Chemistry of Heterocyclic Compounds, Vol. 31, No. 3, 1995

DERIVATIVES OF 1-(2-PYRIDYL)-4,5,6,7-TETRAHYDROINDAZOLE

I. A. Strakova, A. Ya. Strakov, and M. V. Petrova

In reactions of oxidation of 1-(2-pyridyl)-3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindazole, the corresponding 4,5-dioxoindazole is obtained, and then 1-(2-pyridyl)-3-methyl-4-carboxy-5-(2-methyl-2-carboxypropyl)pyrazole; in bromination reactions, a series of 5-bromo and 7-bromo derivatives is obtained. From 4,5-dioxoindazole with hydrazides of acids, a series of 4-oxo-5-acylhydrazono derivatives is obtained, and also 1-(2-pyridyl)-3,6,6-trimethyl-4-oxo-5-tosylhydrazono-4,5,6,7-tetrahydroindazole, which, under the action of caustic, gives the 4-oxo-5-diazo derivative.

Derivatives of indazole and other pyrazole-containing condensed systems are attracting attention because of their biological activity and the possibilities of further conversions [1-7]. Therefore, continuing the work reported in [8-14], we have obtained a number of derivatives of 1-(2-pyridyl)-4,5,6,7-tetrahydroindazole.

The oxidation of 1-(2-pyridyl)-3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindazole by selenious acid, following the procedure used in [9], gives the α-diketone Ib. In the IR spectrum of the 4,5-dioxo derivative Ib, intense absorption bands of carbonyl groups are observed at 1725 and 1676 cm^{-1}, and in the PMR spectrum a signal of protons of the $C_{(7)}$-methylene group at 3.73 ppm. Oxidation of the diketone Ib with hydrogen peroxide in a mixture of formic acid and acetic anhydride, in accordance with [9, 15], gives the dicarboxylic acid II. Boiling of the acid II with acetic anhydride leads to the formation of an anhydride – the oxepinopyrazole III, the structure of which is confirmed specifically by the presence of characteristic IR absorption bands of anhydrides at 1777 and 1730 cm^{-1}, and also the corresponding signals of protons in the PMR spectrum (corresponding in number and character).

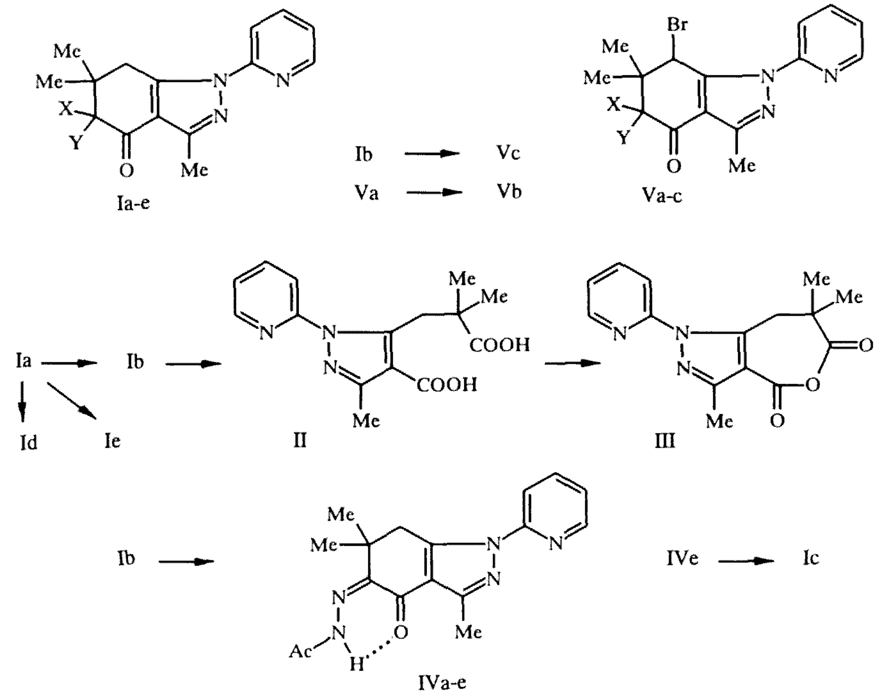
In reactions of the 4,5-dioxo derivative Ib with hydrazides of nicotinic, isonicotinic, salicylic, and 3-bromobenzoic acids, the corresponding 4-oxo-5-acylhydrazonoindazoles IVa-d are obtained; their PMR spectra exhibit downfield signals of NH protons involved in an H-chelate ring (δ_{NH} 14.33-14.61 ppm).

We also obtained the tosylhydrazone IVe, which, when subjected to the action of alkali, is converted to the 4-oxo-5-diazo derivative Ic.

Bromination of the indazole Ia by N-bromosuccinimide (NBS) affords the 7-bromo derivative Va, even with excess of the brominating agent; but bromination of Ia by pyridinium bromide–perbromide (PBP), depending on the mole ratio of reagents, gives the 4-oxo-5-bromo derivative (Id) and the 4-oxo-5,5-dibromo derivative (Ie), respectively. This is consistent with the relationships in the bromination of 4-oxo-4,5,6,7-tetrahydroindazoles that were noted in [9, 11]. The 5,7-dibromo derivative Vb was obtained by the action of PBP on the 7-bromoindazole Va. The 4,5-dioxo-7-bromoindazole Vc was obtained from the 4,5-dioxoindazole Ib by the action of either N-bromosuccinimide or pyridinium bromide–perbromide, which is observed for the first time in the 6,6-dimethyl-4,5,6,7-tetrahydroindazole series.

As a result of the introduction of a bulky substituent – bromine – into position 5 or 7, the $C_{(6)}$-methyl groups become magnetically nonequivalent and are observed in the PMR spectrum, in contrast to 5,7-unsubstituted 6,6-dimethyl-4,5,6,7-tetrahydroindazoles and their 5-oxo (Ib), 5-diazo (Id), and 5-hydrazono (IV) derivatives, in the form of two signals. The signal of the remaining $C_{(7)}$ proton in compounds Va-c undergoes a considerable downfield shift to 6.36 ppm (Va), 6.53 ppm (Vb), and 6.58 ppm (Vc).

Riga Technical University, Riga LV-1658. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 351-354, March, 1995. Original article submitted December 29, 1994.



1) I,Va) X = Y = H; Ib) XY = O; Ic) XY = N^+ = N^-; Id) X = H, Y = Br; Ie) X = Y = Br; Vb) X = H, Y = Br; Vc) XY = O; IVa) Ac = nicotinyl; IVb) Ac = isonicotinyl; IVc) Ac = salicylyl; IVd) Ac = 3-bromobenzoyl; IVe) Ac = tosyl.

EXPERIMENTAL

The IR spectra were taken in a Specord 75-IR spectrometer on suspensions of the substances in white mineral oil (1500-1800 cm^{-1}) or hexachlorobutadiene (2000-3600 cm^{-1}) without indication of C–H stretching vibration frequencies in the 2800-3050 cm^{-1} interval. The PMR spectra were taken in $CDCl_3$ or DMSO-D_6 in a Bruker WH-90/DS spectrometer (90 MHz), internal standard TMS.

Elemental analyses of the compounds for C, H, N, S, and Br matched the calculated values.

1-(2-Pyridyl)-3,6,6-trimethyl-4,5-dioxo-4,5,6,7-tetrahydroindazole (Ib, $C_{15}H_{15}N_3O_2$). A mixture of 1.02 g (4 mmoles) of the indazole Ia (obtained in accordance with [14]) and 0.52 g (4 mmoles) of selenious acid in 6 ml of glacial acetic acid was left for 48 h at 20°C, heated for 1 h on a boiling water bath, and then refluxed for 1 h. After cooling, the selenium was filtered off, 2 ml of water was added, and the solution was neutralized with a concentrated aqueous ammonium hydroxide solution. The resulting precipitate was crystallized from acetic acid. Obtained 1.00 g (92%) of Ib, mp 162-164°C. IR spectrum, cm^{-1}: 1725, 1670, 1620, 1596, 1580, 1540. PMR spectrum ($CDCl_3$), ppm: 1.36 (6H, s, $2CH_3$), 2.56 (3H, s, CH_3), 3.73 (2H, s, CH_2), 7.02-8.44 mp. (4H, m, C_5H_4N).

1-(2-Pyridyl)-3-methyl-4-carboxy-5-(2-methyl-2-carboxypropyl)pyrazole (II, $C_{15}H_{17}N_3O_4$). To a solution of 1.62 g (6 mmoles) of Ib in a solution of 5.5 ml of 90% formic acid and 7.0 ml of acetic anhydride, with cooling, 1.6 ml of a 30% solution of H_2O_2 was added cautiously, dropwise. The mixture was heated for 1.5 h on a boiling water bath, the hot mixture was filtered, and the filtrate was diluted with 50 ml of water. Obtained as a precipitate 1.40 g (77%) of II, mp 234-236°C (from 50% acetic acid). IR spectrum, cm^{-1}: 1690, 1680, 1630, 1590, 1580, 1550, 2500-3200. PMR spectrum (DMSO-D_6), ppm: 0.90 (6H, s, $2CH_3$), 2.47 (3H, s, CH_3), 3.96 (2H, s, CH_2), 7.43-8.30 (4H, s, C_5H_4N), 12.23 (2H, 2COOH).

4,4,8-Trimethyl-6-(2-pyridyl)-1,3-dioxo-1,3,4,5-tetrahydro-6H-oxepino[3,4-c]pyrazole (III, $C_{15}H_{15}N_3O_3$). A 1.52 g quantity (5 mmoles) of the acid II in 30 ml of acetic anhydride was refluxed 4 h. The acetic anhydride was removed in a rotary evaporator, the residue was dissolved in a minimum quantity of benzene, and hexane was added to the solution. Obtained 0.85 g (60%) of III, mp 93-95°C. IR spectrum, cm^{-1}: 1777, 1730, 1600, 1580, 1555. PMR spectrum ($CDCl_3$), ppm: 1.44 (6H, s, $2CH_3$), 2.56 (3H, s, CH_3), 3.64 (2H, s, CH_2), 7.27-8.47 mp (4H, m, C_5H_4N).

1-(2-Pyridyl)-3,6,6-trimethyl-4-oxo-5-acylhydrazono-4,5,6,7-tetrahydroindazoles (IVa, IVb, $C_{21}H_{20}N_6O_2$; IVc, $C_{22}H_{21}N_5O_3$; IVd, $C_{22}H_{20}BrN_5O_2$). A 0.52-g quantity (2 mmoles) of Ib and an equimolar quantity of the appropriate hydrazide, in 10 ml of ethanol, was refluxed for 2 h. In the cases of IVa and IVb, after cooling, the reaction mixture was diluted with 20 ml of water, and compounds IVa-d were obtained.

IVa. Yield 65%, mp 166-167°C (from ethanol). IR spectrum, cm^{-1}: 1700, 1693, 1640, 1590, 1543, 1510, 3220, 3060. PMR spectrum ($CDCl_3$), ppm: 1.36 (6H, s, $2CH_3$), 2.56 (3H, s, CH_3), 3.61 (2H, s, CH_2), 7.25-9.14 (8H, m, $2C_5H_4N$), 14.47 (1H, NH).

IVb. Yield 63%, mp 164-165°C (from ethanol). IR spectrum, cm^{-1}: 1700, 1690, 1635, 1595, 1580, 1545, 1505, 3202-3160. PMR spectrum ($CDCl_3$), ppm: 1.42 (6H, s, $2CH_3$), 2.62 (3H, s, CH_3), 3.57 (2H, s, CH_3), 7.27-8.78 (8H, m, $2C_5H_4N$), 14.50 (1H, NH).

IVc. Yield 56%, mp 222-223°C (from DMF). IR spectrum, cm^{-1}: 1655, 1633, 1615, 1595, 1580, 1545, 1515, 1510, 3450, 3150, 3080. PMR spectrum ($CDCl_3$), ppm: 1.47 (6H, s, CH_3), 2.61 (3H, s, CH_3), 3.61 (2H, s, CH_2), 6.91-8.44 (8H, m, C_5H_4N), 12.05 (1H, OH), 14.61 (1H, NH).

IVd. Yield 69%, mp 187-189°C (from DMF). IR spectrum, cm^{-1}: 1687, 1633, 1580, 1565, 1540, 3165, 3100, 3080. PMR spectrum ($CDCl_3$), ppm: 1.44 (6H, s, $2CH_3$), 2.61 (3H, s, CH_3), 3.56 (2H, s, CH_2), 7.27-8.44 (8H, m, C_6H_4, C_5H_4N), 14.33 (1H, NH).

1-(2-Pyridyl)-3,6,6-trimethyl-4-oxo-5-tosylhydrazono-4,5,6,7-tetrahydroindazole (IVe, $C_{22}H_{23}N_5O_3S$). A 1.35-g quantity (5 mmoles) of the diketone Ib and 0.93 g (5 mmoles) of tosylhydrazide in 20 ml of methanol was refluxed for 2 h. After cooling, obtained 1.65 g (75%) of IVe, mp of yellowish crystals 160°C (decomp.) (from an ethanol–DMF mixture, 1:1). IR spectrum, cm^{-1}: 1633, 1595, 1580, 1550, 3120, 3070. PMR spectrum ($CDCl_3$), ppm: 1.22 (6H, m, $2CH_3$), 2.42 (3H, s, CH_3), 2.56 (3H, s, CH_3), 3.46 (2H, s, CH_2), 7.28-8.44 (8H, m, C_6H_4, C_5H_4N), 12.71 (1H, NH).

1-(2-Pyridyl)-3,6,6-trimethyl-4-oxo-5-diazo-4,5,6,7-tetrahydroindazole (Ic, $C_{15}H_{15}N_5O$). Suspended 0.87 g (2 mmoles) of the tosylhydrazone IVe in 30 ml of an aqueous caustic solution containing 0.40 g (10 mmoles) of NaOH; the mixture was heated for 1 h on a water bath while stirring, after which 12 ml of ethanol was added. The precipitate was filtered off and crystallized from a 1:1 mixture of benzene and hexane. Obtained 0.50 g (90%) of bright yellow crystals of Ic, mp 157-158°C (decomp.). IR spectrum, cm^{-1}: 1620, 1595, 1580, 1543, 1520, 3090, 3070, 2090. PMR spectrum ($CDCl_3$), ppm: 1.37 (6H, s, $2CH_3$), 2.60 (3H, s, CH_3), 3.46 (2H, s, CH_2), 7.22-8.40 (4H, m, C_5H_4N).

1-(2-Pyridyl)-3,6,6-trimethyl-4-oxo-5-bromo-4,5,6,7-tetrahydroindazole (Id, $C_{15}H_{16}BrN_3O$). A 0.40-g quantity (1.5 mmoles) of the indazole Ia, 0.50 g (1.5 mmoles) of pyridinium bromide–perbromide (PBP), and 0.1 ml of H_2SO_4 in 5 ml of acetic acid was refluxed for 10 min. The mixture was diluted with 50 ml of water. The resinous substance that solidified upon triturating was crystallized from ethanol. Obtained 0.48 g (96%) of Id, mp 132-133°C. IR spectrum, cm^{-1}: 1680, 1650, 1595, 1580, 1550, 1515, 3080. PMR spectrum ($CDCl_3$), ppm: 1.20 (3H, s, CH_3), 1.40 (3H, s, CH_3), 2.58 (3H, s, CH_3), 3.42 (2H, s, CH_2), 4.11 (1H, s, CH), 7.22-8.53 (4H, m, C_5H_4N).

1-(2-Pyridyl)-3,6,6-trimethyl-4-oxo-5,5-dibromo-4,5,6,7-tetrahydroindazole (Ie, $C_{15}H_{15}Br_2N_3O$). A 0.40-g quantity (1.5 mmoles) of the indazole Ia, 1.00 g (3 mmoles) of PBP, and 0.1 ml of H_2SO_4 in 5 ml of acetic acid was refluxed for 10 min, after which the reaction mixture was cooled and diluted with 50 ml of water. The colorless solid substance was crystallized from 80% ethanol. Yield 0.59 g (95%), mp 150-152°C. IR spectrum, cm^{-1}: 1688, 1632, 1610, 1595, 1580, 1555. PMR spectrum ($CDCl_3$), ppm: 1.22 (3H, s, CH_3), 1.62 (3H, s, CH_3), 2.56 (3H, s, CH_3), 3.53 (1H, CH), 3.58 (1H, CH), 7.22-8.40 (4H, m, C_5H_4N).

1-(2-Pyridyl)-3,6,6-trimethyl-4-oxo-7-bromo-4,5,6,7-tetrahydroindazole (Va, $C_{15}H_{16}BrN_3O$). A 1.28-g quantity (5 mmoles) of the indazole Ia and 0.89 g (5 mmoles) of NBS in 25 ml of dry CCl_4 was refluxed for 3 h; the succinimide was filtered from the hot mixture, two-thirds of the volume of CCl_4 was driven off, and 15 ml of hexane was added to the residue. Obtained 1.30 g (78%) of Va, mp 146-148°C. IR spectrum, cm^{-1}: 1680, 1650, 1637, 1600, 1588, 1556. PMR spectrum ($CDCl_3$), ppm: 1.27 (3H, s, CH_3), 1.38 (3H, s, CH_3), 2.53 (3H, s, CH_3), 2.24 (1H, dd, $C_{(5)}-H_A$, J = 16.8, 1.3 Hz), 2.91 (1H, dd, $C_{(5)}-H_B$, J = 16.8, 0.9 Hz), 6.36 (1H, dd, $C_{(7)}-H$, J = 1.3, 0.9 Hz), 7.22-8.49 (4H, m, C_5H_4N).

Compound Va was also obtained with a 1:2 mole ratio of Ia to NBS.

1-(2-Pyridyl)-3,6,6-trimethyl-4-oxo-5,7-dibromo-4,5,6,7-tetrahydroindazole (Vb, $C_{15}H_{15}Br_2N_3O$). A 0.50-g quantity (1.5 mmoles) of the indazole Va and 0.5 g (1.5 mmoles) of PBP in 5 ml of acetic acid was refluxed for 10 min, cooled, and diluted with 50 ml of water. The precipitated Vb was crystallized from ethanol. Obtained 0.55 g (88%) of colorless crystals, mp 180-182°C. IR spectrum, cm^{-1}: 1695, 1648, 1610, 1590, 1582, 1560. PMR spectrum ($CDCl_3$), ppm: 1.24 (3H, s, CH_3), 1.62 (3H, s, CH_3), 2.56 (3H, s, CH_3), 5.17 (1H, s, $C_{(5)}-H$), 6.53 (1H, s, $C_{(7)}-H$), 7.31-8.44 (4H, m, C_5H_4N).

1-(2-Pyridyl)-3,6,6-trimethyl-4,5-dioxo-7-bromo-4,5,6,7-tetrahydroindazole (Vc, $C_{15}H_{14}BrN_3O_2$). A 0.26-g quantity (1 mmole) of the diketone Ib, 0.33 g (1 mmole) of PBP, and 0.1 ml of H_2SO_4 in 10 ml of acetic acid was refluxed for 1 h, cooled, and diluted with 80 ml of water. The precipitate was recrystallized from 90% ethanol. Obtained 0.25 g (72%) of Vc, mp 178-180°C. IR spectrum, cm^{-1}: 1740, 1693, 1685, 1650, 1622, 1598, 1585, 1555, 1525. PMR spectrum ($CDCl_3$): 1.47 (3H, s, CH_3), 1.64 (3H, s, CH_3), 2.58 (3H, s, CH_3), 6.58 (1H, s, $C_{(7)}-H$), 7.28-8.49 (4H, m, C_5H_4N).

Compound Vc was also obtained with a 65% yield from Ib and NBS by refluxing for 3 h in CCl_4, separating off the succinimide, and driving off the CCl_4.

REFERENCES

1. O. Barbet, M. Minjat, A.-F. Petavy, and J. Paris, Eur. J. Med. Chem., **21**, 359 (1986).
2. Y. Fujimura, Y. Sharaki, Y. Nowata, and I. Matsunaga, Yakugaku Zasshi, **106**, 1002 (1986).
3. H. Kawabuko, T. Sone, K. Wakigawa, and T. Narita, Yakugaku Zasshi, **107**, 28 (1987).
4. S. Sequeria and S. Seshadri, Indian J. Chem. B, **26**, 436 (1987).
5. Ta-Shue Chou, Rnei-Chih Chang, J. Org. Chem., **58**, 493 (1993).
6. U. Wrzeciono, E. Linkowska, K. Majewska, A. Gzella, and K. Stochla, Pharmazie, **48**, 582 (1993).
7. D. B. Rubinov, A. G. Mikhailovskii, and F. A. Lakhvich, Khim. Geterotsikl. Soedin., No. 12, 1617 (1992).
8. É. Yu. Gudrinietse, I. A. Strakova, A. Ya. Strakov, D. R. Zitsane, and A. F. Ievin'sh, Dokl. Akad. Nauk SSSR, **210**, 1362 (1973).
9. É. Yu. Gudrinietse, A. Ya. Strakov, I. A. Strakova, D. R. Zitsane, and A. F. Ievin'sh, Dokl. Akad. Nauk SSSR, **216**, 1293 (1974).
10. A. Ya. Strakov, I. A. Strakova, D. R. Zitsane, and É. Yu. Gudrinietse, Izv. Akad. Nauk Latv. SSR, Ser. Khim., No. 6, 737 (1973).
11. A. Ya. Strakov, I. A. Strakova, D. R. Zitsane, and É. Yu. Gudrinietse, Izv. Akad. Nauk Latv. SSR, Ser. Khim., No. 1, 68 (1974).
12. I. A. Strakova, A. Ya. Strakov, L. R. Yapinya, D. R. Zitsane, and É. Yu. Gudrinietse, Izv. Akad. Nauk Latv. SSR, Ser. Khim., No. 1, 100 (1975).
13. D. R. Zitsane and A. Ya. Strakov, Izv. Akad. Nauk Latv. SSR, Ser. Khim., No. 6, 742 (1976).
14. I. A. Strakova, A. Ya. Strakov, and M. V. Petrova, Latv. Khim. Zurn., No. 6 (1994) (in press).
15. H. Frank and J. Turovski, Lieb. Ann. Chem., **724**, 94 [year not given].