The Reaction of 2,2,4,4-Tetramethyl-1,3-cyclobutanedione with *o*-Aminophenols, *o*-Aminothiophenol and with Aliphatic 2- and 3-Hydroxy- and -Mercaptoamines.

Siegfried Linke

Chemisch-wissenschaftliches Laboratorium Pharma of BAYER AG, D 56 Wuppertal-Elberfeld, Germany

Received March 30, 1973

Studies of the reaction of the dione dimer of dimethylketene (**1**) with a series of *o*-aminophenols and with *o*-aminothiophenol have been carried out. These reactions give 2-[2-(2,4-dimethyl-3-oxopentyl)]benzoxazoles and -benzothiazole, respectively. Aliphatic 2- and 3-hydroxy- and 2- and 3-mercaptoamines yield 2-substituted 2-oxazolines, 5,6-dihydro-4*H*-1,3-oxazines, 2-thiazolines and 5,6-dihydro-4*H*-1,3-thiazines.

The reaction of 2,2,4,4-tetramethyl-1,3-cyclobutanedione (**1**), the normal dimer of dimethylketene (1,2), with amines as nucleophiles has been demonstrated to be dependent on the reaction conditions and on steric and nucleophilic parameters. In general, two types of products result from the reaction of **1** with amines: either Schiff bases with an intact cyclobutane ring are formed or ring opening occurs and 2,2,4-trimethyl-3-oxopentanamides are obtained (3-5). By using diamino compounds a subsequent reaction can take place and heterocyclic products like imidazolines (5), 4,5-dihydro-1*H*-pyrimidines (5), benzimidazoles (5,6) and perimidines (6) are formed.

This investigation reports the reaction of **1** with *o*-aminophenols, *o*-aminothiophenol, with aliphatic 2- and 3-hydroxyamines and with aliphatic 2- and 3-mercaptoamines.

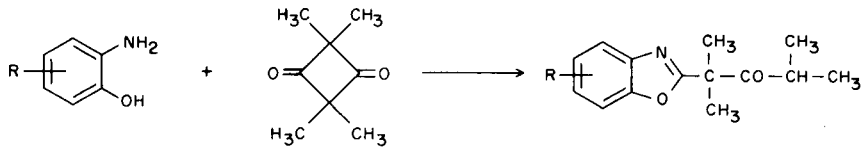
o-Aminophenols react with **1** to form 2-[2-(2,4-dimethyl-3-oxopentyl)]benzoxazoles:

The preparation of the benzoxazoles can be carried out in refluxing toluene or xylene in the presence of *p*-toluenesulfonic acid with azeotropic removal of the water formed. In general good yields are obtained.

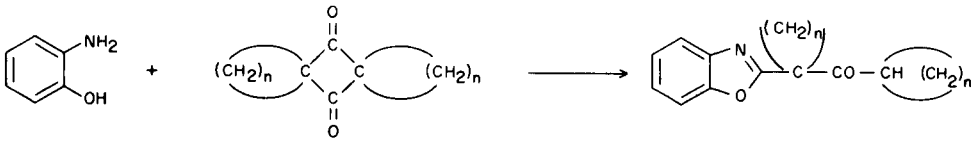
o-Aminothiophenols react in an analogous manner as shown by the formation of 2-[2-(2,4-dimethyl-3-oxopentyl)]benzthiazole (**9**) from **1** and *o*-aminothiophenol.

The structures of the compounds **2-9** were elucidated from their elemental analyses and their spectral data. The infrared spectra show λ max 1730-1720 cm^{-1} for the keto group. Their nmr spectra contain a doublet at δ 1.1 ppm for the six methyl protons of the isopropyl group, a singlet at δ 1.7 ppm for the six 2-C methyl protons, and multiplets for the methine proton of the isopropyl group centered at δ 2.2 and for the aromatic protons at δ 7.2 ppm. The products prepared and their physico-chemical data are summarized in Table I.

The dispirocyclobutanedione compounds **10** (7) and **11** (8) give, in an analogous reaction with *o*-aminophenol, the benzoxazoles **12** and **13**.

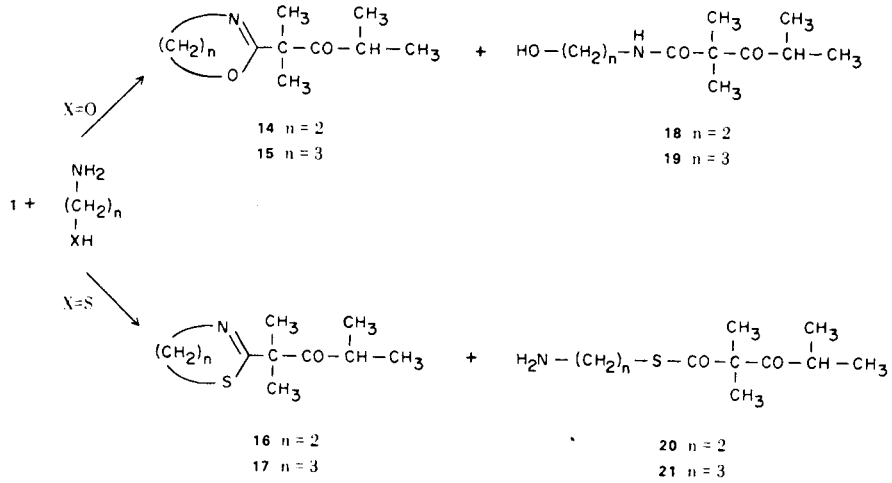


1 **2 - 8**



10 n = 3
11 n = 5

12 n = 3
13 n = 5

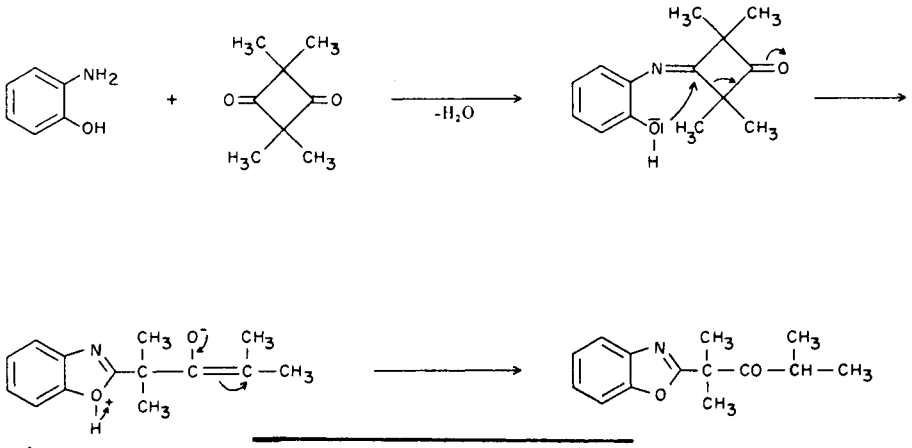


Hydroxy (or mercapto)alkylamines also undergo a reaction with **1** under standard reaction conditions. In addition to the expected heterocycles **14-17** the ring opened compounds **18-21** are formed as shown below and as listed in Table I. In all cases the two reaction products formed could be easily separated by distillation.

The structure elucidation fo these compounds is based on their elemental analyses and on their ir and nmr data: the nmr spectra of products **14-21** contain the isopropyl group [δ 1.1 (d, 6, CH_3, J = 7 Hz), 2.2 (m, 1, CH, J = 7 Hz)] and a singlet of the geminal methyl groups at δ 1.7 ppm. The ir spectra of **14-21** show λ max 1730-1720 cm^{-1} for the keto carbonyl. The amides **18** and **19** exhibit the amide group at 1650 (amide I) and 1530 cm^{-1} (amide II) and a very strong band at 3400 cm^{-1} indicates the hydroxy group. The ir spectra of **20** and **21** show, in addition to the band of the keto carbonyl, the thiolester carbonyl at 1690 cm^{-1} and the amino group at 3500 and 3350 cm^{-1}.

Hansen and DeMarco showed that the reaction of **1** with aliphatic primary amines proceeds via an *N*-substituted imine (5). Opening of the cyclobutane ring takes place in a secondary reaction step initiated by nucleophilic attack of the water formed leading finally to the 2,2,4-trimethyl-3-oxopentamides.

The formation of the 2-substituted benzoxazoles **2-8** from **1** and *o*-aminophenols should follow a similar pathway. Intramolecular attack of the *o*-hydroxy group on the double bond of the Schiff base formed initially (9) generates the benzoxazole while cleaving the cyclobutane ring according to the following scheme:



An analogous mechanism can be assumed for the formation of the 2-oxazoline **14** and the 5,6-dihydro-4*H*-1,3-oxazine **15**. In a side reaction hydrolysis of the initially formed imines (5) leads to the amides **18** and **19**.

Evidence for a plausible mechanism for the reaction of **1** with mercaptoalkylamines provides the formation of the byproducts **20** and **21**. The first step would then be the attack of the mercapto group (as the stronger nucleophile) upon the carbonyl function of **1**. In a secondary reaction step opening of the cyclobutane ring occurs (4), forming

TABLE I

Reaction of **1** with *o*-Aminophenols, *o*-Aminothiophenol and Hydroxy- and Mercaptoamines

Starting material	Reaction product	Yield %	M.p., °C	Analyses			
o-Aminophenol	2-[2-(2,4-dimethyl-3-oxopentyl)]-benzoxazole (**2**).	62	44-46	$C_{14}H_{17}NO_2$ (231.3)			
				Calcd.:	C, 72.70;	H, 7.41;	N, 6.06.
				Found:	C, 72.7;	H, 7.5;	N, 6.0.
2-Amino-4-methylphenol	2-[2-(2,4-dimethyl-3-oxopentyl)]-5-methylbenzoxazole (**3**).	81	b.p. 110-114 /0.4 mm	$C_{15}H_{19}NO_2$ (245.3)			
				Calcd.:	C, 73.44;	H, 7.81;	N, 5.71.
				Found:	C, 73.9;	H, 7.9;	N, 5.7.
2-Amino-4-methoxyphenol	2-[2-(2,4-dimethyl-3-oxopentyl)]-5-methoxybenzoxazole (**4**).	91	53	$C_{15}H_{19}NO_3$ (261.3)			
				Calcd.:	C, 68.94;	H, 7.33;	N, 5.36.
				Found:	C, 69.0;	H, 7.6	N, 5.2.
2-Amino-4-nitrophenol	2-[2-(2,4-dimethyl-3-oxopentyl)]-5-nitrobenzoxazole (**5**).	68	94-97	$C_{14}H_{16}N_2O_4$ (276.3)			
				Calcd.:	C, 60.86;	H, 5.84;	N, 10.14.
				Found:	C, 61.2;	H, 6.0;	N, 10.2.
3-Amino-4-hydroxybenzoic acid	2-[2-(2,4-dimethyl-3-oxopentyl)]-benzoxazole-5-carboxylic acid (**6**).	69	143-145	$C_{15}H_{17}NO_4$ (275.3)			
				Calcd.:	C, 65.44;	H, 6.22;	N, 5.09.
				Found:	C, 65.4;	H, 6.4;	N, 5.1.
2-Amino-4,6-dichlorophenol	2-[2-(2,4-dimethyl-3-oxopentyl)]-5,7-dichlorobenzoxazole (**7**).	39	74-76	$C_{14}H_{15}Cl_2NO_2$ (300.3)			
				Calcd.:	C, 56.02;	H, 5.04;	Cl, 23.62; N, 4.67.
				Found:	C, 56.3;	H, 5.1;	Cl, 23.8; N, 4.5.
3-Amino-2-naphthol	2-[2-(2,4-dimethyl-3-oxopentyl)]-naphtho[2,3-*d*]oxazole (**8**).	62	110-112	$C_{18}H_{19}NO_2$ (281.4)			
				Calcd.:	C, 76.84;	H, 6.81;	N, 4.98.
				Found:	C, 76.9;	H, 6.7;	N, 5.0.
2-Aminobenzenethiol	2-[2-(2,4-dimethyl-3-oxopentyl)]-benzothiazole (**9**).	97	46-47	$C_{14}H_{17}NOS$ (247.4)			
				Calcd.:	C, 67.98;	H, 6.93;	N, 5.66; S, 12.96.
				Found:	C, 68.1;	H, 6.8;	N, 5.6; S, 13.2.
2-Aminoethanol	2-[2-(2,4-dimethyl-3-oxopentyl)]-2-oxazoline (**14**).	48	b.p. 106-116 /12 mm	$C_{10}H_{17}NO_2$ (183.3)			
				Calcd.:	C, 65.54;	H, 9.35;	N, 7.64.
				Found:	C, 65.4;	H, 9.5;	N, 7.7.
	N-(β-hydroxyethyl)-3-oxo-2,2,4-trimethylpentanamide (**18**).	7,5	b.p. 145-155 /0.8 mm	$C_{10}H_{19}NO_3$ (201.3)			
				Calcd.:	C, 59.68;	H, 9.52;	N, 6.96.
				Found:	C, 59.6;	H, 9.5;	N, 7.0.
3-Amino-1-propanol	2-[2-(2,4-dimethyl-3-oxopentyl)]-5,6-dihydro-4*H*-1,3-oxazine (**15**).	48	b.p. 123-128 /12 mm	$C_{11}H_{19}NO_2$ (197.3)			
				Calcd.:	C, 66.97;	H, 9.71;	N, 7.10.
				Found:	C, 66.8;	H, 9.9;	N, 7.0.

TABLE I (Continued)

Starting material	Reaction product	Yield %	M.p., °C	Analyses		
	N(γ-hydroxypropyl)-3-oxo-2,2,4-trimethylpentanamide (**19**).	38	b.p. 160-164 /0.8 mm	$C_{11}H_{21}NO_2$ (215.3) Calcd. C, 61.37; Found: C, 61.3;	H, 9.83; H, 9.6;	N, 6.51. N, 6.6.
2-Aminoethanethiol	2-[2-(2,4-dimethyl-3-oxopentyl)]-2-thiazoline (**16**).	54	b.p. 126-135 /12 mm	$C_{10}H_{17}NOS$ (199.3) Calcd.: C, 60.26; Found: C, 60.4;	H, 8.60; H, 8.9;	N, 7.03; S, 16.09. N, 7.1; S, 15.7.
	S(β-aminoethyl) 3-oxo-2,2,4-trimethylthiopentanoate (**20**).	7	b.p. 160-170 /0.5 mm	$C_{10}H_{19}NO_2S$ (217.3) Calcd.: C, 55.27; Found: C, 56.5;	H, 8.81; H, 8.5;	N, 6.44; S, 14.75. N, 6.0; S, 15.0.
3-Amino-1-ethanethiol	2-[2-(2,4-dimethyl-3-oxopentyl)]-5,6-dihydro-4*H*-1,3-thiazine (**17**).	48	b.p. 115-120 /1.0 mm	$C_{11}H_{19}NOS$ (213.3) Calcd.: C, 61.93; Found: C, 62.2;	H, 8.98; H, 9.2;	N, 6.57; S, 15.03. N, 6.5; S, 14.7.
	S(γ-aminopropyl) 3-oxo-2,2,4-trimethylthiopentanoate (**21**).	19	74-76	$C_{11}H_{21}NO_2S$ (231.4) Calcd.: C, 57.11; Found: C, 57.0;	H, 9.15; H, 9.0;	N, 6.05; S, 13.86. N, 5.9; S, 14.0.

the thiolesters **20** or **21**, while ring opening and cyclodehydration lead to **16** or **17**.

EXPERIMENTAL

The boiling and melting points are uncorrected. The ir spectra were taken in chloroform and were recorded on a Perkin-Elmer-Spectrophotometer, Model 256. The nmr spectra were taken as 10% solution sin deuteriochloroform with TMS as an internal standard.

Reaction of **1** with *o*-Aminophenols, *o*-Aminothiophenol and with Aliphatic Hydroxy- and Mercaptoamines; General Procedure.

The hydroxy- or mercaptoamine (0.15 mole), a trace of *p*-toluenesulfonic acid and 0.15 mole of **1** were refluxed in 200 ml. or dry toluene or xylene. The water formed was removed by a water trap. When no further water was formed (2-48 hours) the solution was filtered, the solvent was evaporated and the residue distilled or recrystallized from petroleum ether (b.p. 40-80°) or ligroin (b.p. 80-110°).

The products synthesized are listed in Table I.

The reactions of dispiro[3.1.3.1]decane-5,10-dione (**10**) and of dispiro[5.1.5.1]tetradecane-7,14-dione (**11**), with *o*-aminophenol yielding **12** and **13**, respectively, were carried out according to the general procedure.

1-(2-Benzoxazolyl)biscyclobutyl Ketone (**12**).

This compound had b.p. 120-130°/0.3 mm, yield 61%; ir (chloroform): 1715 cm^{-1} (CO); nmr (deuteriochloroform): δ 1.5-3.0 (m, 8, CH_2), 2.8 (t, 4, CH_2, J = 7 Hz), 3.1-3.9 (m, 1, CH), 7.2-7.9 (m, 4, aromatic H) ppm.

Anal. Calcd. for $C_{16}H_{17}NO_2$ (255.3): C, 75.27; H, 6.71; N, 5.49. Found: C, 75.4; H, 6.6; N, 5.9.

1-(2-Benzoxazolyl)biscyclohexyl Ketone (**13**).

This compound had m.p. 104° (methanol), yield 91%; ir (chloroform): 1720 cm^{-1} (CO); nmr (deuteriochloroform): δ 1-2 (m, 16, CH_2), 2-3.1 (m, 5, CH, CH_2), 7.1-7.8 (m, 4, aromatic H) ppm.

Anal. Calcd. for $C_{20}H_{25}NO_2$ (311.4): C, 77.14; H, 8.09; N, 4.50. Found: C, 77.3; H, 8.3; N, 4.2.

REFERENCES

(1) D. Borrmann in Houben-Weyl, "Methoden der Organischen Chemie," E. Müller, Ed., Vol. 7/4. Georg Thieme Verlag, Stuttgart 1968, p. 265.

(2) Tetramethyl-1,3-cyclobutanedione, 2,2,4,4-Tetramethyl-1,3-cyclobutanediol, Properties, Reactions; Technical Data Report, Eastman Chemical Products, Inc., May 1960.

(3) R. H. Hasek, E. U. Elam and J. C. Martin, *J. Org. Chem.*, **26**, 4340 (1961).

(4) G. R. Hansen and T. E. Burg, *J. Heterocyclic Chem.*, **4**, 653 (1967).

(5) G. R. Hansen and R. A. DeMarco, *ibid.*, **6**, 291 (1969).

(6) S. Linke and C. Wünsche, *ibid.*, 10, 333 (1973).

(7) J. L. E. Erickson, F. E. Collins, B. L. Owen, *J. Org. Chem.*, **31**, 480 (1966).

(8) D. Koch, U.S. patent 3,113,421 (1960); *Chem. Abstr.*, **60**, 9083d, (1964).

(9) Under the reaction conditions used, aniline yields the Schiff base (2,3).