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Thiation of Enamine of Cyclohexanone with Arensulfenamides

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Arylthiation of the nucleophilic β-carbon atom of 1-morpholino-1-cyclohexene with arensulfensuccinimides and arensulfenamides was successfully carried out. Moreover, benzylthiosulfenylation of morpholine and thiophenol with benzylthiosulfenphthalimide was examined and found to give successfully benzylthiosulfenmorpholide and benzyl phenyl trisulfide.

Recently we reported the arylthiation of morpholine enamine of cyclohexanone with arensulfenamides or with arensulfenimides in the communication.[2] Details and further extensions of this work are now reported.

It is well known that the β-carbon atom of enamines readily undergoes an electrophilic attack. Recently, it has been reported that alkan or arensulfenimides act as an efficient thiation reagent for thiols,[3] alkoxides,[4] amines,[5] arensulfinates[6] and active methylene compounds[7] to give disulfides, sulfenates, sulfenamides, thiosulfonates and thiated active methylene compounds. These reactions may occur by the nucleophilic attack to the sulfur atom of the sulfenimides. Thus, the thiation of the β-carbon atom of an enamine, 1-morpholino-1-cyclohexene which is the most stable enamine, with arensulfenimides and with arensulfenamides. Although the alkylation and acylation of carbonyl compounds through the enamines with alkyl halides,[8] electrophilic olefins[9] and acyl halides[8,10] are well known, little has been reported relating to the thiation of enamines.

When *p*-nitrobenzenesulfensuccinimide (Ia)[11] was allowed to react with two equivalent amounts of 1-morpholino-1-cyclohexene (II) in dry dichloromethane at room temperature for 5 hours, 1-morpholino-6-*p*-nitrophenylthio-1-cyclohexene (IIIa) was obtained in 50% yield, as the only product isolated. The structure of IIIa was established by the satisfactory elemental analysis and infrared (IR), nuclear magnetic resonance (NMR) and mass spectra. The IR spectrum exhibited absorptions assignable to the nitro group at 1331 cm^{-1} and 1513

1) Location: *Oe-hon machi, Kumamoto.*
2) M. Furukawa, Y. Kojima, S. Tsuiji, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 2738 (1972).
3) *a*) K.S. Boustany and A.B. Sullivan, *Tetrahedron Letters*, **1970**, 3547; *b*) D.N. Harpp, D.K. Ash, T.G. Back, J.G. Gleason, B.A. Orwig, W.F. Van Horn, and J.P. Snyder, *Tetrahedron Letters*, **1970**, 3551; *c*) D.N. Harpp and T.G. Back, *J. Org. Chem.*, **36**, 3828 (1971).
4) D.H.R. Barton, G. Page, and D.A. Widdowson, *Chem. Commun.*, **1970**, 1466.
5) *a*) K.S. Boustany, *Chimia*, **1970**, 396; *b*) D.N. Harpp and T.G. Back, *Tetrahedron Letters*, **1971**, 4953.
6) Y. Abe and J. Tsurugi, *Chemistry Letters*, **1972**, 441.
7) *a*) T. Mukaiyama, S. Kobayashi, and T. Kumamoto, *Tetrahedron Letters*, **1970**, 5115; *b*) T. Mukaiyama and K. Saigo, *Bull. Chem. Soc. Japan*, **44**, 3077 (1971); *c*) T. Mukaiyama, S. Kobayashi, and H. Takei, *Chemistry Letters*, **1972**, 237.
8) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).
9) G. Stork and H. Landesman, *J. Am. Chem. Soc.*, **78**, 5128 (1956).
10) *a*) G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954); *b*) S. Hünig and E. Lücke, *Chem. Ber.*, **92**, 652 (1959); *c*) S. Hünig and W. Lendle, *ibid.*, **93**, 913 (1960); *d*) S. Yurugi, M. Numata, and T. Fushimi, *J. Pharm. Soc. Japan*, **80**, 1165 (1960).
11) M. Furukawa, Y. Fujino, Y. Kojima, M. Ono, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 2024 (1972).

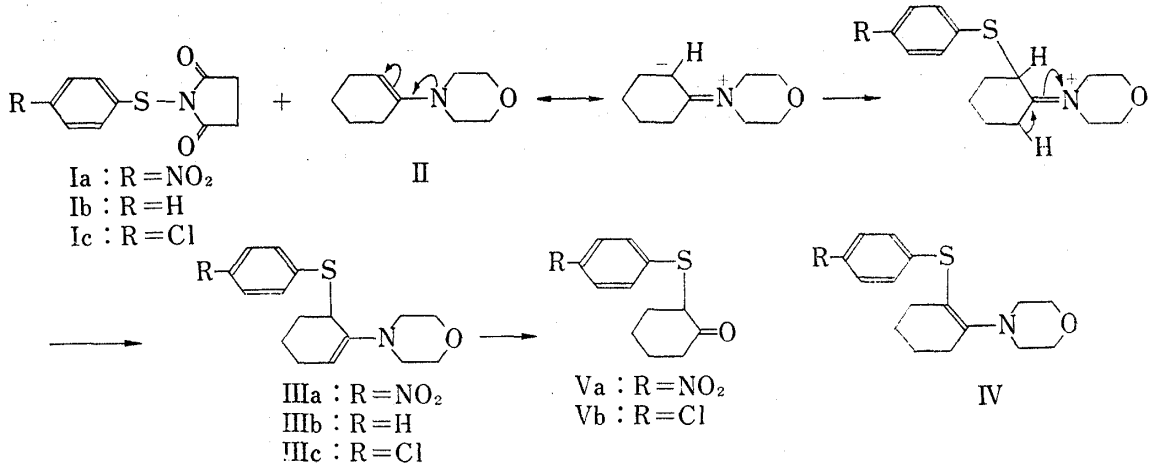


Chart 1

cm^{-1} and due to the ether group at 1119 cm^{-1}. The molecular ion was observed at *m/e* 319 as the most abundant peak in the mass spectrum. The fragment ion corresponding to the elimination of the nitrophenylthio group was also observed at *m/e* 165 as the abundant peak. These results indicate evidently that the introduction of a nitrophenylthio group to II was successfully carried out. However, the isomeric 1-morpholino-2-*p*-nitrophenylthio-1-cyclohexene (IV, R=O_2N-C$_6$H$_4$-) due to the difference of the position of the double bond is also possible. In C-alkylation of enamines of cycloalkanones, Risaliti[12] has reported that the preferred formation of one of the two possible isomeric enamines depends on the nature of the dienophile and the presence of hindering groups at the electrophilic carbon atom of the dienophile favors the less substituted isomer. The distinct evidence for the position of the double bond in IIIa was provided by the NMR spectrum, in which a triplet and broad singlet assignable to the vinyl and methine hydrogens were observed at τ 5.00 and 5.75, respectively. This is possible only in IIIa but not IV. Support for IIIa was also provided by facile conversion into 2-(*p*-nitrophenylthio)cyclohexanone (Va) by hydrolysis with 10% hydrochloric acid. It is presumed that IIIa would be formed by the nucleophilic attack of the β-carbon atom of II to the sulfur atom of I followed by the elimination of the hydrogen atom at C_2. Attempts of the introduction of two nitrophenylthio groups to II by use of a great excess of I resulted in failure, providing IIIa in a lower yield as the only product isolated. It is well known that the alkylation of α-substituted ketoenamines is generally difficult.[13]

The reaction of benzenesulfensuccinimide (Ib)[11] with II under the similar conditions gave satisfactorily 1-morpholino-6-phenylthio-1-cyclohexene (IIIb) in 23% yield. IIIb gave a satisfactory elemental analysis and had IR, NMR and mass spectra consistent with the structure.

In the reaction of *p*-chlorobenzenesulfensuccinimide (Ic)[11] with II under the similar conditions, 2-(*p*-chlorophenylthio)cyclohexanone (Vb) was obtained in 28% yield by hydrolysis of the reaction mixture with 10% hydrochloric acid after completion of the reaction, though the isolation of the intermediate of 1-morpholino-6-*p*-chlorophenylthio-1-cyclohexene (IIIc) was unsuccessful. The structure of Vb was established by the satisfactory elemental analysis and IR, NMR and mass spectra. The distinct evidence was provided by identification with an authentic sample[14] prepared by the reaction of II with *p*-chlorophenyl *p*-chlorobenzenethiosulfonate.

12) A. Risaliti, S. Fatutta, M. Forchiassin, and E. Valentin, *Tetrahedron Letters*, **1966**, 1821.
13) W.R.N. Williamson, *Tetrahedron*, **3**, 314 (1958).
14) M. Furukawa, S. Tsuiji, Y. Kojima, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **21**, 2391 (1973).

Arylthiation of II with benzenesulfenamides was successfully carried out similarly to the case of arensulfensuccinimides but under more drastic conditions. When equivalent amounts of N,N-diethylbenzenesulfenamide (VI) and II in dry benzene were heated for 5 hours under reflux, 1-morpholino-6-phenylthio-1-cyclohexene (IIIb) was obtained in a low yield, which was identified by comparison with an authentic sample obtained by the reaction of Ia with II.

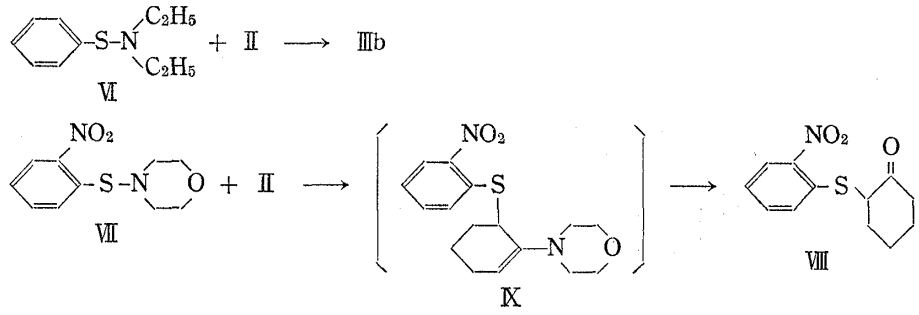


Chart 2

Similarly, heating of *o*-nitrobenzenesulfenmorpholide (VII)[11] with II in benzene under the similar conditions followed by hydrolysis with 10% hydrochloric acid gave 2-(*o*-nitrophenylthio)cyclohexanone (VIII) in 21% yield, though the efforts for the isolation of the intermediate 1-morpholino-6-*o*-nitrophenylthio-1-cyclohexene (IX) resulted in failure. The structure of VIII was established by the satisfactory elemental analysis and the spectral data.

Owing to the structural similarity, it may be anticipated that benzylthiosulfenphthalimide (X)[15] reacts with II similarly to I. Prior to the reaction with II, the reactions with thiophenol and morpholine were examined. Harpp[16] has reported that alkylthiosulfenphthalimide reacted with piperazine to give bis-alkylthiosulfenpiperazide, but little has been known relating to the reactivity toward thiols.

When X was heated with an equivalent amount of morpholine in dichloromethane for 53 hours under reflux, phthalamoylmorpholide (XI) and benzylthiosulfenmorpholide (XII) were obtained in 71% and 20% yields, respectively. The structure of XI was confirmed by

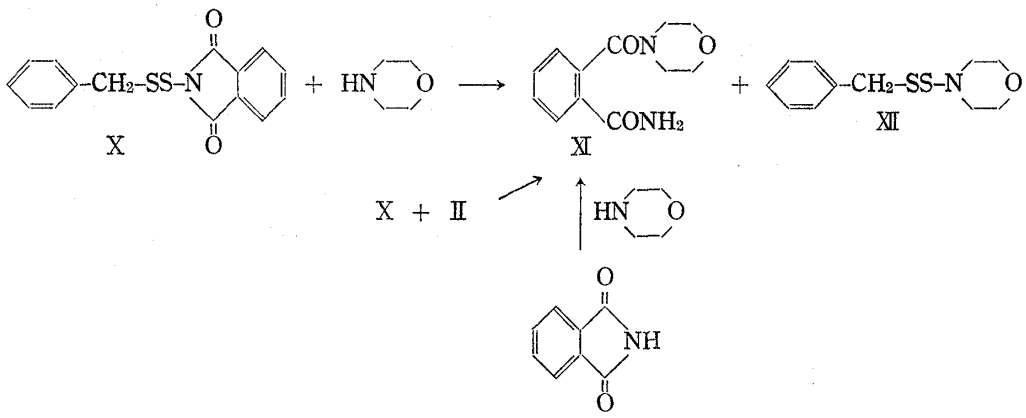


Chart 3

identification with an authentic sample prepared by the reaction of phthalimide with morpholine, and XII was established by the satisfactory elemental analysis and spectral data.

The reaction of X with thiophenol was successfully carried out by treating in benzene at room temperature for 3.5 hours to give a 13% yield of benzyl phenyl trisulfide (XIII).

15) M. Behforouz, H. Firouzabadi, and A.A. Ardakani, *J. Chem. Soc.* (*C*), **1971**, 3550.
16) D.N. Harpp and T.G. Back, *Tetrahedron Letters*, **1972**, 1481.

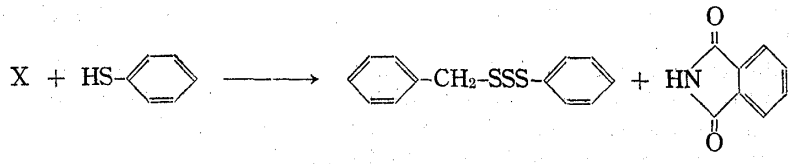
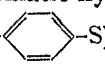


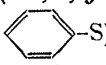
Chart 4

This reaction should be noted for the novel and convenient synthesis of asymmetric trisulfides. By these results, it is evident that the sulfur atom adjacent to the nitrogen atom in X can undergo nucleophilic attack.

However, contrary to our expectation, the anticipated reaction of X with II resulted in failure. When X was heated with two equivalent amounts of II in dichloromethane for 54 hours under reflux, XI was obtained in 26% yield and XII was also detected by TLC. It is presumed that XI was afforded by the reaction between phthalimide and morpholine formed independently by hydrolysis of X and II. In fact, heating of phthalimide with morpholine and with II under the similar conditions gave XI in 56% and 34% yields, respectively.

Experimental

1-Morpholino-6-*p*-nitrophenylthio-1-cyclohexene (IIIa)——To a solution of 2.5 g (0.01 mole) of *p*-nitrobenzenesulfensuccinimide in 50 ml of dry CH_2Cl_2 was added slowly with stirring 3.3 g (0.02 mole) of 1-morpholino-1-cyclohexene and the stirring was continued for additional 6 hr at room temperature. The deposited precipitates, succinimide, were filtered off and the filtrate was evaporated under a reduced pressure. The residue was washed with hot MeOH to remove succinimide and recrystallized from AcOEt to give 1.6 g (50%) of light yellow needles melting at 138°. *Anal.* Calcd. for $C_{16}H_{20}O_3N_2S$: C, 59.99; H, 6.29; N, 8.75. Found: C, 60.01; H, 6.19; N, 9.01. IR ν_{max}^{KBr} cm^{-1}: 1331, 1513 (NO_2); 1119 (–O–). NMR ($CDCl_3$) τ: 8.45—7.60 (6H, m, 3,4,5-CH_2), 7.50—6.75 (4H, m, CH_2NCH_2), 6.23 (4H, t, J=5 Hz, CH_2OCH_2), 5.75 (1H, broad s, CH), 5.00 (1H, t, J=3 Hz, CH=), 2.75—2.40 (2H, m, aromatic hydrogens), 1.95—1.70 (2H, m, aromatic hydrogens). Mass Spectrum *m/e*: 319 (M^+), 165 (M^+– O_2N-  -S).

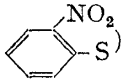
1-Morpholino-6-phenylthio-1-cyclohexene (IIIb)——a) To a solution of 2.1 g (0.01 mole) of benzenesulfensuccinimide in 50 ml of dry CH_2Cl_2 was added slowly with stirring 3.3 g (0.02 mole) of 1-morpholino-1-cyclohexene and the solution was stirred for additional 6 hr at room temperature. Resulted precipitates of succinimide was filtered off and the filtrate was evaporated under a reduced pressure. Recrystallization of the residue from MeOH gave 0.6 g (23%) of colorless needles melting at 83—85°. *Anal.* Calcd. for $C_{16}H_{21}$-ONS: C, 69.78; H, 7.69; N, 5.09; S, 11.66. Found: C, 69.93; H, 7.59; N, 5.03; S, 11.82. NMR ($CDCl_3$) τ: 8.70—7.75 (6H, m, 3,4,5-CH_2), 7.50—6.80 (4H, m, CH_2NCH_2), 6.32 (4H, t, J=5 Hz, CH_2OCH_2), 6.05 (1H, broad s, CH), 5.18 (1H, t, J=3 Hz, CH=), 3.00—2.40 (5H, m, aromatic hydrogens). Mass Spectrum *m/e*: 275 (M^+), 166 (M^+—  -S).

b) To a solution of 1.6 g (0.01 mole) of N,N-diethylbenzenesulfenamide in 20 ml of dry benzene was added with stirring 1.7 g (0.01 mole) of 1-morpholino-1-cyclohexene and the solution was heated with stirring for 5 hr under reflux. After the solution was evaporated under a reduced pressure, the residue was recrystallized from MeOH to give 0.1 g (4.5%) of colorless needles melting at 83—85°. This compound was identified with an authentic sample prepared by method (a) by the mixed melting point determination and comparison of the IR spectra.

2-(*p*-Nitrophenylthio)cyclohexanone (Va)——A suspension of 0.32 g (0.001 mole) of 1-morpholino-6-*p*-nitrophenylthio-1-cyclohexene in 30 ml of 10% HCl was stirred for 3 hr. The precipitates deposited were collected by filtration and recrystallized from MeOH to give 0.13 g (52%) of light yellow needles melting at 99—100°. *Anal.* Calcd. for $C_{12}H_{13}O_3NS$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.26; H, 4.90; N, 6.02. IR ν_{max}^{KBr} cm^{-1}: 1707 (CO); 1331, 1508 (NO_2). NMR ($CDCl_3$) τ: 8.45—6.90 (8H, m, 3,4,5,6-CH_2), 5.90 (1H, t, J=6 Hz, CH), 1.87 (2H, d, J=9 Hz, aromatic hydrogens adjacent to the nitro group), 2.58 (2H, d, J=9 Hz, aromatic hydrogens adjacent to the thio group).

2-(*p*-Chlorophenylthio)cyclohexanone (Vb)——A solution of 2.4 g (0.01 mole) of *p*-chlorobenzenesulfensuccinimide in 50 ml of dry benzene was added with stirring 3.3 g (0.02 mole) of 1-morpholino-1-cyclohexene and the solution was heated with stirring for 10 hr under reflux. After the solution was evaporated, the residue was stirred with 50 ml of 10% HCl solution at room temperature. The oily product separated was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated to dryness under a reduced pressure. The residue was recrystallized from EtOH to give 0.7 g (28%) of colorless crystals melting at 53.5—

55°. This compound was identified with an authentic sample[14] by mixed melting point determination and comparison of the IR spectrum.

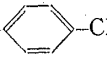
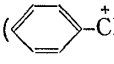
2-(*o*-Nitrophenylthio)cyclohexanone (VIII)——To a solution of 2.4 g (0.01 mole) of *o*-nitrobenzenesulfenmorpholide in 50 ml of dry benzene was added with stirring 3.3 g (0.02 mole) of 1-morpholino-1-cyclohexene and the solution was heated with stirring for 18 hr under reflux. After the solution was evaporated under a reduced pressure, the residue was stirred with 10% HCl aqueous solution at room temperature for 3 hr. The precipitates deposited were collected by filtration and recrystallized from EtOH to give 0.5 g (21%) of light yellow needles melting at 112—112.5°. *Anal.* Calcd. for $C_{12}H_{13}O_3NS$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.26; H, 5.00; N, 5.32. IR ν_{max}^{KBr} cm^{-1}: 1705 (CO); 1336, 1513 (NO_2). NMR ($CDCl_3$) τ: 8.50—6.80 (8H, m, 3,4,5,6-CH_2), 5.93 (1H, t, J=6 Hz, CH), 2.90—2.30 (3H, m, aromatic hydrogens), 1.87 (1H, d, J=7 Hz, aromatic hydrogen adjacent to the nitro group). Mass Spectrum *m/e*: 251 (M^+), 97 (M^+– ).

Phthalamoylmorpholide (XI)——a) A solution of 0.85 g (0.005 mole) of phthalimide and 0.87 g (0.01 mole) of morpholine in 30 ml of EtOH was heated for 63 hr under reflux. The solution was concentrated and the precipitates deposited on cooling were collected and recrystallized from benzene to give 0.65 g (56%) of colorless needles melting at 130—131°. *Anal.*Calcd. for $C_{12}H_{14}O_3N_2$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.09; H, 5.68; N, 12.14. IR ν_{max}^{KBr} cm^{-1}: 3333, 3140 ($CONH_2$); 1704 (CO); 1108 (–O–). Mass Spectrum *m/e*: 234 (M^+), 148 (M^+–O ).

b) A mixture of 1.5 g (0.005 mole) of benzylthiosulfenphthalimide, 1.7 g (0.01 mole) of 1-morpholino-1-cyclohexene and 30 ml of dry CH_2Cl_2 was heated for 54 hr under reflux. The precipitates deposited were collected by filtration and recrystallized from EtOH to give 0.5 g (68%) of phthalimide melting at 232—234°. The filtrate was concentrated by distillation and the precipitates deposited on cooling were collected by filtration and recrystallized from benzene to give 0.3 g (26%) of colorless needles melting at 130—131°. This compound was identified with an authentic sample prepared by method (a) by the mixed melting point determination and comparison of the IR spectrum.

c) A mixture of 0.85 g (0.005 mole) of phthalimide, 1.62 g (0.01 mole) of 1-morpholino-1-cyclohexene and 30 ml of EtOH was heated for 54 hr under reflux. The mixture was concentrated and the precipitates deposited on cooling were collected by filtration and recrystallized from benzene to give 0.4 g (34%) of colorless needles melting at 130—131°, which was identified with an authentic sample prepared by method (a) by mixed melting points determination and comparison of the IR spectra.

Benzylthiosulfenmorpholide (XII)——A mixture of 0.9 g (0.003 mole) of benzylthiosulfenphthalimide, 0.52 g (0.006 mole) of morpholine and 20 ml of dry CH_2Cl_2 was heated for 53 hr under reflux. The mixture was concentrated and the precipitates deposited on cooling were collected and recrystallized from benzene to give 0.5 g (71%) of phthalamoylmorpholide melting at 130—131°, which was identified with an authentic sample prepared by the method described above. The filtrate was allowed to stand for one week in a refrigerator and the resulting precipitates were collected by filtration and recrystallized from EtOH to give 0.15 g (20%) of colorless prisms melting at 42—43°. *Anal.* Calcd. for $C_{11}H_{15}ONS_2$: C, 54.76; H, 6.27; N, 5.81. Found: C, 54.72; H, 6.39; N, 6.19. Mass Spectrum *m/e*: 241 (M^+), 91 ().

Benzyl Phenyl Trisulfide (XIII)——A solution of 2.7 g (0.009 mole) of benzylthiosulfenphthalimide and 2.0 g (0.018 mole) of thiophenol in 50 ml of dry benzene was stirred for 3.5 hr at room temperature. After completion of the reaction, the precipitates deposited from the reaction mixture were collected by filtration to give 1.3 g (98%) of phthalimide melting at 233—234°. The filtrate was concentrated and cooled. Resulting precipitates were collected by filtration and recrystallized from pet. ether to give 0.3 g (13%) of colorless prisms melting at 52—53°. *Anal.* Calcd. for $C_{13}H_{12}S_3$: C, 59.09; H, 4.58. Found: C, 59.54; H, 4.66. Mass Spectrum *m/e*: 264 (M^+), 200 (M^+– 2S), 123 (M^+–  –SS), 109 (M^+–  –CH_2SS), 91 ().