ACTA CHEMICA SCANDINAVICA 25 (1971) 551–558

Base-catalyzed Cyclizations of Some Acetylenic Oxoquinazolines and Related Open Amides*

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When treated with various basic reagents, 3,4-dihydro-4-oxo-3-propargylquinazoline (I) afforded the isomeric 3-propadienyl derivative (II) in good yield. This allene, as well as the original propargyl derivative, gave the oxazole III upon prolonged reaction with base. A 2-vinylquinazolone VII was also formed, which implies that the C-2 of the original quinazoline ring of I or II is eliminated and replaced by the C-1 of the propargylic or allenic side-chain.

It is assumed that both cyclizations proceed *via* a common intermediate, *viz.* a 2-formamidobenzoic acid amide formed by cleavage of the heterocyclic ring. This assumption is supported by the fact that 2-formamidobenzoic acid propargylamide (XIV) afforded the oxazole III and the vinylquinazolone VII under basic conditions; since these reactions did not take place with some other 2-formamidobenzamides, it is concluded that a propargyl (or propadienyl) group is essential for these cyclizations to occur.

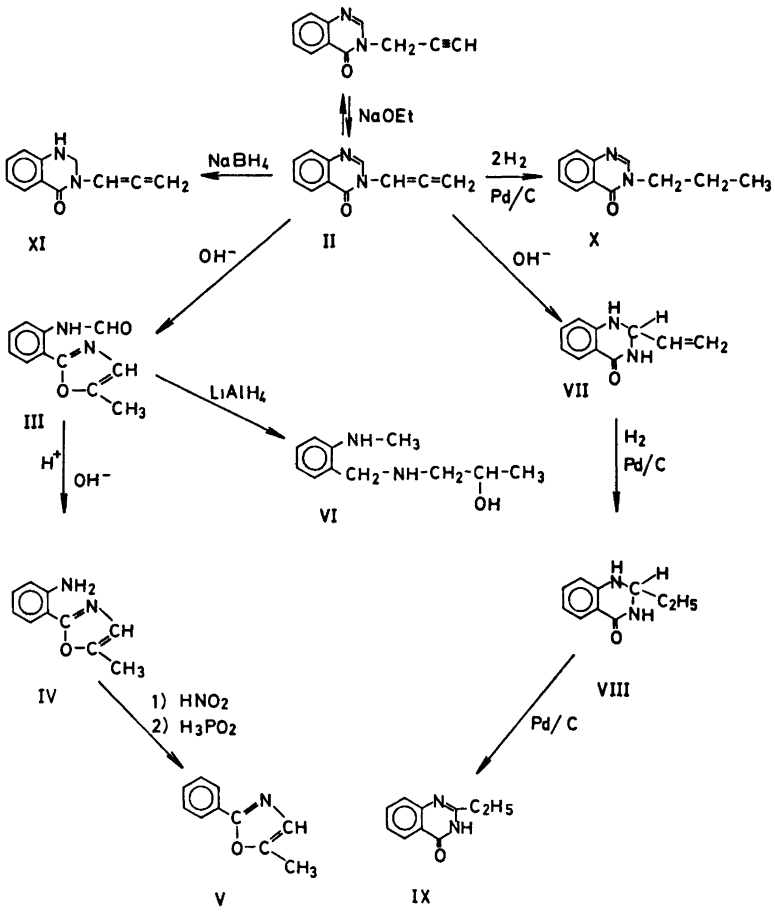
In continuation of our investigations on the medicinal chemistry of oxoquinazolines, we tried to reduce the carbonyl group of 3,4-dihydro-4-oxo-3-propargylquinazoline (I) with lithium aluminium hydride. This reagent, however, only induced transformation of I to the allene II and the same isomerization was effected by other basic reagents, such as sodium ethoxide.

Most of the experimental results are summarized in Schemes 1 and 2.

DISCUSSION

In this section, some of the reactions described in the experimental part and in the schemes are commented upon. The Roman numerals refer to the compound numbers in the experimental part and in the schemes.

* Studies on the medicinal chemistry of oxoquinazolines IX. Part VIII: *Acta Pharm. Suecica* 7 (1970) 257. A preliminary report has appeared.[1]



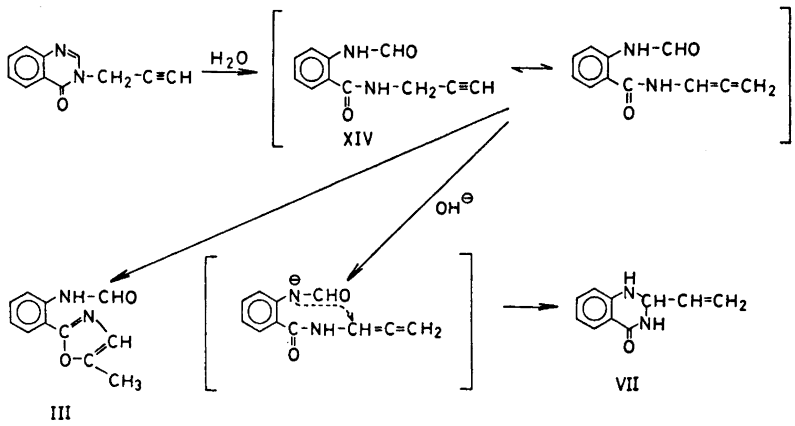
Scheme 1

Scheme 1. Reactions of 3,4-dihydro-4-oxo-3-propadienylquinazoline.

Reaction I→II. The base-catalyzed rearrangement of acetylenic compounds affords a mixture of products including allenic derivatives; *cf.* the recent review by Iwai [2] and references cited therein.

According to text-books, allenes may be readily recognized by their IR absorption in the 1920–2000 cm^{-1} range. Interestingly, however, the two allenes prepared in the present investigation either display a weak band (II) or no band at all (XI) in this range. The compounds, however, were identified as allenes on NMR-spectroscopic evidence and by hydrogenation (II→X; II→XI).

The interaction of compound I and alkali might also be expected to transform *N*-propargyl to an *N*-(1-propynyl) group.[2] This structure, however, was



Scheme 2

easily ruled out on account of the NMR-spectrum of II, which did not show any methyl signals.

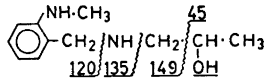
Reaction (I→) II→III. This transformation implies oxazole formation in a basic medium, a reaction which does not seem to have been accomplished before. Preparation of oxazolidines upon ring-closure of *N*-alkyl-*N*-propargyl-ethanolamines under basic condition was studied by Bottini and co-workers.[3] Acid-catalyzed cyclization of acetylenes to oxazoles has been accomplished as described, *e.g.* in Refs. 4, 5.

We have earlier suggested [1] that the first step in the sequence of reactions leading from compound I (or II) to the oxazole III might be hydrolytic cleavage of the heterocyclic ring, which would give a 2-formamidobenzoic acid amide.

This hypothetical intermediate (XIV, Scheme II) was not observed in the TLC-analysis of the reaction mixture, but evidence for its occurrence is given below. The cyclization step seems to involve nucleophilic attack of the amide oxygen on the central carbon of the propargyl group (or its re-arranged allenic equivalent). An analogous mechanism has been proposed for the ring-closure of propargylammonium halides.[2,6]

Partial hydrolysis (deformylation) of III to give IV occurred in these experiments. The identity of the oxazole III was established by hydrolysis to compound IV, deamination and comparison with authentic material.

Reaction III→VI. Upon reduction with $LiAlH_4$ in ether, the formyl group of III was reduced to methyl, as expected. The oxazole ring was opened to give a secondary alcohol, in analogy with early findings of Fischer [7] in connection with reductions of oxazoles with sodium in ethanol. The mass spectrum of VI has prominent peaks corresponding to the fragmentation outlined in the formula.



VI

Reaction II→VII. As stated below, there is evidence for the 2-formamidobenzoic amide XIV being an intermediate also in the reaction II→VII, although it was not trapped in the reaction mixture. A reasonable mechanism for the cyclization would require loss of the hydrogen at the formamidic nitrogen, followed by nucleophilic attack of this nitrogen on C−1 of the propargyl group (or its rearranged allenic equivalent), as sketched in Scheme II, where all hypothetical species are enclosed in brackets.

A process which very much resembles this formation of a vinylquinazolone is the preparation of vinyloxazolidines, described by Bottini *et al.*[3] The latter reaction was understood as occurring *via* an intramolecular nucleophilic addition to C-1 of the allenic moiety of an allenic aminoalcohol, formed by base-induced prototropic rearrangement of a propargylethanolamine.

The identity of the vinylquinazolone VII was established by hydrogenation of the vinyl group to VIII and dehydrogenation of the heterocyclic ring to IX, both compounds being known and available for comparison.

Reaction XII→XIII. Since we were interested to investigate whether oxazole formation also took place with 2-substituted 4-quinazolones, we made some similar experiments with 2-ethyl-3,4-dihydro-4-oxo-3-propargylquinazoline. We found that the reaction in ethanolic sodium hydroxide afforded 5-methyl-2-(2-propionamidophenyl)oxazole, in analogy with compound I. In these experiments there were no signs of allene formation.

Cyclizations of 2-formamidobenzoic acid amides. In order to test the validity of the assumption that a 2-formamidobenzoic acid amide might be a common precursor for the oxazole III and the vinylquinazolone VII, we studied the reactions of 2-formamidobenzoic acid propargyl amide in alkaline media. When performing the reaction in the presence of potassium *t*-butoxide in *t*-butanol we were able to isolate III and VII from the reaction mixture, both in reasonable yields.

We also found it interesting to investigate the behaviour of other 2-formamidobenzoic acid amides in the same alkaline media. It was found that the 1,1-dimethylpropargylamide XV was deformylated to compound XVI, no cyclization taking place. The butynylamide XVII, as well as the allyl- and propylamides all afforded the corresponding 3-substituted quinazolones; *cf.* Ref. 8. There were no indications of oxazole formation in these cases.

It is thus reasonable to assume that a propargyl (or propadienyl) group is essential for these cyclizations to occur.

EXPERIMENTAL

General. Melting points (uncorrected) were taken in open capillary tubes in an electrically heated metal block using calibrated Anschütz thermometers. Elementary analyses were performed in the laboratories of Dr. A. Bernhardt, Mülheim, West Germany.

TLC was performed on silica gel G plates of 0.3 mm (analytical) and 1 mm (preparative) thickness. The plates were heated at 130° for 1.5 h and were stored in a dry cabinet until used. When not otherwise stated, they were developed in chloroform containing 2 % methanol. For visualization of the spots, the plates were exposed to iodine vapour and sprayed with $KMnO_4$ solution. IR spectra were run on a Perkin-Elmer Infracord 337 using the KBr pellet technique. NMR spectra were obtained in $CDCl_3$ using a Varian A 60 spectrometer. Chemical shifts are expressed in ppm relative to tetramethylsilane ($\delta_{TMS}=0.00$ ppm). Mass spectra were run on an LKB 9000 mass

spectrometer using a direct probe heated to a suitable temperature. The ionizing energy was maintained at 70 eV, the accelerating energy at 3500 V, and the temperature of the ion source was kept at 270°C.

In the syntheses described below, no special efforts were made at obtaining maximum yields.

3,4-Dihydro-4-oxo-3-propadienylquinazoline (II). 3,4-Dihydro-4-oxo-3-propargylquinazoline (I)[9] (2 g, 0.011 mol) was dissolved in a freshly prepared solution of 0.05 g (0.002 mol) of sodium in 40 ml of absolute ethanol and the solution refluxed for 5 min. After cooling, the crystalline solid that separated out was filtered off and recrystallized from ligroin. Yield 50 %. M.p. 130–131°C. Mol.wt. 184 (MS). NMR: Doublet at ppm 5.65 (2H, terminal allene, $J = 6.6$ cps); spectrum featureless at higher field. IR: 1955 cm^{-1} (weak), no bands indicating acetylene. (Found: C 71.6; H 4.42; N 15.32. Calc. for $C_{11}H_8N_2O$: C 71.7; H 4.38; N 15.21.) TLC analysis of the filtrate from the reaction mixture showed that it contained small amounts of what was later identified as III and VII.

Compound II was also obtained by treating I with other basic reagents, *e.g.* $LiAlH_4$ in THF (no reduction of the carbonyl group in refluxing THF after 24 h; *cf.* Ref. 10).

3,4-Dihydro-4-oxo-3-propylquinazoline (X) was obtained by catalytic hydrogenation of II in ethyl acetate solution over Pd/C (10 %) at room temperature and atmospheric pressure. Compound X was identified by spectroscopic (IR, NMR) comparison with an authentic specimen.[11]

1,2,3,4-Tetrahydro-4-oxo-3-propadienylquinazoline (XI). Compound II (1 g) was dissolved in the minimum amount of a mixture of methanol and benzene (3+1) and the solution cooled in an ice-bath. Sodium borohydride (1.5 g) was added cautiously and the mixture stirred in the ice-bath for 12 h. After evaporation of the solvent, water was added in order to dissolve inorganic material. The solid residue was isolated and recrystallized from hexane. Yield *ca.* 15 %. M.p. 91–92°C. NMR: Doublet at ppm 5.40 (2H, terminal allene, $J = 6.7$ cps); singlet at ppm 4.66 (2H, HN-CH_2-N). No bands at higher field. IR: No band in the 1920–2000 cm^{-1} range. (Found: C 71.2; H 4.90; N 15.19. Calc. for $C_{11}H_{10}N_2O$: C 71.0; H 5.41; N 15.04.)

2-(2-Formamidophenyl)-5-methyloxazole (III). 3,4-Dihydro-4-oxo-3-propargylquinazoline (I)[9] (18.4 g; 0.1 mol) in 400 ml of *t*-butanol was treated with 4.6 g (0.05 mol) of potassium *t*-butoxide and the mixture heated to 80°C in an atmosphere of nitrogen. The course of the reaction was followed by periodic TLC analysis ($CHCl_3$, ligroin, CH_3OH, 20+4+1 ml). It was found that the allene II was formed initially, but it was consumed in the further reaction and after 2 h it had disappeared entirely. The mixture was neutralized with sulphuric acid and the solvent evaporated. The solid residue was extracted with hot ligroin, from which compound III deposited on cooling. The residue also contained compound VII (see below). Yield 25–30 %. M.p. 74–75°C (from ligroin). Mol.wt. 202 (MS). NMR: Singlet at ppm 2.32 (3H, methyl). The base peak of the mass spectrum (174) corresponds to a loss of 28 (CO) from the molecular ion, which we have also observed in other formamides. (Found: C 65.6; H 5.08; N 13.53. Calc. for $C_{11}H_{10}N_2O_2$: C 65.3; H 4.98; N 13.85.)

Upon hydrolysis with potassium hydroxide in 96 % ethanol or with HCl in moist ether, compound III afforded *2-(2-aminophenyl)-5-methyloxazole* (IV). M.p. (hydrochloride, from absolute ethanol): 207–208°C. (Found: C 57.5; H 5.61; N 13.36. Calc. for $C_{10}H_{10}N_2O \cdot HCl$: C 57.0; H 5.26; N 13.30.)

Compound IV was deaminated by diazotization and reduction with hypophosphorous acid, *cf.* Ref. 12. The deaminated product was identified as *5-methyl-2-phenyloxazole* (V) by spectroscopic comparison (IR) with a specimen prepared from *N*-propargylbenzamide.[4]

Compound III (5 g) was reduced with $LiAlH_4$ (2 g) in 300 ml of ether at room temperature under nitrogen for 30 h, affording *N-(2-hydroxypropyl)-N-(2-methylaminobenzyl)amine* (VI). M.p. (oxalate) 164–166°C. Mol.wt. 194 (MS). NMR: Doublet at ppm 1.02 (3H, CH-CH_3); singlet at ppm 2.70 (3H, NH-CH_3); singlet at ppm 3.60 (2H, benzylic CH_2). (Found: C 54.3; H 7.09; N 9.69. Calc. for $C_{11}H_{18}N_2O \cdot (COOH)_2$: C 54.9; H 7.09; N 9.85.) Mass spectrum: Principal peaks at *m/e* 194 (M^+, 12 %); 149 (6 %); 135 (5 %); 121 (11 %); 120 (100 %); 119 (7 %); 118 (19 %); 91 (16 %); 65 (6 %); 46 (8 %) and 45 (13 %).

1,2,3,4-Tetrahydro-4-oxo-2-vinylquinazoline (VII). As mentioned above, this compound was formed as a by-product in the reaction I→II. It was also prepared by reacting

equimolar amounts of I and potassium hydroxide in refluxing 96 % ethanol for 1.5 h. The reaction mixture was cooled and neutralized with dilute sulphuric acid, whereupon the solvents were removed under reduced pressure. The solid residue was extracted with hot toluene, which upon cooling deposited VII as a crystalline precipitate. This was filtered off and recrystallized from toluene. Yield 20 %. The mother liquor contained a considerable amount of the oxazole III. Compound VII was also formed as above from the allene II. M.p. 151 – 152°C. Mol.wt. 174 (MS). (Found: C 68.8; H 5.73; N 15.93. Calc. for $C_{10}H_{10}N_2O$: C 69.0; H 5.79; N 16.08.) The identity of VII was established by hydrogenation over Pd/C at atmospheric pressure for 30 min in absolute ethanol. The hydrogenation afforded *2-ethyl-1,2,3,4-tetrahydro-4-oxoquinazoline* (VIII), identified by spectroscopic comparison with a specimen prepared by an unambiguous method.[13] M.p. 120-121°C (from toluene). (Found: C 68.1; H 6.82; N 15.73. Calc. for $C_{10}H_{12}N_2O$: C 68.2; H 6.86; N 15.90.)

When the reaction over Pd/C was prolonged to 60 h, dehydrogenation to *2-ethyl-3,4-dihydro-4-oxoquinazoline* (IX) had occurred. The latter quinazolone was also identified by comparison (IR) with an authentic sample.

Reactions of 2-ethyl-3,4-dihydro-4-oxo-3-propargylquinazoline (XII). (a) Compound XII (0.2 g) was refluxed with an equimolar quantity of potassium hydroxide in 96 % ethanol for 1.5 h. The reaction mixture was cooled and neutralized with dilute sulphuric acid and the solvents removed under reduced pressure. The residue was extracted with hot ligroin. From the extract was isolated a small amount of *5-methyl-2-(2-propionamidophenyl)oxazole* (XIII). The yield was low because of difficulties in purification. It was obtained in better yield according to method (b) where analytical data are given.

(b) Compound XII was left standing for 2 days in a mixture of 0.5 M sodium hydroxide and sufficient ethanol to dissolve the compound. From this mixture the oxazole XIII separated out in 25 % yield, no further purification being necessary. M.p. 84 – 85°C. The NMR-spectrum of *5-methyl-2-(2-propionamidophenyl)oxazole* in $CDCl_3$ displayed a singlet at ppm 2.43 (3H, methyl); triplet at ppm 1.33 (3H, $-COCH_2CH_3$) and an obscured quartet at ppm 2.58 (2H, $-COCH_2CH_3$). (Found: C 68.0; H 5.82; N 12.36. Calc. for $C_{13}H_{14}N_2O_2$: C 67.8; H 6.13; N 12.17.)

(c) When XII was treated with sodium in ethanol as described above for the formation of the allene II from the propargyl compound I, no allenic compound could be detected in the reaction product.

(d) Equimolar amounts of compound XII and potassium *t*-butoxide in *t*-butanol were heated at 60°C for 4 h and the solvent was evaporated. The residual solid was recrystallized from aqueous ethanol and further purified by passing through an Al_2O_3 column (solvent: $CHCl_3$), affording a white solid in 20 % yield, identified as the propionamidophenyloxazole XIII.

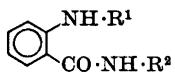
2-Formamidobenzoic acid propargylamide (XIV). Anthranilic acid propargylamide[14] (18 g, 0.1 mol) was refluxed with formic acid (11 g, 0.25 mol) in 300 ml of toluene for 2 h, using a Dean-Stark water separator. The solvent was evaporated and the residue washed with ether and recrystallized. Pertinent data are given in Table 1.

Reactions of 2-formamidobenzoic acid propargylamide (XIV). (a) A mixture of 1 g of XIV and an equimolar amount of potassium hydroxide (0.27 g) was refluxed in 15 ml of 96 % ethanol. After 2 min, TLC analysis indicated the occurrence of the vinylquinazolone VII in the reaction mixture, and after 10 min, the starting material had disappeared entirely although a spot corresponding to anthranilic acid propargylamide could be detected. The experiment was repeated, but in no case could the oxazole III be traced on the TLC plates. Compound VII was isolated from the reaction mixture and identified by IR.

(b) A mixture of XIV (0.5 g) and 0.35 g of potassium *t*-butoxide was refluxed in 10 ml of *t*-butanol. The reaction taking place was completed after 2 min (identical TLC after 2 and 30 min). Three spots were observed, corresponding to anthranilic acid propargylamide and compounds III and VII. The latter compounds, 0.2 g and 0.1 g, respectively, were isolated from the reaction mixture upon dilution with water and extraction with hot toluene. Compound VII separated out from the toluene upon cooling, while III remained in solution, from where it was obtained upon evaporation of the solvent.

2-Formamidobenzoic acid 1,1-dimethylpropargylamide (XV) was prepared in analogy with compound XIV by formylation of anthranilic acid 1,1-dimethylpropargylamide (preparation: see below). See Table 1 for data.

Table 1. Substituted anthranilamides.



No.	R^1	R^2	Formula	Yield %	Analysis: Calc. % / Found % C	H	N	Recryst. solvent	M.p. °C
XIV	HCO	$-CH_2C{\equiv}CH$	$C_{11}H_{10}N_2O_2$	35	65.3 65.2	4.98 5.04	13.85 13.90	ethanol	136–138
XV	HCO	$-C(CH_3)_2\cdot C{\equiv}CH$	$C_{13}H_{14}N_2O_2$	82	67.8 67.9	6.13 5.79	12.17 12.38	ethanol	149–151
XVI	H	$-C(CH_3)_2\cdot C{\equiv}CH$	$C_{12}H_{14}N_2O$	11	71.3 71.2	6.98 7.06	13.85 13.76	ligroin	118–120
XVII	HCO	$-CH_2CH_2C{\equiv}CH$	$C_{12}H_{12}N_2O_2$	46	66.7 66.6	5.59 5.76	12.95 12.85	toluene-ethanol (2+1)	106–107
XVIII	H	$-CH_2CH_2C{\equiv}CH$	$C_{11}H_{12}N_2O$	32	70.2 69.7	6.43 6.71	14.88 14.89	ligroin	69–71
XIX	HCO	$-CH_2CH_2CH_3$	$C_{11}H_{14}N_2O_2$	33	64.1 64.0	6.84 6.78	13.58 13.54	toluene	109–111

Anthranilic acid 1,1-dimethylpropargylamide (XVI) was synthesized according to the method given for anthranilic acid propargylamide [14] using isatoic anhydride and 1,1-dimethylpropargylamine.[15] Data: see Table 1.

2-Formamidobenzoic acid but-3-ynylamide (XVII) was obtained in the same way as compound XIV, using anthranilic acid but-3-ynylamide as starting material. The latter amide (XVIII) was prepared from but-3-ynylamine [16] as described above for compound XVI. Data for compounds XVII and XVIII are given in Table 1.

2-Formamidobenzoic acid propylamide (XIX) was also prepared in analogy with compounds XIV, starting with anthranilic acid propylamide.[17] *Cf.* Table 1 for data.

2-Formamidobenzoic acid allylamide (XX) was prepared according to Hanford *et al.*[11]

Reactions of the 2-formamidobenzoic acid amides XV, XVII, XIX, and XX. The amides were reacted with an equimolar quantity of potassium hydroxide in ethanol as described above for the reaction of compound XIV, method (a). The reaction was followed by TLC-analysis and was stopped when there was no further change in the appearance of the plates.

It was found that compound XV was deformylated to XVI. The other amides were cyclized to the corresponding 3-substituted 3,4-dihydro-4-oxoquinazolines. The 3-propyl derivative (from XIX) and the 3-allyl-3,4-dihydro-4-oxoquinazoline (from XX) were identified by comparison (IR) with authentic material prepared by alkylation of 3,4-dihydro-4-oxoquinazoline.

Compound XVII afforded *3-(but-3-ynyl)-3,4-dihydro-4-oxoquinazoline.* M.p. 132–134°C (from ligroin-toluene). (Found: C 72.5; H 5.33; N 14.16. Calc. for $C_{12}H_{10}N_2O$: C 72.7; H 5.08; C 14.13.)

These amides were also treated with potassium *t*-butoxide in *t*-butanol as described for compound XIV, method (b). The results were the same as described above.

Acknowledgement. We wish to thank Miss Maria Kvist for skilful technical assistance.

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Received June 27, 1970.