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SOME REACTIONS WITH 2-ACETONYL-4H-3, 1-BENZOXAZIN-4-ONE AND 2-ACETONYL-3-PHENYL-4 (3H) QUINAZOLINONE

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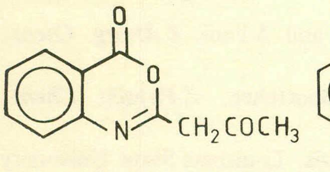
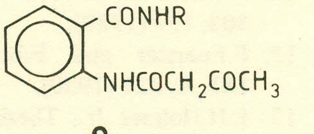
Abstract. The benzoxazone 1 reacted with amines to give 2 and 4. Compounds 2 were converted to the quinazolinones 3. The benzoxazone 1 and the quinazolone 3a were condensed with aldehydes to give 5 and 7. Compound 1 gave 11a, 13,15,17-19 and 21 with hydrazines, hydroxylamine, formamide, sodium azide and active methylene compounds respectively. With Friedel-Crafts reaction and Grignard reagents 1 yielded 22 and 23 P_2S_5 reacted with 1 and gave 24 which underwent the ring opening and yielded 25.

Benzoxazones such as 2-acetonyl-3,1-(4H) benzoxazone 1 reacts with primary amines and piperidene to give products(2a–h)[1-3] and 4 which arise as a result of ring opening of 1. The compounds 2a-h were converted to the quinazolinones (3a–h) by treatment with boiling acetic anhydride.



1



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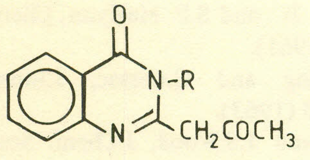

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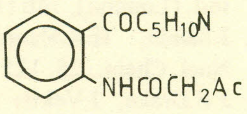


2 or 3 a,R=C_6H_5; b, R=*p* - CH_3-C_6H_4; c, R=2,,4 $(CH_3)_2$ C_6H_3; d, R=*p*-HOOC-C_6H_4;e,R=HO-C_6 H_4; f, R=C_2 H_5; g, R = C_4H_9 (n); h,R = CH_2 CH_2 OH.

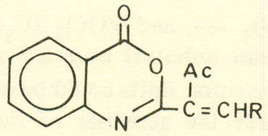
IR of 2 shows absorption at (3475-3200 cm^{-1}) ν_{max} of 2NH, (1710.1680 and 1660 cm^{-1}) ν_{max} of 3C=O. The IR spectra of 3 showed absorption of 2C=O at (1715-1680 cm^{-1}). The IR spectrum of 4 showed bands at 1720,1700 and 3270 cm^{-1} due to νC=O and ν NH.

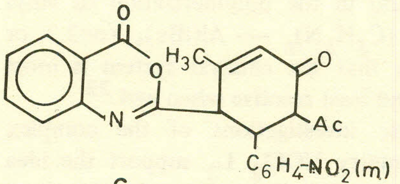
1 and 3a condensed with aromatic aldehydes by fusion in the presence of $ZnCl_2$ and yielded styrylbenzoxazones 5a-f[3] and styrylquinazolinones 7a-e.

Acetylacetone readily condensed with 5c in presence of sodium methoxide via Michael condensation followed by cyclisation to give 2-cyclohexen-1-one derivative 6. Treatment of 5b with boiling Ac_2O yield 5g.

5 shown in the IR bands in the region (1715-1700 cm^{-1}) and (1690-1670 cm^{-1}) for ν_{max} of 2 C=O groups. Also, the presence of CH out of plane deformation in the region (840-800 cm^{-1}) for the compound 5 was taken as indication for the presence of di-substituted ethylenes structure (this means the condensation involved the methylene group rather than the methyl groups).

5





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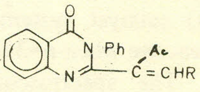


7

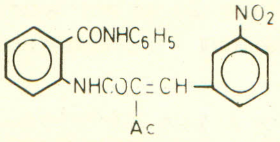
5 or 7 a,R=C_6 H_5; b,R = *o*-HO-C_6H_4;C,R = *m*-O_2 NC_6 H_4; d R = *p*-H_3 COC_6 H_4; e,R = - CH = CHPH; f,R = 3,4 CH_2 O_2 C_6 H_3; g, R = *o* -AcO-C_6 H_4.

The NMR Spectrum of 5e in $CDCl_3$ showed signals at δ 1.9 ppm (s) (CH_3CO), δ 6.1 (s) for 1H (olefinic proton), δ 6.4(4) for 2H (olefinic protons near the ring), δ 7.2 and δ 7.6 (m) for 9H (aromatic protons).

The IR spectrum of 6 exbibits bands in the region of 1705 cm^{-1}, 1700, 1680 cm^{-1} and a broad band at 1610 cm^{-1} due to ν_{max} of 3C=O groups, one being conjugated and enolic group[4]. The IR spectra of 7 show bands at (1700-1690 cm^{-1}), (1670-1660 cm^{-1}) due to ν_{max} of 2C=O groups and (1630-1620 cm^{-1}) due to ν C=N. The NMR spectrum of 7a in $CDCl_3$ showed a signals at δ 2.1 (s) (CH_3 protons), δ 6.1(s) for olefinic proton and two multiplet as δ 7.7 and δ 8.1 for 14H (aromatic protons).

Aniline reacted with 5C in boiling ethanol to give cinnamanilide 8, which was converted to the quinazolinone 7c by boiling with Ac_2O.

Self condensation of 1 resulted in the formation of 9, the latter undergoes ring opening by phenylhydrazine to give acetoacetanilide derivative 10.



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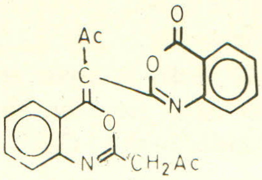
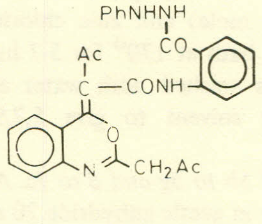


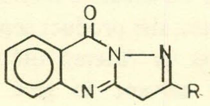
9



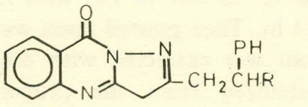
10

IR Spectrum of 10 shows bands at 1700 cm^{-1}, 1670 cm^{-1} 1620 cm^{-1} and 3300 cm^{-1} due to ν C=O groups, ν C=N and ν NH respectively.

The reaction of 1 with hydrazine hydrate in boiling ethanol resulted in the formation of 3-methyl-1,5-quinazolinopyrazoline 11a[3,5]. The latter condensed with benzaldehyde to give 3-styryl derivative llb. The IR absorption spectra of ll have ν C=O (1680-1670 cm^{-1}, ν_{max} of 2C=N at (1650, 1630 cm^{-1}).

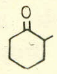


11



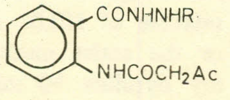
12

a, $R=CH_3$; b, R=-CH=CHPh

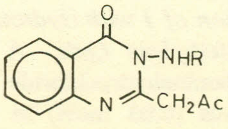
a, R=SPh ; b, R= 

Base catalyzed addition of thiophenol or cyclohexanone to llb gave the corresponding Michael adducts 12a and b respectively.[6] The IR spectra of 12 showed strong absorption at (1715,1670 cm^{-1}) ν_{max} of 2C=O groups, (1620 cm^{-1}) for ν C=N. The NMR spectrum of 12a in $CDCl_3$ showed signals at δ 0.6(m) (5 protons), at δ 7.2 (m), δ 7.6 (m) corresponding to (14 protons).

On the other hand, phenyl hydrazine and 2,4-dinitrophenylhydrazine reacted with 1 and yielded the hydrazide 13a and b, which were converted to quinazolinones 14a and b by treatment with Ac_2O!



13

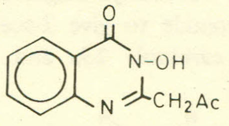


14

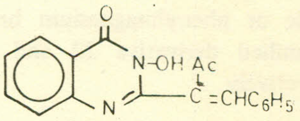
a, $R=C_6H_5$; b, $R=2,4-(O_2N)C_6H_3$

The IR spectra of 13 have bands at (1708,1670 and 1655 cm^{-1}) due to ν_{max} of 3C=O groups and ν NH at (3370 and 3200 cm^{-1}). Compound 14 showed bands at (1705,1670 cm^{-1}), (1620 cm^{-1}) and at the region (3310-3240 cm^{-1}) for ν C=O, ν C=N and ν NH respectively.

By analogy with the recently reported reaction of benzoxazones with hydroxylamine,[5] it is found that interaction of 1 with hydroxylamine hydrochloride in boiling pyridine formed the quinazolinone 15. The latter condenses with benzaldehyde to give 2-styryl quinazolinone 16.



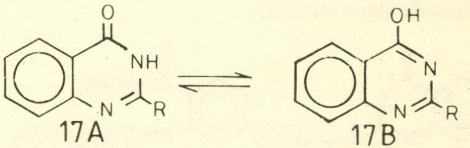
15



16

IR spectra of compounds 15 and 16 characterized by a bands at (1710, 1670 cm^{-1}) for ν_{max} of 2C=O groups, ν C=N at (1625 cm^{-1}, and ν NH in the region (3250-3300 cm^{-1}).

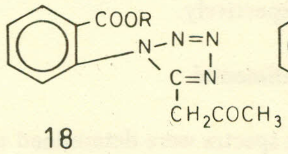
Interaction of 1 or 5c with formamide formed 4 (3H)-quinazolinones 17a and 17b[5] via ammonolysis followed by cyclisation. The IR spectrum of 17a showed bands at (3425 cm^{-1}), (3200 cm^{-1}), (1710 cm^{-1}, 1695 cm^{-1}) and (1640, 1620 cm^{-1}) attributable to bonded OH, NH and ν_{max} of 2C=O and 2C=N groups respectively. These reveal that 17a actually exists in the lactam-lactim toutomeric equilibrium 17 A ⇌ 17 B)



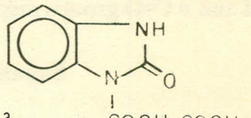
17A 17B

a, $R=CH_2COCH_3$; b, R $-\underset{Ac}{C}=CHC_6H_4NO_2(\underline{m})$

1 reacted with NaN_3 in boiling acetic acid to give a mixture of the tetrazole 18a and benzimidazolone derivative 19. The former converted to the ester 18b by refluxing with $(CH_3)_2SO_4$, anhydrous K_2CO_3 and dry acetone.[7]



18

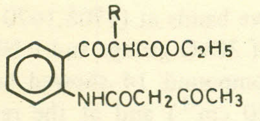


19

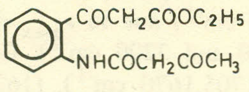
a, R=H ; b, $R=CH_3$

IR spectra of the above compounds showed bands at (1060 cm^{-1}) due to ν tetrazole[8] for 18a, (1735 cm^{-1}) due to ν C=O of ester for 18b, (1705, 1660 and 3200 cm^{-1}) due to ν C=O groups and ν NH.

The benzoxazone 1 reacts with ethylacetate, ethyl cyanoacetate or diethylmalonate in boiling pyridine to give acetate 21,[5] through ring opening with the formed



20



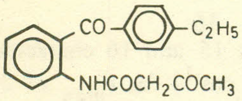
21

R=CH₃CO , CN or −COOC₂H₅

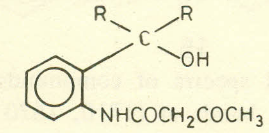
carbanion to give the intermediate 20.

The IR spectrum of 21 exhibited band for keto ester at (1737 cm^{-1}). 21 undergoes acid hydrolysis to give N-acetoacetyl anthranilic acid.

The benzoxazone 1 reacts with ethylbenzene under Friedel Crafts conditions,[5] and with ethyl magnesium iodide or phenylmagnesium bromide to give 2-acetoacetanilied derivative 22 and carbinols 23a and b[9] respectively.



22

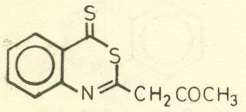


23

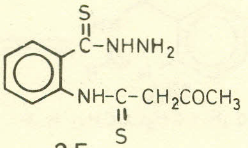
a, $R=-C_2H_5$; b, $R=C_6H_5$

IR spectrum of 22 exhibited bands at (1700, 1675, 1650 and 3340 cm^{-1}) due to ν_{max} of C=O and NH groups respectively. IR spectra of 23 showed ν_{max} of 2 C=O, ν NH and ν OH at (1705,1665,3200 and 3500 cm^{-1}).

1 Reacts with P_2S_5 in dry xylene[10] to give thione 24. The latter undergoes ring opening with hydrazine hydrate in boiling ethanol[11] to give thioanthranilic acid hydrazide derivative 25.



24



25

IR spectrum of 24 showed bands at (1700 cm^{-1}, and 1325 cm^{-1}) for ν C=O, ν C=N and ν C=S respectively.

Compound 25 showed absorption bands at (1315, 1345,3315,3290 and 1690 cm^{-1}) for (ν_{max} of 2 C=S, 2 NH and ν C=O groups respectively.

Experimental

The infrared absorption spectra were determined with Unicam SP 1200, SP 200G and Pye Unicam Ltd. Cambridge England part No. 633791 Spectro-photometers using KBr Wafer technique. The NMR spectra were determined with Thompson Packard (TPV 60 T).

Reaction of 1 and 5c with Amines. A solution of 1 or 5c (0.01 mole) and amines (0.01 mole) in 50 ml of ethanol was heated under reflux for 4 hr. The products 2a-h, 4 and 8 that separated on cooling were crystallized from the suitable solvent (Table 1).

Conversion of 2 to the Quinazolones 3. A solution of 2(0.01 mole) in acetic anhydride 20 ml was heated under reflux for 4 hr. The mixture was concentrated and cooled to give 3 (Table 1).

Condensation of 1,3a, 11a or 15 with Aldehydes and Self Condensation of 1. A mixture of 1,3a 11a or 15(0.01 or 0.025 mole in case of self condensation), the aldehyde (0.015 mole) and zinc chloride (0.5 g) was heated in an oil bath at 170° for 5-7 hr. After cooling the product was washed with water and crystallized from a suitable solvent to give 5,7,9, 11b and 16 (Table 2).

Conversion of 5b to 5g and 8 to 7c. A solution of 5b or 8 (0.01 mole) in acetic anhydride 20 ml was refluxed for 4 hr. The mixture was concentrated and cooled. The product was isolated from compound 8, was identified as the previous quinazolone 7c by m.p. and mixed m.p. determination (yield 55 %). While 5b yielded the corresponding acetate 5g as colourless crystals had m.p. 165°, $C_{20}H_{15}NO_5$, calculated C, 68.76; H, 4.33; Found, C,68.43; H, 4.12

Michael Condensation with 5c and 11b. A mixture of acetylacetone or cyclohexanone (0.01 or 0.02 mole); 5c or 11b (0.01 mole) and (0.01 mole) sodium methoxide was heated at 120° for 3 hr in case of 5c, or heated at 40° in case of 11b with 15 ml absolute methanol for 24 hr. Then poured upon water, the product separated out was extracted with ether or filtered off and recrystallized from the proper solvent to give the Michael adducts 6 and 12b (Table 3).

Reaction of 11b with Thiophenol. A mixture of 11b (0.01 mole) and thiophenol (0.01 mole) was treated with few drops piperidine and then heated in a water bath for one hr. The cooled mixture was washed with light petrol to give the sulphide 12a (Table 3).

Reaction of 1 with Hydrazines and 9 with Phenylhydrazine. A solution of 1 or 9 (0.01 mole) and hydrazinehydrate, phenylhydrazine or 2,4-dinitrophenylhydrazine (0.01 mole) in 50 ml ethanol was heated under reflux for 6 hr. The solid separated on cooling was crystallized from the suitable solvent to give 10, 11a and 13 (Table 3).

Conversion of Hydrazide 13 to the Quinazolinone 14. A solution of hydrazide 13 (0.01 mole) in Ac_2) (20 ml) ml) was heated under reflux for 10 hr. The mixture was concentrated and cooled to give the quinazolinones 14 (Table 3).

Reaction of 1 with Hydroxylaminehydrochloride and Active Methylene Cpds. A mixture of 1(0.01 mole, hydroxylaminehydrochloride or the active methylene compounds (0.03 mole) in dry pyridine 30 ml was refluxed for 15 hr. The reaction mixture was poured on ice-cold dil HCl to give 15 and 21 (Table 4).

TABLE 1. PRODUCTS FROM THE REACTION OF AMINES WITH 1 AND QUINAZOLONES 3.

Compound	m.p.°C	Solvent	Formula	Analysis	
	colour	yield %	(mol. wt.)	Calcd. /	Found
				C%	H%
2a	105	B	$C_{17}H_{16}N_2O_3$	68.90	5.44
	brownish	85	(296)	68.40	5.52
2b	109	B	$C_{18}H_{18}N_2O_3$	69.66	5.85
	colourless	82	(310)	69.22	5.91
2c	250	E	$C_{19}H_{20}N_2O_3$	70.35	6.22
	colourless	81	(324)	69.80	5.91
2d	122	p(80-100)	$C_{18}H_{16}N_2O_5$	63.52	4.74
	colourless	78	(340)	63.00	4.30
2e	128	p(60-80)	$C_{17}H_{16}N_2O_4$	65.37	5.17
	Yellow	75	(312)	65.00	5.70
2f	52	p(60-80)	$C_{13}H_{16}N_2O_3$	62.89	6.50
	colourless	77	(248)	62.60	6.92
2g	158	B	$C_{15}H_{20}N_2O_3$	65.19	7.30
	colourless	83	(276)	65.61	7.65
2h	175	B	$C_{13}H_{16}N_2O_4$	59.08	6.10
	colourless	89	(264)	59.10	6.18
3a	144	T	$C_{17}H_{14}N_2O_2$	73.36	5.07
	colourless	80	(278)	73.36	5.24
3b	96	B	$C_{18}H_{16}N_2O_2$	73.95	5.52
	colourless	79	(292)	73.37	5.57
3c	179	E	$C_{19}H_{18}N_2O_2$	74.49	5.92
	colourless	78	(306)	74.10	5.57
3d	183	T	$C_{18}H_{14}N_2O_4$	67.07	4.38
	colourless	75	(322)	66.78	4.00
3e	154	B	$C_{17}H_{14}N_2O_3$	69.37	4.80
	colourless	70	(294)	69.72	5.00
3f	172	E	$C_{13}H_{14}N_2O_2$	67.81	6.13
	colourless	74	(230)	67.12	6.40
3g	170	T	$C_{15}H_{18}N_2O_2$	69.74	7.02
	colourless	80	(258)	69.47	6.73
3h	150	T	$C_{13}H_{14}N_2O_3$	63.40	5.73
	colourless	85	(246)	63.00	5.52
4	95	p(80-100)	$C_{16}H_{20}N_2O_3$	66.64	6.99
	colourless	98	(288)	67.15	6.93
8	168	E	$C_{24}H_{19}N_3O_5$	67.12	4.46
	colourless	84	(429)	66.82	4.15

B = benzene; E = ethanol; p=pet. ether; T = toluene

TABLE 2. PRODUCTS FROM THE CONDENSATION OF ALDEHYDES AND SELF CONDENSATION

Compound	m.p. °C	solvent	Formula	Analysis	
	colour	yield %	(mol. wt.)	Calcd.	Found
				C %	H %
5a	112	p(80-100)	$C_{18}H_{13}NO_3$	74.21	4.50
	brownish	53	(291)	74.62	4.83
5b	182	B	$C_{18}H_{13}NO_4$	70.35	4.26
	colourless	51	(307)	70.71	4.54
5c	201	E	$C_{18}H_{12}N_2O_5$	64.28	3.60
	colourless	55	(336)	64.55	3.82
5d	275	A	$C_{19}H_{15}NO_4$	71.02	4.71
	yellowish	57	(321)	70.87	4.53
5e	161	B	$C_{20}H_{15}NO_3$	75.69	4.76
	colourless	52	(317)	75.50	4.52
5f	252	A	$C_{19}H_{13}NO_5$	68.06	3.91
	brownish	56	(335)	67.89	3.72
7a	177	p(80-100)	$C_{26}H_{20}N_2O_3$	76.47	4.90
	colourless	62	(408)	76.77	5.44
7b	88	B	$C_{24}H_{18}N_2O_3$	75.38	4.74
	colourles	67	(382)	75.66	4.93
7c	200	B	$C_{24}H_{17}N_3O_4$	70.06	4.17
	yellow	72	(411)	69.85	3.91
7d	174	E	$C_{25}H_{20}N_2O_3$	75.74	5.09
	brown	75	(396)	75.52	5.00
7e	220	B	$C_{26}H_{20}N_2O_2$	79.57	5.14
	brownish	68	(392)	79.47	5.00
9	242	E	$C_{22}H_{16}N_2O_5$	68.03	4.15
	colourless	58	(388)	68.47	4.31
11b	185	B	$C_{18}H_{13}N_3O$	75.24	4.56
	colourless	71	(287)	75.05	4.93
16	116	B	$C_{18}H_{14}N_2O_3$	70.58	4.61
	yellowish	68	(306)	70.35	4.50

A = acetic acid; E = ethanol B = benzene; P = pet. ether

Action of Formamide on 1 and 5c. A mixture of 1 or 5c (0.01 mol) and formamide(0.015 mole) was heated at 175° for 3 hr. The product obtained was crystallized from a suitable solvent to give 17 (Table 4).

Action of Sodium azide on 1. A mixture of 1(0.01 mole) and sodiumazide (0.05 mole) in boiling acetic acid 40 ml was refluxed for 3 hr. The product obtained after concentration was fractionally crystallized to give the tetrazole 18a and the benzimidazolone 19 (Table 4).

Conversion of the Tetrazole 18a to 18b. A Mixture of 18a (0.01 mole), anhydrous K_2CO_3 (0.03 mole) and dimethyl sulphate (0.03 mole) in acetone 60 ml was

TABLE 3.

Compound	m.p. °C colour	Solvent yield %	Formula (mol. wt.)	Analysis Calcd.	Found
				C %	H %
6	182	B	$C_{23}H_{18}N_2O_6$	66.02	4.34
	brown	40	(386)	66.41	4.52
10	201	B	$C_{28}H_{24}N_4O_5$	67.73	4.87
	colourless	60	(496)	67.41	4.50
11a	137	B	$C_{11}H_9N_3O$	66.32	4.55
	colourless	78	(199)	66.61	4.73
12a	95	p(60-80)	$C_{24}H_{19}N_3O$	72.54	4.79
	colourless	76	(397)	72.37	4.53
12b	164	B	$C_{24}H_{22}N_3O_2$	75.00	3.64
	colourless	71	(384)	75.38	3.94
13a	168	p(80-100)	$C_{17}H_{17}N_3O_3$	65.58	5.50
	brown	72	(311)	65.58	5.28
13b	190	T	$C_{17}H_{15}N_5O_7$	50.87	3.74
	brown	69	(401)	50.52	3.30
14a	199	E	$C_{17}H_{15}N_3O_2$	69.61	5.15
	brown	68	(293)	69.88	5.33
14b	202	A	$C_{17}H_{13}N_5O_6$	53.26	3.39
	brown	63	(383)	53.14	3.03

TABLE 4.

Compound	m.p. °C colour	Solvent yield %	Formula (mol. wt.)	Analysis Calcd.	Found
				C %	H %
15	208	T	$C_{11}H_{10}N_2O_3$	60.54	4.62
	brown	55	(218)	60.22	4.55
17a	213	E	$C_{11}H_{10}N_2O_2$	65.33	4.98
	yellow	78	(202)	65.63	5.21
17b	180	T	$C_{18}H_{13}N_3O_4$	64.47	3.91
	yellow	70	(335)	64.74	4.15
18a	237	E	$C_{11}H_{10}N_4O_3$	53.66	4.90
	colourless	46	(246)	53.93	5.18
18b	86	p(60-80)	$C_{12}H_{12}N_4O_3$	55.38	4.65
	colourless	46	(260)	55.60	4.81
19	135	B	$C_{11}H_{10}N_2O_3$	60.54	4.62
	colourless	34	(218)	60.81	4.83
21	247	T	$C_{15}H_{17}NO_5$	61.85	5.88
	colourless	46	(291)	62.12	5.62

TABLE 5.

Compound	m.p. °C ·	Solvent	Formula	Analysis	
	colour	yield %	(mol wt.)	Calcd.	Found
				C %	H %
22	194	E	$C_{19}H_{19}NO_3$	73.76	5.19
	colourless	40	(309)	73.53	5.02
23a	140	B	$C_{15}H_{21}NO_3$	68.40	8.04
	colourless	60	(263)	68.00	7.81
23b	169	A	$C_{23}H_{21}NO_3$	76.86	5.89
	colourless	70	(359)	76.55	5.63
24	104	p(80-100)	$C_{11}H_9NOS_2$	56.17	3.83
	brown	65	(235)	56.40	4.15
25	130	T	$C_{11}H_{13}N_3OS_2$	49.44	4.87
	brownish	60	(267)	49.73	4.24

refluxed for 10 hr after removal of the solvent 18b was obtained (cf Table 4).

Friedel-Crafts Reaction of 1 . A solution of 1 (0.01 mole) in ethylbenzene 50 ml was treated with (0.04 mole) $AlCl_3$ while stirring. Stirring was continued for 10 hr at room temperature. The reaction mixture was decomposed by ice-cold HCl then steam distilled to remove excess ethylbenzene. The soild obtained was crystallized from ethanol to give 22(Table 5).

Reaction of 1 with Grignard Reagents. A solution of 1 (0.01 mole) in dry benzene 100 ml was treated with a solution of Grignard reagent (0.03 mole). The reaction mixture was heated under reflux for 3 hr and then worked up as usual to give the carbinols 23 (Table 5).

Reaction of 1 with P_2S_5. A solution of 1 (0.01 mole), P_2S_5 (0.01 mole) in dry xylene 100 ml was refluxed for 6 hr. The reaction mixture was filtered upon hot, the product separated on cooling was crystallized from suitable solvent to give the thione 24 (Table 5).

Reaction of Thione 24 with Hydrazinehydrate: A solution of thione (0.01 mole) and hydrazinehydrate (0.02 mole) in ethanol 30 ml was refluxed for 3 hr. The solid product separated on cooling gave 25 (Table 5).

References

1. D.T.Zentmeyer and E.C.Wagner, J.Org. Chem., **14**, 967 (1949).
2. M.T.Bogort and H.Amberose, J.Am.Chem. Soc., **27**, 1305 (1905).
3. A.Sammour, M.I.B.Selim and M.Ablo, J.Chem. U.A.R., **14**,197 (1971).
4. L.J. Bellamy, *The IR Spectra of Complex Molecules* (Methuen London 1966),p.132.
5. A.Sammour, A.F.M.Fahmy and M.Mahmoud, Indian J.Chem., **2** , 222 (1973).
6. A.Sammour and M.A.El Hashash, J. F. Prackt, Chemie Band, 314, 906 (1972).
7. M.F. El. Newaihy and M.A.El Hashash, J, C.S. (C) p.2373 (1971).
8. W.I.Awad, A.F.M.Fahmy and A.Sammour, J.Org. Chem., **30**, 2222 (1965).
9. A.Sammour, T.Zimaity and M.Abdo,J.Chem. U.A. R., **16**, 215 (1973).
10. L.Legrand, J.Bull. Soc. Chim. France, 337 (1960).
11. A.Sammour, M.I.B.Selim, A, F, M, Fahmy, K.Elewa Indian J. Chem., **2** , 437 (1973).