Quinoline Alkaloids. Part XIII.[1] A Convenient Synthesis of Furoquinoline Alkaloids of the Dictamnine Type

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The furoquinoline alkaloids dictamnine, γ-fagarine, and skimmianine have been synthesised (48—66% yield) from 4-methoxy-3-(3-methylbut-2-enyl)-2-quinolones or from the corresponding 2,4-dimethoxy-derivatives by ozonolysis or by reaction with osmium tetroxide–periodate and cyclisation of the resultant aldehydes with polyphosphoric acid. The *N*-methyl-4-quinolone, isodictamnine, was prepared similarly. The starting isoprenyl derivatives were obtained by alkylation of 2,4-dimethoxyquinolines as well as by established methods. The rearrangement of linear into angular furoquinolines is discussed.

THE furo[2,3-*b*]quinoline alkaloids dictamnine (4a) and γ-fagarine (4c) were first synthesised in 1956 by two independent routes;[2,3] these procedures and later modifications have been applied extensively to the synthesis of alkaloids of this type.[4,5] In connection with our studies of the biosynthesis of furoquinoline alkaloids,[6] we required furoquinolines of the dictamnine group specifically labelled with ^{14}C in the furan ring, and since the existing routes produce low overall yields we have developed a more efficient synthesis.

The new method[7] is related to Sheshadri's synthesis of furocoumarins,[8] and involves oxidative cleavage of 4-methoxy-3-(3-methylbut-2-enyl)-2-quinolones (2) and cyclisation of the resultant aldehydes (3) to linear furoquinolines (4).

The starting quinolones (2) have been prepared previously[9,10] by reaction of aromatic amines with substituted malonic esters followed by selective methylation with diazomethane, but the yields are not high (19—28%) and isolation of pure products in the initial cyclisation step is sometimes difficult. Direct alkylation of a quinoline derivative seemed a promising alternative,

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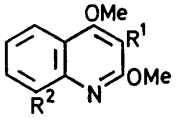
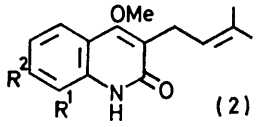
[2] M. F. Grundon and N. J. McCorkindale, *Chem. and Ind.*, 1956, 1091; *J. Chem. Soc.*, 1957, 2177.
[3] H. Tuppy and F. Böhm, *Angew. Chem.*, 1956, **68**, 388; *Monatsh.*, 1956, **87**, 720.
[4] R. G. Cooke and H. F. Haynes, *Austral. J. Chem.*, 1958, **11**, 225; T. Ohta and Y. Mori, *Chem. and Pharm. Bull. (Tokyo)*, 1957, **5**, 87; *Yakugaku Zasshi*, 1962, **82**, 549; Y. Kuwayama and Y. Matsuda, *ibid.*, 1965, **85**, 731.
[5] N. S. Narasimhan and M. V. Paradikar, *Chem. and Ind.*, 1967, 831; 1968, 515; N. S. Narasimhan, M. V. Paradhar, and R. H. Alurka, *Tetrahedron*, 1971, **27**, 1351.
[6] J. F. Collins and M. F. Grundon, *Chem. Comm.*, 1969, 621; M. F. Grundon and K. J. James, *ibid.*, 1971, 1311.
[7] Preliminary communication, J. F. Collins, G. A. Gray, M. F. Grundon, D. M. Harrison, and (Mrs.) C. G. Spyropoulos, *Chem. Comm.*, 1972, 1029.
[8] R. Aneja, S. K. Mukerjee, and T. R. Sheshadri, *Tetrahedron*, 1958, **14**, 256.
[9] E. A. Clarke and M. F. Grundon, *J. Chem. Soc.*, 1964, 4190.
[10] R. M. Bowman and M. F. Grundon, *J. Chem. Soc.* (*C*), 1966, 1504.

since Narasimham *et al.*[5] succeeded in alkylating 2,4-dimethoxyquinolines with ethylene oxide. Reaction of 2,4-dimethoxyquinoline in tetrahydrofuran with n-butyl-lithium and 3,3-dimethylallyl bromide furnished



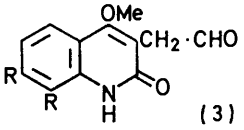
(1)

a; $R^1 = CH_2 \cdot CH{=}CMe_2$, $R^2 = H$
b; $R^1 = Me$, $R^2 = H$
c; $R^1 = CH_2 \cdot CH{=}CMe_2$, $R^2 = OMe$
d; $R^1 = [CH_2]_2 \cdot CHMe_2$, $R^2 = OMe$



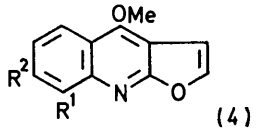
(2)

a; $R^1 = R^2 = H$
b; $R^1 = R^2 = OMe$
c; $R^1 = OMe$, $R^2 = H$



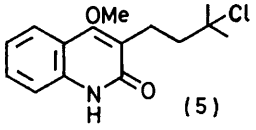
(3)

a; R = H
b; R = OMe



(4)

a; $R^1 = R^2 = H$
b; $R^1 = R^2 = OMe$
c; $R^1 = OMe$, $R^2 = H$



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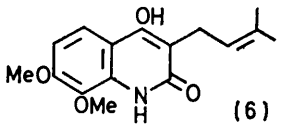
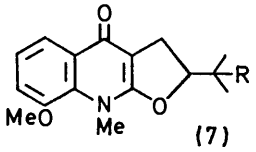


(6)



(7)

a; R = H
b; R = OH

the dimethoxyquinoline (1a) in 81% yield with the alkylated 2-quinolone (2a) as a by-product (17%). This is apparently a general method for the preparation of 3-alkylated 2,4-dimethoxyquinolines, and 2,4-dimethoxy-3-methylquinoline (1b) and the trimethoxyquinolines (1c and d) were prepared similarly.

The required 2-quinolones (2a and c) were obtained from the corresponding 2,4-dimethoxyquinolines by treatment with dry hydrogen chloride. This selective reaction of 2,4-dimethoxyquinolines has been observed previously [11] and proceeds in high yield even for compounds (1a and c) containing side-chain double bonds. It appears that addition of hydrogen chloride to the double bond is a slower process; prolonged reaction of the dimethoxyquinoline (1a) gave the chloro-derivative (5) almost quantitatively. The structure of this compound was indicated by i.r. absorption at 1665 cm^{-1} (NHCO), by its n.m.r. spectrum [τ 6·0 (3H, s, OMe), 7·02 (2H, m, $ArCH_2 \cdot CH_2$), 7·88 (2H, m, $ArCH_2 \cdot CH_2$), and 8·29 (6H, s, CMe_2)], and by the mass spectrum (M^+ at *m/e* 279). Treatment of the chloro-compound with base in an aprotic solvent furnished the quinolone (2a) (86%).

The alkylation route to the prenylquinolones (2) is preferred when the requisite 2,4-dimethoxyquinolines are readily available, as in the preparation of (2a) and (2c) already described. The trimethoxyquinolone (2b) required for the synthesis of skimmianine (4b) was prepared, however, by the older route.[9] Reaction of 2,3-dimethoxyaniline with diethyl (3-methylbut-2-enyl)-malonate furnished the 4-hydroxy-2-quinolone (6) (19%), converted by brief treatment with diazomethane into the 4-methoxy-derivative (2b) (49%). The structures of the two quinolones were confirmed by i.r. and n.m.r. spectroscopy (see Experimental section). The 4-methoxy-2-quinolone (2b) was isolated recently from *Dictamnus albus* and named preskimmianine.[12]

Oxidative cleavage of the prenylquinolone (2a) was carried out by ozonolysis in methanol or by reaction with osmium tetroxide–periodate. The aldehyde (3a) was obtained in >90% yield and its structure was indicated by its n.m.r. spectrum [τ −2·2br (1H, s, NH), 0·61 (1H, t, CHO), 6·0 (3H, s, OMe), and 6·4 (2H, d, CH_2)]. Cyclisation by heating with polyphosphoric acid furnished dictamnine (4a). The overall yield in the four-stage synthesis of the alkaloid from 2,4-dimethoxyquinoline was 50%, a clear improvement on existing methods.

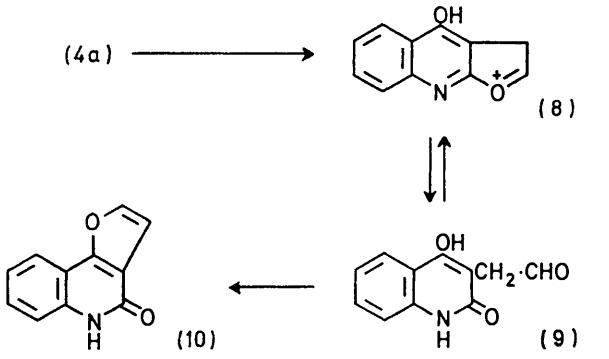
The alkaloids γ-fagarine (4c) and skimmianine (4b) were synthesised similarly. Oxidation of the dimethoxyquinolone (2c) proved to be unsatisfactory, but ozonolysis of the trimethoxy-derivative (1c) and cyclisation of the aldehyde with polyphosphoric acid gave γ-fagarine; the overall yield of the alkaloid from 2,4,8-trimethoxyquinoline was 40%. The alkaloid skimmianine (4b) was prepared most conveniently (48%) from the trimethoxy-prenylquinolone (2b) by oxidation with osmium tetroxide–periodate to the aldehyde (3b) and subsequent cyclisation with polyphosphoric acid.

All furoquinoline alkaloids of the dictamnine type isolated so far and alkaloids related to lunacrine (7a) and balfourodine (7b) have a linear arrangement of the three rings. Synthetic methods have been plagued hitherto by the greater thermodynamic stability of the unnatural angular arrangement and the factors involved in the quinoline series have been discussed previously in relation to the acid-catalysed cyclisation of 3-prenyl 2,4-dioxygenated quinolines [9] and to the Claisen rearrangement of the 3,3-dimethylallyl ether of 4-hydroxy-1-methyl-2-quinolone.[13]

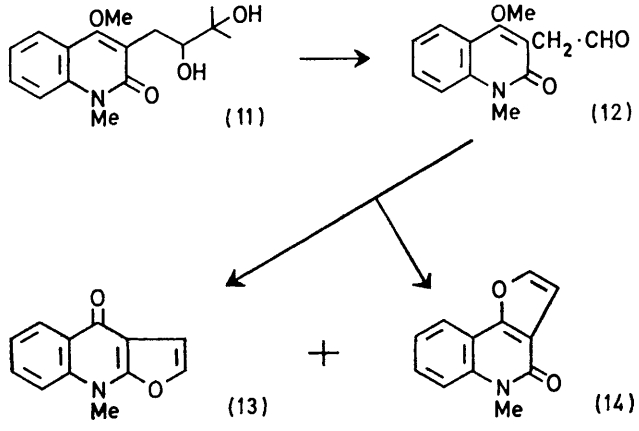
In the present work the isolation of the angular compound (10) (5%) from the cyclisation of the aldehyde (3a) with polyphosphoric acid suggested that the same

[11] M. Terasaka, *Chem. and Pharm. Bull.* (*Tokyo*), 1960, **8**, 523.
[12] R. Storer and D. W. Young, *Tetrahedron Letters*, 1972, 2199.
[13] T. R. Chamberlain and M. F. Grundon, *J. Chem. Soc.* (*C*), 1971, 910.

problem might exist. We find, in fact, that heating dictamnine with polyphosphoric acid at 180° for 40 min results in partial conversion (20%) into the angular 2-quinolone (10). The latter compound has been



synthesised previously [14] and was obtained during attempts to demethylate dictamnine with hydrogen bromide.[15] The mechanism of the dictamnine rearrangement can be formulated as initial cleavage of the methyl ether to the protonated vinyl ether (8) followed by formation of the aldehyde (9), which cyclises to the more stable angular derivative (10). It appears from these results that to obtain maximum yields of furoquinolines in the aldehyde cyclisation reaction the temperature and reaction time must be controlled carefully.



We also studied the synthesis of 4-hydroxy-*N*-methylfuroquinolines (the 'iso'-alkaloids) by the new procedure, choosing isodictamnine (13) as an example. The required aldehyde (12) was prepared in high yield by periodate oxidation of the diol edulinine (11). The structure of the aldehyde was confirmed by its n.m.r. spectrum, τ 0·2 (1H, t, CHO), 6·2 (2H, d, CH_2), and 6·1 and 6·3 (each s, Me). Cyclisation of the aldehyde with polyphosphoric acid afforded isodictamnine (13) (47%). Formation of angular ring compounds provides more serious competition than in the synthesis of 4-methoxy-alkaloids, and the isomer (14) was isolated in 29% yield. Apparently, rearrangement is again involved: reaction of isodictamnine (13) with polyphosphoric acid at 160° led to 18% conversion into the isomer (14).

[14] M. F. Grundon, N. J. McCorkindale, and M. N. Rodger, *J. Chem. Soc.*, 1955, 4284.

EXPERIMENTAL

The n.m.r. spectra were determined with a Varian HR-100 spectrometer (tetramethylsilane as internal standard).

2,4-Dimethoxy-3-(3-methylbut-2-enyl)quinoline (1a).—2,4-Dimethoxyquinoline (6·1 g) in tetrahydrofuran (50 ml) under nitrogen was treated with n-butyl-lithium in hexane (17% w/v; 18 ml), and 3,3-dimethylallyl bromide (12 g) in tetrahydrofuran (50 ml) was added dropwise. After 1 h water was added, and the product was recovered with ether. Trituration with light petroleum (b.p. 40—60°) gave 4-methoxy-3-(3-methylbut-2-enyl)-2-quinolone (1·1 g, 17%), m.p. and mixed m.p. 119—121°. Chromatography of the residue on neutral alumina and elution with light petroleum (b.p. 40—60°)–ether (4 : 1) furnished the *dimethoxyquinoline* as an oil (6·4 g, 81%), b.p. 138—140° at 0·9 mmHg (Found: C, 74·9; H, 7·7; N, 5·9. $C_{16}H_{19}NO_2$ requires C, 74·7; H, 7·4; N, 5·4%).

2,4,8-Trimethoxy-3-(3-methylbut-2-enyl)quinoline (1c).—By the procedure described for the dimethoxy-derivative, except that benzene was used as reaction solvent, 2,4,8-trimethoxyquinoline [5,16] was converted into the trimethoxyquinoline (1c) which was obtained from pentane in plates (79%), m.p. 59—60°, τ ($CDCl_3$) 2·47 (q, H-5), 2·64—3·16 (m, H-6 and H-7), 4·74 (t, =CH–), 5·84, 5·96, and 6·07 (each s, OMe), 6·54 (d, CH_2), and 8·18 and 8·30 (=CMe_2).

2,4,8-Trimethoxy-3-(3-methylbutyl)quinoline (1d).—Reaction of 2,4,8-trimethoxyquinoline with n-butyl-lithium and 1-bromo-3-methylbutane in benzene furnished the *3-alkylquinoline* in prisms (33%) (from pentane), m.p. 55—56° (Found: C, 70·8; H, 8·1; N, 4·8. $C_{17}H_{23}NO_3$ requires C, 70·6; H, 8·0; N, 4·8%).

Reduction of the 3-methylbut-2-enyl derivative (1c) with hydrogen and platinum in ethanol gave the alkylquinoline, m.p. and mixed m.p. 55—56°.

2,4-Dimethoxy-3-methylquinoline (1b).—The *compound* was obtained from 2,4-dimethoxyquinoline, n-butyl-lithium, and methyl iodide in ether as prisms (69%) (from aqueous ethanol), m.p. 45—46° (Found: C, 71·2; H, 6·6; N, 7·0. $C_{12}H_{13}NO_2$ requires C, 71·0; H, 6·5; N, 6·9%).

4,8-Dimethoxy-3-(3-methylbut-2-enyl)-2-quinolone (2c).—A solution of the trimethoxy-quinoline (1c) (2·87 g) in ether (10 ml) was added to a saturated solution of hydrogen chloride in anhydrous ether (100 ml) and kept for 12 h. Water (20 ml) was added and the ether layer was washed with aqueous sodium carbonate and with water. Evaporation, chromatography of the residue on alumina, and elution with chloroform furnished the dimethoxy-quinolone in prisms (from hexane) (2·07 g, 76%), m.p. and mixed m.p. with an authentic sample 119—121° (lit.,[9] 119—120°).

4-Methoxy-3-(3-methylbut-2-enyl)-2-quinolone (2a).—Dry hydrogen chloride was passed through a refluxing solution of the dimethoxy-quinoline (1a) (0·3 g) in di-isopropyl ether (50 ml) for 1·5 h. The solution was washed with aqueous sodium carbonate and evaporated to give the required quinolone (2a) in plates (from ether–hexane) (0·25 g, 92%), m.p. 132—134°, identical (i.r. and mixed m.p.) with an authentic sample (lit.,[10] m.p. 132—134°).

When heating with hydrogen chloride was continued for

[15] H. Tuppy and F. Böhm, *Monatsh.*, 1956, **87**, 735.

[16] G. H. Patel and C. M. Mehta, *J. Sci. Ind. Research (India)*, 1960, **19B**, 436.

5 h 3-(3-chloro-3-methylbutyl)-4-methoxy-2-quinolone (94%) was obtained, and separated from ether–light petroleum (b.p. 40—60°) in needles, m.p. 148—149°, $\nu_{max.}$ 1665 cm^{-1} (NHCO), *m/e* 279 (M^+). Treatment of the chloro-compound with potassium t-butoxide in dimethyl sulphoxide at 70° furnished the quinolone (2a) (86%).

Dictamnine (4a).—(*a*) Ozone–oxygen was passed through a solution of the quinolone (2a) (1·0 g) in methanol (30 ml) at −78° until an excess of ozone was present. Dimethyl sulphide (5 ml) was added, and the mixture was stirred at 20° for 2 h. Solvent was removed, and methylene chloride (50 ml) and water (50 ml) were added. Evaporation of the organic solvent furnished the aldehyde (3a) (0·82 g, 92%), m.p. 154—157° (for n.m.r. data see Discussion section), which was not purified further. The aldehyde (0·3 g) in polyphosphoric acid (15 g) was heated at 150° for 30 min and then added to water (50 ml). The precipitate was sublimed *in vacuo* to give the angular compound (10) (0·012 g, 5%), m.p. 239—241° (lit.,[14] 249—250°), identical (mixed m.p. and i.r.) with an authentic sample. The filtrate was made alkaline and dictamnine was obtained with dichloromethane and separated from light petroleum (b.p. 60—80°) in needles (0·17 g, 72%), m.p. and mixed m.p. 132—133° (lit.,[2] 132°). When heated with polyphosphoric acid at 180° for 40 min dictamnine (0·10 g) gave the angular compound (10) (0·02 g, 20%).

(*b*) The quinolone (2a) (0·243 g) in dioxan–water (3 : 1; 60 ml) was stirred at 20° with osmium tetroxide (9 mg), and sodium periodate (0·78 g) was added slowly. After 24 h the aldehyde (3a) (0·197 mg, 91%), m.p. 154—157°, was obtained by extraction with chloroform, and was cyclised to dictamnine as described in (*a*).

γ-Fagarine (4c).—The trimethoxyquinoline (1c) (0·28 g) was similarly ozonised and the crude aldehyde was heated with polyphosphoric acid at 170—175° for 45 min. Work-up in the usual way gave γ-fagarine (0·13 g, 50%), m.p. and mixed m.p. 141—142°.

4-Hydroxy-7,8-dimethoxy-3-(3-methylbut-2-enyl)-2-quinolone (6).—*2,3-Dimethoxyaniline* [17] (11·5 g) in diphenyl ether (75 ml) was added during 1 h to a solution of diethyl (3-methylbut-2-enyl)malonate [9] (22·5 g) in diphenyl ether (175 ml) refluxing under nitrogen, and the ethanol formed in the reaction was allowed to escape. After 2·5 h the solvent was evaporated off and a solution of the residue in chloroform was extracted with 2N-sodium carbonate. Acidification of the alkaline solution with hydrochloric acid gave the *quinolone* as a precipitate (3·85 g, 19%), separating from aqueous ethanol in needles, m.p. 215—217°, $\nu_{max.}$ 1640 cm^{-1} (NHCO), τ [$(CD_3)_2SO$ at 60 MHz] 2·15 (d, *J* 9 Hz, 5-H), 2·93 (d, *J* 9 Hz, 6-H), 4·7 (t, *J* 7 Hz, CH), 6·05 and 6·15 (each s, OMe), 6·67 (d, *J* 7 Hz, CH_2), and 8·22 and 8·32 (=CMe_2) (Found: C, 66·1; H, 6·6. $C_{16}H_{19}NO_4$ requires C, 66·4; H, 6·6%).

4,7,8-Trimethoxy-3-(3-methylbut-2-enyl)-2-quinolone (2b).—The 4-hydroxy-quinolone (6) (3 g) in methanol (50 ml) was treated with an excess of diazomethane, and after 5 min acetic acid was added and the solvent was evaporated off. Chromatography of the residue on alumina and elution with ether–light petroleum (b.p. 40—60°) (4 : 1) afforded the *trimethoxy-quinolone* (prisms from ether) (1·5 g, 49%), m.p. 153—155°, $\nu_{max.}$ 1640 cm^{-1} (NHCO), τ ($CDCl_3$ at 60 MHz) 2·56 (d, *J* 9 Hz), 3·15 (d, *J* 9 Hz), 4·67 (t, *J* 7 Hz, CH), 6·05 (6H, s, 2 × OMe), 6·10 (3H, s, OMe), 6·67 (d, *J* 7 Hz, CH_2), and 8·22 and 8·32 (=CMe_2) (Found: C, 67·4; H, 6·9. $C_{17}H_{21}NO_4$ requires C, 67·3; H, 6·9%).

Skimmianine (4b).—Reaction of the trimethoxy-quinolone (2b) (0·10 g) with osmium tetroxide–periodate as described for dictamnine (*b*) furnished the aldehyde (3b) (0·077 g, 82%), m.p. 148—151°, $\nu_{max.}$ 1740 (CHO) and 1640 (NHCO) cm^{-1}. The crude aldehyde (98 mg) was heated with polyphosphoric acid at 150° for 30 min and then added to water (50 ml). After filtration, the solution was made alkaline and the product, obtained with chloroform, was purified by preparative t.l.c. on silica gel with ethyl acetate–chloroform (1 : 4) as developer. Skimmianine was obtained from ethanol as prisms (53 mg, 58%), m.p. 176—177°, identical (mixed m.p., i.r., n.m.r., and mass spectra) with a natural sample, m.p. 176—178°.

3-Formylmethyl-4-methoxy-1-methyl-2-quinolone (12).—An excess of periodic acid was added to (±)-edulinine [18] (11) (0·2 g) in methanol–water (3 : 7; 15 ml) and the solution was kept for 12 h and then extracted with dichloromethane. Evaporation of the solvent gave the *aldehyde*, separating from di-isopropyl ether in prisms (0·16 g, 94%), m.p. 113—115° (Found: C, 67·1; H, 5·5; N, 6·3. $C_{13}H_{13}NO_3$ requires C, 67·5; H, 5·6; N, 6·1%).

Isodictamnine (13).—The aldehyde (12) (60 mg) in polyphosphoric acid (13 g) was heated at 170—175° for 30 min and then added to water. The products were extracted with dichloromethane and chromatographed on alumina. Elution with ether gave the angular compound (14) (15 mg, 29%), m.p. and mixed m.p. with an authentic sample 129—130° (lit.,[14] 129—130°). Further elution, with ether–chloroform, afforded isodictamnine, separating from aqueous ethanol in needles (24 mg, 47%), m.p. and mixed m.p. 185—188° (lit.,[19] 188°). The authentic sample was prepared in 82% yield by reaction of dictamnine with methyl iodide; [19] the n.m.r. spectrum ($CDCl_3$) showed τ 1·45 (1H, d, H-5), 2·2—2·75 (3H, m), 2·78 (1H, d), 3·0 (1H, d), and 6·19 (3H, s, NMe).

Heating isodictamnine (100 mg) with polyphosphoric acid (10 ml) at 160° for 40 min gave the angular compound (14) (18%) and unchanged isodictamnine (75%).

We thank the Ministry of Education for Northern Ireland for postgraduate studentships (to J. F. C. and G. A. G.).

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[17] N. Mauthner, *Math. naturw. Anz. ungar. Akad. Wiss.*, 1938, **57**, 252.

[18] D. R. Boyd and M. F. Grundon, *J. Chem. Soc.* (*C*), 1970, 556.

[19] Y. Asahina, T. Ohta, and M. Inubuse, *Ber.*, 1930, **63**, 2045.