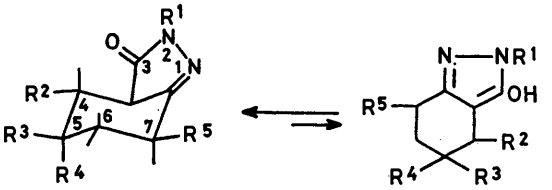
Positional Isomers in the 4,5,6,7-Tetrahydro-3-oxo-2*H*-indazolecarboxylic Acid Series

By **Vinko Škarić** * and **Vera Turjak-Zebić**, Laboratory of Stereochemistry and Natural Products, Institute ' Rudjer Boskovic ', 41001 Zagreb, Croatia, Yugoslavia

The synthesis of previously inaccessible diethyl 2-oxocyclohexane-1,4-dicarboxylate (10) and its conversion into 4,5,6,7-tetrahydro-3-oxo-2*H*-indazole-6-carboxylic acid (5) is described. The indazole ring formation was shown to be dependent upon the reaction media.

In previous publications [1] we described the synthesis and dimerisation of some isomeric 4,5,6,7-tetrahydro-3-oxo-2*H*-indazole-4- (1), -5- (2), and -7-carboxylic acids (3) (R = R^1 = H), their ethyl esters (R = Et, R^1 = H) and 2-phenyl derivatives (R = H, R^1 = Ph or R = Et, R^1 = Ph). The complexing behaviour of the related 5,5-dicarboxylic acid (4) with divalent metal ions has been examined [2] and exploited for the separation of barium, strontium, and calcium.[3] As part of our continuing interest in the stereochemical characteristics of the reductive ring opening of 4,5,6,7-tetrahydroindazolecarboxylic acids,[4] the synthesis of all possible positional isomers in 4,5,6,7-tetrahydro-3-oxo-2*H*-indazolecarboxylic acid series was necessary. Moreover, our earlier reported biological screening results on indazole-5,5-dicarboxylic acid [3] and similar evaluation of some independently prepared 4,5,6,7-tetrahydroindazole derivatives [5] indicated that these compounds were well tolerated as shown by their LD_{50} values. Some of the latter compounds also showed anti-adrenaline and acetylcholine activities, while the intermediary hydrazone derivatives exhibited good anti-inflammatory activity in mice.

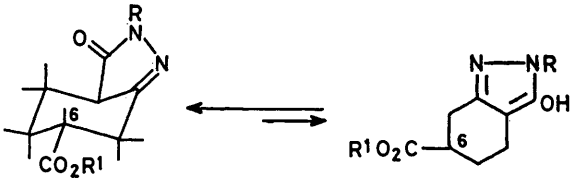


(1) R^2 = CO_2R
(2) R^3 = CO_2R
(3) R^5 = CO_2R
(4) R^3 = R^4 = CO_2R

R=H or Et; R^1=H or Ph; R^2,R^3,R^4,R^5=H unless otherwise stated

In order to complete the title series we now describe the synthesis and properties of the least approachable compounds, namely 4,5,6,7-tetrahydro-3-oxo-2*H*-indazole-6-carboxylic acid (5), its ethyl ester (6), and the corresponding 2-phenyl derivatives (7) and (8).

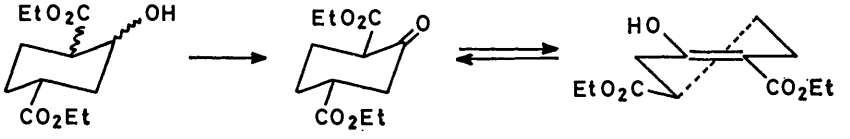
The undesired cyclisation of triethylpentane-1,2,5-tricarboxylate into diethyl 3-oxocyclohexane-1,2-dicarboxylate [6] had, hitherto, prevented the synthesis of the 6-ethoxycarbonyl isomer (7). In considering a new method for the synthesis of the hitherto unknown diethyl 2-oxocyclohexane-1,4-dicarboxylate (10), the oxidation of the stereoisomeric diethyl 2-hydroxycyclohexane-1,4-dicarboxylate [7] (9; a—d) appeared to offer the most convenient route. Thus, the cyclohexanols (10a—d) afforded 2-oxocyclohexane (10) in 38.0, 32.2, 43.4, and 49.5% yields, respectively using Sarett's reagent [8] for oxidation. It is worth noting that the n.m.r. spectrum of compound (10) substantiated its



(5) R = R^1 = H
(6) R = H, R^1 = Et
(7) R = Ph, R^1 = H
(8) R = Ph, R^1 = Et

enolic form as the predominant one, showing an n.m.r. singlet for OH at τ −1.96.

The alicyclic β-keto-ester (10) treated with hydrazine hydrate or phenylhydrazine in 50% ethanol yielded ethyl 4,5,6,7-tetrahydro-3-oxo-2*H*-indazole-6-carboxyl-



(9) (10)

a; *c*-2, *t*-4
b; *t*-2, *t*-4
c; *t*-2, *c*-4
d; *c*-2, *c*-4

ate (7) and ethyl 2-phenyl-4,5,6,7-tetrahydro-3-oxoindazole-6-carboxylate (8), respectively. The hydrolysis of the esters (6) and (8) in 10% hydrochloric acid or 20% methanolic potassium hydroxide gave rise to the corresponding monocarboxylic acids (5) and (7).

The potentiometric titration curves for the tetrahydroindazoles (5), (6), and their 2-phenyl derivatives (7) and (8) in water–dioxan (1 : 1) are in good accord with our previously reported results [1] and show the expected pK values (see the Table). Thus, the lower acidities of the 6-carboxyindazolone (5) and of the already described 5-substituted isomer (2), compared with those of the 4- and 7-isomers, compounds (1) and (3) respectively, is a result of lower inductive effect of the π-electron system of indazolone on the more remote carboxy-group in the former compounds.

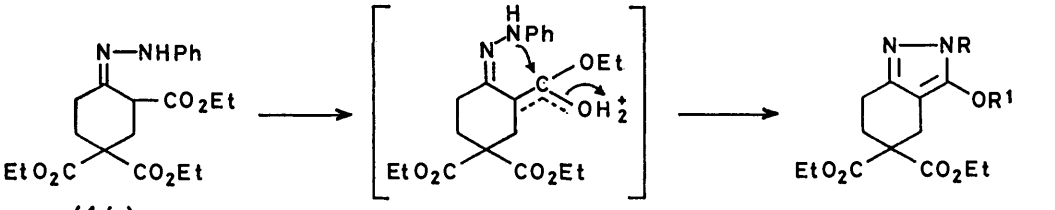
The potentiometric titration curves have also revealed that the isomeric tetrahydroindazolones (1)—(4), as well as the isomer reported here, exist in two tautomeric forms. It is worth noting that the n.m.r. spectrum of the indazolone (4; R = Et, R^1 = Ph, R^3 = R^4 = CO_2R) in $CDCl_3$ solution supported the existence of these two forms exhibiting, for example, signals both at τ 8.83 (6 H, t, 2 × Me) for the enolic form and τ 8.68 and 8.76 (3 H, each, t, 2 × Me) for the keto-form, the latter being also supported by the partial appearance of the 3a-proton at τ 6.5—7.0. In contrast the 2*H*-indazolone (4; R = Et, R^1 = H, R^3 = R^4 = CO_2R) did not exhibit the same resonance characteristics for the 3a-proton, but showed a larger proportion of the enolic form as evidenced by one triplet at τ 8.79 (6 H, 2 × Me) and a quartet at τ 5.82 (4 H, 2 × OCH_2) as well as by broad resonances for OH (enolic) and HN around τ 2.15 (disappearing in D_2O).

Compound	pK_a CO_2H	pK_a −OH(enol)	c/10^{-3}M	ΔpK
(6)		9.73	1.28	
(8)		8.61	1.33	
(5)	6.21	10.55	0.99	4.34
(7)	6.11	9.67	0.77	3.56

The spectral ambiguities with respect to the keto–enol tautomeric forms prompted us to undertake the synthesis of diethyl 3-benzoyloxy-4,5,6,7-tetrahydro-2*H*-indazole (11) and its 2-phenyl derivative (12) which, in turn, showed very convenient solubilities for spectral analyses. Thus, the n.m.r. spectrum of the latter compound (XII) in its benzoylated enolic form exhibited one singlet at τ 6.95 for the isolated methylene protons at position 4. The remaining cyclohexane protons in position 6 and 7 appeared as symetrical triplets centred at τ 7.55 and 7.14. The analogous 3-*O*-ethylindazole derivative (13) obtained in the course of a preparation of indazolone (4; R = Et, R^1 = Ph, R^3 = R^4 = CO_2R) in the acidic media (see below) exhibited a similar spectra pattern for the cyclohexane protons.

It seems likely that the high-yield formation of indazolone in ethanol–water is suppressed in methanolic hydrochloric acid by the formation of an intermediary oxonium ion. Namely, the intermediary hydrazone of triethyl 2-oxocyclohexane-1,5,5-tricarboxylate (14) prepared independently from the corresponding 2-oxocyclohexane,[9] partly cyclised into the unexpected *O*-ethylindazole (20%), possibly through an intermediary oxonium ion and by an elimination of H_2O rather than EtOH.

Thus the *O*-ethylindazole obtained indicated that the hydrazone rather than tautomeric enhydrazine [10] might contribute to this peculiar intramolecular cyclisation.



EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. I.r. spectra were obtained for potassium bromide pellets on a Perkin-Elmer 137 or 257 spectrophotometer. U.v. spectra were taken for solutions in ethanol (unless otherwise stated) with a Beckman DU-2 spectrophotometer. N.m.r. spectra were measured for solutions in deuteriochloroform (unless otherwise stated) on a Varian A60 spectrometer with tetramethylsilane as the internal standard for organic solutions. Mass spectra were measured with a Varian MAT CH7 spectrophotometer. The silica gel (Merck HF_{254}, type 60) which was used for column chromatography and for t.l.c. was activated at 110 °C for 60 min. The products were developed in methylene chloride–methanol (9 : 1) unless otherwise stated and located by exposure to iodine vapour and by u.v. illumination.

Diethyl 2-Oxocyclohexane-1,4-dicarboxylate (10).—Each hydroxy-diester [7] (9; a—d) (0.11—0.29 mmol) dissolved in freshly distilled pyridine (0.54—1.4 ml) was added to the precipitated yellow complex [8] obtained from freshly distilled anhydrous pyridine (0.27—0.7 ml) and chromic anhydride (0.27—0.7 mmol) at 0 °C. The mixture was set aside at room temperature for 24 h in the dark and then the solvent evaporated under diminished pressure. The residue was partitioned between 0.5N-H_2SO_4 (1.35—3.5 ml) and chloroform (4 × 10 ml). The organic layer was washed, dried, and evaporated to leave an oily product which was chromatographed on a silica gel (Merck, 0.08 mm) column.

Methylene chloride eluted an oily product in 38.0, 32.2, 43.4, and 49.5% yields, respectively, b.p. 85 °C at 5×10^{-2} mmHg (Found: C, 59.25; H, 7.6. $C_{12}H_{18}O_5$ requires C, 59.5; H, 7.5%), $\nu_{max.}$ 3 021, 1 739, 1 661, 1 621, and 1 220 cm^{-1}; τ 8.71 and 8.68 (each 3 H, t, 2 × Me), 7.00—8.52 (7 H, m, 3-, 4-, 5-, 6-H), 5.86 and 5.82 (each 2 H, q, 2 × OCH_2), and −1.96 (1 H, s, OH).

Ethyl 4,5,6,7-*Tetrahydro*-3-*oxo*-2-*phenylindazole*-6-*carboxylate* (8).—To a solution of diethyl oxocyclohexane-1,4-dicarboxylate (10) (27.4 mg, 0.11 mmol) in 50% ethanol (1.1 ml) phenylhydrazine (12.5 mg, 1.116 mmol) was added, the mixture heated under reflux for 6 h, and then set aside for 16 h at 0 °C. The crystalline product separated (24 mg, 74%), m.p. 172—173 °C (EtOH–n-hexane) (Found: C, 67.15; H, 6.55; N, 9.5%; Equiv. wt. 284.6. $C_{16}H_{18}N_2O_3$ requires C, 67.1; H, 6.35; N, 9.8%; Equiv. wt. 286.3), $\lambda_{max.}$ 248.5 nm (log ε 4.17), $\lambda_{infl.}$ 269 nm (log ε 4.02), and $\lambda_{min.}$ 221 nm (log ε 3.84); $\nu_{max.}$ 2 882, 1 715, 1 616, 1 600, 1 567, and 750 cm^{-1}.

Ethyl 4,5,6,7-*Tetrahydro*-3-*oxo*-2H-*indazole*-6-*carboxylate* (6).—A solution of oxocyclohexanecarboxylate (10) (56 mg, 0.23 mmol) in 50% ethanol (1 ml) was treated with hydrazine hydrate (14.4 mg, 0.31 mmol) under reflux for 15 h and then for 16 h at 0 °C. The crystals were collected (32.3 mg) in 66.8% yield, m.p. 240—242 °C (EtOH) (Found: C, 56.9; H, 6.65; N, 13.55%; Equiv. wt. 206.6. $C_{10}H_{14}N_2O_3$ requires C, 57.15; H, 6.7; N, 13.35%; Equiv. wt. 210.2); $\lambda_{infl.}$ 239 nm (log ε 3.63), $\lambda_{max.}$ 250 nm (log ε 3.74), and $\lambda_{min.}$ 217 nm (log ε 3.43); $\nu_{max.}$ 3 490, 2 888, 2 703, 1 703, 1 613, and 1 587 cm^{-1}.

4,5,6,7-*Tetrahydro*-3-*oxo*-2-*phenylindazole*-6-*carboxylic Acid* (7).—A solution of ethyl tetrahydro-3-oxo-2-phenylindazole-6-carboxylate (8) (27 mg, 0.096 mmol) in 20% methanolic potassium hydroxide (0.5 ml) was heated under reflux for 4 h and then evaporated to dryness. The residue was dissolved in water and a crystalline product separated by acidification with 10% hydrochloric acid; yield 19 mg (76.8%), m.p. 246—248 °C (EtOH–H_2O) (Found: C, 64.85; H, 5.4; N, 11.0%; Equiv. wt. 259.17. $C_{14}H_{14}N_2O_3$ requires C, 65.1; H, 5.45; N, 10.85%; Equiv. wt. 258.27), $\lambda_{max.}$ 249 nm (log ε 4.18), $\lambda_{infl.}$ 266 nm (log ε 4.03), and $\lambda_{min.}$ 219.5 nm (log ε 3.83); $\nu_{max.}$ 3 130, 2 933, 1 704, 1 610, 1 587, and 753 cm^{-1}.

4,5,6,7-*Tetrahydro*-3-*oxo*-2H-*indazole*-6-*carboxylic Acid* (5).—A solution of ethyl tetrahydro-2-oxo-2*H*-indazole-6-carboxylate (7) (23 mg, 0.11 mmol) in 10% hydrochloric acid (0.7 ml) was heated under reflux for 15 h and then evaporated to dryness after having been dissolved several times in anhydrous ethanol and benzene. The residue crystallised from methanol–water in 12.8 mg (64.2%) yield (Found: C, 52.75; H, 5.7%; Equiv. wt. 182.93. $C_8H_{10}N_2O_3$ requires C, 52.75; H, 5.55%; Equiv. wt. 182.18), $\lambda_{infl.}$ 238 nm (log ε 3.62), $\lambda_{max.}$ 250 nm (log ε 3.75), $\lambda_{min.}$ 217 nm (log ε 3.41); $\nu_{max.}$ 3 145, 2 924, 2 849, 1 681br, and 1 582br cm^{-1}.

Diethyl 3-*Benzoyloxy*-4,5,6,7-*tetrahydro*-2-*phenylindazole*-5,5-*dicarboxylate* (12).—To a solution of 2-phenylindazoledicarboxylate (4) (183.3 mg, 0.52 mmol) in anhydrous pyridine (3.8 ml) benzoyl chloride (0.058 ml, 0.5 mmol) was added. The mixture was stirred for 65 h at room temperature and then poured into chilled water. The methylene chloride extract was washed with 5% hydrochloric acid, 5% sodium hydrogen carbonate, and water, and then dried ($MgSO_4$) and evaporated to give the crude product (231 mg). Preparative t.l.c. [in methylene chloride–methanol (9 : 1); recovery with methylene chloride], gave the product (201 mg, 87%), R_F *ca.* 0.86; m.p. 122—123 °C (ether–n-hexane) (Found: C, 67.7; H, 5.4%; M^+, 462. $C_{26}H_{26}N_2O_6$ requires C, 67.5; H, 5.65%; *M*, 462.48); $\lambda_{max.}$ 240 nm (log ε 4.42), $\lambda_{infl.}$ 254 nm (log ε 4.26), and $\lambda_{min.}$ 218 nm (log ε 4.05); $\nu_{max.}$ 3 070, 2 980, 1 765, 1 755, 1 740, 1 601, 763, 715, and 709 cm^{-1}; τ 8.77 (6 H, t, 2 × Me), 7.55 (2 H, t, 6-H), 7.14 (2 H, t, 7-H), 6.95 (2 H, s, 4-H), 5.79 (4 H, q, 2 × OCH_2) [2.26—2.69 (8 H, m), 1.73—1.98 (2 H, m) aromatic].

Diethyl 3-*Benzoyloxy*-4,5,6,7-*tetrahydroindazole*-5,5-*dicarboxylate* (11).—Following the previously described procedure diethyl tetrahydroindazoledicarboxylate (4), R_F *ca.* 0.22 (282.3 mg, 1 mmol) dissolved in pyridine (7.5 ml) was treated with an equimolar amount of benzoyl chloride at room temperature for 90 min. Chromatography on a silica gel–Celite (1 : 1, 9 g) column and methylene chloride–methanol (99.5 : 0.5) elution afforded the unstable oily product (176 mg, 45.2%), R_F *ca.* 0.49; τ 8.80 (6 H, t, 2 × Me), 7.67 (2 H, t, 6-H), 7.29 (2 H, t, 7-H), 7.02 (2 H, s, 4-H), 5.82 (4 H, q, 2 × OCH_2), 2.10br (1 H, s, NH; disappearing in D_2O) [2.25—2.62 (3 H, m), 1.70—1.90 (2 H, m) aromatic].

Diethyl 3-*Ethoxy*-4,5,6,7-*tetrahydro*-2-*phenylindazole*-5,5-*dicarboxylate* (13).—A solution of triethyl 2-oxocyclohexane-1,5,5-tricarboxylate [9] (172 mg, 0.55 mmol) in methanol (4 ml) and concentrated hydrochloric acid (0.027 ml, 0.33 mmol) was added to a solution of phenylhydrazine (71.38 mg, 0.66 mmol) in methanol (2 ml). The mixture was heated under reflux for 1 h and then set aside for 16 h at room temperature; it was then evaporated to dryness and the residue triturated with methylene chloride. From the methylene chloride solution a mixture of four products (192 mg) was obtained. Preparative t.l.c. [R_F 0.67, in methylene chloride–methanol (9 : 1)] gave diethyl 2-phenyl-4,5,6,7-tetrahydroindazole-5,5-dicarboxylate monohydrate [11] (57 mg, 49.5%) showing the lowest mobility. Rechromatography of the more mobile fractions (five developments with methylene chloride) separated the starting material (76 mg) and the product (24 mg, 20.0%), m.p. 77—78 °C (ether–n-hexane) (Found: C, 65.5; H, 7.0. $C_{21}H_{26}N_2O_5$ requires C, 65.25; H, 6.80%); $\lambda_{max.}$ 253 nm (log ε 4.19), $\lambda_{min.}$ 223 nm (log ε 3.62); $\nu_{max.}$ 3 472, 2 967, 1 751, 1 730, 1 592, 1 580, 752, and 694 cm^{-1}; τ 8.72 and 8.67 (3 H each, t, 2 × Me), 7.63 (2 H, t, 6-H), 7.24 (2 H, t, 7-H), 6.85 (2 H, s, 4-H), 5.82 and 5.79 (2 H, q, 2 × OCH_2), and 2.16—2.82 (5 H, m, aromatic).

Triethyl 2-*Oxocyclohexane*-1,5,5-*tricarboxylate Phenylhydrazone* (14).—To a solution of triethyl 2-oxocyclohexane-1,5,5-tricarboxylate [9] (330 mg, 1.05 mmol) in chloroform (7.5 ml) phenylhydrazine (125 mg, 1.16 mmol) dissolved in chloroform (6.8 ml) was added; the mixture was then heated under reflux for 6 h. This solution was evaporated to leave an oily product (475 mg) which was dissolved in methylene chloride and chromatographed on a silica gel (Merck, 0.05—0.2 mesh, 45 g) column. By elution with methylene chloride–methanol (99 : 1) first the product (320 mg, 75.2%) and then diethyl 2-phenyl-4,5,6,7-tetrahydro-3-oxoindazole-5,5-dicarboxylate monohydrate (58 mg, 14.7%) was obtained. The main product was precipitated from ether–n-hexane as a yellow oil (Found: C, 62.65; H, 7.15; N, 6.95. $C_{21}H_{28}N_2O_6$ requires C, 62.35; H, 6.90; N, 6.95%); $\lambda_{max.}$ 239 and 278 nm (log ε 3.82 and 4.18), $\lambda_{infl.}$ 291 nm (log ε 4.06), $\lambda_{min.}$ 224 and 247 nm (log ε 3.70 and 3.78); $\nu_{max.}$ 3 344, 2 976, 1 724, 1 656, 1 600, and 752 cm^{-1}; τ 8.57—8.87 (9 H, m, 3 × Me), 7.17—8.07 (6 H, m, 3-, 4-, 6-H),

5.85 (4 H, q, 2 × OCH_2), 5.78 (2 H, q, OCH_2), 4.46br (>1 H, s, NHPh), 2.70—3.42 (5 H, m, aromatic), and 0.17br (>1 H, s, NH–N–Ph).

Diethyl 4,5,6,7-Tetrahydro-3-oxo-2-phenylindazole-5,5-dicarboxylate (4).—A solution of the phenylhydrazone of triethyl 2-oxocyclohexane-1,5,5-tricarboxylate [9] (44 mg, 0.109 mmol) in 50% ethanol (2.6 ml) was heated under reflux for 6 h and then cooled and refrigerated overnight. The crystalline product separated in the form of a monohydrate (23 mg, 56%), R_F 0.44 identical (mixed m.p., and u.v. and i.r. spectra) with that obtained previously.[11]

The authors thank Mrs. A. Poturić for technical assistance.

[8,1298 *Received*, 12*th July*, 1978]

REFERENCES

[1] V. Škarić, L. Stuhne, D. Škarić, and V. Turjak-Zebić, *J. Chem. Soc.* (*C*), 1969, 2783.

[2] V. Turjak-Zebić, D. Škarić, and V. Škarić, *Croat. Chem. Acta*, 1969, **41**, 235.

[3] V. Škarić, V. Turjak-Zebić, M. Branica, and D. Škarić, *Croat. Chem. Acta*, 1964, **36**, 221.

[4] D. Škarić, V. Škarić, and V. Turjak-Zebić, *Croat. Chem. Acta*, 1963, **35**, 267.

[5] Babu Lal and A. P. Bhaduri, *Indian J. Chem.*, 1977, **15B**, 359.

[6] Kalianmay Sen and P. Bagchi, *J. Org. Chem.*, 1958, **23**, 1125.

[7] V. Škarić, V. Turjak-Zebić, and D. Škarić, *J.C.S. Perkin I*, 1974, 1406.

[8] G. J. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.

[9] E. Hardegger, P. A. Plattner, and F. Blanck, *Helv. Chim. Acta*, 1944, **27**, 793.

[10] T. A. Favorskaya, S. I. Yakimovich, and V. A. Khrustalev, *Zhur. Org. Khim.*, 1972, **8**(1), 61.

[11] D. Škarić, V. Škarić, V. Turjak-Zebić, and Z. Veksli, *Croat. Chem. Acta*, 1962, **34**, 75.