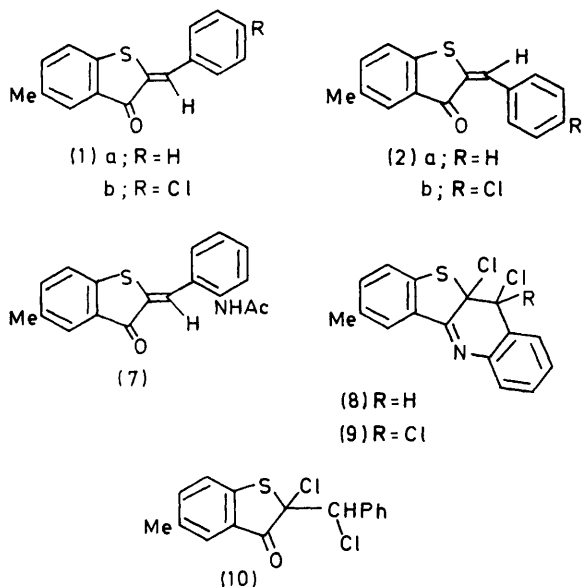


## Configuration of 2-Arylmethylene-2,3-dihydro-5-methylbenzo[*b*]thiophen-3-ones

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The configurations of 2-arylmethylene-2,3-dihydro-5-methylbenzo[*b*]thiophen-3-ones, prepared by the condensation of 2,3-dihydro-5-methylbenzo[*b*]thiophen-3-ones with aromatic aldehydes, and of their photoisomers are assigned on the basis of n.m.r. spectroscopic and chemical evidence.

2-ARYLMETHYLENE-2,3-DIHYDROBENZO[*b*]THIOPHEN-3-ONES (thioaurones) † are generally prepared<sup>1</sup> by the acid-catalysed condensation of aromatic aldehydes with 2,3-dihydrobenzo[*b*]thiophen-3-ones. Only one of the



two possible geometrical isomers [*e.g.* (1) and (2)] is reported to have been isolated in each case of synthesis

† The need for a simple name for 2-benzylidene-2,3-dihydrobenzo[*b*]furan-3-ones was met by Bate-Smith and Geissman (*Nature*, 1951, **167**, 688), whose term 'aurone' has found general acceptance (see for example B. A. Bohm in 'The Flavonoids,' ed. T. J. Mabry and H. Mabry, Chapman and Hall, London, 1975, p. 467). For convenience we use the term 'thioaurone' as a trivial name for the sulphur analogues of these compounds.

‡ The terms *cis* and *trans* in this paper refer to the relative positions of the carbonyl and the side-chain aryl groups.

§ For example see refs. 5–8.

<sup>1</sup> K. Auwers and F. Arndt, *Ber.*, 1909, **42**, 543; P. Friedländer, *Monatsh.*, 1909, **30**, 349; P. Friedländer and N. Woroschzow, *Annalen*, 1912, **10**, 388; G. A. Yagai and M. A. Mostoslavskii, Yu L. Yagupol'skii, and N. P. Makshanova, *Khim. geterotsikl. Soedinenii*, 1972 (8), 1148, and leading references cited therein.

by this method. We required to know the configuration of the thioaurones thus prepared in order to establish the stereochemistry of the products of oxidation of these compounds.<sup>2</sup> Mostoslavskii and his co-workers<sup>3</sup> obtained a less stable thioaurone isomer by u.v. irradiation of the more stable condensation product. The photoisomer had weaker u.v. absorption, greater solubility in organic solvents, and lower m.p. than the original product. It was also readily reconverted into the original isomer either by heating or by treatment with base. It was concluded<sup>3a</sup> that the photoisomer had the *cis*-configuration, ‡ because the greater steric compression between the side-chain aryl group and the carbonyl oxygen atom in this isomer, as compared with that between the side-chain aryl group and the sulphur atom in the *trans*-isomer, would account for these properties. Although the properties described can generally help to distinguish between a pair of geometrical isomers<sup>4</sup> this is not universally so, § and caution has to be exercised in taking this evidence alone as proof of structure.

Steric factors alone do not determine the stereochemistry of  $\alpha$ -arylmethylene ketones prepared by the condensation of aromatic aldehydes with ketones. Electronic factors were shown to be more important than steric factors in determining the reaction stereochemistry in the Perkin and related reactions.<sup>9</sup> The requirement of maximum overlap of electrons in the transition state of the elimination step favours products with unhindered

<sup>2</sup> L. S. S. Réamonn and W. I. O'Sullivan, *J.C.S. Chem. Comm.*, 1976, 642, 1013.

<sup>3</sup> (a) V. A. Izmail'skii and M. A. Mostoslavskii, *Ukrain. khim. Zhur.*, 1961, **27**, 234; (b) M. A. Mostoslavskii and V. A. Ismail'skii, *Zhur. obshchei Khim.*, 1961, **31**, 17; (c) M. A. Mostoslavskii and M. O. Kravchenko, *Khim. geterotsikl. Soedinenii*, 1968, (1), 58.

<sup>4</sup> E. L. Eliel, 'Stereochemistry of Carbon Compounds,' McGraw-Hill, London, 1962, p. 325.

<sup>5</sup> A. Hassner and T. L. Mead, *Tetrahedron*, 1964, **20**, 2201.

<sup>6</sup> D. N. Kevill, E. D. Weiler, and N. H. Cromwell, *J. Org. Chem.*, 1964, **29**, 1276.

<sup>7</sup> J. S. Hastings and G. H. Heller, *J.C.S. Perkin I*, 1972, 2128.

<sup>8</sup> M. Hooper and W. N. Pitkethly, *J.C.S. Perkin I*, 1972, 1607.

<sup>9</sup> H. E. Zimmerman and L. Ahramjian, *J. Amer. Chem. Soc.*, 1959, **81**, 2086.

electron delocalising groups.<sup>9</sup> The arylmethylene derivatives of acetophenones,<sup>10</sup> cyclohexanones,<sup>5</sup> tetralones,<sup>6</sup> flavanones,<sup>11</sup> indanones,<sup>6</sup> and aurones<sup>7,12</sup> as prepared by acid- or base-catalysed condensation of the parent compounds with aromatic aldehydes have all been shown to be *trans*-isomers, which are the expected products from a consideration of 'overlap control';<sup>9</sup> the only exceptions were when there was a high degree of steric crowding which rendered the *trans*-isomers unstable.\* In the case of condensation of benzaldehyde with 2,3-dihydrobenzo[*b*]thiophen-3-ones the expected products, from both steric and electronic considerations, are *trans*-thioaurones. That the products indeed have the *trans*-configuration is further supported by n.m.r. spectroscopic and by chemical evidence described below.

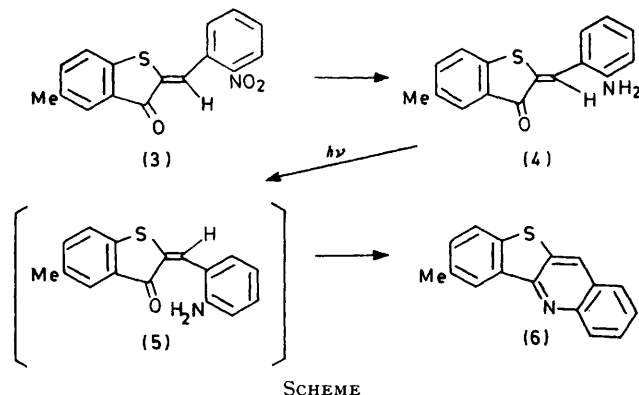
The assignments of configurations to the compounds listed above, except aurones, were made on the basis of the chemical shifts of the  $\beta$ -protons, which in the *trans*-isomers give signals at considerably lower field than the signals of the corresponding protons in the *cis*-isomers. The configurations of the geometrical isomers of aurones could not be assigned on this basis because of the small differences between the chemical shifts of the  $\beta$ -protons of these compounds.<sup>7,12</sup> However, n.m.r. spectral analysis was more useful in enabling configurations to be assigned to thioaurones.

*trans*-2-Benzylidene-2,3-dihydro-5-methylbenzo[*b*]thiophen-3-one (1a) and *trans*-2-(4-chlorobenzylidene)-2,3-dihydro-5-methylbenzo[*b*]thiophen-3-one (1b) were prepared by acid-catalysed condensation of 2,3-dihydro-5-methylbenzo[*b*]thiophen-3-one with benzaldehyde and with *p*-chlorobenzaldehyde, respectively. U.v. irradiation of solutions of these thioaurones in *n*-hexane with a high-pressure mercury-vapour lamp through a water-cooled Pyrex sleeve gave the second geometrical isomer (2a or b) in each case. Previously<sup>3</sup> solutions of the *cis*-isomers were obtained by exposure of solutions of the *trans*-isomers to sunlight. In the present work mixtures of *cis*- and *trans*-isomers were obtained in estimated (n.m.r.) ratios of 13 : 1 [(2a) : (1a)] and 12 : 1 [(2b) : (1b)]. Crystals of the *cis*-isomers were obtained by mechanical separation from the crystalline mixtures.

The  $\beta$ -proton signals in the n.m.r. spectra of the condensation products occurred at lower field [ $\tau$  2.08 in (1a) and 2.19 in (1b)] than the signals of the  $\beta$ -protons in the corresponding photoisomers [ $\tau$  2.80 in (2a) and 2.77 in (2b)]; thus the condensation products were assigned the *trans*-configuration and the photoisomers the *cis*-configuration. The identity of the  $\beta$ -proton signals in the n.m.r. spectra of the thioaurones (1a) and (2a) was confirmed by the absence of signals at  $\tau$  2.08 and 2.80 in the n.m.r. spectra of the corresponding thioaurones in

which the  $\beta$ -protons were replaced by  $\beta$ -deuterium atoms. The ring sulphur atom in the isomeric 5-methylthioaurones (1) and (2) is expected to have a smaller shielding effect on the  $\beta$ -protons of these compounds<sup>13</sup> as compared with the shielding effect of the oxygen atom on the  $\beta$ -proton<sup>14</sup> of the corresponding aurones, and to shield the *cis*- $\beta$ -proton to a greater extent (*ca.* 0.2 p.p.m.) than the *trans*- $\beta$ -proton. The difference between the chemical shifts of the  $\beta$ -protons of isomeric 5-methylthioaurones is, thus regarded as being predominantly due to the greater effect of the anisotropy of the carbonyl group on the  $\beta$ -proton in the *trans*-isomer. Further evidence of the configuration of the thioaurones (1) and (2) was obtained from the chemical shift values of the 2'- and 6'-protons. It was previously shown<sup>12</sup> that the differences in chemical shifts between the 2'- and 6'-protons of isomeric 6-methoxyaurones were sufficiently large to enable assignments of configuration to be made. The low-field absorptions of the 2'- and 6'-protons in *cis*-thioaurones (2a and b) ( $\tau$  1.93 and 1.70—2.02) may be attributed to the deshielding effect of the carbonyl group. The 2'- and 6'-protons in the *trans*-isomers (1a and b) are further removed from the carbonyl group and should not be significantly deshielded by it; the signals due to these protons were hidden in the aromatic multiplets in each case.

The foregoing assignments of configuration to thioaurones is supported by chemical evidence (Scheme).<sup>15</sup> 5-Methyl-2'-nitrothioaurone (3), prepared by the condensation of 2,3-dihydro-5-methylbenzo[*b*]thiophen-3-one with 2-nitrobenzaldehyde, on treatment with tin(II) chloride and hydrochloric acid at room temperature, gave 2'-amino-5-methylthioaurone (4). The latter on



irradiation with u.v. light gave the quinoline (6), the isolation of which indicated that *cis*-2'-aminothioaurone (5) was formed by isomerisation of the more stable *trans*-isomer (4) and cyclised immediately. It is concluded that the 2'-aminothioaurone (4) and 2'-nitrothioaurone (3) are both *trans*-isomers. The possibility that the

\* See examples in refs. 8 and 11.

<sup>10</sup> W. B. Black and R. E. Lutz, *J. Amer. Chem. Soc.*, 1955, **77**, 5134.

<sup>11</sup> D. D. Keane, K. G. Marathe, W. I. O'Sullivan, E. M. Philbin, R. M. Simons, and P. C. Teague, *J. Org. Chem.*, 1970, **35**, 2286.

<sup>12</sup> B. A. Brady, J. A. Kennedy, and W. I. O'Sullivan, *Tetrahedron*, 1973, **29**, 359.

<sup>13</sup> L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Spectroscopy in Organic Chemistry,' 2nd edn., Pergamon, Oxford, 1969, p. 185.

<sup>14</sup> J. W. Emsley, J. Feeney, and H. Sutcliffe, 'High Resolution Nuclear Magnetic Resonance Spectroscopy,' vol. 2, Pergamon, Oxford, 1966, p. 721.

<sup>15</sup> Cf. method used in ref. 12.

original 2'-nitrothioaurone was the *cis*-isomer, which isomerised to the *trans*-isomer (3) under the conditions of the reduction reaction, was discounted when thioaurone (1a), formed by condensation of 2,3-dihydro-5-methylbenzo[*b*]thiophen-3-one and benzaldehyde, was unchanged under the same conditions. The possibility that the reduction product was the *cis*-2'-aminothioaurone, which underwent photocyclisation, was also discounted when a chloroquinoline derivative was obtained on treatment of the 2'-aminothioaurone with chlorine in the dark. Addition of chlorine to the olefinic bond of the *trans*-2'-aminothioaurone (4) would enable free rotation about the  $\alpha\beta$ -bond and thus allow the amino- and oxo-groups to collide and cyclisation to occur. Direct cyclisation of the 2'-aminothioaurone to give the quinoline (6) would have been expected had the initial product of reduction of 2'-nitrothioaurone been the *cis*-2'-aminothioaurone (5). Furthermore, treatment of the 2'-aminothioaurone with acetic anhydride-acetic acid gave the acetamido-derivative (7) only. Cyclisation, at least in part, would have been expected under such acidic conditions had the 2'-aminothioaurone been the *cis*-isomer.

The chloroquinoline derivative mentioned above was not the expected dichloro-derivative (8) but a trichloro-derivative assigned structure (9) on the basis of elemental analysis and spectroscopic data. There were no peaks in the i.r. spectrum attributable to oxo- or amino-groups, or to saturated C-H. The n.m.r. spectrum had aromatic signals integrating for seven protons but had no signals in the  $\tau$  3—5 region, indicating the absence of a 4-proton. In the n.m.r. spectrum of 5-methylthioaurone dichloride (10), prepared by chlorination of 5-methylthioaurone, the  $\beta$ -proton gave a signal at  $\tau$  4.40.

#### EXPERIMENTAL

N.m.r. spectra were recorded with a Perkin-Elmer R-12 spectrometer at 60 MHz for solutions in deuteriochloroform with tetramethylsilane as internal standard. I.r. spectra were recorded with a Perkin-Elmer 700 spectrophotometer.

*trans*-2-Benzylidene-2,3-dihydro-5-methylbenzo[*b*]thiophen-3-one (1a).—Prepared by the method of Auwers and Arndt<sup>1</sup> from 2,3-dihydro-5-methylbenzo[*b*]thiophen-3-one [m.p. 102° (lit., 102°),  $\tau$  2.45 (1 H, s, 4-H), 2.7 (2 H, m, 6- and 7-H), 6.25 (2 H, s, CH<sub>2</sub>), and 7.65 (3 H, s, 5-CH<sub>3</sub>)] and benzaldehyde, the aurone (1a) had m.p. 146° (lit.,<sup>1</sup> 146°),  $\nu_{\max}$  (Nujol) 1 655 and 1 580 cm<sup>-1</sup>,  $\tau$  2.08 (1 H, s,  $\beta$ -H), 2.1—2.7 (8 H, m, ArH), 2.29 (1 H, m, 4-H), and 7.61 (3 H, s, 5-CH<sub>3</sub>);  $\lambda_{\max}$  in agreement with data reported previously.<sup>3c</sup>

*trans*-2-( $\alpha$ -Deuteriobenzylidene)-2,3-dihydro-5-methylbenzo[*b*]thiophen-3-one (0.98 g, 80%) was prepared in the same way from 2,3-dihydro-5-methylbenzo[*b*]thiophen-3-one (1.5 g) and benz[<sup>2</sup>H]aldehyde<sup>16</sup> (0.5 g); m.p. 146° alone or when mixed with a non-labelled sample.

*cis*-2-Benzylidene-2,3-dihydro-5-methylbenzo[*b*]thiophen-3-one (2a).—A solution of the *trans*-isomer (1a) (0.1 g) in n-hexane (200 ml) was irradiated for 1 h through a water-cooled Pyrex sleeve with a Philips HPK 125 W high-pressure mercury vapour lamp. Removal of the solvent *in vacuo* afforded a mixture of the *cis*- and *trans*-isomers in

an estimated (n.m.r.) ratio of ca. 13 : 1. Lemon yellow crystals of the *cis*-isomer (2a) were separated mechanically; m.p. ca. 87° (Found: C, 76.25; H, 4.8; S, 12.55. C<sub>16</sub>H<sub>12</sub>OS requires C, 76.2; H, 4.75; S, 12.3%),  $\nu_{\max}$  (Nujol mull) 1 660 and 1 580 cm<sup>-1</sup>,  $\tau$  1.80—2.05 (2 H, m, 2'- and 6'-H), 2.30—2.75 (5 H, m, ArH), 2.80 (1 H, s,  $\beta$ -H), and 7.61 (3 H, s, 5-CH<sub>3</sub>);  $\lambda_{\max}$  in agreement with data reported previously.<sup>3c</sup>

*cis*-2-( $\alpha$ -Deuteriobenzylidene)-2,3-dihydro-5-methylbenzo[*b*]thiophen-3-one was obtained in the same way by irradiation of a solution of *trans*-2-( $\alpha$ -deuteriobenzylidene)-2,3-dihydro-5-methylbenzo[*b*]thiophen-3-one in n-hexane; m.p. 87° alone or when mixed with a non-labelled sample.

*trans*-2-(4-Chlorobenzylidene)-2,3-dihydro-5-methylbenzo[*b*]thiophen-3-one (1b).—This was prepared as previously described;<sup>17</sup> m.p. 176° (lit.,<sup>17</sup> 178°) (Found: C, 67.15; H, 3.9; Cl, 12.05; S, 11.25. Calc. for C<sub>16</sub>H<sub>11</sub>ClOS: C, 67.0; H, 3.85; Cl, 12.35, S, 11.2%),  $\nu_{\max}$  (Nujol) 1 680 and 1 590 cm<sup>-1</sup>,  $\tau$  2.19 (1 H, s,  $\beta$ -H), 2.30 (1 H, m, 4-H), 2.4—2.7 (6 H, m, ArH), and 7.59 (3 H, s, 5-CH<sub>3</sub>);  $\lambda_{\max}$  in agreement with data reported previously.<sup>3c</sup>

*cis*-2-(4-Chlorobenzylidene)-2,3-dihydro-5-methylbenzo[*b*]thiophen-3-one (2b).—A solution of the *trans*-isomer (1b) (0.1 g) in n-hexane (200 ml) was irradiated as above. Removal of the solvent *in vacuo* left a mixture of the *cis*- and *trans*-isomers, in an estimated (n.m.r.) ratio of 12 : 1. Yellow crystals of the *cis*-isomer (2b) were separated mechanically; m.p. 135° (Found: C, 67.1; H, 3.7; Cl, 12.55; S, 11.05. C<sub>16</sub>H<sub>11</sub>ClOS requires C, 67.0; H, 3.85; Cl, 12.35; S, 11.2%),  $\nu_{\max}$  (Nujol) 1 670 and 1 590 cm<sup>-1</sup>,  $\tau$  1.70—2.02 (2 H, m, 2'- and 6'-H), 2.25 (1 H, m, 4-H), 2.3—2.7 (4 H, m, ArH), 2.77 (1 H, s,  $\beta$ -H), and 7.59 (3 H, s, 5-CH<sub>3</sub>);  $\lambda_{\max}$  in agreement with data reported previously.<sup>3c</sup>

*trans*-2,3-Dihydro-5-methyl-2-(2-nitrobenzylidene)benzo[*b*]thiophen-3-one (3).—Hydrochloric acid (1.5 ml; s. g. 1.18) was added to a solution of 2,3-dihydro-5-methylbenzo[*b*]thiophen-3-one (0.5 g) and 2-nitrobenzaldehyde (0.5 g) in ethanol (35 ml) at 60 °C. The product which separated was collected and crystallised from ethanol to give orange leaves of the thioaurone (3) (0.46 g, 47%), m.p. 192° (Found: C, 64.9; H, 3.9; N, 4.35; S, 10.85. C<sub>16</sub>H<sub>11</sub>NO<sub>3</sub>S requires C, 64.65; H, 3.75; N, 4.7; S, 10.75%),  $\nu_{\max}$  (KBr) 1 690 and 1 560—1 610 cm<sup>-1</sup>,  $\tau$  1.93 (1 H, s,  $\beta$ -H), 2.0—2.9 (7 H, m, ArH), and 7.62 (3 H, s, 5-CH<sub>3</sub>).

*trans*-2-(2-Aminobenzylidene)-2,3-dihydro-5-methylbenzo[*b*]thiophen-3-one (4).—Dry hydrogen chloride was passed into a stirred suspension of anhydrous tin(II) chloride (3 g) in anhydrous acetic acid (60 ml) until dissolution was effected. The thioaurone (3) (1.5 g) was added, over 30 min, to the stirred solution (kept at <12 °C). The mixture was allowed to reach room temperature. The orange precipitate which had formed after 10 h was collected and added to water, and the pH was adjusted to 8 with dilute aqueous alkali. The resulting precipitate crystallised from aqueous dimethyl sulphoxide in red needles of the *trans*-2'-amino-compound (4) (1.03 g, 80%), m.p. 217° (Found: C, 71.8; H, 4.9; N, 5.05; S, 12.3. C<sub>16</sub>H<sub>13</sub>ONS requires C, 71.9; H, 4.85; N, 5.25; S, 12.0%),  $\nu_{\max}$  (KBr) 3 350, 1 665, and 1 590—1 560 cm<sup>-1</sup>.

7-Methyl[1]benzothieno[3,2-*b*]quinoline (6).—A suspension of compound (4) (0.05 g) in n-hexane (300 ml) was

<sup>16</sup> A. Streitwieser, jun., and J. R. Wolfe, jun., *J. Amer. Chem. Soc.*, 1957, **79**, 903.

<sup>17</sup> S. K. Guha, *J. Indian Chem. Soc.*, 1935, **12**, 659.

irradiated for 3 h through a water-cooled Pyrex sleeve. The residue obtained on removal of the solvent crystallised from methanol in light brown needles of the *quinoline* (6) (0.042 g, 89%), m.p. 142° (Found: C, 76.95; H, 4.35; N, 5.45; S, 13.25.  $C_{16}H_{11}NS$  requires C, 77.1; H, 4.4; N, 5.6; S, 12.95%),  $\nu_{\max}$  (KBr) 2 780  $cm^{-1}$  ( $CH_3$ ),  $\tau$  1.5—2.9 (8 H, m, ArH) and 7.50 (3 H, s, 7- $CH_3$ ).

10a,11,11-Trichloro-10a,11-dihydro-7-methyl[1]benzo-thieno[3,2-b]quinoline (9).—Carbon tetrachloride saturated with chlorine (1 ml; ca. 10%) was added in the absence of light to a stirred suspension of the 2'-amino-compound (0.1 g) in carbon tetrachloride (20 ml) and the mixture was kept in the dark for 20 h. The residue obtained on removal of the solvent gave crystals of the *quinoline* (9) (0.08 g, 61%), m.p. 215—216° (from chloroform-methanol) (Found: C, 54.3; H, 2.75; Cl, 30.1; N, 3.7; S, 9.35.  $C_{16}H_{10}Cl_3NS$  requires C, 54.2; H, 2.85; Cl, 30.0; N, 3.95; S, 9.05%),  $\nu_{\max}$  (KBr) 2 920  $cm^{-1}$  ( $CH_3$ ),  $\tau$  1.50—2.65 (7 H, m, ArH) and 7.40 (3 H, s, 7- $CH_3$ ).

Acetylation of the 2'-Aminothioaurone (4).—A suspension of compound (4) (0.1 g) in acetic acid-acetic anhydride (1 : 1; 4 ml) was heated on a steam-bath for 3 min, then diluted with water. The resulting precipitate crystallised

from chloroform-light petroleum to give yellow needles of *trans*-2-(2-acetamidobenzylidene)-2,3-dihydro-5-methylbenzo[b]thiophen-3-one (7) (0.076 g, 63%), m.p. 219° (Found: C, 70.35; H, 4.9; N, 4.2; S, 10.55.  $C_{18}H_{15}NO_2S$  requires C, 69.9; H, 4.9; N, 4.55; S, 10.35%),  $\nu_{\max}$  (KBr) 3 360, 1 660, and 1 580  $cm^{-1}$ ,  $\tau$  1.90 (1 H, s,  $\beta$ -H), 2.0—2.7 (8 H, m, NH and ArH), 7.61 (3 H, s, CO- $CH_3$ ), and 7.68 (3 H, s, 5- $CH_3$ ).

2-Chloro-2-( $\alpha$ -chlorobenzyl)-2,3-dihydro-5-methylbenzo[b]thiophen-3-one (10).—Carbon tetrachloride saturated with chlorine (6.5 ml; ca. 10%) was added to a stirred solution of *trans*-2-benzylidene-2,3-dihydro-5-methylbenzo[b]thiophen-3-one (1 g) in carbon tetrachloride (100 ml). After 2.5 h the solvent was removed under reduced pressure. The residue crystallised from chloroform-methanol in needles of *compound* (10) (0.97 g, 76%), m.p. 157° (Found: C, 59.05; H, 3.55; Cl, 21.8; S, 10.15.  $C_{16}H_{12}Cl_2OS$  requires C, 59.15; H, 3.7; Cl, 21.95; S, 9.95%),  $\nu_{\max}$  (KBr) 3 000—2 850 and 1 700  $cm^{-1}$ ,  $\tau$  2.1—2.8 (8 H, m, ArH), 4.40 (1 H, s,  $\beta$ -H), and 7.56 (3 H, s, 5- $CH_3$ ).

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