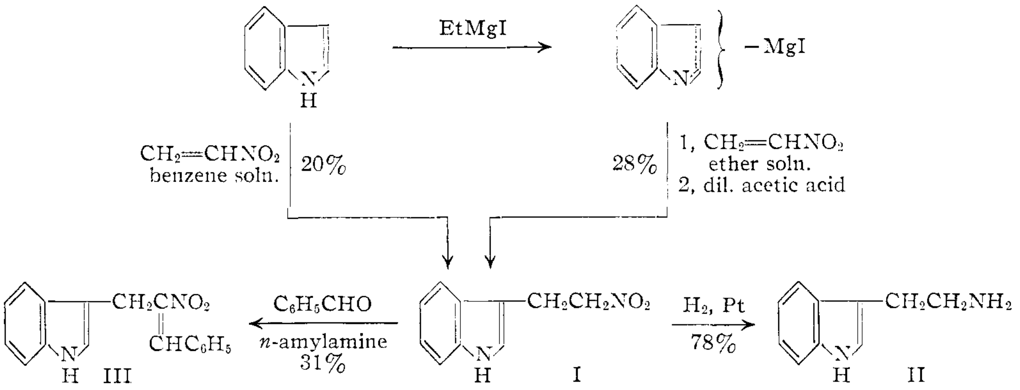
The Nitroethylation of Indole. A New Synthesis of Tryptamine

By Wayland E. Noland and Philip J. Hartman[1]

Received February 8, 1954

An earlier attempt to add nitroethylene to indole resulted in a base-soluble polymer.[2] In the present work 3-(2-nitroethyl)-indole (I) was obtained in 20% yield by chromatographing the products from the reaction of nitroethylene with indole in benzene solution. The yield of I was increased to 28% by reaction of nitroethylene with indolemagnesium iodide in ether solution. Refluxing of 2-nitroethyl acetate with indole in benzene solution for 24 hours yielded none of the desired product, I.



3-(2-Nitroethyl)-indole (I) was obtained in dimorphic forms, m.p. 56.5–57° and 68–68.5°, which were interconvertible and had identical infrared and ultraviolet spectra. The lower melting form appeared to be the favored product of fast crystallization under conditions of supercooling or supersaturation.

Table I

Ultraviolet Absorption Maxima in 95% Ethanol of Tryptamine and Related Compounds

Wave lengths of absorption maxima are given in mμ and intensities in log ε after them in parentheses

Tryptamine (II)	222(4.50)	276(3.70)	282(3.72)	291(3.65)	
Tryptamine hydrochloride[a]	221(4.52)	275(3.73)	281(3.75)	290(3.69)	
N-Benzoyltryptamine[b]	223(4.58)	275(3.75)	281(3.75)	291(3.68)	
3-(2-Nitroethyl)-indole (I)	220(4.56)	274(3.76)	281(3.79)	290(3.72)	
β-(3-Indolemethyl)-β-nitrostyrene (III)	221(4.56)	276(3.99) inflect.	283(4.04)	291(4.04)	308(3.88) inflect.
β-Methyl-β-nitrostyrene[c]	223(3.90)	276(3.80) not a max.	283(3.89) not a max.	291(3.96) not a max.	307(4.02)

[a] Previously studied by M. Kotake, K. Mori and T. Mitsuwa, *J. Sci. Research Inst.* (*Tokyo*), **31**, 333 (1937), but numerical values were unobtainable from their data. [b] Prepared essentially according to the method of A. J. Ewins, *J. Chem. Soc.*, **99**, 270 (1911); found m.p. 141–142° (cor.). [c] Determined previously by E. A. Braude, E. R. H. Jones and G. G. Rose, *J. Chem. Soc.*, 1104 (1947): $\lambda_{\max}^{\text{EtOH}}$ 226 (4.01), 305 (4.09).

The point of attachment of the nitroethyl group to the indole nucleus was established by the catalytic hydrogenation of I to tryptamine (II) in 78% yield. This provides a new synthesis of tryptamine.[3]

The close similarity of the ultraviolet spectra of III (the benzal derivative of I) and tryptamine, as well as I, shows that the double bond is not in conjugation with the indole system.

Nitroethylene and β-nitrostyrene react with pyrrole in benzene solution, but the yellow or orange solutions darken upon standing, and, in the case with nitroethylene, deposit dark solids. No identifiable products were obtained. Similarly, nitroethylene reacted with pyrrolemagnesium iodide. After hydrolysis, a benzene solution was left which darkened upon standing and deposited dark solids.

Experimental

Ethylene Iodohydrin.—Ethylene iodohydrin was prepared by slight modification of the method of Henry[4] by refluxing for four hours a mixture of sodium iodide (990 g., 6.60 moles), ethylene chlorohydrin (483 g., 6.00 moles) and absolute ethanol (1200 cc.). Removal of the precipitated sodium chloride and ethanol, extraction of the residue with ether, and distillation yielded a fraction (928 g., 5.40 moles, 90.0%) b.p. 52–55° (5 mm.), consisting principally of ethylene iodohydrin. Further purification yielded ethylene iodohydrin, $n^{20}\text{D}$ 1.5708, $n^{24}\text{D}$ 1.5682, b.p. 90–95° (40–45 mm.); reported b.p. 85° (25 mm.), 176–177° (with decomposition) (762 mm.).[4]

2-Nitroethanol.—2-Nitroethanol was prepared by slight modification of the method of Wieland and Sakellarios[5] by adding silver nitrite (1003 g., 6.52 moles) in small portions with vigorous stirring to a solution of ethylene iodohydrin (928 g., 5.40 moles) in absolute ether (1440 cc.). The mixture was refluxed for three hours, the silver iodide was removed, and the fraction (304 g., 3.34 moles, 61.8%) distilling at 65–66° (1.2 mm.), $n^{25.6}\text{D}$ 1.4383, was collected; reported $n^{19}\text{D}$ 1.4438,[6] $n^{20}\text{D}$ 1.443,[7] b.p. 63° (0.5 mm.).[7]

---

(1) From the M.S. Thesis of Philip J. Hartman, January, 1954.

(2) Bernhard Witkop and Wayland E. Noland, unpublished work, Harvard University, 1948.

(3) For references to previous syntheses see: (a) for tryptamine: J. Thesing and F. Schulde, *Chem. Ber.*, **85**, 324 (1952); (b) for 3-(2-alkyl-2-aminoethyl)-indoles; H. R. Snyder and L. Katz, This Journal, **69**, 3140 (1947).

(4) L. Henry, *Bull. classe sci. acad. roy. Belg.*, [3] **18**, 182 (1889).

(5) H. Wieland and E. Sakellarios, *Ber.*, **53B**, 201 (1920).

(6) I. M. Gorsky and S. P. Makarov, *ibid.*, **67B**, 996 (1934).

(7) N. Levy, C. W. Scaife and A. E. Wilder Smith, *J. Chem. Soc.*, 1096 (1946).

Nitroethylene.—Nitroethylene was prepared by heating 2-nitroethanol with phthalic anhydride under reduced pressure, according to the method of Buckley and Scaife.[8]

3-(2-Nitroethyl)-indole (I). (a) From Indole and Nitroethylene.—A solution of nitroethylene (10.0 g., 0.137 mole) in benzene (50 cc.) was added over a period of 50 minutes, with vigorous stirring, to a solution of indole (20.2 g., 0.172 mole) in benzene (50 cc.), maintained at 40–50°. The indole solution became reddish and darkened throughout the addition period. Stirring was continued for 40 minutes at 40–50° and finally the solution was refluxed for one hour. Some brown fumes of nitrogen dioxide were evolved. At the end of the reflux period the odor of nitroethylene was still detectable. A small amount of black precipitate was removed. The filtrate was chromatographed on alumina, using benzene as developer and eluant. A dark brown zone formed at the top of the column. A diffuse, pale yellow band moved down the column quite rapidly. After this yellow band was completely eluted, the column was eluted with 20% chloroform–80% benzene. Nearly all of the dark material remaining on the column was then washed out with 20% ethanol–80% benzene. Evaporation of the first benzene fractions yielded a small amount of indole. The chloroform–benzene fractions were colorless, but upon standing turned yellow, red and finally dark brown. Evaporation of the solvent left tars. Evaporation of the ethanol–benzene fractions also left tars.

Evaporation of the benzene from the yellow band fractions left a yellowish solid. Several recrystallizations from dilute ethanol, with charcoal, yielded 5.3 g. (0.028 mole, 20%) of colorless platelets greatly resembling indole; m.p. 68–68.5° (cor.). ν_{N-H} (cm.$^{-1}$) 3480 in $CHCl_3$, 3450 in CCl_4, Nujol; ν_{NO_2} (cm.$^{-1}$) 1550 in Nujol, 1385 in CCl_4, 1378 in $CHCl_3$.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$ (190.20): C, 63.15; H, 5.30; N, 14.73. Found: C, 63.11; H, 5.01; N, 14.62.

The product obtained by evaporation of the chromatographic solutions usually had a dual melting point when determined on a melting point block. Part of the sample would melt at 54–56° and the remainder at 68–70°. Recrystallization usually yielded the higher melting form, but on one occasion the lower melting form was obtained as colorless platelets, m.p. 56.5–57°.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$ (190.20): C, 63.15; H, 5.30; N, 14.73. Found: C, 63.23; H, 5.42; N, 14.87.

(b) From Indolemagnesium Iodide and Nitroethylene.—Indolemagnesium iodide was prepared by the method of Baker[9] from magnesium turnings (1.15 g., 0.047 g. atom), ethyl iodide (7.6 g., 0.049 mole) and indole (5.5 g., 0.047 mole) in absolute ethyl ether (40 cc.). A solution of nitroethylene (3.3 g., 0.045 mole) in absolute ethyl ether (20 cc.) was added slowly, with vigorous stirring, to the ice-cooled solution of indolemagnesium iodide. During the addition, a yellow solid formed in the yellow solution. The mixture was stirred for one hour at room temperature, and finally refluxed for one-half hour. During this time the mixture, which still contained solid, turned brown. The mixture was cooled and stirred into a solution of acetic acid (30 cc.) in water (100 cc.). The ethereal and aqueous layers were separated. The aqueous layer was neutralized with sodium carbonate and the ether layer washed with sodium carbonate solution until the evolution of carbon dioxide was no longer evident. The original neutralized aqueous layer and the sodium carbonate washings were extracted with ether and the ether added to the original washed ether layer. The combined ether solutions were washed with water and dried over anhydrous calcium chloride. Distillation of the ether left a brown, tarry residue, which was chromatographed according to the method of part a. A minute amount of indole was obtained, followed by crude, yellowish 3-(2-nitroethyl)-indole. Two recrystallizations from dilute ethanol yielded 2.4 g. (0.0126 mole) of platelets, m.p. 67–68° (cor.); mixed m.p. with sample from part a, 67–68.5°.

Tryptamine (3-(2-Aminoethyl)-indole) (II).—3-(2-Nitroethyl)-indole (7.8 g., 0.041 mole) in 95% ethanol (150 cc.) and platinic oxide (0.45 g.) were treated with hydrogen at 41 p.s.i. in a Parr low pressure hydrogenation apparatus until no further pressure drop was observed. The catalyst was filtered off and the ethanol distilled at reduced pressure. The light brown residue, which crystallized upon cooling in an ice-bath, was dissolved in ether and the solution filtered. Glacial acetic acid was added to the filtrate until precipitation was complete. The precipitated tryptamine acetate was dissolved in water and basified with 2 *N* sodium hydroxide solution. The precipitated tryptamine was filtered off, washed with water, dissolved in benzene and the solution dried over sodium sulfate. Part of the benzene was distilled in a nitrogen atmosphere. Cooling the concentrated solution caused the formation of tan, granular crystals (5.1 g., 0.032 mole, 78%), m.p. 115–117° (cor.) (reported m.p. 116–117°[3a]). An aqueous solution of Eastman Kodak Co. white label tryptamine hydrochloride was basified with 5% sodium hydroxide solution to yield tryptamine, m.p. 113–114.5°; mixed m.p. with sample obtained above, m.p. 113–116.5°. The infrared spectra of the two samples were identical.

β-(3-Indolemethyl)-β-nitrostyrene (III).—The procedure for the preparation of β-nitrostyrenes developed by Knoevenagel and Walter[10] and Hass, Susie and Heider[11] was used in this preparation. A solution of 3-(2-nitroethyl)-indole (2.01 g., 0.0106 mole), benzaldehyde (1.13 g., 0.0106 mole), *n*-amylamine (2 drops) and absolute ethanol (2 cc.) was refluxed in a test-tube on the steam-bath for 11 hours. Crystals formed slowly over a period of 48 hours when the dark brown solution was kept at −20°. Two recrystallizations from absolute ethanol yielded 0.93 g. (0.0033 mole, 31%) of glistening orange flakes, m.p. 151–152° (cor.); ν_{N-H} (cm.$^{-1}$) 3490 in $CHCl_3$, 3480 in CS_2, 3410 in Nujol; ν_{NO_2} (cm.$^{-1}$) 1524 in Nujol, 1329 in Nujol, $CHCl_3$, 1325 in CS_2. (Compare with β-methyl-β-nitrostyrene ν_{NO_2} 1534, 1330 cm.$^{-1}$ in Nujol.)

Anal. Calcd. for $C_{17}H_{14}N_2O_2$ (278.30): C, 73.36; H, 5.07; N, 10.07. Found: C, 73.34; H, 5.25; N, 10.05.

---

[8] G. D. Buckley and C. W. Scaife, *J. Chem. Soc.*, 1471 (1947).

[9] J. W. Baker, *ibid.*, 461 (1946).

[10] E. Knoevenagel and L. Walter, *Ber.*, **37**, 4502 (1904).

[11] H. B. Hass, A. G. Susie and R. L. Heider, *J. Org. Chem.*, **15**, 8 (1950).

SCHOOL OF CHEMISTRY
UNIVERSITY OF MINNESOTA
MINNEAPOLIS 14, MINN.

Compounds Derived from the Addition of Amines to 2,4-Pentadienenitrile

BY JOHN M. STEWART

RECEIVED DECEMBER 3, 1953

In recent years several reports have appeared dealing briefly with the addition reactions of amines and 2,4-pentadienenitrile.[1–4] At the time of the appearance of these articles a more comprehensive study of these reactions was in progress in this Laboratory and the results of this work are reported herewith.

The mixture of *cis* and *trans* forms of 2,4-pentadienenitrile obtained by the pyrolysis of the benzoate of crotonaldehyde cyanohydrin, according to the method of Snyder, Stewart and Myers,[5] was used throughout this investigation. It has been reported previously[1,4] that no apparent difference in reactivities was noted when the *cis* and *trans* isomers were carefully separated and used individually with the same amines, and the products obtained were identical.

Aliphatic primary and secondary amines added readily to 2,4-pentadienenitrile at room tempera-

---

[1] M. Frankel, H. S. Mosher and F. C. Whitmore, THIS JOURNAL, **72**, 81 (1950).

[2] S. J. Allen and J. G. Drewitt, U. S. Patent 2,527,510 (Oct. 31, 1950).

[3] P. Kurtz, *Ann.*, **572**, 23 (1951).

[4] Ph.D. Thesis of K. H. Takemura, Univ. of Illinois, 1950 (private communication from Prof. H. R. Snyder).

[5] H. R. Snyder, J. M. Stewart and R. L. Myers, THIS JOURNAL, **71**, 1055 (1949).