INDOLE DERIVATIVES

IV. Reaction of Indole with α,β-Unsaturated Ketones

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 5, pp. 878–880, 1968

UDC 547.753

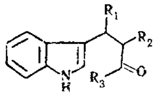
A series of α-, β-substituted β-(3-indolyl) ketones was obtained by the reaction of indole with α,β-unsaturated ketones in the presence of perchloric acid.

A study of the reactions of indole with α,β-unsaturated ketones (I) was undertaken with the aim of developing a procedure for obtaining β-(3-indolyl) ketones substituted in the α- and β-positions with respect to the carbonyl group.

The literature reports a series of investigations of the Michael addition of indolic compounds to an activated double bond. The interactions of indole with methyl vinyl ketone [1, 2] and with various acrylic acid derivatives [3–5] were described. In most cases the reaction proceeded in an acetic acid solution in the presence of acetic anhydride. The addition of indole to mesityl oxide under the influence of hydrogen chloride [6] has been reported, although the yield of the addition product was very low.

It is known that substitution at the double bond significantly decreases the activity of the acceptor in the Michael reaction. Therefore we expected that the substitution of ketones (I) would require more rigorous conditions than those employed in the previously mentioned publications. In fact, none of the ketones studied did react with indole under the influence of a mixture of acetic acid and acetic anhydride. It might have been expected that strong acids would increases the "enamine activity" [7, 8] of the indole nucleus, with a consequent increase in its capacity to react with an electrophilic double bond. And in fact, when a mixture of α-ethylene ketones and indole were treated with strong mineral acids, an addition reaction took place with the formation of the expected adducts (II–IX). The yield of these adducts increased parallel to the increase in the strength of the acid, and reached a maximum when $HClO_4$ was employed.

By presenting eight examples, this paper will show the above reaction to be a practical method for obtaining α-β-monosubstituted, as well as α, β and β,β-disubstitued β-(3-indolyl) ketones. These compounds were synthesized by the action of a catalytic quantity of 70% $HClO_4$ on a solution of indole in a small excess of an α-ethylene ketone. Since the unsaturated compounds used varied greatly in their reactivity to indole, it was necessary to use different reaction conditions to find those most suitable for each individual case. Most of the indole ketones obtained were amorphous substances. They were purified by chromatography on aluminum oxide, and then converted to crystalline oximes. It was not possible to obtain crystals of the



Compound	R^1	R^2	R^3	Conditions of synthesis			Oxime				
				temperature, °C	time, hrs	yield, %	mp, °C	element	empirical formula	found, %	calculated, %
II	$2CH_3$	H	CH_3	95—100	0.5	30	161—162 (chloroform)	C H N	$C_{14}H_{18}N_2O$	73.3; 73.4 7.4; 7.7 12.1; 12.2	73.0 7.9 12.2
III	n-C_3H_7	H	CH_3	7—8	1.5	51	127—129 (benzene)	C H N	$C_{15}H_{20}N_2O$	74.1; 73.9 8.7; 8.7 11.3; 11.3	73.7 8,3 11.5
IV	C_6H_5	H	CH_3	10—20	4	44	122 and 141 (benzene)	C H N	$C_{18}H_{18}N_2O$	77.7; 77.6 6.8; 6,7 10.1; 10.2	77.7 6.5 10.1
V	C_6H_5	H	C_6H_5	80—95	0.25	83	204—205 (ethanol)	C H N	$C_{23}H_{20}N_2O$	81.1; 81.2 6.1; 6.1 8.2; 8.2	81.2 5.9 8.2
VI	i-C_4H_9	H	CH_3	0	24	69	108—109 (petroleum ether)*	C H N	$C_{16}H_{22}N_2O$	73.9; 74.0 8.5: 8.5 11.0; 11.0	74.4 8.5 10.8
VII	CH_3	CH_3	CH_3	90—100	0.25	55			$C_{14}H_{18}N_2O$		
VIII	H	CH_3	CH_3	0	8	76	122—123 (ethanol)	C H N	$C_{13}H_{16}N_2O$	72.0; 72.0 7.4; 7.5 13.3; 13.1	72.2 7.5 13.0
IX	C_6H_5	CH_3	CH_3	100—105	1	29					

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*O-Acetyl derivative, mp 151–153° (benzene). Found, %: C 70.24, 70.4; H 7.4, 7.3; N 10.3, 10.4. Calculated for $C_{16}H_{20}N_2O_2$, %: C 70.6; H 7.4; N 10.3. IR spectrum: 885, 1077, 1218, 1637, 1751, 3350 cm⁻¹.

oxime of 3-methyl-4-(3'-indolyl)pentane-2-one (VII); it was identified instead by its O-acetyl derivative, which was obtained by the action of acetic anhydride in pyridine.

EXPERIMENTAL

2-Methyl-2-(3'-indolyl)pentan-4-one (II). To a solution of 11.7 g (0.1 mole) of indole in 14.7 g (0.15 mole) of mesityl oxide, well stirred and heated to 80–85°, 1.2 g of 70% $HClO_4$ was added at a rate such that the temperature remained below 95°. This operation required 30 min. After cooling, water and ether were added to the red solution. The ethereal layer was separated and washed with a sodium bicarbonate solution. The residue left after distilling off the ether was chromatographed on aluminum oxide (activity grade III). The substance obtained by elution with a mixture of petroleum ether and chloroform (1:1) was crystallized twice (carbon tetrachloride), mp 87–88°; the literature reports 86–88° [6]. Found, %: C 78.9, 78.7; H 6.9, 7.1; N 6.9, 6.8. Calculated for $C_{14}H_{15}NO$, %: C 78.9; H 7.0; N 6.6.

2-Methyl-1-(3'-indolyl)butan-3-one (VIII) was obtained similarly to (II) from indole and methyl isopropenyl ketone, mp 88–90° (benzene-hexane). Found, %: C 77.5, 77.3; H 7.2, 7.3; N 7.0, 7.2. Calculated for $C_{13}H_{15}NO$, %: C 77.6; H 7.5; N 7.0.

2-Methyl-1-phenyl-1-(3'-indolyl)butan-3-one (IX). Obtained similarly to (II) from 7 g (0.06 mole) of indole and 13.6 g (0.09 mole) of 2-methyl-1-phenyl-1-butene-3-one-3, mp 129–130° (ethanol). Found, %: C 82.2, 82.2; H 6.9, 6.7; N 5.1, 5.0. Calculated for $C_{19}H_{19}NO$, %: C 82.3; H 6.9; N 5.1.

1,3-Diphenyl-3-(3'-indolyl)propan-1-one (V). To a well-stirred mixture of 10 g (0.046 mole) of benzylidene acetophenone and 3.8 g (0.033 mole) of indole at 80°, 0.4 g of 70% $HClO_4$ was added. After 15 minutes, the mixture was heated to 95°. To the hot solution, 10 ml benzene and 10 ml of a saturated sodium bicarbonate solution were added. The crystals which precipitated after cooling, were filtered off and carefully washed with benzene, mp 136–137° (benzene). Found, %: C 85.1, 85.2; H 6.1, 6.1; N 3.9, 4.0. Calculated for $C_{23}H_{19}NO$, %: C 84.9; H 5.9; N 4.3.

Oximes of β-(3-indolyl) ketones. The remaining ketones were amorphous compounds, and were synthesized similarly to (II). The substances obtained after chromatographing the reaction mixture on aluminum oxide (1:1) were dissolved in a tenfold quantity of pyridine and ethanol, treated with the calculated quantity of hydroxylamine hydrochloride, and allowed to stand for 40–50 hrs. The solution was then poured into water, and the oximes extracted with ether or ethyl acetate. Pyridine was removed from the organic layer by washing with 5% hydrochloric acid. After evaporation, the residue was crystallized from suitable solvent. The table summarizes the conditions for the synthesis, the yield of oximes, and the constants of the oximes.

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11 July 1966

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