Some Reactions of 2-Amino-1,4-dihydro-1-methylquinazoline with Electrophilic Reagents

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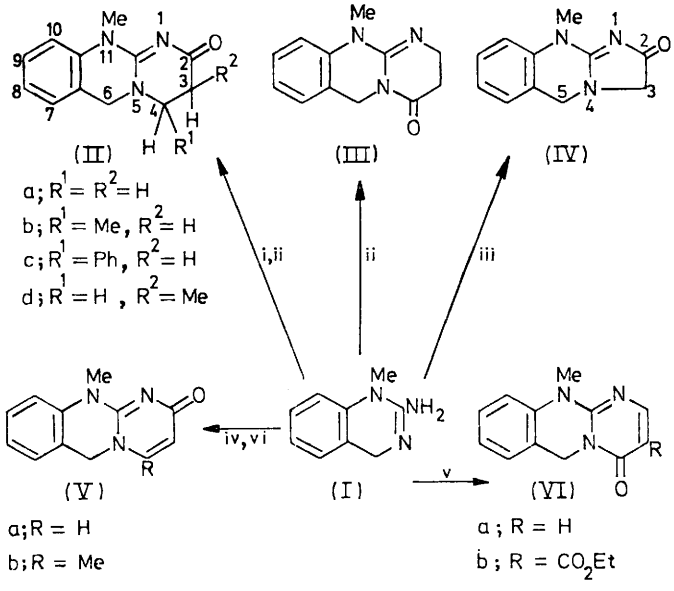
The preparation of the title compound and its reactions with acrylic and propiolic esters, acryloyl chloride, chloro- and aceto-acetic esters, and ethoxymethylenemalonate to give imidazo- and pyrimido-[2,1-*b*]quinazolines are reported. Structures are assigned principally on the basis of ^{1}H n.m.r. and u.v. spectral data.

THE sulphate salt of the previously unreported 2-amino-1,4-dihydro-1-methylquinazoline (I) was prepared by treatment of 2-methylaminobenzylamine with *S*-methylthiouronium sulphate; reactions of (I) with various bifunctional electrophiles have revealed preparative methods for both 2-oxo- (II and V) and 4-oxo- (III and VI) derivatives of 6,11-dihydropyrimido[2,1-*b*]quinazoline. Thus, treatment of (I) with ethyl acrylate in refluxing ethanol yielded the tetrahydro-derivative (IIa) as a white crystalline solid. Similarly, reactions with ethyl crotonate, ethyl cinnamate, and methyl methacrylate afforded compounds (IIb—d). The related 2-oxo-derivatives (V) were obtained by similar treatment of (I) with propiolic ester or ethyl acetoacetate. The unsubstituted derivative (IIa) could also be prepared, although in lower yield (31%), by treatment of (I) with freshly distilled acryloyl chloride in dimethylformamide solution. Also obtained from this reaction, in 14% yield, was the isomeric 4-oxo-derivative (III); the related 4-oxo-dihydro-compounds (VI) were readily obtained from (I) and diethyl ethoxymethylenemalonate.



Reagents: i, $R^1CH{:}CR^2{\cdot}CO_2Et$(or Me); ii, $CH_2{:}CH{\cdot}COCl$; iii, $ClCH_2{\cdot}CO_2Et$; iv, $CH{:}C{\cdot}CO_2Et$; v, $EtO{\cdot}CH{:}C(CO_2Et)_2$; vi, $MeCO{\cdot}CH_2{\cdot}CO_2Et$.

The yields, m.p.s, and spectroscopic data (i.r., u.v., and ^{1}H n.m.r.) for these and other compounds described are recorded in Tables 1 and 2.

The structural assignments are based mainly on the n.m.r. spectral data. Thus in the n.m.r. spectrum of (IIa) in trifluoroacetic acid, the four pyrimidone ring protons (at C-3 and C-4) were observed as a typical two-triplet A_2X_2 system, and the methylene protons at C-6 gave a singlet at τ 4·97 (Table 1). The spectra of (IIb) and (IIc) were more complex. In the former, the C-4 proton was further coupled to the adjacent methyl group and gave a multiplet at τ 5·62, whilst in the latter this proton was the X part of an ABX system and gave rise to a well defined quartet at τ 4·52. In both examples the C-6 methylene protons gave AB quartets, presumably because of the asymmetry at C-4. The protons at C-6 in (IId), although more distant from the asymmetric centre, now at C-3, also gave rise to an AB quartet.

The n.m.r. spectrum of (III) in deuterium oxide showed an A_2X_2 coupling pattern for the C-2 and C-3 protons, similar to that observed for the C-3 and C-4 protons of (IIa) in both deuterium oxide and trifluoroacetic acid. The structure was assigned in the light of the spectrum of the corresponding protonated species (VII) which revealed additional coupling of the C-2 methylene protons (multiplet at τ 5·90). This coupling is clearly not possible in (VIII), the hypothetical protonated species derived from (IIa).

Reactions analogous to those described have been reported previously for 2-aminopyridine,[1-5] 3-aminopyridazine,[6] and various other amino-heterocycles.[7] Thus, the reactions of (I) with derivatives of acrylic ester to give (II) are analogous to the formation of 3,4-dihydropyrido[1,2-*a*]pyrimidin-2-one from 2-aminopyridine and ethyl acrylate,[1,2] where initial attack by the β-carbon atom of the electrophile also occurs at the ring nitrogen. In the case of acryloyl chloride, competition for the two electrophilic sites presumably accounts for the formation of both (II) and (III).

The imidazo[2,1-*b*]quinazoline (IV) was obtained by treatment of (I) with ethyl chloroacetate in refluxing ethanol. The n.m.r. spectrum of the protonated species in trifluoroacetic acid showed a singlet at τ 5·26 for the C-3 methylene protons, in agreement with this formu-

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lation. The alternative 3-oxo-structure is excluded since coupling between the C-2 methylene protons and the adjacent NH would be expected in the corresponding protonated species, by analogy with the C-2 protons in (VII).

Similarly, treatment of (I) with ethyl propiolate afforded (Va) in 45% yield. Evaporation of the filtrate left a red oil containing one major component (t.l.c.), thought to be mainly the uncyclised *trans*-derivative (IX). The n.m.r. spectrum of the unpurified oil in deuteriochloroform revealed the presence of an ethyl ester group and two *trans*-olefinic protons (doublets centred at τ 4·55 and 1·4, J 14 Hz). Ethyl propiolate has been reported [3,4] to react in a similar manner with 2-aminopyridine, to give pyrido[1,2-*a*]pyrimidin-2-one and a noncrystalline uncyclised *trans*-derivative with the imino-structure analogous to (IX). The relationship between (IIa) and (Va) was established by dehydrogenation of (IIa) (palladium–charcoal in refluxing xylene) to give (Va) in good yield. The isomeric 4-oxo-compound (VIa) was obtained by acidic hydrolysis and decarboxylation of the ester (VIb). This ester was produced at room temperature in a rapid (<2 min.) reaction which ensued when (I) was treated with diethyl ethoxymethylenemalonate in ethanolic solution. The comparable reaction with 2-aminopyridine has been reported [1,5] to proceed in the same manner to give ethyl 4-oxopyrido[1,2-*a*]pyrimidine-3-carboxylate.

Significant differences were observed in the u.v. spectra of (Va) and (VIa). Thus the 2-oxo-derivative (Va) showed a maximum at 236 nm. (ε 20,050) with a shoulder at 267 nm. (ε 13,900), whilst the 4-oxo-isomer (VIa) exhibited maxima at considerably longer wavelengths, 254 (ε 8700) and 314 (ε 10,200) nm. A similar

TABLE 1

^{1}H N.m.r. spectra of compounds (II)—(VI) *

			τ Values					
	R^1	R^2	2-H	3-H	R^2	4-H	R^1	6-H
(IIa)	H	H		6·78(t)	6·78(t)	5·82(t)	5·82(t)	4·97(s)
(IIa) [a]				6·85(t)	6·85(t)	5·82(t)	5·82(t)	4·97(s)
(IIb)	Me	H		7·03(q)	6·38(q)	5·62(m)	8·38(d)	4·90(q)
(IIc)	Ph	H		6·58(q)	6·14(q)	4·52(q)	2·3(m)	4·98(q)
(IId)	H	Me		6·60(m)	8·52(d)	6·0(m)	6·0(m)	4·96(q)
(III)			5·90(m)	6·78(t)				4·74(s)
(III) [a]			6·00(t)	6·89(t)				4·89(s)
(IV)				5·26(s)				4·91(s) [b]
(IV) [a]				5·52(s)				5·14(s) [b]
	R							
(Va)	H			3·87(d)			1·57(d)	4·95(s)
(Vb)	Me			3·51(s)			7·34(s)	4·68(s)
(VIa)	H		2·02(d)	3·41(d)			3·41(d)	4·60(s)
(VIb)	CO_2Et		0·95(s)				5·3(q), 8·5(t)	4·45(s)

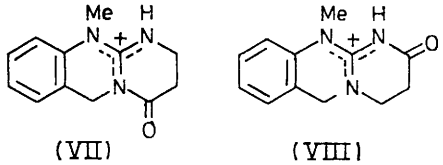
[a] In D_2O solution. [b] 5-H.
* Recorded with a Varian A60 spectrometer, with tetramethylsilane as internal standard; solutions in trifluoroacetic acid.

TABLE 2

Compound	Yield (%)	M.p.	Carbonyl $\nu_{max.}$ in cm.$^{-1}$ (Nujol mull)	$\lambda_{max.}$ (MeOH) in nm. (ε)	Formula	Found (%) C	H	N	Required (%) C	H	N
(IIa) [a]	64	181—182° 226—228 [b]	1658 1755 [b]	265 (13,360) 280sh (13,320)	$C_{12}H_{13}N_3O$	66·9	6·1	19·4	66·95	6·1	19·5
(IIb) [c]	62	145—146	1648	262 (17,100) 280sh (17,000)	$C_{13}H_{15}N_3O$	68·35	6·6	18·1	68·1	6·6	18·3
(IIc) [c]	41	176—178	1640	261 (16,800) 280sh (16,760)	$C_{18}H_{17}N_3O$	73·9	5·8	14·3	74·2	5·9	14·4
(IId) [a]	75	176—177	1658	261 (18,400) 280sh (18,350)	$C_{13}H_{15}N_3O$	68·0	6·35	18·5	68·1	6·6	18·3
(III) [d]	14	273—275 [b]	1730 [b]	265 (12,400)	$C_{12}H_{13}N_3O$,HCl	57·1	5·9	16·45	57·25	5·6	16·7
(IV) [a]	30	182—183	1688	253 (9550)	$C_{11}H_{11}N_3O$	65·3	5·4	21·1	65·7	5·5	20·9
(Va) [a]	45	180—182	1639	236 (20,050) 267sh (13,900)	$C_{12}H_{11}N_3O$	67·3	5·3	19·5	67·2	5·2	19·8
(Vb) [a]	32	248—250	1650	238 (18,000) 272sh (9000)	$C_{13}H_{13}N_3O$	68·4	5·9	18·05	68·7	5·7	18·5
(VIa) [d]	68	237 [b]	1720 [b]	254 (8700) 314 (10,200)	$C_{12}H_{11}N_3O$·HCl	57·5	4·85	16·9	57·7	4·8	16·8
(VIb) [d]	66	180—182	1675 1700	230 (10,400) 248 (10,000) 336 (17,580)	$C_{15}H_{15}N_3O_3$	62·95	5·3	14·6	63·15	5·3	14·7

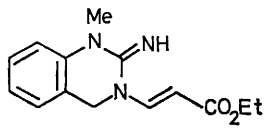
[a] Recrystallised from ethyl acetate containing a trace of methanol. [b] HCl salt. [c] Recrystallised from ethyl acetate–light petroleum (b.p. 60—80°). [d] Recrystallised from ethanol.

bathochromic shift was observed [1] in the longer wavelength absorption maxima of pyrido[1,2-*a*]pyrimidin-2-one and its 4-oxo-isomer [$\lambda_{max.}$ (MeOH) 325 and 340 nm., respectively]. Treatment of compound (I) with ethyl



(VII)

(VIII)



(IX)

acetoacetate in refluxing ethanol gave the pyrimidoquinazoline (Vb); this structure was assigned on the basis of the u.v. spectrum, which was virtually identical with that of the unsubstituted derivative (Va). In contrast, the reaction of ethyl acetoacetate with 2-aminopyridine is reported [1,5] to proceed in the opposite manner to give 2-methylpyrido[1,2-*a*]pyrimidin-4-one.

EXPERIMENTAL

2-Methylaminobenzylamine.— 2-Methylaminobenzamide [8] (30 g.) was slowly added to M-diborane in tetrahydrofuran (900 ml.); the mixture was heated under reflux for 8 hr., then cooled. The excess of diborane was cautiously decomposed with 5N-hydrochloric acid (250 ml.), the solvent was evaporated off, and the residue was dissolved in water. Insoluble tars were filtered off and the filtrate was basified and extracted with methylene chloride. The extract was dried, filtered, and evaporated; the residual oil was distilled to give the product (15·2 g., 62%), b.p. 75—77°/0·1 mm. Addition of ethereal hydrogen chloride afforded the *dihydrochloride*, m.p. 208—210° (Found: C, 46·2; H, 6·5; Cl, 33·8; N, 13·1. $C_8H_{12}N_2$,2HCl requires C, 46·0; H, 6·75; Cl, 33·9; N, 13·4%).

2-Amino-1,4-dihydro-1-methylquinazoline (I).—2-Methylaminobenzylamine (6·80 g.) was refluxed with *S*-methylthiouronium sulphate (10·0 g.) in ethyl Cellosolve (175 ml.) for 24 hr. The solution was then concentrated and cooled; the white precipitate yielded the sulphate salt of (I), m.p. 291—295° (from acetone–water). Basification with aqueous sodium hydroxide and extraction with chloroform, followed by drying and evaporation of the extract afforded a white residue, which gave the pure *product* (4·9 g., 61%), m.p. 171—173° (from benzene), $\lambda_{max.}$ 250 nm. (ε 5800), $\nu_{max.}$ (Nujol) 3448 and 1665 cm.$^{-1}$, pK_a 10·76 (±0·04) (Found: C, 66·6; H, 6·7; N, 25·7. $C_9H_{11}N_3$ requires C, 67·05; H, 6·8; N, 26·1%). The tautomeric composition of this compound has not been determined.

6,11-Dihydro-11-methyl-4H-pyrimido[2,1-b]*quinazolin-2(3H)-one* (IIa).—A mixture of ethyl acrylate (5·3 g.) and 2-amino-1,4-dihydro-1-methylquinazoline (I) (8·0 g.) was dissolved in ethanol (50 ml.) and heated under reflux for 6 hr. Evaporation left a white residue that yielded the product (6·9 g., 64%) [from ethyl acetate–methanol (10 : 1)].

The following compounds were obtained similarly. *6,11-Dihydro-4,11-dimethyl-4H-pyrimido*[2,1-b]*quinazolin-2(3H)-one* (IIb) was obtained from compound (I) and ethyl crotonate, *6,11-dihydro-11-methyl-4-phenyl-4H-pyrimido*[2,1-b]*quinazolin-2(3H)-one* (IIc) from ethyl cinnamate, *6,11-dihydro-3,11-dimethyl-4H-pyrimido*[2,1-b]*quinazolin-2(3H)-one* (IId) from methyl methacrylate, *5,10-dihydro-10-methylimidazo*[2,1-b]*quinazolin-2(3H)-one* (IV) from ethyl chloroacetate, *6,11-dihydro-11-methyl-2H-pyrimido*[2,1-b]*quinazolin-2-one* (Va) from ethyl propiolate, and *6,11-dihydro-4,11-dimethyl-2H-pyrimido*[2,1-b]*quinazolin-2-one* (Vb) from ethyl acetoacetate. *Ethyl 6,11-dihydro-11-methyl-4-oxo-4H-pyrimido*[2,1-b]*quinazoline-3-carboxylate* (VIb) was prepared by the reaction of (I) with diethyl ethoxymethylenemalonate in cold ethanol; the product precipitated out from solution after 2 min. without the necessity of refluxing the mixture.

6,11-Dihydro-11-methyl-4H-pyrimido[2,1-b]*quinazolin-4-one* (VIa).—The ester (VIb) (2·0 g.) was added to 5N-hydrochloric acid (30 ml.) and the mixture was warmed on a steam-bath for 18 hr. Evaporation to dryness, and recrystallisation of the residue from ethanol gave the *hydrochloride* of the product (1·2 g.).

6,11-Dihydro-11-methyl-2H-pyrimido[2,1-b]*quinazolin-4(3H)-one* (III).—Freshly distilled acryloyl chloride (1·9 g.) was slowly added with stirring to a solution of compound (I) (3·2 g.) in dry dimethylformamide (75 ml.); the mixture was heated at 100° for 3·5 hr., then cooled. The solvent was removed and water (100 ml.) was added to the residue. The solution was made just basic with sodium carbonate and extracted with ether; the extract was dried, filtered, and evaporated. Addition of ethereal hydrogen chloride to the residue gave the *hydrochloride* salt of the product (III) (0·7 g.).

The basic aqueous phase was then extracted with chloroform; the extract was dried, filtered, and evaporated to give a red oil. Column chromatography on neutral alumina in chloroform gave the 2-oxo-isomer (IIa) (1·3 g., 31%).

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