[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

The Reaction of Nitroölefins with Indole

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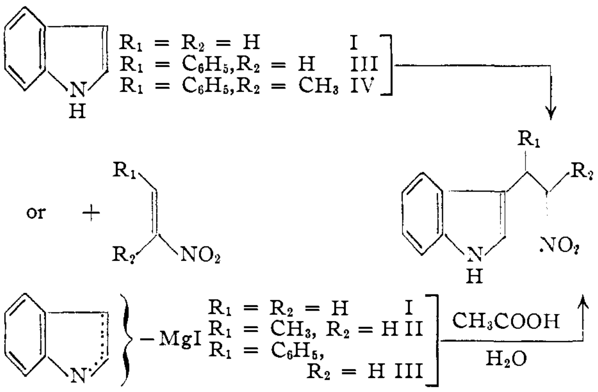
Indole or its Grignard reagent has been found to add to typical nitroölefins containing aliphatic and/or aromatic substituents to give sidechain-substituted 3-(2-nitroethyl)-indoles.

In order to determine the generality of the reaction previously reported[1] between nitroethylene and indole or indolemagnesium iodide, we have carried out corresponding reactions with several typical nitroölefins. Crystalline products were obtained from reactions with 1-nitropropene, β-nitrostyrene and β-methyl-β-nitrostyrene.



The structures of the products are assigned from analogy with the reaction between nitroethylene and indole,[1] as well as from the close similarity of the ultraviolet spectra, characteristic of 3-alkylindoles, with the product of that reaction, 3-(2-nitroethyl)-indole (I) (see Table I). The narrow melting point range (161–162°) of the β-methyl-β-nitrostyrene adduct (IV) suggests that only one of the two possible racemates may have been obtained.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA IN 95% ETHANOL OF 3-(2-NITROETHYL)-INDOLE AND DERIVATIVES

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

Indoles	Wave length, mμ			
3-(2-Nitroethyl)-(I)[a]	220 (4.56)	274 (3.76)	281 (3.79)	290 (3.72)
3-(1-Methyl-2-nitroethyl)-(II)	220 (4.60)	275 (3.80)	281 (3.82)	290 (3.76)
3-(1-Phenyl-2-nitroethyl-(III)	219 (4.61)	273 (3.80)	280 (3.82)	290 (3.75)
3-(1-Phenyl-2-aminoethyl)-(IIIa)	221 (4.56)	274 (3.75)	282 (3.78)	291 (3.72)
3-(1-Phenyl-2-nitropropyl)- (IV)	220 (4.58)	274 (3.80)	281 (3.83)	290 (3.78)

[a] Reference (1).

The reaction with β-nitrostyrene to give III was particularly favorable, proceeding in a yield as high as 78%. It would appear that the increased steric hindrance to bond formation afforded by the phenyl group is more than offset by its favorable electrical effect. As would be expected from both the steric and electrical effects of the methyl group, the yield of IV (16%) from β-methyl-β-nitrostyrene was much lower than that of III (78%) from β-nitrostyrene. The adduct II from 1-nitropropene, however, was obtained in higher yield (37%) than the adduct I (28%) from nitroethylene. Since both the steric and electrical effects of the methyl group of 1-nitropropene should inhibit bond formation with indole, other factors, such as polymerization of the nitroölefin, may also affect the success of the addition reaction.

The reaction between nitroölefins and indole may serve as a route to side-chain substituted tryptamines, as shown by catalytic hydrogenation of the β-nitrostyrene adduct (III) to the corresponding tryptamine, 3-(1-phenyl-2-aminoethyl)-indole (IIIa) in 55% yield. Several attempts to form a β-nitrostyrene derivative from III, analogous to the β-(3-indolemethyl)-β-nitrostyrene[1] from I, resulted only in the recovery of unchanged III, probably because of the additional steric hindrance provided by the phenyl group.

Experimental

All melting points are corrected.

3-(1-Methyl-2-nitroethyl)-indole (II).—Indolemagnesium iodide was prepared by the method of Baker[2] from magnesium turnings (1.15 g., 0.0211 g. atom), ethyl iodide (7.6 g., 0.049 mole) in absolute ethyl ether and indole (5.5 g., 0.047 mole) in absolute ether. 1-Nitropropene[3] (3.9 g., 0.045 mole) in absolute ether was added slowly, with vigorous stirring, to the ice-cold solution of indolemagnesium iodide according to the procedure of Noland and Hartman for the nitroethylene case,[1] with the following observations and modifications. A vigorous reaction ensued and a yellow-orange solid separated. As more 1-nitropropene solution was added, the solid disappeared and a lower, deep red, oily layer separated and persisted during the remainder of the reaction. After acidification with aqueous acetic acid the deep red oil became ether soluble. There was no odor of 1-nitropropene. Chromatography on alumina of the dark red benzene solution of the products gave no distinct yellow band, and evaporation of the benzene eluates gave no indole but tan-colored crystals, m.p. 86–88°. Further elution with 10–20% chloroform–90–80% benzene gave more tan crystals, m.p. 87–88°. Final elution with chloroform yielded darker-colored crystals, m.p. 86–87°. Two recrystallizations of each fraction, with charcoal, from ethanol–water gave a combined yield of 3.4 g. (0.0166 mole, 37%) of white needles, m.p. 90°. Three more recrystallizations from ethanol-water yielded the analytical sample of 3-(1-methyl-2-nitroethyl)-indole, m.p. 90–91°; ν_{NH} (cm.$^{-1}$) 3480 in $CHCl_3$, 3390 in Nujol; ν_{NO_2} (cm.$^{-1}$) 1535 in Nujol, 1382 in $CHCl_3$.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$ (204.22): C, 64.69; H, 5.92; N, 13.72. Found: C, 64.50; H, 5.87; N, 13.70.

When the melting point was determined on a Kofler block, it was observed that only part of the crystals melted at 90–91°, and the remainder dissolved slowly in the melt, disappearing rapidly and completely at 114–116.5°. This suggests another case of dimorphism, similar to that of 3-(2-nitroethyl)-indole.[1]

3-(1-Phenyl-2-nitroethyl)-indole (III). (a) **From β-Nitrostyrene and Indole at Room Temperature** (with Pa-

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(1) W. E. Noland and P. J. Hartman, THIS JOURNAL, **76**, 3227 (1954).

(2) J. W. Baker, *J. Chem. Soc.*, 458 (1940); 461 (1946).

(3) E. Schmidt and G. Rutz, *Ber.*, **61**, 2142 (1928).

tricia A. McVeigh).—β-Nitrostyrene[4] (7.46 g., 0.0500 mole) and indole (5.86 g., 0.0500 mole) were warmed on a steam-bath just long enough to form a clear, homogeneous, orange-red solution. The container was stoppered and set aside for two months. At the end of this period the solution had become a clear, immobile, reddish glass. The glass was dissolved in ethanol by warming on a steam-bath. Hot water was added to the point of incipient cloudiness and the solution was allowed to crystallize. Addition of water to the mother liquor from the first crystallization yielded a small second crop of crystals. The combined crude yield of tan-colored crystals was 10.4 g. (0.0391 mole, 78%). Two or three recrystallizations from ethanol-water yielded 3-(1-phenyl-2-nitroethyl)-indole (8.8 g., 0.033 mole, 66%), m.p. 99–100°.

(b) **From β-Nitrostyrene and Indole at Steam-bath Temperature.**—β-Nitrostyrene (13.9 g., 0.0932 mole) and indole (10.0 g., 0.0854 mole) were heated on a steam-bath for 4.5 hours until the odor of β-nitrostyrene was no longer evident. Crystallization of the reaction solution from ethanol yielded 3-(1-phenyl-2-nitroethyl)-indole (12.3 g., 0.0462 mole, 54%), m.p. 99–100°.

(c) **From β-Nitrostyrene and Indolemagnesium Iodide.**—Indolemagnesium iodide was prepared by the method of Baker[2] from magnesium turnings (1.36 g., 0.0560 g. atom), ethyl iodide (7.78 g., 0.0499 mole) in absolute ethyl ether (20 cc.) and indole (5.85 g., 0.0499 mole) in absolute ethyl ether (35 cc.). A solution of β-nitrostyrene (7.15 g., 0.0479 mole) in absolute ethyl ether (40 cc.) was added slowly, with stirring, to the ice-cooled solution of indolemagnesium iodide. During the addition a yellow-brown, gummy residue formed. The mixture was stirred for one-half hour at room temperature and then treated with a solution of acetic acid (60 cc.) in water (200 cc.). The aqueous and ethereal layers were separated. The aqueous layer was neutralized with sodium carbonate and then extracted three times with ether. The ethereal layer was washed with aqueous sodium carbonate solution until the evolution of carbon dioxide ceased. The ethereal layer was then combined with the ether extracts and the combined solution dried over calcium chloride. The ether solvent was replaced by ethanol and the solution treated with decolorizing charcoal. The solution was concentrated by vacuum distillation and allowed to crystallize at −10°. The crude product was recrystallized twice from ethanol-water, yielding white, rod-like crystals of 3-(1-phenyl-2-nitroethyl)-indole (5.0 g., 0.0188 mole, 39%), m.p. 99–100°; ν_{NH} (cm.$^{-1}$) 3480 in $CHCl_3$, 3380 in Nujol; ν_{NO_2} (cm.$^{-1}$) 1532 in Nujol, 1380 in $CHCl_3$.

Anal. Calcd. for $C_{16}H_{14}N_2O_2$ (266.29): C, 72.16; H, 5.30; N, 10.52. Found: C, 72.23; H, 5.29; N, 10.29.

3-(1-Phenyl-2-aminoethyl)-indole (IIIa).—3-(1-Phenyl-2-nitroethyl)-indole (5.7 g., 0.0214 mole) in absolute ethanol (60 cc.) and platinic oxide (0.100 g.) were treated with hydrogen at 36 p.s.i. in a Parr low pressure hydrogenation apparatus for ten hours. The catalyst was filtered off and the filtrate concentrated by vacuum distillation. The solution slowly turned deep brown in contact with air. Since cooling produced no crystals, the ethanol solvent was replaced by benzene, from which the product readily crystallized. Recrystallization yielded white 3-(1-phenyl-2-aminoethyl)-indole (2.8 g., 0.0118 mole, 55%), m.p. 130.5–131.5°; ν_{NH} (cm.$^{-1}$) 3510, 3400 in $CHCl_3$.

Anal. Calcd. for $C_{16}H_{16}N_2$ (236.30): C, 81.32; H, 6.83; N, 11.86. Found: C, 81.47, 81.59; H, 7.08, 6.95; N, 11.69.

3-(1-Phenyl-2-nitropropyl)-indole (IV).—β-Methyl-β-nitrostyrene[5,6] (5.33 g., 0.0327 mole) and indole (3.83 g., 0.0327 mole) were warmed on a steam-bath until a clear, orange-red solution was formed. The flask was stoppered and set aside for 70 days. The dark solution was treated with absolute ethanol and, after being allowed to evaporate overnight, deposited pink crystals (0.14 g.), m.p. 159–160°. Three more crops of crystals were increasingly impure. Recrystallization from ethanol-water, with charcoal, yielded a total of 1.53 g. (0.00546 mole, 16%), m.p. 159–161°. The analytical sample of 3-(1-phenyl-2-nitropropyl)-indole melted at 161–162°; ν_{NH} (cm.$^{-1}$) 3480 in $CHCl_3$, 3440 in CS_2, 3420 in Nujol; ν_{NO_2} (cm.$^{-1}$) 1557 or 1540 in Nujol, 1391 or 1362 in $CHCl_3$.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$ (280.31): C, 72.84; H, 5.75; N, 9.99. Found: C, 72.84, 73.07; H, 5.75, 6.06; N, 9.59, 9.98.

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[4] D. E. Worrall in "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 413.

(5) E. Knoevenagel and L. Walter, *Ber.*, **37**, 4502 (1904).

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

[CONTRIBUTION FROM THE MOORE LABORATORY OF CHEMISTRY, AMHERST COLLEGE]

7-Azaindole. I. Synthesis and Conversion to 7-Azatryptophan and Other Derivatives

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7-Azaindole (II) has been prepared in yields as high as 51% by the Madelung cyclization of 2-formamido-3-picoline (I) in the presence of sodium anilide and potassium formate. The indole was converted to 7-azagramine (III) which was used to alkylate acetamidomalonic ester. The product (IV) was converted to 7-azatryptophan (V) by hydrolysis and decarboxylation. That the side-chain was attached at the 3-position was shown by conversion of the intermediate gramine to 3-methyl-7-azaindole (VIII) which was prepared for comparison by cyclization of 2-formamido-3-ethylpyridine (XI). Several new derivatives of 3-ethylpyridine also are described.

7-Azaindole (II, 1-pyrrolo[2,3-b]pyridine) was obtained first from coal tar by Kruber,[1] who prepared derivatives and obtained evidence for the constitution of the compound by oxidation of its benzenesulfonamide to 2-benzenesulfonamidonicotinic acid and conversion of the latter to the known 2-aminonicotinic acid. The structure was confirmed later by the work of Clemo and Swan[2] who synthesized the substance in 3% yield by cyclization of 2-formamido-3-picoline in the presence of sodium ethoxide. These workers also prepared 2-methyl- and 2-ethyl-7-azaindole from the acetyl and propionyl derivatives of 2-amino-3-picoline. Miescher and Kägi[3,4] earlier prepared 7-azaoxindole and other compounds in which the pyrrole ring is partially oxidized, and Sucharda[5] synthesized several of the corresponding indoxyl compounds. Very little work has been reported, however, on the chemistry of 7-azaindole itself.

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(1) O. Kruber, *Ber.*, **76**, 128 (1943).

(2) G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 603 (1945).

(3) K. Miescher and H. Kägi, *Helv. Chim. Acta*, **24**, 1471 (1941).

(4) H. Kägi, *ibid.*, **24**, 141E (1941).

(5) E. Sucharda, *Roczniki Chem.*, **3**, 236 (1923); *C. A.*, **19**, 72 (1925).