_2O$: C, 63.07; H, 6.88; N, 7.35. Found: C, 63.89; H, 7.16; N, 6.96.

A sample, after further drying and before air exposure gave N, 7.34.

1-Methyl-3-benzyl-3-(β-dimethylaminoethyl)-5,6-dimethoxy-2-indolinone hydrochloride (XIXe).—Colorless crystals had m.p. 245–246° dec.; λ_{max}^{Nujol} broad 3.9–4.3, 5.85–5.87, and 6.16 μ; λ_{max}^{MeOH} 209 and 281 mμ (ϵ 31,150 and 5850, respectively) with inflection 296 mμ (ϵ 5280).

Anal. Calcd. for $C_{22}H_{29}ClN_2O_3$: C, 65.25; H, 7.22; N, 6.92. Found: C, 65.17; H, 7.33; N, 6.62.

1-Methyl-3-cyclopentyl-3-(β-dimethylaminoethyl)-2-indolinone (XIXf) was characterized as the **picrate**: m.p. 153–155°; λ_{max}^{Nujol} 3.64, 5.86, and (doublet) 6.12–6.23 μ.

Anal. Calcd. for $C_{24}H_{29}N_5O_8$: C, 55.91; H, 5.67; N, 13.59. Found: C, 55.71; H, 5.85; N, 13.41.

1-Phenyl-3-methyl-3-(β-dimethylaminoethyl)-2-indolinone hydrochloride (XIXg) had m.p. 251–253°; λ_{max}^{Nujol} broad 4.17–4.27 ionic band, 5.90, and 6.19 μ; λ_{max}^{MeOH} 244 mμ (ϵ 12,120) with inflection 292 mμ (ϵ 620).

Anal. Calcd. for $C_{19}H_{23}ClN_2O$: C, 68.97; H, 7.01; N, 8.47. Found: C, 68.42; H, 7.30; N, 8.50.

Also prepared by the same procedure was the known compound **1-methyl-3-phenyl-3-(β-dimethylaminoethyl)-2-indolinone**,[11] b.p. 190–195° (3 mm.), hydrochloride hygroscopic, and **1-benzyl-3-phenyl-3-(β-dimethylaminoethyl)-2-indolinone hydrochloride (XIXh)**, m.p. 199–200°, λ_{max}^{Nujol} broad ionic bands 5.89 and 6.20 μ, λ_{max}^{EtOH} 256 (ϵ 6910) with inflections 264 and 283 (ϵ 5800 and 1550, respectively).

Anal. Calcd. for $C_{25}H_{27}ClN_2O$: C, 73.70; H, 6.68; N, 6.87. Found: C, 73.81; H, 6.95; N, 6.76.

Alkylation with β-dimethylaminoethyl chloride could not successfully be applied to XIV or to XIIb.

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