with ether (3 × 30 ml) gave the amine products. The ether layer was washed with water (2 × 10 ml), and dried over magnesium sulfate.

In the case of amines IIIa-e (IVa-e), the ether was removed, and the residue distilled in vacuo. In preparing the amines IIIg-k (IVg-k), the ether extract was partially evaporated, and the crystals which separated were filtered off and recrystallized from ether.

LITERATURE CITED

1. É. O. Chukhadzhyan, L. A. Manasyan, and A. T. Babayan, Khim. Geterotsikl. Soedin., No. 11, 1481 (1988).
2. A. T. Babayan, É. O. Chukhadzhyan, and G. T. Babayan, Zh. Org. Khim., 6, 1161 (1970).
3. El. . Chukhadzhyan, É. O. Chukhadzhyan, and A. T. Babayan, Zh. Org. Khim., 10, 46 (1974).
4. A. T. Babayan, É. O. Chukhadzhyan, and L. A. Manasyan, Arm. Khim. Zh., 31, 489 (1978).
5. A. T. Babayan, K. Ts. Tagamazyan, and G. T. Babayan, Arm. Khim., Zh., 19, 678 (1966).
6. A. T. Babayan, É. O. Chukhadzhyan, K. G. Shakhatuni, S. V. Lindeman, and Yu. T. Struchkov, Arm. Khim. Zh., 37, 44 (1985).

SYNTHESIS AND PROPERTIES OF 2,7-DIAZABICYCLO[2.2.2]OCTANE-3,8-DIONES AND -3,8-DITHIONES

Z. A. Kalme, É. É. Liepin'sh,
Yu. É. Pelcher, and G. Yu. Dubur

UDC 547.825'824:
543.422

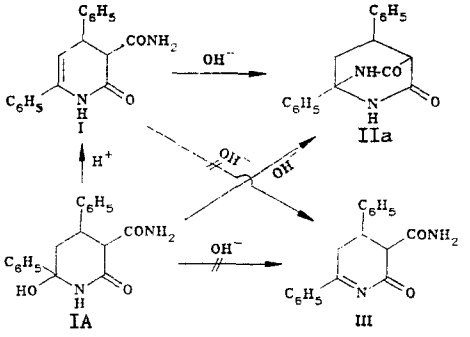
In an alkaline medium, 3,4-dihydropyridin-2(1H)-ones form 2,7-diazebicyclo[2.2.2]-octane-3,8-diones, which are thiolated to the corresponding dithiones. The alkylation of the last proceeds at the sulfur atoms with the formation of 2,7-diazabicyclo[2.2.2]octa-2,7-dienes.

The formation of bicycles in the series of 1,4-dihydropyridines is known when they are alkylated with dibromopropane [1], as a result of the reaction of ortho substituents in 4-aryl-substituted 1,4-dihydropyridines with the dihydropyridine ring [2], as well as in the cycloaddition of styrene or allyl-trimethylsilane to dihydropyridines [3].

We investigated the formation of 2,7-diazabicyclo[2.2.2]-octane-3,8-diones based on 3-amido-substituted 3,4-dihydropyridin-2(1H)-ones.

It was found that 3-carbamoyl-4,6-diphenyl-3,4-dihydropyridin-2(1H)-one (I) and 3-carbamoyl-4,6-diphenyl-6-hydroxy-3,4-dihydropyridin-2(1H)-one (IA) undergo intramolecular cyclization in an alkaline medium with the formation of 2,7-diaza-1,5-diphenylbicyclo[2.2.2]-octane-3,8-dione (IIa).

It was shown that the bicycle (IIa) is identical to the product obtained by the condensation of benzylidenacetophenone and malonic diamide, for which the structure of 3,4-dihydropyridin-2(5H)-one (III) was proposed on the basis of the ^{1}H NMR spectrum [4, 5].



Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 620-625, May, 1989. Original article submitted October 30, 1987.

0009-3122/89/2505-0516$12.50

TABLE 1. Parameters of the ^{13}C NMR Spectra of the Compounds (II), (IV), and (V)

Compound	Chemical shifts, δ, ppm								
	$C_{(1)}$	$C_{(3)}$ and $C_{(8)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(C_6H_5)}$	$C_{(R^1)}$	$C_{(R^2)}$	$C_{(SR^3)}$
IIa	70,73	169,79; 171,33	59,77	38,82	44,51	141,70 (α); 127,41 (β); 128,54 (γ); 126,90 (δ)	—	136,31 (α); 126,47 (β), 128,54 (γ); 129,00 (δ)	—
IIc	66,34	169,90; 171,52	59,79	38,22	44,79	141,98; 127,31; 128,54; 126,85	—	20,76	—
IId	67,75	169,79; 171,38	59,63	45,56	51,66	141,46; 128,54; 127,41; 126,92	30,43*; 30,24*; 24,34*; 20,46*		—
IVa	75,48	196,48; 198,69	76,89	40,71	41,14	139,60; 127,87; 127,46; 127,11	—	134,01; 128,62; 128,33; 129,78	—
IVb	73,92	196,13; 198,37	76,35	47,18	49,74	139,00; 128,00; 128,77; 127,19	16,58	17,30	—
IVc	70,76	196,98; 199,38	75,76	41,02	43,16	139,06; 127,31; 127,96; 126,93	—	19,99	—
IVd	73,16	196,29; 198,93	76,45	47,57	49,75	139,28; 128,04; 128,33; 127,20	30,47*; 28,96*; 23,92*; 20,63*		—
Va	85,64	168,13; 169,94	57,43	41,25	42,98	139,79; 127,84; 128,27; 126,90	—	145,05; 127,76; 128,27; 127,06	12,02
Vb	85,54	167,39; 169,17	56,67	45,64	50,30	139,73; 127,98; 128,30; 126,98	16,90	25,12	12,10 12,05
Vc	82,94	168,19; 170,07	57,10	39,57	42,10	139,94; 127,48; 128,13; 126,83	—	27,36	12,17
Vd	84,56	167,70; 168,86	56,71	48,24	48,51	139,90; 127,98; 128,33; 126,95	36,91*; 31,30*; 25,07*; 22,19*		12,08
Ve	82,76	166,79; 168,68	56,73	39,07	41,39	140,01; 127,96; 128,14; 126,88	—	27,75	R^3=CH: 34,30; $R^3=(CH_3)_2$: 22,65; 22,65; 22,19; 22,00

*Signals of the CH_2 groups.

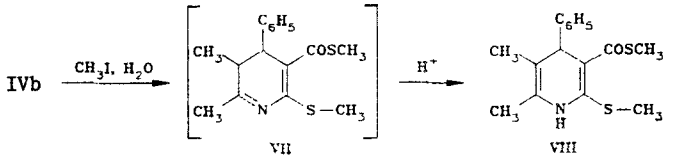
However, the data of the ^1H NMR spectrum proved to be insufficient for the definitive choice between the structure of the compounds (IIa) and (III) due to the small difference in the CSs of their protons [6]. The signal of the sp^3-hybridized quaternary carbon atom at 70.73 ppm is present in the ^{13}C NMR spectrum of the product of the alkaline conversion of the pyridone (I) (Table 1); this clearly corresponds to the $C_{(1)}$ atom in the bicyclic structure (II) [7]. The ^{15}N NMR spectrum also testifies in favor of the structure of the bicyclooctanedione (IIa): the CSs of the ^{15}N atoms at −240.1 and −243.0 ppm correspond to the amide nitrogen atoms [8]. The data of the ^{13}C NMR spectra of the compounds (IIb-d) (Table 1), which were obtained directly from the corresponding benzylidene derivative and malonic diamide, also confirm their bicyclic character.

The bicycles (IIa-d) are readily thiolated by the Lawesson reagent — the dimer of p-methoxyphenylthionophosphine sulfide — with the formation of the dithiones (IVa-d). The bicyclodithiones (IV) are stable in contrast to the readily oxidized 3,4-dihydropyridine-2-(1H)-thiones, which can often only be isolated in the form of the piperidinium salts [9]. The alkylation of the dithiones (IVa-d) with alkyl halides proceeds at both sulfur atoms with the preservation of the structure of the bicycle and the formation of the alkylthiodienes (Va-e).

The structure of the 2,7-diazabicyclo[2.2.2]octanedithiones (IVa-d) and their alkylation products (Va-d) was confirmed by the data of the ^1H NMR (Table 2) and the ^{13}C NMR (Table 1) spectra. Thus, the thiolation of the bicycle (IIa) displaces the CSs of the ^{15}N in the spectrum of the compound (IVa) to −203.4 and −204.9 ppm; this corresponds with the thioamide atoms of nitrogen [8]. The alkylation of the dithione (IVa) leads to the significant low-field shift of the ^{15}N signals. In the case of compound (Va), the CSs are registered at −65.5 and −69.7 ppm; this corresponds with the imine atoms of nitrogen [8].

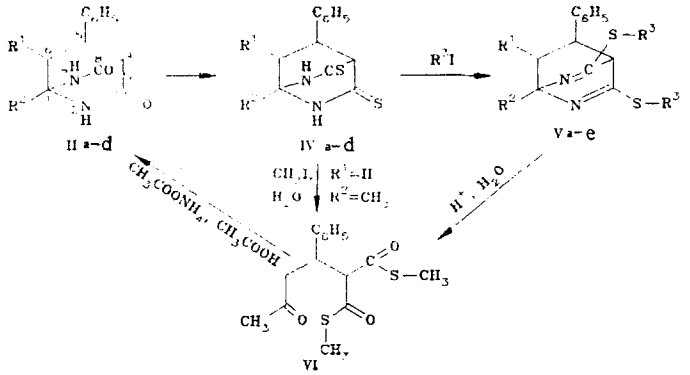
It should be noted that if the octanediones (IIa-d) absorb in the near ultraviolet (Table 3), then the sulfur-containing bicyclooctanes (IVa-d) have the λ_{max} at 296...297 nm. In the case of the alkyl products (Va-e), the hypsochromic shift is registered with the λ_{max} 245... 250 nm (Table 2).

The 1,4-dihydropyridine (VIII), and not the dialkyldiene (Vb), was obtained by the methylation of the 1,6-dimethyloctane-dithione (IVb) in the presence of water.



The intermediate product in this reaction is evidently the hydrolysis product - the 4,5-dihydropyridine (VII), which is readily converted to the 1,4-dihydropyridine (VIII) in the acidic medium similarly to its analogs [10]. The IR spectra of the compound (VIII) show the vibration $\nu_{C=O}$ of the (methylthio)carbonyl group at 1703 cm^{-1}; the UV spectra show the absorption band with the maximum at 365 nm which is characteristic of 1,4-dihydropyridines [11].

When the dithione (IVc), which is unsubstituted at the 6 position, is alkylated in the presence of water, the product is also formed by both the hydrolysis of the thioamide group and the cleavage of the pyridine ring; the product is the dithiomethoxycarbonyl α-[acetonyl-1(H)]-



II, IV a R^1=H, R^2=C_6H_5; b R^1=R^2=CH_3; c R^1=H, R^2=CH_3; d R^1+R^2=—$(CH_2)_4$—;
V a R^1=H, R^2=C_6H_5, R^3=CH_3; b R^1=R^2=R^3=CH_3; c R^1=H, R^2=R^3=CH_3; d R^1+R^2= =—$(CH_2)_4$—, R^3=CH_3; e R^1=H, R^2=CH_3, R^3=$CH(CH_3)_2$

TABLE 2. Parameters of the ^1H NMR Spectra of the Bicycles (IVa-d) and (Va-e)

Compound	Chemical shifts of the protons, δ, ppm (in DMSO)						SSCC, Hz		
	4-H (d, 1H)	5-H (m, 1H)	6-H (d, d 2H) or (d 1H)	5-C_6H_5 (5H)	2NH (d 2H)	other protons	J_{45}	J_{56}	J_{66}
IVa	4,30	3,57	2,97; 2,56	7,30	11,62	7,8...7,4 (m, 5H, 1-C_6H_5)	1,5	10,0; 5,0	12,1
IVb	4,00	2,62	2,22	7,25	11,47; 11,38	0,92 (d, 3H, 6-CH_3); 1,55 (s, 3H, 1-CH_3)	2,0	6,0	6,0 (CH_3)
IVc	4,21	3,47	2,49; 2,16	7,30	11,47; 11,37	1,72 (s, 3H, 1-CH_3)	2,0	9,0; 5,1	12,0
IVd	4,13	2,72	2,13	7,30	11,43	2,2...1,0 (m, 8H, $(CH_2)_4$)	1,8	5,8	—
Va	4,03	3,07	2,16; 1,80	7,3...7,0	—	2,33 (s, 3H, S—CH_3); 2,42 (s, 3H, S—CH_3); 8,1...7,4 (m, 5H, 1-C_6H_5)	1,5	9,4; 5,6	12,1
Vb	3,69	2,17	1,78	7,3...7,0	—	0,88 (d, 3H, 6-CH_3); 1,91 (s, 3H, 1-CH_3); 2,77 (s, 3H, S—CH_3); 2,33 (s, 3H, S—CH_3)	1,8	5,0	6,0 (CH_3)
Vc	4,03	3,07	2,16; 1,80	7,3...7,0	—	2,33 (s, 3H, S—CH_3); 2,42 (s, 3H, S—CH_3); 8,1...7,4 (m, 5H, 1-C_6H_5)	1,5	9,4; 5,6	12,1
Vd	3,70	—	—	7,3...7,0	—	2,3...0,7 (m, 8H, $(CH_2)_4$); 2,29 (s, 3H, S—CH_3); 2,37 (s, 3H, S—CH_3)	1,2	—	—
Ve	3,55	2,88	1,94; 1,63	7,3...7,0	—	3,68 & 3,64 (m, 2H, $2CH(CH_3)_2$); 1,94 (s, 3H, 1-CH_3); 1,31, 1,27, 1,26 & 1,17 (m, 12H, $2CH(CH_3)_2$)	2,0	9,8; 5,2	12,0

TABLE 3. Characteristics of the Compounds Synthesized

Compound	Empirical formula	mp, °C	UV spectrum, λ_{max}, nm (log ε)	Yield,%
IIa	$C_{18}H_{16}N_2O_2$	250...251	205 (8,6)	65*
IIb	$C_{14}H_{16}N_2O_2$	271...272	203 (3,6)	40
IIc	$C_{13}H_{14}N_2O_2$	261...262	209 (10,2)	65
IId	$C_{16}H_{18}N_2O_2$	249...251	203 (10,1)	60
IVa	$C_{18}H_{16}N_2S_2$	220...223	245 sh (3,97), 278 (4,32), 297 sh (4,12)	76
IVb	$C_{14}H_{16}N_2S_2$	242...243	243 (4,00), 278 (4,33), 277 sh (4,17)	53
IVc	$C_{13}H_{14}N_2S_2$	239...241	242 (4,02), 277 (4,31), 296 sh (4,12)	80
IVd	$C_{16}H_{18}N_2S_2$	240...243	242 (3,89), 277 (4,16), 296 sh (3,96)	70
Va	$C_{20}H_{20}N_2S_2$	137...138	225 sh (4,11), 250 (3,91)	75
Vb	$C_{16}H_{20}N_2S_2$	123...124	225 sh (4,08), 250 (3,99)	67
Vc	$C_{15}H_{18}N_2S_2$	136...137	225 sh (4,00), 243 (3,88)	48
Vd	$C_{18}H_{22}N_2S_2$	131...132	225 sh (4,02), 245 (3,89)	58
Ve	$C_{19}H_{26}N_2S_2$	60...62	225 sh (3,93), 245 (3,83)	50
VI	$C_{15}H_{18}O_3S_2$	121...122	242 (3,94)	75†
VIII	$C_{16}H_{19}NOS_2$	151...153	280 (3,88), 365 (3,92)	58

*By the method B.
†By the method A.

benzylmalonic ester (VI). The ready hydrolysis of alkylthioimides in the acidic medium is known in the series of acyclic compounds [12, 13]. The thioester (VI) was also obtained by the acid hydrolysis of the dialkylthiodiene (Vc).

EXPERIMENTAL

The IR spectra were recorded on the Perkin-Elmer 580B instrument (in mineral oil). The UV spectra were recorded on the Specord UV-vis spectrophotometer (in ethanol). The ^1H, ^{13}C, and ^{15}N NMR spectra were obtained on the WH-90/DS and WH-360 spectrometers (90, 90.5, and 36.6 MHz correspondingly). The internal standard was tetramethylsilane (^1H and ^{13}C) and nitromethane (^{15}N).

The main characteristics of the compounds synthesized are presented in the Tables 1-3. The data of the elemental analysis of the compounds for C, H, N, and S correspond with the calculated values.

2,7-Diaza-1,5-diphenylbicyclo[2.2.2]octane-3,8-dione (IIa). A. To the solution of 0.5 g (1.7 mmole) of the dihydropyridin-2(1H)-one (I) in 5 ml of ethanol are added 2 ml of a 1 N alcoholic solution of NaOH, and the mixture is boiled for 1.5 h. After 1 day, the reaction mixture is diluted with water and acidified with hydrochloric acid to the pH ∿ 2; the dione (IIa) is filtered off. The yield is 60%.

B. The mixture of 1.0 g (3.4 mmole) of the hydroxypiperidone (IA) and 10 ml of an 8.5% solution of sodium methoxide is maintained for 20 h at room temperature. The solution is neutralized with hydrochloric acid, and the residue of sodium chloride is separated. The filtrate is acidified to the pH ∿ 2, and the dione (IIa) is separated. The yield is 60%.

C. The mixture of 5.0 g (24.0 mmole) of benzylidenacetophenone, 2.45 g (24 mmole) of malonic diamide, 5 ml of an 8.5% solution of sodium methoxide, and 20 ml of abs. ethanol is boiled for 3.5 h. The mixture is cooled and poured into acidified water (pH ∿ 2), and the dione (IIa) is separated.

D. To the solution of 1.5 g (4.8 mmole) of the benzylthiomalonic ester (VI) in 10 ml of acetic acid are added 3.25 g (48.5 mmole) of ammonium acetate. The mixture is boiled for 30 min, cooled, and diluted with ice water; the precipitated residue is filtered off. The yield is 62%.

Compounds (IIb-d). These are obtained analogously to (IIa) by the method B.

2,7-Diaza-5-phenyl-1-methylbicyclo[2.2.2]octane-3,8-dithione (IVa). The mixture of 3.0 g (13 mmole) of the dione (IIa) and 5.25 g (13 mmole) of Lawesson's reagent is boiled for 3 h in 200 ml of benzene. The mixture is cooled, and the residue is filtered off, washed with ether, and recrystallized from ethanol.

The compounds (IVb-d) are obtained analogously.

2,7-Diaza-5-phenyl-1-methyl-3,8-di(methylthio)bicyclo[2.2.2]octa-2,7-diene (Va). To the suspension of 1.0 g (4.35 mmole) of the dithione (IVa) in 50 ml of ethanol is added 0.5 g of NaOH. The mixture is stirred for 0.5 h at room temperature prior to the addition of 3.1 g (21.75 mmole) of methyl iodide; the mixture is boiled for 10 min. After cooling it, 30 ml of ice water are added to the reaction mixture with energetic stirring. The residue is filtered off and crystallized from ethanol.

The compounds (Vb-d) are obtained analogously.

2,7-Diaza-5-phenyl-1-methyl-3,8-di(thioisopropyl)bicyclo-[2.2.2]octa-2,7-diene (Ve). This compound is obtained analogously to the diene (Va), but the reaction mixture is concentrated after the boiling. The remaining oil is dissolved in hot ethanol, and the solution is cooled and left overnight in a refrigerator. The precipitated residue is filtered off and recrystallized from ethanol.

Dithiomethoxycarbonyl α-[Acetonyl-(1)]benzylmalonic Ester (VI). A. To the suspension of 1.0 g (3.81 mmole) of the dithione (IVa) in 30 ml of ethanol are added 0.25 g of NaOH and 0.3 ml of water. The reaction mixture is stirred for 2 h, left overnight at room temperature, and then poured into acidified water. The oil which separated out is crystallized with energetic stirring. The residue is separated and recrystallized from ethanol. The yield is 75%.

B. To the suspension of 1.0 g of the compound (Va) in 50 ml of ethanol are added, with stirring, 5 ml of hydrochloric acid. The mixture is stirred for 1 h; it is poured into water, and the residue is filtered off. The yield is 70%. The IR spectrum is as follows: 1660, 1695, and 1718 cm^{-1}. The PMR spectrum (DMSO-D_6) is as follows: 1.89 ppm (s, 3H, $COSCH_3$), 2.04 ppm (s, 3H, $CSCH_3$), 2.34 ppm (s, 3H, $COCH_3$), 2.60 and 2.96 ppm (m, 2H, CH_2, J = 16.1 Hz), 3.86 ppm (m, 1H, CH—CH_2, J = 9.8 and J = 3.0 Hz), 4.53 ppm (d, 1H, CH—CO, J = 10.1 Hz), and 7.20 ppm (s, 5H, C_6H_5).

3-Thiomethoxycarbonyl-4-phenyl-5,6-dimethyl-2-methylthio-1,4-dihydropyridine (VIII). To the suspension of 1.0 g (3.62 mmole) of the dithione (IVb) in 30 ml of ethanol are added 0.25 g of NaOH and 0.3 ml of water. The reaction mixture is stirred and heated at 70-80°C until the solution is achieved. To the mixture are then added 10.0 g (72.40 mmole) of methyl iodide, and it is heated with stirring for 2 h. The reaction mixture is then cooled, poured into acidified water, and left overnight at room temperature. The precipitated residue is filtered off and recrystallized from ethanol. The IR spectrum is as follows: 1702 cm^{-1} (C=O) and 3320 cm^{-1} (NH). The PMR spectrum (DMSO-D_6) is as follows: 1.57 ppm (s, eH, 6—CH), 1.82 ppm (s, 3H, 5-CH_3), 2.08 ppm (s, 3H, S-CH_3), 2.42 ppm (s, 3H, S-CH_3), 4.27 ppm (broad s, 1H, 4-CH), 7.20 ppm (s, 5H, C_6H_5), and 7.53 ppm (s, 1H, NH).

LITERATURE CITED

1. J. W. Patterson, J. Heterocycl. Chem., 23, 1689 (1986).
2. G. D. Hartman, B. T. Phillips, and W. Halczenko, J. Org. Chem., 50, 2423, 2427 (1985).
3. G. D. Hartman, B. T. Phillips, and W. Halczenko, J. Org. Chem., 52, 1136 (1987).
4. Z. A. Bomika, Yu. É. Pelcher, G. Ya. Dubur, A. A. Krauze, and É. É. Liepin'sh, Khim. Geterotsikl. Soedin., No. 10, 1377 (1979).
5. Z. A. Bomika, M. B. Andaburskaya, Yu. É. Pelcher, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 8, 1108 (1975).
6. L. M. Jackman and S. Sternhell, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, Pergamon Press, Oxford (1969), p. 172.
7. W. Bremser, B. Franke, and H. Wagner, Chemical Shift Ranges in Carbon-13 NMR Spectroscopy, Verlay Chemie, Weinheim (1982), p. 724.
8. G. J. Martin, M. L. Martin, and J. P. Gouesnard, ^{15}N-NMR Spectroscopy, Springer, Berlin (1981), pp. 138, 140, and 153.
9. A. A. Krauze, Z. A. Kalme, Yu. É. Pelcher, É. É. Liepin'sh, I. V. Dipan, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 11, 1515 (1983).
10. A. A. Krauze, É. É. Liepin'sh, Yu. É. Pelcher, Z. A. Kalme, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 1, 75 (1987).
11. U. Eisner and J. Kuthan, Chem. Rev., 72, 24 (1972).
12. W. Walter and J. Krohn, Chem. Ber., 102, 3786 (1969).
13. R. K. Chaturvedi, A. E. MacMahon, and G. L. Schmir, J. Am. Chem. Soc., 89, 6984 (1967).