190–191°), and 0.282 g. (7.5%) of 1-phenylpropane-1,2-dione 2,4-dinitrophenylosazone,[35] m.p. 263–264°.

Anal. Calcd. for $C_{21}H_{16}N_8O_8$: C, 49.6; H, 3.2; N, 22.0 Found: C, 49.4; H, 3.1; N, 21.9.

Propiophenone, when treated with mercuric sulfate and sulfuric acid in the presence of excess DNPH reagent, yielded 81% of the normal derivative and 12% of the osazone. After similar treatment, 1-phenyl-2-propanone yielded 89% of the osazone and none of the normal derivative, while 1-phenylpropyne yielded 74% of propiophenone 2,4-dinitrophenylhydrazone and 11% of the osazone.

When 1.54 g. of oil G was chromatographed on silicic acid and developed with Skellysolve B, four fractions were obtained: the first fraction, H (0.521 g.), was shown by infrared spectrum to be solely hydrocarbon. The second fraction was treated with DNPH reagent to yield 0.579 g. (7.8%) of the acetophenone derivative, m.p. 248–249°. The third fraction was 0.525 g. (12.8%) of additional IX. The fourth fraction was 0.211 g. of tar.

When 0.403 g. of H was ozonized[19a,b] and worked up as previously described, 0.606 g. (10.5%) of the acetophenone 2,4-dinitrophenylhydrazone, m.p. 248–249°, was obtained. When a portion of H was treated with DNPH reagent before ozonolysis, no carbonyl derivative was obtained.

Pyrolysis of 3-Nitroso-1-oxa-3-azaspiro[4.5]decan-2-one (III).—In a dried flask connected to a gas collecting device, 8.20 g. of III was decomposed at 185° in the manner previously described. The decomposition was moderate initially but became violent as the reaction proceeded. Gas evolution ceased after 40 minutes: the dry gas collected (963 ml., S.T.P.) represented 0.965 mole per mole of III. As in the case of the pyrolysis of I, no carbon monoxide was detected.

After cooling, the brown-black, tarry mass was made up to 10 ml. with chloroform to give solution J. When 5 ml. of J was treated with excess DNPH reagent, no derivative was obtained. When 5 ml. of J was chromatographed on a column packed with alumina and developed with 10% ether in Skellysolve B, two fractions were obtained. One fraction, a tar, remained on the column. The other fraction, concentrated and cooled, yielded 1.96 g. (56.8%) of 1-oxa-3-azaspiro[4.5]decan-2-one (X), m.p. 101–102° (reported[6a] m.p. 101.0–102.4°).

Pyrolyses of Nitroso Compounds I, II and III in the Presence of Solvents.—A typical reaction is described: a 25 × 200 mm. test-tube, which contained the nitroso compound (3.5–5.0 g.) and redistilled solvent (15–25 g.), was provided with an air condenser and maintained at 153 or 168° for 2 hr. or at 185° for 40 minutes.

Recovery of Decomposition Products. A. Nitroso Compound I.—After cooling, solid oxazolidone V was removed by filtration and the solvent carefully removed by distillation to yield an oil. Benzophenone was determined as the 2,4-dinitrophenylhydrazone and diphenylacetylene as desoxybenzoin 2,4-dinitrophenylhydrazone. When the solvent was adsorbed strongly enough on alumina so that the diphenylacetylene-1,1-diphenylethylene mixture could be selectively removed, multicomponent ultraviolet spectrophotometric analysis was used. The results are listed in Table II.

B. Nitroso Compounds II and III.—The recovery of the decomposition products was carried out as was previously described for II and III at 185°. In some cases in the decomposition of nitroso compound III, treatment of an aliquot of the reaction mixture with DNPH reagent yielded the cyclohexanone derivative, m.p. 161–162° (reported[36] m.p. 162°).

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(35) 1-Phenylpropane-1,2-dione was prepared according to J. Wegmann and H. Dann, *Helv. Chim. Acta*, **29**, 1248 (1946).

(36) Reference 15, p. 262.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

The Reaction of Substituted Indoles with Methyl Vinyl Ketone. New Synthesis of 2-Methylcarbazole

BY J. SZMUSZKOVICZ

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The reactions of indole, 2-methylindole and skatole with methyl vinyl ketone were investigated and the products characterized.

There are a number of examples in the literature which illustrate the behavior of the indole nucleus toward electrophilic components in the Michael-type reaction.

In the case of C_3-unsubstituted indoles, *under acidic conditions*, the negatively polarized C_3 undergoes reaction, *e.g.*, with acetamidoacrylic acid in acetic acid solution containing acetic anhydride,[1] with nitroethylene in benzene solution,[2] with propiolactone in the absence of solvent,[3] with diketene in the absence of solvent[4] and with acrylonitrile in acetic acid solution in the presence of copper borate.[5]

On the other hand, *the base-catalyzed* Michael-type reaction occurs at the 1-position. Thus, in a benzene solution containing potassium hydroxide, indole and acrylonitrile react to give 1-(β-cyano)-ethylindole,[6] 2-phenylindole reacts with acrylonitrile in the presence of trimethylbenzylammonium hydroxide to give 1-(β-cyano)-ethyl-2-phenylindole,[7] indole and methacrylonitrile in ethanolic sodium ethoxide solution gives rise to 1-(β-cyano-β-methyl)-ethylindole,[8] ethyl α-(3-indolyl)-isobutyrate afforded 1-(β-carboxypropyl)-3-indoleisobutyric acid on reaction with methacrylonitrile in ethanolic sodium methoxide and subsequent hydrolysis,[8] 2,3-dimethylindole reacts with acrylonitrile and sodium methoxide to give 1-(β-cyano)-ethyl-2,3-dimethylindole[9]; in some cases 1,3-dicyanoethylindoles are obtained as by-products

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(1) H. R. Snyder and J. A. MacDonald, THIS JOURNAL, **77**, 1257 (1955).

(2) W. E. Noland and P. J. Hartmann, *ibid.*, **76**, 3227 (1954).

(3) J. Harley-Mason, *J. Chem. Soc.*, 2433 (1952).

(4) J. Harley-Mason, *Chemistry & Industry*, 886 (1951).

(5) W. Reppe and H. Ufer, German Patent 698,273 [*Frdl.*, **25**, 173 (1938)].

(6) A. P. Terentyev, A. N. Kost and V. A. Smit, *J. Gen. Chem. (USSR)* in English translation, **25**, 1905 (1955).

(7) R. C. Blume and H. G. Lindwall, *J. Org. Chem.*, **10**, 255 (1945).

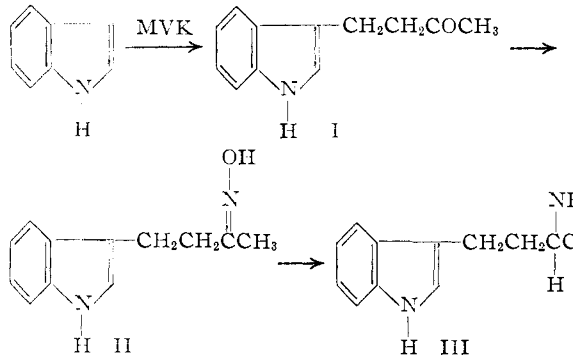
(8) H. Erdtmann and Ä. Jörnson, *Acta Chem. Scand.*, **8**, 119 (1954).

(9) C. Y. Almond and F. G. Mann. *J. Chem. Soc.*, 1870 (1952).

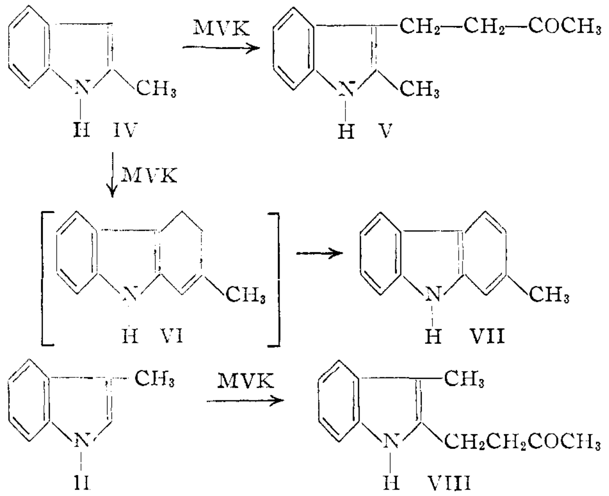
from the reaction of 2-substituted indoles with acrylonitrile.[10,11]

It has now been found that indole reacts with methyl vinyl ketone (MVK) in acetic acid medium with or without anhydride to give 75 and 69% yield, respectively, of 1-(3′-indolyl)-butanone-3 (I). The reaction also proceeds in the absence of solvent to give I in 22% yield.

Compound I was converted in a quantitative yield to a mixture of isomeric oximes (II) which was reduced with lithium aluminum hydride to 3-(3′-indolyl)-1-methylpropylamine (III), characterized as the creatinine sulfate complex.



Holland and Nayler[12] prepared I by treatment of gramine methosulfate with ethyl sodioacetoacetate in ethanol, the product subsequently being hydrolyzed with sodium hydroxide.



2-Methylindole (IV) reacted with MVK at 160° (5 hr. reaction time) in the absence of solvent to give a 28.6% yield of 1-[3′-(2′-methyl)-indolyl)]-butanone-3 (V). In acetic acid solution containing acetic anhydride the yield advanced to 84%. When hydroquinone was added to the two reactants and the temperature raised to 280°, 2-methylcarbazole (VII)[13] was isolated in 10% yield.[14] The reaction probably proceeded through an intermediate (VI) which was not isolated.

Skatole did not react with MVK in the absence of solvent even on prolonged heating (19 hr.). On the other hand, in acetic acid solution containing *acetic anhydride*[15,16] a moderate yield of 1-[2′-(3′-methyl)-indolyl]-butanone-3 (VIII) was obtained. When the reaction was conducted in acetic acid alone, the product VIII could not be isolated.

Experimental[17,18]

Preparation of 1-(3′-Indolyl)-butanone-3 (I).—Indole (2.34 g., 0.02 mole) was dissolved in glacial acetic acid (12 ml.), 4 ml. of acetic anhydride was added, then 4.2 g. (0.06 mole) of commercial methyl vinyl ketone. The solution was allowed to stand at room temperature for 5 minutes and then heated on the steam-bath (condenser, Drierite tube) for 25 minutes. The initial yellow solution turned dark brown. It was cooled in ice, 100 ml. of water was added and, after standing for a few minutes, the precipitate was filtered and washed with water. The crude product was recrystallized from benzene–petroleum ether (30–60°) as pale yellow needles, m.p. 93–94°, yield 2.8 g. (75%).

Anal. Calcd. for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N, 7.48. Found: C, 77.25; H, 7.13; N, 7.43.

Infrared spectrum: NH (3305 cm.$^{-1}$), C=O (1699), C=C (1621, 1572, 1555, 1492), *o*-disubstituted benzene (734, 725). **Ultraviolet spectrum:** λ_{max} 223 mμ (36,675), 275 (5,475), 283 (5,900), 291.5 (5,050).

When acetic anhydride was omitted[15] from the above procedure, the product I was obtained in 69.6% yield (m.p. 93–94°).

Preparation of the Oxime II.—One gram of I was dissolved in 10 ml. of 95% ethanol by warming. A solution of 2 g. of hydroxylamine hydrochloride and 3 g. of anhydrous sodium acetate in 10 ml. of water was added and the resulting solution refluxed for 15 minutes. It was then allowed to stand at room temperature for 45 hr., diluted with water and induced to crystallize by scratching. After cooling in ice for 1 hr., the crystals were filtered and washed with water; m.p. 89–115° (97% yield). Recrystallization from benzene–petroleum ether (30–60°) gave clusters, m.p. 89–111°.

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.34; H, 7.14; N, 13.58.

Lithium Aluminum Hydride Reduction of the Oxime II. Synthesis of III.—A solution of II (0.9 g.) in 10 ml. of anhydrous ether was added dropwise with ice-cooling and swirling to a solution of 1.2 g. of lithium aluminum hydride in 70 ml. of ether. The resulting mixture was refluxed for 2 hr. and then allowed to stand overnight at room tempera-

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[10] N. Roh and W. Wolff, German Patent 641,597 [*Frdl.*, **23**, 152 (1936)]; *C. A.*, **32**, 4602 (1938).

[11] The more drastic conditions used in these base-catalyzed Michael-type reactions suggest that thermodynamic control of products applies and that the 1-substituted product is the more thermodynamically stable isomer under the conditions of its formation. The milder acid conditions might favor kinetic control of products which result in 3-substitution. A test of this idea would involve submitting the adduct to the conditions under which the 1-adduct is prepared to see if 3-adduct yields 1-adduct [see also I. M. Bassett, R. D. Brown and A. Penfold in *Chemistry & Industry*, 892 (1956)].

[12] D. O. Holland and J. H. Nayler, *J. Chem. Soc.*, 280 (1953).

[13] For a review of carbazole syntheses see R. C. Elderfield, "Heterocyclic Compounds," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 296.

[14] This yield very likely could be improved on further experimentation.

[15] It is interesting that acetic anhydride seems to be essential for the reaction of skatole with MVK, especially in view of a similar observation of Snyder and MacDonald[1] in the case of indole and α-acetamidoacrylic acid.

[16] The crude product showed a weak band in the infrared at 1747 cm.$^{-1}$ and a strong band at 1662 cm.$^{-1}$. The 1747 cm.$^{-1}$ band could be eliminated by mild alkaline treatment (see Experimental). The 1662 cm.$^{-1}$ band persisted after this alkaline treatment and may be due to either the N-acetyl compound being present or, less likely, to the amidic character of the carbonyl imposed by interaction with the indolic nitrogen.

[17] All melting points are uncorrected. Ultraviolet spectra were determined in 95% ethanol using Cary spectrophotometers, models 11 and 14. Infrared spectra were determined in Nujol (except when otherwise specified) using a Perkin-Elmer recording infrared spectrophotometer, model 21.

[18] The author is indebted to Prof. D. J. Cram for an interesting discussion, to Dr. J. L. Johnson and his staff for spectral data, to Mr. W. A. Struck and his associates for microanalyses, and to Mr. L. G. Laurian for laboratory assistance.

ture. Water was added, cautiously at first, then excess of 10% potassium hydroxide solution, and the mixture was extracted four times with ether. The ethereal extracts were washed once with water and then extracted three times with 10% hydrochloric acid. The acidic solution was reëxtracted with ether and then basified with excess potassium hydroxide. The resulting oily mixture was extracted three times with ether, washed twice with saturated salt solution, dried over sodium sulfate and evaporated to give 0.8 g. (95% yield) of pale yellow oil which could not be crystallized.

The amine (0.253 g.) was dissolved in 1.45 ml. of 1 *N* sulfuric acid and 4 cc. of water by gentle warming, the solution was filtered and 0.210 g. of creatinine sulfate was added. The solution was warmed to *ca.* 60° and 45 ml. of acetone was added. After 2 hr., the crystalline precipitate was filtered and washed with acetone–water (6:1); yield 0.436 g. (80%), m.p. 150–153°. The complex was recrystallized by dissolving in 4 ml. of warm water and adding 50 ml. of acetone. The needles were filtered, washed with cold acetone–water solution (4:1), then acetone and finally ether; m.p. 153–156° (completely clear at 160°).

Anal. Calcd. for $C_{16}H_{25}N_5O_5S + 1.5H_2O$: C, 45.06; H, 6.77; N, 16.42; S, 7.52. Found: C, 44.90; H, 6.73; N, 16.16; S, 8.26.

Synthesis of 2-Methylcarbazole (VII).—A mixture of 2-methylindole (6.6 g., 0.05 mole), MVK (4.2 g., 0.06 mole) and 0.3 g. of hydroquinone was heated for 1.5 hr. (outside bath temperature 155–160°). The temperature was then raised to 280–290° and maintained for 20.5 hr. The resulting reaction mixture crystallized within 1 hr. on standing at room temperature. On treatment with 20 ml. of benzene a slightly oily material was obtained which was recrystallized from the same volume of benzene to give 0.6 g. of plates melting at 261.5–262.5°.[19]

Anal. Calcd. for $C_{13}H_{11}N$: C, 86.15; H, 6.12; N, 7.73. Found: C, 86.33; H, 6.20; N, 7.66.

Infrared spectrum: NH (3400), C=C (1627, 1608, 1486), *o*-disubstituted and trisubstituted benzene (806, 763, 744, 725). **Ultraviolet spectrum**: flex. 230 mμ, λ_{max} 235.5 (48,270), flex. 246, λ_{max} 259.5 (19,225), flex. 286, λ_{max} 297.5 (17,200), 323 (3,900), 335 (2,900).

The second crop amounted to 0.140 g. (m.p. 261–262°). The combined filtrates and washings were evaporated to dryness and the residual dark oil was distilled from an oil-jacketed flask at 0.1 mm. The first fraction, b.p. 120–160° (3.46 g.), was discarded. The second fraction, b.p. 180–270° (3.26 g.), solidified overnight and was crystallized from 5 ml. of benzene and 9 ml. of petroleum ether (30–60°) with seeding to give a third crop of VII (0.2 g., m.p. 252–255°). The fourth crop amounted to 14 mg. (m.p. 237–242°). The total yield of VII was 10.5% (0.954 g.). The picrate was formed in ethanol as orange-red needles, m.p. 168° (lit.[19] m.p. 168°).

Synthesis of 1-[3′-(2′-Methyl)-indolyl]-butanone-3 (V).—A mixture of 2-methylindole (13.1 g., 0.1 mole) and MVK (8.4 g., 0.12 mole) was heated under nitrogen at 155–162° for 5 hr. The resulting oil was allowed to stand overnight at room temperature. It was then distilled from an oil-jacketed flask at 0.05 mm. to give: (1) 5.97 g. of unchanged 2-methylindole, b.p. 120–160° (mainly 135–140°); (2) 10.82 g. of viscous yellow oil, b.p. 160–190°.

Fraction 2 was redistilled carefully at 0.05 mm. and material boiling at 180–190° was collected; 5.76 g. (28.6% yield), $n^{27.5}D$ 1.5833. The analytical sample showed b.p. 185°, $n^{27.5}D$ 1.5835.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.74; H, 7.59; N, 6.70.

Infrared spectrum: NH (3340), C=O (1698), C=C (1617, 1582, 1565, 1487), *o*-disubstituted benzene (740). Quantitative infrared comparison with I in the NH region indicated the presence of 92.9% of NH absorption.

The trinitrofluorenone derivative was formed in acetic acid–ethanol as black plates, m.p. 139–142°.

Anal. Calcd. for $C_{26}H_{40}N_4O_8$: C, 60.46; H, 3.90; N, 10.85. Found: C, 60.11; H, 3.98; N, 10.87.

When the reaction was run in acetic acid containing acetic anhydride (as described above) and the product extracted with ether, washed and distilled, an 84.6% yield of a yellow oil was obtained, b.p. 170–195° (0.05 mm.).

Infrared spectrum: NH (3400), C=O (1710), extraneous band at 1676 (probably due to N-acetyl impurity), C=C (1636, 1607, 1593, 1571, 1561, 1536, 1480), *o*-disubstituted benzene (746).

Synthesis of 1-[2′-(3-Methyl)-indolyl]-butanone-3 (VIII).—A solution of skatole (10 g., 0.0765 mole), MVK (16.2 g., 0.232 mole), 46 ml. of acetic acid and 15.5 ml. of acetic anhydride was heated on the steam-bath for 25 minutes. The resulting dark green solution was cooled to room temperature, 400 ml. of water was added and the heating continued on the steam-bath for 2 hr. The cooled mixture was extracted with ether (4 × 150 ml.). The ethereal extracts were washed once with water, twice with saturated salt solution and dried over sodium sulfate. The product (brown oil, 12.52 g.) was distilled from an oil-jacketed flask to give: (1) 4.12 g. of recovered skatole, b.p. 120–135° (0.1 mm.); and (2) 4.72 g. of an oil boiling at 170–210° (0.1 mm.). Redistillation of fraction 2 afforded 2.76 g. of material which was collected at 170–190° (0.05 mm.), $n^{25}D$ 1.5835.

Infrared spectrum: NH (3380), weak band at 1747, C=O (1702), strong band at 1662, C=C (1600, 1537, 1477), *o*-disubstituted benzene (757).

The product (0.641 g.) was dissolved in 10 ml. of methanol, a solution of 1.0 g. of potassium hydroxide in 10 ml. of water was added and the solution heated on the steam-bath for 5 minutes. It was then cooled and extracted with ether (4 × 30 ml.). The ethereal extracts were washed twice with saturated salt solution, dried over sodium sulfate and evaporated. The resulting oil (0.4868 g.) was distilled from an oil-jacketed flask; b.p. 170–175° (0.05 mm.), 0.3296 g.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 76.81; H, 7.49; N, 5.98.

Infrared spectrum: essentially the same as above, but the band at 1747 no longer was present.

Apparently this product represents a mixture of the desired material VIII and the corresponding N-acetyl derivative. Quantitative infrared comparison with I in the NH region indicated 21.5% NH absorption.

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[19] G. R. Clemo and D. G. I. Felton, *J. Chem. Soc.*, 700 (1951); B. M. Barclay and N. Campbell, *ibid.*, 530 (1951); W. Borsche, A. Witte and W. Bothe, *Ann.*, **359**, 52 (1908).