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2-AMINO-6-PHENYL-7,8-DIHYDROINDAZOLO[4,5-d]THIAZOLES

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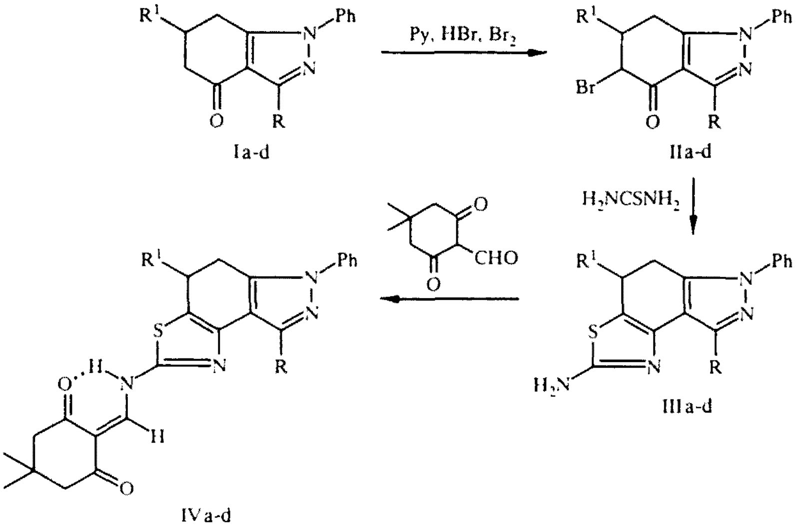
Treatment of 4-oxo-1-phenyl-4,5,6,7-tetrahydroindazole and its 3-methyl, 6-phenyl, and 3-methyl-6-phenyl substituted derivatives with pyridinium bromide-perbromide and subsequent reaction of the 5-bromo derivatives obtained with thiourea gave 2-amino-6-phenyl-7,8-dihydroindazolo[4,5-d]thiazole and its corresponding substituted derivatives. The condensation of these products with 2-formyldimedone led to their 4,4-dimethyl-2,6-dioxocyclohexylidene derivatives.

Various condensed systems have been obtained by us previously from 4,5-difunctional 4,5,6,7-tetrahydroindazoles. These include indazolo[4,5-d]imidazoles [1], indazolo[4,4-5',4']isoxazoles [2], indazolo[4,5-c]pyrazoles [3], indazolo[4,5-d]pyrimidines [2], pyazolo[4,3-*a*]acridines [4], pyrazolo[4,3-*a*]phenazines [5-7], and indazolo[4,5-b]diazepines [8]. In view of the current increasing interest in condensed systems containing thiazoles [9, 10] we have synthesized the indazolo[4,5-d]thiazoles (IIIa-d) and (IVa-d) starting from the 4-oxo-4,5,6,7-tetrahydroindazoles (Ia-d) through their 4-bromo derivatives (IIa-d) by the scheme indicated below.



I—IVa $R = R^1 = H$; b $R = H$; $R^1 = Ph$; c $R = Me$, $R^1 = H$; d $R = Me$, $R^1 = Ph$

The bromination of the tetrahydroindazoles (I) was carried out with pyridinium bromide-perbromide by briefly (10-30 min) boiling the reactants in glacial acetic acid. This method has already been used previously to obtain 5-bromo-4-oxo-4,5,6,7-tetrahydroindazoles [11], including compound (IId) [12].

Reaction of the bromides (IIa-d) with thiourea occurred on extended (5-7 h) boiling of the reactants in ethanol. After diluting the reaction mixture with water it was expedient to add an aqueous solution of ammonium hydroxide to alkaline reaction. The aminodihydroindazolothiazoles (III) precipitated in this way were recrystallized from ethanol. The 4,6-diphenyl substituted product (IIIb) crystallized with a molecule of ethanol. It melted losing ethanol at 135-140°C, then resolidified, and melted a second time at 189-190°C.

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The primary amines (III) readily condense at the amino group with 2-formyldimedone in alcohol at 70-75°C being converted into the corresponding 4,4-dimethyl-2,6-dioxocyclohexylidenemethyl derivatives (IVa-d).

The structures of all the compounds synthesized were confirmed by data of PMR and IR spectra. The frequency of the carbonyl group absorption of the bromoketones (II) was raised compared to ketones (I) by 15 cm^{-1} on average and was detected at 1676-1682 cm^{-1}. The stretching vibrations of the amino group of compounds (IIIa) and (IIIc) were displaced as a narrow maximum at 3430-3440 and a wide band at 3280-3370 cm^{-1}, while amines (IIIb) and (IIId) were characterized by only a wide intense absorption band at 3260-3360 cm^{-1}. The primary amino group of compounds (III) is also displayed clearly in the PMR spectra as a broadened singlet at 5.00-6.00 ppm. The data of PMR and IR spectra of the condensation products (IV) corresponded with the characteristic spectra of N-monosubstituted 2-amino-methylenedimedones reported in [13, 14].

EXPERIMENTAL

The IR spectra were taken on a Specord 75 IR spectrometer for suspensions of substances in Nujol (1500-1800 cm^{-1}) and hexachlorobutadiene (2000-3600 cm^{-1}). The frequencies of the stretching vibrations of C – H bonds in the 2800-3050 cm^{-1} region are not given. The PMR spectra were taken in $CDCl_3$ on a Bruker WH 90/DS (90 MHz) instrument, the internal standard was TMS.

The initial indazoles (Ia-d) were obtained by known procedures [15-17].

5-Bromo-4-oxo-1-phenyl-4,5,6,7-tetrahydroindazole (IIa). A solution of pyridinium bromide-perbromide (1.60 g: 5 mmole) in acetic acid (25 ml) was added to a solution of compound (Ia) (1.06 g: 5 mmole) in acetic acid (10 ml). The mixture was boiled for 15 min and water (50 ml) was added to the hot reaction mixture. The oily substance formed readily hardened and was recrystallized from ethanol. Yield was 0.85 g (58%) of mp 151-153°C. IR spectrum: 1682, 1650, 1600, 1545, 1505 cm^{-1}. PMR spectrum: 2.51-3.49 (4H, m, 6- and 7-H); 4.57 (1H, t, J = 3 Hz, 5-H); 7.41-7.56 (5H, m, H_{Ph}); 8.09 ppm (1H, s, 3-H). Found, %: C 53.50; H 3.99; Br 27.30; N 9.70. $C_{13}H_{11}BrN_2O$. Calculated, %: C 53.63; H 3.81; Br 27.44; N 9.62.

The bromo compounds (IIb-d) were obtained by the procedure described above from equivalent quantities of 4-oxo-4,5,6,7-tetrahydroindazoles (Ib-d) and pyridinium bromide-perbromide.

5-Bromo-4-oxo-1,6-diphenyl-4,5,6,7-tetrahydroindazole (IIb). Yield was 49%, mp 167-169°C (from glacial CH_3COOH). IR spectrum: 1682, 1646, 1598, 1544, 1500 cm^{-1}. PMR spectrum: 3.04 (1H, m, 6-H); 3.56 (2H, m, 7-H); 4.53 (1H, d, J = 2 Hz, 5-H); 7.33-7.41 (10H, m, H_{Ph}); 8.16 ppm (1H, s, 3-H). Found, %: C 62.32; H 4.14; Br 21.60; N 7.60. $C_{19}H_{15}BrN_2O$. Calculated, %: C 62.14; H 4.12; Br 21.76; N 7.63.

5-Bromo-3-methyl-4-oxo-1-phenyl-4,5,6,7-tetrahydroindazole (IIc). Yield was 66%, mp 160-161°C (from ethanol). IR spectrum: 1674, 1602, 1544, 1516 cm^{-1}. PMR spectrum: 2.53 (3H, s, 3-Me); 2.51-3.42 (4H, m, 6- and 7-H): 4.56 (1H, d, J = 4 Hz, 5-H); 7.42 ppm (5H, m, H_{Ph}). Found, %: C 54.98; H 4.30; Br 26.06; N 9.12. $C_{14}H_{13}BrN_2O$. Calculated, %: C 55.10; H 4.29; Br 26.18; N 9.18.

5-Bromo-3-methyl-4-oxo-1,6-diphenyl-4,5,6,7-tetrahydroindazole (IId). Yield was 51%, mp 182-184°C (from ethanol). IR spectrum: 1682, 1598, 1550, 1514 cm^{-1}. PMR spectrum: 2.57 (3H, s, 3-Me); 3.0 (1H, m, 6-H); 3.53 (2H, m, 7-H); 4.49 (1H, d, J = 3 Hz, 5-H); 7.29-7.49 ppm (10H, m, H_{Ph}). Found, %: C 63.10; H 4.37; Br 20.81; N 7.30. $C_{20}H_{17}BrN_2O$. Calculated, %: C 63.00; H 4.50; Br 20.96; N 7.35.

2-Amino-6-phenyl-7,8-dihydroindazolo[4,5-d]thiazole (IIIa). The bromoketone (IIa) (0.87 g:3 mmole) was boiled with thiourea (0.23 g: 3 mmole) in ethanol (20 ml) for 7 h. The mixture was cooled, and water (50 ml) and conc. NH_4OH solution (1 ml) were added. The precipitate of product (IIIa) was filtered off and recrystallized from ethanol. Yield was 0.42 g (53%), mp 229-231°C. IR spectrum: 1632, 1598, 1564, 1524, 1505, 3440, 3280-3340, 3100 cm^{-1}. PMR spectrum: 2.82-3.24 (4H, m, 7- and 8-H); 6.00 (2H, br s, NH_2); 7.42 (5H, m, H_{Ph}); 7.67 ppm 1H, s, 4-H). Found, %: C 62.50; H 4.38; N 20.70; S 12.01. $C_{14}H_{12}N_4S$. Calculated, %: C 62.66; H 4.51; N 20.88; S 11.95.

Amines (IIIb-d) were synthesized analogously from equivalent quantities of bromoketones (IIb-d) and thiourea.

2-Amino-6,8-diphenyl-7,8-dihydroindazolo[4,5-d]thiazole (IIIb). IIIb·C_2H_5OH. Yield was 63%, mp 135-140°C (from ethanol). IR spectrum: 1658, 1635, 1618, 1602, 1564, 1530 1502, 3300-3350, 3100 cm^{-1}. PMR spectrum: 1.22 (3H, t, J = 7 Hz, Me_{Et}); 1.53 (1H, br s, OH_{Et}); 3.31 (2H, m, 7-H); 3.71 (2H, q, J = 7 Hz, H_{Et}); 4.33 (1H, m, 8-H); 5.09 (2H, br s, NH_2); 7.27-7.58 (10H, m, H_{Ph}); 7.84 ppm (1H, s, 4-H). Found, %: C 67.51; H 5.58; N 14.49; S 8.20. $C_{20}H_{16}N_4S \cdot C_2H_5OH$. Calculated, %: C 67.66; H 5.68; N 14.35; S 8.21. Compound (IIIb)·C_2H_5OH was melted to remove ethanol and amine (IIIb) obtained in quantitative yield. mp 189-190°C. IR spectrum: 1655, 1630, 1600, 1570, 1530, 1500, 3380, 3260, 3100 cm^{-1}. PMR spectrum: 3.27 (2H, m, 7-H); 4.35 (1H, m, 8-H); 5.76 (2H, br s, NH_2); 7.24-7.78 (10H, m, H_{Ph}); 7.80 ppm (1H, s, 4-H). Found, %: C 69.82; H 4.77; N 16.20, S 9.20. $C_{20}H_{16}N_4S$. Calculated, %: C 69.74; H 4.68; N 16.27; S 9.31.

2-Amino-4-methyl-6-phenyl-7,8-dihydroindazolo[4,5-d]thiazole (IIIc). Yield was 71%, mp 180-182°C (from 70% ethanol). IR spectrum: 1634, 1600, 1578, 1558, 1530, 1510, 3440, 3270-3300, 3100 cm^{-1}. PMR spectrum: 2.56 (3H, s, 4-Me); 2.72-3.13 (4H, m, 7- and 8-H); 5.07 (2H, br s, NH_2); 7.40 ppm (5H, m, H_{Ph}). Found, %: C 63.63; H 5.02; N 19.90; S 11.25. $C_{15}H_{14}N_4S$. Calculated, %: C 63.80; H 5.00; N 19.84; S 11.35.

2-Amino-4-methyl-6,8-diphenyl-7,8-dihydroindazolo[4,5-d]thiazole (IIId). Yield was 55%, mp 114-116°C (from ethanol). IR spectrum: 1646, 1600, 1570, 1550, 1530, 1510, 3260-3340, 3160 cm^{-1}. PMR spectrum: 2.58 (3H, s, 4-Me); 3.22 (2H, m, 7-H); 4.29 (1H, m, 8-H); 5.00 (2H, br s, NH_2); 7.24-7.35 ppm (10H, m, H_{Ph}). Found, %: C 70.30; H 5.18; N 15.60; S 8.78. $C_{21}H_{18}N_4S$. Calculated, %: C 70.36; H 5.06; N 15.36; S 8.94.

2-(4,4-Dimethyl-2,6-dioxocyclohexylidenemethylamino)-6-phenyl-7,8-dihydroindazolo[4,5-d]thiazole (IVa). A solution of 2-formyldimedone (0.37 g: 2 mmole) in ethanol (10 ml) heated to 70-75°C was added to a solution of amine (IIIa) (0.54 g: 2 mmole) in ethanol (10 ml) at the same temperature. The precipitated solid was filtered off and recrystallized from DMF−water (10:1). Yield was 0.46 g (55%), mp 225-227°C. IR spectrum: 1678, 1606, 1570, 1514, 3100 cm^{-1}. PMR spectrum: 1.11 (6H, s, Me_{chx}); 2.44 (2H, s, H_{chx}); 2.49 (2H, s, H_{chx}); 3.17 (4H, m, 7- and 8-H); 7.42 (5H, m, H_{Ph}); 7.92 (1H, s, 4-H); 8.75 (1H, d, J = 15 Hz, =C−); 13.08 ppm (1H, d, J = 15 Hz, NH). Found, %: C 66.16; H 5.30; N 13.50; S 7.71. $C_{23}H_{22}N_4O_2S$. Calculated, %: C 66.00; H 5.30; N 13.39; S 7.66.

Compounds (IVb-d) were obtained analogously from equimolar quantities of amines (IIIb-d) and 2-formlydimedone.

2-(4,4-Dimethyl-2,6-dioxocyclohexylidenemethylamino)-6,8-diphenyl-7,8-dihydroindazolo[4,5-d]thiazole (IVb). Yield was 48%, mp 228-230°C (from DMF−water, 10:1). IR spectrum: 1686, 1614, 1572, 1500, 3070 cm^{-1}. PMR spectrum: 1.04 (6H, s, Me_{chx}); 2.40 (2H, s, H_{chx}); 2.42 (2H, s, H_{chx}); 3.26-3.37 (2H, m, 7-H); 4.44 (1H, m, 8-H); 7.37-7.42 (10H, m, H_{Ph}); 7.93 (1H, s, 4-H); 8.71 (1H, d, J = 12.3 Hz, =CH−); 12.93 ppm (1H, d, J = 12.3 NH). Found, %: C 70.28; H 5.20; N 11.41; S 6.40. $C_{29}H_{26}N_4O_2S$. Calculated, %: C 70.42; H 5.30; N 11.33; S 6.48.

2-(4,4-Dimethyl-2,6-dioxocyclohexyldienemethylamino)-4-methyl-6-phenyl-7,8-dihydroindazolo[4,5-d]thiazole (IVc). Yield was 81%, mp 258-259°C (from DMF−water, 10:1). IR spectrum: 1668, 1608, 1568, 1510, 3080 cm^{-1}. PMR spectrum: 1.08 (6H, s, Me_{chx}); 2.42 (2H, s, H_{chx}); 2.47 (2H, s, H_{chx}); 2.58 (3H, s, 4-Me); 3.07 (4H, m, 7- and 8-H); 7.39 (5H, m, H_{Ph}); 8.72 (1H, d, J = 11.5 Hz, =CH−); 13.08 ppm (1H, d, J = 11.5 Hz, NH). Found, %: C 66.50; H 5.48; N 12.90; S 7.30. $C_{24}H_{24}N_4O_2S$. Calculated, %: C 66.64; H 5.59; N 12.95; S 7.41.

2-(4,4-Dimethyl-2,6-dioxocyclohexylidenemethylamino)-4-methyl-6,8-diphenyl-7,8-dihydroindazolo[4,5-d]thiazole (IVd). Yield was 63%, mp 188-189°C (from ethanol). IR spectrum: 1665, 1610, 1570, 1505, 3090 cm^{-1}. PMR spectrum: 1.08 (6H, s, Me_{chx}); 2.42 (2H, s, H_{chx}); 2.47 (2H, s, H_{chx}); 2.61 (3H, s, 4-Me); 3.22-3.36 (2H, m, 7-H); 4.42 (1H, m, 8-H); 7.23-7.40 (10H, m, H_{Ph}); 8.69 (1H, d, J = 12.5 Hz, =CH−); 13.08 ppm, (1H, d, J = 12.5 Hz, NH). Found, %: C 70.64; H 5.50; N 11.15; S 6.30. $C_{30}H_{28}N_4O_2S$. Calculated, %: C 70.84; H 5.55; N 11.02; S. 6.30.

REFERENCES

1. Yu. B. Sliede, A. Ya. Strakov, and E. Yu. Gudrinietse, Izv. Akad. Nauk Latv. SSR, Ser. Khim., No. 1, 111 (1977).
2. A. Ya. Strakov, M. T. Opmane, and E. Yu. Gudrinietse, Izv. Akad. Nauk Latv. SSR, Ser. Khim., No. 2, 234 (1976).
3. I. A. Strakova, A. Ya. Strakov, and E. Yu. Gudrinietse, Izv. Akad. Nauk Latv. SSR, Ser. Khim., No. 5, 610 (1974).
4. A. Ya. Strakov, M. T. Opmane, and E. Yu. Gudrinietse, Izv. Akad. Nauk Latv. SSR, Ser. Khim., No. 1, 101 (1976).
5. E. Yu. Gudrinietse, A. Ya. Strakov, I. A. Strakova, D. R. Zitsane, and A. F. Ievinyl, Dokl. Akad. Nauk SSSR, **216**, 1293 (1974).
6. A. Ya. Strakov, Yu. B. Sliede, D. R. Zitsane, and I. A. Strakova, Akad. Nauk Latv. SSR, Ser. Khim., No. 1, 81 (1977).
7. I. A. Strakova, A. Ya. Strakov, and M. V. Petrova, Khim. Geterotsikl. Soedin., No. 3, 351 (1995).
8. I. A. Strakova, A. Ya. Strakov, and E. Yu. Gurinietse, Izv. Akad. Nauk Latv. SSR, Ser. Khim., No. 6 627 (1972).
9. A. Shaffie and M. Rezayazdi, J. Heterocycl. Chem., **32**, 177 (1995).
10. V. A. Azimov, N. P. Solov'eva, amd V. G. Granik, Khim.-farm. Zh., No. 8, 43 (1994).

11. A. Ya. Strakov, I. A. Strakova, D. R. Zitsane, and E. Yu. Gudrinietse, Izv. Akad. Nauk Latv. SSR, Ser. Khim., No. 1, 68 (1974).
12. D. R. Zitsane, I. A. Strakova, A. Ya. Strakov, and E. Yu. Gudrinietse, Izv. Akad. Nauk Latv. SSR, Ser. Khim., No. 1, 114 (1974).
13. A. Ya. Strakov, T. F. Kzolovskaya, M. V. Petrova E. Yu. Gudrinietse, and A. Dmitriev, Latv. Khim. Zh., No. 2, 179 (1991).
13. A. Ya. Strakov, T. F. Kozlovskaya, M. V. Petrova, E. Yu. Gudrinietse, and A. Dmitriev, Latv. Khim. Zh., No. 2, 179 (1991).
14. M. V. Petrova, V. V. Negrebetskii, A. Kh. Rekis, A. Ya. Strakov, and E. Yu. Gudrinietse, Latv. Khim. Zh., No. 6, 731 (1993).
15. G. Lehmann, H. Wehhan, and G. Hilgetag, Chem. Ber., **100**, 2967 (1967).
16. I. A. Strakova, A. Ya. Strakov, and E. Yu. Gudrinietse, Izv. Akad. Nauk Latv. SSR, Ser. Khim., No. 5, 593 (1973).
17. H. Smith, J. Chem. Soc., 803 (1953).