residue showed only one spot (Rf 0.28) and *d*-arabinose employed as control gave a spot with the same Rf value (0.28).

A solution of the residue (120 mg.) and propionic anhydride (630 mg.) dissolved in pyridine (860 mg.) was left at room temperature for 5 days. The reaction mixture was poured into ice-water and extracted with Et$_2$O. The Et$_2$O extract was washed successively with 10% HCl and water, dried over Na$_2$SO$_4$, and evaporated. The residue was distilled *in vacuo* and gave a colorless viscous oil (200 mg.), b.p$_{0.0003}$ 160~165°(bath temp.), whose analytical values agreed with those for arabinose tetrapropionate. The infrared spectrum of this oil in CHCl$_3$ solution was identical with that of D-arabinose tetrapropionate prepared analogously. *Anal.* Calcd. for $C_{17}H_{26}O_9$: C, 54.54; H, 7.00. Found: C, 54.59; H, 6.96.

The authors wish to express their deep gratitude to Prof. K. Tsuda, The Institute of Applied Microbiology, University of Tokyo, and to Mr. M. Matsui, Director of this Laboratory, for their kind guidance and encouragement throughout the course of this investigation. The measurement of infrared spectra was carried out by Messrs O. Amakasu and H. Higuchi, and by Miss N. Sawamoto, and microanalyses were made by Messrs. T. Onoe and H. Nagashima, and Misses C. Furukawa and H. Ohtsuka.

Summary

DL-Arabinose was stereospecifically synthesized starting from 5-ethoxy-4-penten-2-yn-1-ol, which was prepared by the Grignard reaction of formaldehyde with 4-ethoxy-3-buten-1-yn-1-yl magnesium bromide.

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152. **Tohru Hino**: Synthetic Approaches to Calycanthaceae Alkaloids. II.[*1] A Synthesis of 1,1'-Dimethyl-3,3'-bis(2-aminoethyl)-3,3'-bioxindole.

(*Faculty of Pharmaceutical Sciences, University of Tokyo*[*2])

The structure of calycanthine,1) the main alkaloid of Calycanthaceae plants, has been investigated by Barger,1a) Manske,1b) Späth,1c) and others, since its first isolation by Eccles in 1888. In 1954, Robinson and Teuber2) pointed out that the previously suggested structure for the alkaloid appeared to be unnecessarily complicated and proposed its structure as (I), an N-methyltryptamine dimer, by clarifying the structure of calycanine, a degradation product of the alkaloid, and by the biogenetic consideration. Recently, Woodward, Harley-Mason, *et al.*3) proposed a new structure (II), derived from β,β-coupling of N-methyltryptamine as in the case of Robinson's structure, by the synthetic proof of calycanine and conformational consideration with biogenetic speculation. The structure (II) was proved by X-ray work by Glasgow group.4)

[*1] The paper by T. Hino and T. Shioiri (This Bulletin, 8, 839 (1960)) is designated as Part I of this series.

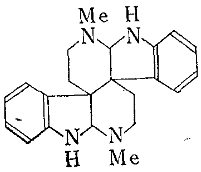
[*2] Hongo, Tokyo (日野 亨).

1) *a*) G. Barger, *et al.*: J. Chem. Soc., **1939**, 510; *b*) R.H.F. Manske, *et al.*: Can. J. Research, **B16**, 432 (1938); **B17**, 293 (1939), **B24**, 224 (1946); *c*) E. Späth, K. Eiter, *et al.*: Monatsh. **79**, 11, 17, 22 (1948); **80**, 607 (1949); **81**, 404 (1950); **83**, 916 (1952). cf. Léo Marion; R.H.F. Manske, H.L. Holmes: "The Alkaloids," Vol. II, Chapter XIII, pp. 434 (1952). Academic Press Inc., New York. J.E. Saxton: Quart. Rev., **10**, 108 (1956).

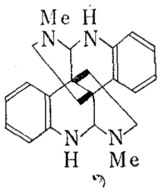
2) R. Robinson, H.J. Teuber: Chem. & Ind. (London), **1954**, 783.

3) R.B. Woodward, J. Harley-Mason, *et al.*: Proc. Chem. Soc., **1960**, 76.

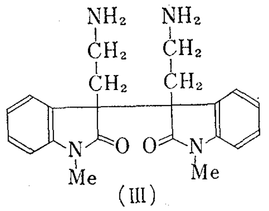
4) T.A. Hamor, J.M. Robertson, *et al.*: *Ibid.* **1960**, 78.



(I)

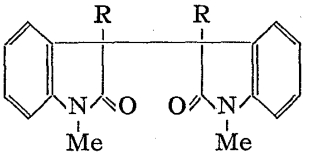


(II)



(III)

The author has been interested in the type of structure (I) and (II), and considered that a compound (III) was an attractive intermediate for the synthesis of the compounds of type (I) or (II). This paper deals with the synthesis of (III) and related compounds (IV) by the alkylation of bioxindole (IV : R=H).



(IV)

Though the alkylation of oxindole at 3-position has been well investigated by Julian,5) Wenkert,6) and others,7) these compounds (IV) are scarcely found in the literature, except the compound (IV : R=CH_3), which was synthesized by the oxidative dimerization of 1,3-dimethyloxindole by Harley-Mason,8) who reported the failure of dimethylation of bioxindole.

The starting material (V), m.p. 194~196°, was prepared in a good yield from 1,1′-dimethylisoindigotin,8,9) obtained by the condensation10) of 1-methylisatin and 1-methyloxindole, by reduction10) with zinc in acetic acid containing a small amount of conc. hydrochloric acid. This starting material might be a mixture of diastereoisomers but their separation did not succeed.

The methylation was carried out as a preliminary test for the alkylation of (V). When (V) was treated with methyl iodide in benzene, using sodium hydride (1 mole) and following Wenkert procedure,6a) (VIa), m.p. 216~217°, and (VIb), m.p. 165~167°, were obtained after fractional recrystallization. Both isomers gave the same dimethyl derivative8) (VIIa), m.p. 223~224°, by second methylation using sodium hydride in benzene and (VIIb) was not detected. (VIIa) was also obtained besides a small amount of (VIa) by direct dimethylation with 2 moles of sodium hydride in benzene. These compounds were identical with the higher-melting isomer obtained by oxidative dimerization of 1,3-dimethyloxindole, following Harley-Mason's procedure,8) however, the lower-melting isomer (VIIb), m.p. 177~179°, of (VII) was obtained besides a small amount of (VIIa) when (V) was treated with excess methyl iodide in liquid ammonia, using 2 moles of sodium amide. (VIIb) was identical with the lower-melting isomer of dimerization products. This stereospecific reaction, which was not clearly observed in the dimerization reaction, may be due to the difference of the reaction temperature which might affect the structure of sodium salts.

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5) *a*) P.L. Julian, J. Pikl, D. Boggess : J. Am. Chem. Soc., **56**, 1797 (1934); *b*) P.L. Julian, J. Pikl: *Ibid.*, **57**, 539, 563 (1935); *c*) P.L. Julian, J. Pikl, E. Wantz : *Ibid.*, **57**, 2026.

6) *a*) E. Wenkert, N.K. Bhattacharyya, *et al.* : *Ibid.*, **78**, 797 (1956); *b*) E. Wenkert, B.S. Bernstein, *et al.* : *Ibid.*, **80**, 4899 (1958); *c*) E. Wenkert, N.V. Bringi : *Ibid.*, **80**, 5575 (1958).

7) *a*) B. Witkop, J.B. Patrick : *Ibid.*, **75**, 2572 (1953); *b*) E.C. Horning, M.W. Ruthenberg : *Ibid.*, **72**, 3534; *c*) T. Hino, T. Shioiri : This Bulletin, 8, 839 (1960).

8) J. Harley-Mason, R.F.J. Ingleby : J. Chem. Soc., **1958**, 4782.

9) *a*) R. Stolle : J. prakt. Chem., **128**, 1 (1930); *b*) H. King, J. Wright : J. Chem. Soc., **1948**, 2314; *c*) F.G. Mann, R.C. Haworth : J. Chem. Soc., **1944**, 670.

10) cf. H. de Diesbach, E. Heppner : Helv. Chim. Acta, **32**, 687 (1949); A. Wahl, G. Fericean : Ann. chim. (Paris), **9**, 277 (1928).

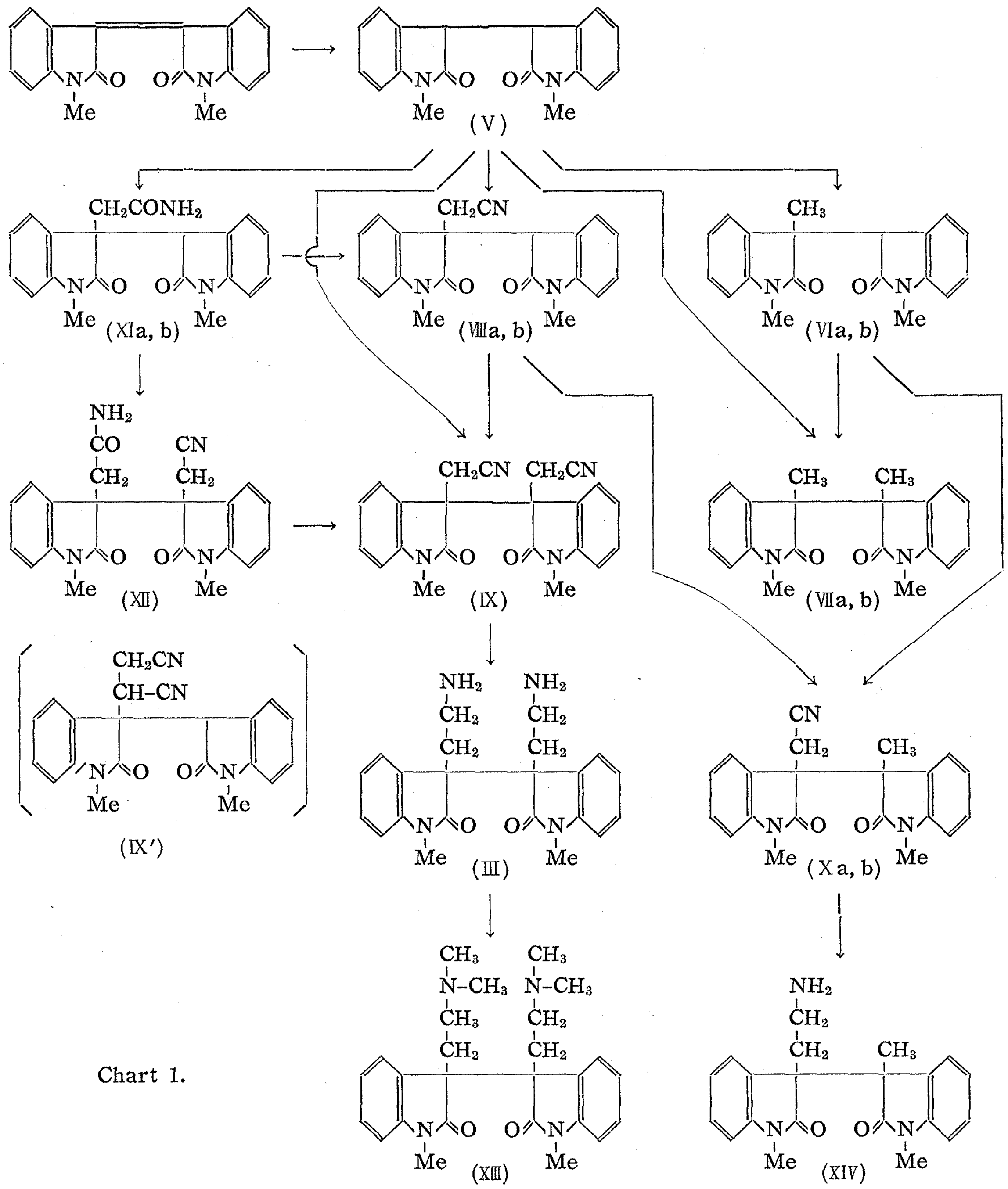

Chart 1.

As the third method of methylation, (V) was boiled for 10 hours with excess of methyl iodide and anhydrous potassium carbonate in dry acetone,6a) and this resulted in a formation of (VIa).

The cyanomethylation was then carried out, applying above methods. With 1 mole of sodium hydride and 2 moles of chloroacetonitrile in benzene, (V) gave higher-melting isomer (VIIIa), m.p. 258~260°, in 60% yield, accompanied with a small amount of lower-melting isomer (VIIIb). Almost the same result was obtained by the use of sodium ethoxide in ethanol, sodium powder in benzene, or potassium carbonate in acetone. The second cyanomethylation of (VIII) and *bis*-cyanomethylation of (V) encountered difficulties. Treatment of (VIIIa) with sodium hydride in toluene, dioxane, or dimethylformamide, mostly gave unreacted starting material with some uncharacterized products. When (VIIIa) was treated with 2 moles of chloroacetonitrile and 1 mole of sodium amide (or lithium amide) in liquid ammonia, dicyanomethyl derivative (IX), m.p. 263~264°, was obtained in a low yield after complicated separation from the starting material. Though the melting point of (IX) was close to that of the starting material, a depression was observed in a mixed fusion test and the analytical data of (IX) agreed with dicyanomethyl derivative.

Surprisingly, (IX) was obtained in a fair yield (56% based on reacted (VIIIa)) when (VIIIa) was refluxed with 1 mole of sodium iodide, 2.4 moles of potassium carbonate, and 3 moles of chloroacetonitrile in dry acetone for 12 hours.[6b)] The addition of sodium iodide showed a marked effect, but a larger amount of sodium iodide decreased the yield of (IX), with increased recovery of (VIIIa). By the use of 0.25 mole of potassium iodide instead of sodium iodide, with potassium carbonate in acetone, (VIIIa) gave (IX) in the same yield as in the use of 1 mole of sodium iodide. A good effect of sodium iodide was observed in the bis-cyanomethylation of (V). (IX) was obtained in 50% yield in almost pure state when (V) was refluxed with 3 moles potassium carbonate, 0.6 mole of sodium iodide, and 3 moles of chloroacetonitrile in acetone, while only (VIIIa) was obtained in 50% yield by a similar reaction without sodium iodide.

Treatment with sodium amide in liquid ammonia,[*3] by which dimethylation of (V) was successful, was applied to dicyanomethylation of (V), resulting in the formation of non-characterized crystals, having no CN in its infrared spectrum, besides a small amount of (VIIIa). In these reactions, definite isomer of (IX) was not isolated.[*4]

In the reaction of (VIIIa) with sodium amide in liquid ammonia, α-position of the cyano group in (VIII) might be attacked by a strong base such as NH_2^- to give (IX′). However, the fact that the same compound (IX) was obtained from (VIII) by chloroacetonitrile in the presence of potassium carbonate in acetone showed that such as that above-mentioned was not the case, because it was not probably the α-position of cyano group that would be attacked by a weak base such as potassium carbonate.

The structure of (IX) was also supported by the following reactions, by which two bioxindoles substituted with different alkyl group at 3- and 3′-positions were prepared. The methylation of (VIIIa) with sodium amide in liquid ammonia gave (Xa), m.p. 203~204.5° and (Xb), m.p. 163~165°, and the same (Xa) was also obtained by cyanomethylation of (VI) with sodium amide in liquid ammonia. Cyanomethylation of (VI) with sodium hydride in benzene was unsuccessful. On catalytic reduction, (Xa) gave methyl-(2-aminoethyl) derivative (XIV), m.p. 208~209°(decomp.).

Two isomers of monoacetamido derivative (XI) were obtained from (V) by treatment with sodium ethoxide in ethanol and with sodium hydride in benzene with chloroacetamide, former method mainly giving the higher-melting isomer (A), m.p. 255~256°, and the latter, the lower-melting isomer (B), m.p. 231~232°. When (XIa) was treated with tosyl chloride in pyridine (VIIIb), lower-melting isomer of (VIII) was obtained, while (VIIIa) was obtained from (XIb) by the same condition.

The cyanomethyl-acetamido derivative (XII) was obtained by cyanomethylation of (XI) with sodium amide in liquid ammonia, though the carbamoylmethylation of (VIII) did not succeed with various metal amides in liquid ammonia. The compound obtained by dehydration of (XII) with tosyl chloride in pyridine was identical with (IX) obtained by the cyanomethylation of (V) or (VIIIa). By these reactions the structure of (IX) has been further confirmed.

The catalytic hydrogenation of (IX) in acetic acid[7b)] gave *bis*-(2-aminoethyl) derivative (III), m.p. 227~228°(decomp.), which formed dihydrochloride, m.p. 268~269°(decomp.), as

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[*3] By this method, 1-methyloxindole with chloroacetamide gave 1-methyl-3,3-bis(carbamoylmethyl) oxindole, m.p. 258~259°(*Anal.* Calcd. for $C_{13}H_{15}O_3N_3$: C, 59.76; H, 5.79; N, 16.08. Found : C, 59.43; H, 5.94; N, 15.71.).

[*4] The oxidative dimerization of 1-methyl-3-cyanomethyl oxindole with $K_3Fe(CN)_6$ did not succeed.

dihydrate, and dipicrate, m.p. 247°(decomp.). The tetramethyl derivative (XIII), m.p. 130∼132°, was obtained by N-methylation of (III) with formaldehyde solution and formic acid. The same compound was obtained by the direct dimethylaminoethylation of (V) with dimethylaminoethyl chloride and sodium hydride in benzene after chromatographic separation.

The infrared spectra of these 3,3′-bioxindole derivatives have strong carbonyl stretching vibration of the oxindole at 1710[11] cm^{-1}, aromatic bands at 1615 and 1495 cm^{-1}, defomation vibration[11b,12] of N-Me at 1380 cm^{-1}, in chloroform solution and out-of-plane C-H bending vibrations of benzene at 750 cm^{-1} in KBr disc. Comparing infrared spectra of (V), (VIIa), and (IX), with those of their monomers, 1-methyloxindole, 1,3-dimethyl- and 1-methyl-3-cyanomethyloxindole, all of the main bands in the higher-frequency region to 1300 cm^{-1} are identical, but the bands are different in the lower-frequency region, especially in the out-of-plane vibration region, in which (V), (VIIa), and (IX) have doublet absorption while their monomers have only a single peak. Infrared spectra of (VIIa) and (VIIb) are closely similar, but different in the region of 1100 cm^{-1} in chloroform solution.

Thus the synthesis of (III) and other 3,3′-disubstituted 3,3′-bioxindoles has been established. The Ladenburg and lithium aluminium hydride reduction of (III), (XIII), and (VII) will be discussed in the following paper.

Experimental[*5]

1,1′-Dimethylisoindigotin——A mixture of 1-methyloxindole[9a] (60 g., 0.408 mole), 1-methylisatin[13] (66.0 g., 0.41 mole), AcOH (360 cc.), and conc. HCl (4 cc.) was heated in a boiling water bath for 2 hr. On warming, the mixture formed a clear red solution in the beginning, which turned dark red, and began to separate dark red crystals. After cool, the crystals were collected, washed with AcOH, and dried. The crude product was obtained as dark red crystals (95 g., 80%) of m.p. 270∼273° (decomp.). Recrystallization from glacial AcOH afforded dark red needles, m.p. 272∼273°(decomp.) (reported m.p. 263∼264°,[9c] 265°,[9a] and 268°[9b]). *Anal.* Calcd. for $C_{18}H_{14}O_2N_2$: C, 74.49; H, 4.86; N, 9.65. Found: C, 74.53; H, 5.03; N, 9.79.

1,1′-Dimethyl-3,3′-bioxindole (V)——A suspension of the isoindigotin (90 g.) in glacial AcOH (500 cc.) containing conc. HCl (4 cc.) was warmed in a boiling water-bath. Zn powder (35 g.) was added in small portions to the mixture during 1 hr. The dark red color gradually faded to pale brown. After cool, Zn was filtered off, washed with AcOH, and the filtrate was concentrated *in vacuo* to ca. 150 cc. The residue was poured into H_2O (ca. 500 cc.) with stirring, the white solid that formed was collected, and dried in a vacuum desiccator. The crude bioxindole (83.0 g., 91.6%), m.p. 180∼182°, was recrystallized from benzene to colorless prisms, m.p. 194∼196°. *Anal.* Calcd. for $C_{18}H_{16}O_2N_2$: C, 73.98; H, 5.52; N, 9.59. Found: C, 74.00; H, 5.72; N, 9.43. UV: $\lambda_{\max}^{\mathrm{EtOH (J.P.)}}$ 253 mμ (log ε 4.15).

1,1′,3-Trimethyl-3,3′-bioxindole (VI)——a) To a suspension of NaH (150 mg., 0.006 mole) in dehyd. benzene, bioxindole (V) (1.7 g., 0.0058 mole) in benzene was added in N_2 stream and the mixture became dark green on stirring at room temperature. The mixture was heated at 80∼90°(bath temperature) for 30 min., cooled, and MeI (2.5 g., 0.018 mole) in benzene was added dropwise, giving a dark red mixture. The whole was stirred at room temperature for 2 hr., then at 80°(bath temperature) for 4 hr. After being kept overnight, the mixture was filtered, the benzene layer was washed with H_2O, and dried. After evaporation of benzene, a brown solid (1.6 g.), m.p. 150∼160°, was obtained as a mixture of the isomers (VIa and b). Several recrystallizations from benzene afforded small plates, m.p. 217∼219°, as the higher-melting isomer (VIa). *Anal.* Calcd. for $C_{19}H_{18}O_2N_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74,22; H, 5.92; N, 9.43.

From the mother liquor, another isomer was obtained after Al_2O_3 chromatography. Several recrystallizations from benzene-hexane afforded minute crystals, m.p. 165∼167°. *Anal.* Found: N, 9.41.

[*5] All melting points are uncorrected. Infrared spectra were taken by Koken Model DS-301 and ultraviolet spectra, by Carry Model 11 spectrophotometer.

11) *a*) E. Wenkert, A.K. Bose, T.L. Reid: J. Am. Chem. Soc., **75**, 5514 (1953); *b*) A.E. Kellie, D.G.O. Sullivan, P.W. Sadler: *Ibid*. **1956**, 3809.

12) A.R. Katritzky, R.A. Jones: J. Chem. Soc., **1959**, 2067.

13) W. Steinkopf, H. Wilhelm: Ann., **546**, 221 (1941); J. Harley-Mason, R.F.J. Ingleby: J. Chem. Soc., **1958**, 3639.

b) A mixture of (V) (8.8 g.), K_2CO_3 (12.4 g.), and MeI (17.0 g.) in dehyd. Me_2CO (150 cc.) was gently refluxed for 8 hr., giving a dark red mixture. After cool, the mixture was filtered, washed with Me_2CO, and the acetone-insoluble fraction was treated with H_2O, giving a white solid (3.0 g., 32%), m.p. 214~217°. Recrystallization from benzene afforded colorless plates, m.p. 215~217°, which were identical with (VIa) obtained as above on admixture and in their IR spectra. From the acetone-soluble part, some (VIa) was obtained besides a colored substance which was not further investigated, and (VIb) was not isolated.

1,1′,3,3′-Tetramethyl-3,3′-bioxindole (VII)——a) From (VIa): To a suspension of NaH (40 mg.) in benzene (30 cc.), (VIa) (400 mg.) was added in N_2 stream and the mixture was stirred at room temperature for 1 hr., then refluxed for 1 hr., giving a dark red mixture. MeI (3.0 g.) in benzene was added to the mixture at 60° (bath temperature), the whole was stirred at this temperature for 6 hr., and finally heated to reflux for 2 hr. After cool, the mixture was filtered, the residue was washed with benzene, the combined benzene solution was washed with H_2O, and dried. Evaporation of benzene *in vacuo* afforded crude (VIIa) (0.4 g.) as dark brown solid, m.p. 200~210°. Repeated recrystallization from benzene gave pure (VIIa) as colorless prisms, m.p. 223~224°. When it was mixed with the starting material, melting point depressed to 195~205°. *Anal.* Calcd. for $C_{20}H_{20}O_2N_2$: C, 74.97; H, 6.29; N, 8.74. Found: C, 74.94; H, 6,28; N, 8.55.

b) From (VIb): When (VIb) (0.8 g.) was treated with NaH (80 mg.) and MeI (5.0 g.) in benzene as above, crude (VIIa) (0.7 g.) was obtained as reddish brown solid, m.p. 210~217°. Recrystallization from benzene afforded colorless prisms, m.p. 222~223°, which were identical with the sample obtained as above, on admixture. Both samples were identical with (VIIa) obtained by oxidative dimerization of 1,3-dimethyloxindole, on admixture and in their IR spectra.

c) From (V) by direct dimethylation with NaH in benzene: (V) (9.7 g.) was treated with NaH (1.6 g., 2 mol. equiv.) and MeI (20 g., over 4 mol. equiv.) in benzene by essentially the same procedure as above with longer heating (8 hr.), crude (VIIa) (5.8 g., 53%), m.p. 217~218°, was obtained from benzene-soluble portion as a cold benzene-insoluble solid. Recrystallization from benzene afforded colorless prisms, m.p. 218~220°, which were identical with the sample obtained as above, on admixture and in IR spectra. From the cold benzene-soluble portion, a small amount of (VIa) was obtained besides a small amount of (VIIa).

1,1′,3,3′-Tetramethyl-3,3′-bioxindole (VIIb)——To $NaNH_2$ (prepared from 1.0 g. of Na) in liq. NH_3 (300 cc.), (V) (5.8 g.) was added as a powder at the boiling point of NH_3, yielding greenish solution. After stirring for 1 hr. at the boiling point of NH_3, CH_3I (18.0 g., large excess) in dehyd. toluene (50 cc.) was added to the mixture during 20 min. The whole mixture was stirred at the room temperature for 3 hr., and then kept overnight to evaporate NH_3, giving a dark red toluene solution with insoluble materials. The mixture was filtered, the residue was washed with benzene and H_2O, toluene-benzene solution was washed with H_2O, and dried. Toluene-benzene solution was evaporated *in vacuo*, and the reddish brown solid (5.3 g.) gave crude (VIIb) (3.5 g., 52%), m.p. 160~170°, on recrystallization from benzene-hexane. It was recrystallized from benzene-hexane to large prisms, m.p. 177~178°. *Anal.* Calcd. for $C_{20}H_{20}O_2N_2$: C, 74.97; H, 6.29; N, 8.74. Found: C, 75.20; H, 6.39; N, 8.50.

From the mother liquor, further crop of (VIIb) (800 mg.), m.p. 173~177°, was obtained by Al_2O_3 chromatography (total yield of (VIIb) 4.3 g., 66%). A small amount of (VIIa) was obtained from the chromatography. (VIIb) was identical with the lower-melting isomer obtained by oxidative dimerization of 1,3-dimethyloxindole, on admixture and IR spectra.

3-Cyanomethyl-1,1′-dimethyl-3,3′-bioxindole (VIII)——a) NaH in benzene: To a suspension of NaH (2.40 g,) in dehyd. benzene (300 cc.), (V) (29.2 g.) was added as a fine powder with stirring. The whole mixture was refluxed for 5.5 hr. in N_2 stream with stirring and formed a dark greenish black mixture. After cool, chloroacetonitrile[14] (15.5 g., ca. 2 mol. equiv., freshly distilled) in benzene was added dropwise to the mixture during 30 min., resulting in a reddish brown mixture with a brown precipitate. The mixture was refluxed for 7.5 hr., filtered after cool, and the precipitate was washed with benzene. The insoluble residue was treated with H_2O and EtOH (to destroy unreacted NaH) and the resultant brown solid was washed with EtOH to give a light brown crystalline solid (19.3 g., 59%), m.p. 256~258° (decomp.). Recrystallization from glacial AcOH afforded colorless plates, m.p. 258~259°, (VIIIa). This was identical with (VIIIa) obtained from (XIb) (see below) on admixture and IR spectra. *Anal.* Calcd. for $C_{20}H_{17}O_3N_2$: C, 72.49; H, 5.17; N, 12.69. Found: C, 72.60; H, 5.28; N, 12.62. IR: $\nu_{\max}^{\text{Nujol}}$ 2260 cm^{-1} (C≡N). UV: $\lambda_{\max}^{\text{EtOH(J.P.)}}$ 256 mμ (log ε 4.08).

The benzene filtrate was washed with H_2O, dried, and evaporated *in vacuo*, leaving reddish brown solid (13.0 g.), m.p. 145~160°. It was recrystallized from benzene to a crystalline powder (1.0 g.), m.p. 180~190°, which showed $\nu_{C\equiv N}$ absorption at 2260 cm^{-1} in its IR spectrum. Recrystallization from EtOH afforded a small amount of colorless crystals, m.p. 233~235° (sint.)/260~263°, which was assumed to be the isomer b contaminated with isomer a. *Anal.* Found: C, 72.24; H, 5.08; N, 12.63.

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[14] Org. Syntheses, **30**, 22 (1950); cf. M. Nakazaki: Bull. Chem. Soc. Japan, **32**, 588 (1959).

Its IR spectrum was almost identical with that of (VIIIb) obtained from (XIa) (see below). Na-sand substituted for NaH gave about the same result.

b) NaOEt in EtOH: To a boiling mixture of (V) (4.3 g.) and chloroacetonitrile (3.5 g., freshly distilled) in dehyd. EtOH (40 cc.), NaOEt in dehyd. EtOH (prepared from 700 mg. of Na and 20 cc. of EtOH) was added dropwise in N_2 stream with stirring during 20 min., giving a dark brown mixture. The mixture was heated for further 2 hr., filtered after cool, and washed with EtOH. The insoluble residue was treated with H_2O and formed a brown solid, m.p. 250~255°(decomp.) (3.0 g., 61%), as a crude product. The crude material was recrystallized from glacial AcOH to pure (VIIIa), m.p. 256~257°. *Anal.* Found: C, 72.46; H, 5.41; N, 13.11.

c) K_2CO_3 in acetone: A mixture of (V) (5.0 g.), dehyd. K_2CO_3 (4.5 g.), and chloroacetonitrile (2.7 g. 2 mol. equiv.) in dehyd. Me_2CO (100 cc.) was heated to reflux for 16 hr. When cooled, the dark red mixture was filtered and the residue was washed with Me_2CO. Insoluble residue was treated with H_2O and gave crude (VIIIa) as a colorless solid (2.8 g., 50%), m.p. 252~257°(decomp.). Recrystallization from glacial AcOH afforded pure (VIIIa).

d) From (XIa); formation of (VIIIb): A mixture of (XIa) (120 mg.) and TsCl (200 mg.) in pyridine (2 cc.) was warmed on a water bath for 35 min. After cool, the yellow solution was poured into cold water, the precipitate was collected, and recrystallized from EtOH to colorless crystals (50 mg.), m.p. 235~240°. Two recrystallizations from the same solvent afforded pure (VIIIb) as fine pillars, m.p. 233~235°. *Anal.* Calcd. for $C_{20}H_{17}O_2N_3$: C, 72.49; H, 5.17; N, 12.69. Found: C, 72.47; H, 5.08; N, 12.65.

e) From XIb; formation of (VIIIa): (XIb) (200 mg.) was treated with TsCl (400 mg.) in pyridine (2 cc.) as in (d). Crude (VIIIa) was obtained as fine crystals (100 mg.), m.p. 253~258°, by recrystallization of H_2O-insoluble solid. It gave pure (VIIIa) (40 mg.), m.p. 260°, on recrystallization from glacial AcOH and was identical with (VIIIa) obtained as above, on admixture and IR spectra.

3-Carbamoylmethyl-1,1′-dimethyl-3,3′-bioxindole (XI)——a) NaOEt in EtOH: To a boiling solution of (V) (3.0 g.) and chloroacetamide[15] (2.0 g.) in dehyd. EtOH (30 cc.), NaOEt in EtOH (500 mg. of Na (ca. 2.2 atoms equiv.) in 30 cc. of dehyd. EtOH) was added dropwise during 30 min. with stirring. After the addition, the mixture was heated to reflux for 6 hr., forming a dark red mixture. After cool, the mixture was filtered and the residue was washed with EtOH. The insoluble residue was treated with H_2O, filtered, and washed with EtOH, giving a light brown powder (2.0 g.), m.p. 245°, as a crude product. From the hot EtOH-insoluble fraction (600 mg.), pure (XIa) was obtained as colorless prisms, m.p. 255~256°, after recrystallization from BuOH. *Anal.* Calcd. for $C_{20}H_{19}O_3N_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 69.22; H, 5.41; N, 11.87. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3540, 3320, 3240 (prim. amide), 1645 ($CONH_2$); $\nu_{\max}^{CHCl_3}$ cm^{-1}: 3570, 3360 (prim. amide), 1700 (C=O), 1598 (amide II).

From the hot EtOH-soluble portion, colorless prisms, m.p. 233~234°/249~251°, were obtained after recrystallization from EtOH. It was assumed to be a mixture of (XIa) and (XIb).

b) NaH in benzene: (V) (4.5 g.) was treated with NaH (380 mg., 1 mole equiv.) and chloroacetamide 2.0 g.) in benzene as in the methylation or cyanomethylation. The reaction mixture was filtered, washed with benzene, and the residue was treated with H_2O. This was filtered, washed with EtOH, and gave a colorless powder (fraction A), m.p. 220~225° (2.3 g., 42%). Fraction A was recrystallized several times from EtOH to colorless prisms, m.p. 231~232°, as pure (XIb). *Anal.* Found: C, 68.63; H, 5.35; N, 11.92. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3470, 3380 (NH), 1675 ($CONH_2$); $\nu_{\max}^{CHCl_3}$ cm^{-1}: 3560, 3490 (NH), 1700 (C=O of oxindole and $CONH_2$), 1605 (amide II band).

Another crop of crystals, m.p. 230°/250~252°, was obtained from the mother liquor after recrystallization from BuOH, as a mixture of isomers a and b. *Anal.* Found: C, 68.60; H, 5.47; N, 11.73.

From the EtOH-soluble portion, a brown solid, m.p. 235~245° (300 mg., fraction B), was obtained. From fraction B, colorless crystals, m.p. 249~251°, were obtained by recrystallization from BuOH, and it was found to be identical with (XIa) obtained as in above (a).

3-Cyanomethyl-1,1′,3′-trimethyl-3,3′-bioxindole (X)——a) From (VIII): To a suspension of $NaNH_2$ (prepared from 350 mg. of Na) in liquid NH_3 (250 cc.), (VIIIa) (5.0 g.) was added in several portions at the boiling point of NH_3, giving a light green mixture. The mixture was stirred in a dry ice-EtOH freezing mixture for 2.5 hr., resulting in a dark red mixture. MeI (5.0 g,) in dehyd. Et_2O (10 cc.) was added to the mixture during 15 min., the mixture was stirred in the cooling bath for 1.5 hr., then at the boiling point of NH_3, and added dropwise with Et_2O to evaporate NH_3. The resulting dark red mixture was filtered and the precipitate was washed with Et_2O. The insoluble residue was washed thoroughly with H_2O to a brown solid, m.p. 190~195°, which was treated with benzene and H_2O. From the insoluble portion the starting material, m.p. 253~257° (500 mg.), was recovered. From the benzene layer, crude (Xa) was obtained as a brown crystalline solid (2.2 g., 42%), m.p. 203~205°, which was recrystallized twice from benzene to pure (Xa), m.p. 203~204.5°. *Anal.* Calcd. for $C_{21}H_{19}O_2N_3$: C, 73.04; H, 5.50; N, 12.17. Found: C, 73.17; H, 5.32; N, 12.02. IR: $\nu_{\max}^{\text{Nujol}}$ 2260 cm^{-1} ($C\equiv N$).

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[15] Org. Syntheses, Coll. Vol. I, 153.

From the Et_2O solution, a brownish red solid, m.p. 155~185°(1.0 g., 19%), was obtained when the Et_2O was washed with H_2O, dried, and evaporated. Repeated recrystallizations from benzene afforded (Xb) as colorless needles, m.p. 163~165°. *Anal.* Found: C, 72,78; H, 5,46; N, 12.79. IR: ν_{max}^{Nujol} 2250 cm^{-1} ($C\equiv N$).
b) From VI: (VI) (mixture of a and b, 1.6 g.) was treated with $NaNH_2$ and chloroacetonitrile (2.0 g.) in liquid NH_3 as above. The reaction mixture was filtered and washed with Et_2O. The filtrate was washed with H_2O, dried, and evaporated to leave a red resinous solid (1.0 g.), m.p. 165~175°. It was recrystallized several times from benzene-hexane to colorless prisms, m.p. 200~202°, which showed no depression with (Xa) obtained by the method (a) on admixture and agreed in IR spectra.

3-(2-Aminoethyl)-1,1′,3′-trimethyl-3,3′-bioxindole (XIV)——(Xa)(500mg.) was hydrogenated in EtOH containing HCl (50 cc. EtOH, 5 cc. H_2O, and 1 cc. conc. HCl) with PtO_2 (50 mg.) at atmospheric pressure. After removal of the catalyst, the colorless solution was evaporated *in vacuo*, leaving a white solid (500 mg.), which was dissolved into H_2O and extracted with benzene. The aqueous acid solution was basified with 10% KOH and extracted with benzene. The benzene solution was washed with H_2O, dried, and evaporated *in vacuo*, leaving a white solid (150 mg.), m.p. 190~196°, as a crude (XV). Recrystallization from benzene-hexane afforded colorless prisms, m.p. 209~210°. *Anal.* Calcd. for $C_{21}H_{23}O_2N_3$: C, 72.18; H, 6.63; N, 12.03. Found: C, 72.66; H, 6.29; N, 11.72.
Hydrochloride: m.p. 257~258°(from EtOH-Et_2O). *Anal.* Calcd. for $C_{21}H_{23}O_2N_3 \cdot HCl$: C, 65.28; H, 6.23; N, 10.80. Found: C, 64.93; H, 5.82; N, 10.53.
Picrate: Yellow prisms, m.p. 220°(from EtOH). *Anal.* Calcd. for $C_{21}H_{23}O_2N_3 \cdot C_6H_3O_7N_3$: C, 56.05; H, 4,53. Found: C, 56.43; H, 4.43.

3-Carbamoylmethyl-3′-cyanomethyl-1,1′-dimethyl-3,3′-bioxindole (XII)——a) From (XIa): To a suspension of $LiNH_2$ (prepared from 50 mg. of Li) in liquid NH_3 (200 cc.), (XIa)(2.0 g.) was added at the boiling point of NH_3 and the whole was stirred at this temperature for 30 min. The mixture was chilled in a cooling bath and added with chilled chloroacetonitrile (1.2 g.) in dehyd. toluene. The mixture was stirred in the cooling bath for 2 hr., then at the boiling point of NH_3 for 2 hr., and kept overnight. The resinous mixture was treated with benzene and H_2O, and the brown solid (500 mg.), m.p. 160~180°, obtained as benzene-H_2O-insoluble solid was recrystallized 5 times from EtOH to pure (XII) as colorless needles, m.p. 258~259°. *Anal.* Calcd. for $C_{22}H_{20}O_3N_4$: C, 68.03; H, 5.19; N, 14.43. Found: C, 68.17; H, 4.85; N, 14.20. IR ν_{max}^{KBr} cm^{-1}: 3510, 3370 (NH), 2250 ($C\equiv N$), 1670$^{(sh)}$ (CH_2CONH_2).
b) From (XIb): From (XIb) (2.0 g.), $NaNH_2$, and chloroacetonitrile (1.5 g.), crude (XII) (200 mg.), m.p. 253~255°, was obtained by essentially the same procedure as (a). It gave pure (XII), m.p. 257~258°, on recystallization from EtOH, and showed no depression with above sample on admixture. *Anal.* Found: C, 68.19; H, 5.31; N, 14.07.

1,1′-Dimethyl-3,3′-dicyanomethyl-3,3′-bioxindole (IX)——a) From (V): A mixture of (V) (20.4 g., 0.07 mole), dehyd. K_2CO_3 (30.4 g., 0.22 mole), fused NaI (6.0 g., 0.04 mole), and chloroacetonitrile (16.5 g., 0.218 mole) in dehyd. Me_2CO (250 cc.) was refluxed for 12 hr., giving a dark brown solution with a precipitate. After cool, the mixture was filtered and the precipitate was washed with Me_2CO. From the insoluble portion, a pale brown solid (12.2 g., fraction A) was obtained after dissolving inorganic salts in H_2O. Me_2CO filtrate and washings were evaporated *in vacuo* to leave a dark brown resinous solid which was treated with benzene. From the benzene-soluble portion, some lachrymatory oil, which showed strong $C\equiv N$ band at 2260 cm^{-1}, was obtained but was not investigated further.

From the benzene-insoluble portion, a brown solid (8.0 g., fraction B), m.p. 253~258°(decomp.), insoluble in H_2O and soluble in $CHCl_3$, was obtained. Almost pure (IX) (12.3 g., 47%), m.p. 258~260°, was obtained from the fraction B on recrystallization from AcOH (5.5 g.) and from benzene-insoluble portion of fraction A on repeated recrystallization from AcOH (6.8 g.). This was further recrystallized from the same solvent to pure (IX) as colorless prisms, m.p. 263~265°, which depressed to 240~245° when mixed with (VIIIa). This was identical with (IX) obtained as in (b) below, on admixture and in IR spectra. *Anal.* Calcd. for $C_{22}H_{18}O_2N_4$: C, 71.34; H, 4.90; N, 15.12. Found: C, 71.07; H, 4.58; N, 15.36. IR: ν_{max}^{KBr} 2260 cm^{-1} ($C\equiv N$). UV: $\lambda_{max}^{EtOH(J.P.)}$ 257 mμ (log ε 4.08).
b) From (XII): A mixture of (XII) (200 mg.) and TsCl (400 mg.) in pyridine (3 cc.) was warmed in a water bath for 35 min., giving a clear yellow solution. After cool, the mixture was poured into cold water, filtered, and the precipitate was washed with H_2O to give crude (IX) (150 mg.) as a pale brown solid, m.p. 258~260°. Recrystallization from glacial AcOH afforded colorless prisms, m.p. 261~262.5°. *Anal.* Found: 71.32; H, 4.72; N, 14.91.
c) From (VIIIa) with NaI: A yellow mixture of (VIIIa) (8.0 g., 0.02417 mole), fused NaI (3.6 g., 0.024 mole), dehyd. K_2CO_3 (8.0 g., 0.058 mole), and freshly distilled chloroacetonitrile (4.0 g., 0.053 mole) in dehyd. Me_2CO (150 cc,) was heated to reflux for 12.5 hr., during which time further chloroacetonitrile (2.0 g., 0.026 mole) was added. The resulting dark brown mixture was filtered after cool, and the residue was washed with Me_2CO to leave crystals (3.0 g.) of m.p. 250~255°(fraction A) after treatment with H_2O. The Me_2CO filtrate combined with washings was evaporated to leave a dark brown resinous

solid, which was treated with benzene and left an insoluble powder. After treatment with H_2O, it gave crude (IX) (4.1 g.), m.p. 252～255°, on recrystallization from glacial AcOH. Further crop of (IX) (1.0 g. total 4.2 g., 47%), m.p. 263～265°, was obtained from the hot Me_2CO-soluble portion of fraction A. This was identical with (IX) in its IR spectrum. From the hot Me_2CO-insoluble portion of fraction A, the starting material (430 mg.), m.p. 260°, was recovered. When the amount of NaI was increased, the yield of (IX) decreased, with increasing recovery of the starting material and formation of a lachrymatory oil which showed strong $C\equiv N$ absorption. When the reaction was carried out in MeCN instead of Me_2CO, (IX) was obtained in a lower yield.

d) From (VIIIa) with KI: A mixture of (VIIIa) (6.6 g., 0.02 mole), KI (0.8 g., 0.005 mole), dehyd. K_2CO_3 (5.5 g., 0.04 mole), and chloroacetonitrile (3.0 g., 0.04 mole) in Me_2CO (150 cc.) was gently refluxed for 12 hr. The reaction mixture was treated as above and afforded the starting material (2.4 g.), m.p. 255～258°, from the Me_2CO-insoluble portion, and crude (IX) (3.3 g., 44%, 70% based on reacted (VIIIa)), m.p. 250～257°, from the Me_2CO-soluble and benzene-insoluble fraction. Crude (IX) was recrystallized from glacial AcOH to pure (IX) (2.2 g.), m.p. 263°, which was identical with the authentic sample obtained as above, on admixture and in IR spectra.

e) From (VIIIa) and $NaNH_2$ in liquid NH_3: (VIIIa) (4.6 g.) was treated with $NaNH_2$ (prepared from 350 mg. of Na) and chloroacetonitrile (2.1 g.) in liquid NH_3 as in the methylation of (VIIIa). The reaction mixture was filtered, and the precipitate was washed with H_2O to leave a reddish powder (2.8 g.), m.p. 230～235°. It was treated with hot benzene, from which pale brown crystals (550 mg.), m.p. 245～250°, were obtained from the cooled benzene solution. This was recrystallized from glacial AcOH and then from benzene to colorless prisms, m.p. 260～263°. This was identical with (IX) obtained above on admixture and in IR spectra. *Anal.* Found: C, 71.65; H, 4.78; N, 14.42.

From the benzene mother liquor, the starting material (100 mg.) was recovered. About the same result was obtained by the use of $LiNH_2$ instead of $NaNH_2$.

1,1′-Dimethyl-3,3′-bis(2-aminoethyl)-3,3′-bioxindole (III)——(IX) (3.4 g.) was hydrogenated in glacial AcOH (200 cc.) using PtO_2 as a catalyst, at ordinary temperature and pressure. The initial susyension of (IX) in AcOH became a clear solution when a small excess of H_2 was consumed. After removal of the catalyst, colorless clear solution was evaporated *in vacuo*, and the residue was dissolved in dil. HCl. The acid solution was again evaporated *in vacuo* after shaking with $CHCl_3$ to remove neutral substances and gave a crude hydrochloride, m.p. 250～255° (decomp.). This was dissolved in H_2O and basified with NaOH solution to give a white precipitate (2.2 g.), m.p. 220° (decomp.), which was collected and washed with a small amount of H_2O. It was recrystallized from tetrahydrofuran to colorless prisms, m.p. 227～228° (decomp.). Further crop of crude (XIII) was obtained from the $CHCl_3$ extract of the alkaline filtrate. *Anal.* Calcd. for $C_{22}H_{26}O_2N_4$: C, 69.81; H, 6.92; N, 14.80. Found: C, 69.41; H, 6.85; N, 14.56. IR: ν_{max}^{KBr} 3375 (NH_2). UV: $\lambda_{max}^{EtOH(J.P.)}$ 257 mμ (log ε 4.11).

Dihydrochloride: Colorless pillars, m.p. 268～269° (decomp.) (from EtOH). *Anal.* Calcd. for $C_{22}H_{26}O_2N_4 \cdot 2HCl \cdot 2H_2O$: C, 54.21; H, 6.61; N, 11.49; Cl, 14.55. Found: C, 54.20; H, 6.53; N, 11.4; Cl, 14.26. IR: ν_{max}^{KBr} ～3500 (H_2O), ～3000 (NH_3^+).

Dipicrate: Yellow needles, m.p. 247° (decomp.) (from EtOH). *Anal.* Calcd. for $C_{22}H_{26}O_2N_4 \cdot 2C_6H_3O_7N_3$: C, 48.81; H, 3.86; N, 16.74. Found: C, 48.45; H, 3.66; N, 16.33.

1,1′-Dimethyl-3,3′-bis(2-dimethylaminoethyl)-3,3′-bioxindole (XIII)——a) From (XIII): (III) (1.6 g.) was added to a cooled mixture of 35% formaldehyde solution (3.0 g.) and 80% HCOOH (2.0 g.), and the mixture was shaken for a while to give pale brown solution. The solution was warmed in an oil bath at 70～80°, by which the mixture started to foam, and became dark brown which color faded after warming at 100～110° for a while. The mixture was heated at 120～125° (bath temperature) for 10 hr., cooled, the viscous solution was added with 10% HCl (2 cc.), and evaporated *in vacuo*, leaving a brown oil. It was dissolved in H_2O (30 cc.), basified with NaOH solution, and the separated oil was extracted with Et_2O and AcOEt. AcOEt-Et_2O solution was washed with H_2O, dried, and evaporated *in vacuo*, leaving a brown viscous oil (1.4 g.), which soon solidified, m.p. 110～116°. It was recrystallized from hexane, after purification through Al_2O_3, to colorless leaflets, m.p. 130～132°. *Anal.* Calcd. for $C_{26}H_{34}O_2N_2$: C, 71.86; H, 7.89; N, 12.89. Found: C, 71.89; H, 7.52; N, 12.90.

It gave a yellow picrate which was recrystallized from glacial AcOH to fine yellow crystals, m.p. 263～264° (decomp.). *Anal.* Calcd. for $C_{26}H_{34}O_2N_4 \cdot 2C_6H_3O_7N_3$: C, 51.12; H, 4.51; N, 15.69. Found: C, 51.23; H, 4.86; N, 15.42.

b) From (V): When (V) (5.8 g.) was treated with NaH and dimethylaminoethyl chloride (prepared from its hydrochloride) in benzene as in the dimethylation of (V), a small amount of crude (XIV), m.p. 110～120°, was obtained after chromatographic separation of the reaction mixture. Recrystallization from hexane afforded colorless leaflets, m.p. 125～127°, which was found to be identical with the sample obtained as above, on admixture and in IR spectra. The picrate was also identical with that of the sample obtained as above. The other products were not investigated further.

The author expresses his deep gratitude to Prof. Emeritus S. Sugasawa and Prof. S. Yamada for their interest and encouragement throughout this work. Thanks are also due to Mr. K. Tanikawa, Miss M. Ninomiya, and Mrs. E. Tanaka for infrared spectral data, and to the members of the Analysis Center of this Faculty for microanalytical and ultraviolet spectral data.

Summary

Alkylation of 1,1′-dimethyl-3,3′-bioxindole (V) was carried out. A higher-melting isomer (VIIa) was obtained by dimethylation of (V) with sodium hydride in benzene, while a lower-melting isomer (VIIb) was obtained by dimethylation of (V) with sodium amide in liquid ammonia. Cyanomethylation of (V) with sodium hydride in benzene afforded (VIIIa), which was further cyanomethylated by chloroacetonitrile with potassium carbonate, sodium iodide, and acetone to give (IX), which was also obtained by direct biscyanomethylation with the latter reagents. Two other 3,3′-disubstituted 3,3′-bioxindoles (X, XII) were also prepared by analogous alkylation.

The compound (III), which was considered to be an attractive intermediate for the synthesis of (I) and (II), was obtained by catalytic reduction of (IX).

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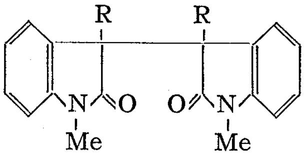
153. Tôhru Hino : Synthetic Approaches to Calycanthaceae Alkaloids. III.[*1] Reductive Cyclization of 3,3′-Bioxindoles. (1). A Formation of 5,7-Dimethyl-11b,11c-bis(2-dimethylaminoethyl)-5,5a,6a,7,11b,11c-hexahydrofuro[2,3-*b*:5,4-*b*′]diindole.

(*Faculty of Pharmaceutical Sciences, University of Tokyo*[*2])

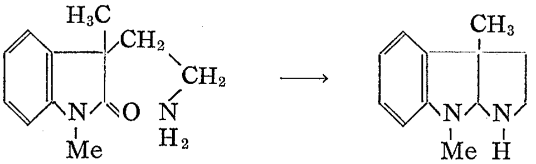
In the preceding paper,[*1] the author reported the synthesis of several kinds of 3,3′-disubstituted bioxindoles including (Ia, b), (II), and (III). Now the reductive cyclization of these compounds was investigated. Julian[1] reported, in his brilliant synthesis of physostigmine, that the reductive cyclization of (IV) with sodium in ethanol gave (V). Sugasawa



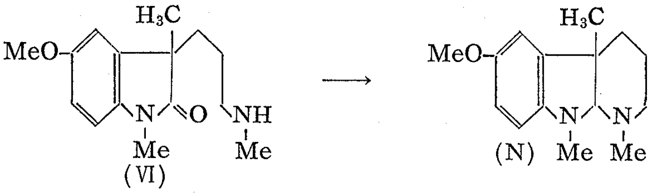
(I) R: CH_3

(II) R: $CH_2CH_2NH_2$

(III) R: $CH_2CH_2N\langle{}^{CH_3}_{CH_3}$



(IV) (V)



(VI) (N)

[*1] Part II. This Bulletin, 9, 979 (1961).

[*2] Hongo, Tokyo (日野 亨).

1) P.L. Julian, J. Pikl, *et al.* : J. Am. Chem. Soc., **57**, 539, 564, 755 (1935).