INDOLE DERIVATIVES

V*. SKATYLIDENEACETONE IN THE MICHAEL REACTION

A. A. Semenov, K. I. Kuchkova, and
E. P. Styngach

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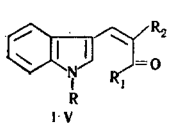
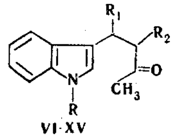
The reactions of indolecarbaldehyde and N-benzylindolecarbaldehyde with acetone have given skatylideneacetone and its N-benzyl and N-acetyl derivatives. The behavior of these substances under the conditions of the Michael reaction has been studied.

In order to investigate synthetic routes to 1-(indol-3'-yl)butan-3-one derivatives bearing functional substituents in position 1, we have studied the reactions of skatylideneacetone (I) and its analogs with various reagents typical for the Michael reaction. Compound I was obtained by the crotonic condensation of indolecarbaldehyde with acetone under the action of concentrated caustic potash solution. When acetophenone was used, compound II, described previously [2], was obtained. Similarly, acetone and N-benzylindolecarbaldehyde gave N-benzylskatylideneacetone (IV). Another method was also tested for the synthesis of I. Under the conditions of the Knoevenagel reaction, N-acetylindolecarbaldehyde reacted with tert-butyl acetoacetate with the formation of III; however, attempts to eliminate the butoxycarbonyl group by pyrolysis proved unsuccessful.

Compound I takes part in the Michael reaction with very great difficulty. A satisfactory result was obtained only in the reaction with potassium cyanide. The nitrile VI so formed can easily be saponified to the acid VII. In contrast to I, its N-benzyl derivative IV acts as an active acceptor in the Michael reaction and readily adds HCN, nitrobutane, and malonic esters, forming the corresponding adducts VIII, IX, and X. Compound X was saponified to the diacid XI, which, after decarboxylation and esterification gave the oxo ester XI, isolated in the form of the oxime.



I-V



VI-XV

I $R=R_2=H$, $R_1=CH_3$; II $R=R_2=H$, $R_1=C_6H_5$; III $R=H$, $R_1=CH_3$, $R_2=CO_2C(CH_3)_3$; IV $R=CH_2C_6H_5$, $R_1=CH_3$, $R_2=H$; V $R=COCH_3$, $R_1=CH_3$, $R_2=H$; VI $R=R_2=H$, $R_1=CN$; VII $R=R_2=H$, $R_1=CO_2H$; VIII $R=CH_2C_6H_5$, $R_1=CN$, $R_2=H$; IX $R=CH_2C_6H_5$, $R_1=C_3H_7CH-NO_2$, $R_2=H$; X $R_2=H$, $R=CH_2C_6H_5$, $R_1=CH(CO_2C_2H_5)_2$; XI $R=CH_2C_6H_5$, $R_2=H$, $R_1=CH(CO_2H)_2$; XII $R=CH_2C_6H_5$, $R_1=CH_2CO_2CH_3$, $R_2=H$; XIII $R=COCH_3$, $R_1=CH(CO_2C_2H_5)_2$, $R_2=H$; XIV $R=R_2=H$, $R_1=CH_2CO_2C_2H_5$; XV $R=COCH_3$, $R_1=CH_2NO_2$, $R_2=CO_2C(CH_3)_3$

To obtain compounds not substituted on the indole nitrogen, we used the acetyl derivative of the skatylideneacetone V, which was obtained from I by acetylation with acetic anhydride. Compound V reacts smoothly with diethyl malonate to form the oxo ester XIII. Compound XIV was obtained from XIII by selective saponification and the elimination of the carboxy group formed by heating in pyridine. In the reactions of I, III, IV, and V with nitromethane, no individual products were isolated. Consequently we tried another method for the synthesis of the corresponding nitro derivative. N-Acetyl-3-(2'-nitrovinyl)indole was caused to react with tert-butyl acetoacetate, which led to the formation of the expected product XV. Unfortunately, all efforts to decarboxylate it proved unsuccessful.

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*For Communication IV, see [1].

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EXPERIMENTAL

All the melting points were determined on a Kofflerblock and are uncorrected. The infrared spectra were taken in KBr tablets on a UR-10 instrument and the ultraviolet spectra in ethanol on an SF-4 spectrophotometer.

4-(Indol-3'-yl)but-3-en-2-one (I). With stirring and ice-water cooling, 207 ml of a 60% aqueous solution of KOH was slowly added to a suspension of 30 g (0.21 mole) of indolecarbaldehyde in 172 ml of methanol and 76 ml (1.05 mole) of acetone. The mixture was left at room temperature for 120 hr, and was then poured into water, acidified with the calculated amount of acetic acid, and extracted with ether. The residue, after drying and distillation of the solvent, was crystallized from a mixture of ethanol and trichloroethylene. Yield 20.71 g (54.3 %). A sample for analysis was chromatographed on alumina and recrystallized from a mixture of the same solvents. Yellow crystals with mp 141-142°C. Found, %: C 78.1; H 6.2; N 7.4. Calculated for $C_{12}H_{11}NO$, %: C 77.8; H 6.0; N 7.6. IR spectrum, cm^{-1}: 770; 1615 (C ═C); 1660 (C = O); 3170 (N – H). UV spectrum, λ_{max}, nm (log ε); 221 (4.54); 275 (4.23); 352 (4.65).

1-Phenyl-3-(indol-3'-yl)prop-2-en-1-one (II). A mixture of 20 g (0.14 mole) of indolecarbaldehyde, 16.5 g (0.14 mole) of acetophenone, and 60 ml of ethanol was treated with 60 ml of 60 % KOH solution, as in the preparation of I. Yield 62 %. mp 165-167°C (from ethanol). Found, %: C 82.8; H 5.3; N 5.7. Calculated for $C_{17}H_{13}NO$, %: C 82.6; H 5.3; N 5.7. IR spectrum cm^{-1}: 770; 1600 (C═C); 1650 (C = O); 3430 (N–H). According to the literature [2], mp 166-167°C.

4-(1'-Benzylindol-3'-yl)but-3-en-2-one (IV). This was obtained in a similar manner to I from N-benzylindolecarbaldehyde [3] and acetone with a reaction time of 24 hr. Yield 90 %. mp 135-137°C (from isopropanol). Found, %: C 82.7; H 6.3; N 5.1. Calculated for $C_{19}H_{17}NO$, %: C 82.9; H 6.2; N 5.1. IR spectrum cm^{-1}: 750,770; 1590 (C═C); 1675 (C = O).

3-tert-Butoxycarbonyl-1-(indol-3'-yl)but-3-en-2-one (III). With cooling and stirring, 0.45 ml of piperidine was added to 0.6 g (3.2 mmoles) of N-acetylindolecarbaldehyde and 0.62 g (3.55 mmoles) of tert-butyl acetoacetate in 6 ml of anhydrous methanol. After 20 hr of continuous stirring at room temperature, the mixture was poured into water containing acetic acid and extracted with ethyl acetate. The oily residue after the elimination of the solvent solidified on trituration with ether. The compound was purified by recrystallization first from trichloroethylene and then from ethanol. mp 132-133°C. Found, %: C 71.6; H 6.8; N 4.9. Calculated for $C_{17}H_{19}NO_3$, %: C 71.6; H 6.7; N 4.9. IR spectrum cm^{-1}: 775; 1610 (C═C); 1650 (C = O); 1715 (COOt-Bu); 3350 (N–H).

4-(1'-Acetylindol-3'-yl)but-3-en-2-one (V). A mixture of 0.5 g (2.7 mmoles) of I, 1.37 g (13.4 mmoles) of acetic anhydride, and 0.6 g (7.3 mmoles) of anhydrous sodium acetate was heated at 97-104°C for 5 hr, poured into 10 ml of water, and left overnight. The crystals that had deposited were filtered off, washed with water, and recrystallized from methanol. Yield 75%. mp 121-122°C. Found, %: C 74.0; H 5.8; N 6.2. Calculated for $C_{14}H_{13}NO_2$, %: C 74.0; H 5.8; N 6.2. IR spectrum, cm^{-1}: 780; 1610 and 1630 (C═C); 1690 and 1715 (C = O) (mixture of cis and trans isomers); 1665 (C = O, amide).

4-Cyano-4-(indol-3'-yl)butan-2-one (VI). A mixture of 1.48 g (7 mmoles) of I, 1.04 g (16 mmoles) of potassium cyanide, 16 ml of dimethylformamide, and 10 ml of water was heated in the boiling water bath for 2 hr 30 min. The hot solution was poured into water, acidified with acetic acid, and extracted with ether. The residue after the distillation of the solvent was crystallized from ethanol. Yield 0.95 g (56 %). Colorless crystals with mp 138-139°C. Found, %: C 73.6; H 5.6; N 13.0. Calculated for $C_{13}H_{12}N_2O$, %: C 73.6; H 5.7; N 13.2. IR spectrum, cm^{-1}: 780; 1710 (C = O); 2260 (CN); 3330 (NH). UV spectrum, λ_{max}, nm (log ε): 218 (4.52); 270 (3.80) (inflection); 280 (3.83); 290 (3.70) (inflection); 315 (2.60).

4-(1'-Benzylindol-3'-yl)-4-cyanobutan-2-one (VIII). The crude product, obtained in a similar manner to VI from 2.9 g of IV and KCN, was chromatographed on alumina of activity grade 3. A mixture of benzene and petroleum ether (4 : 1) eluted 1.2 g (38 %) of the cyano ketone VIII in the form of an oil. IR spectrum, cm^{-1}: 770; 780; 1720 (C = O); 2270 (CN). Thiosemicarbazone, mp 94-96°C (from ethanol). Found, %: C 66.9; H 5.8; N 18.7; S 8.2. Calculated for $C_{21}H_{21}N_5S$, %: C 67.2; H 5.6; N 18.7; S. 8.5.

4-Carboxy-1-(indol-3'-yl)butan-2-one (VII). A mixture of 3.87 g of VI, 68 ml of ethanol, and 19.4 ml of 25% aqueous NaOH was boiled for 2 hr. The ethanol was distilled off in vacuum and the residue was diluted with water and filtered. The filtrate was acidified with oxalic acid and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated to a volume of 5-10 ml. On standing, 3.15 g

(74.8%) of colorless crystals of VII deposited. mp 167-168°C (from isopropanol). Found, %: C 67.6; H 5.7; N 5.8. Calculated for $C_{13}H_{13}NO_3$, %: C 67.5; H 5.7; N 6.1. IR spectrum, cm^{-1}: 775; 1265; 1420; 1695; 3000-3100 (COOH); 1710 (C = O); 3300-3380 (NH).

4-(1'-Benzylindol-3'-yl)-5-nitrooctan-2-one (IX). To a solution of 0.36 g (0.016 g-at) of sodium in 165 ml of anhydrous methanol were added 16.5 g (0.06 mole) of IV and 18.8 g (0.18 mole) of nitrobutane, and the mixture was boiled for 20 hr. The yellow solution was poured into water, neutralized with acetic acid, and extracted with ether. The crude product obtained after the distillation of the solvent was chromatographed on alumina. A mixture of petroleum ether and benzene (7 : 3) eluted 9.2 (40 %) of the nitro ketone IX. mp 88-90°C (from isopropanol). Found, %: C 73.0; H 6.7; N 7.2. Calculated for $C_{23}H_{26}N_2O_3$, %: C 73.0; H 6.9; N 7.4. IR spectrum, cm^{-1}: 765; 770; 1360; 1550 (NO_2); 1720 (C = O).

Ethyl 3-(1'-Benzylindol-3'-yl)-2-ethoxycarbonyl-5-oxohexanoate (X). A solution of 2.32 g (0.11 g-at) of sodium in 139 ml (0.91 mole) of malonic ester was treated with 27.7 g (0.11 mole) of IV and the suspension was stirred at room temperature for 24 hr. Then the resulting solution was diluted with water, acidified with acetic acid, and extracted with ether. The extract was washed with water and sodium bicarbonate solution and was dried with Na_2SO_4. The solvent and the excess of malonic ester were distilled off in vacuum. The residue was twice recrystallized from isopropanol. This gave 35.5 g (81 %) of colorless crystals with mp 70-71°C. Found, %: C 71.7; H 6.6; N 3.2. Calculated for $C_{26}H_{29}NO_5$, %: C 71.7; H 6.7; N 3.2. IR spectrum, cm^{-1}: 760, 770; 1710 (C = O); 1730 ($COOC_2H_5$).

Ethyl 3-(1'-Acetylindol-3'-yl)-2-ethoxycarbonyl-5-oxohexanoate (XIII). This was obtained in a similar manner to X from V and sodiomalonic ester with a reaction time of 8 hr. Yield 65.4 %. mp 102-103°C (from ethanol). Found, %: C 65.3; H 6.6; N 3.8. Calculated for $C_{21}H_{25}NO_6$, %: C 65.1; H 6.5; N 3.6. IR spectrum, cm^{-1}: 780; 1680 (CO, amide); 1715 (CO, ketone); 1735 (CO, ester).

3-(1'-Benzylindol-3'-yl)-2-carboxy-5-oxohexanoic Acid (XI). A mixture of 27.4 g of X, 137 ml of ethanol, and 137 of 4N NaOH was stirred until the solid matter had dissolved completely and was then left overnight at toom temperature, after which it was poured into water and extracted with ether. The aqueous layer was acidified with oxalic acid and again extracted with ether. After drying, the solvent was distilled off to dryness and the residue was recrystallized from benzene. Yield 20 g (83.7 %). mp 126-128°C. Found, %: C 69.3; H 5.5; N 3.8. Calculated for $C_{22}H_{21}NO_5$, %: C 69.6; H 5.6; N 3.7. IR spectrum, cm^{-1}: 760, 780, 1260, 1420; 2900-2990 (COOH); 1690-1700 (CO and COOH).

Oxime of Methyl 3-(1'-Benzylindol-3'-yl)-5-oxohexanoate (XII). A mixture of 18.7 g (43 mmoles) of XI and 44 ml of pyridine was heated at 110-114°C for 40 min. Then the solution was cooled and 44 ml of methanol and 3.76 g (54 mmoles) of hydroxylamine hydrochloride were added and the mixture was left at room temperature for 20 hr. After this, it was poured into water, acidified with oxalic acid, and extracted with ether. The dried extract was treated with an ethereal solution of diazomethane (from 13 g of nitrosomethylurea), and 16.03 g (90 %) of the oxo ester oxime XII was isolated. mp 107-108°C (from ethanol). Found, %: C 72.4; H 6.9; N 7.6. Calculated for $C_{22}H_{24}N_2O_3$, %: C 72.5; H 6.6; N 7.7. IR spectrum, cm^{-1}: 765, 775; 1670 (C=N); 1740 ($COOCH_3$); 3300 (OH).

Ethyl 3-(Indol-3'-yl)-5-oxohexanoate (XVI). At -10 to -15°C, 10 ml of 1 N ethanolic caustic potash was added over 1 hr to 2 g of XIII in 10 ml of ethanol, and the mixture was stirred at the same temperature for another 4 hr. The cold solution was poured into water and extracted with ether, and then it was acidified with conc HCl and again extracted with ether. The residue obtained from the second ethereal extract was dissolved in 4 ml of pyridine and the solution was heated at 110-115°C for 40 min. Then it was poured into water and extracted with ether, and the extract was washed with dilute HCl and with ether. The crystals obtained after the elimination of the ether were recrystallized from isopropanol. Yield 0.62 g (44 %). mp 90-91°C. Found, %: C 70.5; H 6.7; N 5.4. Calculated for $C_{16}H_{19}NO_3$, %: C 70.3; H 7.0; N 5.1. IR spectra cm^{-1}: 780; 1710 (C=O); 1720 ($CO_2C_2H_5$); 3360 (NH).

4-(1'-Acetylindol-3'-yl)-3-tert-butoxycarbonyl-5-nitropentan-2-one (XV). To 0.153 (6.3 mmoles) of sodium hydride in 11 ml of anhydrous dimethylformamide was added 1 g of tert-butyl acetoacetate (7 mmoles) and the mixture was stirred until the hydride had dissolved completely. The resulting solution was cooled to -17°C and, with stirring, 1.44 g of N-acetyl-3-(2'-nitrovinyl)indole [4] was scattered into it in portions. Mixing was continued for 1 hr during which the temperature rose to -5°C. Then the mixture was neutralized with acetic acid, poured into water, and extracted with ethyl acetate. The product that remained after the distillation of the solvent was crystallized from benzene. Yield 1.45 g (63 %). mp 162-163°C (from ethanol).

Found, %: C 61.5; H 6.1; N 7.2. Calculated for $C_{20}H_{24}N_2O_6$, %: C 61.8; H 6.2; N 7.2. IR spectrum, cm^{-1}: 775; 1370; 1560 (NO_2); 1610 (C=C, enol); 1680 (C=O, amide); 1710 (C=O, ketone); 3440 (OH, enol).

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