THE REACTION OF O-ETHYL SUCCINIMIDE WITH PRIMARY AND SECONDARY AMINES. A SIMPLE SYNTHESIS OF SOME 4(3H)-QUINAZOLONES AND QUINAZOLINES HAVING PROPIONIC ACID AT 2-POSITION

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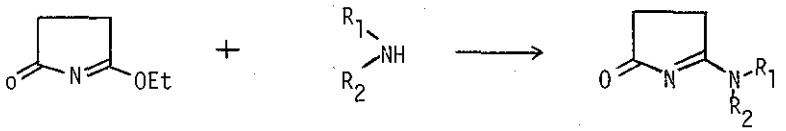
The reaction of O-ethyl succinimide (I) with various primary and secondary amines (II) afforded keto-amidines (III) in satisfactory yields. The treatment of keto-amidines (IIIi, IIIj, and IIIk) prepared from anthranilate and o-acylanilines with sodium in alcohol afforded quantitatively quinazolones (VIa and VIb) and quinazolines (VId and VIe) having propionic acid ester at 2-position. The sequence of these reactions for quinazolones and quinazolines can be carried out in the same reaction-vessel by successive addition of the reagents.

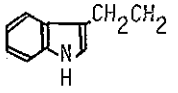
O-Ethyl succinimide (I) was first prepared by Comstock and Wheeler[1] in 1891. After long silence, some interesting behaviors of this compound (I) were reported by two groups in recent years.[2] I seems to be a hopeful synthon because of the reactive imidate group included in its structure.[3] In this paper we wish to report a simple one-pot synthesis of 4(3H)-quinazolones and quinazolines having propionic acid at 2-position[4] from I and ortho carbonyl aniline derivatives.

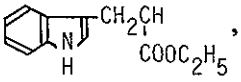
As the reported examples[5], we observed that the reaction of various amines (II) with I yielded keto-amidines (III) in satisfactory yields. The physical and



I II a - o III a - o

a : R_1=R_2=H[6], b : R_1=H, R_2=CH_3[6], c : R_1=H, R_2=$C_6H_5CH_2$[6],

d : R_1=H, R_2=$CH_3O(p)C_6H_4$, e : R_1=H, R_2=C_6H_5CONH, f : R_1=H, R_2= 

g : R_1=H, R_2=  , h : R_1=H, R_2=$CF_3(o)C_6H_4$,

i : R_1=H, R_2=$CH_3OOC(o)C_6H_4$, j : R_1=H, R_2=$C_6H_5CO(o)C_6H_4$,

k : R_1=H, R_2=$CH_3CO(o)C_6H_4$, l : R_1-R_2=-$(CH_2)_4$-, m : R_1-R_2=-$(CH_2)_5$-

n : R_1=R_2=CH_3, o : R_1=R_2=-$(CH_2)_2O(CH_2)_2$-

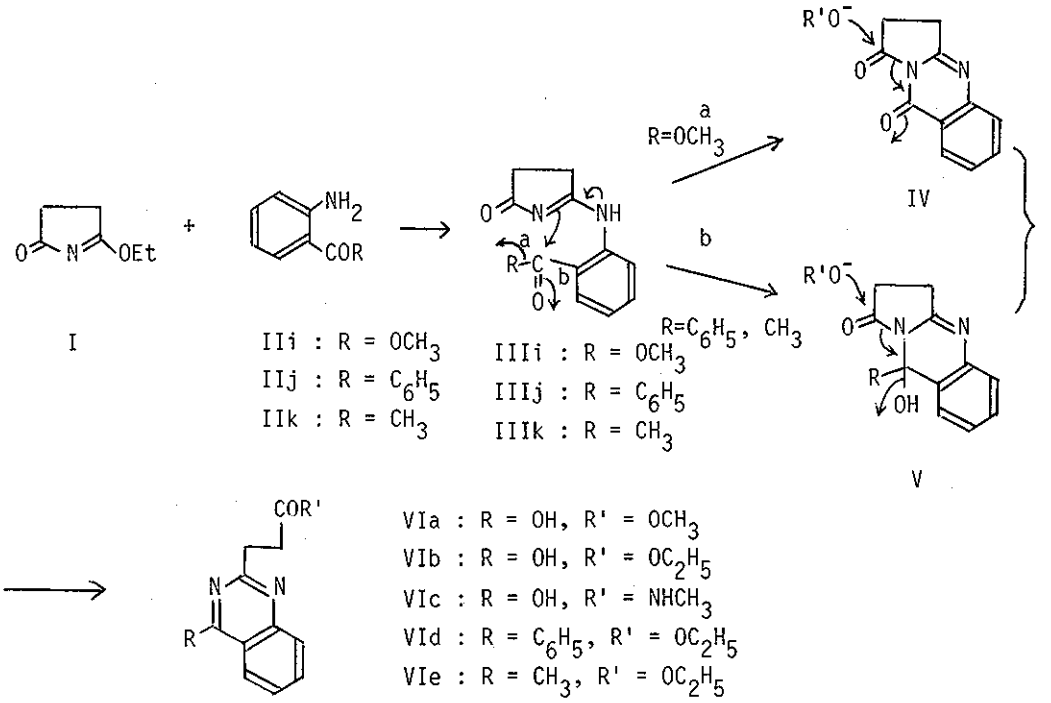
spectral properties of III are summarized in Table 1. This synthetic method of III, which seems to be an usual one, is superior to the former ones, for instance, the past synthetic methods of 5-amino-$\Delta^{1(5)}$-pyrrolin-2-one (IIIa) need three steps from ethyl β-bromopropionate[7], two steps from succinonitrile and liquid ammonia[8], and one step from succinonitrile and 1,1,3,3-tetramethylbutyl hypoperoxide.[9] By our method, the just mixing of the EtOH solution of I (1 eq mol) and the concentrated aqueous ammonia (28%, 1.1 eq) is sufficient to give the pure solid (IIIa). In the cases of aniline derivatives (IIh, IIi, IIj, and IIk) having the electron-withdrawing groups at ortho position, the reactions in EtOH were very slow at room temperature (Table 1) and lowered yields at reflux temperature. However, no solvent-condition at elevated temperature (80-140°) overcame this disadvantage and gave good results.

From above observation, a simple one-pot reaction of quinazolones and quinazolines (VI) was attempted and accomplished. The typical procedure employed was as follows : A mixture of I(2 mmol) and IIi(2 mmol) was heated at 130-140° (bath

Table 1. Keto-amidines (III)

Compound	Reaction Time[a]	Yield (%)	m.p. (°C)	Spectral Data[b]
IIIa	2.5 h	98	250-251 (dec)[c]	UV 226, M^+ 98, IR 1710, 1690, 1630, NMR(d_6-DMSO) 2.30(2H,m), 2.60(2H,m), 8.0(1H,b)
IIIb	3 h	95	149-152	UV 231, M^+ 112, IR 1720, 1660, 1600, NMR(d_6-DMSO) 2.3(2H,m), 2.55(2H,m), 2.80(3H,d), 8.4(1H,b)
IIIc	4 h	69	195-196	UV 234, M^+ 188, IR 1700, NMR(d_6-DMSO) 2.3(2H,m), 2.6(2H,m), 4.25(2H,d), 7.23(5H,s), 8.9(1H,b)
IIId	4 h	92	212-213	UV 212, 278, M^+ 204, IR 1700, 1630, NMR(d_6-DMSO) 2.40(2H,m), 2.80(2H,m), 3.70(3H,s), 6.90(2H,d), 7.85(2H,d)
IIIe	4 h	98	271-273 (dec)	UV 203, 264, M^+ 217, IR 1760, NMR (d_6-DMSO) 2.50(2H,m), 2.80(2H,m), 7.5(3H,m), 7.8(2H,m)
IIIf	10 h	45	214-216	UV 223, 272, 282, 290, M^+ 241, IR 1715, 1690, NMR(d_6-DMSO) 2.2-2.7(4H, m), 2.90(2H,t), 3.55(2H,m),6.80-7.60 (5H,m), 8.60(1H,b)
IIIg	10 h	86	215-216	UV 222, 272, 282, 290, M^+ 313, IR 1740, 1710, NMR(d_6-DMSO) 1.1(3H,t) 2.3(2H,m), 2.6(2H,m), 3.2(2H,d), 4.05 (2H,q), 4.7(1H,q), 6.9-7.6(5H,m)
IIIh	2 months	58	178-179	UV 204, 227, 278, M^+ 242, IR 1750, NMR($CDCl_3$) 2.4-3.0(4H,m), 6.7-7.6 (5H,aromatic)
IIIi	1 day	54	141-142	UV 212, 267, 302, M^+ 232, IR 1730, 1690, 1610, NMR($CDCl_3$) 2.60(2H,m), 3.00(2H,m), 3.90(3H,s), 7.0-7.20 (2H,m), 7.55(1H,t), 8.00(1H,d),8.90
IIIj	1 month	78	241-242 (dec)	M^+ 278, IR 1770
IIIk	80 h	34	152-153 (dec)	UV 217, 267, 277, 295, M^+ 216, IR 1760, 1645, NMR(d_6-DMSO), 2.00(3H,s), 2.40-2.90(4H, m), 7.05-7.60(4H,m)
IIIl	4 h	93	127-129	UV 238, M^+ 152, IR 1705, 1670, NMR (CD_3OD) 2.50(4H,m),2.55(2H,m), 2.90 (2H,m), 3.60(4H,m)
IIIm	4 h	90	101-102	UV 241, M^+ 166, IR 1700, NMR($CDCl_3$) 1.70(6H,s), 2.70(4H,m), 3.50(2H,m), 3.90(2H,m)
IIIn	3 h	90	119-120	UV 239, M^+ 126, IR 1700,1660, NMR ($CDCl_3$) 2.65(4H,m), 3.10(3H,s), 3.24 (3H,s)
IIIo	4 h	63	168-169	UV 242, M^+ 168, IR 1690, NMR($CDCl_3$) 2.70(4H,m), 3.40-4.00(8H,m)

a) The reaction time for the reaction in EtOH at room temperature is listed. This is not always an optimum condition. b) UV (λmax, EtOH, nm), IR (KBr, cm^{-1}), PMR (ppm). c) lit. 227-230(dec)[7], 250(dec)[8], 238-240(dec)[9]



temp.) for 2 h. After cooling, the reaction mixture was suspended in EtOH and sodium (60 mg) was added with stirring to this suspension at room temperature. After stirring for 30 min, the clear reaction mixture was poured in water, and the usual work-up gave white solid, which was recrystallized from EtOH. The physical and spectral properties of VI were summarized in Table 2.

The mechanism of formation of quinazolones and quinazolines may be visualized as above. Tricyclic compound (IV), mp 173-176° (dec), UV (EtOH, λmax, nm) 210, 229, 254, 263, 273, 313, 325, MS (M^+) 200, IR (KBr, cm^{-1}) 1790, 1690, 1620, NMR ($CDCl_3$) ppm 2.90 (2H,m), 3.10 (2H,m), 7.20-7.80 (3H,m), 8.25 (1H,d), was also isolated as a by-product from the reaction of I with IIi. IIIi and IV were easily separated by recrystallization from benzene. IIIi was also converted to IV by heating at 142° (mp. of IIIi). Refluxing IV in MeOH (for 14 h), EtOH (for 14 h), and EtOH containing CH_3NH_2 (for 1 h) gave quantitatively 2-substituted quinazo-

Table 2. Quinazolones and Quinazolines

Compound	Yield (%)	m.p. (°C)	Spectral Data[a]
VIa	quant.[b] 65[c]	188-190	UV 203,225, 263, 305, 316, M^+ 232, IR 1730, 1680, 1620, NMR($CDCl_3$) 3.05(4H,m), 3.70(3H,s), 7.20-7.80(3H,m), 8.25(1H,d)
VIb	quant.[b] 68[c]	175-177	UV 202, 225, 263, 305, 316, M^+ 246, IR 1725, 1665, 1615, NMR(d_6-DMSO) 1.15(3H,t), 2.85(4H, m), 4.05(2H,q), 7.40-7.80(3H,m), 8.05(1H,d)
VIc	quant.[b]	246-248(dec)	UV 202, 224, 264, 304, 316, M^+ 231, IR 1680, 1645, 1610, NMR(d_6-DMSO) 2.60(2H,m), 2.85(2H, m), 3.35(3H,s), 7.40-8.00(3H,m), 8.10(1H,d)
VId	quant.[d] 60[c]	93-94	UV 206, 226, 260, 320, M^+ 306, IR 1720, NMR ($CDCl_3$) 1.10(3H,t), 3.00(2H,t), 3.65(2H,t), 4.05(^{3}2H,q), 7.4-8.5(9H,m)
VIe	quant.[e] 37[c]	40-41	UV 203, 226, M^+ 244, IR 1735, NMR($CDCl_3$) 1.15 (3H,t), 2.95(2H,t), 3.50(2H,t), 4.05(2^3H,q), 7.50-8.20(4H,m)

a) UV (λmax, EtOH, nm), IR (KBr, cm^{-1}), PMR (ppm). b) From IV. c) By one-pot reaction. d)From IIIj. e) From IIIk.

lones (VIa, VIb, and VIc) and the reactions were very accelerated by addition of sodium. These results indicate that IV is the intermediate of VIa, VIb, and VIc.

In conclusion, the above investigation clarifies that O-ethyl succinimide (I) is suitable as a starting material for synthesis of quinazolones and quinazolines having propionic acid group at 2-position. Synthetic approach for pharmacologically active derivatives is now under progress.

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REFERENCES AND FOOTNOTES

* Satisfactory analytical data have been obtained for all compounds described in this paper.

1 S. J. Comstock and H. L. Wheeler, Am. Chem. J., 1891, 13, 522.

2 a) T. H. Koch and R. J. Slusk, Tetrahedron Lett., 1970, 2391. b) K. Matoba and

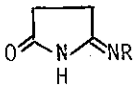
T. Yamazaki, Chem. Pharm. Bull. (Tokyo), 1974, 22, 2999; T. Yamazaki, K. Matoba, S. Imoto, and M. Terashima, Chem. Pharm. Bull.(Tokyo), 1976, 24, 3011.

3 "The Chemistry of Amidines and Imidates", edited by S. Patai, 1975, John Wiley & Sons, New York.

4 Although many biologically active quinazolones and quinazolines are known, no derivative having propionic acid at 2-position is prepared yet. Synthesis of them seems comparatively difficult; cf. R. Hardman and M. W. Partridge, J. Chem. Soc., 1954, 3878.

5 The reactions of I with aniline[1)] and phenylhydrazine[2b)] are reported.

6 Katritzky et al. state that the potentially tautomeric structure for IIIa is 5-amino-$\Delta^{1(5)}$-pyrrolin-2-one; S-O. Chua, M. J. Cook, and A. R. Katritzky, J. Chem. Soc. Perkin II, 1974, 546. We could also confirmed the predominant tautomeric forms for IIIb and IIIc. Namely, PMR spectra (d_6-DMSO) of IIIb and IIIc show doublet signals for methyl and methylene protons, respectively, which are converted to singlet signals by adding D_2O. The another tautomeric isomer (III') can be neglected from this fact.



III'

7 M. Protiva, V. Rericha, and J. O. Jilek, Chem. Listy, 1950, 44, 231 [C. A. 45, 7953c (1951)].

8 J. A. Elvidge and R. P. Linstead, J. Chem. Soc., 1954, 442.

9 D. B. Denney and J. D. Rosen, Tetrahedron, 1964, 20, 271.

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