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Spiro Heterocyclic Compounds. I. Synthesis of Spiro[imidazolidine-4,3'-indoline]-2,2',5-triones

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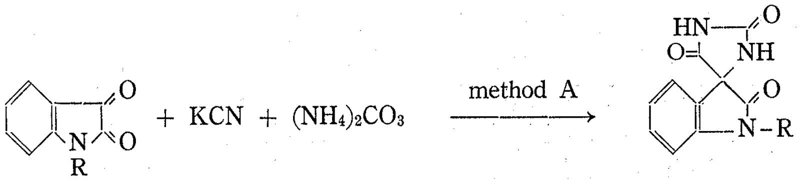
1'-Substituted spiro[imidazolidine-4,3'-indoline]-2,2',5-triones (**5**—**8**) were prepared by the reaction of 1-substituted indoline-2,3-diones with KCN and $(NH_4)_2CO_3$. The reaction of indoline-2,3-diones with KCN and amines afforded 3-amino-3-cyanoindolin-2-ones (**9**—**11**), which on reacting with KOCN, only **9** gave 3-methyl derivative of the spiro compound (**16**). By the methylation of **6** with $(CH_3)_2SO_4$, 1',3-dimethyl- (**17**) and 1,1',3-trimethyl-spiro[imidazolidine-4,3'-indoline] compound (**18**) were obtained.

There are some naturally occurring heterocyclic compounds containing spiro-cyclic structure and having strong biological activity. It was recently found that several alkaloids, *e.g.*, Rhynchophylline,[2] Elegantine,[3] and Surugatoxin[4] (a toxic principle of shellfish), were heterocyclic compounds combined with a spiro-system at the position-3 of the 2-indolinone skeleton. These facts prompted us to synthesize the various 3-spiro-heterocyclic compounds of 2-indolinone skeleton for their pharmacological evaluation.

Taking advantage of the high reactivity of the keto group at the position-3 of 2-indolinone, the formations of various 3-spiro-heterocyclates of 2-indolinone are expected. In our first trial, spiro[imidazolidine-4,3'-indoline] compounds were successfully synthesized from indoline-2,3-diones according to Bucherer's Hydantoin synthesis.[5]



1: $R=H$
2: $R=CH_3$
3: $R=CH_2CH=CH_2$
4: $R=CH_2C_6H_5$

5: $R=H$
6: $R=CH_3$
7: $R=CH_2CH=CH_2$
8: $R=CH_2C_6H_5$

Chart 1

The indoline-2,3-dione compounds **1**—**4** were refluxed for 2 hr in aqueous methanol with potassium cyanide and ammonium carbonate. The analytical and spectral data of the reaction products **5**—**8** thus obtained were listed in Table I.

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1) Location: *Ebara 2-4-41, Shinagawa-ku, Tokyo.*

2) J.C. Seaton, M.D. Nair, O.E. Edwards, and L. Marion, *Can. J. Chem.*, **38**, 1035 (1960); T. Nozoe, *Chem. Pharm. Bull.* (Tokyo), **6**, 309 (1958); N. Finch and W.I. Taylor, *J. Am. Chem. Soc.*, **84**, 3871 (1962); Y. Ban and T. Oishi, *Tetrahedron Letters*, **1961**, 791; *idem*, *Chem. Pharm. Bull.* (Tokyo), **11**, 451 (1963); Y. Ban, M. Seto, and T. Oishi, *Tetrahedron Letters*, **1972**, 2113.

3) J. Bhattacharyya and S.C. Pakrashi, *Tetrahedron Letters*, **1972**, 159.

4) T. Kosuge, H. Zenda, A. Ochiai, N. Masaki, M. Noguchi, S. Kimura, and H. Narita, *Tetrahedron Letters*, **1972**, 2545; H. Hirayama, K. Sugihara, K. Wakigawa, S. Tsuyama, T. Sugihara, H. Ohkuma, and K. Gohgi, *Folia Pharmacol. Japon*, **69**, 583 (1973).

5) H.T. Bucherer and V.A. Lieb, *J. Prakt. Chem.*, **141**, 5 (1934); E. Ware, *Chem. Rev.*, **46**, 403 (1950).

Bucherer's reaction of the red colored indoline-2,3-diones produced colorless products whose ultraviolet (UV) spectra showed that they should have the unconjugated 2-indolinones. Infrared (IR) spectra of the products **5**—**8** showed the absorption of carbonyl groups of imidazolidine-2,5-diones, and their nuclear magnetic resonance (NMR) spectra showed three singlets of N-H protons which disappeared upon deuteration. These results along with the analytical data indicated that the compounds **5**—**8** have the structure of spiro[imidazolidine-4,3'-indoline]-2,2',5-triones.

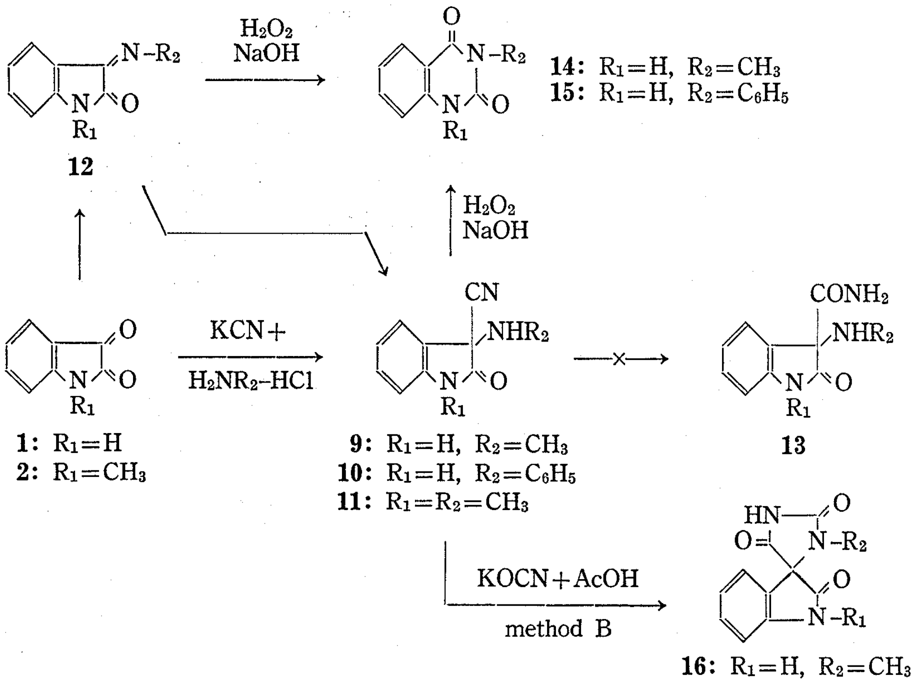

Chart 2

Since this modified Bucherer's reaction gave only 1-substituted 2-indolinone moieties, we examined another route for the syntheses of the title compound.

Strecker's reaction[6] of indoline-2,3-diones using potassium cyanide and amine produced 3-amino-3-cyanoindolin-2-ones (**9**—**11**) in fairly good yield. In this reaction, **10** was also obtained from 3-phenyimino-2-indolinone (**12**) by reacting with potassium cyanide in acetic acid solution. For the purpose of obtaining imidazolidine derivatives, some ring formation reactions with the compounds **9**—**11** were carried out.

First, we thought that the amides (**13**) might be prepared by hydrolysis of **9**—**11** and these amides cyclized to form the imidazolidine nucleus. However, the heating of compounds **9**—**11** with 90% sulfuric acid at 70°, caused the materials to decompose, and yielded solids of unknown structure.

Hydrolysis of **9** and **10** with sodium hydroxide and hydrogen peroxide yielded colorless needles of mp 234° (**14**) and mp 274° (**15**), respectively. The respective molecular ion peaks (M^+) on their mass (MS) spectra appeared each at *m/e* 176 and 238. IR spectra of **14** and **15** showed the presence of two carbonyl groups at 1720 and 1660—1670 cm^{-1}. These results suggested that the products were 3-methyl- (**14**) and 3-phenyl-1,2,3,4-tetrahydroquinazoline-2,4-dione (**15**), and this assumption was confirmed by the identification with the specimens prepared by known method.[7,8] Jacini[9] reported that β-imino derivative of 2-indolinone

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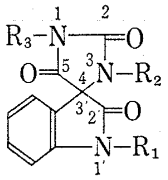
6) A. Strecker, *Ann.*, **75**, 27 (1850).
7) R.P. Staiger and E.C. Wagner, *J. Org. Chem.*, **18**, 1427 (1953).
8) Br. Paulewski, *Ber.*, **38**, 130 (1905).
9) G. Jacini, *Gazz. Chim. Ital.*, 73, 85 (1943) [*C.A.*, **38**, 5825 (1944)].

rearranged to 3-substituted 1,2,3,4-tetrahydroquinazoline-2,4-dione with hydrogen peroxide in alkaline solution. Therefore, these quinazoline-diones (**14** and **15**) we obtained might have been derived from the imino compounds which were formed by the loss of cyano group during the reaction.

Table I. Spiro[imidazolidine-4,3′-indoline]-2,2′,5-triones



Compd. No.	R_1	R_2	R_3	Method (Yield %)	mp °C[a)]	Formula
5	H	H	H	A (62)	280	$C_{10}H_7O_3N_3$
6	CH_3	H	H	A (89)	295	$C_{11}H_9O_3N_3$
7	$CH_2CH=CH_2$	H	H	A (58)	254	$C_{13}H_{11}O_3N_3$
8	$CH_2C_6H_5$	H	H	A (68)	268	$C_{17}H_{13}O_3N_3$
16	H	CH_3	H	B (27)	283	$C_{11}H_9O_3N_3$
17	CH_3	CH_3	H	C (50)	288	$C_{12}H_{11}O_3N_3$
18	CH_3	CH_3	CH_3	C (69)	179	$C_{13}H_{13}O_3N_3$

Compd. No.	Analysis % Calcd (Found) C	H	N	IR Nujol (cm^{-1}) C=O			UV λ_{max}^{EtOH} nm (log ε)		
5	55.30 (55.26)	3.25 (3.26)	19.35 (19.43)	1780	1740	1690	206 (4.40)	243 (3.76)	290 (3.28)
6	57.14 (57.47)	3.92 (4.27)	18.18 (17.88)	1780	1740	1710	216 (4.28)	255 (3.58)	288 (3.08)
7	60.69 (60.30)	4.35 (4.60)	16.34 (16.24)	1780	1740	1680	207 (4.24)	250 (3.49)	288 (3.07)
8	66.44 (66.44)	4.30 (3.89)	13.68 (14.01)	1780	1740	1690	209 (4.50)	250 (3.75)	288 (3.20)
16	57.14 (57.38)	3.92 (3.64)	18.18 (17.99)	1780	1730	1695	209 (4.38)	245 (3.77)	290 (3.27)
17	58.77 (58.84)	4.52 (4.64)	17.14 (16.88)	1780	1740	1720	208 (4.34)	248 (3.67)	290 (3.15)
18	60.22 (59.77)	5.05 (5.06)	16.21 (15.74)	1780	1730	1710	209 (4.43)	248 (3.77)	290 (3.30)

a) All of the compounds were obtained as colorless needles from a mixt. of MeOH+C_6H_6

Reduction experiments of **9**—**11** either catalytically, or by use of lithium aluminum hydride were unsuccessful, and only amorphous products yielded. Finally, the reactions of the compounds **9**—**11** with potassium cyanate in 90% acetic acid at 100° were carried out. Only **9** gave the product as colorless needles of mp 283° (**16**), though in poor yield, whose structure was determined by its spectral and analytical data to be 3-methyl-spiro[imidazolidine-4,3′-indoline]-2,2′,5-trione. The reactions of **10** and **11** caused the material to decompose, and the original indoline-2,3-diones were recovered.

Subsequently, in expectation of obtaining the other imidazolidine derivatives, methylation of **5** and **6** by use of dimethylsulfate (DMS) was carried out. Methylation of **5** with two molar equivalents of DMS in alkaline solution gave a 50% yield of **6**. Similar treatment of **6** yielded a dimethyl derivative (**17**) of mp 288°, M^+ 245. When **6** was heated with a mixture of three molar equivalents of DMS, powdered sodium carbonate and a small amount of toluene, color-

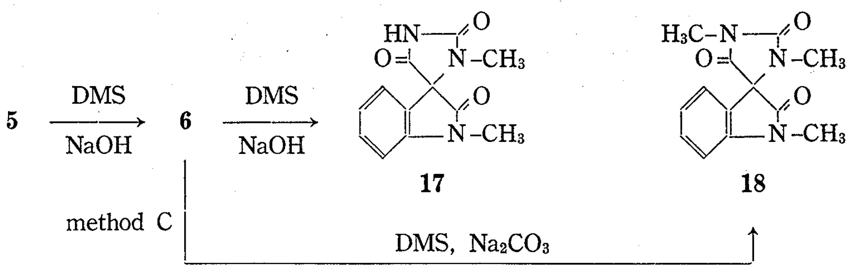


Chart 3

less needles of mp 179°, M+ 259, agreeing with the molecular weight of trimethyl derivative (**18**) were obtained.

To verify the position of methyl groups in these compounds **17** and **18**, their NMR spectra were compared with those of the compounds **5**, **6** and **16**. These are summerized in Table II.

Signals for three protons of the compound **5** were observed as three singlets at 11.05, 10.65 and 8.45 ppm. Among those signals, the peak of the lowest field is assigned to the most electron depressed 1-NH proton, and one in the highest field is to the 3-NH proton which has the smallest electron negativity, and the singlet in the medium field is considered to be the N-H proton of 2-indolinone. These assignments are clearly supported when compared to the signals of the N-H protons of the compounds **6** and **16**. Compound **6** showed two singlet peaks, one at the lowest field and the other at the highest field, in addition to a singlet due to 1′-NCH_3 proton at 3.2 ppm. In contrast, compound **16** indicated two singlets, one at the lower field and the other at the intermediate field along with a singlet 3-NCH_3 proton at 2.55 ppm. Product **17** is certain to be 1′,3-dimethyl derivative, because a singlet of N-H proton located in the lowest field and two singlets of NCH_3 appeared at 3.2 and 2.55 ppm which corresponded respectively to 1′- and 3-position of the spiro structure. Product **18** is undoubtedly 1,1′,3-trimethyl spiro-compound, in terms of the absence of all three N-H proton peaks, and the three singlets due to the presence of three NCH_3 protons. If an O-methyl structure were formed, these O-methyl proton would be observed at the field lower than those of the N-methyl derivative.

TABLE II. Signals of N–H and N–CH_3 Protons of Spiro[imidazolidine-4,3′-indoline]-2,2′,5-triones[a]

Compd. No.	1-NH	1′-NH	3-NH	1-NCH_3	1′-NCH_3	3-NCH_3
5	11.05	10.65	8.45			
6	11.30		8.60		3.20	
16	11.40	11.00				2.55
17	11.48				3.20	2.55
18				3.00	3.20	2.60

a) in *d*-dimethylsulfoxide(ppm)

From the above mentioned observations, the attribution of three singlets of the compound **18** at 3.2, 3.0, and 2.60 ppm were respectively assigned to the 1′-, 1-, and 3-NCH_3 protons. However, considering the order of electron negativity of the three nitrogen atoms as well as the case of the compound **5**, the signal of 1-NCH_3 proton must be assigned to the one in the lowest field. The NCH_3 proton in the upper field is reasonably considered to be of the 1-methyl group placed between the two carbonyl groups, which maintained the strain on the N-CH_3 bond and lessened the influence of the electron depression towards the methyl group.

Experimental

All melting points are uncorrected. IR spectra were recorded with a Hitachi Model-215 and UV spectra with a Shimadzu UV-200 instrument. NMR spectra were determined on a Hitachi–Perkin–Elmer R-20 spectrometer using tetramethylsilane as the internal standard. Mass spectra were run on a Hitachi RMS-4 spectrometer.

Materials——1-Methyl- (2),[10] 1-allyl- (3)[11] and 1-benzylindoline-2,3-dione (4)[12] were prepared by known method.

Preparation of 1′-Substituted Spiro[imidazolidine-4,3′-indoline]-2,2′,5-triones (5—8)——A solution of indoline-2,3-dione (2.9 g, 0.02 mole) in MeOH (60 ml) was added a solution in water (60 ml) and gently refluxed for 2 hr. The reaction mixture was highly concentrated by a rotary evaporater, after diluted with 60 ml of water, purified with "Norit A," and the solution was acidified with 50% AcOH to yield 2.7 g (62%) of white solid. Recrystallization from a mixture of MeOH and benzene gave colorless needles of mp 280° (**5**). Analytical and spectral data are listed in Table I.

3-Cyano-3-methylaminoindoline-2-one (9)——To a mixture of indoline-2,3-dione (25 g, 0.17 mole) and $CH_3NH_2 \cdot HCl$ (13.6 g, 0.20 mole) in EtOH (60 ml) and water (100 ml) was added a solution of KCN (13.0 g, 0.20 mole) in water (60 ml) at room temperature with stirring. The mixture was kept standing over night at room temperature, then poured into 300 ml of water, white solid separated was filtered and washed with water. Yield 24.0 g, 75%. Recrystallization from benzene gave colorless needles of mp 128°. IR ν_{max}^{Nujol} cm^{-1}: 2200w (CN); 1720 (C=O). *Anal.* Calcd. for $C_{10}H_9ON_3$: C, 64.14; H, 4.85; N, 22.45. Found: C, 63.99; H, 4.62; N, 22.30.

3-Anilino-3-cyanoindolin-2-one (10)——To a mixture of indoline-2,3-dione (5 g, 0.034 mole) and aniline (3.2 g, 0.034 mole) in AcOH (70 ml) was added a solution of KCN (3.9 g, 0.06 mole) in water (30 ml) at 40° over 30 min with stirring, and the stirred mixture was kept standing at room temperature for 20 hr. Colorless crystals (**10**) separated were collected and washed with water. The filtrate was diluted with water to give another crop of **10**. Total yield 6.9 g, 81%. Combined crops of **10** were recrystallized from benzene to give colorless needles of mp 139°. IR ν_{max}^{Nujol} cm^{-1}: 2240w (CN); 1720 (C=O). *Anal.* Calcd. for $C_{15}H_{11}ON_3$: C, 72.27; H, 4.45; N, 16.86. Found: C, 71.98; H, 4.35; N, 16.51. The same product was also obtained by the reaction of 3-phenyliminoindoline-2-one in AcOH with KCN solution.

3-Cyano-1-methyl-3-methylaminoindoline-2-one (11)——Similar treatment of **2** (5.0 g), $CH_3NH_2 \cdot HCl$ (2.7 g) and KCN (2.6 g) as described for **9** followed by recrystallization from ligroin gave colorless needles, mp 120°. Yield, 4.3 g, 70%. IR ν_{max}^{Nujol} cm^{-1}: 2200w (CN): 1720 (C=O). *Anal.* Calcd. for $C_{11}H_{11}ON_3$: C, 65.67; H, 5.51; N, 20.88. Found: C, 65.35; H, 5.32; N, 20.59.

3-Methyl-1,2,3,4-tetrahydroquinazoline-2,4-dione (14)——To a solution of **9** (1.9 g) and H_2O_2 (30%, 1.5 ml) in MeOH (30 ml) was added a solution of NaOH (1 g) in 10 ml of water dropwise over 30 min at room temperature with stirring. The stirring was continued for 1 hr, the solution was filtered to remove a small amount of insoluble product and diluted with 5% AcOH to give 1.2 g of white solid. Recrystallization from iso-PrOH gave colorless needles of mp 234°. Mass Spectrum *m/e*: 176 (M$^+$). IR ν_{max}^{Nujol} cm^{-1}: 1720, 1670 (C=O). This compound was identical with the sample prepared by Staiger, *et al*'. method.[7]

3-Phenyl-1,2,3,4-tetrahydroquinazoline-2,4-dione (15)——Similar treatment of **10** (2.5 g), H_2O_2 and NaOH solution as described above followed by recrystallization from iso-PrOH gave colorless needles of mp 274°. Yield, 80%. Mass Spectrum *m/e*: 238 (M$^+$). IR ν_{max}^{Nujol} cm^{-1}: 1720, 1660 (C=O). This compound was identical with the sample prepared by Paulewski' method.[8]

3-Methyl-spiro[imidazolidine-4,3′-indoline]-2,2′,5-trione (16)——To a mixture of **9** (3 g, 0.015 mole) and KOCN (1.8 g, 0.02 mole) in 15 ml of EtOH–H_2O (10: 5) was added AcOH (70%, 20 ml) and heated at 100° for 1 hr. The mixture was then added conc. HCl (2 ml) and heating was continued for 10 min. The resulting mixture was concentrated to a thick syrup *in vacuo*, the residue was mixed with water and a solid remained was dried and washed with benzene. Yield, 1.0 g (Table I).

Methylation of 5: Formation of 6——To a solution of **5** (2.1 g) in NaOH solution (20%, 7 ml) was added $(CH_3)_2SO_4$ (2.3 g) at 60° with vigorous shaking. After cooling, a solid separated was collected and recrystallized from a mixture of MeOH and benzene to give 1.5 g of colorless needles, mp 288°, which were identical to the foregoing sample.

1′,3-Dimethyl-spiro[imidazolidine-4,3′-indoline]-2,2′,5-trione (17)——This compound was obtained from **6** (1.8 g) in NaOH solution (20%, 8 ml) with $(CH_3)_2SO_4$ (2.0 g) according to the same procedure as described above. Yield, 1 g (Table I).

1,1′,3-Trimethyl-spiro[imidazolidine-4,3′-indoline]-2,2′,5-trione (18)——A mixture of **6** (1.2 g), well powdered Na_2CO_3 (3 g), $(CH_3)_2SO_4$ (2.5 g) and toluene (10 ml) was heated at 110° for 2 hr. After cooling, the mixture was added 30 ml of water and shaked with benzene. The organic layer was dried over $MgSO_4$ and evaporated to give colorless needles. Yield, 0.8 g (Table I).

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10) P. Friedlander and St. Kielbasinski, *Ber.*, **44**, 3098 (1911).

11) F. Knotz, *Sci. Pharm.*, **38**, 98 (1970) [*C.A.*, **73**, 55911*k* (1970)].

12) H. Hellmann, G. Hellmann, and F. Lingens, *Chem. Ber.*, **86**, 1346 (1953).