NUCLEOPHILIC ADDITION OF INDOLE AND ITS DERIVATIVES TO β-AROYLACRYLIC ACIDS

S. G. Agbalyan, G. V. Grigoryan, and A. A. Dzhaninyan

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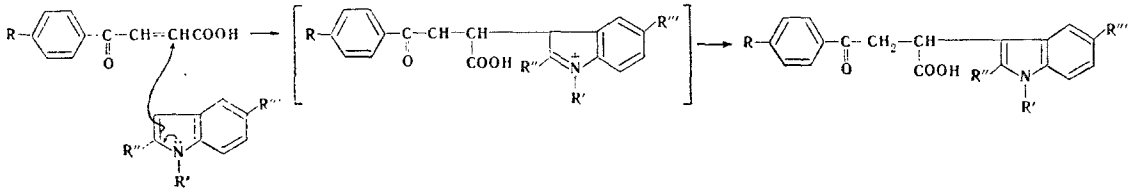
Condensation of β-benzoyl- and β-toluylacrylic acids with indole and its derivative gave β-benzoyl- and β-toluyl-α-(3-indolyl)propionic acids and their derivatives.

Indole and its derivatives react with unsaturated compounds in which the double bond is activated by conjugation with one or several electron-acceptor groups. The reaction with some monosubstituted and α,β-disubstituted ethylenes, for example, with nitrostyrene and chalcone, proceeds at the $C_{(3)}$ atom of the indole ring in the presence of acid catalysts [1-5]. Attempts to obtain adducts of indole with cinnamic acid and some other α,β-disubstituted olefins under the same conditions were unsuccessful [6]. Consequently, the success of the reaction depends on the nature of the substituting groups that promote electron depletion of the ethylene bond.

The aim of our investigation was to study the nucleophilic addition of indole and its derivatives to the α,β-disubstituted double bond of β-aroylacrylic acids.

The research of a number of investigators has shown that in the case of olefins with unsymmetrical structures the orientation of nucleophilic attack is determined by the relative stability of the intermediately formed carbanions, and an unambiguous direction of attack of a nucleophilic agent to give a carbanion of the acetophenone type [7] has been established for aroylacrylic acids.

In the reaction of indole and its derivatives with β-aroylacrylic acids one might similarly expect the intermediate formation of a zwitterion σ complex that is subsequently stabilized to the corresponding β-aroyl-α-(3-indolyl)propionic acid.



When benzoylacrylic and p-toluylacrylic acids are refluxed in benzene, in the absence of catalysts, with indole and its derivatives, β-aroyl-α-indolylpropionic acids are formed in satisfactory yields (Table 1). The IR spectra of the latter contain absorption bands characteristic for an acid carbonyl group at 1700 cm^{-1} and for a carbonyl group conjugated with an aromatic ring at 1670-1680 cm^{-1}.

The UV spectra of β-benzoyl-α-substituted propionic acids (λ_{max} 280 nm, λ_{min} 265 nm) differ substantially from the spectra of β-toluyl-α-substituted propionic acids (λ_{max} 255 nm, λ_{min} 235 nm).

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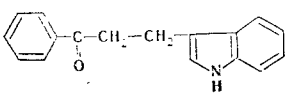
TABLE 1. α-R'-β-Aroylpropionic Acids $RC(=O)CH_2CH(R')COOCH_3$

R	R'	Reaction time, h	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
C_6H_5	3-Indolyl	6	150	$C_{18}H_{15}NO_3$	74,1	4,8	4,6	73,7	5,2	4,8	41
C_6H_5	1-Methyl-3-indolyl	6	137	$C_{19}H_{17}NO_3$	74,0	5,5	5,0	74,2	5,6	4,6	55
C_6H_5	1-(β-Cyanoethyl)-3-indolyl	6	170	$C_{21}H_{18}N_2O_3$	73,1	5,5	7,9	72,8	5,2	8,1	42
C_6H_5	2-Methyl-3-indolyl	0,2	145—147	$C_{19}H_{17}NO_3$	73,9	5,7	4,7	74,2	5,6	4,5	55
C_6H_5	1,2-Dimethyl-5-methoxy-3-indolyl	0,2	180	$C_{21}H_{21}NO_4$	71,6	5,7	4,2	71,8	6,0	4,0	80
p-$CH_3C_6H_4$	3-Indolyl	12	200	$C_{19}H_{17}NO_3$	74,1	5,9	4,9	74,2	5,6	4,6	98
p-$CH_3C_6H_4$	1-Methyl-3-indolyl	12	185	$C_{20}H_{19}NO_3$	74,9	5,6	4,4	74,8	5,9	4,6	99
p-$CH_3C_6H_4$	1-(β-Cyanoethyl)-3-indolyl	12	178	$C_{22}H_{20}N_2O_3$	72,9	5,3	7,7	73,3	5,6	7,8	99
p-$CH_3C_6H_4$	2-Methyl-3-indolyl	0,2	190	$C_{20}H_{19}NO_3$	74,8	6,3	4,5	74,7	5,9	4,3	81
p-$CH_3C_6H_4$	1,2-Dimethyl-5-methoxy-3-indolyl	0,2	123	$C_{22}H_{23}NO_4$	72,6	6,5	3,5	72,3	6,3	3,8	87

In order to determine the site of addition of indole we carried out the decarboxylation of β-benzoyl-α-(3-indolyl)propionic acid to the ketone, the structure of which could be represented by the following formulas, depending on the structure of the starting acid:



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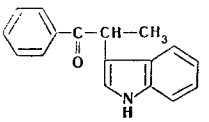
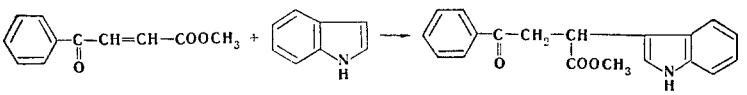


II

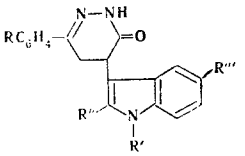
The formation of II is negated by the PMR spectra (the absence of a CH_3 group). Thus, indole adds to the α-carbon atom of β-benzoylacrylic acid in accordance with the scheme presented above.

The methyl esters were obtained from the synthesized acids. Inasmuch as the probability of the formation of a dimer and trimer of indole under the influence of β-aroylacrylic acids is not excluded, we realized the synthesis of methyl β-benzoyl-α-(3-indolyl)propionate from methyl β-benzoylacrylate and indole:



The formation of the methyl esters was confirmed by mass-spectral determination of the molecular weights. The IR spectra of the esters contain absorption bands characteristic for a conjugated carbonyl group at 1720-1730 cm^{-1} and for a carbonyl group conjugated with an aromatic ring at 1670-1680 cm^{-1} [8].

Condensation of α-keto acids with hydrazine hydrate gave 6-phenyl- and 6-(p-tolyl)-4-substituted 2,3,4,5-tetrahydro-3-pyridazinones, the IR spectra of which contain absorption bands characteristic for a carbonyl group in a pyridazine system (1600-1680 cm^{-1}).



According to the results of preliminary tests, the sodium salts of the synthesized acids have gibberellin-like activity in doses of 0.1 mg/ml. They do not have auxin-like activity.

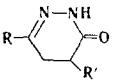
EXPERIMENTAL

The synthesized acids were chromatographed on Silufol in acetone–chloroform (1:2). The IR spectra of mineral oil suspensions were recorded with a UR-10 spectrometer. The UV spectra were obtained with an SF-4 spectrophotometer. The PMR spectra were recorded with a Varian spectrometer (60 MHz).

TABLE 2. Methyl α-R'-β-Aroylpropionates

R	R'	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
C_6H_5	3-Indolyl	115	$C_{19}H_{17}NO_3$	74,6	5,0	4,8	74,2	5,6	4,6	77
C_6H_5	1-Methyl-3-indolyl	103	$C_{20}H_{19}NO_3$	72,3	5,8	4,1	72,8	6,0	4,4	83
C_6H_5	1-(β-Cyanoethyl)-3-indolyl	109	$C_{22}H_{20}N_2O_3$	73,7	5,8	7,4	73,3	5,6	7,8	75
C_6H_5	2-Methyl-3-indolyl	50	$C_{20}H_{19}NO_3$	74,8	5,9	4,4	74,8	5,9	4,4	43
C_6H_5	1,2-Dimethyl-5-methoxy-3-indolyl	128	$C_{22}H_{23}NO_4$	72,4	6,3	3,8	72,3	6,3	3,8	44
p-$CH_3C_6H_4$	3-Indolyl	139	$C_{20}H_{19}NO_3$	74,5	5,9	4,3	73,8	6,0	4,4	86
p-$CH_3C_6H_4$	1-Methyl-3-indolyl	117	$C_{21}H_{21}NO_3$	75,1	5,9	4,2	75,2	6,3	4,2	89
p-$CH_3C_6H_4$	1-(β-Cyanoethyl)-3-indolyl	111	$C_{23}H_{22}N_2O_3$	73,9	5,6	7,2	73,8	5,9	7,5	90
p-$CH_3C_6H_4$	3-Methyl-3-indolyl	81	$C_{21}H_{21}NO_3$	75,5	6,7	4,5	75,2	6,3	4,2	50
p-$CH_3C_6H_4$	1,2-Dimethyl-5-methoxy-3-indolyl	154	$C_{23}H_{25}NO_4$	72,5	6,6	3,9	72,8	6,6	3,7	48

TABLE 3. 6-R-4-R'-2,3,4,5-Tetrahydro-3-pyridazinones



R	R'	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
C_6H_5	3-Indolyl	202	$C_{18}H_{15}N_3O$	74,9	5,2	14,4	74,9	5,2	14,5	82
C_6H_5	1-Methyl-3-indolyl	216	$C_{19}H_{17}N_3O$	74,1	5,9	14,2	75,2	5,6	13,9	98
C_6H_5	1-(β-Cyanoethyl)-3-indolyl	208	$C_{21}H_{18}N_4O$	74,5	5,2	16,6	74,7	5,3	16,5	88
C_6H_5	2-Methyl-3-indolyl	174	$C_{19}H_{17}N_3O$	75,1	5,4	13,7	75,2	5,6	13,8	81
C_6H_5	1,2-Dimethyl-5-methoxy-3-indolyl	196	$C_{21}H_{21}N_3O_2$	73,0	5,9	11,7	72,6	6,1	12,1	61
p-$CH_3C_6H_4$	3-Indolyl	250	$C_{19}H_{17}N_3O$	75,3	6,1	13,9	75,2	5,6	13,9	97
p-$CH_3C_6H_4$	1-Methyl-3-indolyl	245	$C_{20}H_{19}N_3O$	75,4	6,0	13,2	75,7	6,0	13,2	35
p-$CH_3C_6H_4$	1-(β-Cyanoethyl)-3-indolyl	237	$C_{22}H_{20}N_4O$	73,8	5,7	15,7	74,1	5,7	15,7	90
p-$CH_3C_6H_4$	2-Methyl-3-indolyl	256	$C_{20}H_{19}N_3O$	75,7	6,4	13,4	75,7	6,1	13,2	57
p-$CH_3C_6H_4$	1,2-Dimethyl-5-methoxy-3-indolyl	216	$C_{22}H_{23}N_3O_2$	73,5	6,5	11,8	73,1	6,4	11,6	6

β-Aroyl-α-(3-indolyl)propionic Acid. A mixture of 1.17 g (0.01 mole) of indole and 0.01 mole of aroylacrylic acid in 10 ml of dry benzene was heated on a water bath for 0.5-12 h. The resulting precipitate was removed by filtration and dissolved in 5% sodium hydroxide solution. The sodium hydroxide solution was then filtered to remove impurities, and the filtrate was treated with dilute HCl to precipitate the product, which was washed with hot benzene.

The products of condensation with substituted indoles were similarly obtained and purified by recrystallization from benzene (Table 1).

Decarboxylation of β-Benzoyl-α-(3-indolyl)propionic Acid. A 2.93-g (0.01 mole) sample of β-benzoyl-α-(3-indolyl)propionic acid was added to 20 ml of glycerol heated to 140°. The mixture was then heated at 150-160° for 10-15 min to complete the decarboxylation. A transparent solution formed during the heating period. Water (70 ml) was added to it, and the following day the resulting phenyl β-(3-indolyl)-ethyl ketone was removed by filtration to give 2.3 g (79%) of a product with mp 121-122° (benzene) and R_f 0.42. IR spectrum: 1674 cm^{-1} (C=O). The doublet of a methyl group was not detected in the PMR spectrum (pyridine). Found: C 81.5; H 6.1; N 5.3%. $C_{17}H_{15}NO$. Calculated: C 81.9; H 6.11; N 5.6%. The oxime was obtained as cream-colored crystals with mp 172°. Found: N 10.4%. $C_{17}H_{16}N_2O$. Calculated: N 10.6%.

Methyl β-Aroyl-(3-indolyl)propionates. A) A 10-ml sample of a 0.5% solution of hydrogen chloride in methanol was added to 0.05 mole of the appropriate β-aroyl-α-(3-indolyl)propionic acid, and the mixture was allowed to stand at room temperature for a few days. It was then heated on a water bath for 1 h, after which it was cooled and poured into water. The resulting precipitate was removed by filtration, dried, and recrystallized from ethanol, or the methanol was evaporated, and the residue was recrystallized from dilute ethanol (Table 2).

B) A 0.58-g (0.005 mole) sample of indole and 10 ml of benzene were added to 0.005 mole of the methyl ester of the appropriate β-aroylacrylic acid, and the mixture was refluxed for 6 h. The resulting precipitate was removed by filtration, washed with dry ether, and recrystallized from dilute ethanol.

6-Aryl-4-R'-2,3,4,5-tetrahydro-3-pyridazinones. A mixture of 0.005 mole of the appropriate β-aroyl-α-(3-indolyl)propionic acid and 4 ml of 80% hydrazine hydrate was heated on a water bath for 2-4 h. The resulting precipitate was washed with hot alcohol or recrystallized from alcohol (Table 3).

LITERATURE CITED

1. G. W. Saüsen, V. A. Engelhardt, and W. J. Widdleton, J. Amer. Chem. Soc., 80, 2815 (1958).
2. N. E. Noland, W. C. Kuryla, and R. F. Lange, J. Amer. Chem. Soc., 81, 6010 (1959).
3. Z. Rappoport, J. Chem. Soc., 4498 (1963).
4. R. Foster, P. Foster, and P. Hanson, Tetrahedron, 21, 255 (1965).
5. Y. Shirota, S. Esaki, S. Kusabajashi, and H. Mikawa, Bull. Chem. Soc. Japan, 45, 836 (1972).
6. J. R. Merchant, K. M. Chhatriwalla, S. S. Salgar, and J. R. Partell, J. Ind. Chem. Soc., 48, 613 (1971).
7. A. N. Nesmeyanov, M. I. Rybinskaya, and L. V. Rybin, Usp. Khim., 36, 1089 (1967).
8. J. A. Ballantine, C. B. Barrett, R. J. S. Beer, B. G. Boggiano, S. Eardly, B. E. Jennings, and A. Robertson, J. Chem. Soc., 2227 (1957).