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2-Phenyl-4,5,6,7-tetrahydroindazol-3-one-carboxylic acids. I. Synthesis and Properties

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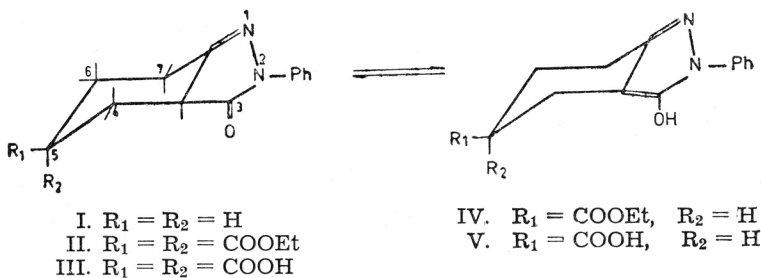
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The properties and synthesis of 2-phenyl-4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylic acid (III), 2-phenyl-4,5,6,7-tetrahydroindazol-3-one-5-carboxylic acid (V) and their ethyl esters II and IV were described.

Indazolone dicarboxylic acid III showed the exceptional properties that indicated chelating tendencies of this compound. It formed a monohydrate which built in the molecule of crystal water steadily. The content of water was determined by proton magnetic resonance.

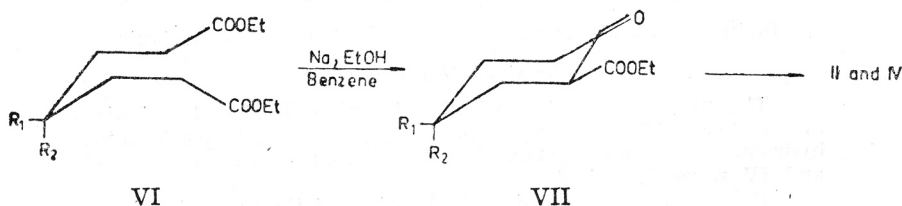
Potentiometric titrations gave the number of the acidic groups of acids and corresponding esters, as well as the existence of enol form of these compounds. The ultraviolet and infrared absorption spectra were recorded.

The derivatives of indazolone type* are considered attractive ones. Besides of expected physiological interest¹ these compounds drew attention to their possibility to form complexes and chelating systems. Namely, the functional groups of indazolone (II—V) could show the different tendencies at the forming of chelates and complexes, and so contribute to the selective separation of metals. The indazolone III, with work presently underway, seems to be most promising having axial carboxylic group in the key position. It is hoped to describe these properties in the following paper.



* The nomenclature of published compound I is the subject of controversy and it is described as follows: 1-phenyl-3,4-cyclotetramethylene-pyrazol-(5)-one¹, 1-phenyl-3,4-cyclohexane-pyrazol-(5)-one², 1-phenyl-3,4,1',2'-hexahydrobenzo-pyrazol-(5)-one³ and 2-phenyl-4,5,6,7-tetrahydroindazolone¹. The above compound was named in accordance with Definite Rules for Nomenclature of Organic Chemistry, *J. Am. Chem. Soc.* **82** (1960) 5545.

Synthesis of indazolone dicarboxylate II proceeded through tetraethyl ester of 1,3,3,5-pentanetetracarboxylic acid⁴ (VI, $R_1 = R_2 = \text{COOEt}$) and triethyl cyclohexanone-2,4,4-tricarboxylate⁵ (VII, $R_1 = R_2 = \text{COOEt}$). The former was prepared from diethyl malonate and ethyl ester of β -bromopropionic acid. Compound VII was obtained by Dieckmann reaction of VI. The alicyclic β -ketoester VII when treated with phenylhydrazine in 50% ethanol yielded diethyl-2-phenyl-4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylate (II) as monohydrate.



Compound II, as well as compound IV, behaved as monobasic acids upon potentiometric titration (Fig. 1). The position of inflexion point corresponds to one equivalent of added base. The complete enolization takes place and hydroxyl group of the enol form will give off a proton at the pH at which the jump of potential is observed.

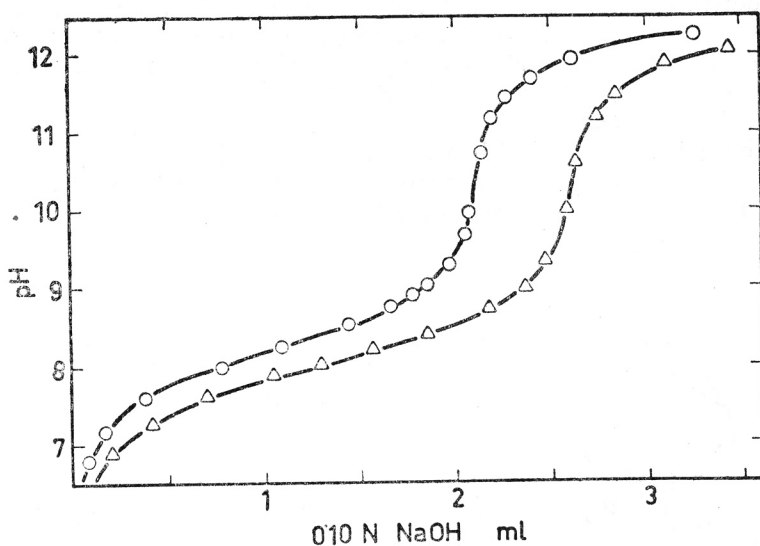


Fig. 1. Potentiometric titration. Δ : Compound II; \circ : Compound IV.

UV-absorption spectra of compounds II and IV were recorded showing the maxima at λ_{max} 249 μ , 249.5 μ and shoulders at λ 267 μ , 266.5 μ , respectively. The addition of acid or base influenced the shift of the maxima, which can be brought in connection with the dynamic keto-enol tautomerism

of these systems (Fig. 2). The same direction of the illustrated shifts is the common characteristic of all compounds described in this paper.

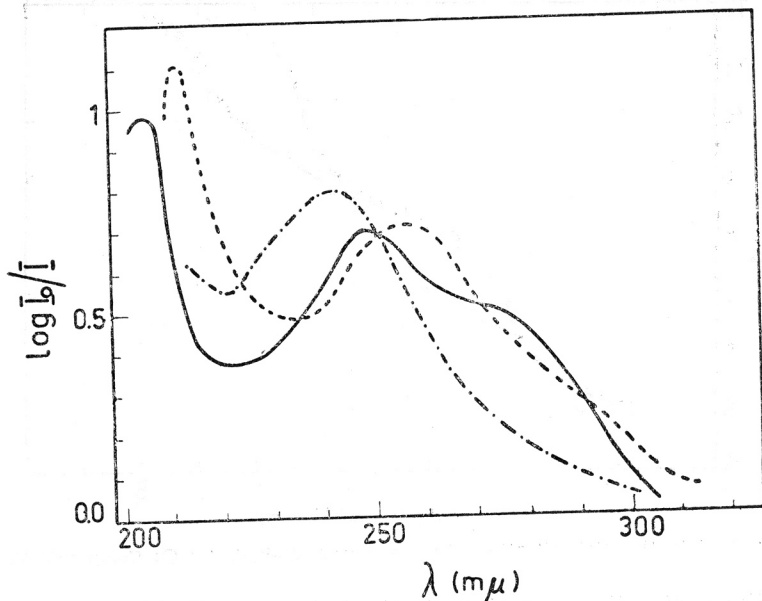


Fig. 2. Ultraviolet absorption spectrum of compound IV. —: in ethanol; ---: triethylamine added; -.-: methanolic hydrochloric acid added.

The hydrolysis of diester II with 20% methanolic potassium hydroxide or with 10% hydrochloric acid gave rise to a diacid III in 94% yield, as monohydrate, m.p. 163—165°. Attempts to remove the molecule of crystal water of this hydrate by heating under reduced pressure failed. At the melting point decarboxylation occurred resulting in the formation of monocarboxylic acid V. Only by refluxing in acetic acid the diacid III crystallized in anhydrous form, m. p. 250°, with softening at 210°.

The starting material for ethyl indazolone-carboxylate IV was triethyl ester of 1,3,5-pentanetricarboxylic acid⁶ (VI, $R_1 = \text{COOEt}$, $R_2 = \text{H}$) obtained from tetraethyl ester of 1,3,3,5-pentanetetracarboxylic acid by hydrolysis, decarboxylation and esterification. The compound VI was then converted by the Dieckmann reaction into diethyl cyclohexanone-2,4-dicarboxylate⁶ (VII, $R_1 = \text{COOEt}$, $R_2 = \text{H}$). The latter treated with phenylhydrazine yielded ethyl-2-phenyl-4,5,6,7-tetrahydroindazol-3-one-5-carboxylate (IV). The hydrolysis of indazolone IV gave monocarboxylic acid, which was identical with compound V, obtained from the decarboxylation either of the hydrate or the anhydrous form of diacid III. Therefore, there it is reasonable to present the conformation of compounds IV and V with the substituent in the equatorial position.

The curves of potentiometric titrations of the diacid III monohydrate, and monoacid V are presented in Figure 3. The titrations and the neutralization equivalents show the compound III as tribasic and the compound V as dibasic acid. The obvious jumps of potential are seen claiming three, two and one

equivalent of 0.1 N sodium hydroxide, respectively. This means that enolization was complete at the last jump of potential.

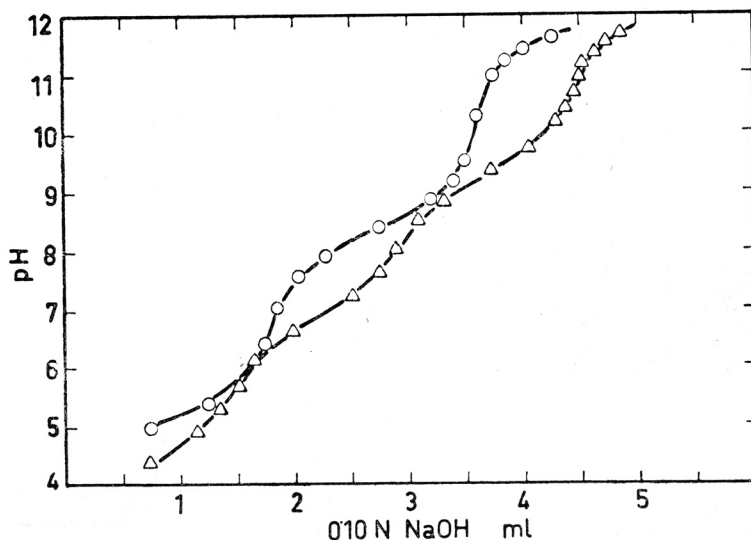


Fig. 3. Potentiometric titration. Δ : Compound III hydrate; \circ : Compound V.

Additional attention was given to the indazolone diacid III, as regards its content of the water of crystallization. The low solubility of this compound prevented determination of water by Karl Fischer method. Besides of determined molecular weights, elemental analyses, IR and UV spectra, diacid III as monohydrate was examined by proton magnetic resonance. The NMR spectra and calculations of second moments were used to provide a supplemental proof of the existence of a monohydrate.

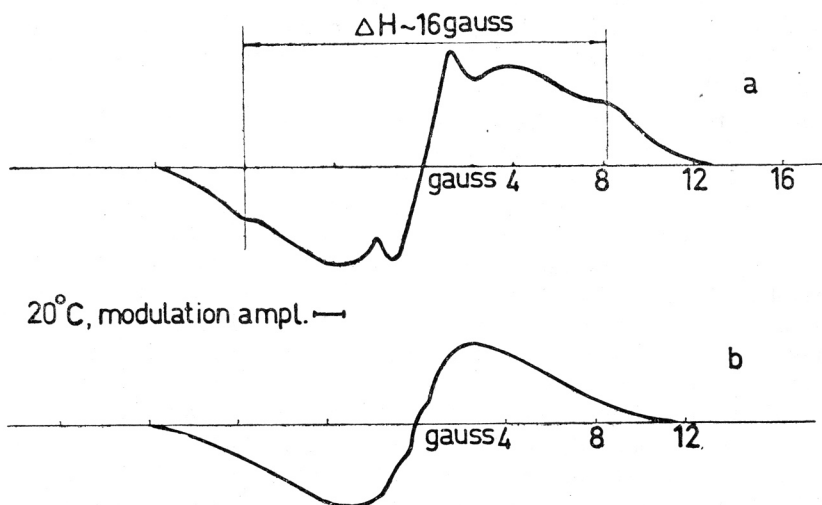


Fig. 4. Proton magnetic resonance. a) Compound III hydrate; b) Compound III, anhydrous form.

The NMR spectrum of the hydrate revealed the characteristics of a two-spin water-line with $\Delta H_{H_2O} = 14\text{--}16$ gauss² (Fig. 4a). It showed that at 20° there was no vivid motion within the molecule. Therefore, the calculation of second moments⁷ was done according to the Van Vleck's formula:

$$S = \frac{716.16}{N} \sum_{j > k} r_{jk}^{-6} (r_{jk} \text{ in } \text{Å}) \quad (1)$$

The experimental second moment of anhydrous form III (Fig. 4b) was about 3 gauss² lower in comparison to that of the hydrate. This difference corresponds to the second moment of water⁸. The calculations gave the values, which were in agreement with the experimental data (Table I).

TABLE I

Compound	Second moment, found	Second moment, calc'd.
III (hydrate)	13.3 ± 1.0 gauss ²	$10.1 + S_{\text{inter}}$ gauss ²
III (anhydrous form)	10.5 ± 1.2 gauss ²	$7.1 + S_{\text{inter}}$ gauss ²

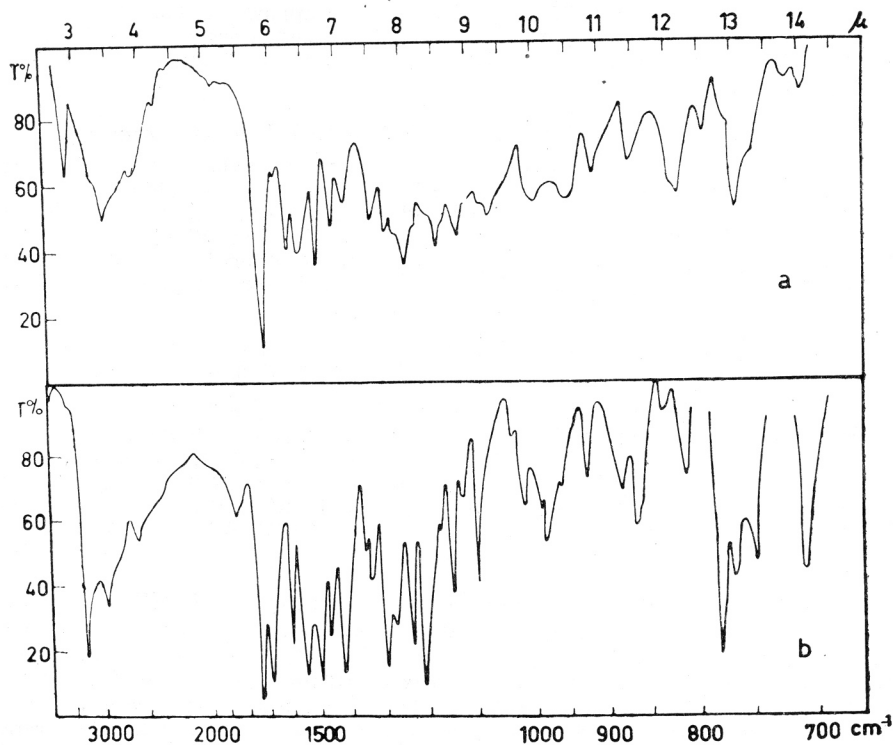


Fig. 5. Infrared absorption spectra: a) Compound III hydrate; b) Compound III, anhydrous form.

The infrared absorption spectrum of diethyl ester of indazol-3-one-5,5-dicarboxylic acid (II) as monohydrate showed similarities with the monoester V and monoacid IV spectra. The anhydrous form of compound II expressed the slight shifts of absorption bands in the region between 8 and 12 μ . It was supposed that the molecule of water in compound II was more labile built in, than in the case of the indazolone diacid III.

The marked difference of IR spectra of anhydrous indazolone diacid III and monohydrate of diacid III (Fig. 5a and 5b) pointed out the structural peculiarities in water-diacid relation indicating firm insertion of molecule of crystal water in the structure of indazolone diacid III.

EXPERIMENTAL

Melting points, uncorrected, were taken on a Kofler hot stage. UV-spectra were measured in 95% ethanol on a Perkin-Elmer model 137 UV spectrophotometer with automatic gain control. The IR-absorption bands were recorded in potassium bromide plates on a Perkin-Elmer infracord model 137. The infrared absorption were reported in wavelength followed by a number in brackets which designates transmittance (%). The instrument used for the potentiometric titrations was Pye Universal pH-meter and millivoltmeter with universal glass electrode and calomel reference electrode with wick-type liquid junction. The titrations were measured in ethanol-water (1:1). Twenty five ml. of 0.008 M indazolones were titrated with sodium hydroxide in a 50 ml. beaker unless stated otherwise at 20°. The stirring was accomplished by a magnetic stirrer. The average time per titration was about 2.5 hrs. The water content was determined by Karl Fischer titration in absolute ethanol. The instrument used for titration was a Baird and Tatlock electrometric apparatus. The NMR measurements were done with an apparatus described earlier⁹. Care was taken to avoid saturation distortion of the spectra. All the results were obtained at 20.0°C using a thermostated probe.

Diethyl-2-phenyl-4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylate (II)

To a solution of triethyl cyclohexanone-2,4,4-tricarboxylate⁵ (1.18 g., 3.8 mmole) in 50% ethanol (18 ml.), phenylhydrazine (0.42 g., 3.9 mmole) was added. The mixture was refluxed for 6 hours and then cooled and refrigerated overnight. The crystalline product which separated was filtered and washed with ether. Yield 1.1 g. (78%). The compound was a monohydrate. Crystallization from ethanol gave the analytical sample as colourless prisms, m. p. 76°. It crystallized from ethylacetate-petroleum ether as colourless plates with the same melting point.

Anal. C₁₉H₂₂N₂O₅·H₂O (376.70) calc'd.: C 60.62; H 6.52; N 7.44%
found: C 60.68; H 6.20; N 7.63%

Water content calc'd: 18.02 mg. per mole; found: 18.36 mg. per mole. Potentiometric titration of anhydrous form with a 0.0974 N solution of sodium hydroxide, is graphically represented in Figure 1. Neutral. equivalent calc'd.: 358.4; found: 361.1.

The ultraviolet spectrum: $\lambda\lambda_{\max}$ 206.5 m μ , log ϵ 4.225; 249 m μ , log ϵ 4.145 and shoulder λ 267 m μ , log ϵ 4.016; λ_{\min} 223 m μ , log ϵ 3.884. Infrared spectrum of hydrate: 3.12(55), 5.72(27), 6.25(30), 6.35(25), 6.67(28), 8.1(16), 8.93(47), 9.3(48), 9.78(59), 11.7(68), 13.15(46), 14.3(51) μ .

2-Phenyl-4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylic acid (III) monohydrate

a) Hydrolysis with methanolic potassium hydroxide. — Diethyl-2-phenyl-4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylate monohydrate (1.0 g., 2.7 mmole) was dissolved in 20% methanolic potassium hydroxide (10 ml.) and refluxed for 4 hours. The methanolic solution was evaporated at the water pump and the residue dissolved in water (10 ml.). The solution was made just acid to Congo red by the dropwise addition of 10% hydrochloric acid. A crystalline precipitate separated soon. It was filtered off and washed well with water. Yield 0.8 g. (94%). Crystallization from

ethanol-water gave the analytical sample as colourless prisms, m. p. 163—165°, extended with decomposition. The analysis indicated a monohydrate.

Anal. $C_{15}H_{14}N_2O_5 \cdot H_2O$ (320.29) calc'd.: C 56.26; H 5.04; N 8.75%
found: C 55.80; H 4.96; N 8.76%

Water content was determined by proton magnetic resonance (Fig. 4a). Second moment calc'd.: ~ 13.1 gauss²; found: 13.3 ± 1.0 gauss² (Table I). From the potentiometric titration (Fig. 3) with a 0.0974 *N* solution of sodium hydroxide neutral equivalents calc'd.: 320.3, 160.1, 106.8; found: 325.0, 161.9, 105.4.

Ultraviolet spectrum: $\lambda_{\lambda_{\max}}$ 206.5 m μ , log ϵ 4.251; 249.5 m μ , log ϵ 4.150 and shoulder λ 266.5 m μ , log ϵ 4.007; λ_{\min} 221 m μ , log ϵ 3.854. The infrared spectrum is given in Figure 5a.

b) Hydrolysis with hydrochloric acid. — A suspension of diethyl-2-phenyl-4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylate monohydrate (1.0 g., 2.7 mmole) in 10% hydrochloric acid (10 ml.) was refluxed for 8 hours. The solution was then evaporated to dryness at the water pump. The residue was suspended in water, filtered off, washed with water and dried. Yield 0.8 g. (94%). It crystallized from ethanol-water as colourless prisms, m. p. 163—165°, extended (dec.), undepressed on admixture with the sample obtained from hydrolysis with methanolic potassium hydroxide. The infrared spectra of both samples were superimposable.

2-Phenyl-4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylic acid (III)

2-Phenyl-4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylic acid monohydrate (0.5 g., 1.56 mmole) was suspended in glacial acetic acid (50 ml.) and refluxed for one hour. On cooling a crystalline product separated. Yield 0.42 g (89%). Crystallization from ethanol gave the analytical sample as colourless prisms, m. p. 249—250° (dec.) with softening at 210°. It gave analysis corresponding to the anhydrous form.

Anal. $C_{15}H_{14}N_2O_5$ (302.28) calc'd.: C 59.60; H 4.67; N 9.27%
found: C 59.40; H 4.72; N 9.51%

Neutralization equivalents (potentiometric titration with 0.0993 *N* solution of sodium hydroxide) calc'd.: 302.3, 151.1, 100.8; found: —, 154.4, 100.0. Proton magnetic resonance second moment calc'd.: ~ 10.1 gauss²; found: 10.5 ± 1.2 gauss² (Fig. 4b).

Ultraviolet spectrum: $\lambda_{\lambda_{\max}}$ 206.5 m μ , log ϵ 4.277; 249 m μ , log ϵ 4.182 and shoulder λ 266.5 m μ , log ϵ 4.045; λ_{\min} 220 m μ , log ϵ 3.884. The infrared spectrum is reported in Figure 5b.

Ethyl-2-phenyl-4,5,6,7-tetrahydroindazol-3-one-5-carboxylate (IV)

To a solution of diethyl cyclohexanone-2,4-dicarboxylate⁶ (0.969 g., 4.0 mmole) in 50% ethanol (35 ml.), phenylhydrazine (0.44 g., 4.1 mmole) was added. The mixture was refluxed for 6 hours and then allowed to cool in ice overnight. Crystalline product as needles separated, filtered off and washed with ether. Yield 0.7 g. (62%). Crystallization from ethanol gave the analytical sample as colourless needles, m. p. 168—169°.

Anal. $C_{18}H_{18}N_2O_3$ (286.32) calc'd.: C 67.11; H 6.34; N 9.78%
found: C 66.95; H 6.23; N 9.78%

Potentiometric titration with a 0.1005 *N* solution of sodium hydroxide is graphically represented in Figure 1. Neutral equivalent calc'd.: 286.3; found: 289.5.

Ultraviolet spectrum (Fig. 2): $\lambda_{\lambda_{\max}}$ 205 m μ , log ϵ 4.323; 249.5 m μ , log ϵ 4.169 and shoulder λ 266.5 m μ , log ϵ 4.035; λ_{\min} 221 m μ , log ϵ 3.880. The infrared spectrum: 5.78(24), 6.13(39), 6.22(30), 6.32(20), 6.69(36), 7.13(38), 7.59(46), 8.5(41), 12.35(58), 13.26(46) μ .

2-Phenyl-4,5,6,7-tetrahydroindazol-3-one-5-carboxylic acid (V)

a) Hydrolysis of compound IV. — Ethyl-2-phenyl-4,5,6,7-tetrahydroindazol-3-one-5-carboxylate (0.9 g., 3.1 mmole) was dissolved in 20% ethanolic potassium hydroxide (10 ml.) and refluxed for 4 hours. The product was isolated as described for

compound III. Yield 0.7 g. (86.4%). It crystallized from methanol-water, m. p. 249⁰ (dec.).

Anal. C₁₄H₁₄N₂O₃ (258.27) calc'd.: C 65.10; H 5.46; N 10.85%
found: C 65.13; H 5.73; N 10.66%

From potentiometric titration (Fig. 3) in a 50% ethanol solution (40 ml.) with 0.1003 N solution of sodium hydroxide neutral equivalents calc'd.: 258.3, 129.1; found: 259.7, 130.9.

Ultraviolet spectrum: $\lambda\lambda_{\max}$ 205.5 m μ , log ϵ 4.297; 249 m μ , log ϵ 4.169 and shoulder λ 266.5 m μ , log ϵ 4.027; λ_{\min} 220 m μ , log ϵ 3.862. The infrared spectrum: 3.38(47), 3.42(44), 5.87(20), 6.20(18), 6.29(23), 6.68(24), 7.16(33), 7.64(33), 12.42(64), 13.14(41) μ .

b) Pyrolysis of hydrate III. — 2-Phenyl-4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylic acid monohydrate, m. p. 163—165⁰ (0.25 g., 0.78 mmole) was shortly pyrolyzed at 260⁰. It was cooled and crystallized from methanol-water. Yield 0.16 g. (80%), m.p. 251⁰. Crystallization from methanol gave the analytical sample as colourless hexagonal prisms, m.p. 248.5—249⁰, undepressed on admixture with the sample obtained by hydrolysis of compound IV. The infrared spectra of both samples were superimposable.

Anal. C₁₄H₁₄N₂O₃ (258.27) calc'd.: C 65.10; H 5.46; N 10.85%
found: C 64.97; H 5.38; N 10.97%

c) Pyrolysis of III, anhydrous form. — 2-Phenyl-4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylic acid, m. p. 250⁰ (0.2 g., 0.66 mmole) was shortly pyrolyzed at 265⁰, cooled and crystallized from methanol, m.p. 248⁰. Yield 0.1 g. (59.4%). No depression on admixture with the sample obtained above, and their infrared spectra were superimposable.

Anal. C₁₄H₁₄N₂O₃ (258.27) calc'd.: C 65.10; H 5.46; N 10.85%
found: C 64.89; H 5.84; N 10.69%

Calculations of NMR second moment of III (hydrate and anhydrous form)

The molecule of diacid III monohydrate contains 16 protons. There are 8 isolated protons (S_{isol}): two of them belong to carboxylic groups, 5 are in benzene ring and 1 belongs to the tertiary carbon. Six protons are attached to the secondary carbons of the cyclohexane (S_{sec}) and are main contributors to the sum of the NMR second moments. The remaining two protons are in the water molecule. The total NMR second moment can be calculated from equation (2). S_{inter} indicates intermolecular contribution to the sum. $S_{\text{sec}} + S_{\text{isol}} = S_{\text{intra}}$ give the intramolecular second moment of the organic part of compound III, calculated according to the Van Vleck's formula (1).

$$S_{\text{tot}} = 1/8 S_{\text{H}_2\text{O}} + 3/8 S_{\text{sec}} + 1/2 S_{\text{isol}} + S_{\text{inter}} \quad (2)$$

The model of this molecule was constructed from Dreiding-stereomodels (W. Büchi), and based on $r_{\text{C-C}} = 1.54 \text{ \AA}$, $r_{\text{C=C}} (\text{conj}) = 1.39 \text{ \AA}$, $r_{\text{C-H}} = 1.09 \text{ \AA}$, $r_{\text{C-OH}} = 1.41 \text{ \AA}$, ($r_{\text{O-H}} = 0.96 \text{ \AA}$), $r_{\text{C=N}} = 1.39 \text{ \AA}$ and corresponding bond angles. Different conformational relations between cyclohexane and benzene ring were taken into account, as well as van der Waals interactions. Second moment, $S_{\text{sec}} + S_{\text{isol}}$, of outermost conformations give the values 7.33 and 6.81 gauss², respectively (average 7.1 gauss²). It means that S_{tot} , including second moment of water, gives 10.1 gauss² + S_{inter} , where S_{inter} amounts to 3 gauss² (corresponding to 30% of S_{intra}).

The same calculations of second moment of monocyclic phenylhydrazone of cyclohexane-2,4,4-tricarboxylic acid gives the values 8.15 and 7.54 gauss², on the average 7.8 gauss². If this value has to satisfy the total second moment $S_{\text{tot}} = 13.3 \pm 1.0$ gauss², which is obtained experimentally (Fig. 4a), then S_{inter} should be about 6 gauss². Such a relatively high intermolecular second moment, S_{inter} , is very unlikely.

In the NMR spectrum of anhydrous indazolone III (Fig. 4b) the characteristic line of water disappeared, and the corresponding second moment is: $S_{\text{tot}} = 10.5 \pm 1.2$

gauss². The difference between two experimental values (Table I) corresponds to the second moment of water⁸.

Acknowledgments. We acknowledge with thanks our indebtedness to Mr. M. Bratica and Dr. S. Maričić for helpful discussion. We also thank to Mrs. N. Zambelli for the microanalyses and to Mr. T. Magjer for recording the infrared spectra.

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IZVOD

2-Fenil-4,5,6,7-tetrahidroindazol-3-on karbonske kiseline. I. Sinteza i svojstva

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Opisana su svojstva i sinteza 2-fenil-4,5,6,7-tetrahidroindazol-3-on-5,5-dikarbonske kiseline (III), 2-fenil-4,5,6,7-tetrahidroindazol-3-on-5-karbonske kiseline (V) i njihovih etilnih estera II i IV.

Indazolon karbonska kiselina III pokazuje posebna svojstva sa mogućim sklonošćima da stvara helate. Ista tvar ugrađuje vrlo postojano jednu molekulu kristalne vode. Sadržaj te vode je određen protonskom magnetskom rezonancijom.

Potencimetrijske titracije su označile broj kiselinskih funkcija opisanih indazolon kiselina i estera, kao i postojanje njihovih enolnih formi. Ultraljubičasti i infracrveni absorpcijski spektri su priloženi.

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ZAGREB

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