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Studies on Benzoheterocyclic Derivatives. XIV.[1] Synthesis of Spiro[cycloalkane-1',2(1H)quinazolin]-4(3H)-ones and the Related Compounds

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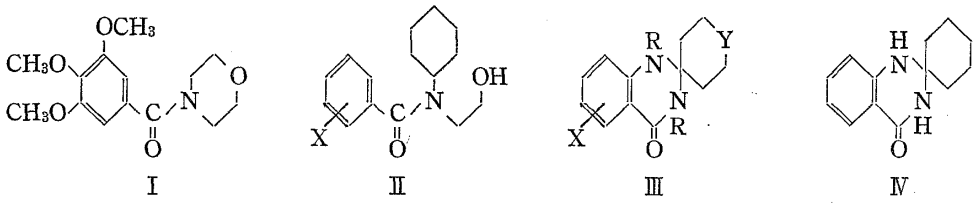
A series of 1- or 3-substituted spiro[cycloalkane-1',2(1H)quinazolin]-4(3H)-ones and the related compounds were synthesized for pharmacological testing. They could be prepared *via* anthranilic acid N-substituted amides or N-substituted anthranilamides with appropriate ketones, but attempts for introduction of the substituents at 1 or 3 position of spiro[cyclohexane-1',2(1H)quinazolin]-4(3H)-one were failed. Mass fragmentation pathways are described for the several representative compounds briefly.

A number of 3,4,5-trihydroxybenzamides have been reported[3] to possess CNS depressant or tranquilizing activity, in particular, trimetozin (I)[4] have been evaluated clinically as a mild tranquilizer. Recently some of N(β-hydroxy)ethyl -N-cyclohexylbenzamide derivatives (II) have been reported[5] as approximately equipotent to chlorpromazine in CNS depressant activity.



I II III IV

Chart 1

These compounds (I and II) may be considered benzamide derivatives which possess lipophylic moiety as N-substituent. On the other hand, numerous studies appeared on the analgetic, antiphlogistic, and antipyretic activity of *o*-amino benzamides (anthranilamides).[6] Thus we intended to synthesize a group of the title compounds (III) which we were able to view as cyclized *o*-amino benzamides.

1) Part XIII: N. Hirose, S. Sohda, S. Kuriyama, and S. Toyoshima, *Chem. Pharm. Bull.* (Tokyo), **21**, 960 (1973).
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3) *a*) Y.G. Perron, U.S. Patent 2870145 (1954); *b*) S. Hayao, *J. Org. Chem.*, **26**, 3414 (1961); *c*) L. Vargha, Hungarian Patent 48503 (1961); *d*) E. Kasztreiner, *Biochem. Pharmacol.*, **1**, 551 (1962); *e*) L. Tody, Hungarian Patent 151642 (1964); *f*) E.G. Tapszeergyar, British Patent 992353 (1965); *g*) R.B. Petigara, *J. Med. Chem.*, **11**, 332 (1968).
4) 4(3,4,5-Trimethoxybenzoyl)morpholine.
5) W.D. Roll, *J. Pharm. Sci.*, **57**, 1671 (1968); *idem*, *J. Med. Chem.*, **13**, 303 (1970); *idem*, *J. Pharm. Sci.*, **50**, 1838 (1970).
6) *a*) K. Thomae, G.m.b.H., German Patent 1091120 (1960); *b*) S.M. Gadekar, *J. Org. Chem.*, **26**, 613 (1961); *c*) L.A. Shabrova, *Khim. Geterotsikl. Soedin.*, **1**, 135 (1967); *d*) Arziende Chimiche Riunite Angelini Francesco, British Patent 1057667.

Various biological activities have been encountered in compounds having the quinazolinone ring system. For example, quinazolinones with CNS activity[7] are known, and methaqualone[8] has been utilized for clinical use as a hypnotic; other quinazolinones have antiphlogistic,[9] muscle relaxant,[9] antihistaminic,[10] diuretic[11] and hypotensive activities.[12]

Literature reports regarding the synthesis of 1,2,3,4-tetrahydroquinazolin-4-ones which have spiro ring in their 2-position are sparse, in fact they elaborate nothing else but attempts[13] of ring closure of spiro[cyclohexane-1′,2(1H)quinazolin]-4(3H)-one. Synthesis of spiro[cycloalkane-1′,2(1H)quinazolin]-4(3H)-one analogs having substituents in their 1 or 3 position and their pharmacological activities have not been reported in any literature to date.

In this paper, the synthesis of a number of the compounds represented by the general formula (III) is described. First, spiro[cyclohexane-1′,2(1H)quinazolin]-4(3H)-one (IV) was prepared by a modified Somasekhara's method.[13a] In an attempt to prepare 1- or 3-substituted analogs of IV, alkylation and acylation of (IV) was studied; to prepare 1-substituted derivatives, compound (IV) was treated with β-bromoethyl chloride in the presence of potassium carbonate in isopropanol solution under reflux, and also (IV) was refluxed with chloroacetyl chloride in the presence of pyridine in chloroform solution, however no reaction occured, and (IV) unreacted was recovered quantitatively. Moreover, in order to prepare 3-substituted derivatives, compound (IV) was alkylated with either ethylene bromohydrin or ethyliodide in the presence of sodium hydride in toluene or dimethylformamide solution under heating, but these attempts of alkylation were also unsuccessful. Accordingly it was assumed that the introduction of alkyl or acyl group to (IV) at the position 1 or 3 was impossible. The unsuccessful attempts to introduce the substituents led us to investigate the cyclization of N-substituted anthranilamides to desired 1- or 3-substituted (IV) analogs.

All of the compounds (III) were prepared by these methods as illustrated in Chart 2.

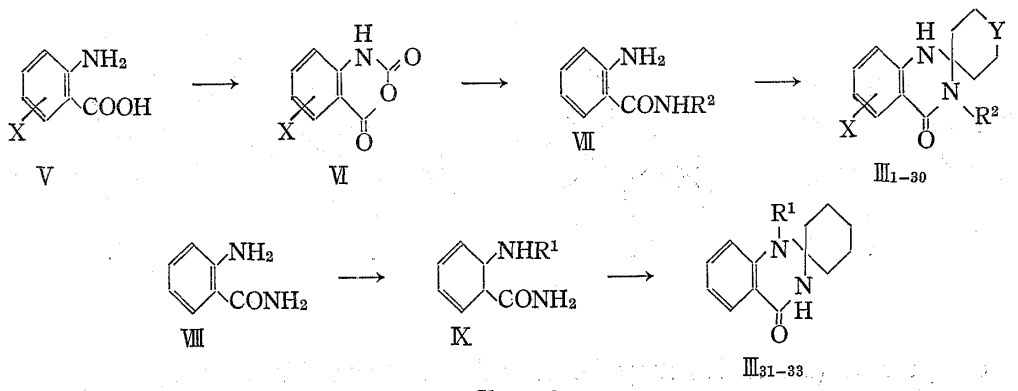


Chart 2

In order to prepare 3-substituted derivatives (III_{1-30}), 4 or 5-substituted isatoic anhydride (VI) were synthesized from corresponding anthranilic acids (V)[14] by the phosgenation

7) *a*) K.H. Bolz, H.D. Dell, and M. Aubert-Schweer, *Arzneimittel. Forsch.*, **13**, 688 (1963); *b*) S. Peterson, H. Herlinger, and W. Siefken, *Angew. Chem.*, **74**, 855 (1962); *c*) C. Saito, S. Sasaki, Y. Yukawa, and H. Takagi, *Arzneimittel. Forsch.*, **19**, 1945 (1969); *d*) J.H. Gogerty, L.C. Iorio, and H.W. Barness, *J. Med. Chem.*, **14**, 878 (1971).

8) 2-Methyl-3(*o*-tolyl)-4(3H)quinazolinone; A. Ravina, *Presse. Med.*, **67**, 891(1959).

9) *a*) G. Heszkovsky, I. Erdély, and L. Tardos, *Acta. Physiol. Acad. Sci. Hung.*, **27**, 81(1964); *b*) M. Vincent, J.C. Poignant, and C. Remond, *J. Med. Chem.*, **14**, 714(1971).

10) G. Muacević, H. Stozer, and H. Wick, *Arzneimittel. Forsch.*, **15**, 613(1965).

11) E. Cohen, B. Klarbert, and J.R. Vaugham, Jr, *J. Am. Chem. Soc.*, **82**, 2731(1960).

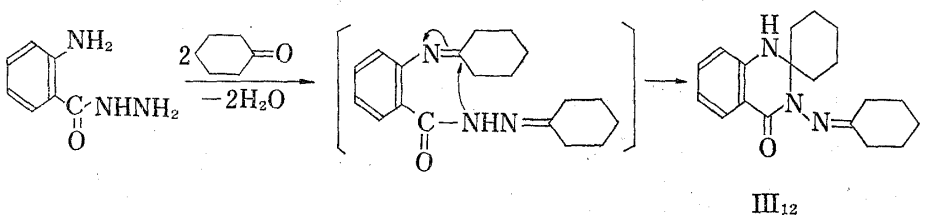
12) S. Hayao, H.J. Havera, and H.E. Harzler, *J. Med. Chem.*, **8**, 807 (1965).

13) *a*) S. Somasekhara, V.S. Dighe, and S.L. Mukherjee, *Current Sci.*, **33**, 645 (1964); *b*) E. Ziegler, *Monatsh. Chem.*, **96**, 411 (1965); *c*) P. Aeberli, *J. Org. Chem.*, *33*, 2402 (1968); *d*) H. Bohme, *Arch. Pharm.*, **293**, 1101 (1960); *e*) W. Steiger, *Monatsh. Chem.*, **100**, 146 (1969).

14) R.E. Rutz, *J. Am. Chem. Soc.*, **68**, 1285 (1946).

technique reported for anthranilic acid.[15,16] Diverse type of anthranilic acid N-substituted amides (VII) were prepared by the nucleophilic ring opening[17,18] of VI with appropriate amines. As this reaction proceeded quantitatively, the crude amides VII were used for next reaction without purification. 3-Substituted spiro[cycloalkane-1′,2(1H)quinazolin]-4(3H)-one analogs (III_{1-30}) were prepared from the corresponding VII with excess cyclic ketone in the presence of *p*-toluenesulfonic acid in ethanol under reflux.

With respect to anthranilic acid N-(γ-phenylpropyl)amide, however, the preparation of corresponding III was not successful under the condition described above, but achieved by refluxing azeotropically with cyclic ketone in the presence of *p*-toluenesulfonic acid in toluene. When a small quantity of *p*-toluene-sulfonic acid was added at ordinary temperature to a solution of anthranilic acid hydrazide and excess of cyclohexanone in ethanol, colorless crystals were separated with violent exothermal reaction immediately. The product was not the expected 3-amino spiro[cyclohexane-1′,2(1H)quinazolin]-4(3H)-one, but 3-cyclohexylideneamino analog (III_{12}) which was formed by condensation of anthranilic acid hydrazide and two moles of cyclohexanone, as indicated in Chart 3.

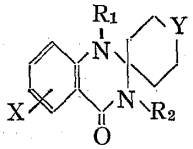


III_{12}

Chart 3

As to the 1-substituted derivatives (III_{31-33}) they were prepared *via* corresponding N-substituted anthranilamides (IX); compounds (IX) were obtained by the reaction[9c] of anthranilamides (VIII) with appropriate alkyl halide in dimethylformamide. Cyclization of (IX) with excess amount of cyclohexanone in the presence of *p*-toluenesulfonic acid in ethanol gave 1-substituted spiro[cycloalkane-1′,2(1H)quinazolin]-4(3H)-ones (III_{31-33}) in the same manner as described for the preparation of 3-substituted derivatives (III_{1-30}).

Table I. Spiro[cycloalkane-1′,2(1H)quinazolin]-4(3H)-ones and Related Compds (III_{1-33})



Compd. No.	X	Y	R_1	R_2	Yield (%)	Formula	mp (°C) (recrystn. solvent)[a]	Analysis (%) Calcd. (Found) C	H	N
III_1	H	CH_2	H	$(CH_2)_2OH$	46	$C_{15}H_{20}O_2N_2$	163—164 (E+H)	69.19 (69.04)	7.76 (7.80)	10.72 (10.62)
III_2	H	CH_2	H	CH_2CHOH CH_3	93	$C_{16}H_{22}O_2N_2$	173—175 (E+H)	70.04 (70.12)	8.08 (8.02)	10.21 (10.20)
III_3	H	CH_2	H	$(CH_2)_2OEt$	87	$C_{17}H_{24}O_2N_2$	170.5—172 (E+H)	70.79 (70.65)	8.04 (8.38)	10.21 (9.57)
III_4	H	CH_2	H	$(CH_2)_2CN$	93	$C_{16}H_{19}ON_3$	127—129 (E+H)	71.33 (71.12)	7.12 (7.10)	15.60 (15.48)

15) E.C. Wagner and M.F. Fegley, *Org. Syn.*, **27**, 45 (1947).
16) M. Shreekrishna, *J. Org. Chem.*, **26**, 613 (1961).
17) N.D. Heindel, W.P. Fives, T.F. Lemke, and R.A. Carrano, *J. Pharm. Sci.*, **60**, 703 (1971).
18) *a*) R.P. Staigner, *J. Org. Chem.*, **24**, 1214 (1959); *b*) C.-M. Lee, *J. Heterocyclic. Chem.*, **1**, 235 (1964).

Compd. No.	X	Y	R_1	R_2	Yield (%)	Formula	mp (°C) (recrystn. solvent)[a]	Analysis (%) Calcd. (Found) C	H	N
III_5	H	CH_2	H	$(CH_2)_2NEt_2$	64	$C_{19}H_{29}ON_3$	156—157 (E+H)	72.32 (72.47)	9.28 (9.44)	13.32 (13.27)
III_6	H	CH_2	H	$(CH_2)_3OH$	91	$C_{16}H_{22}O_2N_2$	167.5—160 (E)	70.04 (69.91)	8.08 (8.24)	10.21 (10.09)
III_7	H	CH_2	H	$(CH_2)_3OMe$	82	$C_{17}H_{24}O_2N_2$	126.5—127 (E+H)	70.79 (71.03)	8.40 (8.50)	9.72 (9.66)
III_8	H	CH_2	H	$(CH_2)_3OCHMe_2$	79	$C_{19}H_{28}O_2N_2$	127.5—129 (E+H)	72.10 (72.34)	8.94 (9.00)	8.55 (8.20)
III_9	H	CH_2	H	$(CH_2)_3NMe_2$	86	$C_{18}H_{27}ON$	170—171 (E+H)	71.71 (71.69)	9.05 (9.09)	13.94 (13.82)
III_{10}	H	CH_2	H	$(CH_2)_3$ 	71	$C_{20}H_{29}O_2N_3$	169.5—171 (A)	69.92 (70.45)	8.53 (8.65)	12.24 (12.29)
III_{11}	H	CH_2	H	$(CH_2)_3C_6H_5$	96	$C_{22}H_{26}ON_2$	125—127 (E+H)	78.93 (78.99)	7.77 (7.81)	8.37 (8.39)
III_{12}	H	CH_2	H	N= 	70	$C_{19}H_{25}ON_3$	220.5—222.5 (M)	73.26 (73.22)	8.11 (8.13)	13.50 (13.52)
III_{13}	H	CH_2	H	$CH_2CH=CH_2$	78	$C_{16}H_{20}ON_2$	146—148 (E+H)	74.95 (74.99)	7.88 (7.99)	10.93 (10.80)
III_{14}	H	none	H	$(CH_2)_2NEt_2$	47	$C_{18}H_{27}ON_3$	150—151 (E+H)	71.71 (71.70)	9.05 (9.14)	13.94 (13.86)
III_{15}	H	NCH_3	H	$(CH_2)_2NEt_2$	55	$C_{19}H_{30}ON_4$	154.5—155.5 (A)	69.04 (68.93)	9.17 (9.21)	16.96 (17.01)
III_{16}	H	$NCH_2C_6H_5$	H	$(CH_2)_2NEt_2$	84	$C_{25}H_{34}ON_4$	164—165 (A+C)	73.84 (73.80)	8.45 (8.46)	13.78 (13.45)
III_{17}	H	$NCH_2C_6H_5$	H	$CH_2CH=CH_2$	98	$C_{22}H_{25}ON_3$	163—164 (A+H)	76.03 (75.96)	7.27 (7.27)	12.09 (12.00)
III_{18}	H	$N(CH_2)_2C_6H_5$	H	CH_3	95	$C_{21}H_{25}ON_3$	208—210 (M)	75.18 (75.13)	7.53 (7.63)	12.53 (12.65)
III_{19}	6-Cl	CH_2	H	$(CH_2)_2CN$	20	$C_{16}H_{18}ON_3Cl$	148—150 (E+H)	63.25 (63.43)	5.98 (5.92)	13.83 (14.03)
III_{20}	6-Cl	CH_2	H	$(CH_2)_2NEt_2$	78	$C_{19}H_{28}ON_3Cl$	124—125 (A+H)	65.21 (65.27)	8.08 (8.12)	12.01 (11.93)
III_{21}	6-Cl	CH_2	H	$(CH_2)_3NEt_2$	75	$C_{18}H_{26}ON_3Cl$	125—127 (A+H)	64.35 (64.29)	7.82 (7.73)	12.51 (12.37)
III_{22}	6-Cl	CH_2	H	$(CH_2)_3$ 	58	$C_{20}H_{28}O_2N_3Cl$	181—181.5 (A)	63.55 (63.60)	7.48 (7.46)	11.12 (11.21)
III_{23}	6-Cl	NCH_3	H	$(CH_2)_3$ 	77	$C_{20}H_{29}O_2N_4Cl$	196—198 (B)	61.12 (61.29)	7.45 (7.36)	14.26 (14.51)
III_{24}	6-Cl	$NCH_2C_6H_5$	H	$(CH_2)_3NEt_2$	20	$C_{24}H_{31}ON_4Cl$	171—173 (A+H)	67.50 (67.57)	7.33 (7.25)	13.12 (13.39)
III_{25}	6-Cl	$N(CH_2)_2C_6H_5$	H	C_2H_5	67	$C_{22}H_{16}ON_3Cl$	198—200 (E)	68.81 (68.78)	6.84 (7.01)	10.95 (10.95)
III_{26}	7-Cl	CH_2	H	$(CH_2)_2CN$	99	$C_{16}H_{18}ON_3Cl$	177.5—179 (A+C)	63.25 (63.17)	5.98 (5.95)	13.83 (13.83)
III_{27}	7-Cl	CH_2	H	$(CH_2)_2OEt$	93	$C_{17}H_{23}O_2N_2Cl$	162—163 (A+C)	63.24 (63.31)	7.19 (7.12)	8.68 (8.65)
III_{28}	7-Cl	CH_2	H	$(CH_2)_2NEt_2$	25	$C_{19}H_{28}ON_3Cl$	147—149 (E+H)	65.21 (65.32)	8.08 (8.02)	12.01 (12.13)
III_{29}	7-Cl	CH_2	H	$(CH_2)_3OH$	72	$C_{16}H_{21}O_2N_2Cl$	182.5—183 (A)	62.22 (62.40)	6.87 (6.87)	9.07 (9.03)
III_{30}	7-Cl	CH_2	H	$(CH_2)_3$ 	82	$C_{20}H_{28}O_2N_3Cl$	198—200 (A)	63.55 (63.57)	7.48 (7.43)	11.12 (10.93)
III_{31}	H	CH_2	$CH_2CH=CH_2$	H	66	$C_{16}H_{20}ON_2$	142—144 (A)	74.95 (75.15)	7.88 (7.94)	10.93 (10.75)
III_{32}	H	CH_2	$CH_2C\equiv CH$	H	96	$C_{16}H_{18}ON_2$	211—213 (M)	75.55 (75.88)	7.15 (7.18)	11.02 (11.09)
III_{33}	H	CH_2	$(CH_2)_2C_6H_5$	H	75	$C_{21}H_2ON_2$	171—173 (E)	78.70 (78.64)	7.56 (7.46)	8.74 (8.81)

a) Recrystn. solvents: E=ethanol, M=methanol, H=*n*-hexane, A=ethyl acetate, B=benzene, C=cyclohexane

Physical properties, yields and results of elementary analyses of the compounds synthesized are summarized in Table I.

In order to prepare 3-substituted analog of III_{13}, compound (III_{13}) was treated with ethyl iodide in the presence of potassium carbonate in dimethylformamide, but the attempt resulted in recovery of unreacted material. For the purpose of chloroacetylation, III_{13} was treated with chloroacetyl chloride in the presence of potassium carbonate in acetone at ordinary temperature, the substance obtained was N-acetyl anthranilic acid N-allyl amide (X), in place of the expected 3-allyl-1-chloroacetyl spiro[cyclohexane-1′,2(1H)quinazolin]-4(3H)-one. The structure of X was assigned on the basis of elemental analysis, IR [ν_{max}^{Nujol} cm^{-1}: 3300, 3100(NH), 1670, 1630(C=O], NMR[($CDCl_3$, TMS) δ: 4.20 ppm (2H, singlet, $COCH_2$), 4.12 (2H, doublet, $NHCH_2$)] and Mass Spectrum [*m/e*: 252 (M^+), 203, 196].

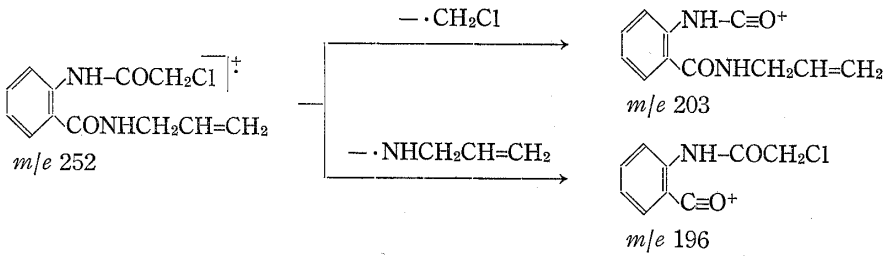


Chart 4

One attempt to prepare 1-benzoyl derivative from (III_{13}) by the reaction with benzoyl chloride in the presence of potassium carbonate in acetone resulted in the failure of 1-benzoylation, but gave 3-allyl-2,2-dimethyl-1,2,3,4-tetrahydroquinazolin-4-one (XI). The structure of (XI) was verified to be identical with the cyclization product of anthranilic acid N-allylamide (XII) with acetone by means of IR spectrum and the mixed melting point. It was supposed that (III_{13}) reacted with acetone used for solvent. Being dissolved in large amount of acetone, and allowed to stand at ordinary temperature, (III_{13}) was converted into (XII) smoothly. It appears that (III_{13}) and (X) are in the equilibrium as indicated in Chart 5.

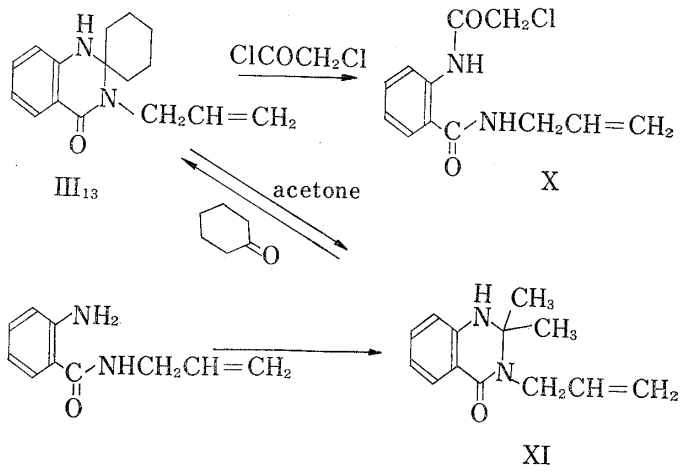


Chart 5

In fact, the latter was converted readily by warming with cyclohexanone at 60° into the former as was expected. Thus to investigate whether analogous equilibrium exists in another compounds or not, the reaction of several analogous compounds, namely 1-allyl (III_{31}), 3-ethoxyethyl (III_3), 3-β-diethylaminoethyl (III_5) and 3-γ-hydroxypropyl (III_6) analogs, with acetone was carried out under the same condition as described for (III_{13}), but they did not react at all. Refluxing them with acetone for more than 20 hours resulted in the recovery of material unreacted too. Accordingly it can be said this equilibrium is specific on 3-allyl analog (III_{13}).

The mass spectra of several compounds synthesized in this study were determined, and furthermore as to three representative compounds (III_{13}, III and IV) selected from them high resolution mass measurements and determination of metastable ions were carried out. Meta-

stable ions were measured according to the method reported by Sasaki, *et al.*[19] Observed metastable transitions are marked by asterisks in Chart 6 and in the Experimental section.[23]

C. Bogentoft and his co-worker[20] reported that mass specra of 1 or 3-substituted-1,2,3,4-tetrahydroquinazolin-4-ones show abundant peaks due to retro-Diels Alder-like fission of heterocyclic ring. Contrary to our expectation, the mass spectra of the compounds (III, IV) which posesss spiro cyclohexane ring at their position 2 do not show the fragmentation due to retro-Diels Alder reaction. For instance, the fragment at *m/e* 119 in the spectrum of IV does not correspond to C_7H_5ON (Calcd. 119.0371) due to retro-Diels Alder cleavage, but $C_7H_7N_2$ (Calcd. 119.0609, Observed 119.0601) by high resolution mass measurement. Moreover in the spectra of III_{31} and III_{32}, the ions due to the retro-Diels Alder cleavage (III_{31}: *m/e* 159, III_{32}: *m/e* 157) are not observed, and in the spectrum of III_{13}, an ion (C_7H_5ON, Calcd. 119.0371, Observed 119.0376) which seems to be due to the fragmentation of retro-Diels Alder cleavage can be observed as a minor fragment, but metastable peak appropriated from ion b—g to ion at *m/e* 119 can not be detected. From these fact the retro-Diels Alder cleavage of spiro[cyclohexane-1′,2(1H)quinazolin]-4(3H)-ones seems to occur hardly differing from 1,2,3,4-tetrahydroquinazolin-4-ones.

The fragmentation pattern of 1 or 3-substituted spiro[cyclohexane-1′,2-(1H)quinazolin]-4(3H)-ones under electron impact was not influenced by the substituents, and they showed similar fragmentation all alike. Their fragmentations are given in experimental section,[21] and the dissociation path is illustrated for the simplest representative, spiro[cyclohexane-1′,-2(1H)quinazolin]-4(3H)-one (IV), in Chart 6.

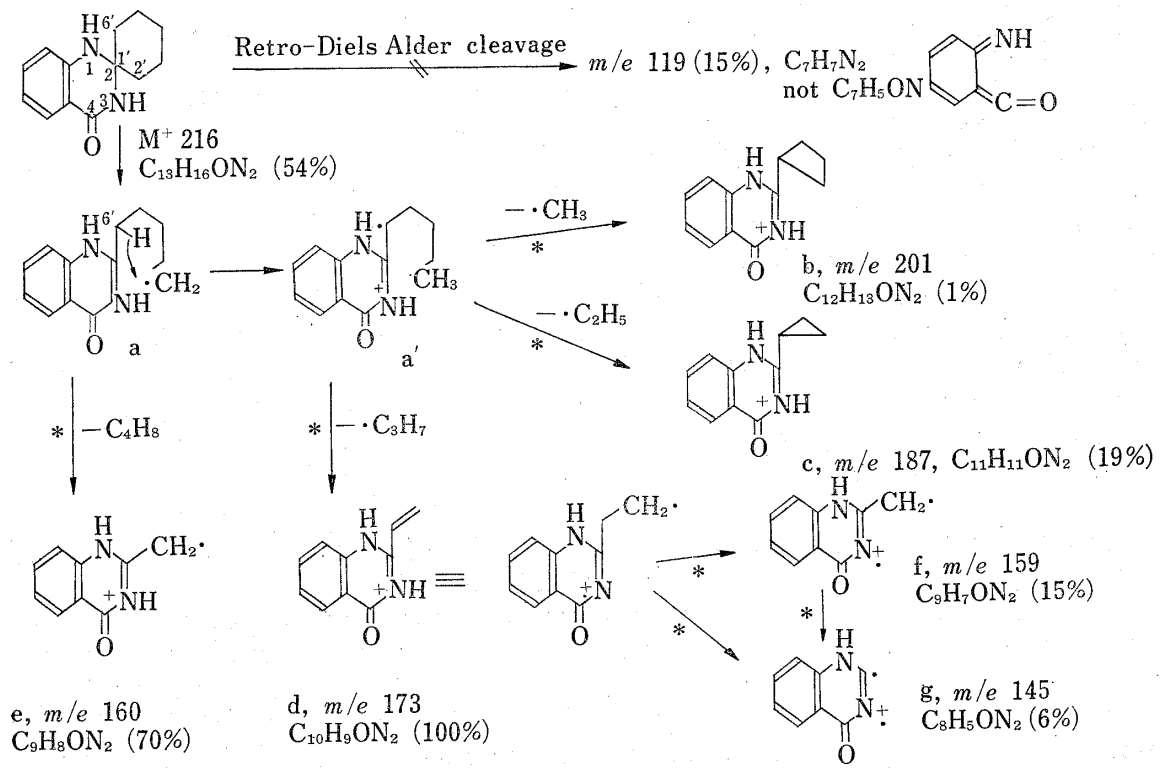


Chart 6

19) S. Sasaki, E. Watanabe, Y. Itagaki, T. Aoyama, and E. Yamauchi, *Anal. Chem.*, **40**, 1000 (1968).
20) C. Bogentoft and B. Danielson, *J. Heterocyclic Chem.*, **9**, 193 (1972).
21) The letters refer to the fragments depicted in Chart 6. The compositions were determined by high resolution mass measurement. Metastable transitions detected are shown by asterisks.

As a first step, cleavage of cyclohexane ring at C–C bond β to the nitrogen atom (Cl′–C2′ linkage) in parent ion M^+ would yield the radical ion a, and all major fragmentation seems to arise from the ion a. Six fragment ion peaks (b—g) are common to all the compounds determined as shown in experimental section.[23]

An initial rupture of one of the C6′ hydrogens by a primary free radical site at C2′ in ion a would afford secondary radical ion a′. The intermediate ion a′ would then undergo fission at C2′–C3′ bond to produce an ion b (M^+–·CH_3), and at C4′–C5′ bond to yield an ion c (M^+–·C_2H_5). Moreover, fragment ion d (M^+–·C_3H_7) would be probably formed by a fission at C5′–C6′ bond in ion a′, and this cleavage would be the main fragmentation pathway, and ion f and g are formed from ion d as indicated in Chart 6. Furthermore homolytic cleavage of C4′–C5′ linkage in ion a would yield the radical ion e (M^+–C_4H_8).

Biological activities of 33 compounds prepared in this study are being investigated in our laboratories. As a preliminary screening test for tranquilizing activity, an examination by open field method[22] was carried out. Moderate or weak tranquilizing activity has been observed in several compounds ($III_{25,32,33}$). The pharmacological activities of these compounds will be presented in detail elsewhere.

Experimental[23]

4(or 5)-Chloroisatoic Anhydrides (VI)——A modification of the method of Shreekrishna[16] was employed. Phosgen was bubbled at room temperature through a solution of 4(or 5)-chloroanthranilic acid (V) 34.3 g (0.2 mole) and Na_2CO_3 21.2 g (0.2 mole) in water 500 ml with stirring. Phosgene bubbling was continued till the pH dropped to about 2. The solid separated was filtered, washed with water and air dried. Crude anhydride was recrystallized from EtOH.

4-Chloroisatoic Anhydride: mp 278—281° (decomp.), blades, yield 74%.

5-Chloroisatoic Anhydride: mp 278—280° (decomp.), blades, yield 69%.

4(or 5)-Chloroanthranilic Acid N-Substituted Amides (VII)——A solution of VI (0.04 mole) and appropriate amine (0.05 mole) in dioxane 100 ml was refluxed for 5 hr. As this nucleophilic ring opening reaction could proceed quantitatively, the colorless pasty residue which was obtained by evaporation *in vacuo* of the reaction mixture was used for next reaction without purification.

General Procedures of 3-Substituted Spiro[cycloalkane-1′,2(1H)-quinazolin]-4(3H)-one Analogs ($III_{1-11,13-30}$)——a) A solution of (VII) (0.01 mole), appropriate cyclic ketone (0.02 mole) and *p*-toluenesulfonic acid 0.1 g in EtOH 150 ml was refluxed for 8 hr. The reaction mixture was concentrated *in vacuo* to dryness, and the resulting residue was crystallized by addition of *n*-hexane. The crude product was purified by recrystallization, $III_{1-10,13-22,24-30}$. The physical canstants and results of micro analysis are summarized in Table I. Spectral data of the representative compounds are shown as follows.

III_3: IR ν_{max}^{Nujol} cm^{-1}: 3350 (NH), 1620 (CON<). NMR ($CDCl_3$, TMS) δ: 8.0—6.7 ppm (4H, m, aromatic H), 4.72 (1H, s, NH, D_2O exchangeable), 3.8—3.4 (6H, m, N-C$\underline{H}_2$C$\underline{H}_2$OC$\underline{H}_2$Me), 2.2—1.2 (10H, cyclohexane CH_2), 1.12 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$).

III_4: IR ν_{max}^{Nujol} cm^{-1}: 3400 (NH), 2250 (CN), 1640 (CON<). NMR ($CDCl_3$, TMS) δ: 7.9—6.6 ppm (4H, m, aromatic H), 4.75 (1H, s, NH, D_2O exchangeable), 3.78 (2H, t, J=7 Hz N-C$\underline{H}_2$$CH_2$CN) 2.71 (2H, t, J=7 Hz, N-CH_2C$\underline{H}_2$CN), 2.3—1.2 (10H, cyclohexane CH_2). Mass Spectrum[21] *m/e*: 269 (M^+, 37%), 254 (b, 2%), 240 (c, 12%), 226 (d, 100%), 213 (e, 25%), 173 (10%), 160 (13%), 119 (12%).

III_{13}: IR ν_{max}^{Nujol} cm^{-1}: 3350 (NH), 1620 (CON<, C=C). NMR ($CDCl_3$, TMS) δ: 7.9—6.7 ppm (4H, m, aromatic H), 5.90 (1H, octet, CH_2–C$\underline{H}$=CH_2), 5.30, 5.22 (2H, a pair of quartet, CH_2–CH=C$\underline{H}_2$), 4.81 (1H, s, NH, D_2O exchangeable), 4.06 (2H, intricately split doublet, N-C$\underline{H}_2$CH=CH_2), 2.2—1.2 (10H, cyclohexane CH_2). Mass Spectrum[21] *m/e*: 256 (M^+, 18%, $C_{16}H_{20}ON_2$), 241 (b, 12%, $C_{15}H_{17}ON_2$), 227 (c, 16%, $C_{14}H_{15}ON_2$), 213 (d, 68%, $C_{13}H_{13}ON_2$), 200 (e, 63%, $C_{12}H_{12}ON_2$), 199 (f, 53%, $C_{12}H_{11}ON_2$), 185 (g, 100%, $C_{11}H_9ON_2$), 173 (16%, $C_{10}H_9ON_2$), 160 (11%, $C_9H_8ON_2$), 119 (11%, C_7H_5ON). Metastable Transitions: ($M^+ \rightarrow$b)*, ($M^+ \rightarrow$c)*, ($M^+ \rightarrow$d)*, ($M^+ \rightarrow$e)*, (d→f)*, (d→g)*, (f→g)*.

b) A mixture of VIII (0.01 mole), appropriate cyclic ketone (0.02 mole) and *p*-toluenesulfonic acid 0.1 g in toluene 200 ml was heated under reflux using a Dean–Stark trap to remove H_2O. When the theore-

22) R. Ader, Experimental Approaches to the Study of Emotional Behavior, *Ann. N.Y. Acad. Sci.*, **159** (3), 791—879 (1960).

23) IR spectra were determined on Hitachi-215 spectrometer, and NMR spectra on a Japan Electron Optics Model JNM-PS 100 spectrometer. The mass spectra were recorded on JEOL double focussing mass spectrometer Model JMS-01 SG. The ionization energy normally used was 75 eV.

tical amount of H_2O had been collected, the solbent was removed at reduced pressure, and the reaidue was crystallized from IPE, ($III_{11,23}$). (Table I).

III_{11}: IR ν_{max}^{Nujol} cm^{-1}: 3310 (NH), 1620 (CON<). NMR ($CDCl_3$, TMS) δ: 7.9—6.6 ppm (9H, m, aromatic H), 5.24 (1H, s, NH, D_2O exchangeable), 3.59 (2H, t, J=8 Hz, N–C$\underline{H}_2$$CH_2$), 2.74 (2H, t, J=8 Hz, $CH_2C\underline{H}_2$-C_6H_5), 2.2—1.1 (12H, m, cyclohexane CH_2 and $CH_2C\underline{H}_2CH_2C_6H_5$).

2-Cyclohexylideneamino Spiro[cyclohexane-1′,2(1H)quinazolin]4(3H)-one (III_{12})——To a stirred solution of hydrazine hydrate (80% soln.) 7.0 g in dioxane 50 ml was added portionwise isatoic anhydride 2.0 g under cooling. The mixture was stirred for 2 hr at ordinary temperature, and then evaporated at reduced pressure. The resulting solid was recrystallized from water to give 1.5 g of 2-aminobenzoic acid hydrazide, mp 122—124°. To a solution of the hydrazide prepared above 1.5 g (0.01 mole) and cyclohexanone 4.9 g (0.05 mole) in EtOH 20 ml was added *p*-toluenesulfonic acid 0.1 g at room temperature. A violent exothermal reaction began immediately, and white solid was separated. After stirring for 2 hr at room temperature, the resulting solid was filtered and recrystallized from MeOH to give 2.1 g (70%) of (III_{12}), mp 220.5—222.5°. (Table I). IR ν_{max}^{Nujol} cm^{-1}: 3340 (NH), 1625, 1615 (CON<, C=N). Mass Spectrum *m/e*: 311 (M), 268 (base peak, M^+–·C_3H_7), 255 (M^+–C_4H_8), 215 (M^+–·$CH_2(CH_2)_4CN$), 200, 96. NMR ($CDCl_3$, TMS) δ: 7.9—6.8 ppm (4H, m, aromatic H), 4.86 (1H, s, NH, D_2O exchangeable), 2.3—1.1 (20H, cyclohexane CH_2).

N-Substituted Anthranilamides (IX)——A solution of anthranilamide 4.1 g (0.03 mole), appropriate alkyl bromide (0.03 mole) and Na_2CO_3 3.5 g (0.033 mole) in DMF 100 ml was stirred for 15 hr at ordinary temperature. The reaction mixture was poured into water, and an oil separated was extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried and evaporated, and then the residue was recrystallized.

N-Allyl anthranilamide: mp 131—135°, blades (from EtOAc), yield 92%.

N-Propargyl anthranilamide: mp 177—178°, blades (from EtOAc), yield 85%.

N-Phenethylanthranilamide: mp 124—126°, needles (from EtOH–H_2O), yield 87%.

General Procedure of 1-Substituted Spiro[cyclohexane-1′,2(1H)-quinazolin]-4(3H)-ones ($III_{31\sim33}$)——A solution of (IX) (0.01 mole), cyclohexanone 2.0 g (0.02 mole) and *p*-toluenesulfonic acid 0.1 g in EtOH 100 ml was refluxed for 7 hr. After removal of EtOH, the residual oil was crystallized from small amount of IPE. Physical constants and the results of micro analysis are summarized in Table I. Spectral data are indicated as follows.

III_{31}: IR ν_{max}^{Nujol} cm^{-1}: 3200 (NH), 1640 (CON<, C=C). NMR ($CDCl_3$, TMS) δ: 7.9—6.7 ppm (4H, m, aromatic H), 6.80 (1H, s, amide NH, D_2O exchangeable), 5.92 (1H, octet, CH_2–C$\underline{H}$=CH_2), 5.30, 5.10 (2H, a pair of quartet, CH_2–CH=C$\underline{H}_2$), 3.98 (2H, intricately split d, N–C$\underline{H}_2$–CH=CH_2), 2.2—1.1 (10H, cyclohexane CH_2). Mass Spectrum[21] *m/e*: 256 (M^+, 24%, $C_{16}H_{29}ON_2$), 241 (b, 13%, $C_{15}H_{17}ON_2$), 227 (c, 27%, $C_{14}H_{15}ON_2$), 213 (d, 77%, $C_{13}H_{13}ON_2$), 200 (e, 70%, $C_{12}H_{12}ON_2$), 199 (f, 51%, $C_{12}H_{11}ON_2$), 185 (g, 100%, $C_{11}H_9ON_2$), 173 (33%, $C_{10}H_9ON_2$), 160 (37%, $C_9H_8ON_2$), 119 (22%, C_7H_5ON). Metastable Transitions: ($M^+ \rightarrow$b), ($M^+ \rightarrow$c), ($M^+ \rightarrow$d), ($M^+ \rightarrow$e), ($M^+ \rightarrow$f), (d→f), (d→g), (f→g).

III_{32}: IR ν_{max}^{Nujol} cm^{-1}: 3300 (C≡CH), 3210 (amide NH), 1655 (CON<). NMR ($CDCl_3$, TMS) δ: 8.12 ppm (1H, s, amide NH, D_2O exchangeable), 7.9—6.8 (4H, m, aromatic H), 4.21 (2H, s, N–CH_2), 2.84 (1H, s, C≡CH), 2.3—1.2 (10H, cyclohexane CH_2). Mass Spectrum[21] *m/e*: 254 (M^+, 8%), 239 (b, 5%), 225 (c, 7%), 211 (d, 32%), 198 (e, 15%), 197 (f, 100%), 196 (52%), 129 (14%).

Reaction of III_{13}——a) With Chloroacetyl Chloride in Acetone: To a stirred solution of (III_{13}) 2.6 g (0.01 mole) and K_2CO_3 1.7 g (0.012 mole) in acetone 500 ml was added dropwise chloroacetyl chloride 1.4 g (0.012 mole) at room temperature. After stirring for 12 hr inorganic substance was filtered off, and the filtrate was condensed *in vacuo* to dryness. The residue obtained was recrystallized from EtOH–H_2O to give N-chloroacetylanthranilic acid N-allylamide (X) 2.0 g, mp 149—150°. *Anal.* Calcd for $C_{12}H_{13}O_2N_2Cl$: C, 57.03; H, 5.20; N, 11.09. Found: C, 56.81; H, 5.05; N, 11.09. IR ν_{max}^{Nujol} cm^{-1}: 3300, 3100 (amide NH), 1670, 1630 (amide C=O). NMR ($CDCl_3$, TMS) δ: 8.6 —7.0 ppm (4H, m, aromatic H), 7.3 (1H, broad s, amide NH), 6.5 (1H, broad s, amide NH), 6.03 (1H, octet, $CH_2C\underline{H}$=CH_2), 5.35, 5.22 (2H, a pair of quartet, $CH_2C\underline{H}$=CH_2), 4.20 (2H, s, $COCH_2Cl$), 4.08 (2H, intricately split d, N–C$\underline{H}_2$CH=CH_2). Mass Spectrum *m/e*: 252 (M^+), 203, 196.

b) With Benzoyl Chloride in Acetone: To a stirred solution of III_{13} 2.6 g (0.01 mole) and K_2CO_3 1.7 g (0.012 mole) in acetone 50 ml was added dropwise benzyol chloride 1.7 g (0.012 mole) at ordinary temperature, and the reaction mixture was continued to stir for 5 hr. After removal of the inorganic substance the resulting filtrate was evaporated under reduced pressure to give white solid. The solid was recrystallized from *n*-hexane–EtOAc to give colorless needles 1.8 g, mp 137—138°. 3-Allyl-2,2-dimethyl-1,2,3,4-tetrahydroquinazoline-4-one (XI) resulted, in place of the expected 1-benzoyl derivative of III_{13}. *Anal.* Calcd. for $C_{13}H_{16}ON_2$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.30; H, 7.25; N, 12.81. IR ν_{max}^{Nujol} cm^{-1}: 3320 (NH), 1630, 1620 (CON<, C=C). NMR ($CDCl_3$, TMS) δ: 8.0—6.7 ppm (4H, m, aromatic H), 6.00 (1H, octet, $CH_2C\underline{H}$=CH_2), 5.30, 5.17 (2H, a pair of quartet, CH_2CH=C$\underline{H}_2$), 4.7 (1H, broad s, NH, D_2O exchangeable), 4.10 (2H, finely split d, NC$\underline{H}_2$CH=CH_2), 1.58 (6H, s, CH_3). Mass Spectrum *m/e*: 216 (M^+), 201, 161, 160, 132, 130, 119.

c) With Acetone: A solution of (III_{13}) 2.6 g in acetone 100 ml was allowed to stand for 1.5 hr at room temperature. After evaporation of the solvent under reduced pressure, the residual oil was recrystallized

from *n*-hexane–EtOAc to give colorless needles (XI) 1.7 g (78%); mixed melting point with (XI) obtained by method b) give no depression.

Reaction of XI with Cyclohexanone——A suspension of XI 2.2 g (0.01 mole) in cyclohexanone 50 ml was stirred for 5 hr at 60°. The clear reaction mixture was evaporated *in vacuo* to dryness, and the oily residue was dissolved in ether 100 ml. The ethereal solution was washed with $NaHSO_3$ solution and water in turn, dried and concentrated. The residual oil was crystallized from *n*-hexane–ether to give colorless needles 1.7 g, mp 147—148°. The substance obtained was verified to be identical with (III_{13}) by mixed melting point and IR spectrum.

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