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# Synthesis of optically Active Deoxytazettine Neomethine[1]

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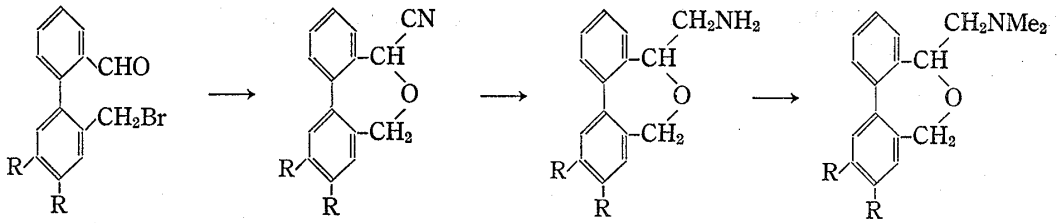
The structure of deoxytazettine neomethine (I), derived from tazettine (III) *via* 5 steps, was confirmed by synthesis of its optically active and racemic forms. A key step in the synthesis, conversion of 2′-bromomethyl-4′,5′-methylenedioxy-2-biphenylcarbaldehyde (VI) to 7-cyano-5,7-dihydro-2,3-methylenedioxydibenz[*c*,*e*]oxepin (VII), was achieved by employing a novel method which had been developed for synthesis of 5-cyano-5,7-dihydrodibenz[*c*,*e*]oxepin (V). The nuclear magnetic resonance spectra of the neomethine (I) and its synthetic intermediates were discussed.

Ikeda, *et al.*[3] obtained deoxytazettine neomethine (I) by Hofmann degradation of deoxytazettine (II) followed by acidic rearrangement of the product and I was valuable for elucidation of the structure of tazettine (III). Ikeda, *et al.* reported that I was optically inactive, but later, Warnhoff,[4] thinking that compound I should be optically active on the basis of the mechanism of the acidic rearrangement, obtained I with $[\alpha]_D^{27}$ −40° (ethanol) from II.

This paper reports results confirming those of Warnhoff[4] and giving final proof of the structure of the neomethine (I) by synthesis of its optically active and racemic forms.

Previously we reported[5] that reaction of 2′-bromomethyl-2-biphenylcarbaldehyde (IV) with sodium cyanide in ethanol at −60° gave the oxepin (V). It seemed likely that this reaction could be used for conversion of the bromoaldehyde (VI) to the corresponding oxepin (VII), a key step in the synthesis of I.




IV: R=H VI: R, R=$OCH_2O$ V: R=H VII: R, R=$OCH_2O$ XXVIII: R=H XVIII: R, R=$OCH_2O$ XXI: R=H I: R, R=$OCH_2O$

Chart 1

To prepare VII, we first tried to obtain 2′-methyl-4′,5′-methylenedioxy-2-biphenylcarbaldehyde (VIII) by Ullmann condensation of accessible 2-bromo-4,5-methylenedioxytoluene (IX) with 2-iodobenzaldehyde (X) or 2-bromobenzaldehyde (XI) but these reactions were

1) This forms Part XI of "Studies on the Syntheses of Benzoheterocyclic Compounds" by S. Kobayashi (Part X is ref. 5).
2) Location: *a*) *Sho-machi-1-chome, Tokushima, 770, Japan*; *b*) *Ikawadani, Tarmi-ku, Kobe, 673, Japan.*
3) T. Ikeda, W.I. Taylor, Y. Tsuda, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, **1956**, 4749.
4) E.W. Warnhoff, "Molecular Rearrangement," Vol. 2, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N.Y., 1964, p. 851.
5) S. Kobayashi, M. Kihara, T. Hashimoto, and K. Kitamura, *Yakugaku Zasshi*, **95**, 1449 (1975).

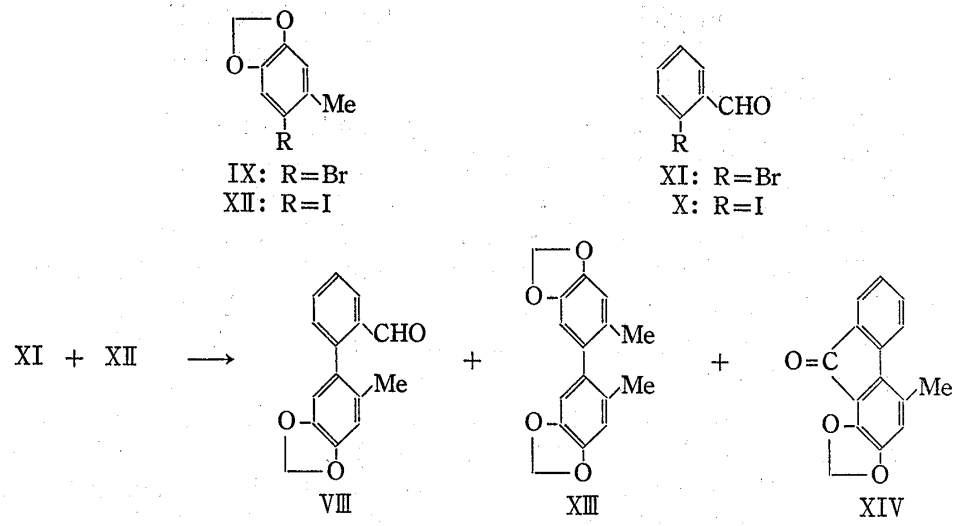



Chart 2

unsuccessful. From the work of Fanta,[6] Ullmann condensation of 2-iodo-4,5-methylenedioxytoluene (XII)[7] with XI is considered to be the most suitable method for synthesis of VIII. Using this procedure we obtained VIII in fair yield with 2,2′-dimethyl-4,5,4′,5′-bismethylenedioxybiphenyl (XIII) and 4-methyl-1,2-methylenedioxyfluorenone (XIV).

Conversion of VIII to VI with N-bromosuccinimide (NBS) could not be achieved by refluxing a solution of VIII in carbon tetrachloride in the presence of benzoyl peroxide and an unexpected product under these conditions was found to be 9,10-methylenedioxydiphenide (XV) from its melting point[3] and infrared (IR) spectrum: $\nu_{max}^{KBr}$ $cm^{-1}$, 1710 (C=O), 1380 (diphenide).[8] This product was confirmed by the independent synthesis: Ullmann condensation of 6-bromopiperonal with methyl 2-bromobenzoate gave methyl 2′-formyl-4′,5′-methylenedioxy-2-biphenylcarboxylate (XVI)[3] and reduction of XVI with sodium borohydride gave XV. The most plausible mechanism for formation of XV from VIII involves (i) benzylic bromination and oxidation of an aldehyde to a carboxylic acid, and (ii) cyclization of the acid (XVII).

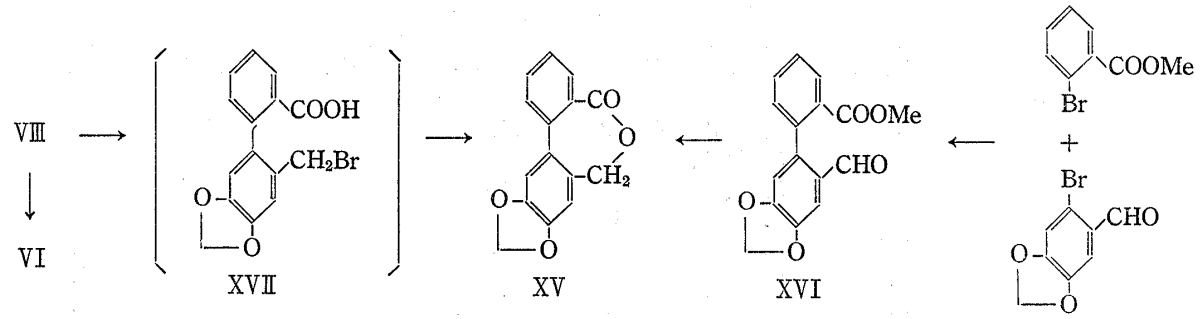



Chart 3

Next, benzylic bromination of VIII with NBS was carried out by irradiation with UV-light at room temperature which gave the crude bromide (VI) in fair yield. Treatment of VI with sodium cyanide in ethanol at −60° by the method reported in the preceding paper[5]

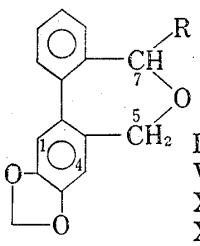
6) P.E. Fanta, *Chem. Rev.*, **64**, 613 (1964).
7) A compound with mp 38—39°, which C.S. Kallianpur and J.R. Merchant [J. Indian Chem. Soc., **38**, 27 (1961)] considered to be 6-iodopiperonylic acid, was found to be XII, since a new compound, 6-iodopiperonylic acid with mp 218.5—221°, could be obtained by oxidation of 6-iodopiperonal with potassium permanganate (see Experimental).
8) S. Kobayashi, F. Senoo, M. Kihara (née Azekawa), K. Sakata, and A. Miura, *Chem. Pharm. Bull.* (Tokyo), **19**, 1262 (1971).

afforded the nitrile (VII) in low yield but use of a mixture of dimethylformamide (DMF) and water instead of ethanol gave VII in moderate yield. The IR spectrum of VII, like that of V,[5] showed no absorption band due to a cyano group.

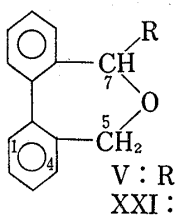
Lithium aluminum hydride reduced VII quantitatively to racemic 7-aminomethyl-5,7-dihydro-2,3-methylenedioxydibenz[*c*,*e*]oxepin (XVIII), mp 108—121°, and XVIII was resolved by recrystallization of the di-*p*-toluoyl D-tartarate. An optically active amine, (—)-XVIII, thus obtained, had mp 121—124.5° and $[\alpha]_D^{19}$ —41°. Methylation of the racemic amine (XVIII) by the Eschweiler-Clarke reaction afforded the racemate of 5,7-dihydro-7-N,N-dimethylaminomethyl-2,3-methylenedioxydibenz[*c*,*e*]oxepin, (±)-I, mp 98—99°. The nuclear magnetic resonance (NMR) and IR spectra of the racemate were found to be identical with those of the optically active neomethine, (—)-I ($[\alpha]_D^{29}$ —35.1°),[4] prepared from III by the procedure[3] described previously. The rotation, $[\alpha]_D^{19}$ —35°, of the synthetic (—)-I obtained from (—)-XVIII was found to identical with that of the above (—)-I. Direct comparison showed that the synthetic racemic methiodide [(±)-XIX] of (±)-I was identical in every respect, except rotation, with natural deoxytazettine neomethine methiodide [(—)-XIX], $[\alpha]_D^{19}$ —6.0.[9]

The NMR spectra of the oxepins given in Table I, show that the C-5 methylene proton signals of the oxepins I, VII, XX, and XV are 0.12—0.2 ppm upfield of those of the oxepins XXI, V, XXII, and XXIII, respectively. This is due to the diamagnetic effect of the methylenedioxy group. Due to a similar effect of this group, the methyl proton signals of the halobenzenes IX and XII are upfield of those of the halobenzenes XXIV and XXV, respectively, as shown in Table II. The assignment of the two aromatic protons, C-1-H and C-4-H, in

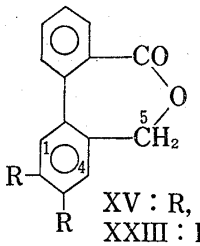
Table I. NMR Spectra of 5,7-Dihydrodibenz[*c*,*e*]oxepins



I : R=$CH_2NMe_2$
VII : R=CN
XVIII : R=$CH_2NH_2$
XX : R=H



V : R=CN
XXI : R=$CH_2NMe_2$
XXII : R=H



XV : R, R=$OCH_2O$
XXIII : R=H

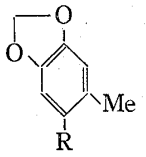
| Compound | Chemical shift[a] | | | | | | |
|---|---|---|---|---|---|---|---|
| | C-1-H | C-4-H | C-5 $H_2$[b] | C-7-H | C-7 $H_2$ | $NCH_3$ | $OCH_2O$ |
| I | 3.00 | 3.13 | 5.64(d, $J$=12)<br>5.96(d, $J$=12) | 5.60(m) | | 7.77 | 4.00 |
| V[c] | | | 5.57(d, $J$=11)<br>5.68(d, $J$=11) | 4.63 | | | |
| VII | 2.98 | 3.10 | 5.76 | 4.72 | | | 3.96 |
| XV | 2.96 | 3.13 | 5.16 | | | | 4.00 |
| XVIII | 3.01 | 3.14 | 5.60(d, $J$=12)<br>5.92(d, $J$=12) | 5.78(m) | | | 4.01 |
| XX[d] | 2.98 | 3.10 | 5.82 | | 5.70 | | 4.00 |
| XXI[d] | | | 5.46(d, $J$=12)<br>5.84(d, $J$=12) | 5.58(m) | | 7.78 | |
| XXII[e] | | | 5.69 | | 5.69 | | |
| XXIII[f] | | | 5.00 | | | | |

*a*) See ref. 11. Signals are for singlets except for those combined with parentheses.
*b*) These signals are AB types or singlets.
*c*) See ref. 5.
*d*) These new compounds were prepared as described in the Experimental.
*e*) This compound was obtained as described by G. Wittig, P. Davis, and G. Koenig [*Chem. Ber.*, **84**, 627 (1951)].
*f*) See ref. 8.

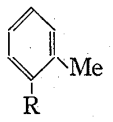
9) Warnhoff reported that the methiodide had $[\alpha]_D^{27}$ —5.4° (See ref. 4).

XX and XV was achieved by study of intramolecular nuclear Overhauser effects (NOE): on saturation of the C-5 methylene proton signals, the C-4-H signals in XX and XV increased in intensity by 15 and 13%, respectively. Furthermore, the signal of C-1-H, *ortho* to the other benzene ring, in XX was found to be 0.12 ppm downfield of that of C-4-H. The C-1-H and C-4-H signals of I, VII, and XVIII were assigned on the basis of the fact that the chemical shifts of the C-1-H and C-4-H in I, VII, and XVIII are similar to those of the corresponding aromatic protons in XX (Table I). Studies on the NOE showed that the chemical shifts of C-6-H in the biphenyls VIII and XIII were 0.08—0.15 ppm upfield of those of C-3-H: on saturation of the C-2-$CH_3$ signals, the C-3-H signals of VIII and XIII increased in intensities by 12 and 10%, respectively. From these findings the chemical shifts of C-6-H and C-3-H in XXVI

Table II. NMR Spectra of Toluene Derivatives




IX: R=Br
XII: R=I

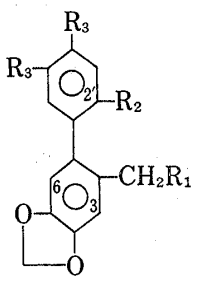



XXIV: R=Br
XXV: R=I

| Compound | Chemical shift[a] | |
|---|---|---|
| | $CH_3$ | $OCH_2O$ |
| IX | 7.76 | 4.12 |
| XII | 7.69 | 4.09 |
| XXIV[b] | 7.64 | |
| XXV[b] | 7.61 | |

*a*) See ref. 11.
*b*) These compounds were obtained from 2-toluidine.

Table III. NMR Spectra of 4,5-Methylenedioxybiphenyls




| Compound | | Chemical shift[a] | | | | |
|---|---|---|---|---|---|---|
| | | C-3-H | C-6-H | $OCH_2O$ | C-2-$CH_2$ | C-2'-$CH_2$ |
| VIII | $R_1=R_3=H$, $R_2=CHO$ | 3.26 | 3.34 | 4.04 | | |
| XIII | $R_1=H$, $R_2=Me$, $R_3$, $R_3=OCH_2O$ | 3.29 | 3.44 | 4.07 | | |
| XXVI[b] | $R_1=OH$, $R_2=CH_2OH$, $R_3=H$ | 3.08 | 3.22 | 4.04 | 5.86[c] | 5.70 |
| XXVII[b] | $R_1=R_3=H$, $R_2=CH(OMe)_2$ | 3.26 | 3.40 | 4.08 | | |

*a*) See ref. 11. All the signals are for singlets.
*b*) These new compounds were prepared as described in the Experimental.
*c*) The fact that this signal is upfield of that (5.70τ) of other methylene protons seems to be due to the diamagnetic effect of the methylenedioxy group.

and XXVII were assigned to those in the higher field and to those in the lower field, respectively, as shown in Table III.

From these NMR data, the ring current effect of the other benzene ring on the aromatic proton, C-6-H, in the biphenyls (VIII, XIII, XXVI, and XXVII) seems to be larger than that on the corresponding aromatic protons, C-1-H, in the oxepins (I, VII, XX, and XV). Therefore, the angle between the planes of the benzene rings in these biphenyls seems to be larger than that (43 and 44.5°)[10] in these oxepins.

## Experimental[11]

**5-Aminomethyl-5,7-dihydrodibenz[*c*,*e*]oxepin (XXVIII)**——To a suspension of $LiAlH_4$ (450 mg) in dry ether (20 ml) was added dropwise a solution of V (300 mg) in dry ether (20 ml) at −5—0° under $N_2$ with stirring for 2 hr. Then ether saturated with $H_2O$ and then 10% NaOH were added and the ether layer was separated, washed with $H_2O$, dried over anhyd. $K_2CO_3$, and evaporated to dryness *in vacuo* at 0°. The resulting oily product was converted to its styphnate (331 mg). Recrystallization from MeOH gave XXVIII-styphnate (286 mg, 60.0%), mp 208—209° (decomp.), as yellow cubes. *Anal.* Calcd. for $C_{15}H_{15}ON \cdot 1/2\text{-}C_6H_3O_8N$: C, 62.15; H, 4.78; N, 10.07. Found: C, 61.90; H, 4.80; N, 9.61.

The mother liquid from which the styphnate (331 mg) was separated afforded 2,2′-bis(hydroxymethyl)-biphenyl[8] (14 mg, 4.8%), as colorless plates.

In a second experiment, in which V (200 mg) was reduced with $LiAlH_4$ (270 mg) at −20 to −40°, XXVIII was obtained in 99.2% yield.

**5-N,N-Dimethylaminomethyl-5,7-dihydrodibenz[*c*,*e*]oxepin (XXI)**——A mixture of XXVIII (37 mg), HCOOH (0.43 ml), and formalin (0.43 ml) was heated at 100° under $N_2$ for 15 hr. Then it was concentrated to dryness and 10% HCl was added to the residue. The acidic solution was washed with ether, made alkaline with $Na_2CO_3$, and extracted with ether. The base (XXI) thus obtained gave a styphnate (33 mg, 52%), mp 166—170° (decomp.), as yellow cubes (from benzene–ether). *Anal.* Calcd. for $C_{17}H_{19}ON \cdot C_6H_3O_8N_3$: C, 55.42; H, 4.45; N, 11.24. Found: C, 55.34; H, 4.45; N, 10.92. NMR ($CDCl_3$) $\tau$: 1.08 (1H, s, aromatic proton in styphnic acid), 2.40—2.68 (8H, m aromatic protons), 5.64 and 5.80 (each 1H, d, $J=12$, AB type of C-5 $H_2$), 5.14 (1H, q, $J=9$ and 4, C-7-H), 6.44—7.00 (2H, m, $CH_2$-N), 7.13 (6H, s, $2\times NCH_3$). The free base of XXI (3 mg) was obtained by passing the styphnate (8.5 mg) through a column of $Al_2O_3$ in acetone–$CHCl_3$.

**2-Iodo-4,5-methylenedioxytoluene (XII)**——To a solution of 3,4-methylenedioxytoluene[7] (10 g) in EtOH (40 ml) were added alternately powdered iodine (17 g) and mercuric oxide (yellow) (9.8 g) with stirring at room temperature for 1.5 hr. The mixture was stirred for additional 0.5 hr and then the solvent was removed. The residue was extracted with ether. The extract was washed successively with a saturated solution of $Na_2S_2O_3$, 10% NaOH, and $H_2O$, and dried over $Na_2SO_4$. On evaporation of the solvent, a yellow oil, bp 148—153° (5 mmHg) was obtained. The oil was triturated with MeOH–$H_2O$ to give XII (12.7 g, 63.2%), mp 38—39°, as white needles. *Anal.* Calcd. for $C_8H_7O_2I$: C, 36.66; H, 2.69. Found: C, 36.19; H, 2.56. NMR ($CDCl_3$) $\tau$: 2.79 (1H, s, C-3-H), 3.27 (1H, s, C-6-H). Mass Spectrum *m/e*: 262 ($M^+$).

**6-Iodopiperonylic Acid**——To a solution of 6-iodopiperonal[12] (1 g) in acetone (20 ml) was added powdered $KMnO_4$ (1.5 g) in portions with stirring at 55—60° for 4 hr. Then the solvent was removed, $H_2O$ was added and the mixture was acidified with $SO_2$. The resulting white precipitate was dissolved in 2.5% KOH and the solution was extracted with $CHCl_3$. 6-Iodopiperonal (57 mg) was recovered from the $CHCl_3$. The aqueous solution was acidified with HCl to afford 6-iodopiperonylic acid (621 mg, 59.3%), mp 218.5—221°, as white needles (from MeOH). *Anal.* Calcd. for $C_8H_5O_4I$: C, 32.90; H, 1.73. Found: C, 32.63; H, 1.59. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1690 (C=O). NMR (DMSO-$d_6$) $\tau$: 3.92 (2H, s, $OCH_2O$), 2.72 (1H, s, C-5-H or C-2-H), 2.53 (1H, s, C-2-H or C-5-H), −3.25 (1H, s, COOH).

**2′-Methyl-4′,5′-methylenedioxy-2-biphenylcarbaldehyde (VIII)**——A mixture of XII (3.27 g), copper powder (8.2 g), and XI [2.83 g, bp 71—80°/3 mmHg, prepared by hydrolysis of 2-bromobenzylidene diacetate

10) These values were reported for the angles of 5,7 dihydrodibenz[*c*,*e*]oxepin (XXII) by D.M. Hall and F. Minhaj (*J. Cem. Soc.*, **1957**, 4548) and by H. Suzuki [*Bull. Chem. Soc. Japan*, **32**, 1357 (1959)], respectively.

11) All melting points given are uncorrected values. The spectrophotometers used were a Hitachi, EPI-G2 model for IR spectra, a Hitachi, EPS-2 model for ultraviolet (UV) spectra, and a JEOL, JNM-PS-100 or a Hitachi, R-22 model for NMR spectra using TMS as an internal standard. Chemical shifts are reported as $\tau$ values and those given in Table I, II, and III were determined in $CDCl_3$ solution. Coupling constants are reported as Hz values. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

12) A. Rilliet and L. Kreitmann, *Helv. Chim. Acta*, **4**, 588 (1921).

(5.79 g) with 9% $H_2SO_4$ (17.6 ml)], was heated in a sealed tube at 209° for 4 hr. The reaction mixture was dissolved in $CHCl_3$. The solvent was evaporated off and the residue was extracted with ether. The extract was evaporated to give a brown oil, which on distillation *in vacuo* afforded a yellow oil (1.75 g, bp 116—129°/0.5 mmHg). The oil was applied to a column of $SiO_2$ in benzene. The first eluate with petr. ether gave XIII (24 mg), mp 120—121.5°, as white needles (from ether–petr. ether). *Anal.* Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.23; H, 5.32. NMR ($CDCl_3$) $\tau$: 8.10 (6H, s, $2\times CH_3$).

The second eluate with petr. ether–benzene (10: 1 v/v) gave VIII as a pale yellow oil (854 mg, 28.5%). *Anal.* Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.67; H, 4.91. IR $\nu_{max}^{film}$ $cm^{-1}$: 1690 (C=O). NMR ($CDCl_3$) $\tau$: 0.18 (1H, s, CHO), 8.04 (3H, s, $CH_3$).

The residue from the distillation gave XIV, mp 204—208°, as yellow needles. *Anal.* Calcd. for $C_{15}H_{10}O_3\cdot 1/4H_2O$: C, 74.29; H, 4.35. Found: C, 74.44; H, 4.06. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1710 (C=O). NMR ($CDCl_3$) $\tau$: 2.24—2.88 (4H, m, aromatic protons), 3.40 (1H, s, C–3–H), 3.92 (2H, s, $OCH_2O$), 7.54 (3H, s, $CH_3$). Mass Spectrum *m/e*: 234 ($M^+$).

**Reaction of VIII with NBS**——A mixture of VIII (121 mg), NBS (189 mg), benzoyl peroxide (5 mg), and $CCl_4$ (3 ml) was refluxed for 3 hr. Then the reaction mixture was filtered and concentrated, and the residue was extracted with ether. The extract was evaporated to dryness and the residue was submitted to preparative thin-layer chromatography (TLC) using $SiO_2$–benzene. Elution of material of *Rf* 0.16—0.30 with $CHCl_3$ gave XV (11 mg), as pale brown plates (from ether), mp 146—149°. The sample was identical with an authentic sample of XV by the mixed melting point test and IR comparison.

**9,10-Methylenedioxydiphenide (XV)**——6-Bromopiperonal (4.8 g), methyl 2-bromobenzoate (3.5 g), and copper powder (9 g) were heated in a sealed tube at 210° for 4 hr. The mixture was extracted first with $CHCl_3$ and then with ether as described for VIII. Then the residue was triturated with ether to give 4,5,4′,5′-bis(methylenedioxy)diphenaldehyde (388 mg, 12.4%), mp 234—238° (lit.[3] mp 238—240°) (from ethyl acetate). The ethereal mother-liquor gave white crystals (938 mg, 15.8% from 6-bromopiperonal), mp 100.5—103°, which were recrystallized from ether as white prisms of XVI, mp 102—103.5° (lit.[3] mp 103—104°). *Anal.* Calcd. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.26. Found: C, 67.85; H, 4.58. The mother-liquor from which XVI had been separated was applied to a $SiO_2$ column. Elution with petr. ether gave dimethyl diphenate (1.19 g, 27.0%) as colorless plates, mp 70—72° (lit.[13] mp 74°). Further elution with petr. ether–benzene (1: 1 v/v) afforded further XVI (357 mg, total yield 1.295 g, 21.7% from 6-bromopiperonal), mp 100—103°.

A mixture of XVI (55 mg) in MeOH (3 ml) and $NaBH_4$ (50 mg) was stood at room temperature overnight. The resulting precipitate was collected and on crystallization from ether gave XV (28 mg, 62.2%) as white prisms, mp 153—155° (lit.[3] mp 151—152°).

**Acetal (XXVII) of VIII**——To avoid oxidation of VIII to XVII by NBS, VIII was converted to its acetal (XXVII). Benzylic bromination of XXVII with NBS was unsuccessful.

A solution of VIII (55 mg) in MeOH (5 ml) and conc. HCl (0.3 ml) was stirred at room temperature for 2.5 hr. Then it was worked up in the usual way and crystallization of the crude product from ether–petr. ether gave XXVII (41 mg, 62.3%), mp 72—74°, as white plates. *Anal.* Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.18; H, 6.39. NMR ($CDCl_3$) $\tau$: 2.28—3.00 (4H, m, aromatic protons), 5.06 (1H, s, $-CH\langle$), 6.82 (6H, s, $2\times OCH_3$), 8.08 (3H, s, $CH_3$).

**7-Cyano-5,7-dihydro-2,3-methylenedioxydibenz[*c*,*e*]oxepin (VII)**——(i) A mixture of VIII (100 mg), NBS (80 mg), benzoyl peroxide (3 mg), and $CCl_4$ (4 ml) was irradiated with UV-light (Toshiba HLS 400 2B) under $N_2$ at room temperature for 30 min. The mixture was filtered and the solvent was evaporated off. The residue was extracted with ether and the extract was washed with $H_2O$, dried, and evaporated to give crude VI as an oil.

A mixture of the oil, NaCN (70 mg), and EtOH (25 ml) was stirred at −60° for 1 hr. The solvent was evaporated off and the residue was extracted with ether. The extract gave a yellow oily residue (108 mg), which was submitted to preparative TLC using $SiO_2$–benzene. Material of *Rf* 0.21—0.37 eluted with $CHCl_3$ gave XV (20 mg, 18.9%), and it was identical with an authentic sample of XV by the mixed melting point measurement. Material of *Rf* 0.45—0.64 eluted with $CHCl_3$ afforded VII (8 mg, 7.3% from VIII) as colorless plates, mp 170—172° (from ether–petr. ether). *Anal.* Calcd. for $C_{16}H_{11}O_3N$: C, 72.44; H, 4.18; N, 5.28. Found: C, 72.12; H, 4.52; N, 5.14. UV $\lambda_{max}^{EtOH}$ nm (log $\varepsilon$): 300 (4.19), 270 (4.19).

(ii) A mixture of VIII (576 mg), NBS (476 mg), benzoyl peroxide (17 mg), and $CCl_4$ (20 ml) was irradiated with UV-light (Riko UVL-400HA) under $N_2$ at 26° for 2 hr. Work up in the same way as that for (i), gave the crude bromide (VI) (729 mg) which was found to contain 72% of pure VI by NMR spectral analysis.

A solution of crude VI (487 mg) in DMF (15 ml) was added to a solution of NaCN (88 mg) in $H_2O$ (15 ml) and stirred at 0° for 30 min. The reaction mixture was then extracted with ether, washed with $H_2O$, dried, and evaporated to give white prisms of VII (145 mg, 34.1% from VIII), mp 167—168.5° (from MeOH).

**7-Aminomethyl-5,7-dihydro-2,3-methylenedioxydibenz[*c*,*e*]oxepin (XVIII)**——A solution of VII (221 mg) in dry ether (50 ml) was reduced with $LiAlH_4$ (140 ml) in the same way as for XXVIII. The pale brown needles (195 mg, 87.1%) thus obtained were recrystallized from $CHCl_3$–ether to give (±)-XVIII, mp 108—

13) F. Ullmann, *Ann.*, 332, 79 (1904).

112°, as white needles. *Anal.* Calcd. for $C_{16}H_{15}O_3N$: C, 71.31; H, 5.61; N, 5.20. Found: C, 71.03; H, 5.55; N, 4.86. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3355 (N–H). NMR ($CDCl_3$) $\tau$: 8.40 (2H, s, $NH_2$), 6.94 (2H, m, $-CH_2-N$), 2.58 (4H, m, aromatic protons).

**Resolution of (±)-XVIII**——A mixture of (±)-XVIII (51 mg), di-*p*-toluoyl D-tartaric acid (80 mg), and MeOH (0.7 ml) was stood at room temperature overnight to give the crude tartarate (113 mg), mp 189—190° (decomp.), as white cubes. Recrystallization from MeOH was repeated several times to afford white needles (32 mg), mp 197—198° (decomp.). The tartarate was dissolved in $H_2O$ (4 ml), made alkaline with 4% NaOH, and extracted with $CHCl_3$. The extract gave (−)-XVIII (12 mg), mp 121—124.5°, as white needles. $[\alpha]_D^{19}$ −41° ($c$=0.73, 95% EtOH). The NMR and IR spectra of (−)-XVIII were identical with those of (±)-XVIII. The crude amine (+)-XVIII, mp 97—105°, $[\alpha]_D^{20}$ +23° ($c$=0.67, 95% EtOH), was obtained from the tartarate of mp 183.5—184°, which could be separated from the mother liquor of the tartarate of mp 189—190° (decomp.).

**5,7-Dihydro-7-N,N-dimethylaminomethyl-2,3-methylenedioxydibenz[*c*,*e*]oxepin (I)**——(i) A mixture of (±)-XVIII (63 mg), HCOOH (1.3 ml), and formalin (0.8 ml) was heated at 100° for 15 hr and then evaporated under reduced pressure. The oily residue was mixed with $H_2O$ (10 ml) and made alkaline with $Na_2CO_3$. Then it was extracted with ether, dried, and evaporated to give crude (±)-I (46 mg, 66.1%) as colorless crystals. Recrystallization of the crystals from ether gave white prisms, mp 98—99°. *Anal.* Calcd. for $C_{18}H_{19}O_3N$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.52; H, 6.45; N, 4.56.

(ii) A mixture of (−)-XVIII (20 mg), HCOOH (0.5 ml), and formalin (0.3 ml) was heated at 90° for 15.5 hr. Work up in the same way as that for (i) gave (−)-I (15.5 mg) as a colorless oil. $[\alpha]_D^{19}$ −35° ($c$=1.0, 95% EtOH). The NMR and IR spectra of (−)-I were identical with those of (±)-I.

The amine, (+)-I (10 mg), was obtained as a colorless oil by treatment of (+)-XVIII (10 mg) with HCOOH (0.5 ml) and formalin (0.3 ml). $[\alpha]_D^{20}$ +19° ($c$=0.67, 95% EtOH).

**5,7-Dihydro-7-N,N-dimethylaminomethyl-2,3-methylenedioxydibenz[*c*,*e*]oxepin Methiodide (XIX)**——A mixture of (±)-I (77 mg), $CH_3I$ (3 g), and MeOH (7 ml) was stood at room temperature for 2 days. The crude product was recrystallized from MeOH–acetone to give white prisms of (±)-XIX (78 mg), mp 255—257° (decomp.). *Anal.* Calcd. for $C_{18}H_{19}O_3N \cdot CH_3I$: C,51.94; H, 5.05; N, 3.19. Found: C, 52.13; H, 5.21; N, 3.15. UV $\lambda_{max}^{EtOH}$ nm (log $\varepsilon$): 272 (4.01), 300 (3.98). NMR (DMSO-$d_6$) $\tau$: 2.32—2.57 (4H, m, aromatic protons), 2.80 (1H, s, C–1–H), 2.87 (1H, s, C–4–H), 3.90 (2H, s, $OCH_2O$), 5.10 (1H, m, C–7–H), 5.68 and 5.94 (each 1H, d, $J$=12, AB type of C-5 $H_2$), 6.20—6.60 (2H, m, $-CH_2-N$), 7.95 (9H, s, $3 \times NCH_3$). The IR, NMR, and UV spectra of synthetic XIX were identical with those of the same compound derived from III.

**5,7-Dihydro-2,3-methylenedioxydibenz[*c*,*e*]oxepin (XX)**——To a suspension of $LiAlH_4$ (1.07 g) in dry ether (20 ml) was added dropwise a solution of XVI (857 mg) in dry ether (60 ml) at 40° over a period of 45 min and the mixture was refluxed with stirring for 3.5 hr. After working up in the usual way, the crude 2,2′-bis(hydroxymethyl)-4,5-methylenedioxybiphenyl (XXVI) was recrystallized from ether to give 677 mg of colorless prisms, mp 132—134°. *Anal.* Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.64; H, 5.35. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3250 (OH).

The diol (XXVI) (425 mg) and 24% HBr (40 ml) were heated at 95°, 30 min. Work up in the usual way gave XX (351 mg, 88.8%) as colorless plates, mp 137—139°. *Anal.* Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.99; H, 4.94. UV $\lambda_{max}^{EtOH}$ nm (log $\varepsilon$): 267.5 (4.31), 297.5 (4.21).

Deoxytazettine neomethine [(−)-I] and its methiodide [(−)-XIX] were derived from tazettine (III) by the method of Ikeda, *et al.*[3] The chemical shifts of the protons in III and its degradation products were assigned by a study of nuclear magnetic double resonance.

**Tazettine (III)**——NMR[14] ($CDCl_3$) $\tau$: 3.16 (1H, s, C–12–H), 3.52 (1H, s, C–9–H), 3.88 (1H, m, $J_{1-2}$=2, C–2–H), 4.12 (2H, s, $OCH_2O$), 4.39 (1H, m, $J_{1-2}$=10, $J_{1-3}$=2, C–1–H), 5.03 and 5.38 (each 1H, d, $J$=15, AB type of C–8 $H_2$), 5.94 (1H, m, C–3–H), 6.55 (3H, s, $OCH_3$), 6.71 and 7.33 (each 1H, d, $J$=10, AB type of C–6 $H_2$), 7.14 (1H, m, $J_{4a-1}$=1, $J_{4a-4l}$=3, C–4a–H), 7.78 [1H, m, $J_{4l-4a}$=3, $J_{4l-4h}$=13, $J_{4l-3}$=6, $J_{4l-2}$=1, C–4–H (lower)], 8.39 [1H, octet, $J_{4h-4l}$=13, $J_{4h-4a}$=2, $J_{4h-3}$=10, C–4–H (higher)].

**Tazettadiol (XXIX)**——The product (XXIX, 603 mg) was obtained by $LiAlH_4$ reduction of III (950 mg), and melted at 117—119° (lit.[3] mp 118—119°). *Anal.* Calcd. for $C_{18}H_{23}O_5N \cdot H_2O$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.71; H, 7.35; N, 3.86. NMR ($CDCl_3$) $\tau$: 3.13 (1H, s, C–3′–H), 3.21 (1H, s, C–6′–H), 4.08 (2H, s, $OCH_2O$), 4.20 (2H, br s, C–4–H and C–5–H), 5.22 and 5.46 (each 1H, d, $J$=12, AB type of C–2 $H_2$), 5.64 (1H, d.d, $J_{3-2h}$=5, $J_{3-2l}$=7, C–3–H), 6.11 (1H, m, $J_{6-7h}$=10, $J_{6-7l}$=6, C–6–H), 6.38 [1H, d.d, $J_{2l-2h}$=11, $J_{2l-3}$=6, C–2–H (lower)], 6.67 (3H, s, $OCH_3$), 6.92 (1H, m, C–7a–H), 7.58 (3H, s, $NCH_3$), 7.59 [1H, m, $J_{7l-7h}$=13, $J_{7l-7a}$=2, $J_{7l-6}$=6, C–7–H (lower)], 7.77 [1H, d.d, $J_{2h-2l}$=11, $J_{2h-3}$=5, C–2–H (higher)], 8.22 [1H, m, $J_{7h-7l}$=13, $J_{7h-7a}$=10, C–7–H (higher)].

**Deoxytazettine (II)**——Colorless plates of II (377 mg, mp 134.5—136°, lit.[3] mp 135—136°) were prepared from XXIX (550 mg). *Anal.* Calcd. for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.48; H, 6.93; N, 4.25. NMR ($CDCl_3$) $\tau$: 3.09 (1H, s, C–12–H), 3.50 (1H, s, C–9–H), 3.98 (1H, m, $J_{1-2}$=10, $J_{2-3}$=2, $J_{2-4}$=2, C–2–H), 4.12 (2H, s, $OCH_2O$), 4.62 (1H, m, $J_{1-2}$=10, $J_{1-3}$=2, $J_{1-4a}$=2, C–1–H), 5.41 (2H, q, AB

14) R.D. Haugwitz, P.W. Jeffs, and E. Wenkert, *J. Chem. Soc.*, **1965**, 2001.

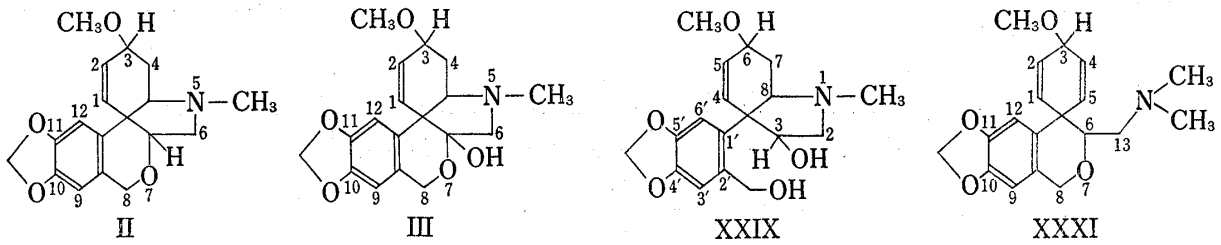



Chart 4

type of C-8 $H_2$), 6.00 (1H, q, $J_{6a-6l}=5$, $J_{6a-6h}=3$, C–6a–H), 6.57 (3H, s, $OCH_3$), 6.57 [1H, q, $J_{6l-6a}=5$, $J_{6l-6h}=11$, C–6–H (lower)], 7.36 (1H, m, C–4a–H), 7.49 [1H, q, $J_{6h-6a}=3$, $J_{6h-6l}=11$, C–6–H (higher)], 7.61 (3H, s, $NCH_3$), 7.76 [1H, m, C–4–H (lower)], 8.30[1H, octet, $J_{4h-4l}=13$, $J_{4h-4a}=3$, $J_{4h-3}=10$, C–4–H (higher)].

**Deoxytazettine Methiodide (XXX)**——The methiodide [XXX, mp 230—232° (decomp.), lit.[3] mp 231—233° (decomp)] was obtained from II (354 mg). *Anal.* Calcd. for $C_{18}H_{21}O_4N\cdot CH_3I$: C, 49.90; H, 5.29; N, 3.06. Found: C, 49.53; H, 5.44; N, 2.73.

**Deoxytazettine Methine (XXXI)**——XXXI (245 mg) was obtained as a colorless oil from XXX (413 mg) by Hofmann degradation. NMR ($CDCl_3$) $\tau$: 3.31 (1H, s, C–12–H), 3.56 (1H, s, C–9–H), 3.72—4.40 (4H, m, C-1,2,4, and 5-H), 4.13 (2H, s, $OCH_2O$), 5.19 (2H, s, C–8 $H_2$), 6.34 (1H, q, $J_{6-13h}=2$, $J_{6-13l}=8$, C–6–H), 5.64 (1H, m, C–3–H), 6.56 (3H, s, $OCH_3$), 7.56 [1H, q, $J_{13l-13h}=13$, $J_{13l-6}=8$, C–13–H (lower)], 7.72 (6H, s, $2\times NCH_3$), 7.78 [1H, q, $J_{13h-13l}=13$, $J_{13h-6}=2$, C–13–H (higher)].

**Deoxytazettine Neomethine[(—)-I]**——The methine (XXXI, 225 mg) was treated with 5% HCl to give a colorless oil (161 mg) of (−)-I. $[\alpha]_D^{29}$ −35.1° ($c=0.83$, 95% EtOH).

**Deoxytazettine Neomethine Methiodide [(—)-XIX]**——On standing a mixture of the above neomethine, (−)-I, (136 mg), MeI (6 g), and MeOH (10 ml) overnight white cubes of (−)-XIX (126 mg) were obtained and had mp 252—254° (decomp.) [lit.[3] mp 251° (decomp.), and lit.[15] mp 254—255.5° and 257—258° (decomp.)]. $[\alpha]_D^{19}$ −6.0° ($c=1.5$, 95% EtOH).

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15) R.J. Highet, J.C.N. Ma, and P.F. Highet, *J. Org. Chem.*, **33**, 3096 (1968).