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Reaction of *o*-Aminobenzamide Derivatives with Ethoxymethylenemalononitrile and Its Analogue

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A new synthetic method of *o*-aminobenzamide derivatives with ethyl ethoxymethylenecyanoacetate or ethoxymethylenemalononitrile gave high yield of 3,4-dihydro-4-oxoquinazoline and 3-aryl-3,4-dihydro-4-oxoquinazoline derivatives, and the mechanism of this synthetic reaction was discussed.

The synthesis of some derivatives of 3,4-dihydro-4-oxo-quinazoline, having the interesting biological activities,[2] have hitherto been reported by many researchers.[3]

In continuation of the works[4] on the reactivity of ethyl ethoxymethylenecyanoacetate (EMCA) and ethoxymethylenemalononitrile (EMMN) to various types of amines, we have newly found a new synthetic method of 3,4-dihydro-4-oxoquinazoline derivatives by the reaction of these reagents with *o*-aminobenzamide derivatives. Heating of *o*-aminobenzamide with equivalents amount of EMCA and EMMN in ethanol under reflux for 6 hr gave, in 92 and 75% yield, the corresponding ethyl (2-carbamoylphenyl)aminomethylenecyanoacetate (IIIa) and (2-carbamoylphenyl)aminomethylenemalononitrile (IIIb). The infrared (IR) absorptions of the products exhibited cyanogen group at 2230 cm^{-1} and carboxamide group at 1650 cm^{-1}, as shown in Chart 1. Next, treatment of compounds (IIIa, IIIb) of these

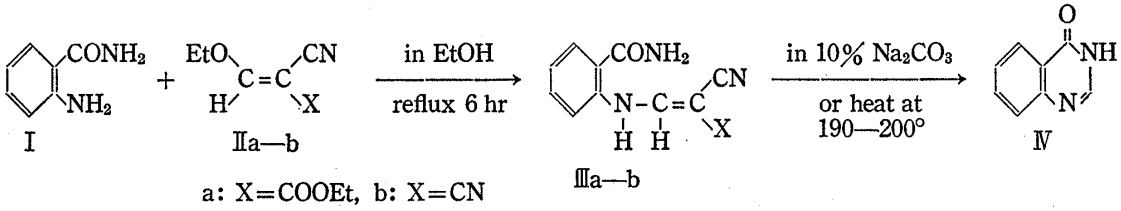


Chart 1

enamines with an aqueous solution of sodium carbonate for 3 hr at 80° afforded 3,4-dihydro-4-oxoquinazoline (IV) in 54 and 79% yield, which was identical with the authentic samples[3a] prepared by the reaction of anthranylamide with triethyl orthoformate under refluxing for 18 hr. Also, pyrolysis of these enamine compounds (IIIa, IIIb) at 190—200° for 1 hr afforded product IV in 54 and 65% yield.

On the other hand, heating of EMCA with equivalent amount of (2-arylcarbamoyl)aniline

1) Location: *Shirokane 5-9-1, Minato-ku, Tokyo, 108, Japan.*

2) *a*) C. Paal and M. Busch, *Chem. Ber.*, **22**, 2683 (1889); *b*) G. Maffei, German Patent 525653 [*C.A.*, **25**, 4664 (1931)]; *c*) I.G. Farbenind. A.G., British Patents 287179, 288159 [*C.A.*, **23**, 396 (1929)]; *idem*, British Patent 330583. *Chem. Zentr.*, **101**, 11, 1773 (1930).

3) *a*) C. Runti, V.D'Osualdo and F. Ulian, *Ann. Chim.* (Rome), **49**, 1668 (1959); *b*) R.H. Clark and E.C. Wagner, *J. Org. Chem.*, **9**, 55 (1944); *c*) N.J. Leonard and W.V. Ruyle, *ibid.*, **13**, 903 (1948); *d*) J.F. Bunnett and J.Y. Bassett. Jr, *ibid.*, 27, 3714 (1962); *e*) S. Rani, O.P. Vig, I.S. Gupta and K.S. Narang, *J. Indian Chem. Soc.*, **30**, 331 (1953); *f*) J.F. Meyer and E.C. Wagner, *J. Org. Chem.*, **8**, 239 (1943); *g*) W.L.F. Armarego, "The Chemistry of Heterocyclic Compounds, Fused Pyrimidines: Part I, Quinazolines," ed. D.J. Brown, John Wiley & Sons, Inc., New York, 1967, p. 87.

4) K. Takagi, K. Nagahara and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **18**, 2353 (1970).

derivatives (V) under the similar conditions gave 49—76% yield of ethyl (2-arylcarbamoylphenyl)aminomethylenecyanoacetate derivatives (VIa).

Thereupon, 3-aryl-3,4-dihydro-4-oxoquinazoline derivatives (VII) were obtained in approximate 73% yield by refluxing compound VIa with an aqueous solution of sodium carbonate (Method A).

On the other hand, heating of EMMN with equivalent amount of compound V in ethanol under reflux for 6 hr gave only the compound VII in 29—96% yield, and the addition product of type VI was not obtained.

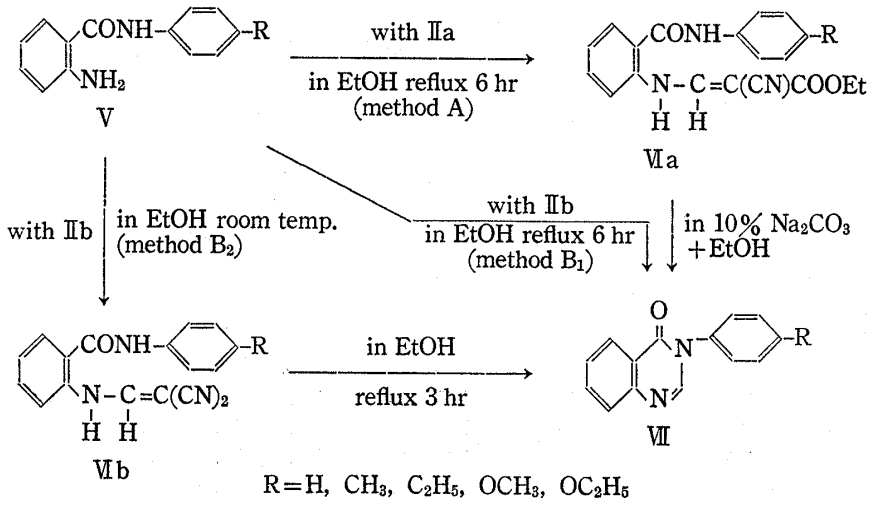
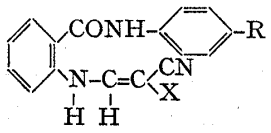


Chart 2

TABLE I. 

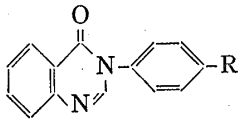
R	X	mp (°C)	Yield[a] (%)	IR ν_{max}^{KBr} (cm^{-1}) [CN CONH– (CO–O–)]	Formula	Analyses (%) Calcd. (Found) C H N	Mass M+
H	COOEt	204—205	75.7	2230 1650 (1685)	$C_{19}H_{17}O_3N_3$	68.05 5.11 12.53 (67.79) (5.09) (12.38)	335
CH_3	COOEt	207—208	49.3	2230 1650 (1685)	$C_{20}H_{19}O_3N_3$	68.75 5.48 12.03 (69.05) (5.44) (12.09)	349
C_2H_5	COOEt	189—191	55.6	2230 1650 (1685)	$C_{21}H_{21}O_3N_3$	69.40 5.83 11.50 (69.62) (5.86) (11.78)	363
OCH_3	COOEt	205—206	70.4	2230 1645 (1690)	$C_{20}H_{19}O_4N_3$	65.74 5.24 11.50 (65.87) (5.29) (11.60)	365
OC_2H_5	COOEt	204—206	65.0	2230 1645 (1685)	$C_{21}H_{21}O_4N_3$	66.48 5.58 11.08 (66.35) (5.61) (11.10)	379
H	CN	201—203	63.2	2230 1630	$C_{17}H_{12}ON_4$	70.82 4.20 19.44 (70.60) (4.25) (19.60)	288
CH_3	CN	170—172	91.9	2215 1640	$C_{18}H_{14}ON_4$	71.51 4.67 18.53 (71.73) (4.70) (18.30)	302
C_2H_5	CN	175—177	71.4	2220 1640	$C_{19}H_{16}ON_4$	72.13 5.10 17.71 (72.34) (5.08) (17.74)	316
OCH_3	CN	176—178	90.6	2220 1645	$C_{18}H_{14}O_2N_4$	67.91 4.43 17.60 (68.06) (4.44) (17.36)	318
OC_2H_5	CN	195—196	86.3	2215 1650	$C_{19}H_{16}O_2N_4$	68.66 4.85 16.86 (68.45) (4.88) (17.08)	332

a) Yields are based on products purified by recrystallization.

Moreover, stirring of EMMN with equivalent amount of the compound V in ethanol at room temperature for 3 hr gave 63—92% yield of (2-arylcarbamoylphenyl)aminomethylenemalononitrile derivatives of addition product of type VIb. These derivatives are listed in Table I.

Next, heating of compound VIb in ethanol under reflux for 3 hr afforded the compound of type VII in approximate 86% yield (Method B). The 3-aryl-3,4-dihydro-4-oxoquinazoline derivatives obtained by these reactions were summarized in Table II. The products V and VII were readily synthesized by the new synthetic methods, which was identical with the authentic material prepared according to the method of Wagner's,[3b] Leonard's[3c] and Rani's.[3e]

Table II.



No.	R	Appearance	Recryst. solvt.	mp (°C)	Yield[a] (%) Method A	Method B		IR ν_{max}^{KBr} (cm^{-1}) [>C=O]	Mass M$^+$
						B_1	B_2		
1	H	needles	C_2H_5OH	125—127[b]	54.4	29.4	90.9	1680	222
2	CH_3	needles	$CH_3COOC_2H_5$	143—145[c]	62.5	95.8	90.9	1690	236
3	C_2H_5	needles	C_2H_5OH	126—128	85.0	48.0	75.0	1680	250
4	OCH_3	needles	C_2H_5OH	189—191[d]	76.1	74.0	91.1	1680	252
5	OC_2H_5	needles	C_2H_5OH	158—160[e]	86.4	59.3	82.5	1690	266

a) Yields are based on products purified by recrystallization.
b) Lit.,[3c] 136—137°, c) Lit.,[3b] 144—145°, d) Lit.,[3e] 186° e) Lit.,[3c] 158°

As described above, it may be said that the mechanism of the formation of compounds types of IV and VII seemed to be similar to that of benzimidazole by the reaction of *o*-phenylenediamine with EMMN or EMCA.[5] Namely, the attack of the amino nitrogen on the *β*-carbon of these enamines (IIIa,b; VIa,b), accompanied by the elimination of the resonance-stabilized anion VIII, results in the ring closure. The tendency to form the 3-aryl-3,4-dihydro-4-oxoquinazoline system VII in the above reactions should act as a strong driving force which favors these reactions.

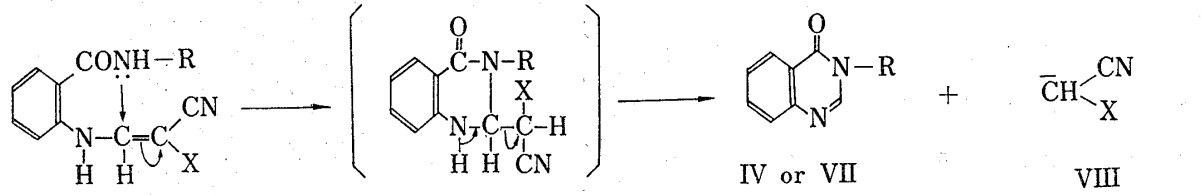


Chart 3

Finally, the new synthetic process of 4-oxoquinazoline derivatives by the reaction of *o*-aminobenzamide derivatives with EMMN or EMCA could easily be synthesized by Method B, and thus it may be excellent for problem in point of view of yield. Also, the cyclization of *o*-aminoamide compound of heterocyclic systems with EMMN or EMCA will be widely available for the preparation of numerous heterocyclic systems containing a fused pyrimidine ring.

5) A.A. Santilli, W.F. Bruce and T.S. Osdene, *J. Med. Chem.*, 7, 68 (1964).

Experimental[6)]

Ethyl (2-Carbamoylphenyl)aminomethylenecyanoacetate (IIIa)——To a solution of 4.0 g (0.029 mole) of *o*-aminobenzamide in 50 ml of EtOH was added 4.9 g (0.029 mole) of ethyl ethoxymethylenecyanoacetate (EMCA) and the mixture was refluxed on a water bath for 6 hr. After cooling, the product was removed by filtration and recrystallized from acetonitrile to give 7 g (91.9%) of IIIa as colorless needles, mp 174—175°. Mass Spectrum *m/e*: 259 (M^+). *Anal.* Calcd. for $C_{13}H_{13}O_3N_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.25; H, 5.05; N, 16.31.

(2-Carbamoylphenyl) aminomethylenemalononitrile (IIIb)——To a solution of 4.9 g (0.036 mole) of *o*-aminobenzamide in 50 ml of EtOH was added of 4.3 g (0.036 mole) of ethoxymethylenemalononitrile (EMMN). The mixture was then refluxed on a water bath for 6 hr. Resulted precipitates were collected and recrystallized from acetonitrile to give 5.7 g (74.6%) of IIIb as colorless powders, mp 196—198°. Mass Spectrum *m/e*: 212 (M^+). *Anal.* Calcd for $C_{11}H_8ON_4$: C, 62.25; H, 3.80; N, 26.40. Found: C, 62.51; H, 3.91; N, 26.66.

3,4-Dihydro-4-oxoquinazoline (IV)——Method 1: To 25 ml of 10% aqueous Na_2CO_3 was added 1 g of IIIa (or IIIb) and warmed at 80° for 3 hr. After cooling, the mixture was acidified with CH_3COOH to precipitate crystals, which were filtered off, washed with H_2O and dried giving 53.6% and 78.6% yield of IV as colorless needles, mp 211—212° (lit.,[3a)] 218°). Mass Spectrum *m/e*: 146 (M^+). *Anal.* Calcd. for $C_8H_6ON_2$: C, 65.74; H, 4.14; N, 19.17. Found: C, 65.55; H, 4.04; N, 19.21.

Method 2: One gram of IIIa (or IIIb) of these enamines were heated on an oil bath for 1 hr at 190—200°. After cooling, the solid product was recrystallized from H_2O to give 53.9% and 64.6% yield of IV, respectively.

General Procedure for Syntheses of Ethyl (2-Arylcarbamoylphenyl)aminomethylenecyanoacetate Derivatives (VIa)——To a solution of 0.01 mole of (2-arylcarbamoyl)aniline derivative (V) in 50 ml of EtOH was added 0.01 mole of EMCA and the mixture was refluxed on a water bath for 6 hr. After cooling, the separated products were collected by filtration and recrystallized from acetonitrile to give as colorless needles. Details of the data were summarized in Table I.

General Procedure for Syntheses of (2-Arylcarbamoylphenyl)aminomethylenemalononitrile Derivatives (VIb)——To a solution of 0.01 mole of V in 50 ml of EtOH was added with stirring 0.01 mole of EMMN. The reaction mixture was continued to stirring for 6 hr at room temperature. Precipitated crystals were filtered by suction, and recrystallized from acetonitrile to give VIb, as colorless needles. Details of the date were summarized in Table I.

3-Aryl-3,4-dihydro-4-oxoquinazoline Derivatives (VII)——Method A: To a solution of 0.03 mole of VIa in 10 ml of EtOH was added 40 ml of 10% Na_2CO_3 solution. The mixture was refluxed on a water bath for 6 hr. After cooling, the mixture was acidified with CH_3COOH to precipitate crystals, which were filtered off, washed with H_2O and dried. Recrystallization from EtOH gave VII.

Method B (Direct Method B_1): To a solution of 0.02 mole of V in 50 ml of EtOH was added 0.02 mole of EMMN and the mixture was refluxed on a water bath for 6 hr. After cooling, the separated products were collected by filtration and treated by the method similar to method A.

(Method B_2): In 50 ml of EtOH was added 1 g of VIb and refluxed on a water bath for 3 hr. After cooling, the reaction product was treated by the method similar to method A. R=C_2H_5 *Anal.* Calcd. for $C_{16}H_{14}ON_2$: C, 76.77; H, 5.64; N, 9.60. Found: 76.65; H, 5.62; N, 9.53. Details of the data were summarized in Table II.

6) All melting points are uncorrected. The IR spectra were recorded on a Japan Spectroscopic Model IRA-1 spectrometer. Mass spectra were obtained on a JMS-OlS spectrometer (Japan Electron Optics Laboratory Co., Ltd.).