# REACTION OF 2-AROYL-1-CYCLOHEXANONES AND THEIR 6-AMINO DERIVATIVES WITH HYDRAZINES

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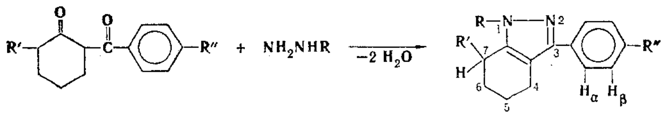
The reaction of 2-aroyl-1-cyclohexanones and their amino derivatives with hydrazines gives substituted 4,5,6,7-tetrahydroindazoles.

Continuing our research on amino derivatives of cycloalkanones [1, 2], we have studied methods for the synthesis of indazole derivatives from them. Aminoindazoles with a nitrogen-containing substituent in the 3 position have analgetic and antiphlogistic properties [3, 4], and polyfunctional tetrahydroindazoles are also physiologically active [5, 6].

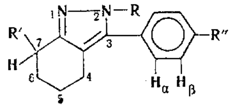
Like other $\beta$-diketones [7], 2-aroyl-1-cyclohexanones and their 6-amino derivatives (I) react with hydrazine and arylhydrazines with closing of a five-membered ring to give 4,5,6,7-tetrahydroindazoles II (III). The results of elementary analysis and the IR and PMR spectral data confirm the general structure of II (III). The absorption of carbonyl groups and hydrazone C = N bonds is absent in the region of double-bond absorption in the IR spectra of the cyclization products; only several compounds obtained in the reaction with 2,4-dinitrophenylhydrazine (Table 1), in which there are evidently admixtures of hydrazones, constitute exceptions to this. A broad maximum at ~1600 $cm^{-1}$, which is related to the absorption of the indazole and aromatic rings [8], is observed in the spectra of II (III).

Indazoles II (III) with an amino group in the ring form salts with one or two molecules of hydrogen chloride, while compounds without an amine residue give salts with only one molecule of hydrogen chloride.



I

II



III

Cyclization of I with phenylhydrazine may lead to two isomeric tetrahydroindazoles (II and III). A diamagnetic shift of the resonance signals of the $H_\alpha$ and $H_\beta$ protons is observed on passing from nitrogen-unsubstituted indazoles IIa-i to compounds having a phenyl substituent attached to the nitrogen atom (IIIj-*l*) (Table 2). This may be explained by the anisotropic effect of the adjacent $N_2$-phenyl grouping. Where there are two phenyl groupings in the 2 and 3 positions of the indazole ring. Dreiding models show that steric interactions that lead to their primarily parallel orientation and, consequently, to a diamagnetic contribution to the shielding of the $H_\alpha$ and $H_\beta$ protons arise between them. Consequently, the reaction of I with phenylhydrazine leads to compounds with structure III rather than structure II.

The low chemical shift of the $H_\alpha$ protons in derivatives IIa-i (7.5-7.8 ppm) is noteworthy, whereas for indazoles with a phenyl substituent attached to the $N_2$ atom (IIIj-*l*) the resonance of these protons is

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TABLE 1. 3-Aryl-4,5,6,7-tetrahydroindazoles (II, III)

| Compound | R | R′ | R″ | mp, °C* | Empirical formula | Found, % | | | | Calculated, % | | | | IR spectra, ν, cm$^{-1}$ | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N | Cl | C | H | N | Cl | 1500–1800 cm$^{-1}$ region | 2800–3600 cm$^{-1}$ region | |
| IIb | H | H | Cl | 129 | $C_{13}H_{13}N_2Cl$ | 66,5 | 5,4 | 11,9 | 15,2 | 67,1 | 5,6 | 12,0 | 15,2 | ~ 1600 | 2850, 2950, 3080 | 43 |
| IIb·HCl | H | H | Cl | 264—266 | $C_{13}H_{14}N_2Cl_2$ | 58,3 | 5,3 | 10,4 | 27,1 | 58,0 | 5,2 | 10,4 | 26,3 | | | — |
| IIc | H | H | $OCH_3$ | 78 | $C_{14}H_{16}N_2O$ | 73,4 | 6,9 | 12,2 | | 73,6 | 7,1 | 12,3 | | ~ 1600 | 3230 | 31 |
| IIc·HCl | H | H | $OCH_3$ | 268—269 | $C_{14}H_{17}N_2OCl$ | 62,9 | 6,7 | 10,4 | 12,4 | 63,5 | 6,5 | 10,6 | 13,4 | | | — |
| IId | H | $N(CH_2)_5$ | H | 159 | $C_{18}H_{23}N_3$ | 76,3 | 7,5 | 14,9 | | 76,8 | 8,2 | 14,9 | | 1600, 1605 | 3290 | 36 |
| IId·2HCl | H | $N(CH_2)_5$ | H | 236—238 | $C_{18}H_{25}N_3Cl_2$ | 61,0 | 7,1 | 11,9 | 20.0 | 61,6 | 7,6 | 11,7 | 21,0 | | | — |
| IIe | H | $N(CH_2)_5$ | Cl | 183 | $C_{18}H_{22}N_3Cl$ | 68,7 | 7,1 | 13,4 | 11,8 | 68,4 | 7,0 | 13,3 | 11,2 | ~ 1590 | 2860, 2950, 3250 | 22 |
| IIe·HCl | H | $N(CH_2)_5$ | Cl | 255—256 | $C_{18}H_{24}N_3Cl_3$ | 56,7 | 6,4 | 10,8 | 27,2 | 55,6 | 6,2 | 10,8 | 27,4 | | | — |
| IIf | H | $N(CH_2)_5$ | $OCH_3$ | 170 | $C_{19}H_{25}N_3O$ | 74,0 | 8,1 | 13,5 | | 73,3 | 8,1 | 13,5 | | ~ 1610 | 3240 | 36 |
| IIf·2HCl | H | $N(CH_2)_5$ | $OCH_3$ | 224—226 | $C_{19}H_{27}N_3OCl_2$ | 59,8 | 7,3 | 10,9 | 18,3 | 59,4 | 7,1 | 10,9 | 18,4 | | | — |
| IIg | H | $N(CH_2CH_2)_2O$ | H | 178 | $C_{17}H_{21}N_3O$ | 73,2 | 7,8 | 14,9 | | 72,1 | 7,5 | 14,8 | | ~ 1600 | 2950, 3070, 3280 | 31 |
| IIg·HCl | H | $N(CH_2CH_2)_2O$ | H | 226—228 | $C_{17}H_{22}N_3OCl$ | 63,3 | 6,9 | 13,1 | 11,3 | 63,8 | 6,9 | 13,1 | 11,1 | | | — |
| IIh | H | $N(CH_2CH_2)_2O$ | Cl | 176 | $C_{17}H_{20}N_3OCl$ | 64.8 | 6,6 | 12,7 | 11,9 | 64,2 | 6,3 | 13,2 | 11,1 | ~ 1600 | 2870, 2950, 2980, 3300 | 41 |
| IIh·HCl | H | $N(CH_2CH_2)_2O$ | Cl | 220—222 | $C_{17}H_{21}N_3OCl_2$ | 56.8 | 6,5 | 11,3 | 20,2 | 57,6 | 6,0 | 11,9 | 20,0 | | | — |
| IIi | H | $N(CH_2CH_2)_2O$ | $OCH_3$ | 154 | $C_{18}H_{23}N_3O_2$ | 69,3 | 7,5 | 22,8 | | 69,0 | 7,4 | 13,4 | | ~ 1600, 1620 | 2875, 2950, 3260 | 36 |
| IIi·2HCl | H | $N(CH_2CH_2)_2O$ | $OCH_3$ | 212—214 | $C_{18}H_{25}N_3O_2Cl_2$ | 55,6 | 6,6 | 10,2 | 17,2 | 56,0 | 6,5 | 10,9 | 18.3 | | | — |
| IIIj | $C_6H_5$ | H | H | 136 | $C_{24}H_{27}N_3$ | 80,8 | 7,9 | 11,4 | | 80,6 | 7,6 | 11,7 | | ~ 1600 | | 14 |
| IIIk | $C_6H_5$ | $N(CH_2)_5$ | Cl | 147 | $C_{24}H_{26}N_3Cl$ | 73,7 | 6,7 | 10,9 | 9,9 | 73,6 | 6,7 | 10,7 | 9,0 | ~ 1600 | 2870, 2940 | 38 |
| III*l* | $C_6H_5$ | $N(CH_2)_5$ | $OCH_3$ | 112 | $C_{25}H_{29}N_3O$ | 76,6 | 7,8 | 11,3 | | 77,5 | 7,,5 | 10,8 | | 1600, 1615 | | 19 |
| IIIm | $C_6H_5$ | H | $OCH_3$ | 125 | $C_{20}H_{20}N_2O$ | 78,7 | 6,7 | 9,2 | | 78,9 | 6,6 | 9,2 | | 1590, 1610 | | 58 |
| IIIn | $C_6H_5$ | H | H | 105 | $C_{19}H_{18}N_2$ | 83,0 | 6,4 | 10,7 | | 83,2 | 6,6 | 10,2 | | ~ 1600 | | 54 |
| IIIn·HCl | $C_6H_5$ | H | H | 169—171 | $C_{19}H_{19}N_2Cl$ | 73,5 | 6,2 | 9,0 | 12,3 | 73,4 | 6,2 | 9,0 | 11,4 | | | — |
| IIIo | $C_6H_3(NO_2)_2$ | H | H | 186 | $C_{19}H_{16}N_4O_4$ | 63,1 | 4,8 | 14,8 | | 62,6 | 4,4 | 15,4 | | ~ 1610 | | 64 |
| IIIp | $C_6H_5$ | $N(CH_2CH_2)_2O$ | H | 133 | $C_{23}H_{25}N_3O$ | 76,7 | 7,1 | 11,5 | | 76,8 | 7,0 | 11,7 | | ~ 1600 | 2860, 2950 | 24 |
| IIIp·HCl | $C_6H_5$ | $N(CH_2CH_2)_2O$ | H | 247—248 | $C_{23}H_{26}N_3OCl$ | 70,8 | 6,6 | 10,8 | 10,0 | 69,8 | 6,6 | 10,6 | 9,0 | | | — |
| IIIq | $C_6H_5$ | $N(CH_2CH_2)_2O$ | $OCH_3$ | 134 | $C_{24}H_{27}N_3O_2$ | 73.2 | 6.9 | 10.8 | | 74,0 | 7,0 | 10,8 | | ~ 1610 | 2850, 2900 2955, 3020, 3060 | 38 |
| IIIq·HCl | $C_6H_5$ | $N(CH_2CH_2)_2O$ | $OCH_3$ | 172—173 | $C_{24}H_{28}N_3O_2Cl$ | 66,5 | 7.0 | 9,2 | 9,6 | 67,7 | 6,6 | 9,9 | 8,3 | | | — |
| IIIr | $C_6H_3(NO_2)_2$ | $N(CH_2CH_2)_2O$ | $OCH_3$ | 105—107 | $C_{24}H_{25}N_5O_6$ | 61.3 | 5,8 | 14,6 | | 60,1 | 5,2 | 14,6 | | ~ 1610, 1680 | 2850, 2950, 3020 | 56 |
| IIIs | $C_6H_5$ | H | Cl | 133 | $C_{19}H_{17}N_2Cl$ | 74,2 | 5.6 | 9.2 | 12,4 | 73.9 | 5,5 | 9,1 | 11,5 | ~ 1600 | 2870, 2940, 3080 | 30 |
| IIIs·HCl | $C_5H_5$ | H | Cl | 172—174 | $C_{19}H_{18}N_2Cl_2$ | 65,5 | 5,2 | 7,7 | 20,1 | 66,1 | 5,2 | 8,1 | 20,5 | | | — |
| IIIt | $C_6H_3(NO_2)_2$ | H | Cl | 180 | $C_{19}H_{15}N_4O_4Cl$ | 57,3 | 3.7 | 13,7 | 9,1 | 57,2 | 3,8 | 14,0 | 8,9 | ~ 1610 | 2870, 2940, 2960, 3070 | 58 |

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*The indazoles were crystallized from ethanol or purified by precipitation from hydrochloric acid solution by the addition of ammonium hydroxide; the hydrochlorides were crystallized from absolute ethanol with the addition of ether.

TABLE 2. Parameters of the PMR Spectra of 3-Aryltetrahydroindazoles (II, III)

| Compound | Chemical shifts, δ, ppm | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | $C_4$-H | $C_5$-H — $C_6$-H | $C_7$-H | H α | H β | R | R′ | R″ |
| IIa | 2,60 | 2,0—1,6 | 2,60 | 7,60 | 7,20 | 11,0 | — | 7,20 |
| IIb | 2,57 | 1,8—1,5 | 2,57 | 7,50 | 7,22 | 10,9 | — | — |
| IIc | 2,56 | 1,8—1,5 | 2,56 | 7,40 | 6,70 | 10,6 | — | 3,70 |
| IId | 2,60 | 2,0—1,5 | 3,96 | 7,80 | 7,3 | 10,0 | 2,57 ($NCH_2$)<br>1,50 ($CCH_2$) | 7,30 |
| IIe | 2,60 | 2,0—1,5 | 3,90 | 7,72 | 7,33 | 11,0 | 2,55 ($NCH_2$)<br>1,50 ($CCH_2$) | — |
| IIf | 2,60 | 2,1—1,6 | 3,80 | 7,58 | 6,84 | 10,0 | 2,50 ($NCH_2$)<br>1,50 ($CCH_2$) | 3,73 |
| IIg | 2,67 | 2,1—1,6 | 3,72 | 7,70 | 7,26 | 10,9 | 2,50 ($NCH_2$)<br>3,50 ($OCH_2$) | 7,30 |
| IIh | 2,60 | 2,0—1,5 | 3,85 | 7,62 | 7,30 | 11,0 | 2,57 ($NCH_2$)<br>3,60 ($OCH_2$) | — |
| IIi | 2,60 | 2,1—1,6 | 3,88 | 7,63 | 6,91 | 10,6 | 2,58 ($NCH_2$)<br>3,65 ($OCH_2$) | 3,80 |
| IIIj | 2,57 | 2,0—1,6 | 2,80 | 7,20 | 7,20 | 7,20 | — | 7,20 |
| IIIk | 2,46 | 2,1—1,6 | 3,74 | 7,20 | 7,03 | 7,18 | 2,68 ($NCH_2$)<br>1,50 ($CCH_2$) | — |
| III*l* | 2,45 | 2,1—1,6 | 3,74 | 7,03 | 6,72 | 7,18 | 2,73 ($NCH_2$)<br>1,50 ($CCH_2$) | 3,74 |

shifted to strong field (7.03-7.2 ppm). These differences apparently should be explained by the equilibrium II $\rightleftarrows$ III for indazole derivatives with a hydrogen atom attached to the nitrogen atom and by the appearance of averaged signals of forms II and III with pronounced predominance of tautomeric forms II. The anisotropy of the $C_3 = N_2$ double bond and the unshared pair of electrons attached to the $N_2$ nitrogen in form II should make an appreciable paramagnetic contribution to the shielding of the $H_\alpha$ protons of the aryl ring as compared with that observed for form III. A comparison of the chemical shifts of the $C_7$ protons for IIa and IIIj also indicates the importance of these anisotropic contributions. The resonance of this group is shifted to weak field when there is a $C = N_1$ double bond in the IIIj molecule.

## EXPERIMENTAL

The PMR spectra of 10% solutions of the compounds in $CDCl_3$ were recorded with a Perkin–Elmer R-12A spectrometer (60 MHz). The internal standard was tetramethylsilane. The IR spectra of Nujol or hexachlorobutadiene suspensions of the compounds were recorded with a UR-10 spectrometer.

3-Phenyl-4,5,6,7-tetrahydroindazole (IIa). A mixture of 4.04 g (0.02 mole) of 2-benzoyl-1-cyclohexanone, 1 g of hydrazine hydrate, and 1 ml of concentrated $H_2SO_4$ was refluxed in 50 ml of absolute ethanol for 5 h, after which the mixture was poured into water, and the pH was brought up to 9-10 by the addition of ammonium hydroxide. After 4 h, the resulting precipitate was separated and crystallized from ethanol to give 2.2 g (55%) of a product with mp 126°. Found: N 14.3%. $C_{13}H_{14}N_2$. Calculated: N 14.1%. IR spectrum: 1600, 3080, 3150, and 3200 $cm^{-1}$.

Hydrochloride (IIa • HCl). The hydrochloride was obtained by saturation of a solution of IIa in ether–benzene with hydrogen chloride. The precipitated salt was separated and crystallized from absolute ethanol with the addition of ether to give a colorless substance with mp 244-245° (dec.); the salt was soluble in water. Found: C 65.9; H 6.4; N 11.9; Cl 14.6%. $C_{13}H_{14}N_2 \cdot HCl$. Calculated: C 66.5; H 6.4; N 11.9; Cl 15.1%.

The properties of the remaining substances, which were similarly synthesized, are presented in Table 1.

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