The Reactions of 2-Ethoxy-2,3-dihydro-4*H*-1,3-benzothiazin-4-one (**6**), 4,4-Diphenyl-2-ethoxyoxazolidin-5-one (**10**), and 1-Benzyl-2-methoxyimidazolidine-4,5-dione (**12**) with Dienes

D. Ben-Ishai, I. Gillon, and A. Warshansky

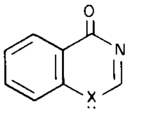
Department of Chemistry, Technion - Israel Institute of Technology, Haifa, Israel

Received November 28, 1972

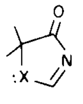
2-Ethoxy-1,3-benzothiazin-4-one (**6**), 4,4-diphenyl-2-ethoxyoxazolin-5-one (**10**) and 1-benzyl-2-methoxyimidazolidine-4,5-dione (**12**) were prepared and were found to react with 1,1-bicyclohexenyl, 1,2,3,4-tetramethylbutadiene and 2,4-dimethyl-1,3-pentadiene to give Diels-Alder adducts (**7**, **8**, **9**, **13-18**).

Cyclic acylimines were found to be reactive compounds, readily adding weak nucleophiles, dienes, and active methylene compounds across the carbon-nitrogen double bond. The reactivity of the acylimine depends on the degree of conjugation involving the carbon-nitrogen double bond. The more conjugated the acylimine the less reactive it is in addition reactions (1-7). In most cases, the free acylimine cannot be isolated, they can be formed *in situ* from various addition products (*e.g.* α-alkoxylactams) thermally or in the presence of an acid catalyst and trapped with dienes or weak nucleophiles.

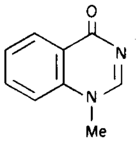
The present investigation was aimed at the preparation of cyclic acylimines in which the carbon-nitrogen double bond is further conjugated with lone pairs of electrons of hetero atoms (*e.g.* **1** or **2**) and the study of their chemical and physical properties.



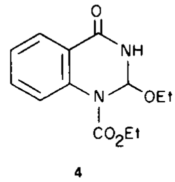
1



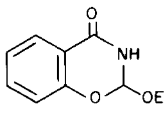
2



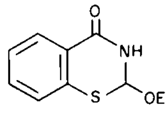
3



4

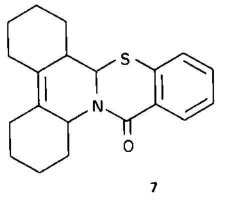


5

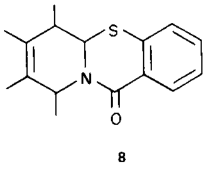


6

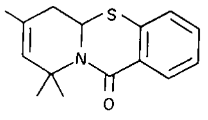
The first series we looked at was the quinazolinones (**3**, **4**) the benzoxazinone (**5**), and the benzothiazinone (**6**). The four compounds two of which (**3**, **5**) were described in the literature (7,8) were prepared from the corresponding *ortho*-substituted benzamide and triethylorthoformate. Under the same experimental conditions, **4**, **5**, and **6** were obtained as the ethanol addition products of **1**, and only **3**, due to enhanced p-π conjugation, is stable in the unsaturated form. In compound **4**, the electron withdrawing property of the carbethoxy group activates the potential carbon-nitrogen double bond (**1**, X = N CO_2Et) and stabilizes the ethanol addition product. Attempts to eliminate ethanol from **4**, **5**, and **6** thermally or in the presence of an acid catalyst, in order to obtain **1** (X = N-CO_2Et; X = O; X = S) led to the formation of polymeric materials. The unsaturated compounds can, however, be trapped as Diels-Alder adducts with dienes. We have already described the reaction of the 2-ethoxybenzoxazinone (**5**) with dienes in the presence of boron trifluoride as catalyst (7). Similarly the sulfur analog was found to react with 1,1′-bicyclohexenyl, 1,2,3,4-tetramethyl butadiene and 2,4-dimethyl-1,3-pentadiene affording **7**, **8**, and **9** respectively. The reactions were carried out thermally or in the presence of boron trifluoride



7



8

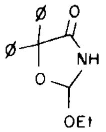


9

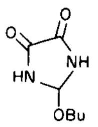
etherate at room temperature. The acid catalyzed reactions gave higher yields than the thermal reactions. According to the nmr spectra, the adducts with the bicyclohexenyl (**7**) and the tetramethylbutadiene (**8**) are most probably the *cis* isomers. The coupling constants of the acetal type hydrogens are 5 and 6 cps respectively (7,8).

The 1-carbethoxy-2-ethoxy-2,3-dihydro-4*H*-quinazolin-4-one (**4**) afforded a mixture of oily products when treated with 1,1′-bicyclohexenyl and 1,2,3,4-tetramethyl butadiene in boiling benzene and in the presence of β-naphthalenesulfonic acid. The 1-methyl-4*H*-quinazolin-4-one (**3**) did not react with the above described dienes.

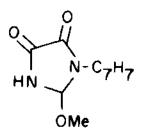
In the five membered ring system we have prepared 5,5-diphenyl-2-ethoxyoxazolidien-4-one (**10**), 2-butoxyimidazolidine-4,5-dione (**11**) and the *N*-benzyl (**12**) and *N*,*N*′-dibenzyl derivative. In the above cases, we also did not succeed in isolating the unsaturated compounds of type **2**. We did succeed, however, in trapping the unsaturated intermediates as Diels-Alder adducts on reacting **10** and **12** with 1,1′-bicyclohexenyl, 1,2,3,4-tetramethylbutadiene and 2,4-dimethyl-1,3-pentadiene to give **13**, **14**, **15**, **16**, **17**, and **18**. The reactions were carried out in boiling benzene and in the presence of β-naphthalenesulfonic acid. The less substituted dienes, 1,4-dimethylbutadiene, 2,3-dimethylbutadiene, piperylene, isoprene, and butadiene reacted sluggishly with the above described dienophiles to give complex mixtures. The thermal reactions gave generally lower yields of Diels-Alder adducts.



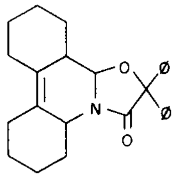
10



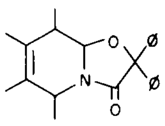
11



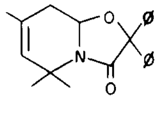
12



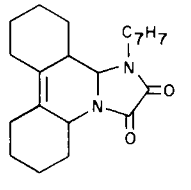
13



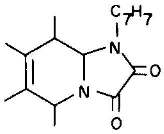
14



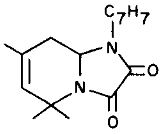
15



16



17



18

According to the nmr spectra, compound **13** was obtained as a mixture of *cis-trans* isomers in a 1:2.5 ratio. The pure *trans* isomer was isolated on crystallization from hexane. Only one isomer was observed in the case of **14** with a coupling constant of the acetal type hydrogen of 7 cps. Compound **16** and **17** were obtained as mixtures of *cis-trans* isomers. Pure samples were obtained on fractional crystallizations.

EXPERIMENTAL

Melting points are corrected, infrared spectra were measured in chloroform solutions and nmr spectra in deuterio chloroform (unless otherwise indicated).

2-Ethoxybenzothiazin-4-one.

A mixture of thiosalicylamide (4.0 g.), triethylorthoformate (12 ml.) and β-naphthalenesulfonic acid (0.4 g.) was refluxed for 1.5 hours. The solution was cooled to room temperature, filtered from undissolved material and dry ether (5 ml.) was added. After standing in the refrigerator over night, the solid was filtered and crystallized from dry ethanol; m.p. 134-136°, yield 1.70 g. (31%). It showed NH and CO absorptions at 3390 and 1675 cm^{-1} in the infrared.

Anal. Calcd. for $C_{10}H_{11}NO_2S$: C, 57.40; H, 5.25; N, 6.70; S, 15.30. Found: C, 57.62; H, 5.40; N, 6.69; S, 15.21.

The Reactions of 2-Ethoxy-2,3-dihydro-4*H*-1,3-benzothiazin-4-one with Dienes.

1,1′-Bicyclohexenyl Affording 7.

A mixture of the ethoxybenzothiazinone (1.045 g., 0.005 mole), diene (0.41 g., 0.0025 mole) and freshly distilled boron trifluoride etherate (0.7 ml., 0.005 mole) in dry ether (50 ml.) was left at room temperature for 4 days with stirring. The mixture was diluted with ether (50 ml.) and aqueous bicarbonate (25 ml., 5%) was added. The ether solution was separated, washed with water, dried and evaporated. The residue was chromatographed over neutral alumina (25 g.) and the product was eluted with benzene. It was crystallized from hexane, m.p. 145-146°, yield 0.41 g. (51%); ir: 1650 cm^{-1} (CO); nmr: δ 8.2-8.0 (m, 1H), 7.4-7.2 (m, 3H), 5.34 (d, 1H, J = 6 cps), 4.7-4.3 (m, 1H), 3.0-1.0 (m, 17H), m/e = 325.

Anal. Calcd. for $C_{20}H_{23}NOS$: C, 73.82; H, 7.09; N, 4.30; S, 9.81. Found: C, 74.02; H, 7.17; N, 4.23; S, 10.02.

The same product was also obtained in 40% yield by refluxing a chloroform solution (20 ml.) of the ethoxybenzothiazinone (0.53 g., 0.0025 mole) the diene (0.42 g., 0.0025 mole) and β-naphthalenesulfonic acid (0.1 g.) for 3 hours.

The same product was also obtained in 24% yield in a thermal reaction by refluxing a *p*-xylene solution (5 ml.) of equimolar quantities (0.001 mole) of the diene and the ethoxybenzothiazinone for 24 hours.

1,2,3,4-Tetramethylbutadiene Affording **8**.

A mixture of the ethoxybenzthiazinone (1.045 g., 0.005 mole), diene (0.4 ml.) and boron trifluoride etherate in dry ether (50 ml.) was treated as described above. The product melted at 116-118° after crystallization from ethyl acetate-hexane; yield 0.34 g. (50%). It showed a CO absorption at 1640 cm^{-1} in the infrared; nmr: δ 8.2-8.0 (m, 1H), 7.4-7.2 (m, 3H), 5.22 (d, 1H, J = 5 cps), 4.65 (q, 1H), 2.60-2.10 (m, 1H), 1.73 (s broad 6H), 1.47 (d, 3H, J = 6 cps), 1.32 (d, 3H, J = 7 cps), m/e = 273.

Anal. Calcd. for $C_{16}H_{19}NOS$: C, 70.31; H, 7.01; N, 5.13; S, 11.72. Found: C, 69.92; H, 6.79; N, 5.30; S, 11.96.

2,4-Dimethyl-1,3-pentadiene Affording **9**.

A mixture of the ethoxybenzothiazinone (2.00 g., 0.001 mole), the diene (0.7 ml., 0.005 mole) and boron trifluoride etherate in dry ether (200 ml.) was refluxed for 3 days. A solid was filtered off and the solution was treated as described above. The oily product 0.53 g. (42%) showed a CO absorption at 1650 cm^{-1}; nmr: δ 8.2-8.0 (m, 1H), 7.40-7.20 (m, 3H), 5.40 (m, 1H), 5.18 (t, 1H, J = 6 cps), 2.70-2.40 (t, broad, 2H), 1.79 (S, 3H), 1.63 (S, 3H), 1.59 (S, 3H), m/e = 259.

Anal. Calcd. for $C_{15}H_{17}NOS$: C, 69.40; H, 6.55; N, 5.44; S, 12.35. Found: C, 69.79; H, 6.78; N, 5.62; S, 11.98.

5,5-Diphenyl-2-ethoxyoxazolidin-4-one (**10**).

A mixture of the amide of benzilic acid (10 g.) triethyl orthoformate (100 ml.) and β-naphthalenesulfonic acid (0.25 g.) was stirred at room temperature for 2 days. The mixture was diluted with ethyl acetate (300 ml.), washed with aqueous bicarbonate (100 ml., 5%), dried and evaporated. The residue was triturated with petroleum ether filtered and crystallized from ethyl acetate-hexane. The yield was 8.0 g. (69%), m.p. 118°. It showed NH absorption at 3430 cm^{-1} and CO absorption at 1740 cm^{-1} in the infrared; nmr: δ 8.40 (broad 1H), 7.70-7.20 (m, 10H), 6.15 (S, 1H), 3.65 (m, 2H), and 1.12 (t, 3H) ppm.

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 72.21; H, 5.96; N, 4.99.

The Reactions of 4,4-Diphenyl-2-ethoxyoxazolidin-5-one (**10**) with Dienes.

1,1′-Bicyclohexenyl Affording **13**.

A suspension of β-naphthalenesulfonic acid (0.1 g.) in benzene (12 ml.) was refluxed to remove traces of water. The ethoxyoxazolidone **10** (0.283 g., 0.001 mole) and diene (0.178 g., 0.001 mole) were added and the mixture was refluxed for an additional 2 hours. The reaction mixture was diluted with more benzene (50 ml.) washed with aqueous bicarbonate (15 ml., 5%), dried and evaporated. The residue was chromatographed over neutral alumina (10 g.) and eluted with benzene. The product (0.13 g., 32%) is a mixture of *cis-trans* isomers in a 1:2.5 ratio according to the nmr spectrum. Crystallization from hexane gave pure *trans*, m.p. 180°. It showed CO absorption at 1710 cm^{-1} and no NH absorption in the infrared. The nmr of the *trans* isomer showed absorptions at δ 7.70-7.20 (m, 10H), 4.90 (d, 1H, J = 7 cps), 4.50-4.00 (m, 1H), and 3.00-0.90 (m, 17H).

The crude mixture showed an additional doublet at 5.07 with a coupling constant of 4 cps attributed to the *cis* isomer.

Anal. Calcd. for $C_{27}H_{29}NO_2$: C, 81.17; H, 7.32; N, 3.51. Found: C, 80.85; H, 7.54; N, 3.56.

1,2,3,4-Tetramethylbutadiene Affording **14**.

A mixture of β-naphthalenesulfonic acid (0.1 g.), ethoxyoxazolidinone (0.283 g., 0.001 mole) and diene (0.33 g., 0.003 mole) was treated as described above. The product was eluted with petroleum ether to give 0.20 g. (62%) of a crystalline product, m.p. 119°. It showed a CO absorption at 1715 cm^{-1}; nmr: δ 7.70-7.20 (m, 10H), 4.89 (d, 1H, J = 7 cps), 4.50-4.20 (m, 1H), 2.50-2.00 (m, 1H), 1.62 (s, 6H), 1.28 (s, 3H), and 1.18 (s, 3H) ppm. According to the nmr, it is the pure *trans* isomer.

Anal. Calcd. for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.28; H, 7.17; N, 4.03.

2,4-Dimethyl-1,3-pentadiene Affording **15**.

A mixture of β-naphthalenesulfonic acid (0.1 g.) ethoxyoxazolidinone (0.283 g., 0.001 mole) and diene (0.4 ml., 0.003 mole) in benzene (10 ml.) was treated as described above. The oily product 0.23 g. (72%) showed CO absorption at 1700 cm^{-1} in the infrared; nmr: δ 7.70-7.20 (m, 10H), 5.19 (s, 1H), 5.07 (t, 1H), 2.40 (d, 2H, J = 7 cps), 1.73 (s, 3H), 1.66 (s, 3H), and 1.35 (s, 3H) ppm.

Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.20; H, 6.94; N, 4.62.

2-Butoxyimidazolidine-4,5-dione (**11**).

To a solution of sodium butoxide in *n*-butanol (3.0 g. sodium in 100 ml. of *n*-butanol) there was added formamidine acetate (10.4 g.) and diethyl oxalate (20 ml.). The suspension was stirred for 4 days at room temperature and was then diluted with ethylacetate (500 ml.). The organic solution was washed with water (50 ml.) dried and evaporated. The residue was triturated with chloroform (20 ml.) and was left in the refrigerator overnight. The solid was filtered and crystallized from ethyl acetate-hexane, yield 4.6 g. (20%), m.p. 179-180°. It showed NH absorption at 3150 cm^{-1} (broad) and CO absorption at 1780, 1760, and 1730 cm^{-1} (potassium bromide); nmr (DMSO-d_6): δ 10.0 (2H, broad); 6.00 (s, 1H), 3.43 (t, 2H), 1.6-0.8 (m, 7H).

Anal. Calcd. for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.03; N, 16.27. Found: C, 48.66; H, 6.68; N, 16.59.

1-Benzyl-2-methoxyimidazolidine-4,5-dione and 1,3-Dibenzyl-2-methoxyimidazolidine-4,5-dione.

A mixture of formamidine acetate (5.3 g., 0.05 mole) diethyloxalate (10 ml., excess) in methanol (100 ml.) containing sodium methylate (3.24 g., 0.06 mole) was refluxed for 2 hours. The solution was cooled and a solution of sodium methylate (3.24 g., 0.06 mole) in methanol (50 ml.) was added followed by benzyl chloride (5.8 ml., 0.05 mole). The solution was refluxed again for 3 hours evaporated and distributed between ethyl acetate (100 ml.) and water (50 ml.). The ethyl acetate was separated, washed with water, and evaporated to dryness. Trituration of the residue with dry ether afforded the monobenzyl derivative, which was crystallized from ethyl acetate-hexane, m.p. 148-150°, yield 1.1 g. (10%). It showed NH absorption at 3420 and CO absorption at 1760 cm^{-1} in the infrared; nmr: δ 8.80 (broad, 1H), 7.33 (s, 5H), 5.80 (s, 1H), 4.97 (d, 1H, J = 15 cps), 4.16 (d, 1H, J = 15 cps), 3.14 (s, 3H).

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.78; H, 5.53; N, 13.00.

The etherial solution was evaporated and the residue was chromatographed over neutral alumina (100 g.). The dibenzyl derivative was eluted with benzene to give (2.9 g.) (19%) of a solid which melted at 112-113° after crystallization from ethyl acetate-hexane. It showed CO absorption at 1770 cm^{-1} in the infrared;

nmr: δ 7.30 (s, 10H), 5.59 (s, 1H), 4.88 (d, 2H, J = 15 cps), 4.20 (*d*, 2H, J = 15 cps), 2.83 (s, 3H), m/e = 310.

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.53; H, 5.70; N, 9.16.

The Reactions of 1-Benzyl-2-methoxyimidazolidine-4,5-dione with Dienes.

1,1′-Bicyclohexenyl to Give **16**.

A mixture of β-naphthalenesulfonic acid (0.2 g.) in benzene (50 ml.) was refluxed to remove traces of water. The methoxyimidazolidinedione (0.88 g., 0.004 mole) and the diene (0.73 g., 0.004 mole) were added and the mixture was refluxed for 24 hours. The solution was diluted with more benzene (50 ml.), washed with aqueous bicarbonate (20 ml., 5%), water, dried and evaporated. The residue was chromatographed over neutral alumina (50 g.) and the product was eluted with benzene, 0.30 g. (21%).

The product is a mixture of two isomers. Two crystallizations from ethylacetate afforded a pure sample of the more polar component (tlc), m.p. 234-235°.

Anal. Calcd. for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.27; H, 7.36; N, 9.70.

Both isomers showed CO absorption at 1750 cm^{-1} and no NH absorptions in the infrared. The nmr spectra is more complex and is not significant.

1,2,3,4-Tetramethylbutadiene to Give **17**.

A mixture of β-naphthalenesulfonic acid (0.1 g.), the methoxyimidazolidinedione (0.44 g., 0.002 mole) and the diene (0.6 g. excess) in benzene (20 ml.) was treated as described above. The crude product is a mixture of two isomers, 0.30 g. (50%). Trituration with ether afforded one of the isomers (0.10 g.) which was crystallized from methanol, m.p. 222-223°. It showed CO absorption at 1750 and no NH absorption in the infrared; nmr: δ 7.35 (s, 5H), 5.25 (d, 1H, J = 15 cps), 4.57 (d, 1H, J = 5 cps), 4.30-4.00 (m, 1H), 4.02 (d, 1H, J = 15 cps), 2.60-2.20 (m, 1H), 4.80-1.50 (9H), 0.78 (d, 3H, J = 6 cps).

Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.33; H, 7.70; N, 9.11.

2,4-Dimethyl-1,3-pentadiene to Give **18**.

A mixture of β-naphthalenesulfonic acid (0.1 g.) the methoxyimidazolidinedione (0.44 g., 0.002 mole) and diene (0.54 ml., 0.004 mole) in benzene (20 ml.) was refluxed for 5 hours. The solution was diluted with benzene (50 ml.) washed with aqueous bicarbonate (20 ml., 5%) and water, dried and evaporated. The residue was chromatographed over neutral alumina (10 g.) and eluted with benzene. The product was triturated with hexane and crystallized from methanol; m.p. 136-137°, yield 0.21 g. (38%). It showed CO absorption in the infrared at 1750 cm^{-1} and no NH absorption; nmr: δ 7.32 (s, 5H), 5.28 (broad 1H), 5.05 (d, 1H, J = 15 cps), 4.15 (t, 1H), 4.38 (d, 1H, J = 15 cps), 2.30-1.80 (m, 2H), 1.70 (s, 6H), 1.38 (s, 3H).

Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 72.04; H, 7.21; N, 10.00.

1-Carbethoxy-2-ethoxyquinazolidin-4-one (**4**).

A mixture of *N*-carbethoxyanthranilamide (1.0 g.), β-naphthalenesulfonic acid (0.1 g.) in triethylorthoformate (10 ml.) was stirred for 24 hours. The solution was diluted with ethyl acetate (100 ml.) washed with aqueous bicarbonate (30 ml., 5%), dried and evaporated. The oily residue was triturated with hexane filtered and crystallized from ethylacetate-hexane, m.p. 96°, yield 65%. It showed NH absorption at 3440 cm^{-1} and a CO doublet at 1710 and 1680 cm^{-1} in the infrared; nmr: δ 8.60 (broad 1H), 8.20-7.40 (m, 4H), 6.65 (d, 1H, J = 6 cps), 4.40 (q, 2H), 3.60 (q, 2H), 1.40 (t, 3H), 1.10 (t, 3H).

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 58.97; H, 5.96; N, 10.66.

REFERENCES

(1) A. Warshawsky and D. Ben-Ishai, *Tetrahedron Letters*, 541 (1968); *J. Heterocyclic Chem.*, 6, 681 (1969).

(2) R. R. Schmidt and E. Schlipf, *Chem. Ber.*, 103, 3783 (1970).

(3) D. Ben-Ishai, Z. Inbal and A. Warshawsky, *J. Heterocyclic Chem.*, 7, 615, 917 (1970).

(4) I. Felner and K. Schenker, *Helv. Chim. Acta*, 52, 1810 (1969).

(5) A. D. Bartfeld, W. Flitsh, and H. Peters, *Tetrahedron Letters*, 757 (1970).

(6) W. L. F. Armarego and S. C. Sharma, *J. Chem. Soc.*, 1600 (1970).

(7) D. Ben-Ishai and A. Warshawsky, *J. Heterocyclic Chem.*, 8, 865 (1971).

(8) N. J. Leonard and W. V. Ruyle, *J. Org. Chem.*, 13, 903 (1948).

(9) D. Ben-Ishai and E. Goldstein, *Tetrahedron*, 27, 3119 (1971).