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SYNTHESIS OF 4-OXO-2-THIOXO-1,2,3,4,5,6-HEXAHYDROSPIRO(BENZO[*h*]QUINAZOLINE-5,1′-CYCLOHEXANE AND ITS REACTION WITH DIBROMOALKANES

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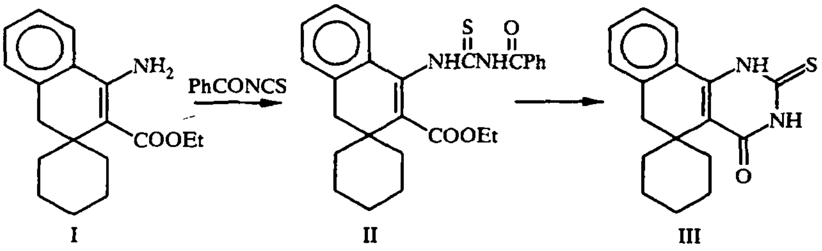
4-(N′-Benzoylthioureido)-3-ethoxycarbonyl-1,2-dihydrospiro(naphthalene-2,1′-cyclohexane), which was synthesized from 4-amino-3-ethoxycarbonyl-1,2-dihydrospiro(naphthalene-2,1′-cyclohexane) and benzoyl isothiocyanate, cyclized to give 4-oxo-2-thioxo-1,2,3,4,5,6-hexahydrospiro(benzo[h]quinazoline-5,1′-cyclohexane). Reaction of the latter with 1,2-dibromoethane or 1,3-dibromopropane gave products of intramolecular dialkylation at the S and $N_{(3)}$ atoms.

We have previously reported the synthesis of 3-substituted 4-oxo-2-thioxo-1,2,3,4,5,6-hexahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexanes) and their reactions with various halides to give 2,3-disubstituted benzo[*h*]quinazolines, the biological activities of which are of definite interest [1]. In a continuation of research in this field we report in this paper the synthesis of 4-(N′-benzoylthioureido)-3-ethoxycarbonyl-1,2-dihydrospiro(naphthalene-2,1′-cyclohexane (II) from 4-amino-3-ethoxycarbonyl-1,2-dihydrospiro(naphthalene-2,1′-cyclohexane) (I) and benzoyl isothiocyanate. Cyclisation of II in aqueous alcoholic potassium hydroxide gave 4-oxo-2-thioxo-1,2,3,4,5,6-hexahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexane) (III).



Products of O-, S-, or N-alkylation can be formed by alkylation of the quinazoline III. With 1,2-dibromoethane and 1,3-dibromopropane formation of products of intramolecular dialkylation are also possible, most likely at atoms S and $N_{(3)}$ (IV, V) or S and $N_{(1)}$ (VI, VII).

According to TLC and ^1H NMR spectroscopic data, only one compound is formed from each of the dibromides and this was confirmed by elemental analysis and mass spectrometry. The IR spectra of the products contain bands characteristic of the carbonyl group, which indicates that the carbonyl group did not take part in the reaction. Mass spectroscopic data showed that $N_{(3)}$, but not $N_{(1)}$, took part in the reaction: the presence of

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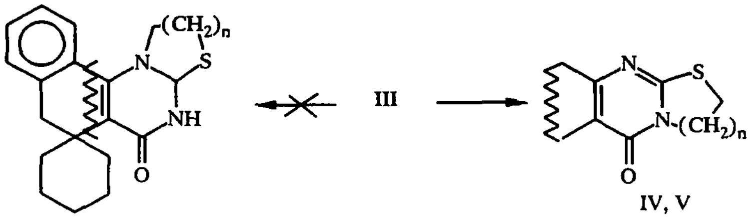

VI, VII

IV, V

IV, VI n = 1; V, VII n = 2

fragment ions with mass numbers M$^+$ -43, M$^+$ -56, and M$^+$ -70 (in the spectrum of the product from dibromoethane) indicate the loss of the fragments HNCO, CH_2NCO, and CH_2CH_2NCO, which is only possible for products IV and V.

The structure of compound IV was confirmed by X-ray crystal analysis (Fig. 1). The thiazolidine ring A has a distorted twist conformation (atoms C(2) and C(3) diverge on opposite sides of the plane formed by atoms $S_{(1)}$, $N_{(4)}$, and $C_{(22)}$ by -0.325(3) and 0.100(3) Å respectively). The cyclohexadiene ring C has the form of a distorted half boat (atoms $C_{(6)}$ and $C_{(7)}$ are displaced from the mean square formed by the remaining atoms of the ring by -0.375(2) and 0.833(2) Å respectively). The cyclohexane ring D has the chair conformation (atoms $C_{(7)}$ and $C_{(10)}$ are on opposite sides of the mean plane formed by the remaining atoms of the ring and are 0.673(2) and -0.650(3) Å from it); rings B and E are planar.

Bond lengths in the molecule are slightly different from corresponding bonds cited in the literature [2]. For example, the $N_{(21)}$—$C_{(22)}$ bond (1.293(3)) is slightly shorter and the $N_{(4)}$—$C_{(5)}$ (1.402(3)) and $C_{(20)}$—$N_{(21)}$ (1.385(3) Å) bonds are slightly longer than the standard value (1.336 Å). The C—C bond in the pyrimidine (1.387 Å) is also slightly elongated. Bond angles are close to standard values (Table 2).

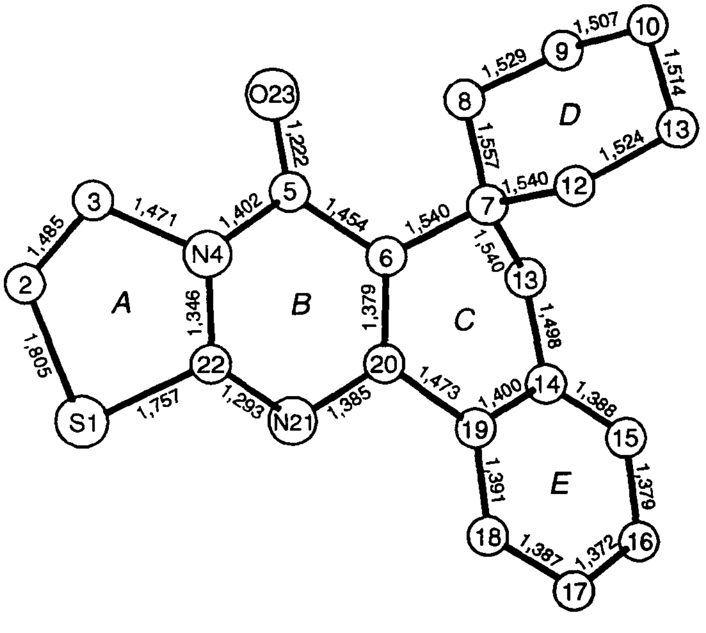

Fig. 1. Structure of the molecule of compound IV.
Atomic numbering and bond lengths (σ = 0.004 Å) are shown.

TABLE 1. Coordinates of Atoms (× 10^4) and Their Equivalent Isotropic Temperature Factors for Molecules of Compound IV

Atom	*x*	*y*	*z*	B_{iso}
$S_{(1)}$	399 (1)	912 (1)	7450 (1)	4,21 (2)
$C_{(2)}$	1963 (3)	1411 (3)	7623 (1)	4,85 (9)
$C_{(3)}$	2498 (3)	340 (3)	7908 (1)	4,01 (8)
$N_{(4)}$	1426 (2)	-357 (2)	8115 (1)	2,98 (6)
$C_{(5)}$	1615 (2)	-1236 (3)	8477 (1)	3,06 (7)
$C_{(6)}$	462 (2)	-1874 (2)	8631 (1)	2,65 (6)
$C_{(7)}$	425 (2)	-2706 (2)	9069 (1)	2,87 (7)
$C_{(8)}$	1699 (3)	-3387 (3)	9191 (1)	3,98 (8)
$C_{(9)}$	1652 (3)	-4073 (3)	9654 (1)	4,47 (9)
$C_{(10)}$	1312 (3)	-3124 (3)	10029 (1)	4,77 (9)
$C_{(11)}$	72 (3)	-2439 (3)	9930 (1)	4,38 (8)
$C_{(12)}$	76 (2)	-1777 (3)	9464 (1)	3,20 (7)
$C_{(13)}$	-574 (3)	-3783 (3)	8993 (1)	3,93 (8)
$C_{(14)}$	-1830 (3)	-3264 (3)	8841 (1)	3,35 (8)
$C_{(15)}$	-2967 (3)	-3812 (3)	8981 (1)	4,37 (9)
$C_{(16)}$	-4099 (3)	-3312 (3)	8825 (1)	4,62 (9)
$C_{(17)}$	-4126 (2)	-2259 (3)	8533 (1)	4,12 (8)
$C_{(18)}$	-3000 (2)	-1700 (3)	8338 (1)	3,44 (7)
$C_{(19)}$	-1851 (2)	-2199 (2)	8540 (1)	2,87 (7)
$C_{(20)}$	-639 (2)	-1621 (2)	8395 (1)	2,75 (7)
$N_{(21)}$	-726 (2)	-799 (2)	8021 (1)	3,09 (6)
$C_{(22)}$	305 (2)	-205 (3)	7905 (1)	2,92 (7)
$C_{(23)}$	2694 (2)	-1369 (2)	8618 (1)	4,87 (6)

EXPERIMENTAL

IR spectra of nujol mulls were recorded with a UR-20 spectrometer, ^1H NMR spectra were recorded with a Varian T-60 machine (deuterated solvents, TMS or HMDS as internal standards), and mass spectra were recorded on an MX-1320 machine with direct insertion of the sample and an ionizing voltage of 70 eV. TLC was carried out on Silufol UV-254 strips with development with iodine vapor.

X-ray crystallographic analysis of compound IV was carried out with Hilger-Watts four circle automatic diffractometer (λMoKα, $\theta/2\theta$ scanning, graphite monochromator, θ_{max} 28°). The crystals were rhombic: a = 10.583(1), b = 10.182(1), c = 29.333(4) Å, V 3160.7(3) Å^3, d_{calc} = 1.364 g×cm^3, Z = 4, space group Pbca. The structure was solved by direct methods using the MULTAN program and refined by least squares using the block diagonal anisotropic approximation for non-hydrogen atoms. Positions of hydrogen atoms were calculated geometrically and included in the least squares refinement with fixed isothermal thermal parameters, B_{iso} = 5 Å^2. All calculations were carried out using the INEXTL program [3] on an Eclipse-200. The final residual factors were R = 4.3 and R_w = 4.6% for 1691 reflexions with $I > 3\sigma(I)$.

Atomic coordinates are given in Table 1, bond angles in Table 2, and the molecular structure with bond lengths in Fig. 1.

4-(N′-Benzoylthioureido)-3-ethoxycarbonyl-1,2-dihydrospiro(naphthalene-2,1′cyclohexane) (II). A mixture of 4-amino-3-ethoxycarbonyl-1,2-dihydrospiro(naphthalene-2,1′cyclohexane) (14.2 g, 0.05 mole) [4] and benzoyl isothiocyanate (8.2 g, 0.05 mole) in ethanol (50 ml) was boiled under reflux for 30 min and kept at room temperature for 10 h. The precipitated crystals were filtered off, washed with ethanol, and dried in the air to give II (15.2 g, 68%), m.p. 197-199°C. R_f 0.55 (1:3 ethyl acetate – hexane). IR Spectrum: 1605 (C=C arom), 1670 (C=O amide), 1715 (C=O ester), 3265 cm^{-1} (NH). ^1H NMR Spectrum ($CDCl_3$): 1.10-1.90 (10H, m, 5-CH_2), 1.27 (3H, t, $CH_2\underline{CH_3}$), 3.00 (2H, s, 1-CH_2), 4.23 (2H, q, OCH_2), 7.00-7.93 (9H, m, H arom), 9.60 and 12.03 ppm (2H, 2 br. s, 2NH). Found, %: C 69.77, H, 6.19, N, 6.07, S 7.26. Calc. for $C_{26}H_{28}N_2O_3S$, %: C 69.62, H 6.29, N 6.25, S 7.15.

TABLE 2. Bond Angles in the Molecule of Compound IV

Angle	ω, deg	Angle	ω, deg
C(2)—S(1)—C(22)	91,2 (1)	C(10)—C(11)—C(12)	112,0 (2)
S(1)—C(2)—C(3)	107,5 (2)	C(7)—C(12)—C(11)	113,8 (2)
C(2)—C(3)—N(4)	107,1 (2)	C(7)—C(13)—C(14)	113,7 (2)
C(3)—N(4)—C(5)	120,8 (2)	C(13)—C(14)—C(15)	122,7 (2)
C(3)—N(4)—C(22)	115,8 (2)	C(13)—C(14)—C(19)	118,3 (2)
C(5)—N(4)—C(22)	123,1 (2)	C(15)—C(14)—C(19)	119,0 (2)
N(4)—C(5)—C(6)	113,6 (2)	C(14)—C(15)—C(16)	120,5 (3)
N(4)—C(5)—C(23)	117,5 (2)	C(15)—C(16)—C(17)	120,8 (3)
C(6)—C(5)—C(23)	129,0 (2)	C(16)—C(17)—C(18)	119,6 (3)
C(5)—C(6)—C(7)	121,7 (2)	C(17)—C(18)—C(19)	120,2 (2)
C(5)—C(6)—C(20)	118,1 (2)	C(14)—C(19)—C(18)	119,9 (2)
C(7)—C(6)—C(20)	119,9 (2)	C(14)—C(19)—C(20)	118,5 (2)
C(6)—C(7)—C(8)	114,5 (2)	C(18)—C(19)—C(20)	121,6 (2)
C(6)—C(7)—C(12)	107,2 (2)	C(6)—C(20)—C(19)	121,2 (2)
C(6)—C(7)—C(13)	106,7 (2)	C(6)—C(20)—N(21)	124,5 (2)
C(8)—C(7)—C(12)	108,0 (2)	C(19)—C(20)—N(21)	114,3 (2)
C(8)—C(7)—C(13)	108,1 (2)	C(20)—N(21)—C(22)	115,7 (2)
C(12)—C(7)—C(13)	112,5 (2)	S(1)—C(22)—N(4)	111,9 (2)
C(7)—C(8)—C(9)	112,3 (2)	S(1)—C(22)—N(21)	123,3 (2)
C(8)—C(9)—C(10)	111,2 (2)	N(4)—C(22)—N(21)	124,8 (2)
C(9)—C(10)—C(11)	111,2 (3)		

4-Oxo-2-thioxo-1,2,3,4,5,6-hexahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexane) (III). A mixture of thiourea II (4.5 g, 0.01 mole), KOH (1.1 g, 0.02 mole), ethanol (25 ml) and water (25 ml) was refluxed for 3 h. After cooling the reaction mixture was acidified to pH 3.0-3.5 with 10% HCl. The precipitated crystals were filtered off, washed with water, and recrystallized from dimethylformamide to give compound III (2.6 g, 87%), m.p. 276-278°C. R_f 0.61 (1:5 ethyl acetate – chloroform). IR Spectrum: 1585, 1615 (C=C arom), 1680 (C=O, 3300-3450 cm^{-1} (NH). Found, %: C 68.33, H 5.90, N 9.52, S 10.68. Calc. for $C_{17}H_{18}N_2OS$, %: C 68.43, H 6.08, N 9.38, S 10.74.

5-Oxo-,2,3,6,7-tetrahydro-5H-spiro(benzo[*h*]thiazolo[2,3-*b*]quinazoline-6,1′-cyclohexane (IV). A mixture of quinazoline (III) (6 g, 0.02 mole), KOH (2.3 g, 0.041 mole) and isopropanol (150 ml) was heated until the quinazoline dissolved and dibromoethane (3.8 g, 0.02 mole) was then added. The reaction mixture was heated for 15 h and water (50 ml) was then added. The precipitate was filtered off, washed with water, and recrystallized from isopropanol to give compound IV (4 g, 62%), m.p. 193-195°C. R_f 0.51 (1:1 ethyl acetate – hexane). IR Spectrum: 1640 (C=O), 1600 cm^{-1} (C=C arom). ^{1}H NMR Spectrum ($CDCl_3$): 1.10-2.80 (10H, , m, 5-CH_2), 3.00 (2H, s, 7-CH_2), 3.36 (2H, t, J = 8 Hz, S-CH_2), 4.43 (2H, t, J = 8 Hz, N-CH_2), 7.00-8.20 ppm (4H, m, H arom). Mass spectrum, *m/z* (*I*, %): M$^+$ 325 (31), 324 (100), 282 (10), 281 (55), 269 (21), 268 (99), 267 (24), 255 (16), 154 (10), 69 (11). Found, %: C 70.18, H 6.15, N 8.52, S 9.38. Calculated for $C_{19}H_{20}N_2OS$, %: C 70.33, H 6.21, N 8.33, S 9.53.

6-Oxo-2,3,7,8-tetrahydro-4H,6H-spiro(benzo[*h*]thiazino[2,3-*b*]quinazoline-7,1′cyclohexane (V) was synthesized analogously to compound IV from quinazoline (III) (6 g, 0.02 mole), KOH (2.3 g, 0.041 mole) and dibromoethane (4 g, 0.02 mole) to give compound V (3 g, 44%), m.p. 189°C (dimethylformamide). R_f 0.50 (1:1 ethyl acetate – hexane). IR Spectrum: 1600 (C=C arom), 1640 cm^{-1} (C=O). ^{1}H NMR Spectrum (pyridine-d_5): 1.10-2.80 (12H, m, 5-CH_2 and 3-CH_2), 2.86 (2H, t, S-CH_2), 2.93 (2H, s, 8-CH_2), 3.83 (2H, t, J = 6 Hz, N-CH_2), 7.00-8.40 ppm (4H, m, H arom). Mass spectrum, *m/z* (*I*, %): M$^+$ 339 (38), 338 (100), 296 (16), 295 (67), 283 (21), 282 (83), 281 (21), 269 (16), 140 (12). Found, %: C 71.15, H 6.31, N 8.05, S, 9.24. Calc. for $C_{20}H_{22}N_2OS$, %: C 70.98, H 6.55, N 8.28, S 9.47.

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