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N-(6,7-METHYLENEDIOXY-3-QUINAZOLINIO)AMIDATES—I† SYNTHESIS SPECTRA AND SOME DARK REACTIONS

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Abstract—The title compounds **5** and/or their dimers **6**, obtained by ring closure of the diacyl derivatives **4**, exist in monomeric and dimeric forms in aprotic solvents, the positions of equilibria being dependent on the nature of the substituents and solvent. In several cases the pure monomeric and dimeric forms were obtained in the crystalline state. In protic solvents adducts of types **7** and **12** are formed, some of which are stable in the crystalline state. IR, NMR and mass spectra of compounds **5**–**7** and **12**, and several dark reactions, are discussed.

In continuation of our studies into the chemistry of heterocyclic ammonioamidates of the π-deficient type[1-4] our attention has been turned to compounds containing a quinazoline ring as the heterocyclic nucleus. In order to facilitate assignments of the NMR spectra of the compounds synthesised, a methylenedioxy group was introduced into positions 6 and 7 of the quinazoline ring. In the present paper we wish to report on the synthesis (Scheme 1), spectra and certain dark reactions of the *N*-(6,7-methylenedioxy-3-quinazolinio)-amidates **5**; their photochemistry will be discussed in subsequent papers.

6-Nitropiperonal **1a**[5] and the corresponding methyl ketone **1e**[6] were selected as the starting compounds for the synthesis of compounds **5**. **1a** reacted smoothly with hydrazides in refluxing ethanol to yield the N-acylhydrazones **2a–c**; the reaction of **1e** with ethyl carbazate required prolonged refluxing in this solvent. The acylhydrazones **2a–c** and **2e** were reduced with excess $Na_2S_2O_4$ at 65–70° in aqueous EtOH to yield the compounds **3**. *N*-Acylation of the latter with acetic and acetic formic anhydride, respectively, in refluxing CH_2Cl_2 furnished the diacyl derivatives **4a–f**.§ Ring closure of the latter was effected with a slight excess of $SOCl_2$ or $POCl_3$ at 0°. The resulting hydrochlorides were treated with base to yield, depending on the nature of the substituents R, R^2, R^4, as well as of the solvent and the conditions used, the quinazolinioamidates **5**, their dimers **6**, or adducts **7** of the former with alcohols or water; in some cases only mixtures of the amidates with their dimers were obtained. The proof of structure of the different types of products as well as their differentiation are based mainly on their IR, NMR and mass spectra as will be discussed below.

Support for the structure of the dimers as well as of the adducts comes from reasoning by analogy. Thus quinazoline-3-oxides (**8**) which are closely related to the amidates **5**, are known from the literature[7] to add easily a molecule of water and to form adducts **9**. Furthermore, an analogous adduct **12**, whose structure is conclusively proven by NMR evidence (see below), is formed from **5c** with NH_3. On the other hand, it appears reasonable to assume that, in the absence of other nucleophiles, the amidates are stabilized by dimerization, between carbon atoms C-4 of **5** and exocyclic nitrogen atoms. Moreover, monomer⇌dimer equilibria which are closely related to the type under discussion but differ from the latter by the absence of the N-acyl groups, e.g. the equilibrium **10**⇌**11**, have been known for some time.[8] Conclusive proof for the structure of the dimers is expected from X-ray structure determination of **6d** which is presently in progress.

The different transformation products **6**, **7** of the amidates **5** and the conditions of their mutual conversions have been studied thoroughly in the **a** series. Although our studies in the **b–f** series were less complete, the qualitatively analogous behaviour of the compounds of the latter series is beyond doubt although there exist considerable quantitative differences between the different series.

Ring closure of **4a** by the method mentioned above and subsequent recrystallization from anhydrous methanol furnished the hydrochloride of the 1:1 methanol adduct (**7a**; R′ = Me). The proton is assumed to be attached to N-1 of **7a**. When this product was treated with water, it was transformed into the hydrochloride of the corresponding hydrate (**7a**; R′ = H). When recrystallized from methanol, the hydrate was converted back into the methanol adduct.

Treatment of the hydrochloride of the hydrate with alkali in the presence of water furnished the hydrate (**7a**; R′ = H) itself. The latter could not be recrystallized because it readily undergoes loss of water and becomes transformed into the dimer **6a** on recrystallization from benzene or toluene. When **6a** was recrystallized from EtOH, it became converted into the 1:1 ethanol adduct (**7a**; R′ = Et). **6a** appears, obviously for steric reasons, to be incapable of adding t-BuOH or i-PrOH; when recrystallized from either of the latter solvents, it is transformed into the more polar monomeric form **5a**. All these changes are reversible. E.g. by recrystallization from toluene, **5a** is reconverted into **6a**, and treatment of

†Part V of Electron Deficient Heteroaromatic Ammonioamidates. Refs 1–4 are considered as parts I–IV of this series.

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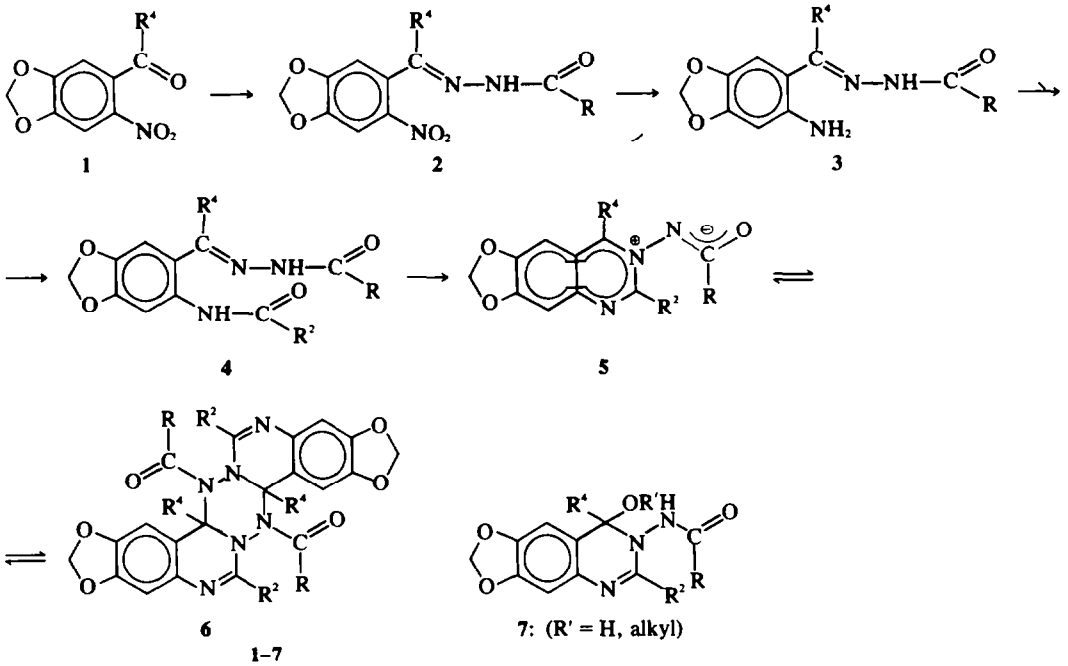
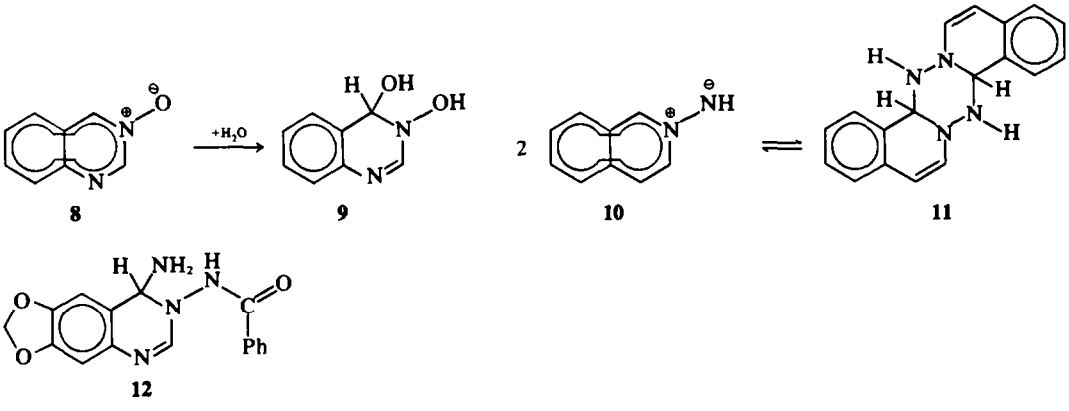
§The synthesis of compounds **2a**, **3a** and **4a** was designed and accomplished first by B. Agai in this Laboratory. He also made the initial ring closure studies of **4a**.



1–7

	a	b	c	d	e	f
R^4	H	H	H	H	Me	Me
R	OEt	OCH_2Ph	Ph	OEt	OEt	OEt
R^2	Me	Me	Me	H	H	Me

Scheme 1.



the latter with ethanolic or methanolic hydrogen chloride and subsequently, with water furnishes the hydrochloride of the hydrate (**7a**; R′ = H).

The adducts **7a** are readily distinguished both from the amidate **5a** and the dimer **6a** of the latter on the basis of their elemental compositions and their IR spectra; NH bands are found only in the spectra of the adducts. In addition, an OH band is also present in the spectrum of the hydrate. The amidate **5a** and its dimer **6a** may also be easily distinguished from each other on the basis of their IR spectra since only the spectrum of the dimer exhibits an amide I band. Similar differences exist between the IR spectra of the type **5**, **6** and **7** compounds in the **b**–**f** series. Considerable differences exist also between the NMR spectra of the type **5**, **6** and **7** compounds; for these and the mass spectra see below.

In the **b** series the pure dimeric and hydrated forms were obtained by decomposing the hydrochloride with bases under properly selected conditions. The dimer **6b** and the amidate **5b** could be converted into each other by thermal treatment and by recrystallization from benzene, respectively. The dimer was obtained also by dehydration of the hydrate which was easily effected by recrystallization from benzene.

In the **c** series only the amidate **5c** and hydrate forms (**7c**; R′ = H) have been obtained. Decomposition of the hydrochloride by base in the **d** series furnished the dimer **6d** which could be transformed by thermal treatment into the amidate **5d**. Recrystallization of **6d** from EtOH furnished (**7d**; R′ = Et). Decomposition of the hydrochlorides of the **e** and **f** series furnished yellow crystalline products which, as judged from the medium intensity amide I band in their IR spectra, contained mainly the amidates **5e** and **f**, respectively, and moderate amounts of the corresponding dimers.

In $CDCl_3$ solutions equilibria between the amidate and

dimeric forms are rapidly established even at room temperature. The NMR spectra of the two pairs of compounds **5a** and **6a**, and **5b** and **6b** are therefore completely identical. By comparing the intensities of characteristic signals the ratio of the two forms may be estimated. E.g. **5a** exists in $CDCl_3$ solution at 35° approximately to 30% as such and to 70% in the dimeric form. Approximately the same ratio of the amidate and dimeric forms was found, under identical conditions, in the **d** series, while in the **b** series the ratio of the two forms is almost exactly reversed (2:1), and **5c**, **5e** and **5f** do not show any tendency to form dimers in $CDCl_3$ solution. The influence of the solvent on the position of the equilibria is shown by the fact that, while forming a 1:2 equilibrium mixture with its dimer in $CDCl_3$, **5d** exists as the practically pure dimer in CCl_4 as well as in benzene solution. A molecular weight of 546 ± 10% was found for the latter compound in benzene solution by osmometry, the calculated value for **6d** being 490.

Increasing solvent polarity and increasing bulk of the substituents R and R^4 thus appear, as might be expected, to stabilize the monomeric amidate forms with respect to their dimers.

In protic (e.g. methanol) or non-anhydrous aprotic (e.g. DMSO) solvents the type **7** adducts of **5a** are present either as the only forms or in equilibrium with one or both of **5a** and **6a**. The NMR spectrum of (**7a**; R′ = H) in DMSO-d_6, e.g. reveals the presence of all three forms. In CD_3OD solutions however, it was only the amidates **5** which, in agreement with the high polarity of the solvent, could be detected in addition to the adduct **7** by inspection of the NMR spectra. The ratio of the two forms depends on the relative stability of the former as discussed above.

A similar adduct **12** is formed, as shown by the NMR spectrum of the solution, when **5c** is dissolved in liquid ammonia. For related adducts see refs 9 and 10.

NMR spectra

The $CDCl_3$ NMR spectra of **5a** and **6a** (Table 1) exhibit two sets of signals corresponding to an equilibrium mixture of these two compounds. The signal of primary diagnostic value is the 0·3H intensity singlet at δ 9·60 ppm which evidently comes from R^4 = H of the amidate form. The intensities of all signals are compared with the 2H + 3H intensity signals of the R = Et group whose positions are coincidentally identical for **5a** and **6a**. Both the R^2 = Me and the O–CH_2–O signals are doubled. The two pairs of signals may, on the basis of their intensity ratios (3:7), be assigned to **5a** and another form of this compound which, in the absence of a protic solvent, must be identical with the dimer **6a**. Additional proof for the presence of the dimeric form comes from the IR spectrum ($CHCl_3$) which, apart from several medium to weak bands due to the amidate form, is practically identical with the IR spectrum (KBr) of **6a**. The ratio of the two forms may conveniently be estimated by comparing the intensities of the two R^2 = Me or of the two O–CH_2–O signals.

The $CDCl_3$ NMR spectra of the remaining compounds shown in Table 1 are largely similar. In the case of **5d** and **6d** the CH_2 parts of the EtO signals of the two compounds do not coincide (while the CH_3 parts do), and a similar situation prevails in the case of **5b** and **6b** where it is the CH_2 parts of the $PhCH_2O$ signals which do not coincide.

The CD_3OD NMR spectrum of compound **6a** (Table 2) also exhibits two methyl and two O–CH_2–O singlets. The assignment of the lower field signals of very low intensity to the amidate form **5a** on the basis of a comparison of their positions with those of the corresponding signals in the $CDCl_3$ spectrum is straightforward. The high intensity—high field methyl singlet cannot be assigned to the dimeric form **6a** because its position is very different from that of the methyl singlet of **6a** in the $CDCl_3$ spectrum. Consequently, it must be assigned to the CD_3OD adduct of **5a** (= **7a**; R′ = CD_3, with –ND– instead of –NH–). The positions of the O–CH_2–O signals of the dimer **6a** in $CDCl_3$ and of the CD_3OD adduct in CD_3OD, on the other hand, are almost identical. By comparing the intensity ratios of the corresponding signals, the ratio of the two forms (**7a**; R′ = CD_3) and **5a** under the conditions applied was found to be 95:5. As a consequence of its low concentration, the R^4 = H signal of **5a** disappears in the noise, and the ArH signal of **5a** is only just observable.

When the CD_3OD solution was evaporated to dryness and the residue was dissolved in $CDCl_3$, the resulting solution had an NMR spectrum which was completely identical with those of compounds **5a** and **6a**, which proves that the formation of the adducts of type **7** is reversible.

The CD_3OD spectra of the remaining type **5** and/or **6** compounds (Table 2) are generally similar to those discussed above and clearly prove the presence of

Table 1. NMR spectra in $CDCl_3$ (TMS, δ values)

Compound introduced	R	R^2	CH_2 (O, O)	R^4	ArH	Compounds present
6a or **5a**	1·36, t + 4·3, q, J = 7Hz	1·75, s 2·95, s	6·00, s 6·28, s	6·72, s[a] 9·60, s	6·95, s + 7·05, s[a] 7·18, s + 7·35, s	**6a** + **5a**, 7:3
6b or **5b**	5·30, s 5·24, s + 7·4, s	1·7, s 2·89, s	5·98, s 6·23, s	6·70, s[a] 9·58, s	6·92, s + 7·00, s[a] 7·12, s + 7·31, s	**6b** + **5b**, 1:2
5c	*o*-protons: ~8·3, m other protons: ~7·55, m	3·08, s	6·34, s	9·62, s	7·21, s + 7·40, s	**5c**
6d	1·35, t + 4·36, q, 4·16, q, J = 7Hz	6·7, s[a] 9·0, s	5·95, s 6·24, s	6·78, s[a] 10·1, s	6·85, s + 6·90, s[a] 7·12, s + 7·35, s	**6d** + **5d**, 2:1
6d[b]	1·38, t + 4·3, q, J = 7Hz	6·6, s[a]	5·93, s	6·68, s[a]	6·74, s + 6·8, s	**6d**
5e + **6e**	1·36, t + 4·23, q, J = 7Hz	9·04, s	6·33, s	2·98, s	7·4, s	**5e**
5f + **6f**	1·37, t + 4·29, q, J = 7Hz	2·9, s or 2·95, s	6·30, s	2·8, s or 2·95, s	7·34, s + 7·36, s	**5f**

[a]The assignment of the three signals in the 6·6–7·3 region to R^4 = H and the two ArH's in **6a–c** as well as of the four signals in the 6·6–6·9 region to R^2 = R^4 = H and the two ArH's in **6d** is arbitrary.

[b]CCl_4 solution.

Table 2. NMR Spectra in CD_3OD (δ scale, reference: CHD_2OH = 3·35 ppm)

Compound introduced	R	R^2	CH_2 O O	R^4	ArH	Compounds present
6a	1·28, t + 4·25, qu, J = 7Hz	2·2, s 2·8, s	5·95, s 6·3, s	5·92, s	6·7, s 7·4, s (?)	**7a** ($R' = CD_3$) + **5a** , ratio 95:5
6b	5·26, s, + 7·43, s	2·2, s 2·78, s	6·02, s 6·4, s	5·96, s	6·73, s	**7b** ($R' = CD_3$) + **5b** , about the same ratio as above
5c	*o*-protons: ~8·05, m, other protons: ~7·5, m	2·3, s 2·87, s	5·96, s 6·3, s	6·03, s 9·36, s	6·66, s + 6·71, s 7·37, s + 7·47, s	**7c** ($R' = CD_3$) + **5c** , ratio 1:2
5c[a]	*o*-protons: ~7·97, m other protons: ~7·35, m	1·91, s	5·92, s	5·37, s	6·47, s + 6·69, s	**12**
5c[b]	*o*-protons: ~8·05, m other protons: ~7·35, m	c/	5·92, s	5·37, t (J = 8Hz)	6·48, s + 6·70, s	**12**
6d	1·41, t + 4·22, qu, J = 7Hz	7·33, s (?)	5·92, s	5·92, s	6·62, s	**7d** ($R' = CD_3$)
5e + **6e**	1·31, t + ~4·2, m J = 7Hz	7·40, s 9·00, s	6·02, s 6·45, s	d/ —	6·67, s + 6·92, s 7·50, s + 7·70, s	**7e** ($R' = CD_3$) + **5e** , ratio 47:53
5f + **6f**	1·35, t + 4·22, qu, J = 7Hz	2·21, s 2·82, s	5·98, s 6·35, s	d/ —	6·6, s 7·35, s + 7·67, s	**7f** ($R' = CD_3$) the amidate form + **5f**, being the main component
7a ($R' = H$)[c]	1·21, t + 3·97, qu 1·27, t + 4·27, qu 1·21, t + 3·97, qu } J = 7Hz	2·03, s 1·64, s 2·67, s	{ 5·97, s + 5·90, s 6·31, s	5·90, s 6·50, s 9·60, s	6·59, s + 6·62, s 6·74, s + 6·90, s 7·35, s + 7·44, s	**7a** ($R' = H$) + **6a** , ratio 1:0·4:1 + **5a**

[a] Solvent: liquid NH_3, reference: NH_3 (δ 0·95 ppm).
[b] Solvent: liquid NH_3, 2 equivalents of KNH_2 added, reference: NH_3 (δ : 0·95 ppm).
[c] See text.
[d] The signals of the R^4 = Me group are, as a result of deuteration, not observable.
[e] Solvent: DMSO-d_6, reference: DMSO-d_5 (δ 2·50 ppm).

equilibrium mixtures of the corresponding type **7** (R′ = CD_3, with –ND– instead of –NH–) and **5** compounds in solution, the positions of the equilibria being dependent on the nature of the substituents R^2, R^4 and R. In the **e** and **f** series the signals of the R^4 = Me groups are not observable, which is the result of rapid and practically complete deuteration of these groups. The H–D exchange obviously takes place in the amidate forms where it is rendered possible by the neighbouring cationic centre.

The NMR spectrum of **5c**, measured in liquid NH_3, is also shown in Table 2. It is completely analogous to that part of the CD_3OD spectrum of the same compound which originates from its CD_3OD adduct, and proves that **5c** exists in liquid NH_3 as the practically pure adduct **12**. The coupling between the protons of the H–C(4)–NH_2 moiety of **12**, which conclusively proves the site of attachment of the NH_2 group, could be observed when the spectrum was run in the presence of two equivalents of KNH_2.†

The NMR spectrum of **7a** (R′ = H) in DMSO-d_6 (Table 2) is exceptional because it demonstrates the simultaneous presence of three forms, viz. of the hydrate, the amidate **5a** and the dimer **6a**, the latter two being formed as a result of partial dehydration by the solvent. When D_2O was added, the signals corresponding to the dimeric form disappeared, and those of the amidate form became considerably less intense.

The chemical shift data are summarized in Table 3 with special reference to the data of diagnostic value.

Mass spectra

No mass spectrometric evidence of a dimeric structure could be found in any of the compounds investigated. Although introduced as pure dimers and recorded at the lowest possible ion source/sample temperatures, compounds **6a**, **6b** and **6d** gave mass spectra corresponding to the monomeric amidates **5** only. The same was found for two samples which were introduced as mixtures of the monomeric and dimeric forms (**5e** + **6e** and **5f** + **6f**, respectively). These results may indicate that the dimeric forms are transformed into the monomeric amidates by evaporation. This is in accordance with the previously mentioned transformation of **6b** and **6d** into **5b** and **5d**, respectively, by thermal treatment.

†The δ 1·9 ppm region where the R^2 = Me signal should appear, is concealed by the low field spinning side band of the solvent. The doublet at δ 2·2 and 2·6 ppm, observed in the presence of KNH_2, might be the low field part of an AB spectrum and, therefore, indicative of the deprotonation of the R^2 = Me group.

Similar results were obtained for the adducts **7**. In no case a molecular ion corresponding to **7** could be detected. Compound **7a** (R′ = H), when recorded at 160°C, gave rise to a spectrum which was identical with that of **5a**. Recorded at higher ion source/sample temperature (200–250°) the spectrum was changed into that of the corresponding quinazoline, **17**. For compound **7a** (R′ = Et) only the quinazoline spectrum could be obtained. This behaviour may be due to a thermal/catalytic decomposition prior to ionization. However, it has not been possible to obtain similar thermolysis of these compounds in preparative work.

The mass spectra of the hydrochlorides of several compounds have also been recorded. They were all identical with those of the corresponding bases.

The mass spectra of the compounds with R = OEt (**5** or **6**; **a**, **d**, **e** and **f**) are shown in Fig 1. They exhibit abundant molecular ions (most abundant when R^4 = Me) and show in all four cases identical primary fragmentation modes which are in good agreement with the amidate structures **5**.

The most abundant fragment ion is formed directly from the molecular ion by loss at the elements $NCO_2C_2H_5$ or by successive losses of $\cdot OC_2H_5$ and ·NCO, as indicated by the application of the metastable defocussing technique. The only other important ion in this mass range is due

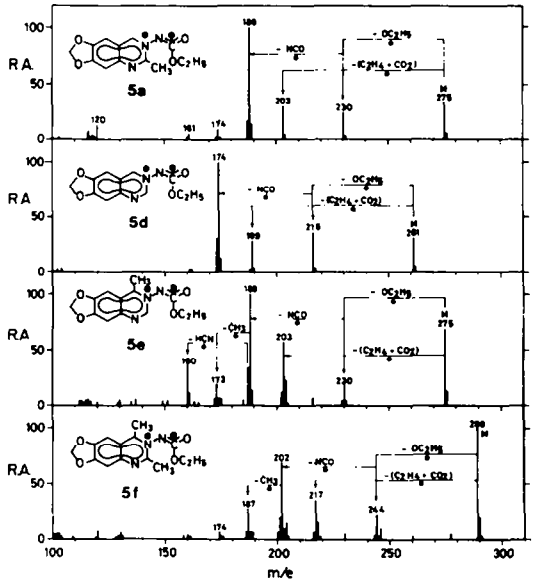
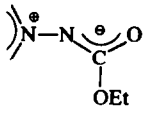


Fig. 1.

Table 3. Summary of NMR data

Group	Solvent \ δ-Value	Amidate form (5)	Dimer (6)	Adduct (7, R′ = H, CD_3)
R^2 = Me	$CDCl_3$	2·9–3·1	1·7–1·75	—
	CD_3OD	2·8–2·9	—	2·2–2·3
	DMSO-d_6	2·7	1·64	2·0
R^2 = H	$CDCl_3$, CCl_4	9·0	around 6·85	—
	CD_3OD	9·0	—	7·4
CH_2 (O, O)	$CDCl_3$	6·25–6·35	5·95–6·00	—
	CD_3OD	6·30–6·45	—	5·92–6·02
	DMSO-d_6	6·31	5·90 or 5·97	5·90 or 5·97
R^4 = H	$CDCl_3$	9·6–10·1	around 6·85	—
	CD_3OD	9·4	—	5·92–6·03
	DMSO-d_6	9·6	6·50	5·90 or 5·97
R^4 = Me	$CDCl_3$	around 2·95	—	—

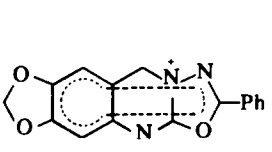
to a rearrangement process involving the elimination of $C_2H_4 + CO_2$ from the molecular ion. These processes are completely analogous to those previously obtained for N - ethoxycarbonyl - N - (2 - isoquinolinio)amide[3] and N - ethoxycarbonyl - N - (1 - quinoxalinio)amide[4] and those reported for N - ethoxycarbonyl - N - (1 - pyridinio)amide[11] and may thus be characteristic processes of the group



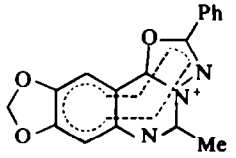
when part of an aromatic system.

The structure of the $[M-NCO_2C_2H_5]^+$ ion corresponds most probably to the molecular ion of the analogous quinazoline. The further decomposition of this ion in the spectra of **a** and **f** is in agreement with that observed for **17** and **18**, respectively, shown in Fig 2.

The mass spectrum of compound **5c** is shown in Fig 3. The initial loss of $R = C_6H_5$ followed by elimination of ·NCO to yield the quinazoline ion at *m/e* 188 is a characteristic feature also in this case. Additionally, important $[M-H]^+$ and $M-Me]^+$ ions are formed. These may be represented by the following structures:



$[M-Me]^+$



$[M-H]^+$

Analogous $[M-H]^+$ and $[M-Me]^+$ ions were reported[11] for N - (2 - methyl - 1 - pyridinio) - benzamidate, in which case also the direct loss of C_6H_5CN was noted (cf Fig 3).

The molecular ion of the compounds with $R = OCH_2Ph$ (**5b** and **6b**) appeared to be extremely unstable. At mass numbers higher than that of the quinazoline ion (*m/e* 188) the spectrum contained only very weak and unreproducible peaks. Thus, the -NCRO moiety is lost very readily yielding the quinazoline ion, and the resulting spectrum corresponds to that of **17** with additional peaks at *m/e* 108, 107, 91, 79 and 77, corresponding to benzyl alcohol. The possibility of a thermal decomposition cannot be completely excluded (cf ref. 11).

Reactions

The catalytic reduction of compounds **6a**, **7a**·HCl (R' = Me) and **7b**·HCl (R' = Me)† may, depending on the nature of the catalyst, the solvent and the conditions used, give rise to the formation of a variety of products, such as the carbamates **13** and **16**, the amine **14**, the dihydroquinazoline **15** and the quinazoline **17**. A by-product of the reduction is ethyl carbamate which is always present in the reaction mixtures, if **15** and/or **17** are formed. The carbamate **13** or its HCl salt were formed as the first reduction product of **6a** and **7a**·HCl (R' = Me), when

†These were the compounds *introduced*; they are certainly modified by reaction with the solvents used, as discussed above for **6a**. Furthermore, in the case of the type **7** compounds exchange of the original OR' groups with solvent ethanol may take place.

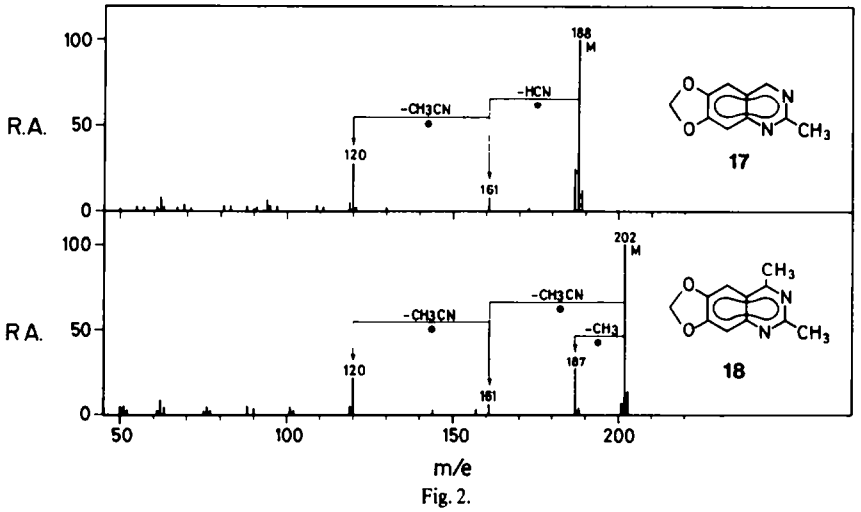


Fig. 2.

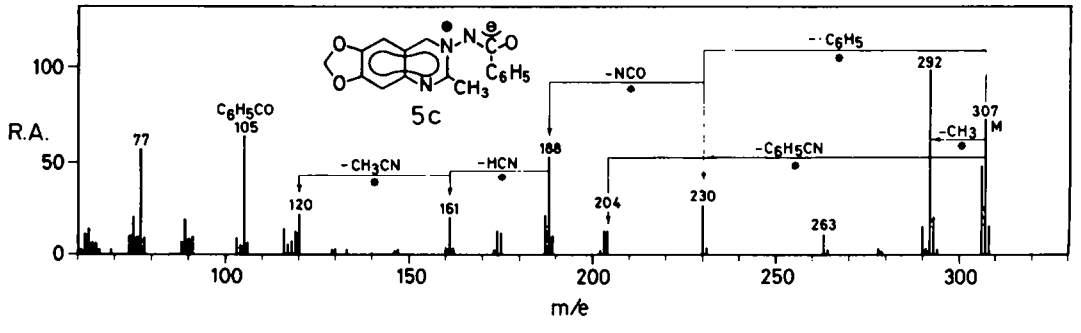


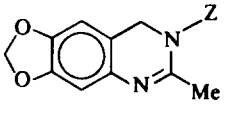
Fig. 3.

Pd–C or slightly alkaline Raney nickel were used as catalysts in aqueous hydrochloric acid or in organic solvents at room temperature. Small amounts of 15·HCl and ethyl carbamate were formed as the by-products when 7a·HCl (R′ = Me) was reduced in ethanol at room temperature in the presence of a Raney nickel catalyst. While 13·HCl proved stable towards hydrogen in the presence of Pd–C at room temperatures the free base 13 is further reduced, to yield the carbamate 16, the reduction being strongly dependent on the organic solvent used (see Experimental). The structure of 13 follows from its spectral properties as well as from its alternative synthesis starting with 14 and ethyl chloroformate.

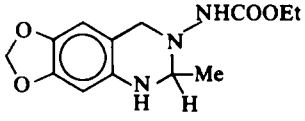
When either 6a or 13 were reduced in hot ethanolic solutions in the presence of Raney nickel, 17 and ethyl carbamate were obtained as the main products, as well as small amounts of 15. An authentic sample of 17 was synthesised by an adaptation of the method of Bogert and McColm.[12] The formation of 17 from 13 does *not* take place by simple thermal elimination of ethyl carbamate, since no trace of 17 is formed if ethanolic solutions of 13 are refluxed in the absence of Raney nickel; it takes place rather by reductive fission of the N–N bond of 13 to yield 15 which, as shown by separate experiments, is in equilibrium with 17 under the conditions applied, the equilibrium being considerably shifted towards the fully aromatic compound 17. Reduction of 7a·HCl (R′ = Me) under the same conditions led to the formation of a similar mixture in which the dihydroquinazoline 15 was, however, replaced by its HCl salt.

Reduction of 7b·HCl (R′ = Me) in ethanol in the presence of a Pd–C catalyst furnished the hydrochloride of 14.

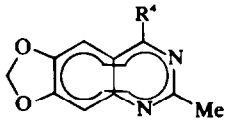
When 6a was refluxed with acrylonitrile in pyridine solution, the 1,3-dipolar cycloadduct 19 was formed, as conclusively proven by the doublet of the 11*b* proton in the NMR spectrum.



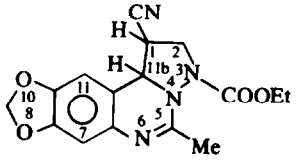
13: Z = NHCOOEt
14: Z = NH_2
15: Z = H



16



17: R^4 = H
18: R^4 = Me



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EXPERIMENTAL

IR, mass, NMR and UV spectra have been obtained with the aid of Hungarian Optical Works (Budapest) Type Spectromom 2000, Zeiss (Jena) Type UR-10 and Perkin-Elmer Type 457 IR, AEI Type MS 902 mass (electron energy 70 eV), Varian Type A-60, Jeol Type JNM-C-60, Perkin-Elmer Type R12 (60 MHz), and Varian Type XL-100 (100 MHz) NMR, and Hungarian Optical Works (Budapest) Type Spectromom 201 UV Spectrometers, respectively. The molecular weight measurement was performed with a Packard Model 302 osmometer.

†Neutralization of the reaction mixtures proved necessary since otherwise the acylhydrazones 3 turned red.

4,5-Methylenedioxy-2-nitroacetophenone 1e

The synthesis of this compound has been described in literature,[6] but in our hands the following synthesis [devised on the analogy of the synthesis of 6-nitropiperonal 1a[5]] proved superior. 3,4-Methylenedioxyacetophenone (41·0 g; 0·25 mole) was added with continuous stirring and external ice-cooling to 65% aq HNO_3 (d 1·4). Heat was evolved, and the mixture was stirred for 15 min at 40°. When the evolution of heat ceased, the mixture was poured onto ice. The product separated partly in the form of a yellow gum, partly as a crystalline material. The aqueous layer (together with most of the crystals) was decanted, and the gummy product was triturated with a small amount of MeOH, whereby it turned crystalline. The aqueous and methanolic mixtures were combined, and the crystalline product was filtered off, thoroughly washed with water until neutral, triturated with three portions (20 ml each) of MeOH and again filtered to yield 37·6 g (72%) of 1e, m.p. 122–3°, lit.[6] 122·5–123·5°.

Acylhydrazones 2a–c *and* e. *General procedures*

Method A. 1a (0·12 mole) was dissolved in hot EtOH (100 ml), the appropriate hydrazide (0·13 mole) was added. The resulting clear brown soln was refluxed for a few minutes until crystallization of the product started. The mixture was allowed to cool, the resulting thick paste was filtered and the product was washed with EtOH.

Method B. A mixture of 1e (50 mmole), EtOH (150 ml), MeOH (3 ml), saturated with HCl gas, and ethyl carbazate was refluxed for 8 h. The dark brown soln was decolorized with Norite and allowed to cool, whereby the light yellow crystals of the product separated. For the yields, microanalyses and IR spectra of the products see Table 4.

Acylhydrazones 3a–c *and* 3e. *General procedure*

Suspensions of the acylhydrazones 2a–c and 2e (80 mmoles) in 40% (v/v) aq EtOH (1000 ml) were treated at 65–70° under continuous stirring with $Na_2S_2O_4$ (70 g). In the a, b and e series a clear yellow soln resulted after about 15 min. At this point further heating of the mixtures was stopped, and crystalline Na_2CO_3 was added until the evolution of CO_2 ceased.† The mixtures were rapidly filtered and allowed to cool, whereby crystallization of mixtures of the desired products and Na_2SO_4 took place. In the c series the reaction mixture remained heterogeneous throughout. After about 30 min further stirring at 65–70°, crystalline Na_2CO_3 was added as above, and the mixture was allowed to cool. The crystalline products were filtered off and thoroughly washed with three portions (100 ml, each) of water. For the yields, microanalyses and IR spectra of the products see Table 5.

NMR (DMSO-d_6, TMS) 3a: δ 8·1, s, 1H, –CH=N; 6·7 and 6·45, both s, 1H, each, ArH's; 5·95, s, 2H, O–CH_2–O; 4·25, q, 2H + 1·3, t, 3H, J = 7 Hz, COOEt.

Diacyl derivatives 4a–f, *see Table* 6

(a) Excess Ac_2O was added under continuous stirring to the refluxing suspensions of 3a–c and e (10–100 mmole) in CH_2Cl_2 (3 ml/mmole 3). A clear soln was initially formed in the case of 3a but turned gradually into a thick purple-red paste. In the case of 3b and 3c the mixtures remained heterogeneous throughout and turned finally into purple-red and yellow pastes, respectively. In the case of 3e a transient clear soln resulted which gradually deposited a white crystalline powder. The products were filtered off (in the case of 3a after dilution with ether) and thoroughly washed with ether to yield about 85% red 4a and 4b, and colourless 4f, which were recrystallized from EtOH to yield colourless pure products. Crude 4c was contaminated with unchanged 3c; recrystallization from EtOH furnished pure 4c, while the unchanged 3c was recovered by dilution of the mother liquor of pure 4c with water.

(b) Mixtures of 3a and 3e (25–50 mmole), CH_2Cl_2 (3 ml/mmole 3) and excess acetic formic anhydride were stirred at room temperature until clear red solns resulted which soon started to deposit colourless crystals of the products. The mixtures were boiled; the crystalline diacyl derivatives 4d and 4e, respectively, obtained in about 80% yields, were filtered off after cooling (in the case of 4e, about 0·1 vol ether was added) and were washed with

Table 4. Acylhydrazones 2

	Method	Yield	M.p. (from)	Formula (Mol wt)	Calc/found C%	H%	N%	IR (KBr) νNH	νC=O
a	A	95%	196° (EtOH)	$C_{11}H_{11}N_3O_6$ (281·22)	46·98 46·73	3·94 3·93	14·94 14·98	3250	1700
b	A	86%	185° (n-BuOH)	$C_{16}H_{13}N_3O_6$ (343·28)	55·98 55·93	3·82 3·92	12·24 12·40	3300	1740
c	A	96%	257–8° (n-BuOH)	$C_{15}H_{11}N_3O_5$ (313·26)	57·51 57·22	3·54 3·78	13·42 13·20	3200	1640
e	B	78%	158–60° (EtOH)	$C_{12}H_{13}N_3O_6$ (295·24)	48·81 48·98	4·44 4·62	14·23 14·30	3200	1710

Table 5. Acylhydrazones 3

	Yield	M.p. (from)	Formula (Mol. wt.)	Calc/found C%	H%	N%	IR (KBr) $\nu NH_2 + \nu NH$	νC=O
a	50%	169° (EtOH)	$C_{11}H_{13}N_3O_4$ (251·24)	52·59 52·73	5·21 5·24	16·74 16·96	3405, 3300, 3280	1710
b	50%	167–8° (MeOH)	$C_{16}H_{15}N_3O_4$ (313·30)	61·33 61·23	4·83 5·10	13·11 13·21	3350, 3250 (b)	1715
c	45%	197° (EtOH)	$C_{15}H_{13}N_3O_3$ (283·27)	63·60 63·47	4·62 4·65	14·83 14·75	3350, 3250 (b)	1640
e	43%	187–8° (MeOH)	$C_{12}H_{14}N_3O_4$ (265·26)	54·33 54·05	5·70 5·68	15·84 15·67	3400, 3300	1740

Table 6. Diacyl derivatives 4

	Excess of acylating agent	Yield[a]	M.p. (from)	Formula (Mol wt)	Calc/found C%	H%	N%	IR (KBr) νNH	νC=O
a	10%	64%	218–20° (EtOH)	$C_{13}H_{15}N_3O_5$ (293·27)	53·24 53·14	5·16 5·13	14·33 14·23	3150, 2950	1730, 1660
b	30%	73%	241–3° (EtOH)	$C_{18}H_{17}N_3O_5$ (355·33)	60·84 60·66	4·82 4·97	11·83 11·60	3200, 3020	1750, 1670
c	30%	49%[b]	273–4° (EtOH)	$C_{17}H_{15}N_3O_4$ (325·31)	62·76 62·56	4·65 4·59	12·92	3120, 2940	1650
d	100%	60%	210–1° (EtOH)	$C_{12}H_{13}N_3O_4$ (279·27)	51·62 51·69	4·58 4·59	15·05 15·24	3160, 3020	1710, 1650
e	100%	79%	183–5° (—)	$C_{13}H_{15}N_3O_5$ (293·27)	53·24 53·56	5·16 5·09	14·23 14·53	3200, 3100	1710, 1675
f	30%	62%	245° (EtOH)	$C_{14}H_{17}N_3O_5$ (307·30)	54·72 54·66	5·58 5·57	13·67 13·85	3200, 2980	1745, 1660

[a]Pure product.
[b]27% of unchanged starting 3c recovered.

ether. The resulting **4e** was colourless and pure, but **4d** was pink and had to be recrystallized from EtOH.

Cyclizations of the diacyl derivative **4a** *and mutual interconversions of compounds* **5a–7a** *and their hydrochlorides*

(a) $SOCl_2$ (1·95 ml; 27 mmole) was added under continuous stirring to a suspension of **4a** (7·35 g; 25 mmole) in CH_2Cl_2 (240 ml); the reaction vessel was kept in an ice-bath in order that the temperature did not exceed 10°. Within 1/2 h a clear, light yellow soln was obtained which gradually deposited a colourless powder. The mixture was stirred for further 2 h under ice-water cooling and cautiously evaporated to dryness in a Rotavapor-R apparatus *in vacuo*. The pink crystalline residue was dissolved in MeOH (80–100 ml), and ether was added to precipitate 7·3 g (85%) of colourless **7a**·HCl (R′ = Me) which turned dark at 170° and melted under effervescence at 209–10°. Found: C, 48·66; H, 5·11; Cl, 10·31; N, 12·23. Calc for $C_{14}H_{16}ClN_3O_5$ (343·76): C, 48·91; H, 5·28; Cl, 10·32; N, 12·22%. IR (KBr): νNH 3100, 2950, 2650; νC=O 1745; νC=N 1660 cm^{-1}. NMR (CD_3OD, reference: CHD_2OD = 3·35 ppm): δ 6·96, s, 2H, ArH; 6·26, s, 1H, 4-H; 6·15, s, 2H, O–CH_2–O; 4·3, q, 2H + 1·3, t, 3H, J = 7 Hz, OEt; 3·35, s, OMe, superimposed on the m of the CHD_2 group of the solvent; 2·6, s, 3H, 2-Me. The spectrum is identical with that of **6a** (see below) taken in CD_3OD/TFA with the difference that the OMe signal is absent in the latter case.

(b) **7a**·HCl (R′ = Me) (2·0 g; 6 mmole) readily dissolved in water (16 ml) at room temperature. After about 5–10 mins the colourless crystals of **7a**·HCl (R′ = H) started to precipitate. The product (1·1 g; 58%), m.p. 135–6°, was filtered off, after the mixture had been allowed to stand for 1/2 h. Found: Cl, 10·81; N, 12·65. Calc for $C_{13}H_{16}ClN_3O_5$ (329·74): Cl, 10·85; N 12·74%.

IR (KBr): νOH + νNH 3500, 3250, 3200, 2950, 2900; νC=O 1750; νC=N 1660 cm^{-1}. NMR (CD_3OD, reference CHD_2OD = 3·35 ppm): almost identical with the spectrum of **7a**·HCl (R′ = Me) with the differences that, in the present case, the ArH signal consists of two 1H singlets at δ 7·00 and 6·97 ppm, and that the OMe signal is absent. The filtrate of the product was made slightly alkaline (pH 8) with 10% aq NaOH to precipitate 0·47 g (28%) of **7a** (R′ = H), m.p. 141–2°. Found: C, 52·92; H, 5·12; N, 14·14. Calc for $C_{13}H_{15}N_3O_5$ (293·26): C, 53·24; H, 5·16; N, 14·33%. IR (KBr): νOH + νNH 3250, 2950, 2850, 2650; νC=O 1720 cm^{-1}.

(c) **7a**·HCl (R′ = H) (0·2 g) was dissolved in anhydrous MeOH (1·5 ml). Ether was added to precipitate 0·15 g of **7a**·HCl (R′ = Me), colourless powder, m.p. 209–10°.

(d) The colourless crystals of **7a**·HCl (R' = H), obtained from the soln of **7a**·HCl (R' = Me) (6·9 g; 20 mmole) in water (55 ml), were dissolved by adding further 120 ml water. The soln was made slightly alkaline (pH 8) by the addition of 10% aq NaOH under ice-cooling. The resulting **7a** (R' = H) was filtered off, dried and recrystallized from anhydrous benzene (60–70 ml) to yield 5·1 g (92%) of **6a**, m.p. 175–6°. Found: C, 56·75; H, 5·01; N 15·46. Calc for $(C_{13}H_{13}N_3O_4)_2$ (550·50): C 56·73; H, 4·76; N 15·27%.

IR (KBr): νC=O 1720; IR ($CHCl_3$): νC=O 1710 cm^{-1}. NMR: see Tables 1–3.

(e) The soln of **6a** (0·5 g) in anhydrous MeOH (3 ml) was treated with a few drops of saturated methanolic HCl. Ether was added to precipitate **7a**·HCl (R' = Me) (0·5 g), colourless crystals, identified by comparison of the IR spectrum with that of an authentic sample.

(f) **6a** was dissolved in refluxing EtOH (20 ml/g of **6a**). The soln was concentrated to about one quarter of its original volume and kept for a few days in a refrigerator to yield a colourless crystalline product, m.p. 110–120° (dec.), which, according to its IR spectrum, proved to be **7a** (R' = Et). IR (KBr): νNH 3200, νC=O 1740.

(g) Recrystallization of **6a** from t-BuOH (30 ml/g **6a**) furnished yellow crystals of **5a**, m.p. 183–5°, 60% recovery. The same transformation was achieved by recrystallization from *i*-PrOH. IR (KBr): no νC=O; NMR: see Tables 1–3. Recrystallization of **5a** either from benzene or from toluene furnished colourless crystals of **6a**.

(h) A mixture of **4a** (0·3 g; 1 mmole), CH_2Cl_2 (10 ml) and $POCl_3$ (0·1 ml; 1·1 mmole) was stirred for 2 days at room temperature whereby the suspension gradually turned into a clear yellow soln. A small amount of gummy material was deposited. The supernatant was evaporated to dryness, the residue (0·25 g) was dissolved in water (10 ml), the aq soln was made alkaline with 10% aq NaOH and extracted with three portions (5 ml each) of $CHCl_3$. The dry residue obtained by conventional work-up of the $CHCl_3$ soln was recrystallized from benzene to yield 0·10 g (36%) of a colourless powder, identical according to m.p.s and IR spectra with **6a** obtained as described under (d).

Cyclization of the diacyl derivative **4b** *and interconversions of compounds* **5b–7b**

(a) $SOCl_2$ (2·2 ml; 30 mmole) was added under stirring and ice-cooling to a mixture of **4b** (8·9 g; 25 mmole) and CH_2Cl_2 (260 ml), and the suspension was stirred for another 2 h. The temperature was kept below 10° throughout. The mixture was evaporated to dryness *in vacuo*, and anhydrous MeOH (40 ml) was added to the residue. From the resulting clear soln the deposition of a colourless powder started soon. The product (8·9 g; 88%), m.p. 180° (dec.), was filtered off and washed with ether. The close resemblance of its KBr-IR spectrum to that of **7a**·HCl (R' = Me) proved this product to be **7b**·HCl (R' = Me). A mixture of the latter (4·1 g; 10 mmole) and water (400 ml) was made slightly alkaline (pH 8) with 10% aq NaOH under continuous stirring and ice-cooling to yield 3·2 g (90%) of colourless **7b** (R' = H), dec. above 160°. Found: C, 60·81; H, 4·68; N, 11·91. Calc for $C_{18}H_{17}N_3O_5$ (355·32) C, 60·84; H, 4·82; N, 11·82%. IR (KBr): νOH + νNH 3300, 3050, 2850, 2700; νC=O 1750 cm^{-1}.

When refluxed with dry benzene (60 ml/g), **7b** (R' = H) gradually dissolved (0·5 h). Light petroleum was added to the hot yellow soln until it became slightly turbid. The mixture was treated with Norite and allowed to cool slowly to yield 2·36 g (70%) of **6b**, m.p. 127–30° and, after resolidification, 174–6°. Found: C, 64·36; H, 4·60; N, 12·50. Calc for $(C_{16}H_{13}N_3O_4)_2$ (674·64): C, 64·09; H, 4·48; N, 12·46%. IR (KBr): νC=O 1700 cm^{-1}. NMR: see Tables 1–3.

(b) A mixture of **7b**·HCl (R' = Me) (4·1 g; 10 mmole), dry $CHCl_3$ (100 ml) and anhydrous Na_2CO_3 (10 g) was stirred for 24 h. The organic salts were filtered off, the yellow filtrate was evaporated to dryness *in vacuo*, and the residue was recrystallized from benzene to yield 3·1 g (92%) of **6b**, m.p. 128–30° and 174–6°.

(c) **6b** (0·15 g) was heated for 10 min at 130°. The colourless starting compound turned into yellow crystals, m.p. 174–6° which, according to their KBr-IR spectra (no νC=O band), proved to be **5b**. When recrystallized from benzene, **5b** was reconverted into **6b**.

Cyclization of the diacyl derivative **4c**

(a) $SOCl_2$ (1·8 ml; 24 mmole) was added under stirring and ice-cooling to a mixture of **4c** (6·5 g; 20 mmole) and CH_2Cl_2 (180 ml), and the suspension was stirred for another 3 h. The temperature was kept throughout below 10°. The mixture was evaporated to dryness in vacuo, and the residue was dissolved in anhydrous MeOH (30 ml). Ether (60 ml) was added to precipitate 7·3 g (97%) of a colourless powder, m.p. 244° (dec), which, according to its KBr-IR spectrum (νNH 3000, 2850, 2600; νC=O 1680 cm^{-1}), proved identical with **7c**·HCl (R' = Me). An aq soln (50 ml) of this salt (0·4 g) was made slightly alkaline (pH 8) with 10% aq NaOH under stirring and ice-cooling to furnish 0·3 g of a light grey product (probably **7c**, R' = H), m.p. 210–1° (after turning yellow above 100°) which, when recrystallized from benzene (50 ml), gave 0·1 g of **5c**, yellow needles, m.p. 210°.

(b) A suspension of **7c**·HCl (R' = Me) (1·9 g; 5 mmole) in CH_2Cl_2 (20 ml) was treated with Et_3N (1 ml) under continuous stirring. The suspension gradually turned yellow. Ether was added to complete crystallization of the product which was filtered off and recrystallized from i-PrOH to yield 1·1 g (61%) of **5c**, yellow needles, m.p. 210°. Found: C, 66·24; H, 4·32; N, 13·78. Calc for $C_{17}H_{13}N_3O_3$ (307·39): C, 66·44; H, 4·23; N, 13·99%. IR (KBr): no νC=O band. NMR: see Tables 1–3.

Cyclization of the diacyl derivative **4d**

(a) $SOCl_2$ (2·2 ml; 30 mmole) was added under stirring and ice-cooling to a suspension of **4d** (7·0 g; 25 mmole) in CH_2Cl_2 (260 ml). A clear yellow soln resulted which was stirred for another 2 h and evaporated to dryness *in vacuo*. The residue was dissolved in MeOH (35 ml). Ether (35 ml) was added to precipitate 6·5 g of colourless crystals, m.p. 84–6°, which, according to their IR (KBr), νNH 3100, 2900, 2700; νC=O 1740; νC=N 1670 cm^{-1}, appeared to be **7d**·HCl (R' = Me). The soln of this product in CH_2Cl_2 (15 ml) was treated with Et_3N (7 ml), and the resulting suspension was evaporated to dryness *in vacuo*. The residue was extracted with two portions (50 ml, each) of boiling benzene to yield 4·45 g (68%) of **6d**, m.p. 178–9°, when the combined solns were allowed to cool. Found: C, 55·30; H, 4·52; N, 16·08. Calc for $(C_{12}H_{11}N_3O_4)_2$ (522·76): C, 55·07; H, 4·24; N, 16·09%. IR (KBr): νC=O 1720 cm^{-1}; NMR: see Tables 1–3.

(b) When **6d** was heated for 2 h at 156°, or for 6 h at 110°, it became transformed into **5d**, m.p. 198–203°. IR (KBr): no νC=O band. When recrystallized from benzene, **5d** was reconverted into **6d**.

(c) Recrystallization of **6d** from EtOH furnished **7d** (R' = Et), m.p. 188–9°. Found: C, 54,56; H, 5·61; N, 13·46. Calc for $C_{14}H_{17}N_3O_5$ (307·30): C, 54·72; H, 5·58; N, 13·67%. IR (KBr): νNH 3120, νC=O 1735, νC=N 1635 cm^{-1}. According to its NMR spectrum, **7d** (R' = Me) at least partly dissociates into **5d** (2-H: δ 9·1; 4-H: δ 10·1) and EtOH.

Cyclization of the diacyl derivative **4e**

$SOCl_2$ (1·8 ml; 24 mmole) was added under ice-cooling and stirring to a suspension of **4e** (5·86 g; 20 mmole) in CH_2Cl_2 (180 ml). A clear yellow soln was obtained, after stirring was continued for about 2 h. Ether was added until precipitation of the light green product (**7e**·HCl, R' = H) (4·7 g), m.p. 208–10°, was complete. IR (KBr): νOH + νNH 3400, 3000, 2800, 2650; νC=O 1725 cm^{-1}. The suspension of the crude salt in CH_2Cl_2 (36 ml) was treated with Et_3N to furnish a yellow powder which was recrystallized twice from benzene. 3·1 g (54·5%) of a mixture of **5e** and **6e**, yellow crystals, m.p. 153–6°, was obtained. Found: C, 57·02; H, 4·88; N, 15·00. Calc for $(C_{13}H_{13}N_3O_4)_n$ (275·25)$_n$: C, 56·73; H, 4·76; N, 15·27%. IR: νC=O 1730 (KBr), 1715 (very weak, $CHCl_3$); νC=N and quinazolinium ring 1630 (KBr) 1615 cm^{-1} ($CHCl_3$). NMR: see Tables 1–3. When recrystallized from EtOH, **5e** + **6e** did not form an EtOH adduct.

Cyclization of the diacyl derivative **4f**

$SOCl_2$ (0·9 ml; 12 mmole) was added under stirring and ice-cooling to a suspension of **4f** (3·1 g; 10 mmole) in CH_2Cl_2 (100 ml). A clear yellow soln resulted within a few minutes and was stirred for further 2 h under ice-cooling. The residue, obtained on evaporation of the solvent and excess reagent *in vacuo*, was

dissolved in anhydrous MeOH. Ether was added, and the resulting greenish gummy material was separated and triturated with ether to yield 3·0 g of a yellow powder, dec. above 80°C.

This crude hydrochloride was dissolved in anhydrous acetone (10–12 ml). Et_3N (1 ml) was added to precipitate 2·45 g of a yellow product which was purified by extraction with boiling acetone (100 ml). A small amount of colourless crystals (Et_3NHCl) remained insoluble, and 1·9 g of a yellow crystalline product was deposited from the acetone soln on cooling. Recrystallization from benzene furnished 1·8 g (62%) of a mixture of **5f** and **6f**, m.p. 150°. Found: C, 57·92; H, 5·50; N, 14·30. Calc for $C_{14}H_{15}N_3O_4$ (289·28): C, 58·11; H, 5·23; N, 14·53%. IR (KBr): νC=O 1740, νC=N + quinazolinium ring 1650 cm^{-1}. NMR: see Tables 1–3.

Reduction of compounds **6a** *and* **7a**·*HCl* (*R' = Me*) *in the presence of Raney nickel*

(a) A mixture of **6a** (0·28 g; 1 mmole), EtOH (25 ml) and slightly alkaline Ni-H_2 (2·0 g) was stirred for 1 h at room temperature. During this period the starting compound has, according to TLC (adsorbent Kieselgel $Pf_{254+366}$; solvent benzene – MeOH, 10:2) completely been used up. The metal was filtered off, the filtrate was evaporated to dryness, and the crystalline residue (228 mg) was taken up with benzene (3 ml) and filtered off to yield 153 mg (55%) of **13**, m.p. 145° from EtOAc. Found: C, 56·31; H, 5·48; N, 15·15. Calc for $C_{13}H_{15}N_3O_4$ (277·27): C, 56·31; H, 5·45; N, 15·15%. IR (KBr): νC=O 1720 cm^{-1}. UV (EtOH): 204 (4·28); 316 (3·90). UV (EtOH + HCl): 228 (4·24); 314 (3·83). NMR ($CDCl_3$, TMS): δ 6·7 and 6·3, both s, 1H, each, ArH's; 5·9, s, 2H, O–CH_2–O; 4·6, s, 2H, 4-H; 4·2, q, 2H + 1·3, t, 3H, J = 7 Hz, COOEt; 2·15, s, 3H, 2-Me. NMR (CD_3OD; reference CHD_2OD = 3·35): δ 6·55 and 6·5, both s, 1H, each, ArH's; 5·95, s, 2H, O–CH_2–O; 4·65, s, 2H, 4-H; 4·25, q, 2H + 1·3, t, 3H, J = 7 Hz, COOEt; s, 3H, 2-Me. MS, principal peaks: *m/e* 277 (M^+, 26%), 248 (3·0), 230 (4·3), 204 (2·8), 189 (38), 188 (100), 187 (7·8).

(b) **7a**·HCl (R' = Me) furnished under the above conditions 74% of **13**. In addition, small amounts of **15** or its hydrochloride were present in the reaction mixture as revealed by TLC (adsorbent and solvent as above).

(c) A mixture of **6a** (2·0 g; 73 mmole), EtOH (250 ml) and slightly alkaline Ni-H_2 (20 g) was refluxed 5 h under continuous stirring. The metal was filtered off, the filtrate was evaporated to dryness, and the greenish residue was taken up in EtOH (5 ml) and filtered off to yield 0·75 g (56%) of **17**, colourless crystals, m.p. 178–80°, identical, according to m.m.p. and IR, with an authentic sample prepared as described below. The filtrate was evaporated to dryness, and the residue was subjected to sublimation at 100° (25 Torr) to yield 0·15 g (18%) of ethyl carbamate. The non-volatile crystalline residue (0·3 g) was shown by TLC (adsorbent, solvent as above) to consist mainly of **17**, contaminated with a small amount of **15**.

(d) A mixture of **13** (0·28 g; 1 mmole), EtOH (25 ml) slightly alkaline Ni-H_2 was refluxed for 3 h under continuous stirring. The metal was filtered off, the filtrate was evaporated to dryness, and the residue was worked up by TLC (size of plates: 20 × 20 cm; adsorbent Kieselgel $PF_{254+366}$; thickness of layer: 2 mm; solvent: benzene-MeOH, 10:2) to yield 0·12 g (62%) of **17** and 0·02 g (9%) of **15**.

(e) A mixture of **7a**·HCl (R' = Me) (2·0 g; 58 mmole), EtOH (250 ml) and slightly alkaline Ni-H_2 was refluxed under continuous stirring until, according to TLC, the starting substance was completely used up. The metal was filtered off, the filtrate was evaporated to dryness, and the residue was recrystallized from EtOH (15–20 ml) to yield 0·65 g (50%) of **15**·HCl, colourless crystals, m.p. 291°, identified by comparison with an authentic sample. Found: C, 53·22; H, 4·92; Cl, 15·20; N, 12·48. Calc for $C_{10}H_{11}ClN_2O_2$ (226·67): C, 52·98; H, 4·89; Cl, 15·64; N, 12·36%. UV (EtOH): 219 (4·36); 310 (3·88). NMR (D_2O, reference: DSS): δ 6·6 and 6·7, both s, 1H, each, ArH; 6·1, s, 2H, O–CH_2–O; 4·7, s, 2H, 4-H; 2·4 ppm, s, 3H, 2-Me. The mother liquor was evaporated to dryness, and the residue was taken up in ether and filtered off. The product proved, according to TLC (adsorbent, solvent as above) to be a mixture of **15**·HCl and **17**. The dry residue of the ether soln was sublimed *in vacuo* to yield 0·16 g of ethyl carbamate. The free base **15** was liberated in 77% yield by treating the aqueous soln of the HCl salt with 10% aq NaOH. Colourless crystals, m.p. 176–8° (from water). Found: C, 62·98; H, 5·23. Calc for $C_{10}H_{10}N_2O_2$ (190·20): C 63·11; H, 5·30;

Equilibration of the quinazoline **17** *and the dihydro derivative* **15** *in the presence of Raney nickel*

(a) A mixture of **17** (0·2 g), EtOH (20 ml) and slightly alkaline Ni-H_2 (2·0 g) was refluxed for 20 h under continuous stirring. The metal was filtered off, the filtrate was evaporated to dryness, and the residue was worked up by TLC (size of plates 20 × 20 cm; adsorbent Kieselgel $PF_{254+366}$; thickness of layer: 2 mm; solvent benzene-MeOH, 10:2) to yield 0·11 g (55%) of unchanged **17** and 0·02 g (10%) of **15**.

(b) A mixture of **15** (0·25 g), EtOH (20 ml) and slightly alkaline Ni-H_2 (2·0 g) was refluxed for 5 h and worked up as described under (a) to yield 0·05 g (20%) of unchanged **15** and 0·10 g (40%) of **17**.

Authentic 2-methyl-6,7-methylenedioxyquinazoline **17**

(a) 6-Nitropiperonal **1a**[5] (9·75 g; 50 mmole) and acetamide (45·0 g; 760 mmole) were thoroughly mixed and heated. At 75° a clear melt was obtained into which a stream of dry HCl was introduced under stirring; simultaneously, the reaction temperature was elevated to 80°. After 30 min the melt solidified. The temperature was raised to 90–100°, and stirring and introduction of HCl was continued for another 30 min. After being allowed to cool, the mixture was triturated with EtOH (50 ml); the insoluble product was filtered off and washed with three portions (25 ml, each) of EtOH, and the resulting colourless crude product (19·5 g) was recrystallized from EtOH (1000 ml) to yield 8·0 g (54%) of N,N' - (4,5 - methylenedioxy - 2 - nitrobenzylidene) - bis - acetamide, colourless needles, m.p. (after another recrystallization from EtOH) 247°. Found: C, 48·91; H, 4·45; N, 14·09. Calc for $C_{12}H_{13}N_3O_6$ (295·24): C, 48·81; H, 4·41; N, 14·23%. IR (KBr): νNH 3250, amide I 1670 cm^{-1}.

(b) AcOH (24 ml) was added under continuous stirring within 5 min to a mixture of the bis-acetamide (7·4 g; 25 mmole), Zn powder (17·8 g) and ice (90 g). The mixture turned yellow. More Zn powder (7·2 g) was added in portions, and the mixture was stirred for another 3 h. The insoluble inorganic material was filtered off and washed with 5% aq AcOH (100 ml). The combined filtrates were treated with NaOH (57 g). The resulting yellowish brown material was separated by centrifugation and taken up in acetone (100 ml). The insoluble parts were removed, and the clear filtrate was evaporated to dryness. The residue was sublimed at 120–130°, 1 Torr to yield 0·7 g (15%) of **17**, light yellow plates, which became colourless after recrystallization from benzene-light petroleum, m.p. 180°. Found: C, 63·93; H, 4·41; N, 14·83. Calc for $C_{10}H_8N_2O_2$ (188·18): C, 63·88; H, 4·29; N, 14·89%. UV (EtOH): 228 (4·53), 328 (3·96). UV (aq HCl): 217 (4·47); 224, sh (4·32); 252 (4·48), 335 (3·96). NMR ($CDCl_3$, TMS): δ 9·0, bs, 1H, 4-H; 7·2 and 7·05, both s, 1H, each, 5-H and 8-H; 6·12, s, 2H, O–CH_2–O; 2·8 ppm s, 3H, 2-Me. NMR (CD_3OD, reference: CHD_2OD = 3·35 ppm): δ 9·1, bs, 1H, 4-H; 7·3 and 7·15, both s, 1H, each, 5-H and 8-H; 6·24, s, 2H, O–CH_2–O; 2·75 ppm, s, 3H, 2-Me. MS: cf Fig 2.

Reduction of compounds **6a**, **7a**·*HCl* (*R' = Me*) *and* **7b**·*HCl* (*R' = Me*) *in the presence of Pd/C*

(a) **6a** (0·3 g; 1 mmole), dissolved in EtOH, dioxan or benzene (25 ml) was reduced at room temperature and normal pressure in the presence of a 9% Pd/C catalyst (0·1–0·3 g). Within 45 min 1 equiv H_2 was absorbed. According to TLC (adsorbent Kieselgel $PF_{254+366}$, solvent EtOAc), the starting **6a** was completely used up, and traces of **16** were present in addition to the main product **13**. The catalyst was filtered off, the filtrate was evaporated to dryness and triturated with a small amount of benzene to yield 0·22 g (70%) of almost pure **13**, m.p. 142–5°, identified by its IR spectrum. HCl salt, m.p. 220–1° (from MeOH–Et_2O) IR (KBr): νNH: 3350, 3150–2650; νC=O 1730 cm^{-1}.

(b) **6a** (0·3 g; 1 mmole), dissolved in benzene (30 ml), was reduced under the above conditions in the presence of 0·3–0·4 g of the Pd/C catalyst. Within 8 h 2 equivalents of H_2 were absorbed. The mixture was conventionally worked up to yield 0·25 g (83%)

of **16**, m.p. 123–4° (from benzene–petroleum ether). Found: C, 55·87; H, 6·12; N, 15·17. Calc for $C_{13}H_{17}N_3O_4$ (279·29): C, 55·90; H, 6·14; N, 15·05%. IR (KBr): νNH 3300, νC=O 1730 cm^{-1}. UV (EtOH): 205 (4·60), 250 (3·86), 317 (3·84). NMR ($CDCl_3$, TMS): δ 6·42 and 6·18, both s, 1H, each, 5-H + 8-H; 5·85, s, 2H, O–CH_2–O; 4·3, s, 2H, 4-H; 4·22, q 2H + 1·25, t, 3H, J = 7 Hz, COOEt; 1·3 ppm, d, J = 5 Hz, 3H, 2-Me. MS, principal peaks: *m/e* 279 ($M^{+\cdot}$, 27%), 264 (3·6), 191 (13), 190 (8·0), 177 (15), 176 ($C_{10}H_{10}NO_2$, 100), 175 (18), 150 ($C_8H_8NO_2$, 67), 149 (21), 148 (19), 146 (C_9H_8NO, 23). **13** was reduced under the above conditions in benzene soln within 8 h, in EtOH soln within 60 h to give **16**.

(c) **7a**·HCl (R′ = Me) (0·3 g; 0·9 mmole), in EtOH (25 ml), was reduced room temperature and normal pressure in the presence of a 9% Pd/C catalyst (0·4 g). One equivalent of H_2 was absorbed within 10 min, and the absorption stopped at this point. The catalyst was removed, the filtrate was evaporated to dryness, and the residue was taken up in MeOH (3 ml) and treated with ether to yield 0·15 g (48%) of **13**·HCl, m.p. 220–1°. Treatment of an aq soln of the latter with aq Na_2CO_3 furnished the free base, m.p. 145°. Reduction of **6a** in ethanolic HCl under otherwise identical conditions furnished 50% of **13**·HCl, m.p. 220–1°.

(d) **7b**·HCl (R′ = Me) (4·1 g; 10 mmole), dissolved in EtOH (300 ml) was reduced at room temperature and normal pressure in the presence of a 9% Pd/C catalyst (2·0 g). Within about 2 h 2 equivalents of H_2 were absorbed. The catalyst was filtered off and washed with 4 portions (20 ml each) of water. The combined filtrates were evaporated to dryness, and the residue was recrystallized from EtOH (100 ml) to yield 1·45 g (59%) of **14**·HCl, colourless crystals, m.p. 273–4°. Found: Cl, 14·80; N, 17·11. Calc for $C_{10}H_{22}ClN_3O_2$ (241·68): Cl, 14·67; N, 17·39%. UV (EtOH): 221 (4·19); 315 (3·92). NMR (D_2O, DSS): δ 6·71 and 6·6, both s, 1H, each, 5-H + 8-H; 6·04, s, 2H, O–CH_2–O; 4·88, s, 2H, 4-H; 2·47 ppm, s, 3H, 2-Me. MS identical with that of **14** (see below).

When the above experiment was repeated, and the dry residue of the reaction mixture was dissolved in water (20 ml) and made slightly alkaline with 10% aq NaOH, 1·4 g (68%) of **14**, colourless crystals, m.p. 174–5° (from benzene) was obtained. Found: C, 58·53; H, 5·48; N, 20·20. Calc for $C_{10}H_{11}N_3O$(205·21): C, 58·53; H, 5·40; N 20·48%. NMR ($CDCl_3$, TMS): δ 6·64 and 6·36, both s, 1H, each, 5-H + 8-H; 5·90, s, 2H, O–CH_2–O; 4·56, s, 2H, 4-H; 3·62, bs, 2H, NH_2; 2·2 ppm, s, 3H, 2-Me. MS, principal peaks: *m/e* 205 (M^+, 90%), 204 (100), 189 (14), 188 (60), 187 (15), 175 (4·6), 174 (5·7), 163 (7·7), 162 (11), 161 (6·0), 120 (18).

Reactions of compound **14**

(a) A mixture of **14** (0·2 g; 1 mmole), p-chlorobenzaldehyde (0·16 g; 1·1 mmole) and anhydrous EtOH (8 ml) was refluxed for 5 h. From the yellow soln 0·08 g of 3 - (p - chlorobenzyl - ideneamino) - 2 - methyl - 6,7 - methylenedioxy - 3,4 - dihydroquinazoline was deposited, yellow crystals, m.p. 201–2°. Found: Cl, 10·58; N, 12·70. Calc for $C_{17}H_{14}ClN_3O_2$ (327·76): Cl, 10·82; N, 12·82%. NMR ($CDCl_3$, TMS): δ 7·65 and 7·39, both d, J = 7·8 Hz, 2H, each, ArH-s of p-ClC_6H_4; 6·78 and 6·56, both s, 1H, each, 5-H + 8-H; 5·94, s, 2H O–CH_2–O; 4·75, s, 2H, 4-H; 2·37 ppm, s, 3H, 2-Me.

(b) Ethyl chloroformate (0·05 ml; 55 mmole) was added under ice-cooling and stirring to a mixture of **14** (105 mg; 0·5 mmole), K_2CO_3 (1·0 g) and dry acetone (5 ml). Stirring was continued at room temperature for 15 h, the inorganic salts were filtered off, and the dry residue of the filtrate was worked up by TLC (size of plate 20 × 20, adsorbent Kieselgel $PF_{254+366}$, thickness of layer 2 mm, solvent benzene–acetone, 1 : 1) to yield 14 mg (10%) of **13**, identified by comparison of the IR spectrum with that of an authentic sample.

Ethyl 1 - cyano - 5 - methyl - 1,11b - dihydro - 3(2H) - [1,3] dioxolo[4,5 - g] - pyrazolo[2,3 - c]quinazoline - 3 - carboxylate **19**.

A mixture of **6a** (0·55 g; 2 mmole), acrylonitrile (0·4 ml) and pyridine (4 ml) was refluxed for 10 min, during which period the starting **6a** was, according to TLC, completely used up. The red soln was evaporated to dryness, and the residue (0·6 g) was triturated with ether, filtered off and recrystallized from benzene (2–3 ml) to yield 0·3 g (46%) of **19**, m.p. 179°. Found: C, 58·68; H, 4·94; N, 17·23. Calc for $C_{16}H_{16}N_4O_4$ (328·32): C, 58·53; H, 4·91; N 17·07%. IR (KBr): νC≡N 2280, νC=O 1700 cm^{-1}. NMR ($CDCl_3$, TMS): δ 6·85 and 6·52, both s, 1H, each, ArH's; 6·02, s, 2H, O–CH_2–O; 4·59, d, J = 6·6 Hz, 1H, 11bH; 4·28, q, 2H + 1·32, t, 3H, J = 7Hz, COOEt; 2·2 ppm, s, 3H 5-Me. MS, principal peaks: *m/e* 328 (M^+, 37%), 275 (26), 230 (14), 203 (43), 188 (100), 174 (5·3), 161 (2·5), 120 (6·6).

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