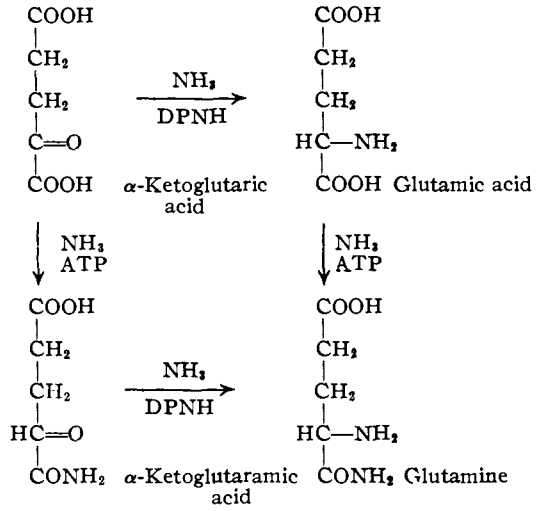
clusively. The increase in total radioactivity in glutamic acid following addition of inhibitor in some experiments is difficult to explain in terms of an inhibition of a transamidation reaction only. Both concentration and total radioactivity of glutamine continue to increase at a constant high rate, even when the level of glutamic acid has fallen from an initial 6 μg. per ml. of 1% suspension to less than 0.2 μg. per ml.

In order to explain these results on the basis of a synthesis of glutamine by way of a reductive amination of α-ketoglutaric acid to glutamic acid followed by amidation to give glutamine, and by no other pathway, it is necessary to call on a separation of the total reservoir of glutamic acid into two more or less isolated reservoirs, capable of possessing different specific activities.

As an alternative explanation of the experimental results, one might invoke the existence of a different route for the synthesis of glutamine, not involving glutamic acid as an intermediate. While no such route has been reported for plants, one might speculate that such a pathway may exist. If, for example, α-ketoglutaric acid were to undergo an amidation in the presence of ammonia and adenosine triphosphate, analogous to the amidation of glutamic acid, the resulting compound would be a α-ketoglutaramic acid, a substance which has been reported as the product of transamination reactions of glutamine in liver.[20-22] Reductive amination of α-ketoglutaramic acid, analogous to the reductive amination of α-ketoglutaric acid, would lead to the formation of glutamine.



Thus, glutamine would have been synthesized by a route not involving glutamic acid. An inhibition of transamidation reactions by which glutamine is converted to glutamic acid would then account for, (1) the continuous increase of radioactivity and concentration of glutamine, (2) the drop in concentration of glutamic acid, (3) a rise in glutamic acid specific activity as more glutamic acid was synthesized directly from α-ketoglutaric acid to replenish its reservoir, and (4) a fluctuation in total glutamic acid radioactivity—first up, then down as its specific activity increased while its concentration was decreasing.

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(20) M. Errera and J. P. Greenstein, *J. Biol. Chem.*, **178**, 495 (1949).

(21) J. P. Greenstein and V. E. Price, *ibid.*, **178**, 695 (1949).

(22) M. Errera, *ibid.*, **178**, 483 (1949).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Reactions of Optically Active Indole Mannich Bases[1]

BY J. D. ALBRIGHT[2] AND H. R. SNYDER

RECEIVED SEPTEMBER 24, 1958

Alkylation of diethyl malonate and diethyl acetamidomalonate with optically active 3-(isopropylaminoethylidene)-indole (I) yields racemic diethyl (3-indolyethylidene)-malonate (IIIa) and diethyl (3-indolylethylidene)-acetamidomalonate (IIIb), respectively. The addition of piperidine, ethanol and diethyl malonate to 3-benzylidene-2-methyl-3H-pseudoindole is reported. Optically active 1-methyl-3-(dimethylaminoethylidene)-indole reacts with diethyl acetamidomalonate to give racemic diethyl (3-N-methylindolylethylidene)-acetamidomalonate. A preliminary kinetic study of the reaction of I with diethyl malonate is described.

The usefulness of carbon alkylations with indole Mannich bases and their quaternary salts has been well established.[3] Syntheses of tryptophan and related compounds have been among the most important applications of the method.[4,5] The synthetic aspects of these reactions have been explored extensively,[3] but some questions concerning the mechanisms by which they operate remain unanswered. A 3H-pseudoindole (*e.g.*, II) has been postulated as an intermediate in alkylation reactions by 3-(dimethylaminomethyl)-indole (gramine),[6] and evidence to support its participation has been discovered.[6,7] Information concerning the mechanism of alkylation by simpler quaternary ammonium salts containing benzyl groups has been obtained by a study of reactions of optically active salts containing the α-phenethyl group,[8] and it has long been recognized that a similar study of an op-

(1) From the dissertation submitted by J. D. Albright in partial fulfillment of the requirements for the Ph.D. degree at the University of Illinois.

(2) National Petro-Chemicals Corporation Fellow, 1957–1958; Phillips Petroleum Co. Fellow, Summer, 1958.

(3) For a critical discussion of the subject of alkylations with amines and their derivatives, see J. H. Brewster and E. L. Eliel, "Organic Reactions," Vol. VII, Chapter 3, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 99.

(4) (a) H. R. Snyder, C. W. Smith and J. M. Stewart, THIS JOURNAL, **66**, 200 (1944); (b) H. R. Snyder and C. W. Smith, *ibid.*, **66**, 350 (1944); (c) N. F. Albertson, S. Archer and C. M. Suter, *ibid.*, **66**, 500 (1944); **67**, 36 (1945).

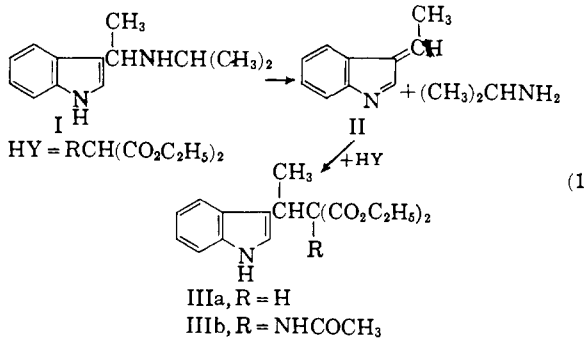
(5) H. R. Snyder and D. S. Matteson, *ibid.*, **79**, 2217 (1957).

(6) H. R. Snyder and E. L. Eliel, *ibid.*, **70**, 1703, 1857 (1948).

(7) H. Hellmann and G. Opitz, *Angew. Chem.*, **68**, 265 (1956); H. Hellmann, *ibid.*, **65**, 473 (1953).

(8) H. R. Snyder and J. H. Brewster, THIS JOURNAL, **71**, 291 (1949).

tically active molecule of the gramine type, carrying a substituent on the carbon atom adjacent to the indole ring to render it asymmetric, would be valuable. However, until recently,[5] such compounds have not been readily accessible. The present work was undertaken as an examination of the reactions of such optically active compounds (*e.g.*, I). Racemic 3-(isopropylaminoethylidene)-indole has been used previously as an alkylating agent.[5]



(1)

3-(Isopropylaminoethylidene)-indole was resolved as its salt with dibenzoyl-(+)-tartaric acid. The less soluble salt yielded the (−)-rotating free base $[\alpha]^{25}D$ ($CHCl_3$) −36 to −41°. The (+)-rotating base was obtained in less pure state ($[\alpha]^{26}D$ ($CHCl_3$) +32 to +36°) from the more soluble salt. Alkylations of diethylacetamidomalonate, diethyl malonate and piperidine all gave racemic products. Racemic 3-(piperidinoethylidene)-indole also was prepared from racemic I, and directly from acetaldehyde, piperidine and indole as well. The replacement of the isopropylamino group of racemic I by morpholine also was effected.

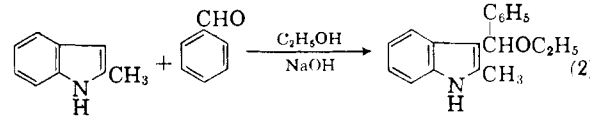
The occurrence of racemization supports the view that the alkylations proceed through addition to II, formed by amine elimination from I. Kinetic studies of the alkylation of malonic ester (*vide infra*) lend further support to this interpretation.

In the hope of carrying out similar experiments on quaternary salts related to optically active I, attempts were made to convert the base to the tertiary amine and its quaternary salt. Unfortunately, no quaternary salt could be isolated. In the original preparation of I from indole and ethylidineisopropylamine it was noted that the yield from this pair was much greater than that from indole and ethylidene-*t*-butylamine, and the low yield in the latter reaction was ascribed to steric hindrance.[5] Thus, it was not surprising that the quaternization of I failed, the steric interference between the methyl groups and additional substituents on the nitrogen atom being prohibitive. Nevertheless, the possibility remained that the quaternary salt might form slowly but decompose rapidly, through an intermediate similar to I, as a result of steric strain. In this event it should be possible to trap the intermediate by carrying out the quaternization in the presence of malonic ester. One of the procedures for effecting alkylations by indole Mannich bases consists in generating a quaternary salt *in situ* in a reaction mixture containing the active methylene compound[4c] or an alcohol.[9,10]

(9) T. A. Geissman and A. Armen, THIS JOURNAL, **74**, 3916 (1952).
(10) J. Thesing and H. Mayer, *Ber.*, **87**, 1084 (1954).

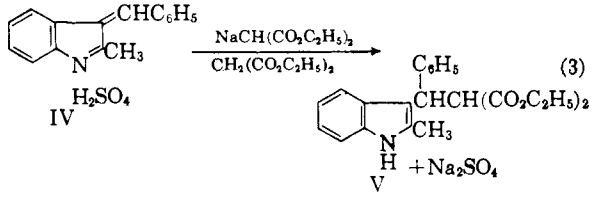
However, when optically active I was allowed to react with methyl iodide and sodium methoxide in methanol over an extended period, only a very low yield (15%) of racemic 3-(methoxyethylidine)-indole was obtained. It is very unlikely that the quaternary salt participated, for a tertiary amine similar to I, 3-(dimethylaminoethylidene)-indole, gave the same ether in excellent yield (93%) under milder conditions. Obviously, it would be of interest to repeat the latter experiment with an optically active form of 3-(dimethylaminoethylidene)-indole, but attempts to resolve this substance have not succeeded.

Salts of 3H-pseudoindoles derived from 2-substituted indoles and aromatic aldehydes are well



(2)

known.[11,12] The free bases are unstable, and few of them have been characterized.[12,13] There is no direct evidence that 3H-pseudoindoles undergo addition of active methylene compounds, alcohols, and amines as proposed in the elimination–addition mechanism of the reactions of gramine and its derivatives (*cf.* equation 1). The formation of 2-methyl-3-(ethoxybenzylidene)-indole from benzaldehyde, 2-methylindole, sodium hydroxide and ethanol[14] (equation 2) occurs under conditions sufficiently similar to those employed in reactions of indole Mannich bases as to suggest a relationship of mechanism, and in this reaction also an elimination–addition process seems most reasonable. To determine whether a 3H-pseudoindole can participate in an addition of the Michael type, the salt IV was prepared and treated with malonic ester containing more than enough of the sodio derivative to convert the salt to the free base. The expected addition occurred at room temperature and the substituted malonic ester (V) was obtained in good



(3)

yield. Similar reactions of IV with piperidine and ethanol were effected. Thus, there can be no doubt concerning the ability of the 3H-pseudoindole system to undergo the proposed addition reactions.

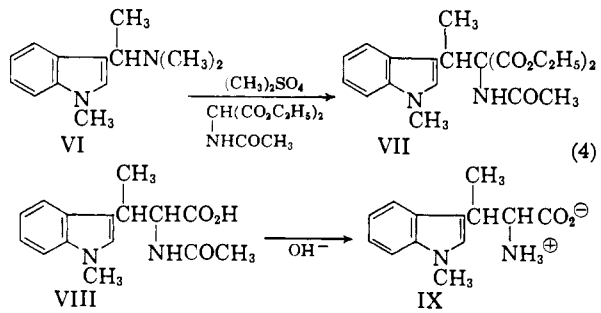
In the course of the present work several 3-(alkoxyethylidene)-indoles and 3-(alkoxymethyl)-indoles were prepared. Although the hydroxyl group of 3-(hydroxymethyl)-indole has been replaced by the cyano and piperidino groups,[15,16] and the ethyl-

(11) R. C. Elderfield, "Heterocyclic Compounds," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 1.
(12) (a) G. Burr and R. Gortner, THIS JOURNAL, **46**, 1224 (1924); (b) H. Teuber and E. Fahrback, *Ber.*, **91**, 713 (1958), and references contained therein.
(13) G. F. Smith, *J. Chem. Soc.*, 3842 (1954).
(14) M. Scholtz, *Ber.*, **46**, 2138 (1913).
(15) C. Runti, *Gazz. chim. ital.*, **81**, 613 (1951); *C. A.*, **49**, 1700 (1955).

thio group of 3-(ethylthiomethyl)-indole[17] has been replaced in similar reactions, there appear to be no recorded examples of the replacement of alkoxyl groups in the ethers. Reactions of the ethers therefore were attempted. 3-(Methoxymethyl)-indole and 3-(ethoxyethylidene)-indole were found to react smoothly with piperidine in the presence of sodium methoxide (but not in its absence) to give 3-(piperidinomethyl)-indole and 3-(piperidinoethylidene)-indole in 65 and 59% yields, respectively. Attempts to alkylate malonic ester with the first of these reagents failed, perhaps because the sodiomalonic ester formed in the reaction mixture is not a sufficiently strong base.

In connection with attempts to resolve 3-(dimethylaminoethylidene)-indole, the related 1-methyl derivative VI, 1-methyl-3-(dimethylaminoethylidene)-indole, was prepared by a condensation of the Mannich type. Unlike the compound lacking the 1-methyl group, this substance was resolved without difficulty. The optically active salt VI was treated with methyl sulfate and the sodium derivative of acetamidomalonic ester, and the expected alkylation product was obtained in about 50% yield. As expected, the alkylation product VII was racemic. The dimethyltryptophan IX was obtained from VII in the usual way.

Although racemic products were obtained when alkylations with optically active I were carried out, the full significance of this fact cannot be determined in the absence of information indicating at which stage of the reaction the racemization occurred. If it were possible to show that the rate of racemization of I and the rate of amine evolution are identical, support for a 3H-pseudoindole would be obtained. The kinetic experiments (see Discussion) were carried out to provide data on this point.



(4)

Experimental[18-20]

Separation of Optical Isomers of 3-(Isopropylaminoethylidene)-indole.—To a solution of 54.9 g. (0.15 mole) of dibenzoyl-(+)-tartaric acid monohydrate[21] in 75 ml. of absolute ethanol was added an ethanol solution containing 20.3 g. (0.15 mole) of 3-(isopropylaminoethylidene)-indole.[5] After cooling overnight at 5°, the product (26 g.) was collected. A second crop of crystals (17 g.) was obtained from the mother liquor. Both the first crop and the second crop of crystals were recrystallized from absolute ethanol yielding 14 and 9.5 g. of salt, respectively. The specific rotation of the salt after only two recrystallizations was usually within the range $[\alpha]^{26}D$ (acetone) −59 to −61°. Attempts to recrystallize the salt from ethanol until a constant rotation was obtained failed because of decomposition of the Mannich base. The (−)-rotating Mannich base was recovered by treatment with aqueous sodium hydroxide and extraction with chloroform. The specific rotation of the 3-(isopropylaminoethylidine-indole used in the following reactions was within the range $[\alpha]^{26}D$ ($CHCl_3$) −36 to −41°. The mother liquor, from which the (−)-rotating salt of dibenzoyl-(+)-tartaric acid and 3-(isopropylaminoethylidene)-indole was separated, was evaporated to a thick red oil by passing air over the solution. To the oil were added water and an aqueous solution of sodium hydroxide. After extracting with chloroform the solvent was removed and the residue recrystallized once from toluene and once from acetone–water. The specific rotation of the 3-(isopropylaminoethylidene)-indole, separated in the manner described above, was usually within the range $[\alpha]^{26}D$ ($CHCl_3$) + 32 to +35°.

Diethyl (3-Indolyethylidene)-malonate.—To 50 ml. of sodium-dried toluene were added 8.01 g. (0.05 mole) of diethyl malonate and 0.1 g. of sodium. The contents of the flask were heated at 85–90° under nitrogen and stirred for 1.5 hours. At this point 10.11 g. (0.05 mole) of 3-(isopropylaminoethylidene)-indole was added. After five hours the reaction mixture was poured into 25 ml. of water and the organic layer separated. The aqueous layer was extracted with three 50-ml. portions of ether. The combined extracts were dried over sodium sulfate and the solvent was removed under vacuum. The residual red oil was dissolved in ethanol and twice treated with Darco. Most of the ethanol then was removed and high-boiling petroleum ether added. On cooling for approximately a week the oil crystallized. The crude product (66% yield) melted at 63–65°. After three recrystallizations from high-boiling petroleum ether–ethanol (60:40) the product melted at 64.5–65.5°.

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.13; H, 6.78; N, 4.87.

Under similar reaction conditions racemic diethyl (3-indolylethylidene)-malonate was obtained from 0.81 g. (0.004 mole) of 3-(isopropylaminoethylidene)-indole ($[\alpha]^{27.5}D$ ($CHCl_3$) −39.0°). Racemic diethyl (3-indolylethylidene)-malonate was also prepared in 77% yield by heating diethyl malonate (0.004 mole), (−)-3-(isopropylaminoethylidene)-indole (0.004 mole) and a catalytic amount of sodium ethoxide in ethanol at 65° for 17 hours.

Diethyl (3-Indolylethylidene)-acetamidomalonate[5] from 3-(Isopropylaminoethylidene)-indole.—To 20 ml. of sodium-dried toluene were added 0.87 g. (0.004 mole) of diethyl acetamidomalonate and a small piece of sodium. After heating at 90° for one hour, 0.81 g. (0.004 mole) of 3-(isopropylaminoethylidene)-indole ($[\alpha]^{27.5}D$ ($CHCl_3$) −39.0°) was added. The reaction mixture was heated under nitrogen for 7.5 hours at 85–90°. On cooling the reaction mixture overnight at 0°, 0.95 g. (67% yield) of racemic diethyl (3-indolylethylidene)-acetamidomalonate was obtained.

3-(Piperidinoethylidene)-indole from 3-(Isopropylaminoethylidene)-indole.—To 0.81 g. (0.004 mole) of 3-(isopropylaminoethylidene)-indole ($[\alpha]^{17}D$ ($CHCl_3$) −36.5°) in 20 ml. of toluene was added 5 ml. of piperidine. The reaction mixture was heated at 85–90° for 18 hours and then heated under vacuum to remove the solvent and excess piperidine. The residual red oil was dissolved in 5 ml. of methylcyclohexane, seeded with a crystal of 3-(piperidinoethylidene)-indole, and cooled at 0°. The yield of crude product was 0.85 g. (93.5%). In order to purify the material to determine its optical rotation it was dissolved in methylcyclohexane, treated with Darco, and recrystallized twice from methylcyclohexane. The yield of pure product (racemic) was 60.4%.

3-(Piperidinoethylidene)-indole.—Indole (23.4 g., 0.2 mole) was dissolved in 150 ml. of glacial acetic acid and the mixture cooled in an ice–salt-bath. To the cooled mixture was added dropwise a solution of 17 g. of piperidine in 10 ml. of thiophene-free benzene. A mixture of acetaldehyde (9.7 g., 0.22 mole) in 50 ml. of thiophene-free benzene was then added dropwise over a period of 10 to 15 minutes. After cooling at 0° for 4 days the reaction mixture was

(16) C. Runti and G. Orlando, *Ann. chim. (Rome)*, **43**, 308 (1953); *C. A.*, **49**, 3940 (1955).

(17) F. Poppelsdorf and S. J. Holt, *J. Chem. Soc.*, 4094 (1954); 1124 (1954).

(18) All melting points are corrected and all boiling points are uncorrected.

(19) The infrared spectra were determined by Mr. James Brader, Mrs. Louise Griffing, Mr. Sy Portnow, Mr. Paul E. McMahon and Miss Mary DeMott.

(20) The microanalyses were performed by Mr. Josef Nemeth, Miss Claire Higham, Mrs. H. Stingl and Mrs. Frederick Ju.

(21) C. L. Butler and L. H. Cretcher, THIS JOURNAL, **55**, 2605 (1933).

poured into 150 ml. of ether and 800 ml. of ice-water. The ether layer was separated and extracted with two 100-ml. portions of 1 *M* potassium bisulfate. The combined aqueous extracts were washed with 100 ml. of ether and then made basic with 10 *N* sodium hydroxide. The temperature of the mixture was kept below 15° during the addition of the alkali by cooling in an ice–salt-bath. The oil that separated was removed by extraction with ether. After drying the ether extracts over sodium sulfate, the solvent was removed under vacuum and 25 ml. of methylcyclohexane added to the remaining oil. The oil crystallized after cooling at 5° for several days. The product (22.6 g.) was obtained in 49.5% yield and after several recrystallizations from methylcyclohexane melted from 99.5–101°. An analytical sample was recrystallized twice from methylcyclohexane and once from toluene–methylcyclohexane.

Anal. Calcd. for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 78.72; H, 8.86; N, 11.87, 11.95.

Hydrochloride of 3-(Piperidinoethylidene)-indole.—An ether solution of 3-(piperidinoethylidene)-indole was treated with 2 *N* hydrochloric acid and the aqueous layer cooled at 0° overnight. The water-insoluble hydrochloride was recrystallized from absolute ethanol, m.p. 165–170° dec.

Anal. Calcd. for $C_{15}H_{20}N_2 \cdot HCl$: C, 68.09; H, 7.94; N, 10.58. Found: C, 67.92; H, 7.85; N, 9.63, 9.73.

3-(Morpholinoethylidene)-indole.—To 20 ml. of sodium-dried toluene were added 3.23 g. (0.016 mole) of 3-(isopropylaminoethylidene)-indole and 10 ml. of morpholine. The reaction mixture was stirred and heated under nitrogen at 95–100° for 15 hours. After removal of the solvent under vacuum, a few milliliters of methylcyclohexane was added and the mixture was cooled. After about two months the oil crystallized. The yield of crude white product (m.p. 98–104°) was 3.68 g. (85%). After recrystallization from toluene–methylcyclohexane, methylcyclohexane and ethanol–water the product melted from 115–118°.

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 73.19; H, 7.95; N, 12.24.

3-(Methoxyethylidene)-indole from 3-(Isopropylaminoethylidene)-indole.—To 15 ml. of absolute methanol were added 0.81 g. (0.004 mole) of 3-(isopropylaminoethylidene)-indole ($[\alpha]^{25}D$ ($CHCl_3$) + 35.1°) and 0.86 g. (0.016 mole) of sodium methoxide. The reaction mixture was cooled in an ice–salt-bath and 2.3 g. (0.016 mole) of methyl iodide added. A slow stream of nitrogen was bubbled through the reaction mixture. The mixture was cooled for the first 10 hours, then allowed to warm to room temperature and stand for 21 hours. The reaction mixture was poured into 25 ml. of ether and 25 ml. of water, the organic layer was separated, and the aqueous layer was extracted with two 25-ml. portions of ether. After drying the ether extracts over sodium sulfate, the solvent was removed under reduced pressure. The oil obtained crystallized from ether–methylcyclohexane (yield 0.61 g., $[\alpha]^{25}D$ ($CHCl_3$) +11.1°). On fractional crystallization from ether–methylcyclohexane, the 3-(methoxyethylidene)-indole formed was separated from unchanged 3-(isopropylaminoethylidene)-indole. Only 0.1 g. (15%) of 3-(methoxyethylidene)-indole was obtained; the remainder of the material appeared to be 3-(isopropylaminoethylidene)-indole and melted from 107–110° after recrystallizing twice from ether–methylcyclohexane, once from acetone–water and once from toluene. The analysis of this material ($[\alpha]^{25}D$ ($CHCl_3$) +19.0°) was very close to that required for 3-(isopropylaminoethylidene)-indole; however, the possibility that the material was 3-(methylisopropylaminoethylidene)-indole cannot be definitely excluded. A mixed melting point with authentic 3-(isopropylaminoethylidene)-indole, m.p. 114–116°, showed very little depression, mixed m.p. 107–111°. The infrared absorption spectrum was identical to that of an authentic sample of 3-(isopropylaminoethylidene)-indole. The 3-(methoxyethylidene)-indole isolated in 15% yield was shown to be racemic.

Anal. Calcd. for $C_{13}H_{18}N_2$: C, 77.18; H, 9.87; N, 13.85. Calcd. for $C_{14}H_{20}N_2$: C, 77.79; H, 9.25; N, 12.96. Found: C, 76.85; H, 8.63; N, 13.34.

3-(Methoxyethylidene)-indole.—A solution of 1.9 g. (0.01 mole) of 3-(dimethylaminoethylidene)-indole[5] in 20 ml. of absolute methanol was prepared. After the addition of 2.7 g. (0.05 mole) of sodium methoxide, the mixture was cooled in an ice–salt-bath. Methyl iodide (3.5 ml.) was then added and a slow stream of nitrogen bubbled through the solution. After 8 hours the reaction mixture was allowed to warm to room temperature and after an additional 14 hours the reaction was terminated. The precipitate which formed was removed by filtration, and the filtrate was poured into 30 ml. of water. On evaporation of the solvent to approximately 25 ml. and cooling at 0°, 1.75 g. (93%) of product was obtained. The crude material melted from 70–72°; it was recrystallized three times from ethanol–water. The purified product melts at 78–79°.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.36; H, 7.43; N, 8.11.

3-Ethoxyethylidene)-indole.—From 1.9 g. (0.01 mole) of 3-(dimethylaminoethylidene)-indole dissolved in ethanol containing (0.05 mole) of sodium ethoxide, 3-(ethoxyethylidene)-indole was prepared. The reaction conditions were essentially the same as those described for the preparation of 3-(methoxyethylidene)-indole. The yield of crude product, m.p. 93–95°, was 1.81 g. or 95.3%. After several recrystallizations from ethanol–water the product melted from 95–97.5°.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 75.98; H, 8.11; N, 7.39.

3-(Isopropoxyethylidene)-indole.—Under reaction conditions similar to those described previously for the preparation of 3-(methoxyethylidene)-indole, 3-(isopropoxyethylidene)-indole was obtained from 3-(dimethylaminoethylidene)-indole (1.9 g.), 2-propanol and the sodium salt of 2-propanol. The yield was 1.3 g. or 64%. An analytical sample was recrystallized from ether–methylcyclohexane and toluene–methylcyclohexane, m.p. 94–96°.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.79; H, 8.40; N, 6.87.

Diethyl (2-Methyl-3-indolylbenzylidene)-malonate.—Sodium (0.23 g., 0.01 mole) was added to 10 ml. of diethyl malonate. The mixture was heated under nitrogen at 90° in an oil-bath until all the sodium had reacted. After cooling in an ice–salt-bath, 0.63 g. (0.002 mole) of the sulfuric acid salt of 2-methyl-3-benzylidene-3H-pseudoindole was added in small portions over a period of approximately 5 minutes. The cooled mixture then was stirred under nitrogen for 3 hours. The reaction mixture was poured into water and extracted with ether and benzene. After drying the extracts over sodium sulfate, the solvent was removed under vacuum. On addition of ether and pentane to the residual oil, a precipitate formed. The white precipitate was removed by filtration and the filtrate diluted with pentane. On cooling overnight, 0.45 g. of product (m.p. 143–145°) was obtained. The yield was 59%. An analytical sample was recrystallized three times from ether–pentane (50:50), m.p. 145–146°.

Anal. Calcd. for $C_{23}H_{25}O_4N$: C, 72.80; H, 6.64; N, 3.69 Found: C, 73.00; H, 6.74; N, 3.88.

2-Methyl-3-(ethoxybenzylidene)-indole.[14]—To 20 ml. of absolute ethanol was added 0.8 g. of sodium. When the sodium had reacted, the mixture was cooled in an ice–salt-bath and 0.3 g. of the sulfuric acid salt of 3-benzylidene-2-methyl-3H-pseudoindole was added slowly while the mixture was stirred under nitrogen. The mixture was allowed to stand for 15 minutes before the addition of 10 ml. of water. The solvent was removed by passing air over the solution and the solid which formed was collected. After washing with water, 0.2 g. (m.p. 118–120°, reported 123°) remained (80%). The crude product was recrystallized twice from ethanol–water and three times from acetone–water; m.p. 122–123°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22. Found: C, 81.42; H, 7.25.

2-Methyl-3-(piperidinobenzylidene)-indole.—To 10 ml. of piperidine cooled in an ice–salt-bath was added 0.5 g. (1.6×10^{-3} mole) of the sulfuric acid salt of 2-methyl-3-benzylidene-3H-pseudoindole in small portions over a period of 15 to 20 minutes. The mixture was stirred under nitrogen during the addition and then allowed to stand for 3 hours at 0°. Ether was added in order to precipitate the sulfuric acid salt of piperidine. After removing the solid formed, the filtrate was heated on a steam-bath under vacuum in order to remove the solvent. The residual oil was dissolved in ether–methylcyclohexane–pentane and cooled for several days. The yield of crystalline product, m.p. 134–136°, was 0.40 g. or 89%. An analytical sample was recrystallized

once from ether–pentane and twice from toluene–methylcyclohexane, m.p. 136–137°.

Anal. Calcd. for $C_{21}H_{24}N_2$: C, 82.85; H, 7.95; N, 9.20. Found: C, 82.72; H, 7.95; N, 9.13.

3-(Piperidinoethylidene)-indole from 3-(Ethoxyethylidene)-indole.—To 20 ml. of piperidine were added 0.57 g. (2.78×10^{-3} mole) of 3-(ethoxyethylidene)-indole and 0.54 g. (0.01 mole) of sodium methoxide. The reaction was heated under nitrogen for 17 hours at 95–100°. After pouring into water, the mixture was extracted with ether. The ether extracts were dried over sodium sulfate and the solvent was removed under vacuum. Since the red oil obtained failed to crystallize from methylcyclohexane on cooling, it was treated with 5 *N* HCl until acidic and cooled at 0°. A crystalline hydrochloride was obtained whose infrared spectrum (Nujol) was identical with the spectrum of the known hydrochloride of 3-(piperidinoethylidene)-indole. The yield of the hydrochloride was 0.44 g. or 59.4%.

3-(Piperidinomethyl)-indole from 3-(Methoxymethyl)-indole.—To 20 ml. of piperidine were added 1.51 g. of 3-(methoxymethyl)-indole[9] and 1.1 g. (0.02 mole) of sodium methoxide. The mixture was stirred under nitrogen and heated at 95–100° for 22 hours. Toluene (15 ml.) then was added and the mixture poured into 25 ml. of water. The aqueous layer was separated and extracted with ether. The combined extracts were dried over sodium sulfate and the solvent was removed under vacuum. The solid obtained was dissolved in methanol and the mixture poured into water. Crystals formed almost immediately, and after cooling overnight the product was collected. The yield was 1.36 g., m.p. 156–158°, or 67.8%. A mixed melting point of the product (after recrystallizing from methanol–water) with an authentic sample of 3-(piperidinomethyl)-indole showed no depression. The infrared spectrum was identical with that of the known 3-(piperidinomethyl)-indole.

1-Methyl-3-(dimethylaminoethylidene)-indole.—A mixture of 13.1 g. (0.1 mole) of N-methylindole,[22] 8.97 g. (0.11 mole) of dimethylamine hydrochloride and 2.76 g. (0.02 mole) of potassium carbonate in 50 ml. of glacial acetic acid and 25 ml. of propionic acid was prepared. To the mixture, cooled in an ice–salt-bath, was added dropwise 4.9 g. (0.11 mole) of acetaldehyde in 25 ml. of thiophene-free benzene. After cooling at 5° for 6 days, the mixture was poured into 150 ml. of ice-water and 100 ml. of ether. The ether layer was extracted with two 50-ml. portions of 1 *M* potassium bisulfate. The aqueous extracts were combined, cooled in an ice–salt-bath, and made basic with 10 *N* sodium hydroxide. During the addition of the alkali the temperature was kept below 20°. A red oil separated and was removed by extracting with ether. The ether extracts were dried over sodium sulfate and the solvent was removed under vacuum. The product was distilled at 1.2–1.3 mm., b.p. 114–116°. The yield after one distillation was 9.5 g. or 47.2%. When the proportions were doubled, the crude product (before distillation) was obtained in a 69% yield. This product without purification was used in the separation of the optical isomers of 1-methyl-3-(dimethylaminoethylidene)-indole.

Anal. Calcd. for $C_{13}H_{18}N$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.38; H, 8.63; N, 13.30.

Separation of Optical Isomers of 1-Methyl-3-(dimethylaminoethylidene)-indole.—Dibenzoyl-(+)-tartaric acid monohydrate (3.66 g., 0.01 mole) was added to 10 ml. of absolute ethanol. After the addition of 2.02 g. (0.01 mole) of 1-methyl-3-(dimethylaminoethylidene)-indole, 10 ml. of ethyl acetate and approximately 1 ml. of ether were added. Cooling for several days at 0° yielded 3.45 g. of crystalline salt. The optical activity of the salt was determined after two recrystallizations from absolute ethanol; $[\alpha]^{23}D$ (ethanol) −67.6°. No attempt was made to obtain optically pure product by recrystallizing the salt until a constant rotation was obtained. The salt was treated with water and 1 *N* sodium hydroxide until the salt dissolved and the mixture was strongly basic. The mixture then was extracted with chloroform and the extracts were dried over sodium sulfate. The solvent was removed by passing dry air over the extracts, leaving the pale yellow liquid, 1-methyl-3-(dimethylaminoethylidene)-indole. The mother liquor from which the (−)-rotating salt was obtained was evaporated to dryness by passing dry air over the solution. The residue was decomposed with dilute sodium hydroxide and the 1-methyl-3-(dimethylaminoethylidene)-indole ($[\alpha]^{26}D$ ($CHCl_3$) −7.3°) isolated in the same manner described for the (+)-rotating isomer.

Diethyl (3-N-Methylindolylethylidene)-acetamidomalonate.—Diethyl acetamidomalonate (1.09 g., 0.005 mole) was added to 15 ml. of ethanol containing 0.23 g. (0.01 mole) of sodium. The mixture under nitrogen was cooled in an ice–salt-bath and 1.01 g. (0.005 mole) of 1-methyl-3-(dimethylaminoethylidene)-indole was added. A solution of dimethyl sulfate (1.26 g., 0.01 mole) in 5 ml. of absolute ethanol was added dropwise over a period of approximately 0.5 hour. The mixture was cooled for 2.5 hours after the addition of the dimethyl sulfate; it was then allowed to stand at room temperature for one hour. The white crystalline material which precipitated was removed by filtration and washed with water. The yield of product, m.p. 186–187°, was 0.78 g. Additional material (0.35 g.) was obtained by extracting the aqueous filtrate with chloroform, drying the extracts over sodium sulfate, and removing the solvent by passing air over the extracts. The total yield was 1.13 g. or 60.5%. The same procedure was used in the preparation of diethyl (3-N-methylindolylethylidene)-acetamidomalonate from optically active 1-methyl-3-(dimethylaminoethylidene)-indole ($[\alpha]^{26}D$ ($CHCl_3$) +19.5°). The product, m.p. 183–185°, 1.20 g. or 64%, was determined to be optically inactive. An analytical sample was recrystallized twice from ethanol, m.p. 186–187°.

Anal. Calcd. for $C_{20}H_{26}N_2O_5$: C, 64.15; H, 7.00; N, 7.48. Found: C, 64.15; H, 7.26; N, 7.21.

2-Acetamido-3-(3-N-methylindolyl)-butyric Acid.—In a 50-ml. flask were added 20 ml. of water, 5 ml. of ethanol and 0.45 g. of diethyl (3-N-methylindolylethylidene)-acetamidomalonate. After the addition of 5 ml. of 2 *N* sodium hydroxide, the mixture was refluxed for 3 hours. The mixture then was cooled in an ice–salt-bath and acidified with hydrochloric acid. On cooling 48 hours the crystals which formed were collected. The yield of crude product (m.p. 210.5–211.5°) was 0.25 g. The sample was purified by recrystallizing from ethanol–water (m.p. 215–217°). The analysis of this sample indicated that the product still contained some material which had not decarboxylated. The product was therefore heated in pyridine at 95° for 5 hours. The solvent was removed and the product recrystallized from ethanol, m.p. 219–220°.

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.79; H, 6.78; N, 9.89.

2-Amino-3-(3-N-methylindolyl)-butyric Acid.—2-Acetamido-3-(3-N-methylindolyl)-butyric acid (0.24 g.) was treated with 2 ml. of 10 *N* sodium hydroxide and 3 ml. of water. The mixture then was heated under reflux for 24 hours. After cooling in an ice–salt-bath the mixture was neutralized with glacial acetic acid. A precipitate formed immediately. The white crystalline solid was collected after cooling overnight; the yield was 0.20 g. The product was purified by dissolving it in dilute sodium hydroxide solution and filtering the solution; after acidification with glacial acetic acid, the mixture was cooled and the product was recovered. An analytical sample was recrystallized from ethanol–water, m.p. 206–208° dec.

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94. Found: C, 67.07; H, 6.86.

Isolation of Diethyl (3-Indolylethylidene)-malonate from Kinetic Runs.—The solvent was removed under vacuum and the residual oil dissolved in a small amount of ethanol. High-boiling petroleum ether was then added and the mixture, seeded with a crystal of diethyl (3-indolylethylidene)-malonate, was cooled at 0° overnight. The yields ranged from 78 to 88%.

Kinetic Experiments.—To a 50-ml. volumetric flask was added, from a pipet, 5 ml. of diethyl malonate which had been redistilled from sodium. The volumetric flask was then filled with xylene at room temperature. In another 50-ml. volumetric flask was added 5.0573 g. (0.025 mole) of 3-(isopropylaminoethylidene)-indole. The flask was filled with xylene so that it contained 50 ml. of solution at the temperature of the bath (94.0°). The xylene (b.p. 137.9–139.6°) was Fisher reagent grade and was dried over sodium before it was used. After sweeping out the reaction flask (a 100-ml. standard taper one-necked flask with

(22) The N-methylindole was supplied by Dr. Allan P. Gray, Irwin Neisler and Co., Decatur, Ill.; A. P. Gray and W. L. Archer, THIS JOURNAL, 79, 3557 (1957).

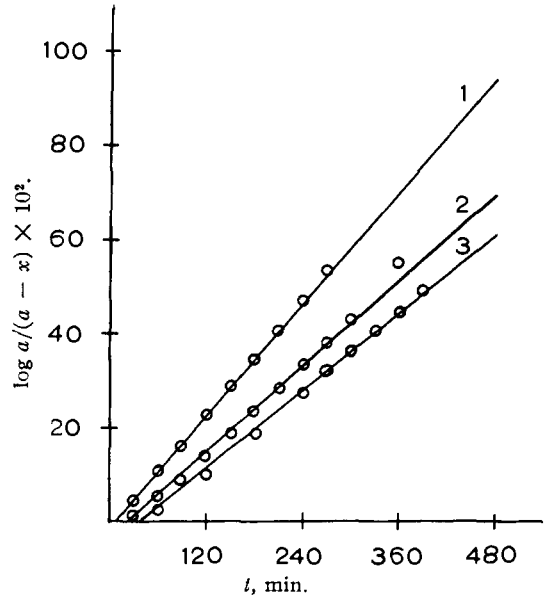


Fig. 1.—Plot showing the effect of catalyst concentration on the rate; amount of $NaOCH_3$ added: (1) 0.10 g., (2) *ca.* 0.02 g., (3) *ca.* 0.01 g.; concentration of I, 0.250 *M*; of diethyl malonate, 0.329 *M*.

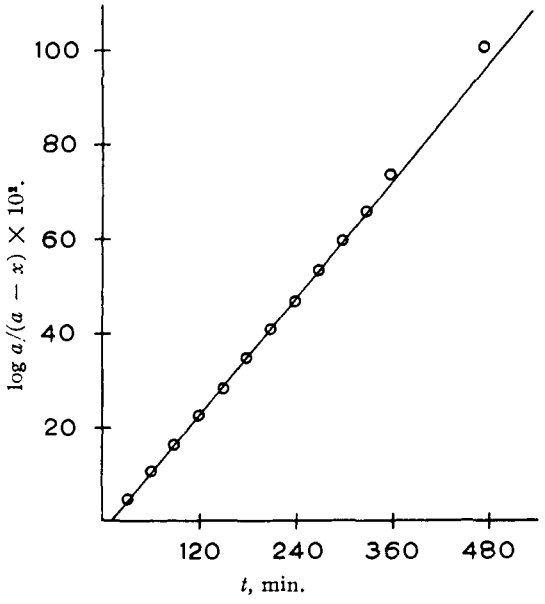


Fig. 2.—Typical first-order plot for the reaction of I (0.250 *M*) with diethyl malonate, 0.329 *M*; amount of $NaOCH_3$ added, 0.05 g. The reaction was approximately 82% complete at 360 min.

small side inlet) with nitrogen, 10 ml. of the malonate solution was pipetted into the flask. Solid sodium methoxide (0.05 g.) then was added and the mixture heated at the temperature of the bath for 0.5 hour. From a pipet was added 10 ml. of the solution, equilibrated at 94.0°, of 3-(isopropylaminoethylidene)-indole. The outlet tube was quickly connected and immersed in a saturated boric acid solution (50 ml.) containing five drops of indicator solution. The indicator solution had the composition 0.25% brom cresol green, 0.07% methyl red in 95% ethanol. The rate of the reaction was followed by titration of the isopropylamine liberated with 0.10 *N* hydrochloric acid. Nitrogen was bubbled through the reaction mixture in order to agitate the mixture and to sweep out the amine eliminated. The rate at which the nitrogen is passed through the system is

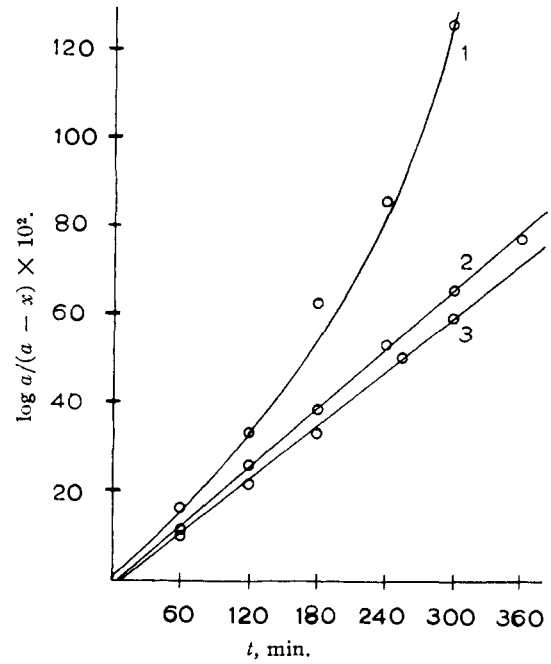


Fig. 3.—Plot showing the effect on the rate of racemization (1) when none of the isopropylamine was removed from the reaction mixture; (2) when nitrogen was bubbled slowly through the reaction mixture (partial removal of the amine eliminated); (3) when the amine eliminated was removed as rapidly as possible; concentration of I, 0.250 *M*; of diethyl malonate, 0.329 *M*.

critical. A very rapid rate tends to evaporate the solvent, causing deviations; however, a very slow rate does not remove all the amine. The rate of the reaction was also followed by determining the change in optical activity of the 3-(isopropylaminoethylidene)-indole. The procedure for preparing the standard solutions was the same as that outlined above. At zero time an aliquot (*ca.* 1.2 ml.) was withdrawn from the reaction mixture, quickly cooled and analyzed polarimetrically. At definite time intervals aliquots were withdrawn and analyzed. From 5 to 10 minutes elapsed between the time the aliquot was withdrawn and analyzed. The sodium methoxide used was commercial grade from Matheson Co., Inc. The temperature of the bath was determined by calibration with a Bureau of Standards thermometer.

Discussion of Kinetic Data

Addition of a greater amount of sodium methoxide (0.10 g.) did not change the rate of amine evolution. A reduction in the amount of sodium methoxide added, however, resulted in a decreased rate of amine evolution (Fig. 1).

It appears that the reaction is homogeneous and that the rate is limited by the solubility of the catalyst in the reaction medium. An increase in the amount of sodium methoxide added increases the amount of diethyl sodiomalonate present but does not change the amount of effective catalyst in solution. An increase in the concentration of diethyl malonate should increase the solubility of the catalyst, diethyl sodiomalonate, and thus increase the rate, if the assumption is made that diethyl sodiomalonate is more soluble in diethyl malonate than xylene. When the concentration of diethyl malonate was doubled, the rate of the reaction did indeed increase (*ca.* 25%).

Pseudo first-order kinetics were observed (Fig. 2) when the rate of the reaction was determined by titration of the amine eliminated; $K_{obsd} = 7.31 \times 10^{-5}$ sec.$^{-1}$ (average of three independent runs). Under identical reaction conditions the rate determined polarimetrically was essentially the same; $K_{obsd} = 7.68 \times 10^{-5}$ sec.$^{-1}$ (average of three independent runs).

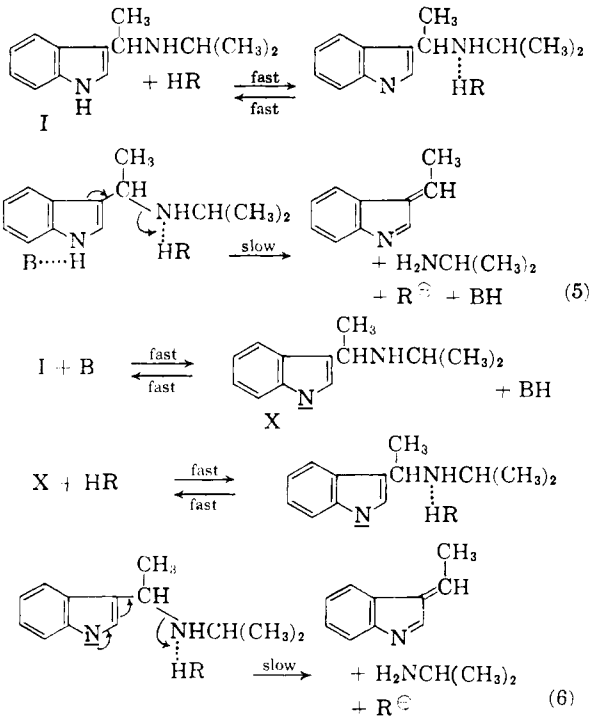
When the isopropylamine eliminated was removed less rapidly (decreased rate of flow of nitrogen through the sys-

tem) the rate of racemization increased. The reaction appeared to be autocatalytic when none of the amine was removed (Fig. 3). It seems reasonable that the amine liberated would act as a catalyst, for in amine replacement reactions with Mannich bases of indole no catalyst except the amine, usually employed as solvent, is needed, the amine acting both as the catalyst and the reactant.

The rate of the reaction depended on the initial concentration of 3-(isopropylaminoethylidene)-indole (I). A plot of K_{obsd} against initial concentration of I yielded a straight line (Fig. 4). The observed rate constants were calculated by use of the integral equation[23]

$$K_{obsd} = \frac{1}{t} \log \frac{a}{a - x} \times 2.303$$

Two possible reaction paths for the alkylation of diethyl malonate with I are illustrated in equations 5 and 6.



The rate expression for the mechanism illustrated in equation 5 is

$$V = kK_{eq}(B)(\text{Mannich base})(HR)$$

The dependence of the rate on the initial concentration of I indicates that HR is another molecule of Mannich base. The logical hydrogen donor is the NH in the indole nucleus; however, the product II, diethyl (3-indolylethylidene)-malonate, would also be expected to hydrogen bond through the hydrogen atom on the indole nitrogen atom. When the concentration of B remains constant and HR is another molecule of I or II, pseudo first-order kinetics should be observed. Since the number of indole residues remains constant, the concentration of HR will remain constant during a given run and be equal to the initial concentration of I. It would thus be possible to obtain pseudo first-order evolution of amine although the rate depends on the initial concentration of I.

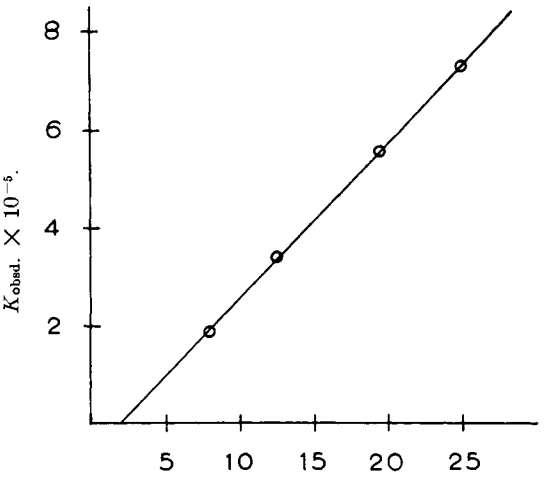


Fig. 4.--Plot showing dependence of the rate on the initial concentration of 3-(isopropylaminoethylidene)-indole.

The rate expression for the mechanism illustrated in equation 6 is

$$V = kK_{eq}K'_{eq}(B/BH)(\text{Mannich base})(HR)$$

If the ratio (B/BH) is assumed to be constant, pseudo first-order kinetics would again be observed when HR is a molecule of I or II. For the ratio (B/BH) to remain constant, it must be assumed that BH can be both diethyl malonate and diethyl (3-indolylethylidene)-malonate (II) and B the corresponding carbanions.

Additional data are needed to determine whether the mode of reaction is best illustrated by equation 5 or 6 or whether the reaction proceeds by some other path. However, the results obtained are consistent with the formation of the intermediate 3H-pseudoindole.

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(23) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 14.