1-Alkyl-4-aryl-3,4-dihydro-2(1*H*)-quinazolinones and Thiones. Synthesis and ^{1}H-NMR Spectra

William J. Houlihan*, George Cooke, Max Denzer (1)
and Joseph Nicoletti

Sandoz, Inc., Preclinical Research, Route 10, East Hanover,
New Jersey 07936

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A series of 1-alkyl-4-aryl-3,4-dihydro-2(1*H*)-quinazolinones and thiones were prepared by a modification of the Pictet-Spengler reaction that involves treatment of an *N*-alkyl-*N*-arylurea or thiourea with an aryl aldehyde in the presence of methanesulfonic acid. The ^{1}H-nmr spectra of several of these compounds gave rise to unusual OCH_2O and isopropyl signals.

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In recent years a number of 1-alkyl-4-aryl-2(1*H*)-quinazolinones and thiones have been reported to possess anti-inflammatory and analgesic activity in animals and man (2). A useful precursor to this class of compounds is the 3,4-dihydro analog **8**. Synthetic methods used to prepare the 2-ones (**8**, X = O) involve the addition of an aryllithium reagent to a 1-alkyl-2(1*H*)-quinazolinone (3) and the borohydride reduction of the quinazolinone (4). The only reported procedure to prepare the 2-thiones (**8**, X = S) is the treatment of a 2-alkylaminobenzhydrol with ammonium thiocyanate in an acidic media (4a).

It seemed to us that the synthesis of **8** could be accomplished by a modification of the Pictet-Spengler (5) reaction which involves the condensation of electron rich β-phenethylamine (**1a**) with an arylaldehyde to form an imine intermediate **2** which in an acidic medium cyclizes to a 1-aryl-1,2,3,4-tetrahydroisoquinoline **3a**. Extension of the reaction to a *N*-arylurea or thiourea (**1b**) could result in the formation of **8** *via* the imine **2b** provided that the phenyl component of **1b** is sufficiently electron rich (6). In the present paper we report that this modification of the Pictet-Spengler reaction can be accomplished to form **8** (X = O, S).

The required *N*-methyl and *N*-ethyl derivatives (**6**) of 3,4-methylenedioxyaniline were prepared by the alkylation of the *N*-trifluoroacetyl derivative **4** followed by hydrolysis with aqueous potassium hydroxide while the *N*-isopropyl compounds were obtained by treatment of anilines **5** with isopropyl iodide in the presence of triethylamine. The ureas **7** (X = O, Table I) were obtained in satisfactory yields by reaction of **6** with sodium isocyanate in acetic acid while the thioureas (**7**, X = S) were prepared from **6** and benzoylisothiocyanate followed by basic hydrolysis.

The aqueous and nonaqueous acids 98% sulfuric, 48% hydrogen bromide, formic, oxalic, benzenesulfonic and methanesulfonic and the Lewis acid boron trifluoride-etherate in either benzene, toluene or xylene at reflux were evaluated in the reaction of benzaldehyde with *N*-isopropyl-*N*-*m*-tolylurea (**7c**) to form the known 1-isopropyl-4-(3-methylphenyl)-3,4-dihydro-2(1*H*)-quinazolinone (**8c**) (4c). The most satisfactory condition found in our laboratories was the use of a catalytic amount of methanesulfonic

Table I

Physical and ^{1}H-NMR Data for Compounds 7

Compound	X	R^1	R^2	Yield %	Mp, °C (Recrystallization Solvent) (a)	^{1}H-NMR (b) N-R^1	^{1}H-NMR (b) R^2	^{1}H-NMR (b) NH_2	Formula	% Calculated C	% Calculated H	% Calculated N
										% Found	% Found	% Found
7a	O	CH_3	3,4-OCH_2O	60	176-178 (A)	3.05, s	6.01, s	5.55, s	$C_9H_{10}N_2O_3$	55.7 55.8	5.2 5.2	14.4 14.2
7b	O	C_2H_5	3,4-OCH_2O	58	90-92 (B)	0,98, t, (7.5), 3.51, q, (7.5)	6.02, s	5.38, s	$C_{10}H_{12}N_2O_3$	57.7 57.8	5.8 5.5	13.5 13.8
7c	O	*i*-C_3H_7	3-CH_3	64	90-91.5 (C)	0.97, d, (7.5), 4.50, qn, (7.5)	2.30, s	5.15, s	$C_{11}H_{16}N_2O$	68.6 68.5	8.3 8.2	14.6 14.3
7d	O	*i*-C_3H_7	4-OCH_3	60	161-162 (A)	0.97, d, 7.5, 4.54, qn, 7.5	3.65, s	5.20, s	$C_{11}H_{16}N_2O_2$	63.4 63.7	7.7 7.9	13.5 13.5
7e	O	*i*-C_3H_7	3,4-$(CH_3)_2$	75	211-213 (C)	0.95, d, 7.5, 4.58, qn, 7.5	2.22, s, 6H	5.00, s	$C_{12}H_{18}N_2O$	69.9 69.7	8.7 8.6	13.6 13.4
7f	O	*i*-C_3H_7	3,4-OCH_2O	48	119-120 (A)	0.97, d, 7.5, 4.37, qn, 7.5	5.96, s,	5.10, s	$C_{11}H_{14}N_2O_3$	59.5 59.3	6.3 6.3	12.6 12.5
7g	S	*i*-C_3H_7	3,4-OCH_2O	75	149-151 (A)	0.98, d, 7.5, 5.52, qn, 7.5	6.08, s	>9.0	$C_{11}H_{14}N_2O_2S$	55.4 55.2	5.9 5.8	11.8 11.7

(a) Recrystallization solvents: A, benzene; B, diethyl ether-benzene; C, ether. (b) See Experimental.

Table II

^{1}H-NMR Data of 1-Alkyl-4-aryl-3,4-dihydro-2(1*H*)-quinazolinones and Thiones (**8**)

Compound	R^1	R^2	R^3	X	^{1}H-NMR (a) N-C(CH$_3$)$_2$H (b)		^{1}H-NMR (a) CH$_3$O* or OCH$_A$H$_B$O (c) (J, Hz)		^{1}H-NMR (a) CH-NH doublets (J, Hz)	H-5 singlets	H-8 singlets
8a	CH_3	6,7-OCH_2O	H	O	3.15 s		5.93, 5.97 (2)	5.38	7.63 (3)	6.82	6.72
8b	C_2H_5	6,7-OCH_2O	H	O	1.12 t	3.85, 3.89 q	5.88, 5.92 (1)	5.37	7.28 (3)	6.70	
8c	i-C_3H_7	7-CH_3	H	O	1.42	4.35	—	5.30	7.40 (3.5)	—	—
8d	i-C_3H_7	6-OCH_3	H	O	1.42	4.34	3.68*	5.28	7.43 (4)	—	—
8e	i-C_3H_7	6-OCH_3	3'-CH_3	O	1.43, 1.49	4.34	3.67*	5.26	7.42 (4)	—	—
8f	i-C_3H_7	6-OCH_3	4'-CH_3	O	1.41, 1.43	4.35	3.69*	5.27	7.42 (4)	—	—
8g	i-C_3H_7	6-OCH_3	3'-CF_3	O	1.41, 1.43	4.32	3.72*	5.47	7.59 (4)	—	—
8h	i-C_3H_7	6-OCH_3	4'-i-C_3H_7	O	1.41, 1.49	4.35	3.68*	5.26	7.39 (4)	—	—
8i	i-C_3H_7	6-OCH_3	2',6'-Cl_2	O	1.45	4.72	3.62*	6.12 (4)	(d)	—	—
8j	i-C_3H_7	6-OCH_3	3',4'-OCH_2O	O	1.42	4.32	3.68*	5.32	7.43 (4.5)	—	—
8k	i-C_3H_7	6,7-$(CH_3)_2$	H	O	1.43, 1.47	4.36	—	5.25	7.45 (3.5)	6.97	6.88
8l	i-C_3H_7	6,7-OCH_2O	H	O	1.41	4.22	5.95, 5.99 (2)	5.23	7.50 (4)	6.88	6.73
8m	i-C_3H_7	6,7-OCH_2O	2'-NO_2	O	1.41, 1.44	4.33	5.98, 6.00 (3)	5.82	7.13 (4)	6.88	6.62
8n	i-C_3H_7	6,7-OCH_2O	3'-NO_2	O	1.40	4.21	5.95, 5.98 (2)	5.42 (4)	(d)	7.02	6.78
8o	i-C_3H_7	6,7-OCH_2O	4'-CH_3	O	1.39	4.21	5.94, 5.98 (4)	5.18	7.42 (3.5)	6.88	6.75
8p	i-C_3H_7	6,7-OCH_2O	3'-CF_3	O	1.40	4.31	5.95, 5.97 (4)	5.40 (3)	(d)	6.92	6.72
8q	i-C_3H_7	6,7-OCH_2O	3'-CO_2H	O	1.42	4.25	6.00, s	5.35	7.62 (4)	6.92	6.80
8r	i-C_3H_7	6,7-OCH_2O	5-chloro-2-thienyl-	O	1.41, 1.43	4.27	6.00, s	5.43	7.71 (4)	6.92	6.82
8s	i-C_3H_7	6,7-OCH_2O	H	S	1.28, 1.56	5.55	6.02, 6.05 (2)	5.30	9.39 (4.5)	7.05	6.95
8t	i-C_3H_7	6,7-OCH_2O	3'-F	S	1.25, 1.55	5.43	6.01, 6.04 (3)	5.35	9.46 (4.5)	7.08	6.95
8u	i-C_3H_7	6,7-OCH_2O	3'-NO_2	S	1.30, 1.58	5.42	6.02, s	5.52	9.57 (4.5)	7.17	7.02
8v	i-C_3H_7	6,7-OCH_2O	4'-i-C_3H_7	S	1.30, 1.57	5.50	5.99, 6.05 (2)	5.26	9.35 (5)	6.98	6.93

(a) The nmr spectra were run in DMSO-d_6 and recorded by a JEOL FX 90Q spectrometer. (b) All methyl signals of the isopropyl group appeared as doublets, J = 7.5 Hz and the methine H as a quintet, J = 7.5 Hz. (c) The H_A-H_B coupling was a doublet when observed. (d) The NH signal was located with the aromatic H signals.

Table III

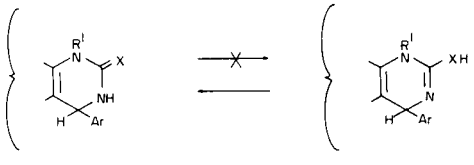
1-Alkyl-4-aryl-3,4-dihydro-2(1*H*)-quinazolinones and Thiones (**8**)

Compound	Yield, %	Mp, °C (Recrystallization Solvent) (a)	Formula	% Calculated C	H	N	Other	% Found C	H	N	Other
8a	25	230-232 (A)	$C_{16}H_{14}N_2O_3$	68.3	4.7	10.0		68.5	5.0	9.9	
8b	39	201-203 (B)	$C_{17}H_{16}N_2O_3$	68.9	5.4	9.5		69.3	5.4	9.2	
8c	46	160-162 (C)	$C_{18}H_{20}N_2O$	77.1	7.1	10.0		76.9	7.1	9.8	
8d	35	164-166 (A)	$C_{19}H_{22}N_2O_3$	69.9	6.7	8.6		69.8	6.7	8.8	
8e	42	166-167(C)	$C_{19}H_{22}N_2O_2$	73.5	7.1	9.0		73.4	7.2	9.0	
8f	32	180-181 (C)	$C_{19}H_{22}N_2O_2$	73.5	7.1	9.0		73.9	7.2	9.0	
8g	43	148-150 (A)	$C_{19}H_{19}F_3N_2O_2$	62.6	5.2	7.7		62.5	5.4	7.6	
8h	13	120-121 (C)	$C_{21}H_{26}N_2O_2$	74.5	7.7	8.3		74.8	7.8	8.3	
8i	22	208-209 (A)	$C_{18}H_{18}Cl_2N_2O_2$	59.2	5.0	7.7	Cl, 19.4	59.5	4.8	7.7	Cl, 19.4
8j	21	155-156 (B)	$C_{19}H_{20}N_2O_4$	67.0	5.9	8.2		67.2	6.0	8.3	
8k	25	158-160 (D)	$C_{19}H_{22}N_2O_2$	73.5	7.1	9.0		73.4	7.0	8.9	
8l	52	175-177 (E)	$C_{18}H_{16}N_2O_3$	69.7	5.8	9.0		69.5	5.6	9.0	
8m	56	202-205 (F)	$C_{18}H_{17}N_3O_5$	60.8	4.8	11.8		60.9	4.8	11.9	
8n	59	230-232 (E)	$C_{18}H_{17}N_3O_5$	60.8	4.8	11.8		60.7	4.9	11.8	
8o	65	192-195 (C)	$C_{19}H_{20}N_2O_3$	70.4	6.2	8.6		70.3	6.1	8.4	
8p	51	151-153 (F)	$C_{19}H_{17}F_3N_2O_3$	60.8	4.6	7.5		60.5	4.7	7.3	
8q	58	270-271 (A)	$C_{19}H_{18}N_2O_5$	64.4	5.1	7.9		64.2	5.0	7.7	
8r	60	162-164 (C)	$C_{16}H_{15}ClN_2O_3S$	54.9	4.3	8.0	Cl, 10.0 S, 9.1	54.8	4.2	7.8	Cl, 9.8 S, 9.0
8s	63	215-218 (C)	$C_{18}H_{18}N_2O_2S$	66.3	5.5	8.6	S, 9.8	66.2	5.6	8.4	S, 9.6
8t	55	200-203 (G)	$C_{18}H_{17}FN_2O_2S$	62.8	4.9	8.1	S, 9.3	62.9	4.8	8.3	S, 9.5
8u	41	225-227 (H)	$C_{18}H_{17}N_3O_4S$	58.2	4.6	11.3	S, 8.6	58.4	4.7	11.4	S, 8.7
8v	37	155-157 (H)	$C_{21}H_{24}N_2O_2S$	68.5	6.6	7.6	S, 8.7	68.3	6.5	7.6	S, 8.8

(a) Recrystallization solvents: A, methanol-methylene chloride; B, ethanol-diethyl ether; C, methanol; D, ethyl acetate; E, 2-propanol; F, diethyl ether; G, dioxane-water; H, benzene.

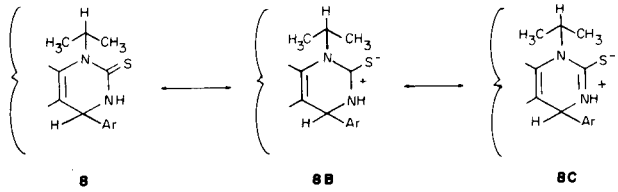
acid in relfluxing toluene for *ca* 20 hours. Under these conditions a 46% yield of **8c** could be isolated. In all acid-solvent systems studied varying amounts of aniline **6** and the polymer of isocyanic acid were isolated or detected by chromatogaphic assays. When the methanesulfonic acid cyclization conditions were applied to *N*-3,4-dimethylphenyl-*N*-isopropyl urea (**7e**) and benzaldehyde, **8h** resulted in 25% yield. Extension of the reaction to *N*-isopropyl-*N*-(4-methoxyphenyl)urea (**7d**) and *N*-isopropyl-*N*-(3,4-methylenedioxyphenyl)urea (**7f**) with a variety of substituted benzaldehydes showed that the yield of **8** followed those expected from the Pictet-Spengler reaction (5). The more electron-rich phenyl ring of **7f** gave rise to a better yield of quinazolinone relative to **7d** (compare **8f/8o** and **8g/8p**). Condensation of *N*-isopropyl-*N*-(3,4-methylenedioxyphenyl)thiourea (**7g**) with four benzaldehyde derivatives also proceeded to form the quinazolinthiones **8s-v** in moderate yields. The location of the methylenedioxy group in the 6,7-position of the quinazolinones and thiones arising from **7a,b** and **7f,g** was confirmed by the presence of two one proton singlets in the δ 6.6-7.1 region of the ^{1}H-nmr spectrum (Table II) that can be assigned to the H-5 and H-8 atoms in **8**. Formation of **8r** from 5-chloro-2-thiophenecarboxaldehyde in 60% yield suggests that the reaction could be extended to prepare a variety of 4-(heterocyclic) substituted derivatives of **8**.

The ^{1}H-nmr spectrum values of selected groups and H atoms of compound **8** given in Table II exhibit several interesting features. A H_AH_B doublet with J = 2-4 Hz separated by δ 0.02-0.06 was observed for most (**8a,b,l,p,s,t,v**) of the quinazolinones and thiones containing the 6,7-OCH_2O group. The C-4 H was found as a doublet of J = 3-5 Hz that integrated as one H atom for all compounds thereby ruling out contribution from the tautomeric hydroxy or mercaptoimine form **8A**.

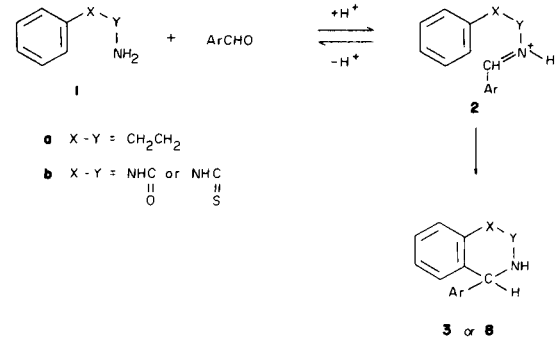


8 **8A**

The position of the C-4 H was markedly influenced by substituents on the phenyl ring. In those compounds with an unsubstituted phenyl group or electron donating groups (**8c-f,h,j,k,l,o,s,v**) the H-4 signal was at *ca* δ 5.25 $\pm$ 0.05 while electron withdrawing groups in the 3′-(**8g,n, p,q,u**) shifted the signal to δ 5.45 $\pm$ 0.05. The presence of a 2′-NO_2 group (**8m**) and a 2′,6′-Cl_2 (**8i**) brought about a marked deshielding effect shift to δ 5.82 and 6.12, respectively. In a number of 1-isopropyl-2-one derivatives (**8**, X = O), the dimethyl signals were found as two sets of doublets (J = 7.5 Hz) of equal weights separated by δ 0.02-0.06 units. No correlation could be found between those compounds that gave one doublet (**8c,d,i,j,l,n,o, p,q**) and those that gave a pair (**8e-h,k,m,r**). All of the 1-isopropyl-5-thione derivatives (**8s-v**) gave a pair of doublets with equal weight with one doublet located at 1.28 $\pm$ 0.03 and the other at δ 1.57 $\pm$ 0.02. One possible explanation for the shift is that the C=S bond in **8s-v** has a large contribution from the polarazied forms **8B** and **8C** which would result in the methyls of the diastereotopic isopropyl group being exposed to two different electronic environments. It is interesting to note that the gem dimethyl signal of the *N*-isopropyl ureas (**7c-f**), thiourea (**7g**; Table I) and all of the 1-isopropyl-4-arylquinazolinones and thiones we have prepared in our laboratories (2f) appeared as one doublet.



8 **8B** **8C**



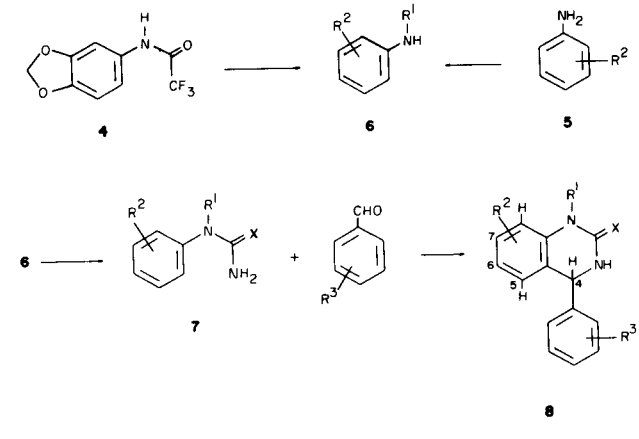
1 **2**

a X-Y = CH_2CH_2

b X-Y = NHC or NHC (O / S)

3 or **8**

Scheme I



4 **6** **5**

6 **7** **8**

EXPERIMENTAL

Infrared (ir) spectra were recorded on a Perkin-Elmer 257 infrared spectrometer and ^{1}H nuclear magnetic resonance (nmr) spectra were recorded by using either a Varian A-60A or JOEL FX 90Q spectrometer. Chemical shifts are reported as δ values in parts per million relative to TMS; coupling constants (J) are given in Hertz. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Silica gel (0.063-0.2 mm) was used in preparing column chromatograms, and analytical thin layer chromatography was conducted on precoated 40 × 80 mm plastic strip sheets of silica gel G with fluorescent indicator for all compounds listed in Tables I and II.

N-Methyl and *N*-Ethyl-3,4-methylenedioxyaniline (**6**).

A stirred solution of 6.86 g (0.05 mole) of 3,4-methylenedioxyaniline and 7.1 g (0.07 mole) of triethylamine in 150 ml of dry toluene was cooled to 10 ± 5° and treated dropwise with a solution of 12.6 g (0.06 mole) of trifluoroacetic anhydride in 25 ml of toluene. After 0.5 hour, 100 ml of water was added. The toluene layer was then dried with anhydrous magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* to give 6.4 g (86%) of **4** mp 117-119° methylene chloride; nmr (deuteriochloroform): δ 5.92 (2H, s, OCH_2O), 10.2 (1H, s, NH).

Anal. Calcd. for $C_9H_6F_3NO_3$: C, 46.3; H, 2.6; N, 6.0. Found: C, 46.8; H, 2.6; N, 6.2.

A solution of 6.05 g (0.03 mole) of **4**, 17 g (0.12 mole) of methyl iodide and 6.73 g (0.12 mole) of powdered potassium hydroxide in 200 ml of dry acetone was refluxed for *ca* 10 minutes. The solvent was removed *in vacuo* and the residue was treated with 50 ml of water and then refluxed for *ca* 20 minutes. The mixture was extracted with chloroform and then the organic layer was dried with anhydrous magnesium sulfate, filtered and then concentrated to give 3.4 g (75%) of **6** (R^1 = CH_3, R^2 = OCH_2O) as an oil; nmr (deuteriochloroform): δ 2.67 (3H, s, CH_3), 3.47 (1H, s, NH), 5.78 (2H, s, OCH_2O). In a similar manner using 13.1 g (0.12 mole) of bromoethane there was obtained 3.56 (72%) of **6** (R^1 = C_2H_5, R^2 = OCH_2O) as an oil; nmr (deuteriochloroform): δ 1.8 (3H, t, J = 15, CH_3), 3.07 (2H, q, J = 15, CH_2), 3.38 (1H, s, NH), 5.82 (2H, s, OCH_2O).

N-Isopropyl-3,4-methylenedioxyaniline (**6**; R^1 = *i*-C_3H_7, R^2 = OCH_2O).

A solution containing 27 g (0.20 mole) of 3,4-methylenedioxyaniline (mp 37°), 15.1 ml (25.4 g, 0.20 mole) of isopropyl iodide, 20.4 g (0.20 mole) of triethylamine and 200 ml of methanol was refluxed for 52 hours. The solvent was removed *in vacuo* and the residue was treated with 150 ml of water and 200 ml of benzene. The benzene layer was separated, dried with anhydrous magnesium sulfate, filtered and distilled to give 26.5 g (74%) of **6** as an oil.

N-Alkyl-*N*-(3,4-methylenedioxyphenyl)ureas (**7**, X = O).

General Procedure.

A stirred solution of *N*-alkylaniline (4 g, 0.08 mole) in 200 ml of acetic acid maintained at 15 ± 5° was treated portionwise with 0.075 mole of sodium isocyanate. After stirring for *ca* 15 hours at room temperature the solvent was removed *in vacuo* and the solid residue treated with 300 ml of 2*N* sodium hydroxide and 250 ml chloroform. The chloroform layer was washed with water, dried with anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to give the **7** (X = O) listed in Table I.

N-Isopropyl-*N*-(3,4-methylenedioxyphenyl)thiourea (**7g**, X = S).

A mixture of 17.3 g (0.12 mole) of benzoyl chloride and 13.6 g (0.17 mole) of anhydrous sodium isothiocyanate was stirred and refluxed for *ca* 3 hours. The mixture was allowed to come to room temperature, filtered, and the filtrate was treated dropwise with a solution of 28.6 g (0.16 mole) of **6** (R^1 = *i*-C_3H_7, R^2 = OCH_2O) in 150 ml of dry benzene. After stirring fro *ca* 30 minutes the solid was collected and then recrystallized from benzene to give 29 g (71%) of N^1-isopropyl-N^1-(3,4-methylenedioxyphenyl)-N^3-benzoylthiourea (**9**), mp 152-157°.

Anal. Calcd. for $C_{18}H_{18}N_2O_3S$: C, 63.2; H, 5.3; N, 8.2; S, 9.4. Found: C, 63.0; H, 5.1; N, 8.3; S, 9.2.

To a solution of 27 g (0.68 mole) of sodium hydroxide in 45 ml of dioxane and 200 ml water there was added portionwise 17 g (0.05 mole) of **4**. The mixture was stirred and refluxed for 48 hours and then allowed to come to room temperature. The resultant solid was collected and then recrystallized from benzene to give 8.9 g (75%) of **7g**, mp 149-151° (Table I).

1-Alkyl-4-aryl-3,4-dihydro-2(1*H*)-quinazolinones and Thiones (**8**).

General Procedure.

A solution of 0.05 mole of *N*-alkyl-*N*-arylurea or thiourea (**7**), 0.06 mole of an aryl aldehyde, 0.5 ml of methanesulfonic acid and 250 ml of toluene was stirred and refluxed for *ca* 20 hours in a flask equipped with a Dean-Stark water separator. The cooled solution was washed with 200 ml water, dried with anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resultant solid was then decolorized with activated charcoal in hot propanol or chromatographed on a silica gel column if necessary and then recrystallized from the appropriate solvent (Table II).

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