ALKYLATION OF 4-OXO-3-METHYL-4,5,6,7-TETRAHYDROINDAZOLES

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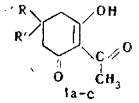
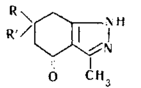
The alkylation of 4-oxo-3,6,6-trimethyl-4,5,6,7-tetrahydroindazole with alkyl halides forms mixtures of 1-alkyl and 2-alkyl derivatives which have been separated by fractional crystallization from n-hexane. The 4-oxo-1-alkyl-, -1-aryl-, and -1-acyl-4,5,6,7-tetrahydroindazoles have characteristic frequencies in their IR spectra at 1540-1530 cm^{-1}, and the corresponding 2-substituted derivatives have frequencies at 1565-1555 cm^{-1}. The introduction of an alkyl substituent at a nitrogen atom decreases the basicity of 4,5,6,7-tetrahydroindazole by 0.6 orders of magnitude, the 1-alkyl isomers being somewhat stronger bases than the 2-alkyl isomers.

Continuing previous investigations [1, 2] we have studied the alkylation of 3,6,6-trimethyl-4-oxo-, 3-methyl-4-oxo-6-phenyl-, and 6-(α-furyl)-3-methyl-4-oxo-4,5,6,7-tetrahydroindazoles (II). In the alkylation of II with alkyl halides in ethanolic solution in the presence of sodium ethoxide, mixtures of the 1- and 2-alkyl derivatives III and IV were obtained, and these were separated by fractional crystallization from n-hexane. The methylation of II with methyl iodide gave the same methyl derivatives as were obtained by the reaction of I with methyl hydrazine.


Ia-c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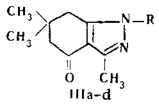
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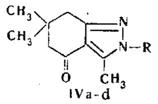
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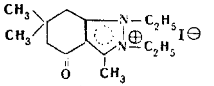
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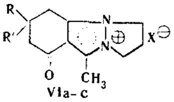
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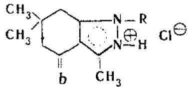
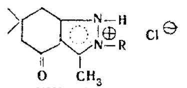

VIIa-d


VIIIa-d

I, II a $R = R' = CH_3$; b $R = H$, $R' = C_6H_5$; c $R = H$, $R' =$ α-furyl; III, IV, VII, VIII a $R = CH_3$; b $R = C_2H_5$; c $R = C_3H_7$-*n*; d $R = CH_2-CH=CH_2$; VI a $R = R' = CH_3$, $X = Br$; b $R = H$, $R' = C_6H_5$, $X = I$; в $R = H$, $R' =$ α-furyl $X = I$

The ethylation of IIIb and IVb gave the same product — 1,2-diethyl-3,6,6-trimethyl-4-oxo-4,5,6,7-tetraindazolium iodide (V). The salt V is soluble in water and the aqueous solution contains the iodide ion.

When II was boiled with 1,3-diiodopropane and with 1,3-dibromopropane in equimolar ratios in ethanolic solution in the presence of potassium carbonate, 4-oxo-1,2-trimethylene-4,5,6,7-tetrahydroindazolium halides (VI), readily soluble in water, were obtained. Halide ions were detected in the aqueous solutions.

When their solutions in absolute diethyl ether were saturated with dry hydrogen chloride, the alkyl derivatives III and IV gave the colorless crystalline hydrochlorides VII and VIII, readily hydrolyzing in aqueous solutions but completely stable in the air.

Since we succeeded in obtaining the chromatographically pure isomers III and IV, we studied their IR and UV spectra. In the 1800-1480 cm^{-1} region (Fig. 1) the absorption of the isomers III coincides with the absorption of 3,6,6-trimethyl-4-oxo-1-phenyl-4,5,6,7-tetrahydroindazole, the structure of which we have proved [1]. In the IR spectra of the 1-phenyl derivative and the 1-alkyl derivatives III, the frequency of the carbonyl group appears at 1665-1654 cm^{-1} and the absorption maximum of the pyrazole ring at 1543-1532 and 1510-1485 cm^{-1}. The absorption of the isomers IV is characterized by a carbonyl frequency increased by 10-15 cm^{-1} and by a strong maximum at 1561-1555 cm^{-1} (Fig. 1). The increase in the frequency of the carbonyl group of III as compared with IV corresponds to the rule [3] according to which when the carbonyl and the double bond in an α,β-unsaturated ketone have the S-cis- arrangement, the carbonyl frequency is higher than with the trans arrangement.

The frequencies of the pyrazole ring in the IR spectra of the N-acyl-3-methyl-4-oxo-4,5,6,7-tetrahydroindazoles appear in the 1575-1560 and 1510-1485 cm^{-1} regions. We assign these derivatives to the 2-substituted series, which corresponds to literature information [4, 5].

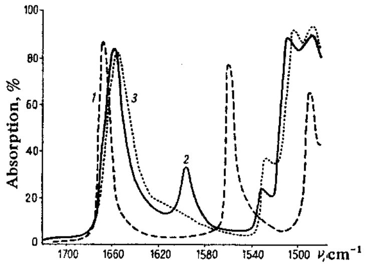


Fig. 1. IR spectra: 1) 3,6,6-trimethyl-4-oxo-2-n-propyl-4,5,6,7-tetrahydroindazole (IVc); 2) 3,6,6-trimethyl-4-oxo-1-phenyl-4,5,6,7-tetrahydroindazole; 3) 3,6,6-trimethyl-4-oxo-1-n-propyl-4,5,6,7-tetrahydroindazole (IIIc).

In our opinion, the IR spectra can be used successfully to distinguish between the 1- and 2-substituted 4-oxo-4,5,-6,7-tetrahydroindazoles.

In the UV spectra, the absorption maxima of the N-alkyl derivatives III and IV are shifted bathochromatically by 3-6 nm as compared with II (Table 1) which is in harmony with Grandberg's results [6]. At the same time, the absorption maxima of all the 2-alkyl isomers, IV, are shifted bathochromically in comparison with the 1-alkyl derivatives, III, which is also in harmony with literature information [7].

The values of pK_{BH^+} (Table 1) for III and IV are 0.5-0.6 units lower than for II. Consequently, N-alkylation causes an increase in the basicity of the 4,5,6,7-tetrahydroindazoles. This is in harmony with the rule reported previously [8]. Compounds III are stronger bases than IV (table). The ratio of the basicities of III and IV agrees with the same characteristics in the pyrazole series [9, 10].

Since at pH ≥ 3 the salts VII and VIII are hydrolyzed almost completely, only the UV absorption spectra taken in strongly acid media (5.5 M HCl) can be used to characterize the hydrochlorides of the 1-alkyl- and 2-alkyl-3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindazoles. The UV absorption of the cationic forms is shifted hypsochromically by about 20 nm as compared with the free bases and the spectra are similar to those of the 1,2-dialkyl-substituted cations V and VI (Table 1).

EXPERIMENTAL

1,3,6,6-Tetramethyl-4-oxo- and 2,3,6,6-tetramethyl-4-oxo-4,5,6,7-tetrahydroindazoles (IIIa and IVa). A) A mixture of 0.9 g (5 mM) of 2-acetyldimedone, 15 ml of absolute ethanol, 0.7 g (5 mM) of methylhydrazine sulfate, and 0.7 g (5 mM) of anhydrous potassium carbonate was boiled until the evolution of carbon dioxide had ceased. Then it was filtered, the ethanol was distilled off in vacuum, and the residue was treated with 10 ml of 5% aqueous NaOH. The oil liberated was extracted with diethyl ether (3 × 10 ml). The ethereal extracts were dried over anhydrous sodium sulfate. The ether was distilled off, and the resinous product, consisting of IIIa and IVa, was dissolved in 15 ml of n-hexane with heating. After the solution had stood at 0°C for 3-4 hr, colorless crystals of IIIa deposited from the solution, while yellow prisms of IVa separated out only after the solution had stood at −15°C (−20°C) for 10 hr. After recrystallization from n-hexane, the IIIa was obtained with a yield of 31% and the IVa with a yield of 23%. Mp of IIIa, 75-78°C. Found %: N 14.72. $C_{11}H_{16}N_2O$. Calculated %: N 14.57. Mp of IVa, 45-48°C. Found %: N 14.53.

B) The sodium ethoxide obtained from 0.28 g (0.012 g-atom) of Na and 20 ml of absolute ethanol was boiled with 2.12 g (0.012 mole) of IIa and 2.24 ml (0.036 mole) of methyl iodide until the reaction was neutral (1 hr). The ethanol was distilled off in vacuum and the residue was treated as in method (A) to give IIIa and IVa, showing no depression of the mp with the compounds obtained by method (A).

1-Ethyl-3,6,6-trimethyl-4-oxo- (IIIb), 2-ethyl-3,6,6-trimethyl-4-oxo-(IVb), 3,6,6-trimethyl-4-oxo-1-n-propyl-(IIIc), 3,6,6-trimethyl-4-oxo-2-n-propyl- (IVc), and 1-allyl-3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindazole (IIId) were

Table 1. N-Alkyl-3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindazoles (III and IV), Their Hydrochlorides (VII and VIII), and the Tetrahydroindazolium Salts V and VI

Compound	Mp, °C	Empirical formula	Found, %		Calculated, %		λ_{max}, nm (ε)	pK_{BH^+}	R_f	yield, %
			N	halogen	N	halogen				
IIIa	75—80	$C_{11}H_{16}N_2O$	14.72	—	14.51	—	254 (12700)	0.58	0,30	34
III b	91—93	$C_{12}H_{18}N_2O$	13.46	—	13.58	—	253 (13200)	0.61	0.32	32
III c	62—68	$C_{13}H_{20}N_2O$	12.75	—	12.71	—	253 (13700)	0.60	0,35	26
III d	68—70	$C_{13}H_{18}N_2O$	12 80	—	12,83	—				31
IVa	45—48	$C_{11}H_{16}N_2O$	14.68	—	14 57	—	256 (12700)	0.53	0.49	23
IV b	57—60	$C_{12}H_{18}N_2O$	13.43	—	13.58	—	255 (13500)	0.59	0,52	30
IV c	61—63	$C_{13}H_{20}N_2O$	12.68	—	12.71	—	256,5 (13500)	0,51	0.58	21
VIIa	145—156	$C_{11}H_{17}ClN_2O$	11,93	15.34	12.25	15,50	232 (10200)		—	—
VII b	110—115	$C_{12}H_{19}ClN_2O$	11.70	14,43	11,54	14.60	233 (10300)		—	—
VII c	120—128	$C_{13}H_{21}ClN_2O$	11,05	13.57	10.91	13,81	233,5 (10700)		—	—
VIIIa	157—166	$C_{11}H_{17}ClN_2O$	11.99	15,58	12 25	15,50	232 (9700)		—	—
VIII b	135—167	$C_{12}H_{19}ClN_2O$	11.48	14.71	11,54	14,60	233 (10200)		—	—
VIII c	106—112	$C_{13}H_{21}ClN_2O$	11.10	13.87	10.91	13.81	233,5 (9800)		—	—
V	167—169	$C_{14}H_{23}IN_2O$	7.67	35.27	7.93	35.03	228,5 (22300)		—	84
VIa	232—234	$C_{13}H_{19}BrN_2O$	9,51	26.94	9,36	26.71	235,5 (11000)		—	53
VI b	157—161	$C_{17}H_{19}IN_2O$	7.10	31,95	7.11	32.19			—	49
VI c	174—179	$C_{15}H_{17}IN_2O$	7,35	32.70	7,29	33,03			—	43

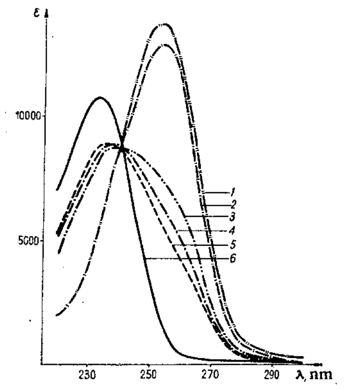


Fig. 2

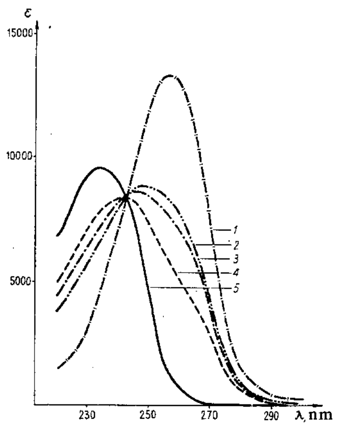


Fig. 3

Fig. 2. UV spectra of solutions of 3,6,6-trimethyl-4-oxo-1-n-propyl-4,5,6,7-tetrahydroindazole (IIIc): 1) in H_2O; 2) in HCl (pH 2); 3) in 0.24 M HCl; 4) in 0.32 M HCl; 5) in 0.40 M HCl; 6) in 7.5 M HCl.

Fig. 3. UV spectra of solutions of 3,6,6-trimethyl-4-oxo-2-n-propyl-4,5,6,7-tetrahydroindazole (IVc): 1) in H_2O; 2) In 0.20 M HCl; 3) in 0.25 M HCl; 4) in 0.40 M HCl; 5) in 7.5 M HCl.

obtained by method (B) by alkylating IIa with ethyl iodide, propyl bromide, and allyl bromide, respectively. The solubilities of the 1-ethyl and the 1-n-propyl derivatives in n-hexane are lower than those of the 2-ethyl and 2-n-propyl derivatives. The allylation of IIa with allyl bromide gave only IIId. For the yields, mp's, and elementary analyses of compounds III and IV, see Table 1.

Chromatography of the 1-alkyl- and 2-alkyl-3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindazoles was carried out in a thin nonfixed layer of alumina (activity grade III) as described by Mistrykov [12]. When the chromatograms were irradiated by means of an ultrachemiscope (BUV-15 lamps, UFS-1 filter) darker spots could be seen on a light zone.

Using chloroform as the eluent, the 1-alkyl derivatives (III) had R_f 0.30-0.35, and the 2-alkyl derivatives (IV) had R_f 0.49-0.58 (Table 1).

The hydrochlorides of the 1-alkyl- and the 2-alkyl-3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindazoles (VII and VIII respectively) were obtained by passing dry hydrogen chloride through solutions of the appropriate compounds III and IV in absolute diethyl ether. They were recrystallized from absolute ethanol. The crystals are stable to the air, but hydrolyze in aqueous solutions Table 1.

1,2-Diethyl-3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindazolium iodide (V). A solution of 1.5 g (7 mM) of IIIb in 3 ml (0.04 mole) of ethyl iodide was heated for 15 hr in a steel tube at 120-130°C. After the cooled mixture had been washed with absolute ether, an orange product was obtained which crystallized from absolute ethanol in the form of colorless crystals with mp 167-169°C. The same product was obtained similarly from IVb and ethyl iodide (Table 1).

3,6,6-Trimethyl-4-oxo-1,2-trimethylene-4,5,6,7-tetrahydroindazolium bromide (VIa). A solution of 0.53 g (3 mM) of IIa in 20 ml of ethanol was boiled for 5 hr with 0.6 ml (6 mM) of 1,3-dibromopropane and 0.41 g (3 mM) of anhydrous potassium carbonate. The mixture was filtered, 15 ml of ethanol was distilled off, and the residue was diluted with absolute diethyl ether. The oil that separated out solidified on trituration. Compound VIa crystallized in the form of colorless needles from absolute ethanol after the dilution of its solution with dry diethyl ether. It is readily soluble in water and the bromide ion can be detected in the aqueous solution (Table 1).

3-Methyl-4-oxo-6-phenyl-1,2-trimethylene-4,5,6,7-tetrahydroindazolium iodide (VIb) and 6-(α-furyl)-3-methyl-4-oxo-1,2-trimethylene-4,5,6,7-tetrahydroindazolium iodide (VIc) were obtained from IIb and IIc, respectively, and 1,3-diiodopropane in a similar manner to VIa (Table 1).

Determination of the pK_{BH^+} values of the N-alkyl-3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindazoles III and IV (Figs. 2 and 3,(Table 1). The UV spectra of 5×10^{-5}–3×10^{-5} M solutions of III-IV were recorded and the pK_{BH^+} values of the compounds were calculated by a published method [2]. Solutions of the substances in 5.5 M HCl ($H_0 = -1.93$) served as standards for the absorption of the cationic forms. The spectra of aqueous solutions of III and IV were used as standards for the absorption of the free bases. The extinctions of solutions of III and IV were also measured in 0.16-0.50 M hydrochloric acid at 250, 255, and 260 nm. The acidities of these solutions expressed in H_0 units [11] were between +0.76 and +0.31. The deviations of the calculated values of pK_{BH^+} from the mean did not exceed ± 0.01 pK units for IIIc and IVc and ± 0.02 pK units for IIIa and b and IVa and b.

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