[Chem. Pharm. Bull. 24(3) 431—436 (1976)]

UDC 547.856.1.04 : 547.867.6.04

Reaction of Triethyloxonium Fluoroborate with Acid Amide. III.[1] Formation of Quinazoline and 4*H*-3,1-Benzoxazin-4-one Derivatives

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(Received June 25, 1975)

Reaction of 2-acetaminobenzamide with triethyloxonium fluoroborate gave 2-methyl-3,4-dihydro-4-quinazolinone. On the other hand, in the reaction of 2-benzoylaminobenzamide in lieu of acetyl derivative with triethyloxonium fluoroborate were obtained 2-phenyl-4*H*-3,1-benzoxazin-4-one and 2-phenyl-4-ethoxyquinazoline. And, the reaction of 2-benzoylaminothiobenzamide with triethyloxonium fluoroborate was obtained 4-ethylthio-2-phenylquinazoline.

In the preceding papers,[1,3] dealing with the reactions between acylaminoacid amides and triethyloxonium fluoroborate (I), it was found that 3-acylaminopropionamide and acylglycinamide afforded 5,6-dihydro-4(3*H*)-pyrimidinone and 4-ethoxyimidazole derivatives respectively, as shown in Chart 1. In sequence of these findings, it was conceived that this reaction could be applied to the synthesis of condenced pyrimidine derivative such as quinazoline, pteridine, purine, *etc.*, by reacting 2-acylaminobenzamide or 2-acylaminoheterocyclecarboxamide having the common skeletal structure, –C–N–C–C–C–N, with I. Taking this assumption into consideration, present investigation was undertaken to elucidate the reaction of 2-acylaminobenzamide derivative with I, using 2-alkanoylaminobenzamide (II), 2-aroylaminobenzamide (III), and 2-acylaminothiobenzamide derivatives (IV).

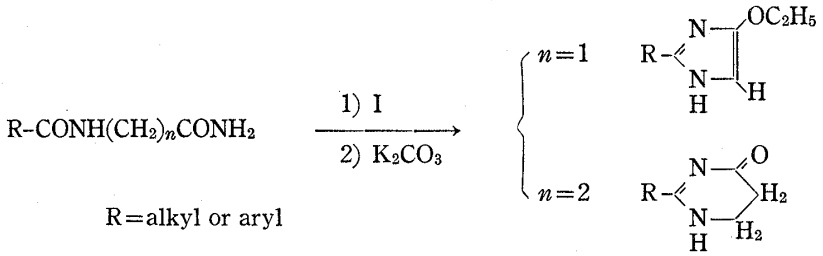


Chart 1

The reaction of one mole of 2-acetaminobenzamide (IIa) with two moles of I in dichloromethane was found to give 2-methyl-3,4-dihydro-4-quinazolinone (Va) in 40% yield as anticipated. The resulting quinazolinone was identified by the mixing melting point test with an authentic sample prepared from the reaction of 2-aminobenzoic acid with acetamide,[4] and by the comparison of their infrared (IR) spectra. The compounds of II and their N-methylamides were similarly reacted with I and corresponding 3,4-dihydro-4-quinazolinone derivatives were obtained. This reaction is illustrated in Chart 2 and the compound synthesized are listed in Table I.

1) Part II: T. Kato, A. Takada, and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **22**, 984 (1974).
2) Location: *Shirokane, Minato-ku, Tokyo.*
3) T. Kato, A. Takada, and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **20**, 901 (1972).
4) Niementowski, *J. Prakt. Chem.*, **51**, 564 (1895).

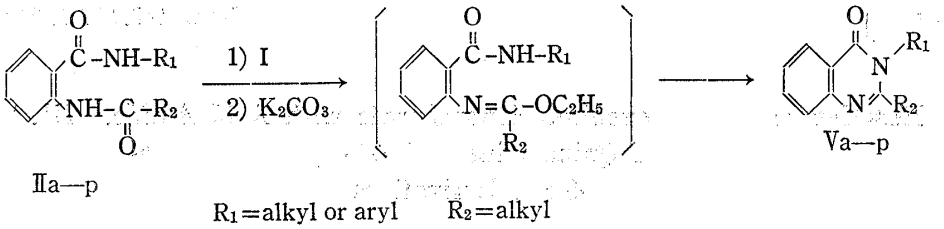
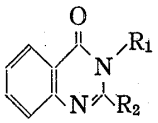
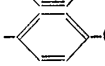
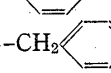


Chart 2

TABLE I.



Compd. V	R_1	R_2	Yield (%)[a]	Appearance (Recryst. solvt.)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
a	H	$-CH_3$	40	needles (EtOH)	233—235	$C_9H_8ON_2$	67.48 (67.33)	5.03 (5.15)	17.49 (17.60)
b	H	$-C_2H_5$	16	powders (dil.EtOH)	226—227	$C_{10}H_{10}ON_2$	68.95 (69.05)	5.79 (5.61)	16.08 (16.12)
c	H	n-C_3H_7	33	powders (dil.EtOH)	190—192	$C_{11}H_{12}ON_2$	70.18 (70.25	6.43 6.33)	14.88 (14.73)
d	H	iso-C_3H_7	16	powders (dil.EtOH)	220—222	$C_{11}H_{12}ON_2$	70.18 (70.39)	6.43 (6.21)	14.88 (14.93)
e	$-CH_3$	$-CH_3$	37	needles (isoPr-O-isoPr)	108—109	$C_{10}H_{10}ON_2$	68.95 (68.81)	5.79 (5.83)	16.08 (16.15)
f	$-CH_3$	$-C_2H_5$	38	needles (EtOH)	120—121	$C_{11}H_{12}ON_2$	70.18 (70.22)	6.43 (6.48)	14.88 (14.92)
g	$-CH_3$	n-C_3H_7	40	powders (EtOH)	77—78	$C_{12}H_{14}ON_2$	71.26 (71.37)	6.98 (6.72)	13.18 (13.29)
h	$-C_2H_5$	$-CH_3$	22	needles (isoPr-O-isoPr)	64— 65	$C_{11}H_{12}ON_2$	70.18 (70.29)	6.43 (6.38)	14.88 (14.69)
i	$-C_2H_5$	$-C_2H_5$	35	needles (isoPr-O-isoPr)	95— 96	$C_{12}H_{14}ON_2$	71.34 (71.26)	6.87 (7.00)	13.86 (13.85)
j	n-C_3H_7	$-CH_3$	65	needles (isoPr-O-isoPr)	81— 82	$C_{12}H_{14}ON_2$	71.26 (71.31)	6.98 (6.88)	13.18 (13.25)
k	n-C_4H_9	$-CH_3$	67	powders (EtOH)	220—222[b]	$C_{13}H_{17}ON_2Cl$	61.78 (61.59)	6.78 (6.67)	11.08 (11.15)
l		$-CH_3$	38	needles (EtOH)	145—146	$C_{16}H_{14}ON_2$	76.25 (76.31)	5.12 (5.02)	11.86 (11.93
m		$-CH_3$	40	needles (EtOH)	148—150	$C_{16}H_{14}ON_2$	76.78 (76.71)	5.64 (5.55)	11.19 (11.28)
n		$-CH_3$	76	needles (EtOH)	168—169	$C_{16}H_{14}O_2N_2$	72.16 (72.31)	5.30 (5.34)	10.52 (10.47)
o		$-CH_3$	60	needles (EtOH)	152—154	$C_{17}H_{16}O_2N_2$	72.84 (72.95)	5.75 (5.87)	9.99 (10.03)
p		$-CH_3$	31	needles (EtOH)	230—232[b]	$C_{16}H_{15}ON_2Cl$	67.01 (67.15)	5.27 (5.38)	9.77 (9.59)

a) from 2-alkanoylaminobenzamide derivative
b) hydrochloride

On the other hand, in the reaction of 2-benzoylaminobenzamide (IIIa) in lieu of acetyl derivative with I, different results to those of acetyl derivative were obtained. When one mole of IIIa was reacted with two moles of I in dichloromethane under warming for 1 hr, a colorless precipitate was separated from the reaction mixture. After treating the precipitate with potassium carbonate solution, 2-phenyl-4*H*-3,1-benzoxazin-4-one (VIa) was obtained in 43.3% yield. This product was identified by the mixing melting point test with an authentic

sample prepared from the reaction of 2-benzoylaminobenzoic acid with acetic anhydride.[5] IR spectrum of VI revealed the presence of carbonyl group in lactone by its absorption band at 1760 cm^{-1}, while in the nuclear magnetic resonance (NMR) spectrum of VI signals of aromatic protons (7.78 ppm, 9H, multiplet) were observed. The mother solution was similarly treated with potassium carbonate solution and 4-ethoxy-2-phenylquinazoline (VIIa) was obtained as a by-product in 27.3% yield. The mass spectrum of VIIa showed its molecular ion peak at *m/e* 223, and IR spectrum of VIIa showed the presence of C=N by its absorption band at 1620 cm^{-1}. In NMR spectrum of VIIa signals of O-ethyl protons (1.52 ppm, 3H, triplet, $J=7.0$ Hz, CH_3; 4.75 ppm, 2H, quartet, $J=7.0$ Hz, O-CH_2-Me) and aromatic protons (7.78 ppm, 9H, multiplet) were observed. When the reaction of IIIa with I was carried out in the molar ratio of 1 : 1, benzoxazinone, VIa, was obtained exclusively, and no quinazoline-type compound was obtained. In the reaction of N-substituted 2-(benzoylamino)benzamide having methyl or phenyl group as the substituent, benzoxazinone derivative was also obtained exclusively in rather low yield, and any compound of quinazoline was not obtained. The process of these reactions are shown in Chart 3 and the compound obtained are listed in Tables II and III.

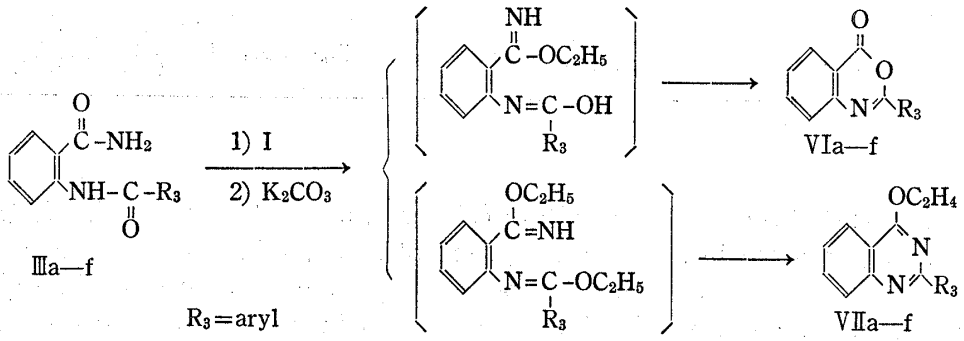
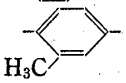
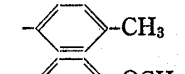
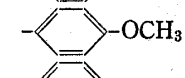
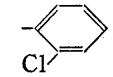
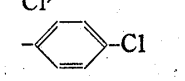


Chart 3

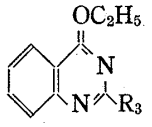
TABLE II.

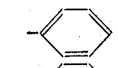
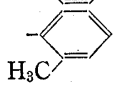
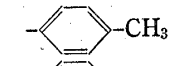
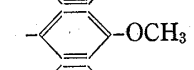
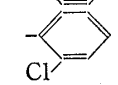
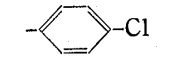
Compd. VI	R_3	Yield (%)[a]	Appearance (Recryst. solvt.)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
a		43	needles (EtOAc)	117—119	$C_{14}H_9O_2N$	75.32 (75.42)	4.06 (4.11)	6.27 (6.48)
b		42	powders (EtOAc)	113—115	$C_{15}H_{11}O_2N$	75.95 (75.75)	4.67 (4.78)	5.90 (5.87)
c		47	powders (EtOH)	152—154	$C_{15}H_{11}O_2N$	75.95 (75.81)	4.67 (4.85)	5.90 (5.71)
d		34	needles (EtOAc)	142—144	$C_{15}H_{11}O_3N$	71.14 (71.25)	4.38 (4.25)	5.53 (5.62)
e		38	powders (EtOH)	137—139	$C_{14}H_8O_2NCl$	65.26 (65.38)	3.13 (3.26)	5.44 (5.56)
f		32	needles (EtOH)	187—189	$C_{14}H_8O_2NCl$	65.26 (65.30)	3.13 (3.17)	5.44 (5.41)

a) from 2-aroylaminobenzamide

5) D.T. Zentmyer and E.C. Wagner, *J. Org. Chem.*, **14**, 967 (1949).

TABLE III.



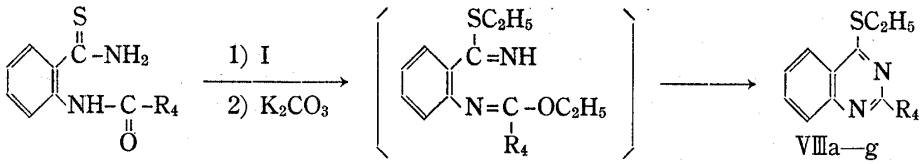
Compd. VII	R_3	Yield (%)[a]	Appearance (Recryst. solvt.)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
a		27	powders (EtOH)	55— 57	$C_{16}H_{14}ON_2$	76.78 (76.67)	5.64 (5.71)	11.19 (11.10)
b		20	powders (EtOH)	57— 59	$C_{17}H_{16}ON_2$	77.25 (77.12)	6.10 (6.02)	10.60 (10.49)
c		41	powders (EtOH)	74— 76	$C_{17}H_{16}ON_2$	77.25 (77.21)	6.10 (6.05)	10.60 (10.50)
d		15	powders (EtOH)	70— 72	$C_{17}H_{16}O_2N_2$	72.84 (72.71)	5.75 (5.59)	9.99 (9.79)
e		12	powders (EtOH)	78— 80	$C_{16}H_{13}ON_2Cl$	67.49 (67.52)	4.60 (4.51)	9.84 (9.72)
f		26	powders (EtOH)	117—118	$C_{16}H_{13}ON_2Cl$	67.49 (67.38)	4.60 (4.48)	9.84 (9.75)

a) from 2-aroylaminobenzamide

It is of interest that the reaction results of III were different to those of II. In the reaction of II with I, oxygen atom in a acylamino group of 2-acylaminobenzamide may react with I, as the first step, and then resulting iminoether may cyclize to corresponding quinazoline, as the second step. In contrast with II, oxygen atom of carboxamide seems to be ethylated with I selectively in the reaction of III, whereas the ethylation of oxygen atom in a benzoyl moiety may be hindered by the electronic effect of both benzene rings, reducing the electron density of oxygen atom in the benzoyl moiety. As the next step of the reaction, it may be infered that resulting mono-iminoether cyclized to 4-iminobenzoxazine by the nucleophilic attack of oxygen atom in the benzoyl moiety to carbon atom in the iminoether moiety and then resulting iminobenzoxazine may be hydrolized under basic condition *via* 4*H*-3,1-benzoxazin-4-one. In the reaction of III with excess amount of I, oxygen atom in the second carbonyl group may be also ethylated with excess amount of I before mono-iminoether may convert to the quinazoline-type compound, just as the similar manner to those described in the preceding paper.[1]

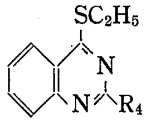
Next, the reaction of acylaminothiobenzamide (IV) in lieu of acylaminobenzamide with I was investigated. On reacting one mole of 2-benzoylaminothiobenzamide (IVa) with one mole of I, 4-ethylthio-2-phenylquinazoline (VIIIa) was obtained exclusively in 50% yield, and in 82% yield on reacting one mole of IVa with two moles of I, but any benzoxazinone derivative was not obtained in both reactions. Mass spectrum of VIIIa showed the molecular ion peak at *m/e* 266 and its fragment ion peak at *m/e* 205 ($M-SC_2H_5^+$) as a base peak. IR spectrum of VIIIa showed the presence of C=N by its absorption band at 1535 cm^{-1} while in NMR spectrum of VIIIa signals of S-ethyl protons (1.53 ppm, 3H, triplet, $J=6.6$ Hz, CH_3; 3.41 ppm, 2H, quartet, $J=6.6$ Hz, S-CH_2-Me) and aromatic protons (7.75 ppm, 9H, multiplet) were observed. The melting point and the other properties of VIIIa agreed with those of obtained by L. Legrand.[6] The compounds of IV having an alkanoyl or an aroyl group similary afforded corresponding ethylthioquinazoline derivatives and no difference in their reactivities could be observed. This reaction is shown in Chart 4 and VIII obtained is listed in Table IV.

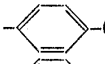
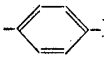
6) L. Legrand and N. Lozac'h, *Bull. Soc. Chim. France*, **1963**, 1161.



IVa—g R4=alkyl or aryl VIIIa—g

Chart 4

TABLE IV. 

Compd. VIII	R_4	Yield (%)[a]	Appearance	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
a		82	needles	52— 54	$C_{16}H_{14}N_2S$	72.15 (72.19)	5.30 (5.51)	10.52 (10.71)
b		65	powders	191—193[b]	$C_{17}H_{17}N_2SCl$	64.44 (64.51)	5.41 (5.47)	8.84 (8.91)
c		69	powders	185—186[b]	$C_{17}H_{17}ON_2SCl$	61.34 (61.21)	5.15 (5.07)	8.42 (8.49)
d		81	needles	135—137	$C_{16}H_{13}N_2SCl$	63.88 (64.01)	4.36 (4.48)	9.31 (9.39)
e		81	needles	155—157	$C_{16}H_{13}O_2N_3S$	61.72 (61.90)	4.21 (4.11)	13.50 (13.41)
f	$-CH_3$	53	powders	196—197[b]	$C_{11}H_{13}N_2SCl$	54.87 (54.93)	5.44 (5.31)	11.64 (11.73)
g	$-C_2H_5$	88	powders	150—152[b]	$C_{12}H_{15}N_2SCl$	56.57 (56.71)	5.93 (6.15)	11.00 (11.17)

a) from 2-acylaminothiobenzamide
b) hydrochloride

As shown in Chart 4, it was assumed in the reaction of IV with I that sulfur atom of thioamide may be ethylated selectively as the first step of the reaction, since it has been well known that sulfur atom in thioamides, thioureas, *etc.* is more easily ethylated by ethylating agents than oxygen atom in amides, ureas, *etc.* As the second step, oxygen atom in amide group of S-ethyl derivative may be ethylated with I successively and, consequently, resulting di-iminoether may cyclize to corresponding ethylthioquinazoline.

As described above, it was found that the reaction products of acylaminobenzamide with I might depend upon the nature of the acyl group; that is, the product was quinazoline derivative, when the acyl group was alkanoyl, and the main product was benzoxazinone, when the acyl group had as electron withdrowing nature. On the other hand, in the reaction of acylthiobenzamide, the product was found to be ethylthioquinazoline regardless of the nature of the acyl group.

Experimental

General Procedure for the Synthesis of 3-Substituted 2-Alkyl-3,4-dihydro-4-quinazolinone (Va—p)——A mixture of 0.01 mole of IIa—p and 3.8 g (0.02 mole) of I in 30 ml of dichloromethane was refluxed for 1 hr. The reaction mixture was treated with a small amount of 50% K_2CO_3 solution below 5° and into the solution further anhyd. K_2CO_3 was added to remove a small amount of water, and extracted with dichloromethane. After filtration of dichloromethane layer by suction, the dichloromethane extract was evaporated *in vacuo*, then the residue was recrystallized from a suitable solvent.

General Procedure for the Synthesis of 2-Aryl-4*H*-3,1-benzoxazin-4-one (VIa—f) and 2-Aryl-4-ethoxyquinazoline (VIIa—f)——A mixture of 0.005 mole of IIIa—f and 1.9 g (0.01 mole) of I in 30 ml of dichloro-

methane was refluxed for 1 hr, a colorless precipitate was separated from the reaction mixture. After filtration of dichloromethane layer by suction, the residual material was treated with a small amount of 50% K_2CO_3 solution below 5° and into the solution further anhyd. K_2CO_3 was added to remove a small amount of water, and extracted with dichloromethane. The dichloromethane extract was evaporated *in vacuo*, then the residue was recrystallized from a suitable solvent, 2-aryl-4*H*-3,1-benzoxazin-4-one was obtained. The mother solution was similarly treated with 50% K_2CO_3 solution and 2-aryl-4-ethoxyquinazoline was obtained.

General Procedure for the Synthesis of 2-Substituted 4-Ethylthioquinazoline (VIIIa—g)——A mixture of 0.01 mole of IVa—g and 3.8 g (0.02 mole) of I in 30 ml of dichloromethane was refluxed for 1 hr. The reaction mixture was treated with a small amount of 50% K_2CO_3 solution below 5° and into the solution further anhyd. K_2CO_3 was added to remove a small amount of water, and extracted with dichloromethane. After filtration of dichloromethane layer by suction, the dichloromethane extract was evaporated *in vacuo*, then the residue was obtained as a crystal or oil. The oil was converted into a hydrochloride.