SOME 2, 3-DISUBSTITUTED 3*H*-4-QUINAZOLONES AND 3*H*-4-THIOQUINAZOLONES

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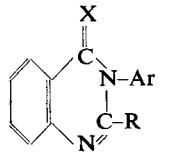
Some 2-alkyl-3-aryl-3*H*-4-quinazolones (I; X = 0) have been prepared and a number of them converted into the thioquinazolones (I; X = S). A new method for the synthesis of 3-alkyl-2-aryl-3*H*-4-quinazolones (VI) has been developed and has been employed for the synthesis of representative derivatives.

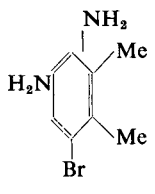
Biological study of the above compounds revealed that some of them, and in particular the 2-alkyl-3-halophenyl-3*H*-4-quinazolones are potent anticonvulsant agents.

OUR interest in quinazolones stemmed from the discovery of Gujral, Saxena and Tiwari[1] that certain 2-alkyl-3-aryl-3*H*-4-quinazolones (I; X = 0) and in particular the 2-methyl-3-*o*-tolyl (I; R = Me, Ar = *o*-Me. C_6H_4, X = 0) and 2-ethyl-3-phenyl (I; R = Et, Ar = Ph, X = 0) derivatives were potent hypnotic agents superior to allobarbitone in the assay. We therefore began in 1955 a systematic study of quinazolones of this type, preparing them by the general method of Grimmel, Guenther and Morgan[2] in which an *o*-acylamidobenzoic acid is condensed with an aromatic amine in the presence of phosphorus trichloride. The compounds listed in Table I which includes, *inter alia* a few derivatives already described in the literature[3–5], were largely synthesised in this way.

In addition to phosphorus trichloride we have found other condensing agents to be effective in the synthesis of the quinazolones (I). Benzenesulphonyl chloride in pyridine previously used by Brewster and Ciotti[6] for the preparation of amides, proved highly satisfactory. Somewhat lower yields followed the use of phosphorus trichloride in pyridine, but reaction was more rapid. Dicyclohexylcarbodiimide in molar proportion in tetrahydrofuran solution at room temperature for 5 hours gave yields of quinazolones (I) of about 50 per cent.



(I)



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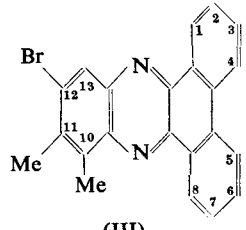

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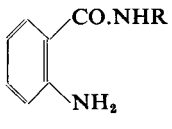

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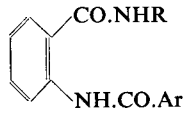

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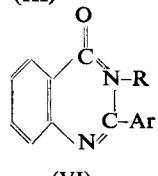


(VI)

Biological study of early members of the series, for which we are indebted to Dr. A. David and Dr. G. Bianchi revealed the pronounced central depressant activity of 3-(4-bromophenyl)-2-methyl-3*H*-4-quinazolone. Extending this observation we prepared 3-(4-bromo-2,3-dimethylphenyl)-3*H*-4-quinazolone. 4-Bromo-2,3-dimethylaniline, required for this purpose has not been described in the literature and was obtained by bromination of 2,3-dimethylacetanilide in acetic acid at 10°, followed by hydrolysis with hydrochloric acid (cf. 7). The orientation of the bromine atom in the acetanilide was established by nitration when 4-bromo-2,3-dimethyl-6-nitroacetanilide was obtained, identified by reduction and hydrolysis to the diamine (II) which passed into 12-bromo-10,11-dimethyldibenzo[*a*,*c*]-phenazine (III) on reaction with phenanthraquinone. 6-Bromo-2-methyl-3-*o*-tolyl-3*H*-4-quinazolone[8] was prepared in order to determine the effect upon biological activity of a bromo-substituent in the benzene ring of the heterocyclic nucleus. In addition a series of new 2-alkyl-3-aryl-3*H*-4-thioquinazolones (I; X = S) (Table II) were prepared from the corresponding 4-oxo-derivatives by the general method of Leonard and Curtin[9].

We next turned our attention to the synthesis of the related 3-alkyl-2-aryl-3*H*-4-quinazolones (VI). 3-Methyl-2-phenyl-3*H*-4-quinazolone (VI; Ar = Ph, R = Me), the only member of this type described in the literature, was prepared by Korner[10] (*a*) by heating 2-benzamido-*N*-methylbenzamide at 230° to 250° and (*b*) by direct methylation with methyl iodide in a sealed tube at 120° of 2-phenyl-3*H*-4-quinazolone, which was itself prepared by the action of boiling aqueous potassium hydroxide on 2-benzamidobenzamide.

Initial attempts to prepare compounds of type (VI) by condensing *N*-alkyl-2-aminobenzamides (IV) with a benzoic acid in the presence of phosphorus trichloride proved unsuccessful. Somewhat better results followed the cyclisation of *N*-alkyl-2-benzamidobenzamides (V) with phosphorus trichloride in pyridine, but the yields of 3-alkyl-2-aryl-3*H*-4-quinazolones (VI) obtained were unsatisfactory. We ultimately found that the required quinazolones (VI) were readily prepared in good yield from the corresponding *N*-alkyl-2-aminobenzamides (IV), which we obtained by reaction between isatoic anhydride and the appropriate amine[11]. Aroylation of the benzamides (IV) was preferably accomplished with the benzoyl chloride in aqueous ethanolic sodium acetate solution when the *N*-alkyl-2-benzamidobenzamides (V) recorded in Table III were obtained. The use of pyridine as solvent for this reaction proved less satisfactory as in the condensation of anthranilamide (IV, R = H) with *p*-bromobenzoyl chloride, for example, substantial quantities of 2-*p*-bromobenzamidobenzonitrile were formed in addition to the usual aroylated product[12]. Conversion of the intermediate *N*-alkyl-2-benzamidobenzamides (V) into the quinazolones (VI) was effected by boiling the compounds with 5 per cent aqueous sodium hydroxide solution (cf. [13,14]) or by heating them to 260° for 1 to 2 hours. The former method of cyclisation was preferred for compounds (V; R = H or Me), but was less satisfactory with ethyl and higher alkylamides. In many cases both methods gave mixtures of product and starting material from which the

quinazolones were obtained by extraction with light petroleum or by precipitation from ethereal solutions as the hydrochloride. 3-Methyl-2-*o*-tolyl-3*H*-4-quinazolone (VI; R = Me, Ar = *o*-Me.C_6H_4) was prepared by direct methylation of 2-*o*-tolyl-3*H*-4-quinazolone with methyl sulphate in alkaline solution. 3-(2,3-Dihydroxypropyl)-2-phenyl-3*H*-4-quinazolone (VI; R = CH_2.CHOH.CH_2OH, Ar = Ph) was obtained by the condensation of 2-phenyl-3*H*-4-quinazolone with 2,3-epoxypropan-1-ol ("glycidol") in ethanolic solution employing pyridine as catalyst.

Biological results have been reported[15].

EXPERIMENTAL

The following examples illustrate the methods used for the preparation of compounds listed in Table I.

3-*p-Bromophenyl*-2-*methyl*-3H-4-*quinazolone* (I; R = Me, Ar = *p*-Br.C_6H_4, X = O).

(*a*) To a stirred mixture of *p*-bromoaniline (34·4 g.) and acetylanthranilic acid (35·8 g.) in toluene (250 ml.) at room temperature, a solution of phosphorus trichloride (8 ml.) in toluene (50 ml.) was added slowly. After the addition was complete the pasty mixture was heated for 2 hours at reflux temperature. After cooling, 15 per cent sodium carbonate solution was added and the toluene removed by distillation in steam. The residual *product* (27 g.) was collected and purified by crystallisation from 95 per cent ethanol. The hydrochloride, prepared by addition of concentrated hydrochloric acid (9 ml.) to a solution of the base (20 g.) in warm 95 per cent ethanol (300 ml.) had m.p. ca *c*, 260° (decomp.) after crystallisation from 95 per cent ethanol.

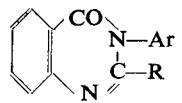
(*b*) To a solution of acetylanthranilic acid (9·0 g.) and *p*-bromoaniline (8·9 g.) in tetrahydrofuran (100 ml.) was added a solution of dicyclohexylcarbodiimide (11·4 g.) in tetrahydrofuran (50 ml.) and the mixture allowed to stand at room temperature for 5 hours. Acetic acid (1·5 ml.) was added and after 2 hours the separated dicyclohexylurea was filtered off. The filtrate was evaporated to dryness at reduced pressure and the residue dissolved in ethyl acetate (150 ml.). The ethyl acetate was shaken with 2N hydrochloric acid when the *hydrochloride* (9 g.) of the product separated and was collected. It had m.p. ca 260° (decomp.) and was identical with the product described under (*a*). The ethyl acetate solution was washed with N sodium bicarbonate solution, then with water and concentrated to ca. 50 ml. to yield, 2-*acetamido*-4'-*bromobenzanilide* (1·5 g.), m.p. 215–216°. Found: C, 53·5; H, 4·0; N, 8·7. $C_{15}H_{13}O_2NBr$ requires C, 54·1; H, 3·9; N, 8·4 per cent.

3-(2,4-*Dichlorophenyl*)-2-*methyl*-3H-4-*quinazolone* (I; R = Me, Ar = 2,4-Cl_2.C_6H_3, X = O)

(*a*) A solution of acetylanthranilic acid (17·9 g.) in pyridine (30 ml.) was treated in one portion with benzenesulphonyl chloride (17·8 g.) followed by 2,4-dichloroaniline (16·2 g.), added in portions with shaking. The mixture was heated on the steam bath for 2 hours. After cooling and dilution with water the resultant gum solidified on trituration with ethanol.

TABLE I

2-ALKYL-3-ARYL-3*H*-4-QUINAZOLONES



R	Ar	Base (B) hydrochloride (H)	M.p. °C.*	Formula	Found per cent				Required per cent			
					C	H	N	Cl	C	H	N	Cl
Me	*p*-Anisyl	H	ca. 240 (*d*)	$C_{16}H_{15}O_2N_2Cl$	63·0	5·1	8·7	11·9	63·5	5·0	9·3	11·7
Me	*o*-Phenetyl	B	115–116	$C_{17}H_{18}O_2N_2$	73·0	6·1	9·7	—	72·9	5·8	10·0	—
		H	ca. 215 (*d*)	$C_{17}H_{17}O_2N_2Cl$	64·1	5·5	9·3	11·6	64·4	5·4	8·9	11·2
Me	*m*-Phenetyl	B	130–132	$C_{17}H_{18}O_2N_2$	73·0	5·9	9·6	—	72·9	5·8	10·0	—
		H	ca. 225 (*d*)	$C_{17}H_{17}O_2N_2Cl$	64·3	5·5	8·7	11·1	64·4	5·4	8·9	11·2
Me	*p*-Phenetyl	H	ca. 240 (*d*)	$C_{17}H_{17}O_2N_2Cl$	64·1	5·2	—	11·3	64·4	5·4	—	11·2
Me	3,4,5-Trimethoxyphenyl	B	150–152	$C_{18}H_{18}O_4N_2$	65·8	5·5	—	—	66·2	5·6	—	—
		H	ca. 250 (*d*)	$C_{18}H_{19}O_4N_2Cl$	59·7	5·1	7·6	9·8	59·6	5·3	7·7	9·8
Me	2,3-Xylyl	B	172–173	$C_{17}H_{16}ON_2$	77·4	6·4	10·3	—	77·3	6·1	10·6	—
		H	ca. 240 (*d*)	$C_{17}H_{17}ON_2Cl$	68·1	5·7	—	11·3	67·9	5·7	—	11·8
Me	2,4-Xylyl	B	100–102	$C_{17}H_{16}ON_2$	77·1	6·3	10·8	—	77·3	6·1	10·6	—
		H	ca. 240 (*d*)	$C_{17}H_{17}ON_2Cl$	68·2	5·8	8·9	11·6	67·9	5·7	9·3	11·8
Me	2,5-Xylyl	B	125–127	$C_{17}H_{16}ON_2$	77·2	6·1	—	—	77·3	6·1	—	—
Me	2,6-Xylyl	H	ca. 215 (*d*)	$C_{17}H_{17}ON_2Cl$	67·5	5·9	9·7	11·6	67·9	5·7	9·3	11·8
Me	3,4-Xylyl	B	134–136	$C_{17}H_{16}ON_2$	77·6	6·0	—	—	77·3	6·1	—	—
Me	*p*-Fluorophenyl	B	133–134	$C_{15}H_{11}ON_2F$	70·7	4·4	—	7·5*a*	70·9	4·5	—	7·6*a*
		H	ca. 280 (*d*)	$C_{15}H_{12}ON_2FCl$	61·4	4·3	9·6	—	61·9	4·2	9·6	—
Me	*o*-Chlorophenyl	B	130–132	$C_{15}H_{11}ON_2Cl$	66·7	4·2	10·3	—	66·5	4·1	10·3	—
Et	*o*-Chlorophenyl	B	124–126	$C_{16}H_{13}ON_2Cl$	66·9	4·6	9·7	11·8	67·5	4·6	9·8	12·4
Me	*m*-Chlorophenyl	B	133–135	$C_{15}H_{11}ON_2Cl$	66·0	4·0	10·2	—	66·5	4·1	10·3	—
Me	*o*-Bromophenyl	B	147–148	$C_{15}H_{11}ON_2Br$	57·4	3·6	8·8	25·1*b*	57·1	3·5	8·9	25·3*b*
		H	ca. 220 (*d*)	$C_{15}H_{12}ON_2ClBr$	51·7	3·5	8·1	32·4*d*	51·2	3·5	8·0	32·8*d*
Me	*m*-Bromophenyl	B	134–136	$C_{15}H_{11}ON_2Br$	57·4	3·5	9·0	25·1*b*	57·1	3·5	8·9	25·3*b*
		H	ca. 260 (*d*)	$C_{15}H_{12}ON_2ClBr$	51·7	3·5	8·2	32·2*d*	51·2	3·5	8·0	32·8*d*
Me	*p*-Bromophenyl	B	170–172	$C_{15}H_{11}ON_2Br$	57·3	3·5	8·7	25·5*b*	57·1	3·5	8·9	25·3*b*
		H	ca. 260 (*d*)	$C_{15}H_{12}ON_2ClBr$	51·6	3·6	8·1	33·4*d*	51·2	3·5	8·0	32·8*d*
Et	*p*-Bromophenyl	B	170–172	$C_{16}H_{13}ON_2Br$	58·3	4·0	8·3	24·0*b*	58·4	4·0	8·5	24·3*b*
Pr	*p*-Bromophenyl	B	139–141	$C_{17}H_{15}ON_2Br$	59·6	4·5	8·2	22·8*b*	59·5	4·4	8·2	23 3*b*
Me	*p*-Iodophenyl	B	178–180	$C_{15}H_{11}ON_2I$	50·0	3·1	7·8	35·3*c*	49·7	3·1	7·7	35·1*c*
		H	ca. 265 (*d*)	$C_{15}H_{12}ON_2ClI$	44·9	3·0	—	40·4*d*	45·2	3·0	—	40·7*d*
Me	2,4-Dichlorophenyl	B	151–152	$C_{15}H_{10}ON_2Cl_2$	59·2	3·5	9·1	23·0	59·0	3·3	9·2	23·3
		H	ca. 250 (*d*)	$C_{15}H_{11}ON_2Cl_3$	52·6	3·3	7·9	31·5	52·7	3·2	8·2	31·2
Me	2,5-Dichlorophenyl	B	161–163	$C_{15}H_{10}ON_2Cl_2$	59·2	3·5	9·1	23·3	59·0	3·3	9·2	23·3
		H	ca. 244 (*d*)	$C_{15}H_{11}ON_2Cl_3$	53·0	3·2	8·3	30·6	52·7	3·2	8·2	31·2
Me	4-Bromo-2,3-xylyl	B	168–170	$C_{17}H_{15}ON_2Br$	58·9	4·1	8·4	23·0*b*	59·5	4·4	8·2	23·3*b*

* All hydrochlorides melted with decomposition over a range of several degrees.
a = Fluorine
b = Bromine
c = Iodine
d = Total halogen

Crystallisation from ethyl acetate-light petroleum (b.p. 60–80°) furnished the product in needles (9·6 g), m.p. 151–152°. The hydrochloride separated from methanol in long needles, m.p. 242–250°.

(*b*) A mixture of acetylanthranilic acid (17·9 g.) and 2,4-dichloroaniline 16·2 g.) in pyridine (50 ml.) was stirred vigorously and treated slowly dropwise with phosphorus trichloride (6·9 g.). After the addition was complete the mixture was heated on the steam bath for 1 hour. It was then cooled and diluted with water. The solid product was washed by decantation, dissolved in ethanol (100 ml.) and treated with a slight excess of hydrogen chloride. The *hydrochloride* (25 g.) separated rapidly from the solution; it had m.p. 240–250° and was identical with the compound described in (*a*)

4-*Bromo*-2,3-*dimethylacetanilide*

A solution of bromine (27·5 ml.) in acetic acid (50 ml.) was added dropwise with stirring to a solution of 2,3-dimethylacetanilide (81·5 g.) in acetic acid (150 ml.) cooling being applied to keep the temperature at 10°. Stirring was continued for a further hour after the addition was complete, when the solids were collected and washed with acetic acid. The *product* crystallised from aqueous ethanol in long colourless needles (82 g.), m.p. 158–160°. Found: C, 49·8; H, 5·2; N, 6·2; Br, 32·9. $C_{10}H_{12}ONBr$ requires C, 49·6; H, 5·0; N, 5·8; Br, 33·0 per cent.

4-*Bromo*-2,3-*dimethylaniline*

A solution of the foregoing compound (81 g.) in ethanol (600 ml.) was treated with concentrated hydrochloric acid (120 ml.) and the mixture heated under reflux for 6 hours. The hydrochloride (77·5 g.), m.p. 268° (decomp.), separated on cooling and was collected. Basification of the hydrochloride with N sodium hydroxide (1 litre) followed by distillation in steam yielded 4-*bromo*-2,3-*dimethylaniline*, which crystallised from light petroleum (b.p. 60–80°) in plates, m.p. 32–34°. Found: C, 47·7; H, 5·1; N, 7·0; Br, 40·1. $C_8H_{10}NBr$ requires C, 48·0; H, 5·1; N, 7·0; Br, 40·0 per cent.

4-*Bromo*-2,3-*dimethyl*-6-*nitroacetanilide*

A hot solution of 4-bromo-2,3-dimethylacetanilide (12·1 g.) in acetic acid (19·2 ml.) was added gradually with stirring to a mixture of acetic acid (7·2 ml.) and fuming nitric acid (21·6 ml.) and the resultant mixture heated on the steam bath for 30 minutes. After cooling and pouring into water (500 ml.) the solids were collected and crystallised from 95 per cent ethanol. The *product* separated in pale-yellow needles of m.p. 207–209°. Found: N, 10·1. $C_{10}H_{11}O_3N_2Br$ requires N, 9·8 per cent.

4-*Bromo*-2,3-*dimethyl*-6-*nitroaniline*

The foregoing acetaniline (10 g.) was heated under reflux with 40 per cent sulphuric acid (400 ml.) for 90 minutes. The solution was cooled, diluted and basified with ammonia solution. The *product* crystallised from 50 per cent ethanol in flat golden-brown needles, m.p. 147–149°. Found: N, 11·1. $C_8H_9O_2N_2Br$ requires N, 11·4 per cent.

5-Bromo-3,4-dimethyl-o-phenylenediamine (II)

A solution of the foregoing nitroamine (2·5 g.) in 50 per cent ethanol (300 ml.) was heated on the steam bath and sodium hydrosulphite (dithionite) (10 g.) added in portions with shaking over 1 hour. The ethanol was removed under reduced pressure when the product (1·5 g.) crystallised on cooling. It had m.p. 85–87° after crystallisation from light petroleum (b.p. 60–80°). Found: N, 12·8; Br, 37·1. $C_8H_{11}N_2Br$ requires N, 13·0; Br, 37·2 per cent.

The diamine (0·5 g.) was characterised by condensation with phenthraquinone (0·4 g.) in hot acetic acid (30 ml.). The product (0·6 g.) separated from chloroform in yellow needles, m.p. 257–259°. Found: N, 7·0; Br, 20·8. $C_{22}H_{15}N_2Br$ requires N, 7·2; Br, 20·6 per cent.

The method used for the preparation of the compounds listed in Table II is illustrated by the following example:

3-o-*Bromophenyl-2-methyl*-3H-4-*thioquinazolone* (I; R = Me, Ar = *p*-Br.C_6H_4, X = S)

A mixture of 3-*p*-bromophenyl-2-methyl-3*H*-4-quinazolone (47·2 g.) and phosphorus pentasulphide (33·3 g.) in xylene (400 ml.) was stirred and heated under reflux for 2 hours. It was then cooled and treated with 10 per cent sodium hydroxide solution (280 ml.) added in portions. The xylene was then removed by distillation in steam. The residual product (47·3 g.) was purified by crystallisation from 95 per cent ethanol when it separated in yellow-brown needles of m.p. 190–192°.

The following three experiments illustrate the methods used for the preparation of the *N*-alkyl-2-benzamidobenzamides recorded in Table III.

2-*Benzamido*-N-*ethylbenzamide* (V; R = Et, Ar = Ph)

To a well stirred solution of 2-amino-*N*-ethylbenzamide (32·8 g.) in 50 per cent aqueous ethanol (700 ml.) containing hydrated sodium acetate (54·4 g.), benzoyl chloride (28·2 g.) was added in portions over 15 minutes. The reaction was completed by heating on the steam bath for 30 minutes. The product was purified by crystallisation from aqueous ethanol.

2-p-*Bromobenzamido*-N-*ethylbenzamide* (V; R = Et, Ar = *p*-Br.C_6H_4)

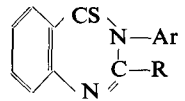
2-Amino-*N*-ethylbenzamide (32·8 g.) was added in small portions with stirring over 30 minutes to a solution of *p*-bromobenzoyl chloride (43·8 g.) in warm pyridine. Reaction was completed by heating on the steam bath for 15 minutes. The mixture was then cooled slightly and poured with stirring into N hydrochloric acid (1,500 ml.). The solids were collected, washed with dilute sodium carbonate solution, then with water and purified by crystallisation from 95 per cent ethanol.

2-p-*Bromobenzamidobenzamide* (V; R = H, Ar = *p*-Br.C_6H_4)

(*a*) Preparation in aqueous ethanol containing sodium acetate, as described for 2-benzamido-*N*-ethylbenzamide except that the reaction was carried out at 60–65°, gave a 60 per cent yield of product m.p. 224–226°.

TABLE II

2-ALKYL-3-ARYL-3*H*-4-THIOQUINAZOLONES

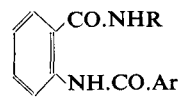


R	Ar	Base (B) hydrochloride (H)	M.p. °C.	Formula	Found per cent				Required per cent			
					C	H	S		C	H	S	
Me	*o*-Tolyl	B	121–123	$C_{16}H_{14}N_2S$	72·3	5·1	11·9	10·6*a*	72·1	5·3	12·0	10·5*a*
		H	228–230	$C_{16}H_{15}N_2SCl$	63·2	5·3	10·8	11·8*b*	63·4	5·0	10·6	11·7*b*
Me	*p*-Fluorophenyl	B	128–130	$C_{15}H_{11}N_2SF$	67·1	4·2	11·5	—	66·6	4·1	11·9	—
Me	*p*-Chlorophenyl	B	183–185	$C_{15}H_{11}N_2SCl$	62·4	3·9	11·3	12·3*b*	62·8	3·9	11·2	12·4*b*
Me	*o*-Bromophenyl	B	174–176	$C_{15}H_{11}N_2SBr$	54·9	3·5	9·3	23·8*c*	54·4	3·4	9·7	24·1*c*
Me	*p*-Bromophenyl	B	190–192	$C_{15}H_{11}N_2SBr$	54·2	3·3	10·2	—	54·4	3·4	9·7	—
Et	*p*-Bromophenyl	B	168–170	$C_{16}H_{13}N_2SBr$	56·0	3·8	8·6	22·9*c*	55·7	3·8	9·3	23·1*c*

a = Nitrogen
b = Chlorine
c = Bromine

TABLE III

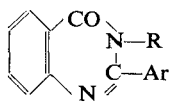
N-ALKYL-2-BENZAMIDOBENZAMIDES



R	Ar	M.p. °C.	Formula	Found per cent				Required per cent			
				C	H	N	Br	C	H	N	Br
H	*p*-Bromophenyl	224–226	$C_{14}H_{11}O_2N_2Br$	52·5	3·4	9·1	25·1	52·7	3·5	8·8	25·0
Me	*o*-Tolyl	167–170	$C_{16}H_{16}O_2N_2$	71·7	6·0	10·1	—	71·6	6·0	10·4	—
Me	*p*-Chlorophenyl	162–164									
		190–192	$C_{15}H_{13}O_2N_2Cl$	62·5	4·5	9·9	—	62·4	4·5	9·7	—
Me	*o*-Bromophenyl	170–172	$C_{15}H_{13}O_2N_2Br$	54·2	3·9	8·4	—	54·0	3·9	8·4	—
Me	*p*-Bromophenyl	165									
		197–199	$C_{15}H_{13}O_2N_2Br$	53·6	4·1	8·3	—	54·0	3·9	8·4	—
Et	Phenyl	158–160	$C_{16}H_{16}O_2N_2$	71·6	6·0	10·6	—	71·6	6·0	10·4	—
Et	*p*-Bromophenyl	174–176	$C_{16}H_{15}O_2N_2Br$	55·1	4·8	8·0	23·0	55·3	4·4	8·1	23·0
Bu^n	Phenyl	125–127	$C_{18}H_{20}O_2N_2$	72·7	6·5	8·9	—	72·9	6·8	9·4	—

TABLE IV

C-ALKYL-2-AMYL-3*H*-4-QUINAZOLONES



R	Ar	Base (B) Hydrochloride (H)	M.p. °C.	Formula	Found per cent				Required per cent			
					C	H	N	Cl	C	H	N	Cl
Me	Phenyl	B	136–138	$C_{15}H_{12}ON_2$	75·7	5·3	12·0	—	76·3	5·1	11·9	—
Me	Phenyl	H	ca. 208 (*d*)	$C_{15}H_{13}ON_2Cl$	66·5	4·6	10·3	13·2	66·1	4·8	10·3	13·0
Et	Phenyl	B	130–132	$C_{16}H_{14}ON_2$	76·7	5·5	11·2	—	76·8	5·7	11·2	—
Et	Phenyl	H	ca. 205 (*d*)	$C_{16}H_{15}ON_2Cl$	67·1	5·2	—	12·4	67·0	5·3	—	12·3
Bu	Phenyl	B	116–118	$C_{18}H_{18}ON_2$	78·0	6·6	10·0	—	77·7	6·5	10·1	—
2,3-Dihydroxypropyl	Phenyl	B	179–181	$C_{17}H_{16}O_3N_2$	69·1	5·4	9·7	—	68·9	5·5	9·5	—
Me	*o*-Tolyl	B	107–109	$C_{16}H_{14}ON_2$	76·4	5·8	11·4	—	76·7	5·7	11·2	—
Me	*o*-Tolyl	H	ca. 205 (*d*)	$C_{16}H_{15}ON_2Cl$	67·1	5·2	9·9	12·1	66·7	5·3	9·8	12·4
Me	*p*-Chlorophenyl	B	170–172	$C_{15}H_{11}ON_2Cl$	66·4	4·1	10·5	13·3	66·5	4·1	10·3	13·1
Me	*o*-Bromophenyl	B	154–156	$C_{15}H_{11}ON_2Br$	57·6	3·6	9·1	25·1*a*	57·1	3·5	8·9	25·3*a*
H	*p*-Bromophenyl	B	313–315	$C_{14}H_9ON_2Br$	55·9	3·1	9·4	26·4*a*	55·8	3·0	9·3	26·5*a*
Me	*p*-Bromophenyl	B	170–172	$C_{15}H_{11}ON_2Br$	57·6	3·7	8·9	25·3*a*	57·1	3·5	8·9	25·3*a*
Et	*p*-Bromophenyl	B	122–124 138–140	$C_{16}H_{13}ON_2Br$	58·4	3·9	8·7	24·1*a*	58·4	4·0	8·5	24·3*a*

a = Bromine

(*b*) Preparation in pyridine as described for 2-*p*-bromobenzamido-*N*-ethylbenzamide gave a mixture which was separated by extraction with chloroform to give the required product in 40 per cent yield, m.p. 224–226° together with 30 per cent of the chloroform-soluble 2-*p*-bromobenzamidobenzonitrile, m.p. 185–187°. Found: C, 56·0; H, 3·3; N, 8·9. $C_{14}H_9ON_2Br$ requires C, 55·8; H, 3·0; N, 9·3 per cent.

Preparation of 3-*alkyl*-2-*aryl*-3H-4-*quinazolones* (VI)

The following examples illustrate the methods used for the preparation of 3-alkyl-2-aryl-3*H*-4-quinazolones in Table IV.

3-*Methyl*-2-*o*-*tolyl*-3H-4-*quinazolone* (VI; R = Me, Ar = *o*-Me.C_6H_4)

(*a*) *N*-Methyl-2-(*o*-methylbenzamido)benzamide (26·7 g.) was heated under reflux for 1 hour with 5 per cent sodium hydroxide solution (300 ml.) containing ethanol (50 ml.). The product (56 per cent) solidified on cooling and was crystallised from light petroleum (b.p. 60–80°), then from aqueous ethanol.

(*b*) 2-*o*-Tolyl-3*H*-4-quinazolone (4 g.) was dissolved in N sodium hydroxide (80 ml.) and methyl sulphate (7·2 ml.) added dropwise with stirring. After the addition was complete a further 20 ml. of N sodium hydroxide was added and stirring continued for 1½ hours at room temperature followed by heating on the steam bath for 15 minutes. The *product* (50 per cent) separated on cooling and was purified as in (*a*). The *hydrochloride* crystallised from ethanol.

3-*Butyl*-2-*phenyl*-3H-4-*quinazolone* (VI; R = Bu, Ar = Ph)

2-Benzamido-*N*-butylbenzamide (29·6 g.) was heated under reflux for 3 hours with 5 per cent sodium hydroxide solution (400 ml.) and ethanol (400 ml.). The solid (27 g.) which separated on cooling was a mixture of the required product and starting material. Extraction with ether followed by treatment of the extract with hydrogen chloride furnished the hydrochloride of the product which was collected. This was dissolved in ethanol, basified with sodium carbonate solution to yield the required *base* (9 g.) and purified by crystallisation from 95 per cent ethanol. Unchanged starting material was recovered by concentration of the ethereal extract.

2-p-*Bromophenyl*-3-*methyl*-3H-4-*quinazolone* (VI; R = Me, Ar = *p*-Br.C_6H_4)

2-*p*-Bromobenzamido-*N*-methylbenzamide (66·6 g.) was finely powdered and heated with stirring at 250–260° for 1 hour. After cooling, the residue was crystallised from ethanol to furnish the product in 68 per cent yield.

3-(2,3-*Dihydroxypropyl*)-2-*phenyl*-3H-4-*quinazolone* (VI; R = CH_2.$CHOH.CH_2OH$, Ar = Ph)

To a suspension of 2-phenyl-3*H*-4-quinazolone (44 g.) in boiling ethanol (800 ml.) was added 2,3-epoxypropan-1-ol (40 ml.) followed by

pyridine (0·5 ml.) and heating continued for 30 minutes after a homogeneous solution was obtained (5 hours). Most of the ethanol was distilled off, the cooled residue diluted well with water and the product isolated with chloroform. After removal of the chloroform the residual solid was purified by crystallisation from ethanol to yield the product (30 g.) in colourless needles.

2-p-*Bromophenyl*-3-*methyl*-3H-4-*thioquinazolone*

A stirred suspension of 2-*p*-bromophenyl-3-methyl-3*H*-4-quinazolone (44·1 g.) in xylene (400 ml.) was treated with phosphorus pentasulphide (37·4 g.) and the mixture heated under reflux for 2 hours. After cooling 10 per cent sodium hydroxide solution (275 ml.) was added cautiously in portions. The xylene was then removed by distillation in steam and the residual *product* (42 g.) purified by crystallisation from a large volume (2 litres) of ethanol, separated in yellow hair-like crystals, m.p. 167–169°. Found: C, 55·0; H, 3·3; S, 10·2. $C_{15}H_{11}N_2SBr$ requires C, 54·4; H, 3·4; S 9·7 per cent.

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