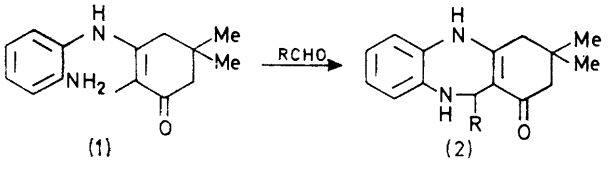
# Reactions of Enamino-ketones. Part II.[1] Synthesis of 4*H*-1,4-Benzothiazines

By **Seiji Miyano,* Nobuhiro Abe, Kunihiro Sumoto,** and **Keisuke Teramoto,** Faculty of Pharmaceutical Sciences, Fukuoka University, Fukuoka 814, Japan

A new synthesis of 4*H*-1,4-benzothiazines, consisting of the condensation of *o*-aminobenzenethiol with cyclohexane-1,3-diones, acetylacetone, benzoylacetone, or ethyl acetoacetate in dimethyl sulphoxide, is described. An oxidative cyclisation mechanism, involving an intramolecular nucleophilic attack in an intermediate enamino-ketone, is suggested.

RECENTLY considerable interest has developed in the reactions of enamino-ketones with a variety of electrophiles.[2] This stems largely from the high nucleophilic reactivity of the α-position of the enamino-ketone system.

In our previous paper [1a] it was shown that a Mannich-type cyclisation of 3-(*o*-aminoanilino)-5,5-dimethylcyclohex-2-enone (1) with aldehydes gave hexahydrodibenzodiazepinones (2) in good yields. This result encouraged us to investigate the extension of the reaction to the synthesis of the hexahydrodibenzothiazepinone counterpart (7) according to the route shown in Scheme 1[(3) ⟶ (5) ⟶ (6) ⟶ (7)]. Condensation of *o*-aminobenzenethiol (3) with 3-chloro-5,5-dimethylcyclohex-2-enone (4) gave 3-(*o*-aminophenylthio)-5,5-dimethylcyclohex-2-enone (5), a sulphur analogue of (1). Mannich-type cyclisation of (5) with *p*-nitrobenzaldehyde was attempted under conditions similar to those employed in the conversion (1) ⟶ (2).[1a] However, the Schiff base (6) was the sole product. The reaction was repeated at an elevated temperature in dimethyl sulphoxide in the hope that cyclisation would occur; however 2,3-dihydro-2,2-dimethyl-1*H*-phenothiazin-4(10*H*)-one (8) was the unexpected product (identified by comparison of m.p. with the literature value,[3] elemental analysis, and spectral properties).




(1) (2)

The vinylogous thiolester (5) turns brown gradually with formation of compound (8). Even keeping its methanolic solution at room temperature for 3 weeks afforded compound (8) in 46% yield. The phenothiazinone (8) was best prepared (59.6% yield) by simply heating compound (5) in dimethyl sulphoxide for 1 h. Thus compound (5) undergoes oxidative cyclisation in dimethyl sulphoxide leading to (8), leaving the *p*-nitrobenzaldehyde intact.

The structural change (5) ⟶ (8) is considered to be the result of the sequence shown in Scheme 2.

These ideas, especially the assumption of the step C (oxidative cyclisation in the presence of dimethyl sulphoxide) as a key reaction, led us to study simple interactions of *o*-aminobenzenethiol (3) with dimedone (10; $R^1 = R^2 = Me$) itself (Scheme 3). We discovered that the phenothiazinone derivative (13; $R^1 = R^2 = Me$) is best prepared (89.8% yield) by merely heating a mixture of (3) and dimedone in dimethyl sulphoxide at 155 °C for

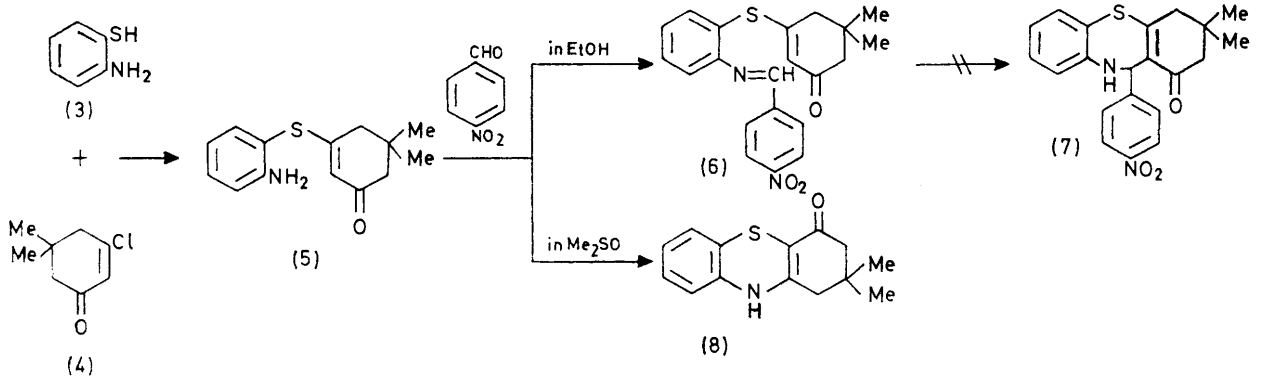
[1] (*a*) Part I, S. Miyano and N. Abe, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1588; (*b*) preliminary report, S. Miyano, N. Abe, and K. Sumoto, *J.C.S. Chem. Comm.*, 1975, 760.

[2] (*a*) G. H. Alt and A. J. Speziale, *J. Org. Chem.*, 1964, **29**, 794; (*b*) H. J. Teuber and R. Braun, *Chem. Ber.*, 1967, **100**, 1353; (*c*) H. J. Teuber, E. Worbs, and D. Cornelius, *ibid.*, 1968, **101**, 3918; (*d*) C. Ruangsiyanand, H.-J. Rimak, and F. Zymalkowski, *ibid.*, 1970, **103**, 2403; (*e*) Y. Yoshimoto, N. Nishida, and T. Hiraoka, *Tetrahedron Letters*, 1973, 39, and references therein.

[3] V. I. Shvedov, L. B. Altukhova, V. M. Lyubchanskaya, and A. N. Grinev, *Khim. geterotsikl. Soedinenii*, 1972, 1901 (*Chem. Abs.*, 1973, **77**, 43395k).

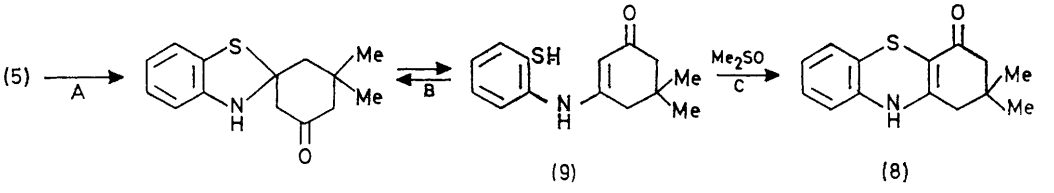
45 min. Similar condensation of (3) with other cyclohexane-1,3-diones (10; $R^1 = R^2 = H$; $R^1 = H$, $R^2 =$ Me; or $R^1 = H$, $R^2 =$ Ph) gave the corresponding products (13) in 42.4, 65.8, and 77.3% yields, respectively.

This hypothesis is borne out by the following two observations. First, the reaction of 2 equiv. of the amino-thiol (3) with dimedone carried out by refluxing the reactants in benzene under nitrogen for 0.5 h (Scheme

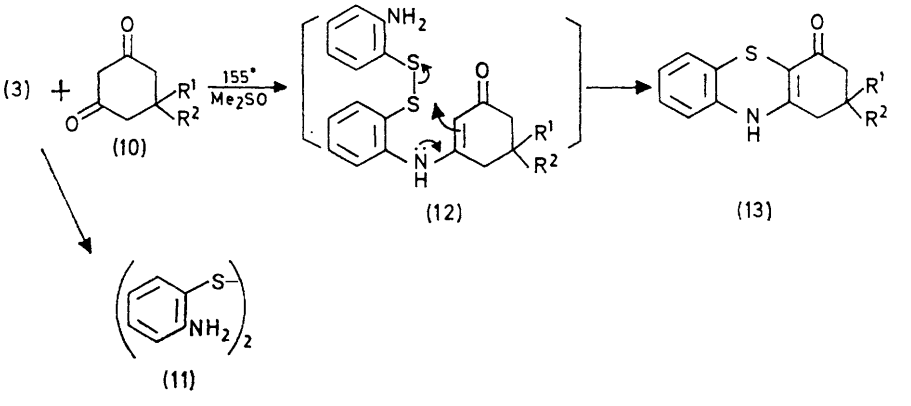



SCHEME 1

Since compound (3) is readily oxidised to bis-(*o*-aminophenyl) disulphide (11) under the reaction conditions,[4] and since we have shown that this disulphide also condenses with cyclohexanediones (10) to give phenothiazines (13), the reaction is considered to proceed *via* 4) gave 2-[3-(benzothiazol-2-yl)-2,2-dimethylpropyl]-2,3-dihydro-2-methylbenzothiazole (14) exclusively in 90% yield. The fact that, in contrast to the reaction in dimethyl sulphoxide, this reaction in a non-oxidising solvent gave no phenothiazinone (8) confirmed the role of




SCHEME 2




SCHEME 3

the intermediate (12), which is cyclised to (13) by scission of the sulphur–sulphur bond[5,6] upon attack by the nucleophilic enaminone system.

dimethyl sulphoxide in the present synthesis. Secondly, compounds (8) and (14) were formed by the reaction of the disulphide (11) with 2 equiv. of dimedone (Scheme 4) under the same conditions. The formation of (8) was apparently the result of ionic cleavage of pre-formed (12)

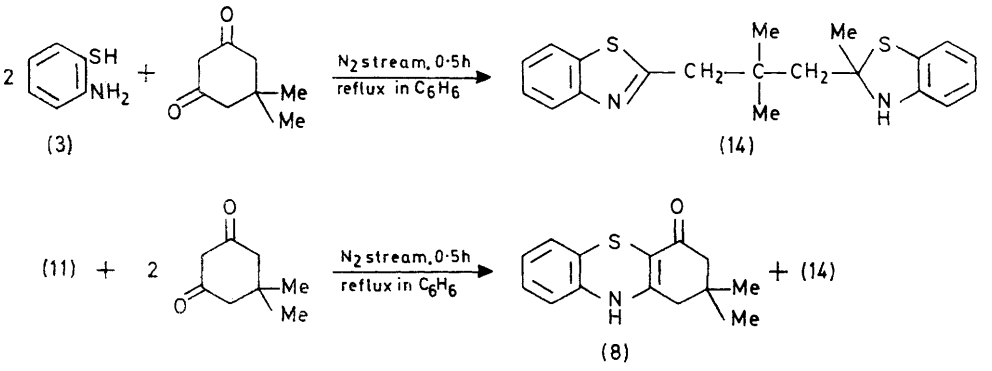
[4] C. N. Yiannios and J. V. Karabinos, *J. Org. Chem.*, 1963, **28**, 3246.

[5] F. M. Moracci, M. Cardellini, F. Liberatore, P. Marchini, G. Liso, and U. Gulini, *Internat. J. Sulphur Chem.*, 1973, **8**, 341 (*Chem. Abs.*, 1974, **82**, 152, 135h)

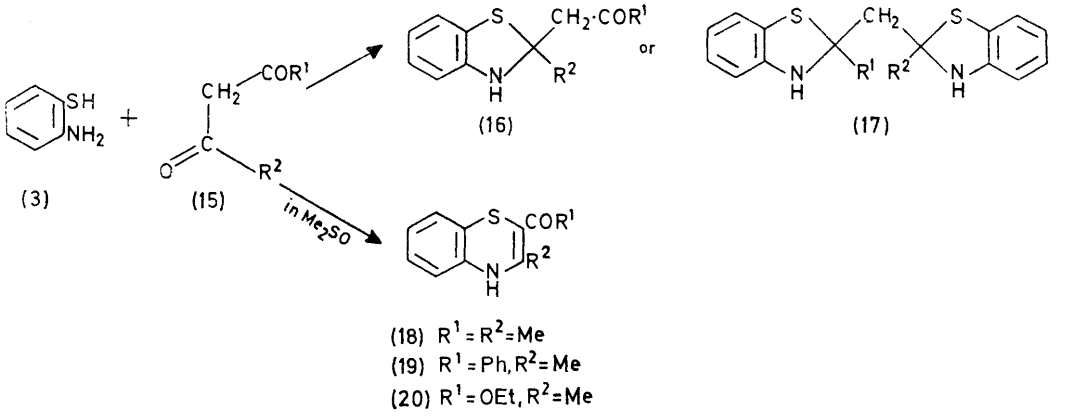
[6] T. Fujiwara, K. Hata, and T. Kojima, *Chem. Letters*, 1973, 287.

(Scheme 3) whereas (14) was the final product of condensation between (3), another fragment of (12), and dimedone.

The condensation described here has been extended successfully to active methylene compounds such as β-diketones and β-oxo-esters, and a general synthesis of 4*H*-1,4-benzothiazines has now been established (Scheme 5). In contrast to the fact that the amino-thiol (3) normally reacts with β-diketones and β-oxo-esters to give dihydrobenzothiazoles (16) or bisdihydrobenzothiazoles (17),[7] its reactions with the β-diketones (15; $R^1 = R^2 =$ Me or $R^1 =$ Ph, $R^2 =$ Me) and the β-oxo-ester (15; $R^1 =$ OEt, $R^2 =$ Me) in dimethyl sulphoxide afforded compounds (18)—(20) in 71.2, 67.2, and 62.1% yields, respectively. In terms of simple manipulation, availability of starting materials, and yields of products, the present synthesis of 4*H*-1,4-benzothiazines and analogues has considerable advantages.




SCHEME 4




SCHEME 5

## EXPERIMENTAL

I.r. spectra were recorded with a Hitachi-EPI-G-3 instrument. N.m.r. spectra were measured with a Hitachi-MH-100 (100 MHz) or Hitachi-R-24 (60 MHz) instrument.

3-(o-*Aminophenylthio*)-5,5-*dimethylcyclohex-2-enone* (5).—To a stirred solution of sodium ethoxide [from sodium (0.23 g, 0.01 mol)] in absolute ethanol (30 ml) were added freshly distilled *o*-aminobenzenethiol (1.25 g, 0.01 mol) and 3-chloro-5,5-dimethylcyclohex-2-enone (4) (1.585 g, 0.01 mol). The mixture was stirred for 1 h at room temperature and the solvent removed under reduced pressure. Ether (20 ml) was added and the solution washed with water, then dried and concentrated to a yellow oil which crystallised on cooling to afford the *vinylogous thiolester* (5) (2.54 g, quantitative) as yellow crystals, m.p. 64—67°, $\lambda_{max.}$ (KBr) 3 433 and 3 324 ($NH_2$), and 1 636 $cm^{-1}$ (C=O), δ($CDCl_3$) 7.45—6.55 (4 H, m, aromatic), 5.52 (1 H, s, CO·C*H*=), 4.20br (2 H, s, $NH_2$), 2.36 (2 H, s, $CH_2$), 2.21 (2 H, s, $CH_2$), and 1.05 (6 H, s, $CMe_2$). Elemental analyses did not give satisfactory values since the compound was rapidly oxidised to (8).

*Attempted Reaction of the Vinylogous Thiolester* (5) *with* p-*Nitrobenzaldehyde.*—(i) *In ethanol.* A solution of compound (5) (1.235 g, 5 mmol) and *p*-nitrobenzaldehyde (0.83 g, 5.5 mmol) in ethanol (8 ml) was kept at room temperature for a few min. The precipitate was filtered off and crystallised from ethanol to afford 5,5-*dimethyl*-3-[o-(p-*nitrobenzylideneamino*)*phenylthio*]*cyclohex*-2-*enone* (6) (1.81 g, 95.3%) as yellow needles, m.p. 142—144°, $\lambda_{max.}$ (KBr) 1 644 $cm^{-1}$ (C=O); δ($CDCl_3$) 8.41 (1 H, s, N=CH), 8.31 (2 H, d, *J* 9.0 Hz, *H*CH), 8.04 (2 H, d, *J* 9.0 Hz, HC*H*), 7.73—6.95 (4 H, m, aromatic), 5.35 (1 H, s, CO·C*H*=C·S), 2.33 (2 H, s, $CH_2$), 2.10 (2 H, s, $CH_2$), and 0.95 (6 H, s, $CMe_2$) (Found: C, 66.1; H, 5.15; N, 7.3. $C_{21}H_{20}N_2O_3S$ requires C, 66.3; H, 5.3; N, 7.35%).

[7] A. I. Kiprianov and V. A. Portnyagina, *Zhur. obshchei Khim.*, 1955, **25**, 2257 (*Chem. Abs.*, 1956, **50**, 9378b).

(ii) *In dimethyl sulphoxide.* A solution of compound (5) (1.235 g, 5 mmol) and *p*-nitrobenzaldehyde (0.38 g, 5.5 mmol) in dimethyl sulphoxide (10 ml) was heated at 170 °C for 45 min and concentrated under reduced pressure to a solid mass. This was washed with acetone to give orange plates (0.62 g, 50.6%), which crystallised from methanol to afford the phenothiazinone (8), m.p. 262—263° (decomp.) (lit.,[3] 264—265°).

*Conversion of the Vinylogous Thiolester* (5) *into the Phenothiazinone* (8).—A solution of compound (5) (1.235 g, 5 mmol) in dimethyl sulphoxide (5 ml) was heated at 170 °C for 1 h and evaporated under reduced pressure to a solid mass. Washing with acetone and crystallisation from methanol gave compound (8) (0.73 g, 59.6%), m.p. 262—263° (decomp.).

2,3-*Dihydro*-1H-*phenothiazin*-4(10H)-*ones* (13; $R^1 = R^2 = H$). —A solution of *o*-aminobenzenethiol (3) (0.01 mol) and cyclohexane-1,3-dione (10; $R^1 = R^2 = H$) (0.01 mol) in dimethyl sulphoxide (5 ml) was heated at 155 °C for 1 h. A small amount of chloroform was added and the product crystallised on cooling; it was filtered off and recrystallised from acetone. 2,3-*Dihydro*-1H-*phenothiazin*-4(10H)-*one* (13; $R^1 = R^2 = H$) was obtained as orange-yellow platelets (0.92 g, 42.4%), m.p. 223—225° (decomp.) (lit.,[3] 203—204°) (Found: C, 66.1; H, 4.95; N, 6.4. $C_{12}H_{11}NOS$ requires C, 66.35; H, 5.1; N, 6.45%). 2,3-*Dihydro*-2-*phenyl*-1H-*phenothiazin*-4(10H)-*one* (13; $R^1 = H$, $R^2 = Ph$) was obtained as orange platelets (2.27 g, 77.3%), m.p. 263—265° (decomp.) (lit.,[3] 194—195°) (from ethanol) (Found: C, 73.55; H, 4.85; N, 4.85. $C_{18}H_{15}NOS$ requires C, 73.7; H, 5.15; N, 4.8%). 2,3-*Dihydro*-2-*methyl*-1H-*phenothiazin*-4(10H)-*one* (13; $R^1 = H$, $R^2 = Me$) was obtained as orange plates (1.52 g, 65.8%), m.p. 266—268° (decomp.) (from ethanol) (Found: C, 67.4; H, 5.55; N, 6.15. $C_{13}H_{13}NOS$ requires C, 67.5; H, 5.65; N, 6.05%). 2,3-Dihydro-2,2-dimethyl-1*H*-phenothiazin-4(10*H*)-one (8) was obtained as orange plates (2.2 g, 89.8%), m.p. 262—263° (decomp.) (lit.,[3] 264—265°) (from methanol), $\lambda_{max.}$ (KBr) 3 240, 3 190, 3 145, 3 100, 1 583, 1 571, and 1 513 $cm^{-1}$ (vinylogous amide), $\delta$[$(CD_3)_2SO$] 8.90 (1 H, s, NH), 7.00—6.43 (4 H, aromatic), 2.20 (2 H, s, $CH_2$), 2.15 (2 H, s, $CH_2$), and 1.00 (6 H, s, $CMe_2$) (Found: C, 68.35; H, 6.05; N, 5.85. Calc. for $C_{14}H_{15}NOS$: C, 68.55; H, 6.15; N, 5.7%).

4H-1,4-*Benzothiazines.*—*o*-Aminobenzenethiol (3) (0.01 mol), the β-diketones or β-oxo-ester (0.01 mol), and dimethyl sulphoxide (5 ml) were heated together at 145—150 °C for 30—45 min. The mixture was concentrated under reduced pressure to give a solid mass which was washed with a small amount of methanol and recrystallised from methanol. 2-*Acetyl*-3-*methyl*-4H-1,4-*benzothiazine* (18) was obtained as orange needles (1.46 g, 71.2%), m.p. 194—196°, Found. C, 64.1; H, 5.15; N, 7.0. $C_{11}H_{11}NOS$ requires C, 64.4; H, 5.4; N, 6.85%). 2-*Benzoyl*-3-*methyl*-4H-1,4-*benzothiazine* (19) was obtained as orange flakes (1.66 g, 67.2%), m.p. 188—190° (decomp.) (Found: C, 71.85; H, 4.7; N, 5.15. $C_{16}H_{13}NOS$ requires C, 71.9; H, 4.9; N, 5.25%). Ethyl 3-methyl-4*H*-1,4-benzothiazine-2-carboxylate (20) was obtained as orange-yellow needles (1.46 g, 62.1%), m.p. 144—145° (lit.,[8] 144—145°) (Found: C, 61.2; H, 5.45; N, 6.0. Calc. for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.55; N, 5.95%).

*Reaction of Bis*-(o-*aminophenyl*) *Disulphide* (11) *with Dimedone.*—(i) *In dimethyl sulphoxide.* The disulphide (11) (1.24 g, 5 mmol), dimedone (1.4 g, 0.01 mol), and dimethyl sulphoxide (5 ml) were heated together at 155 °C for 45 min. The precipitate formed was filtered off and washed with a small amount of methanol to give the phenothiazinone (8) (2.28 g, 93.1%).

(ii) *In benzene.* A solution of compound (11) (1.24 g, 5 mmol), dimedone (1.4 g, 0.01 mol), and toluene-*p*-sulphonic acid (0.1 g) in benzene (60 ml) was refluxed for 0.5 h with a water-separator under a nitrogen stream. The crystals which separated on cooling were filtered off and washed with a small amount of methanol to give compound (8) [0.98 g, 80% based on (11)]. The mother liquor was concentrated under reduced pressure, the residue was extracted with ether, and the extract was evaporated. 2-[3-(*Benzothiazol*-2-*yl*)-2,2-*dimethylpropyl*]-2,3-*dihydro*-2-*methylbenzothiazole* (14) [(0.326 g, 36.8% based on (11)] was obtained as prisms, m.p. 141—142° (from acetone), $\lambda_{max.}$ (KBr) 3 205 $cm^{-1}$ (NH), $\delta(CDCl_3)$ 8.20—6.60 (8 H, m, aromatic), 5.51 (1 H, s, NH), 3.23 (2 H, ABq, *J* 14 Hz, $CH_2$), 2.00 (2 H, s, $CH_2$), 1.71 (3 H, s, $CH_3$), 1.28br (3 H, s, $CH_3$), and 1.17br (3 H, s, $CH_3$) (Found: C, 67.85; H, 6.15; N, 7.95. $C_{20}H_{22}N_2S_2$ requires C, 67.8; H, 6.25; N, 7.9%).

*Reaction of* o-*Aminobenzenethiol* (3) *with Dimedone in Benzene.*—A solution of the thiol (3) (2.50 g, 0.02 mol), dimedone (1.4 g, 0.01 mol), and toluene-*p*-sulphonic acid (0.1 g) in benzene (60 ml) was refluxed for 2 h with a water-separator under a nitrogen stream. The crystals which separated on cooling were filtered off, the benzene was removed under reduced pressure, and the residual solid was washed with methanol. Compound (14) (3.20 g, 90%) was the sole product.

[5/2170 *Received*, 7*th November*, 1975]

[8] Y. Maki, M. Suzuki, and T. Yamada, *Chem. and Pharm. Bull.* (*Japan*), 1966, **14**, 770.