# ELECTRON DEFICIENT HETEROAROMATIC AMMONIOAMIDATES, XV.* *N*-(3-QUINAZOLINIO)AMIDATES, V.**

## NOTE ON THE REACTION OF *N*-(3-QUINAZOLINIO)AMIDATES WITH BUTYLAMINE

By

J. FETTER, G. BARTA-SZALAI,*** A. JABER and F. BERTHA

Department of Organic Chemistry, Technical University, Budapest

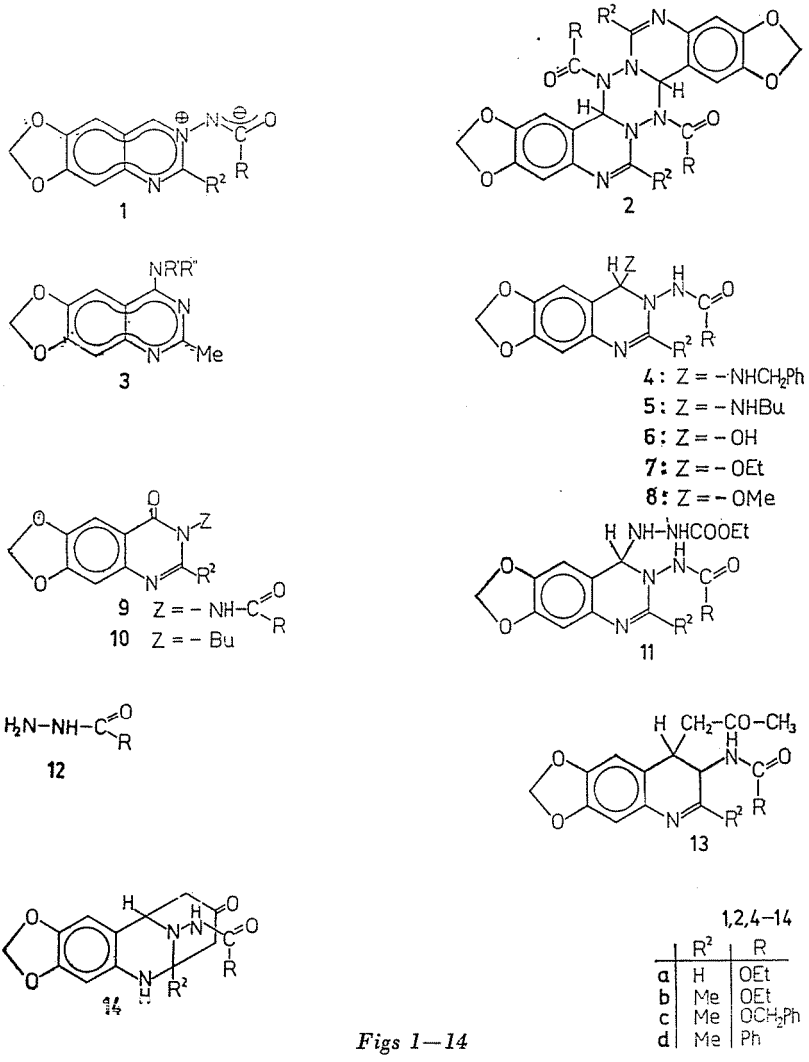
Received May 6, 1977
Presented by Prof. Dr. K. LEMPERT

The *N*-(3-quinazolinio)amidates **1b** [3], when irradiated in the presence of primary or secondary amines, furnished the corresponding 4-aminoquinazolines (**3**) in excellent yields [4].**** Recently we became interested in the thermal reactions of the type **1** compounds with amines.

Refluxing the *N*-(3-quinazolinio)amidates **1a—c** [3] (bearing no substituent attached to C-4) with butylamine, and chromatographic work-up of the resulting mixtures *in the absence of acetone* furnished three types of heterocyclic products, *viz.* **9—11.** In addition, more or less of the hydrazide **12b** was formed, the simplest way of isolating the latter being in form of its acetone adduct. Compound **11b** and the related **11c** (but not compounds **11a!**) also do react with acetone in the presence of catalytic amounts of butylamine***** to yield compounds of types **13** and **14** which have earlier been obtained [5] by allowing to react the type **1** amidates (or their dimers) with acetone in the presence of amines or silica at room temperature. Therefore, if acetone is a component of the solvent used for chromatographic work-up of the mixtures obtained on refluxing compound **1b** with butylamine, at least part of the product **11b** (as well as any unchanged **1b** and adduct **5b,** respectively) are converted into **13b.**

The isolated products and yields are listed in Table I. **9b, 9c** [2, 4] the acetone condensation product of the carbazate **12b,** as well as **13b** [5] were

* For Part XIV, see Ref. [1]
** For Part IV, see Ref. [2]
*** Chinoin Pharmaceutical Works research fellow, 1975—.
**** It was, actually, the dimer **2b** [3] of the amidate **1b** which was subjected to irradiation. A rapid equilibrium is, however, established in solution between the monomeric and dimeric forms [3]; moreover, the amidate **1d** and its dimer are practically completely converted into the adduct **4d** in benzylamine solution at room temperature [4], and a similar situation may be assumed to prevail in the butylamine solutions of the quinazolinioamidates **1a—c** (bearing no substituent attached to C-4). It is, therefore, immaterial whether the monomeric amidates or their dimers are allowed to react with amines and, in the following, we shall discuss all reactions as if they were reactions of the monomers, irrespective of whether the monomers themselves or their dimers have originally been introduced.
***** Acetonolysis of **11b** in the absence of butylamine is extremely slow which suggests that the reactive species is either the enol or the enolate of acetone.




*Figs 1—14*

known compounds and were identified by comparison with authentic samples. The structures of compounds **10a—b** and **11b** were derived from their microanalytical and spectral data, and that of compound **11b** was substantiated by its synthesis from **1b** and ethyl carbazate. Compound **11a** (which was not isolated from the reaction of the amidate **1a** and butylamine) and **11c** were obtained analogously.

Compound **11b** is closely related to the type **6** hydrates and type **7** ethanol adducts [3] of the amidates **1.** In agreement herewith, the MS of compound **11b** is virtually identical with that of **1b,** as has been found [3] to be the case for the mass spectra of the type **7** adducts and the corresponding

**Table I**

Reaction of the *N*-(3-quinazolinio)amidates **1a-c** with amines

| Starting compound | Amine | Reaction conditions | Work-up[a] | Isolated products |
|---|---|---|---|---|
| **1a** | $BuNH_2$ | Refluxing for 20 hrs under air | Method A | 76% **10a** |
| **1b** | $BuNH_2$ | Refluxing for 8 hrs under air | Method A | 12.4% **9b**, 6.3% **10b**, 28.8% **12b**[b], 32.2% **13b** |
| **1b** | $BuNH_2$ | Refluxing for 15 hrs under air | Method B | 26.3% **9b** |
| **1b** | $BuNH_2$ | Refluxing for 13 hrs under oxygen | Method A | 30.6% **9b**, 36.9% **10b** |
| **1b** | $BuNH_2$ | Refluxing for 15 hrs under argon | Method B | 38.6% **11b** |
| **1b** | $BuNH_2$ | Refluxing for 8 hrs under argon | Method A[c] | 28.8% **12b**[b], 25.5% **13b** |
| **1b** | morpholine | Stirring for 80 hrs at 80 °C under air | Method A | 50% **9b** |
| **1c** | $BuNH_2$ | Refluxing for 20 hrs under air | Method A | 15.8% **9c**, 10.2% **10c** (= **10b**) |

[a] See Experimental
[b] Acetone condensation product
[c] The dry residue of the reaction mixture was allowed to stand, prior to chromatographic work up, for 2 days in ethyl acetate solution at room temperature.

amidates **1.** Furthermore, compound **11b** may be converted by thermal treatment into the dimer **2b** (detected by TLC) and by treatment with methanolic hydrogen chloride into the hydrochloride of the methanol adduct **8b.**

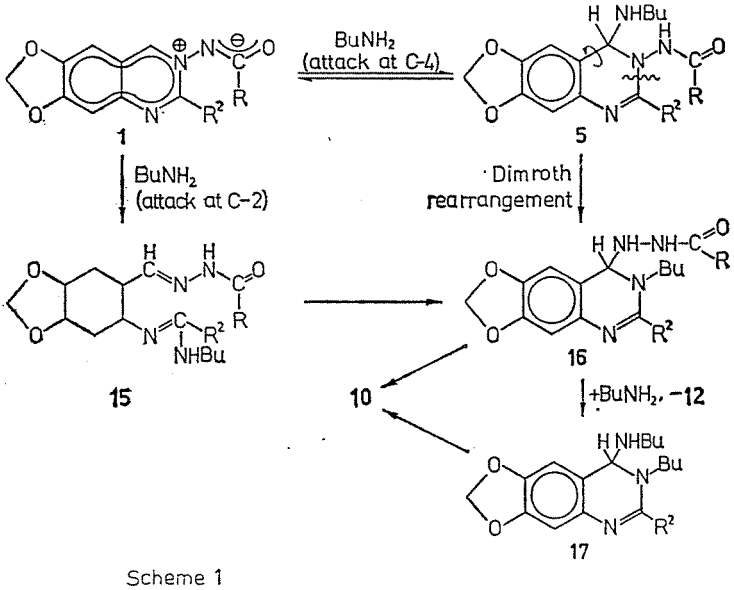
The structures of compounds **9b** and **9c** and the fact that they are formed only in the presence of oxygen suggests that they are oxidation products of the amidates **1.** This oxidation probably involves the intermediacy of type **5** adducts since no oxidation products are formed (indeed, no reaction whatsoever takes place) if compound **1b** is refluxed with triethylamine for 10 hrs under air. (The inertness of **1b** under these conditions is, however, undoubtedly caused in part by the slight solubility of **1b** in triethylamine, even at the b.p. of the latter.)

Compounds **10a** and **10b,** too, are oxidation products. They are certainly *not* formed through the intermediacy of the type **9** compounds, since compound **9b** does not furnish even traces of **10b** when refluxed for 10 hrs with butylamine. We believe, therefore, compounds **16** and **17** (which are closely related to the adducts **5**) to be the precursors of compounds **10.** As shown in Scheme 1, there are two pathways which offer themselves for the rationalization of the

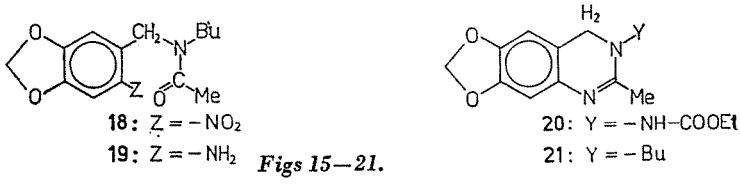
formation of the intermediates **16.** No choice between the two alternatives is possible at present, although the fact that, in contrast to the **b** and **c** Series, only the type **10** oxidation product is obtained in the **a** Series, would appear to be in favour of the path involving the intermediacy of compound **5.** It is, namely, the **a** Series in which the equilibrium **1** $\rightleftharpoons$ **8** has been found to be shifted to the highest degree towards the adduct [3], and a similar situation may be assumed to prevail for the equilibrium **1** $\rightleftharpoons$ **5.**

An important feature of Scheme 1 is that it accounts for the formation of compound **12b** and, by assuming subsequent addition of the latter to **1b**, of compound **11b** as well.

The level of oxidation of the adducts **5, 16** and **17** corresponds to that of benzaldehyde, while the level of oxidation of the products **9** and **10** corresponds to that of benzoic acid. The conversions **5** → **9** and **16** and/or **17** → **10** might, therefore, in principle be envisaged either as autooxidations or as Cannizzaro-type disproportionations. (For a closely related Cannizzaro-type reaction, see Ref. [6].) The fact that we were in no case able to detect the presence of the stable compound **20*** [3] in the reaction mixtures, does not




Scheme 1



18: Z = −NO2
19: Z = −NH2
20: Y = −NH−COOEt
21: Y = −Bu

*Figs 15—21.*

* Compound **20** does not change when refluxed for 45 hrs with butylamine under air.

preclude, in itself, the disproportionation-route because the absence of **20** could be explained by assumption of a selective mixed Cannizzaro-type reaction of **5b** and **16** ($R^2$ = Me, R = OEt) or **17** ($R^2$ = Me) leading to **9b** and **21.** However, although **21** is partially autoxidized to **10b** (cf. Ref. [7]), this process is by far not complete under conditions similar or identical to those used by us for carrying out the reaction of **1b** with butylamine. These results suggest that the type **9** and **10** compounds are formed by an autoxidation, rathe than a disproportion route.

## Experimental

*Reactions of the N-(3-quinazolinio)amidates* **1a—c** *with amines*

a) The amidates (1.0 g) were refluxed with butylamine (25 ml) or stirred at 80 °C with morpholine (25 ml) until, according to TLC the amidates were completely used up. The resulting brown solutions were evaporated to dryness and the oily residues taken up three times in anhydrous benzene or anhydrous dioxane and evaporated to dryness, in order to remove the unchanged amine as completely as possible. The oily products were subsequently dried over $P_2O_5$ in vacuum, taken up in anhydrous benzene (10—15 ml) and worked up according one of the methods A and B.

*Method A:* Chromatography through a column of Kieselgel 60 (Merck, particle size 0.063—0.200; solvent benzene-acetone, 1 : 1) followed, if necessary, by preparative TLC (adsorbent Kieselgel $PF_{254+366}$, Merck, solvent benzene — MeOH, 10 : 1, or benzene-acetone, 10 : 1).

*Method B:* Chromatography through a column of Kieselgel 60 (Merck, as above; solvent: benzene-dioxane 1 : 1).

Isolated products and yields are listed in Table I. Several minor products were also formed.

Compound **10a**, m.p. 90 °C ($Et_2O$). $C_{13}H_{14}N_2O_3$ (246.3). Calcd C 63.40, H 5.73, N 11.38. Found C 63.54, H 5.65, N 11.20%. IR (KBr): 1650 $cm^{-1}$. UV (EtOH): 240 (4.58); 288 (3.56), 310 (3.58); 323 (3.50). NMR ($CDCl_3$): 0.98, distorted t, + 1.3—2.0, m, + 3.98, t, *N*-Bu; 6.10, s, $OCH_2O$; 7.03, s, 8-H; 7.60, s, 5-H; 7.95, ppm, s, 2-H.

Compound **10b**, m.p. 128—9°C ($Et_2O$). $C_{14}H_{16}N_2O_3$ (260.3). Calcd C 64.60, H 6.20, N 10.76. Found C 64.36, H 6.12, N 10.85%. IR (KBr): 1660 $cm^{-1}$. UV (EtOH): 240 (4.54); 287 (3.69); 314 (3.57); 322 (3.49). ($CDCl_3$): 0.98, distorted t, + 1.25—1.7, m, + 4.00, t, *N*-Bu; 2.56, s, 2-Me; 6.10, s, $OCH_2O$; 7.00, s, 8-H; 7.58 ppm, s, 5-H.

Reference compound: 3-ethyl-2-methyl-6,7-methylenedioxy-4(3*H*)-quinazolinone (**10b**, with ethyl replacing the *n*-butyl group). IR (KBr): 1650 $cm^{-1}$. UV (EtOH): 239 (4.56); 287 (3.70); 314 (3.64); 326 (3.56). NMR

($CDCl_3$): 2.63, s, 2-Me; 6.15, s, $OCH_2O$; 7.05, s, 8-H; 7.67 ppm, s, 5-H. MS (60°C): *m/e* 232 (100%, $M^{+\cdot}$), 204 (80%), 203 (13%), 190 (9%), 163 (5%), 149 (16%) [2].

b) Compound **1b** was refluxed for 10 hrs with butylamine, the mixture evaporated to dryness and the residue chromatographed over Kieselgel 60 either as such (solvent as above) or in form of its hydrochloride (solvent: benzene-methanol, 1 : 1). The different fractions were examined by NMR; in none of them could the signals of the 4-$CH_2$ group be detected.

*Ethyl* 3-*(3-ethoxycarbonylamino-6,7-methylenedioxy-3,4-dihydro-4-quinazolinyl)carbazates* (**11a—c**)

a) Compound **1a** (1 mmole) and ethyl carbazate (1.1 mmoles) were dissolved in hot anhydrous benzene (3 ml) to yield, upon cooling, a thick crystalline paste of compound **11a** which was diluted with ether and filtered. Yield: 71%, m.p. 198 °C.

$C_{15}H_{19}N_5O_6$ (365.3). Calcd C 49.31, H 5.24, N 19.17. Found C 49.43, H 5.54, N 18.98%.

IR (KBr): 3300—2700 b, local maxima at 3250, 3140, 2870; 1700 (1725, sh); 1650 $cm^{-1}$. NMR (DMSO-$d_6$): 1.05, t, 1.20, t, + 3.9, qu, 4.05, qu, *two* COOEt groups; 5.3, s, 4-H; 6.05, s, $OCH_2O$; 6.6, s, + 6.85, s, 5-H + 8-H; 7.2 ppm, s, 2-H.

b) Compound **11b**, m.p. 153°C, was similarly prepared in 58% yield, starting with **1b.**

$C_{16}H_{21}N_5O_6$ (379.4). Calcd C 50.66, H 5.58, N 18.46. Found C 50.62, H 5.59, N 18.32%.

IR (KBr): 3400—2650 b, local maxima at 3250, 3180, 2900; 1740, 1710, 1640. NMR ($CDCl_3$): 1.22, t, 1.30, t, + 4.12, qu, 4.24, qu, *two* COOEt groups; 2.10, s, 2-Me; 5.35, s, 4-H; 5.90, s, $OCH_2O$; 6.6 ppm, s, 5-H + 8-H.

The mass spectrum of this product is virtually identical with that of compound **1b.**

c) Compound **11c** was similarly obtained by allowing to react ethyl carbazate and compound **1c.** Yield 88%, m.p. 157 °C.

$C_{21}H_{23}N_5O_6$ (441.4). Calcd N 15.87. Found N 15.60%

IR (KBr): 3500—2700 b, local maxima at 3300, 3200, 2950; 1745, 1690, 1635 $cm^{-1}$.

*Reactions of compounds* **11b** *and* **11c**

a) A few drops of anhydrous methanolic hydrogen chloride were added to the anhydrous methanolic (2 ml) suspension of compound **11b** (379 mg; 1 mmole), and the resulting clear solution was treated with anhydrous ether

to precipitate 326 mg (95%) of the hydrochloride of **8b**, m.p. 205 °C (dec.), identical (m.p., mixed m.p., IR spectrum, conversion into **2b**) with an authentic sample [3].

The filtrate of the above product was evaporated to dryness, the residue dissolved in methanol and worked up by TLC (Kieselgel $PF_{254+366}$, Merck; solvent: benzene-dioxane, 1 : 1) to yield 70 mg (68%) of ethyl carbazate (**12b**), m.p. 40—2 °C, identical (IR spectrum, mixed m.p.) with an authentic sample [8].

b) In another experiment the solution of **11b** (379 mg; 1 mmole) in methanolic hydrogen chloride (obtained as above) was worked up by preparative TLC (adsorbent as above; solvent: benzene-acetone, 1 : 1) to yield 120 mg (84%) of the acetone condensation product of **12b**, m.p. 63 °C (ether — light petroleum), identical (IR, m.p., mixed m.p.) with an authentic product obtained by boiling-up compound **12b** with acetone.

$C_6H_{12}N_2O_2$ (144.2). Calcd C 49.98, H 8.39, N 19.43. Found C 49.68, H 8.25, N 19.26%.

c) Mixtures of compound **11b** and **11c**, respectively, (4 mmoles), butylamine (2 ml), benzene and acetone (10 ml, each) were refluxed for 2 hrs during which period the starting compounds were completely used up. The mixtures were evaporated to dryness and worked up according to Method A (see above) to yield 80% of **13b** [5] and 5% of **14b** [5] as well as 56% of the acetone condensation product of **12b** from **11b**, and 60% **13c** [5] and 91% of **14c** [5] from **11c**. All products were identified (m.p., mixed m.p., IR spectra) with authentic samples.

Under similar conditions, even after prolonged refluxing, **11a** was not converted into either **13a** or **14a**.

*N-Butyl-N-(4,5-methylenedioxy-2-nitrobenzyl)acetamide* (**18**)

2-Nitro-4,5-methylenedioxybenzyl chloride [9] (21.6 g; 0.1 mole) was added with ice-cooling and stirring to butylamine (100 ml). The mixture was refluxed for 1 hr, evaporated to dryness in vacuum and the red oily residue triturated with 10% aqueous NaOH. The amine was isolated by extraction with chloroform and converted into its hydrochloride by treating its anhydrous methanolic solution with methanolic hydrogen chloride. Anhydrous ether was added to precipitate 12.0 g (41.5%) of the yellow crystals of *N-butyl-4,5-methylenedioxy-2-nitrobenzylammonium chloride*, m.p. 177 °C.

1*N* NaOH was added with stirring and ice-cooling to the aqueous solution (600 ml) of the above salt until slightly alkaline, to yield 9.4 g (37%) the free amine, m.p. 45 °C.

Acetic anhydride (1.75 ml; 17 mmoles) was added to the methylene dichloride solution (20 ml) of the above amine (2.5 g; 10 mmoles). The mixture

was refluxed for 2 hrs, evaporated to dryness and the residue triturated with ether to yield 2.1 g (73%) of the title compound, m.p. 112 °C (methanol).

$C_{14}H_{18}N_2O_5$ (294.3). Calcd C 57.13, H 6.16, N 9.52. Found C 57.30, H 6.29, N 9.57%.

IR (KBr): 2950, 1630, 1520, 1320 $cm^{-1}$.

*N-Butyl-N-(2-amino-4,5-methylenedioxybenzyl)acetamide* (**19**)

The above nitro derivative (6.0 g; 20 mmoles) was reduced in ethanolic solution (250 ml) at room temperature in the presence of an 8% Pd-on-charcoal catalyst to yield, after the usual work-up, 4.3 (81%) of an oil which gradually turned crystalline on standing; m.p. 79 °C (benzene — light petroleum).

$C_{14}H_{20}N_2O_3$ (264.3). Calcd C 63.61, H 7.63, N 10.60. Found C 63.47, H 7.49, N 10.53%.

3-*Butyl*-2-*methyl*-6,7-*methylenedioxy*-3,4-*dihydroquinazolinium chloride* (**21** · HCl)

A mixture of compound **19** (0.65 g; 2.5 mmoles) and acetic anhydride (7 ml) was refluxed under argon until, according to TLC, compound **19** was used up completely (about 40 min), and evaporated to dryness in vacuum under argon. The resulting dark oil was dissolved in anhydrous methanol (2 ml), acidified with a few drops of methanolic hydrogen chloride and treated with anhydrous ether. The colourless gummy product was recrystallized from methanol-ether to yield 0.15 g (21%) of the title compound, m.p. 120 °C (dec.).

$C_{14}H_{18}N_2O_2 \cdot HCl$ (282.8). Calcd Cl 12.54, N 9.90. Found Cl 12.87, N 9.87%.

NMR ($CDCl_3$): 1.0, distorted t, + 1.45, m, + 3.45, t, *N*-Bu; 1.65, s, 2-Me; 4.7, s, 4-$H_2$; 5.88, s, $OCH_2O$; 6.35, s, 5-H; 7.07 ppm, s, 8-H.

*Reaction of compound* **21** · HCl *with bases*

a) Treatment of an aqueous solution of the salt with 10% aqueous NaOH furnished a colourless, gradually deliquescent precipitate which, according to its TLC (Kieselgel $PF_{254+366}$, Merck; solvent: benzene-acetone, 1 : 1) and NMR spectrum, proved to be an approximately 1 : 1 mixture of compounds **21** and **10b.**

NMR ($CDCl_3$):* 1.00, distorted t, + 1.6, m, + 3.22 ($\alpha$), t, + 4.07 ($\beta$), t, *N*-Bu; 2.12 ($\alpha$), s, 2.60 ($\beta$), s, 2-Me; 4.4 ($\alpha$), s, 4-$H_2$; 5.85 ($\alpha$), s, 6.05 ($\beta$), s, $OCH_2O$; 6.32 ($\alpha$), s, + 6.60 ($\alpha$), s, ArH-s; 6.95 ($\beta$), s, 8-H, + 7.55 ppm ($\beta$), s, 5-H.

* Signals marked with an $\alpha$ are those of compound **21**, those marked with a $\beta$ those of compound **10b.**

In spite of the large difference in the $R_f$ values of these two compounds, we were unable to obtain, by chromatographic work-up of the mixture, compound **21** in pure form.

The amount of **10b** did not increase and that of **21** did not decrease, according to TLC, when the above mixture was refluxed with butylamine. Nor was any change in the composition of the mixture observed when the mixture was stirred in methanolic solution in the presence of Kieselgel 60, Merck, for 10 hrs under oxygen.

b) Compound **21** · HCl was refluxed with butylamine for 48 hrs. At most only traces of the free base were liberated and no oxidation to yield **10b** took place.

## Acknowledgements

The authors are grateful to Mrs. BALOGH-BATTA and staff for the microanalyses, to Dr. P. KOLONITS and staff for the IR and NMR, to Mrs. BALOGH-BATTA for the UV and to Dr. J. MØLLER (Odense, Denmark) for the mass spectra.

## Summary

Refluxing *N*-(3-quinazolinio)amidates **1a—c** (bearing no substituents attached to C-4) furnished type **9** and **10** oxidation products. Type **12** hydrazides and, in the **b** series, the adduct **11b**. The possible pathways leading to these products are discussed, and the reactions of type 11 adducts with acetone to yield type **13** and **14** products are described.

## References

1. LEMPERT-SRÉTER, M.—LEMPERT, K.—BRUCK, P.—TÓTH, G.: Acta Chim. (Budapest), in press
2. FETTER, J.—LEMPERT, K.—BARTA-SZALAI, G.—MØLLER, J.—PÁRKÁNYI, L.: Acta Chim. (Budapest), in press
3. FETTER, J.—LEMPERT, K.—MØLLER, J.: Tetrahedron **31**, 2559 (1975)
4. FETTER, J.—LEMPERT, K.—MØLLER, J.—SZALAI, G.: Tetrahedron Letters **1975**, 2775
5. FETTER, J.—LEMPERT, K.—MØLLER, J.—BARTA-SZALAI, G., in preparation
6. LEMPERT, K.—GYULAI, P.: Z. Chem. **10**, 384 (1970)
7. ARMAREGO, W. L. F., in *Adv. Heterocyclic Chem.*, Vol. 1 (edited by A. R. Katritzky), Academic Press, New York and London, 1963, p. 285
8. DIELS, O.: Ber. **47**, 2186 (1914)
9. WILKENDORF, R.: Ber. **52**, 611 (1919)

József FETTER
Gizella BARTA-SZALAI
Adel JABER
Ferenc BERTHA
H-1521 Budapest