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CHEMISTRY OF INDOLE

IV. Synthesis of 4-Keto-4, 5, 6, 7-tetrahydroindoles

A. N. Kost, L. G. Ovseneva, and T. G. Shuvaeva

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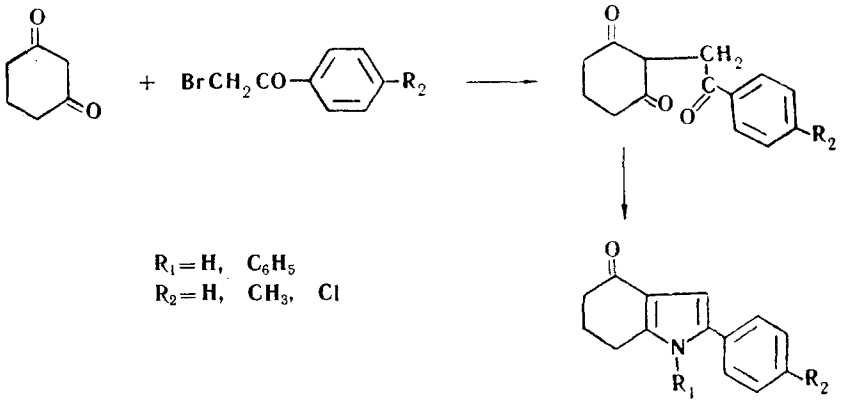
C-alkylation of dihydroresorcinol with substituted phenacylbromides, followed by reaction of the resultant 1, 4-diketones with ammonia or aniline, gives 2-aryl-4-keto-4, 5, 6, 7-tetrahydroindoles. It is shown that a convenient method of synthesizing such compounds is Knorr reduction of a mixture of dihydroresorcinol and α-isonitrosoketone. Some reactions of tetrahydroindoles (hydrolysis, decarboxylation, methylation, keto group reduction) are investigated.

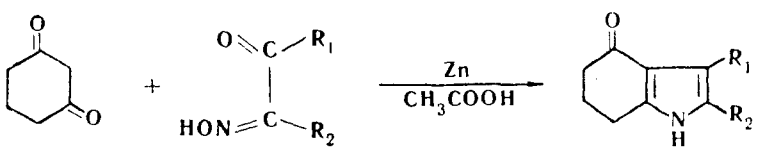
Papers by Stetter [1, 2] describe synthesis of 4-keto-4, 5, 6, 7-tetrahydroindoles by C-alkylating cyclohexane-1,3-diols with α-bromoketones, followed by conversion of the resultant 1, 4-diketones or their cyclization products (i.e., 4-keto-4, 5, 6, 7-tetrabenzoisofurans) to the corresponding tetrahydroindoles. Using para substituted phenacylbromides, the present authors have obtained 4-keto-2-phenyl-4, 5, 6, 7-tetrahydroindoles having various substituents in the benzene ring.

Contrary to what is stated in many papers, C-alkylation of dihydroresorcinols often gives low yields. A further inadequacy of the method is the limited choice of substituents at positions 2 and 3 in the pyrrole ring.

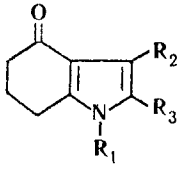


In an attempt to proceed by this route to tetrahydroindoles unsubstituted at positions 1, 2, and 3, dihydroresorcinol was alkylated with bromoacetaldehyde diethylacetal, but only the starting diketone was obtained. Attempts to alkylate with 2-ethoxyethylbromide were also unsuccessful. Use of 2-bromoethylamine did not give a dihydroresorcinol alkylation product, but its bromoethylimine. Reaction of cyclohexane-1, 3-dione with methyl bromoacetate gave a 60-65% yield of the corresponding ester, which on heating with aniline gave a compound melting point 170°-171°, apparently an α-pyrrole derivative. No detailed investigation of its structure was carried out.

As far back as 1929 Nenitzescu obtained a good yield of 3, 6, 6-trimethyl-4-keto-2-ethoxycarbonyl-4, 5, 6, 7-tetrahydroindole by Knorr reduction of a mixture of dimedone and α-isonitrosoacetoacetic ester [3]. We have now carried out this reaction with dihydroresorcinol and some isonitrosoketones. In most cases the 4-keto-4, 5, 6, 7-tetrahydroindole was obtained in rather good yield, reaction being fast (2-3 hr), and it being easy to isolate and purify the product.



$R_1 = CH_3$, C_6H_5, $CH_2COOC_2H_5$.
$R_2 = H$, $COCH_3$, $COOC_2H_5$.

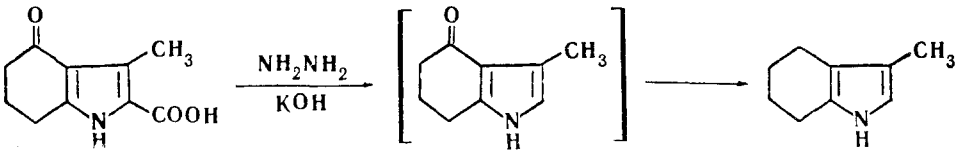


R_1	R_2	R_3	Mp, °C (recrystallization solvent)	UV spectrum in (MeOH) λ_{max}	UV spectrum in (MeOH) lg ε	Formula	C, % Found	C, % Calc.	H, % Found	H, % Calc.	R_f**	Yield %
H	CH_3	$COOC_2H_5$	163—164 (MeOH)	235—237 283	4.42 4.10	$C_{12}H_{15}NO_3$	64.96, 64.95	65.15	6.85, 6.84	6.84	0.52	57
	CH_3	$COCH_3$	168—170 (benzene)	235, 300	4.16 4.19	$C_{11}H_{13}NO_2$	69.20, 69.38	69.09	7.09, 7.00	6.80	0.36	40
	$CH_2COOC_2H_5$	$COOC_2H_5$	127—128 (MeOH)	283—285	4.04	$C_{15}H_{19}NO_5$	60.86, 60.96	61.41	6.79, 6.82	6.53	0.44	36
	C_6H_5	H	228—230 (MeOH)	265	4.10	$C_{14}H_{13}NO$	79.74, 79.73	79.60	6.47, 6.40	6.20	0.48	15
	CH_3	COOH	290 (CH_3COOH)	235 280	3.95 3.97	$C_{10}H_{11}NO_3$	61.00, 61.20	61.31	5.98, 5.91	5.66	—	87
	CH_3	H	204* (MeOH)	242 278	4.28 3.65	$C_9H_{11}NO$	—	—	—	—	0.34	60.5
CH_3	CH_3	$COOC_2H_5$	117—118 (Et_2O)	237	283	$C_{13}H_{17}NO_3$	66.61, 66.54	66.42	7.44, 7.36	7.30	0.74	80
	CH_3	COOH	220	—	—	$C_{11}H_{13}NO_3$	—	—	—	—	—	93
	CH_3	H	130 (benzene+petrol+ether)			$C_{10}H_{13}NO$	73.92, 73.99	73.58	7.84, 7.98	7.96	0.57	66.5

* The literature [2] gives mp 205°–206°.

** R_f values in thin-layer (0.1 cm) chromatography with aluminum oxide (DKhR, activity grade II), solvent system benzene: methanol 10:1, flow distance 12.5 cm.

The ethoxycarbonyl group at the α position in the pyrrole ring is readily hydrolyzed and decarboxylated. The pyrrole nitrogen atom is readily alkylated with dimethyl sulfate, while Kishner reduction of 3-methyl-4-keto-2-carboxy-4,5,6,7-tetrahydroindole is accompanied by decarboxylation, 3-methyl-4,5,6,7-tetrahydroindole being formed.



The UV spectra of the compounds prepared, observed in methanol, have characteristic maxima in the 235–239 and 285–287 mμ regions. The spectrum of 3,5-dimethyl-4-acetyl-2-ethoxycarbonylpyrrole [4] shows precisely the same maxima. This is a further confirmation that 4-keto, 4,5,6,7-tetrahydroindoles have a 3-acylpyrrole structure. The spectrum of 3-phenyl-4-ketotetrahydrindole has only one maximum, displaced to the 256 mμ region, due to additional conjugation with the benzene ring.

When thin-layer chromatographed on aluminum oxide, the tetrahydroindoles prepared show sharp spots, which show up well with iodine visualizer (but which are transparent in the ultraviolet). Their R_f values with the system benzene : methanol 10 : 1 lie within the limits 0.8–0.35 (table). Quite good systems for thin-layer chromatography of these compounds on aluminum oxide are chloroform: hexane 1 : 3, and pure methylene chloride.

Experimental

2-Phenacyclohexane-1,3-dione. 10 g ω-bromoacetophenone in 25 ml MeOH was poured into a solution of 2.8 g KOH in 10 ml water, the mixture stirred for 3 hr at room temperature, then left overnight. The precipitate of KCl was removed, the solvent vacuum-distilled off, and the residue treated with a solution of 3 g NaOH in 50 ml water, filtered to remove the oil which separated, and acidified to pH 2 with concentrated HCl. After some hours 6.6 g (58%) 2-phenacylcylohexane-1,3-dione, mp 158° (ex EtOH) [1] separated from the acid solution.

2-(p-Chlorophenacyl) cyclohexane-1,3-dione. A solution of 2.2 g dihydroresorcinol in 30 ml MeOH was mixed with one of 1.2 g KOH plus 1 g KI in 10 ml water, 3.8 g p, ω-dichloroacetophenone (mp 102° ex MeOH) added, and the mixture heated on a water bath with stirring, for 5 hr and then left overnight. The reaction products were treated with 10 ml 2 N NaOH solution, and extracted with ether. The alkaline solution was brought to pH 2 with concentrated HCl. White crystals of 2-(p-chlorophenacyl) cyclohexane-1,3-dione separated, mp 163° (ex aqueous MeOH). Yield 0.7 g (10%). Found: C 63.35, 63.18; H 5.01, 5.10%. Calculated for $C_{14}H_{13}ClO_3 \cdot H_2O$: C 63.52; H 4.95%.

In the same way, a 30% yield was obtained of 2-(p-methylphenacyl)-cyclohexane-1,3-dione, mp 97°–98° (ex ether). Found: C 73.75, 73.49; H 6.70, 6.37%. Calculated for $C_{15}H_{16}O_3$: C 73.74; H 6.60%.

Synthesis of 4-keto-4,5,6,7-tetrahydroindoles. 30 minutes boiling of a solution of the substituted 2-phenacylcyclohexane-1,3-dione in glacial AcOH with an equimolecular amount of aniline gave the corresponding 1-aryl-4-keto-4,5,6,7-tetrahydroindole, which was precipitated by diluting the reaction products with 6 times the amount of water. In this way were obtained: 1,2-diphenyl-4-keto-4,5,6,7-tetrahydroindole, mp 198° (ex EtOH), yield 98%; 1-phenyl-2-(p-chlorophenyl)-4-keto-4,5,6,7-tetrahydroindole, mp 175°–176° (ex MeOH), yield 80%. Found: C 75.07, 74.91; H 5.32, 5.49%. Calculated for $C_{20}H_{16}ClNO$: C 74.64; H 5.01%; 1-phenyl-2-(p-tolyl)-4-keto-4,5,6,7-tetrahydroindole, mp 196°–197° (ex MeOH), yield 73%. Found: C 83.40, 83.54; H 6.54, 6.65%. Calculated for $C_{21}H_{19}NO$: C 83.70; H 6.35%.

Heating together in a sealed tube for 5 hr at 100° 0.01 mole of a 2-phenacylcyclohexanedione and 2.4 g ammonia in 10 ml MeOH gave: 2-phenyl-4-keto-4,5,6,7-tetrahydroindole, mp 230° (ex EtOH), yield 98%; 2-(p-tolyl)-4-keto-4,5,6,7-tetrahydroindole, mp 270° (ex MeOH), yield 98%. Found: C 79.83; H 6.55%. Calculated for $C_{15}H_{15}NO$: C 79.93; H 6.71%.

Reaction of 2-bromoethylamine with dihydroresorcinol. 3.8 g 2-bromoethylamine hydrobromide was dissolved in 10 ml MeOH, and 1.12 g KOH added, the precipitate of KBr was removed, and the filtrate mixed with a solution of 2.28 g dihydroresorcinol and 1.12 g KOH in 20 ml MeOH. Yield 1.2 g crystals mp 135°. Found: C 44.09, 44.12; H 5.54, 5.66%. Calculated for $C_8H_{12}BrNO$: C 44.06; H 5.54%.

In the same way 1.88 g 4-phenyldihydroresorcinol and 1.9 g 2-bromoethylamine gave a 70% yield of a compound mp 165° (ex MeOH + acetone); UV spectrum (in MeOH): λ_{max} 288 mμ, lg ε 4.37. Found: C 57.56, 57.51; H 5.67, 5.92%. Calculated for $C_{14}H_{16}BrNO$: C 57.18; H 5.48%.

2-Methoxycarbonylmethyldihydroresorcinol. A solution of NaOMe was prepared from 0.8 g Na and 25 ml MeOH, then 2.2 g dihydroresorcinol was added to it, followed, with stirring, by 3 g Me bromoacetate. The mixture was heated

for 3 hr on a water bath, left overnight, the MeOH vacuum-distilled off, the residue neutralized with 2 N H_2SO_4, the mixture extracted with ether, the extract dried over Na_2SO_4, the ether evaporated off, and the residue vacuum-distilled, to give 3 g (58%) 2-methoxycarbonylmethyldihydroresorcinol, bp 145°–150° (20 mm), mp 70°–71°. Found: C 59.11, 59.11; H 6.79, 6.76%. Calculated for $C_9H_{12}NO_4$: C 58.72; H 6.57%.

A mixture of 4 g methoxycarbonylmethyldihydroresorcinol and 2 g freshly-distilled aniline was heated in a metal bath. Evolution of H_2 began at 130°, the temperature was gradually raised to 180° and held there till gas evolution ceased. The products were cooled, and the resinous mass treated with acetone, to give 2 g substance, mp 170° –171° (ex MeOH + Me_2CO). Found: C 73.61, 73.58; H 5.79, 5.79%. Calculated for $C_{14}H_{13}NO_2$: C 73.99; H 5.77%. UV spectrum: λ_{max} 258, 305–310, 450 mμ; lg ε 3.88, 4.45, 1.61 (in MeOH).

Preparation of 4-keto-4, 5, 6, 7-tetrahydroindoles (table) by Knorr's method. A mixture of 0.1–0.2 mole dihydroresorcinol, 25 g Zn dust, fused NaOAc, and 50–80 ml AcOH was heated to 60°–70°, and an equimolecular amount of isonitrosoketoketone added, in small portions, the temperature of the mixture being kept below 115°. Then the mixture was held at its boiling point for 2 hr, cooled, and poured into ice-water. After some time a mass of white crystals had separated, and they were filtered off, dissolved in hot aqueous MeOH, and the Zn dust filtered off. On cooling the MeOH solution, crystals of the tetrahydroindole separated.

Methylation of 4-keto-4, 5, 6, 7-tetrahydroindoles. 5 g KOH in 25 ml water was added to a boiling solution of 1 g of compound in 100 ml acetone, followed by 8 ml Me_2SO_4 over 15 min. Refluxing was continued for 15 min more, the acetone was distilled off, and the crystals of N-methyl-4, 5, 6, 7-tetrahydroindole filtered off.

Hydrolysis of 4-keto-2-ethoxycarbonyl-4, 5, 6, 7-tetrahydroindoles. This was effected by boiling with 10% NaOH until the solid dissolved. After cooling and bringing to pH 5 with concentrated HCl, a white finely-divided crystalline precipitate of acid separated.

Decarboxylation of 4-keto-2-carboxy-4, 5, 6, 7-tetrahydroindoles. 2 g acid, 27 ml MeOH, 6 ml water, and 8 ml concentrated HCl were heated together for 10–15 min, till the solid dissolved completely. The products were cooled, neutralized with $NaHCO_3$, and the MeOH vacuum-distilled off. If crystals of tetrahydroindole did not separate when the aqueous solution was cooled, the latter was extracted with $CHCl_3$, and the solvent then evaporated off, to give 4-keto-4, 5, 6, 7-tetrahydroindole, purified either by recrystallization from petrol ether, or by vacuum-sublimation (10 mm, 170°).

Reduction of 3-methyl-4-keto-2-carboxy-4, 5, 6, 7-tetrahydroindole. 5 g powdered NaOH was dissolved in 35 ml diethylene glycol, with heating, 5 g ketone and 5 ml hydrazine hydrate (85%) added, and the mixture heated for 2 hr at 125° (temperature maintained by adding MeOH). The MeOH was distilled off, along with the water and excess hydrazine hydrate, until the temperature rose to 190°, and heating was continued at that temperature for 3 hr. The products were cooled, 40 ml water added, and the whole then neutralized with 2 N HCl, after which it was extracted with ether, the extract dried over Na_2SO_4, the solvent evaporated off, and the residue vacuum-distilled to give 3 g 3-methyl-4, 5, 6, 7-tetrahydroindole, bp 156° (15 mm), mp 58° [5].

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Lomonosov Moscow State University