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Synthesis of 4-Oxo-2-Thioxo-3,4-Dihydro-2H, 1,3-Substituted Benzoxazine, Their Transformation with Water, Diazomethane and Amines

JASIM M. A. AL-RAWI* and KHALID F. AL-SHAHIRY

Chemistry Department, College of Science, University of Mosul, Mosul, Iraq

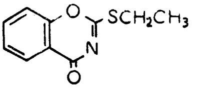
The reaction of five mono-substituted salicyloyl chloride with methyl, ethyl and benzylthiocyanate were studied. A mechanism is suggested for the above reaction. Furthermore these products were treated with water, diazomethane, primary and secondary amines. All structures were studied by ^1H & ^{13}C nmr and IR-spectroscopy.

INTRODUCTION

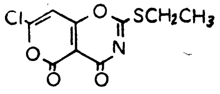
Substituted salicyloyl chloride were used as precursor for the synthesis of a number of new heterocyclic compounds. The reaction with ketones gave the 1,4-cyclo addition, 2,2-dialkyl or aryl -4-oxo-substituted benzo-1, 3-dioxine[1] products. These reactions resemble the reactions of pyronic acid chloride with the ketones[2]. Furthermore salicyloyl chloride reacted with benzylidene aniline[3], camphorimine hydrochloride[4], N-methylene cyclohexylamine[4], S-ethyl-N-N′ diphenylisothiourea and diphenylcarbodiimide[5, 6] yielded derivatives of 1, 3-benzoxazine-4-ones. We are now reporting the reactions of substituted salicyloyl chloride with alkyl thiocyanate and the products transformation with water, amines and diazomethane.

RESULTS AND DISCUSSION

The expected product from the reaction of salicyloylchloride with ethyl thiocyanate was 2-ethyl-thiobenz-1,3-oxazine-4-one (1), by analogy to the reaction of pyranoic acid chloride with ethyl thiocyanate[7] (2).



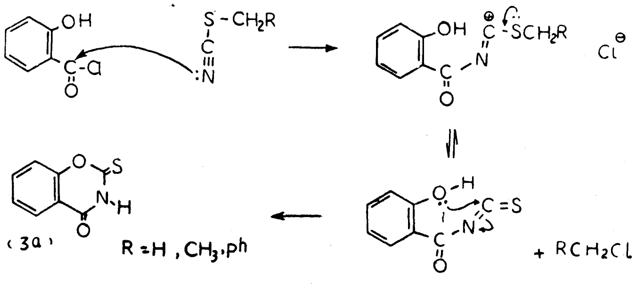
(1)



(2)

However the product showed a molecular ion m/z 179 M^+ and the elemental analysis gave an empirical formula $C_8H_5NO_2S$. Futhermore ^1H nmr spectra of the product showed the absence of the signal for the ethyl group. The reaction of methyl and benzyl thiocyanate gave the same product.

This suggests that the product was not (1) but (3a) (scheme 1). Further structural proof for (3a) comes from the IR measurements (nujol), which showed a broad weak band at 3100 cm^{-1} for the hydrogen bonded NH, 1660 cm^{-1} due to amide carbonyl (4–C=O) and 1200 cm^{-1} a characteristic of C=S group[8]. The ^1H nmr spectra of 3a δ (d_6 acetone) 10.5 (b, 1H, NH) and 8.1–7.4 (m, 4H, aromatic protons); the carbon-13 nmr spectra of 3a showed δ (d_6-DMSO), 182.6, 157.3, 115.6, 126.7, 126.2, 130.5, 116.4, 155.3, which is assigned C-2, C-4, C-4^a, C-5, C-6, C-7, C-8^a respectively (the detail assignment of the ^{13}C nmr spectra is reported elsewhere)[9]. From the above evidence for the structure (3a) the following mechanism can be suggested:

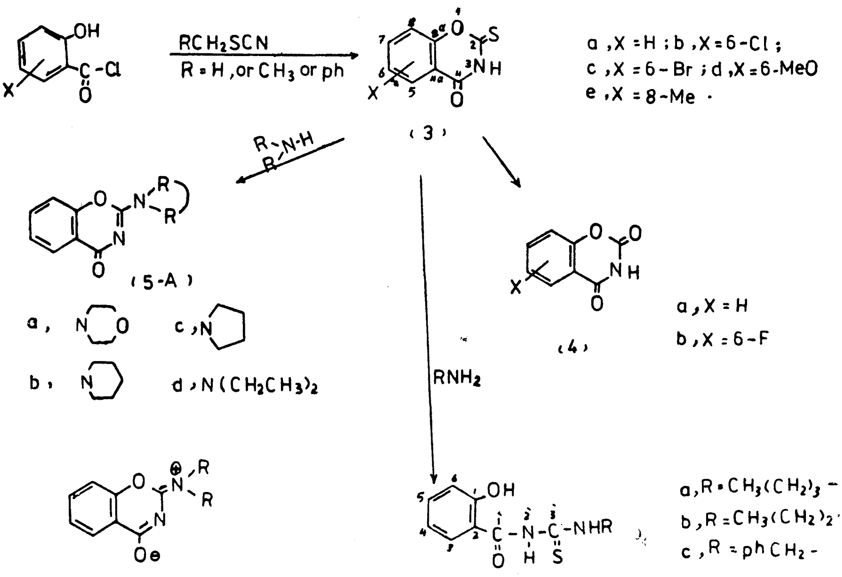


(Scheme 1)

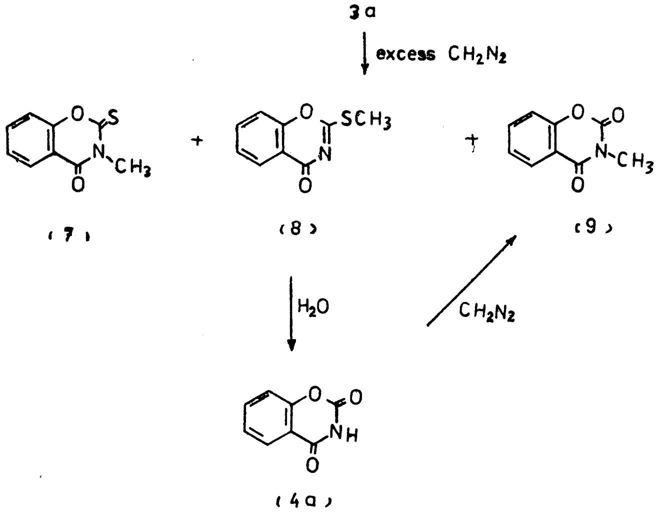
$PhCH_2Cl$ was collected in a trap at liquid nitrogen temperature during the reaction of salicyloyl chloride with benzylthiocyanate and identified by the comparison of its ^1H nmr with an authentic benzylchloride spectra.

Similarly 6-chloro, 6-bromo, 6-methoxy and 8-methyl-4-oxo-2-thioxo-3, 4-dihydro-2H-1, 3-benzoxazines, 3b, 3c and 3e respectively were prepared from the reaction of the corresponding substituted salicyloylchloride with benzylthiocyanate. However the reaction of 5-flourosalicyloyl chloride with benzylthiocyanate did not give the expected 2-thioxo product (3), but gave 2,4-dioxo-6-flouro-3, 4-dihydro-2H-1, 3-benzoxazine (4b). Furthermore on refluxing 4-oxo-2-thioxobenzoxazine (3a) with water in dioxane till the evolution of hydrogen sulphide gas was ceased, the 2,4-dioxobenzoxazine (4a) was obtained.

It is worth noting that the compounds (3) were previously prepared in a good yield by several routes starting from salicylic acid or salicyloyl chloride[10–15] as biological active products, which have fungicidal and bactericidal properties.



On treatment of compound 3a with excess diazomethane in diethyl ether for 1 hr, a mixture of three products 7, 8 and 9 with 25, 33, and 41.6% respectively were obtained. These products were identified from their ^{1}H nmr chemical shift of the methyl groups δ, $CDCl_3$ 3.7 2.7 and 3.5 ppm in compounds 7, 8 and 9 respectively).



But when the reaction time was prolonged to 3 hrs. only two products were detected from the proton chemical shifts for the methyl groups, the products were 7 (35.2%) and 9 (64.8%). This result indicates that compound

8 is a reactive with the water present as moisture in the ether solution of diazomethane hydrolyzed to produce compound 4a which then reacted with diazomethane and gave compound 9.

The above mixture of compounds 7 and 9 were refluxed in a solution of 13% water in dioxan for 120 hrs. to produce 2,4-dioxo-3,4-dihydro-2H, 3-methyl-1,3-benzoxazine (9). Compound (9) showed two carbonyl absorption in the IR (nujol) at ν_{max} 1750 for 2–C=O and 1690 for 4–C=O.

From the above discussion, it is clear that the product from the reaction of 6-flourosalicyloyl chloride with thiocyanate was compound 1 which then reacted with humidity and produced 4b.

Reactions of 2-thioxo-benzoxazine with secondary amines

Reflux 2-thioxo-benzoxazine (3a) with one mole of morpholine in dry dioxan produces 2-morpholino-4-oxo-3,4-dihydro-1,3-benzoxazine (5a). This product gave m/z 232M$^+$ and ν_{max} (nujol) 1650(s)4–C=O, 1600(m) C=C and 1590(m) C=N cm^{-1}, in addition to the ^{1}H nmr (see experimental section). Similarly 2-piperidino (5b), 2-pyrolidino (5c), and 2-diethylamino-4-oxo-3,4-dihydro-1,3-benzoxazine (5d), were prepared.

It is worth mentioning that the $-NCH_2$ of the diethyl amine group are unequivalent, which indicate the double bond character (scheme 2 structure B). Indeed the proton-decoupled carbon-13 nmr spectra of 5d also showed unequivalent chemical shift for the methylene and methyl of the diethyl amino group. $\delta^{13}C(CDCl_3)$, 157.3(C–2), 167.2(C–4), 117.6(C–4^a), 127.6(C–5), 125.4(C–6), 133.7(C–7), 115.4(C–8), 154.0(C–8^a), 43.3, 42.1 for CH_2N and 13.4, 12.8 for the CH_3. Similarly the NCH_2CH_2 of compounds 5b and 5c showed two ^{13}C chemical shifts. (The detail assignments were previously reported)[9]. The rate and activation parameters have been determined for the rotation around C–2N and its double bond character in compound 5 using line shape analysis of the ^{13}C nmr signed over range 226–358°K. ΔG^* (kcal/mole) at 298°K were found to be 6.33, 17.19, 18.05 and 17.75 for compounds 5a, 5b, 5c and 5d respectivly; the detail of this study is reported elsewhere[15].

Reaction of 2-thioxo-benzoxazine (3a) with primary amines

Contrary to the expectation the reaction of compound 3a with one mole of primary amine yielded products (6) where the oxazine ring has been ruptured, and this can be attributed to the fact that primary amines are less basic than secondary amine, where the mode of the reaction depends on the pH of the attacking amine[8]. The structures of 6a, b, and c were confirmed from their ^{1}H nmr, IR, and physical data (see experimental section). Further evidence comes from the ^{13}C nmr spectra of 6b, which showed $\delta(CDCl_3)$, 159.2(C–1), 115.3(C–2), 129.5(C–3), 120.3(C–4), 135.7(C–5), 118.6(C–6), 167.5(C–1$^-$), 180.0(C–3$^-$) and the propyl amine ^{13}C signal were at δ 47.6, 21.7 and 11.3 ppm.

EXPERIMENTAL

UV and IR (nujol) spectra were measured with Unicam sp 800 B and sp 200 spectrometers respectively; ^1H nmr spectra were recorded with a Bruker WH 90 DS FT spectrometer. Microanalysis and mass spectra were measured by Alfred-Bernhardt, West Germany.

Reaction of salicyloyl chloride[11, 12] with thiocyanate[13, 14]

General procedure

Salicyloyl chloride and substituted salicyloyl chloride 0.01 mole and thiocyanate 0.01 mole were heated together on sand bath at 150°C, under anhydrous condition until the evolution of hydrogen chloride gas ceased, and the mixture started to solidify (about 10 hrs). The mixture was then left overnight at room temp.; a dark brown solid product was obtained.

By repeated crystallization from dry chloroform with charcoal a crystalline product (3) was obtained:

(a) 4-Oxo-2-thioxo-3,4-dihydro-2H-1,3-benzoxazine (3a), very pale yellow small needles, 37%, m.pt. 265°C (found C, 53.8; H, 2.9; N, 7.9; S, 17.7; $C_8H_5NO_2S$ requires C, 53.6; H, 2.8; N, 7.8; S, 17.9); ν_{max} (nujol) 3100w (N–H, hydrogen bonded); 1660s (4–C=O); 1600m (C=C); 1590w (C=N); 1200s (C=S) cm^{-1}; δ(d_6-acetone), 10.5 (b, 1, NH), 8.1–7.4 (m, 4, Ar), m/z 179 M^+; λ(dioxane) 272 nm ($\epsilon = 22 \times 10^3$).

(b) 6-Chloro-4-oxo-2-thioxo-3,4-dihydro-2H-1,3-benzoxazine (3b), white small needles, 12.2%, m.pt. 248–250°C (found C, 45.1; H, 1.9; N, 6.5; S, 14.8; Cl, 16.5; $C_8H_4ClNO_2S$ requires C, 45.0; H, 1.9; N, 6.6; S, 15.0; Cl, 16.6); ν(nujol) 3100w (N–H, hydrogen bonded), 1670m (4–C=O), 1600m (C=C), 1590w (C=N), 1200s (C=S) cm^{-1}; δ(d_6-acetone) 10.5 (b, 1, N–H), 8.1–7.3 (m, 3, Ar); m/z 213 M^+, M+2 215 (33)%; λ(dioxane) 272 nm ($\epsilon = 29.6 \times 10^3$).

(c) 6-Bromo-4-oxo-2-thioxo-3,4-dihydro-2H-1,3-benzoxazine (3c), white small needles 9.2%; m.pt. 245°C (found C, 37.3; H, 1.5; N, 5.4; S, 12.3; Br, 31.2; $C_8H_4BrNO_2S$ requires C, 37.2; H, 1.6; N, 5.4; S, 12.4; Br, 31.0); ν(nujol) 3100w (N–H, hydrogen-bonded), 1670s (4–C=O), 1600m (C=C), 1590m (C=N), 1200s (C=S) cm^{-1}; δ(d_6-DMSO) 10.5 (b, 1, NH), 8.1–7.4 (m, 3, Ar); λ(dioxane) 231, 275 nm ($\epsilon = 13, 34 \times 10^3$).

(d) 6-Methoxy-4-oxo-2-thioxo-3, 4-dihydro-2H-1, 3-benzoxazine (3d), pale yellow needles, 21.8%, m.pt. 264°C (found C, 51.6; H, 3.3; N, 6.7; S, 15.2; $C_9H_7NO_3S$ requires C, 51.7; H, 3.4; N, 6.7; S, 15.3); ν(nujol) 3100w (N–H, hydrogen bonded), 1680s (4–C=O), 1600w (C=C), 1590m (C=N), 1200s (C=S) cm^{-1}; δ(d_6-DMSO) 9.8 (b, 1, NH), 8.1–7.4 (m, 3, Ar); 3.7 (S, 3, $-OCH_3$); ν(dioxane) 236, 278 nm ($\epsilon = 15, 25.6 \times 10^3$).

(e) 8-Methyl-4-oxo-2-thioxo-3,4-dihydro-2H-1,3-benzoxazine (3e), pale yellow needles, 38.8%, m.pt. 220–222°C (found C, 56.0; H, 3.6; N, 7.2; S, 16.4; $C_9H_7NO_2S$ requires C, 56.0; H, 3.6; N, 7.3; S, 16.6); ν(nujol) 3100w (NH, hydrogen bonded), 1680s (4–C=O), 1600m (C=C), 1590m (C=N), 1200s (C=S) cm^{-1}; δ(d_6-DMSO) 10.2 (b, 1, NH), 8.1–7.3 (m, 3, Ar), 2.2 (S, 3, CH_3); m/z 193; λ(dioxane) 227, 274 nm ($\epsilon = 14, 31 \times 10^3$).

(f) 2,4-Dioxo-6-flouro-3,4-dihydro-2H-1,3-benzoxazine (4b) recrystallized from dry toluene (charcoal), yellow needles, 11.7%, mp 268°C (found C, 53.0; H, 2.3; N, 7.7; F, 10.4; $C_8H_4FNO_3$ requires C, 53.0; H, 2.2; N, 7.7; F, 10.5); ν(nujol) 3100w (N–H, hydrogen bonded), 1740s (2–C=O); 1680s (4–C=O); 1600m (C=C); 1590w (C=N) cm^{-1}; δ(d_6-acetone) 9.8 (b, 1, NH), 8.1-7.4 (m, 3, Ar); m/z 181; λ(dioxane) 245, 278 nm ($\epsilon = 4, 2.8 \times 10^3$).

2,4-Dioxo-3,4-dihydro-2H-1,3-benzoxazine (4a)

1g (0.005 mole) of compound 3a was dissolved in dioxane (30 ml) and excess of water was added. The mixture was refluxed till the evolution of hydrogen sulphide gas was ceased (120 hrs.), then evaporated to dryness under reduced pressure. The solid product recrystallised from benzene (charcoal), white small needles, 66.6%, m.pt. 238°C; found C, 58.7; H, 2.9; N, 8.5; $C_8H_5NO_3$ requires C, 58.9; H, 3.1; N, 8.6), ν(nujol) 3100w (N–H, hydrogen bonded), 1750s (2–C=O), 1670s (4–C=O), 1600m (C=C), 1590m (C=N) cm^{-1}; δ(d_6-acetone) 10.5 (b, 1, NH), 8.1–7.4 (m, 4, Ar), λ($CHCl_3$) 238, 286 ($\epsilon = 6.2, 9.4 \times 10^3$).

The reaction of 4-oxo-2-thioxo-3,4-dihydro-2H-1,3-benzoxazine (3a) with diazomethane

0.7g (0.004 mole) of compound (3a) was suspended in diethyl ether (5 ml). Excess of ethereal diazomethane was added dropwise, the reaction mixture was kept for 3 hrs. at room temp., then the ether was evaporated. The solid product was found to be a mixture of two compounds from the ^1H nmr, which shows δ($CDCl_3$) 8.2–7.2 (m, Ar); 3.8 (s, CH_3, 35.1%) and 3.5 (S, CH_3, 64.8%). The above mixture was dissolved in dioxane (30 ml) and excess of water (5 ml) was added. The reaction mixture was refluxed till the evolution of hydrogen sulphide gas was ceased (*ca.* 120 hrs.). After evaporating the solvent, the solid product was crystallized from cyclohexane (charcoal), white small needles of 2,4-dioxo-3,4-dihydro-2H-3-methyl-1, 3-benzoxazine (9), 0.4g, 57.1%, m.pt. 133–135°C (found C, 60.9; H, 3.9; N, 7.8; $C_9H_7NO_3$; requires C, 61.0; H, 3.9; N, 7.9); ν(nujol) 1750s (2–C=O); 1690s (4-C=O); 1610s (C=C); 1300s (C-N) cm^{-1}. δ($CDCl_3$) 8.2–7.1 (m, Ar), 3 5 (S, N-CH_3), λ($CHCl_3$) 243, 273 nm ($\epsilon = 2.2, 1.5 \times 10^3$).

The reaction of 4-oxo-2-thioxo-3,4-dihydro-2H-1,3-benzoxazine (3a) with amines

General procedure

0.005 mole of compound (3a) was dissolved in dry dioxane (30 ml) in a 100 ml round-bottomed flask, and 0.005 mole of the corresponding amine in 10 ml dry dioxan was added dropwise, while the mixture was stirred, then the reaction mixture was refluxed till the evolution of hydrogen sulphide gas ceased (*ca.* 2 hrs.) for the secondary amines, and 4 hrs. for the reaction of primary amines. After evaporation of the reaction mixture under reduced pressure to dryness, the solid was washed with diethylether then recrystallized.

(a) *2-Morpholion-4-oxo-3,4-dihydro-1,3-benzoxazine* (*5a*): By repeated crystallization of the solid product (from the reaction of morpholine with 3a) from benzene (charcoal), very pale yellow needles, 54.2%, m.pt. 172°C (found C, 61.9; H, 5.1; N, 11.9; $C_{12}H_{12}N_2O_3$ requires C, 62.1; H, 5.2; N, 12.0); ν(nujol) 1650s (4–C=O); 1600m (C=C); 1590m (C=N) cm^{-1}; δ(d_6-acetone) 8.1–7.4 (m, 4H, Ar); 3.8 (broad singlet, $4CH_2$ of the morpholine); m/z 232 M^+; λ($CHCl_3$) 257, 285 nm ($\epsilon = 13, 5 \times 10^3$).

(b) *2-Piperidino-4-oxo-3,4-dihydro-1,3-benzoxazine* (*5b*): The resulting solid powder from the reaction of piperidine with 3a was crystallized from cyclohexane (charcoal), 66.6%, m.pt. 163°C (found C, 67.7; H, 6.1; N, 12.1; $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.1; N, 12.2); ν(nujol) 1650s (4–C=O), 1600m (C=C), 1590m (C=N) cm^{-1}; δ($CDCl_3$) 8.2–7.1 (m, Ar), 3.8 (m, 2, 6 CH_2 of piperidine), 1.8 (m, 3, 4 and 5 CH_2); λ($CHCl_3$); 258, 287 nm ($\epsilon = 10.3, 4.1 \times 10^3$).

(c) *2-Pyrolidino-4-oxo-3,4-dihydro-1,3-benzoxazine* (*5c*): The resulting solid powder from the reaction of pyrolidine with 3a was crystallized from cyclohexane (charcoal) 33%, m.pt. 189°C (found C, 66.3; H, 5.1; N, 12.1; $C_{12}H_{12}N_2O_2$ requires; C, 66.6; H, 5.5; N, 13.0); ν(nujol) 1640s (4–C=O), 1600m (C=C), 1590m (C=N) cm^{-1}; δ($CDCl_3$) 8.2–7.2 (m, Ar), (m, 2 and 5 CH_2 of the pyrolidine) 2.1 (m, 3 and 4 CH_2), λ($CHCl_3$) 260, 285 nm ($\epsilon = 10.5, 4.7 \times 10^3$).

(d) *2-Diethylamino-4-oxo-3,4-dihydro-1,3-benzoxazine* (*5d*): The resulting solid powder from the reaction of diethylamine with 3a was crystallized from cyclohexane (charcoal), 41.3%, m.pt. 105°C (found C, 66.3; H, 6.4; N, 12.9; $C_{12}H_{14}N_2O_2$ requires C, 66.1; H, 6.4; N, 12.8); ν(nujol) 1650S (4–C=O), 1600m (C=C), 1590m (C=N) cm^{-1}, δ($CDCl_3$) 8.1–7.1 (m, Ar); 3.7–3.5 (m, CH_2–N–CH_2 unequivalent); 1.2 (t, J=8 Hz, $2 \times CH_3$), λ($CHCl_3$) 258, 286 nm ($\epsilon = 10.4, 4 \times 10^3$).

(e) *N-Salicyloyl-N'-butylthiourea* (*6a*): The resulting solid powder from the reaction of n-butyl-amine with 3a was crystallized from cyclohexane (charcoal) 28%, m.pt. 144°C (found C, 57.1; H, 6.3; N, 11.1; S, 12.6; $C_{12}H_{16}N_2O_2S$ requires C, 57.1; H, 6.3; N, 11.1; S, 12.7); ν(nujol) 3200m

(NH), 3100w (OH, hydrogen bonded), 1650S (1–C=O), 1600S (C=C), 1220S (C=S); δ($CDCl_3$) 10.9 and 9.8 (b, –NH and OH) 7.8–6.9 (m, Ar) 3.7 (q, J=5 Hz, N-CH_2) 1.8–1.2 (m, –CH_2CH_2–) 1.0 (t, J=5 Hz, CH_3), λ($CHCl_3$) 255, 295, 315 nm (ϵ = 15, 9.2, 8.4 × 10^3).

(f) *N-Salicyloyl-N'-propylthiourea* (*6b*): The resulting solid powder from the reaction of n-propylamine with 3a was crystallized from cyclohexane (charcoal), 30.3%, m.pt. 143°C (found C, 55.3; H, 5.7; N, 11.6; S, 13.2; $C_{11}H_{14}N_2O_2S$ requires C, 55.5; H, 5.9; N, 11.8; S, 13.4), ν(nujol) 3250m (NH), 3100w (OH, hydrogen bonded), 1650s (1–C=O), 1600s (C=C), 1220s (C=S) cm^{-1}; δ($CDCl_3$) 10.9 and 9.8 (b, –NH and –OH) 7.8–6.9 (m, Ar) 3.7 (q, J=5 Hz, NCH_2) 1.8–1.2 (m, –CH_2CH_2–) 1.0 (t, J=5 Hz, –CH_3) λ($CHCl_3$) 255, 295, 315 nm (ϵ = 15, 9.2, 8.4 × 10^3).

(g) *N-Salicyloyl-N'-benzylthiourea* (*6c*): The resulting solid powder from benzene (charcoal), 46.6%, m.pt. 179°C (found C, 62.9; H, 4.8; N, 9.8; S, 11.0; $C_{15}H_{14}N_2O_2S$ requires C, 62.9; H, 4.9; N, 9.8; S, 11.2); ν(nujol) 3300m (–NH), 3100w (–OH, hydrogen bonded), 1650s (1–C=O), 1600s (C=C), 1200s (C=S) cm^{-1}, δ($CDCl_3$) 10.4 and 9.8 (b, –NH and –OH) 7.8–6.9 (m, Ar) 4.9 (d, J=6 Hz, CH_2NN) λ($CHCl_3$) 256, 295, 317 nm (ϵ = 8.1, 4.7, 4 × 10^3).

REFERENCES

1. (a) E. Ziegler and H. D. Hanus, *Monatsh Chem.*, **95**, 1053 (1964).
   (b) J. M. A. Al-Rawi and K. F. Al-Shahiry, *Iraqi. J. Sci.*, **22**, 300 (1981).
2. S. J. Davis and J. A. Elvidge, *J. Chem. Soc.*, 4109 (1952).
3. E. Ziegler and H. D. Hanus, *Monatsh Chem.*, **96**, 411 (1965).
4. E. Ziegler, G. Kollenze and Th. Kappe, *Monatsh Chem.*, **99**, 804 (1968).
5. ———, *Monatsh Chem.*, **100**, 1722 (1969).
6. ———, *Monatsh Chem.*, **100**, 1735 (1969).
7. J. M. A. Al-Rawi and J. A. Elvidge, *J. Chem. Soc.*, 2432 (1973).
8. L. J. Ballamy, The Infrared of Complex Molecule, 2nd edn., Methuen, London, 1958, p. 350.
9. J. M. A. Al-Rawi and K. F. Al-Shahiry, *Iraqi J. Sci.* (in press).
10. S. Sharma, R. Bindra, and R. N. Iyer, *Indian J. Chem.*, **11**, 1201 (1973).
11. A. Kirpal, *Chem. Ber.*, **638**, 3190 (1930).
12. T. Amakasu and K. Sato, *Bull. Chem. Soc.* (*Japan*), **40**, 1428 (1967).
13. P. Walden, *Chem. Ber.*, **40**, 3215.
14. L. Henry, *Chem. Ber.*, **2**, 634 (1869).
15. J. M. A. Al-Rawi, G. Q. Behnam and M. S. Al-Ajely, *Raf. J. Sci.* (in press).

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