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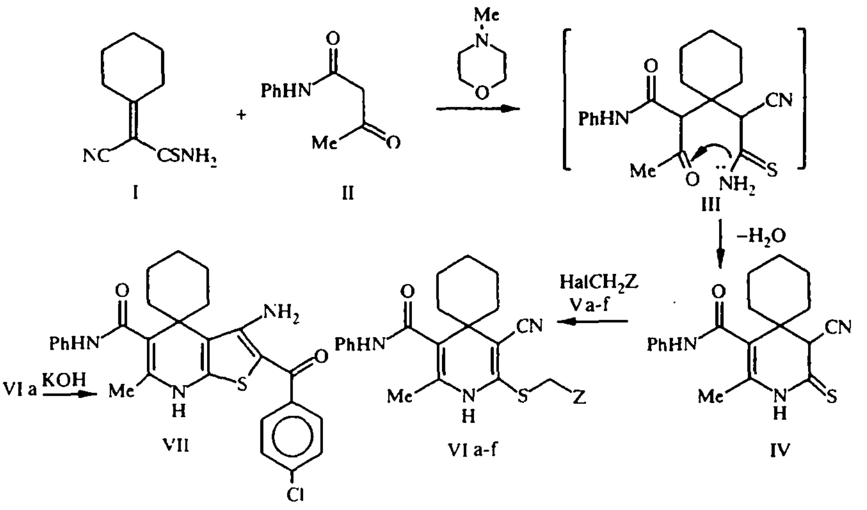
SYNTHESIS OF 6-METHYL-5-PHENYLCARBAMOYL-3,4-DIHYDROPYRIDINESPIRO-4-CYCLOHEXANE-2(1H)-THIONE AND ITS DERIVATIVES

V. D. Dyachenko, S. G. Krivokolysko, and V. P. Litvinov

3-Cyano-6-methyl-5-phenylcarbamoyl-3,4-dihydropyridinespiro-4-cyclohexane-2(1H)-thione was obtained by the condensation of acetoacetic acid anilide with cyclohexylidenecyanothioacetamide. Substituted 2-alkylthio-1,4-dihydropyridines and 3-amino-2-(4-chlorobenzoyl)-6-methyl-5-phenylcarbamoyl-4,7-dihydrothieno[2,3-b]pyridinespiro-4-cyclohexane were synthesized from it.

We previously developed a method of synthesizing 6-amino-3,5-dicyano-3,4-dihydropyridinespiro-4-cyclohexane-2(1H)-thione [1] by the reaction of cyclohexylidenecyanothioacetamide with cyanothioacetamide. Its structural analogs are used to obtain various drugs [2] and certain 1,4-dihydropyridine derivatives containing a carbamoyl group in the 5 position of the dihydropyridine nucleus can display hepatoprotective activity [3]. In view of these facts and continuing the investigation of functionally substituted pyridinespiro-4-cycloalkanes [4] we have developed a method of synthesizing pyridine derivatives containing a spiro linked carbocyclic fragment and a phenylcarbamoyl group as substituents simultaneously.

It has been shown that the adduct (III) is formed by Michael addition on reacting cyclohexylidenecyanothioacetamide (I) with acetoacetic acid anilide (II) in the presence of N-methylmorpholine at 20°C in ethanol. Compound (III) undergoes cyclocondensation to 3-cyano-6-methyl-5-phenylcarbamoyl-3,4-dihydropyridinespiro-4-cyclohexane-2(1H)-thione (IV).



V, VI a Z = 4-ClC$_6$H$_4$CO, b Z = CONH$_2$, c Z = 4-BrC$_6$H$_4$NHCO, d Z = H, e Z = CH$_3$, f Z = Ph;
V, VI a Hal = Br; b,c,f Hal = Cl; d,e Hal = I

The structure of compound (IV) was confirmed by physicochemical investigations (see Experimental) and by chemical conversions. Thione (IV) is alkylated by halides (V) in a basic medium regioselectively with the formation of sulfides (VI) (Tables 1, 2) and the substituted 2-(4-chlorobenzoylmethylthio)-1,4-dihydropyridine (VIa) is converted under the conditions of the Torp–Ziegler reaction into the corresponding thieno[2,3-*b*]pyridine (VII) which confirms their structure.

T. G. Shevchenko Lugansk State Pedagogical Institute, Lugansk 348011, Ukraine. N. D. Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, Moscow 117913. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1533-1535, November, 1997. Original article submitted March 3, 1997.

TABLE 1. Characteristics of the Synthesized Compounds (VIa-f)

Compound	Empirical formula	Found, % / Calculated, % C	H	N	S	mp, °C (recrystallization solvent)	Yield, %
VIa	$C_{27}H_{26}ClN_3O_2S$	66,01 65,91	5,22 5,33	8,65 8,54	6,39 6,52	180...182 (AcOH)	74
VIb	$C_{21}H_{24}N_4O_2S$	63,78 63,61	5,95 6,10	14,00 14,13	7,88 8,09	224...227 (AcOH)	71
VIc	$C_{27}H_{27}BrN_4O_2S$	58,67 58,80	5,15 4,93	10,01 10,16	6,02 5,81	234...235 (AcOH)	84
VId	$C_{20}H_{23}N_3OS$	68,08 67,96	6,40 6,56	12,00 11,89	8,85 9,07	218...220 (AcOH)	68
VIe	$C_{21}H_{25}N_3OS$	68,50 68,63	6,91 6,86	11,35 11,43	8,68 8,72	183...185 (ethanol)	81
VIf	$C_{26}H_{27}N_3OS$	72,54 72,69	6,22 6,34	9,85 9,78	7,39 7,46	228...229 (ethanol)	69

TABLE 2. Spectral Characteristics of Compounds (VIa-f)

Compound	IR spectrum, ν, cm^{-1}			CONH s
	NH	C ≡ N	NHCO	
VIa	3300	2190	1660	10,01
VIb	3280, 3420	2200	1650	10,08
VIc	3270, 3455	2205	1664	10,07
VId	3300, 3472	2190	1648	10,06
VIe	3284, 3450	2198	1670	10,01
VIf	3270, 3480	2200	1680	9,99

Compound	PMR spectrum, δ, ppm					
	NH s	Ph	SCH_2 s	CH_3 s	$(CH_2)_5$ m	Z
VIa	9,31	7,03...7,55 m	4,70	1,82	11,30...1,72	7.99 d and 7.63 d (2H, C_6H_4)
VIb	10,01	7,67 d, 7,30 t, 7,05 t	3,65	1,87	1,15...1,80	7.86 br and 7.54 br.s (1H, NH_2)
VIc	9,61	7,68 d, 7,31 t, 7,05 t	3,96	1,87	1,15...1,70	10.47 (1H, s, CONH); 7.55 (4H, s, C_6H_4)
VId	9,26	7,67 d, 7,30 t, 7,05 t	2,50	1,86	1,20...1,72	—
VIe	9,28	7,65 d, 7,24 t, 7,03 t	3,00 q	1,83	1,30...1,78	1.24 (3H, t, CH_3)
VIf	9,29	7,65 d, 6,95...7,25 m	4,29 s	1,83	1,10...1,64	7.37 (5H, m, Ph)

The signals of the protons of the pentamethylene fragment appearing as multiplets are characteristic signals of the PMR spectra of sulfides (VI) as are the signals of the protons of the SCH_2, 6-CH_3, NH and CONH groups represented as singlets (Tables 1, 2). The IR spectra of compounds (VIa-f) contain characteristic absorption bands for the stretching vibrations of the conjugated cyano group at 2198-2205 cm^{-1}.

EXPERIMENTAL

The IR spectra were recorded on an IKS-29 instrument using Nujol and the PMR spectra on a Bruker WP 100SY (100 MHz) in DMSO-D_6 (internal standard TMS). The monitoring of reactions and a check on the homogeneity of substances was effected by TLC on Silufol UV 254 plates (eluent was acetone–heptane, 3:5).

3-Cyano-6-methyl-5-phenylcarbamoyl-3,4-dihydropyridinespiro-4-cyclohexane-2(1H)-thione (IV). A mixture of cyclohexylidenecyanothioacetamide (I) (10 mmole), acetoacetic acid anilide (10 mmole), and N-methylmorpholine (20 mmole) in abs. ethanol (15 ml) was stirred for 1 h at 20°C. After 48 h, 10% aqueous hydrochloric acid solution was poured in with stirring, to pH 5. After a further 24 h, the resulting precipitate was filtered off, washed with ethanol, and with hexane. Yield was 2.9 g (87%) having mp 212-214°C (AcOH). IR spectrum: 3240, 3314, 3477 (NH), 2248 ($C\equiv N$), 1635 cm^{-1} (CONH). PMR spectrum: 12.03 (1H, s, $N_{(1)}H$); 10.10 (1H, s, CONH); 7.62 (2H, d, Ph); 7.33 (2H, t, Ph); 7.08 (1H, t, Ph); 4.52 (1H, s, $C_{(3)}H$); 1.93 (3H, s, CH_3); 1.20-1.80 ppm [10H, m, $(CH_2)_5$]. Found, %: C 67.50; H 5.59; N 12.51; S 9.63. $C_{19}H_{19}N_3OS$. Calculated, %: C 67.63; H 5.68; N 12.45; S 9.50.

3-Cyano-6-methyl-2-Z-methylthio-5-phenylcarbamoyl-1,4-dihydropyridinespiro-4-cyclohexanes (VIa-f). Aqueous 10% KOH solution (5.6 ml; 10 mmole) was added to a suspension of thione (IV) (10 mmole) in ethanol (15 ml) at 20°C. The mixture was stirred for 1 min, after which halide (V) (10 mmole) was added, and stirring continued for 3 h. The reaction mixture was then diluted with water (10 ml), the precipitate formed was filtered off, and washed with water, ethanol, and hexane. Sulfides (VI) were obtained, data on which are given in Tables 1 and 2.

3-Amino-2-(4-chlorobenzoyl)-6-methyl-5-phenylcarbamoyl-4,7-dihydrothieno[2,3-*b*]pyridinespiro-4-cyclohexane (VII). Aqueous 10% KOH solution (5.6 ml; 10 mmole) was added to a suspension of sulfide (VIa) (10 mmole) in ethanol (20 ml) at 20°C and the mixture stirred for 3 h. The solid was filtered off, washed with 40% aqueous ethanol, and with hexane. Yield was 4.6 g (94%) having mp 213-215°C (ethanol). IR spectrum: 3240-3480 (NH, NH_2), 1710 (C=O), 1665 cm^{-1} (δNH_2). PMR spectrum: 10.40 (1H, s, CONH); 9.89 (1H, s, $N_{(7)}H$); 7.72 d and 7.55 d (2H, C_6H_4); 7.45 (2H, s, NH_2); 7.07-7.31 (5H, m, Ph); 2.25 (3H, s, CH_3); 1.30-1.85 ppm [10H, m, $(CH_2)_5$]. Found, %: C 65.85; H 5.20; N 8.71; S 6.46. $C_{27}H_{26}ClN_3O_2S$. Calculated, %: C 65.91; H 5.33; N 8.54; S 6.52.

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