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Studies on Seven-membered Ring Compounds. XXX.[1] Rearrangement of Dimethylamino Group in Cycloheptoxazole Derivatives

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Rearrangement of amino group on the seven-membered ring of cycloheptoxazole derivatives was examined. Dimethylamino group in 6-dimethylamino-2-phenyl-6*H*-cycloheptoxazole (Ia) underwent rearrangement to C-4 and C-8 on standing in a solution, and the ratio of three isomers, Ia, 4-dimethylamino-2-phenyl-4*H*-cycloheptoxazole (IIa), and 8-dimethylamino-2-phenyl-8*H*-cycloheptoxazole (IIIa), reached an equilibrium at about 3:5:2. By the incorporation of dimethylamino-^{15}N into Ia and interchange between the amino group in 6-dimethylamino-2-phenyl-6*H*-cycloheptoxazole-amino-^{15}N (I-^{15}N) and that of 6-dimethylamino-2-(2-naphthyl)-6*H*-cycloheptoxazole (IX), the rearrangement was presumed to take place intermolecularly. 2-(*p*-Tolyl)-(Ib) and 2-(*p*-nitrophenyl)-6-dimethylamino-6*H*-cycloheptoxazole (Ic) also showed similar rearrangement of the dimethylamino group, while the rearrangement was not observed in 2-phenyl-6-(*p*-toluidino)-6*H*-cycloheptoxazole (VI) and 5-dimethylamino-5*H*-benzocycloheptene (VIII).

Cycloheptatrienes are known to undergo rearrangement of the hydrogen at C-7 on heating,[3] irradiation,[4] or by treatment with a base.[5] Moreover, a superficial methyl shift caused by reorganization of the carbon skeleton was also observed by Berson on heating trimethylcycloheptatriene.[6] The present paper described a new intermolecular rearrangement of the dimethylamino group observed in some dimethylaminocycloheptatrienes having a fused oxazole ring. It will be also notable that 7-dimethylaminocycloheptatriene itself (without a fused ring) has been reported to undergo 7–3 hydrogen shift to give 3-dimethylaminocycloheptatriene.[3e]

In a previous work, 6-dimethylamino-2-phenyl-6*H*-cycloheptoxazole (Ia) was prepared by the reaction of 2-phenyloxazolotropylium cation with dimethylamine, and the NMR spectrum shown in Fig. 1 was observed when measured immediately after solution of Ia in carbon tetrachloride.[7] This spectrum underwent a gradual change at room temperature and finally exhibited the spectrum shown in Fig. 2 after three days. This new spectrum had a strong singlet at 7.91 τ, two doublets at 5.42 and 5.21 τ (J=7.5 cps each), and complicated signals at 3—4 τ. To examine the cause of this change in the spectrum of Ia, its solution was evaporated and an isomer of Ia was obtained as white crystals melting at 62° along with the

1) Part XXIX: M. Watatani, *Chem. Pharm. Bull.* (Tokyo), **16**, 1513 (1968).
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3) *a*) A.P. ter Borg, H. Kloosterziel, and N. van Meurs, *Proc. Chem. Soc.*, **1962**, 359; *idem. Rev. Trav. Chim.*, **82**, 717 (1963); *b*) G. Büchi and E.M. Burgess, *J. Am. Chem. Soc.*, **84**, 3104 (1962); *c*) A.P. ter Borg and H. Kloosterziel, *Rec. Trav. Chim.*, **82**, 741 (1963); *d*) E. Weth and A.S. Dreiding, *Proc. Chem. Soc.*, **1964**, 59; *e*) A.P. ter Borg, E. Razenberg, and H. Kloosterziel, *Rec. Trav. Chim.*, **84**, 1230 (1965); *f*) T. Nozoe and K. Takahashi, *Bull. Chem. Soc. Japan.*, **38**, 665 (1965).
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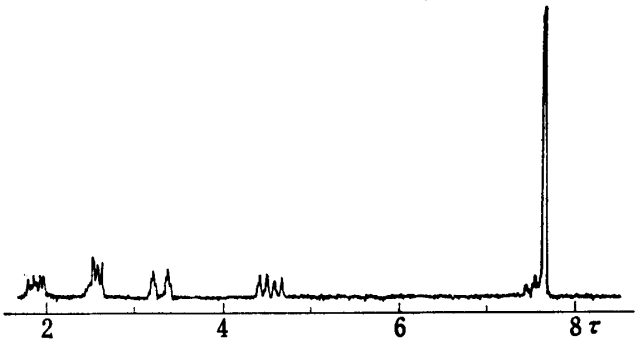


Fig. 1. NMR Spectrum of Ia measured immediately after solution in CCl_4

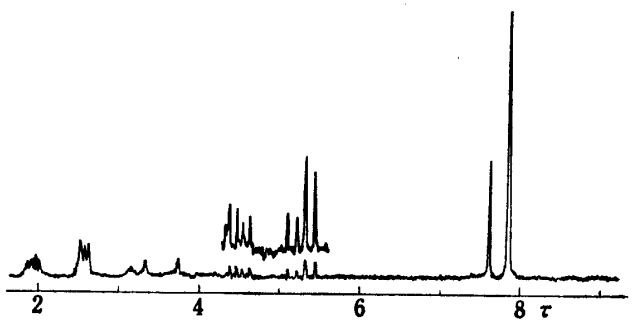
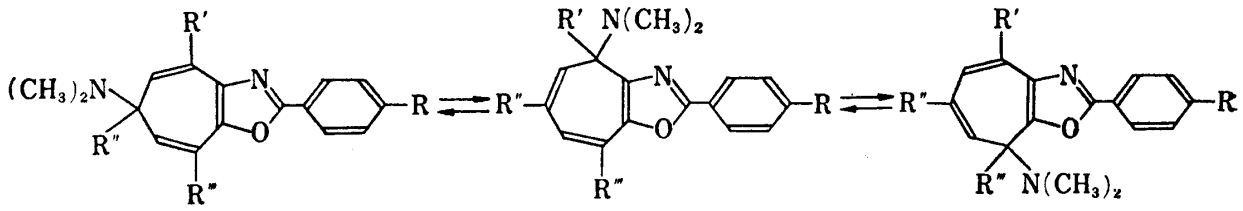


Fig. 2. NMR Spectrum of Ia measured after standing for 3 days

recovery of Ia. This isomer showed a singlet (6H) at 7.91 τ and a doublet (1H, J=7.5 cps) at 5.42 τ in its NMR spectrum, and the similarity of its UV spectrum (in carbon tetrachloride solution) to that of Ia with a 10 mμ red-shift and the absence of an amino or hydroxyl group in its IR spectrum indicate the retention of the cycloheptoxazole ring of Ia. From the following considerations, the structure of this isomer was assumed as 4-dimethylamino-2-phenyl-4*H*-cycloheptoxazole (IIa). When the above isolation of the isomer (IIa) was repeated using 4-deuterio-6-dimethylamino-2-phenyl-6*H*-cycloheptoxazole (Id) instead of Ia, the NMR spec-

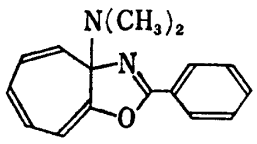


I II III

a : R, R′, R″, R‴=H
d : R′=D; R, R″, R‴=H

b : R=CH_3; R′, R″, R‴=H
e : R‴=D; R, R′, R″=H

c : R=NO_2; R′, R″, R‴=H
f : R‴=D; R, R′, R″=H



IV

Chart 1

trum of the crystals thereby obtained showed disappearance of the doublet at 5.42 τ observed in IIa. Among all the cycloheptoxazole structures having a dimethylamino group on their seven-membered ring, only 3a-dimethylamino-2-phenyl-3a*H*-cycloheptoxazole (IV) and IIa are consistent with this disappearance of a doublet corresponding to one proton by deuteration at C-4. However, the former structure (IV) was excluded by its inconsistency with the above-mentioned high τ-value (5.42 τ) of the doublet and the bathochromic shift relative to Ia in the UV spectrum. The NMR spectrum of the isomer, isolated from the solution of 6-deuterio-6-dimethylamino-2-phenyl-6*H*-cycloheptoxazole (Ie), also supported the structure of IIa. The spectrum of this isomer showed two sets of AB-type signals with the highest doublet at 5.42 τ (J=7.5 cps, same as observed in IIa) anticipated from the seven-membered ring protons of 6-deuterio-4-dimethylamino-2-phenyl-4*H*-cycloheptoxazole (IIe). The NMR spectrum of the isomer (8-deuterio-4-dimethylamino-2-phenyl-4*H*-cycloheptoxazole (IIf)) derived from 8-deuterio-6-dimethylamino-2-phenyl-6*H*-cycloheptoxazole (If) showed the expected retention

of the doublet at 5.42 τ. From these results, it was demonstrated that the dimethylamino group in Ia underwent rearrangement to afford IIa.

Besides the above-mentioned doublet at 5.42 τ due to the methyne proton at C-4 of IIa, one more doublet appeared at 5.21 τ as described above, on standing the solution of Ia. From the close τ-values and the same coupling constant of both doublets, the appearance of the latter doublet was presumed to be due to formation of 8-dimethylamino-2-phenyl-8*H*-cycloheptoxazole (IIIa), that is ,the doublet is assignable to the methyn protons at C-8 in IIIa. This presumption was proved to be correct by the fact that the same doublet did not appear when the solution of If was allowed to stand. This is explainable by the formation of 8-deuterio-8-dimethylamino-2-phenyl-8*H*-cycloheptoxazole (IIIf).

When the measurement of NMR spectrum followed the formation of IIa and IIIa from Ia in carbon tetrachloride solution, an equilibrium was found to be reached after standing the solution for three days at room temperature, and the ratio of Ia:IIa:IIIa was calculated to be about 3:5:2 from the consideration that singlets at 7.59 τ and 7.91 τ correspond, respectively, to the amount of Ia and IIa+IIIa,[8] and the intensity ratio of two doublets at 5.42 and 5.21 τ indicates the ratio of IIa to IIIa. The carbon tetrachloride solution of IIa, on standing at room temperature, also gave the same equilibrium mixture as above, indicating the formation of Ia and IIIa from IIa. The small amount of Ia present in the equilibrium mixture is interesting in contrast with the fact that a high yield of this isomer (Ia) (about 90%) was obtained[7] when the preparation from 2-phenyloxazolotropylium ion was carried out in benzene solution, and the other isomers (IIa and IIIa) were not isolated. Since the isomerization of Ia in benzene solution showed practically the same situation concerning the rate of isomerization and ratio of three isomers in the equilibrium mixture, as observed in the above-mentioned carbon tetrachloride solution, except that the methyl protons of IIa overlapped that of Ia, it may be concluded that the 4- (IIa) and 8-isomers (IIIa) are thermodynamically more stable than the 6-isomer (Ia) and the dimethylamino group of Ia once produced undergoes rearrangement to C-4 and C-8 on standing in a solution. In contrast with the above rather slow rearrangements, an equilibrium was established almost immediately when Ia was dissolved in methanol-d_4. The ratio of three isomers in the equilibrium mixture was the same as observed in carbon tetrachloride solution. This rapid rearrangement in a polar solvent, methanol, suggests that the dimethylamino group undergoes ionic rearrangement.

Next, 6-dimethylamino-2-(*p*-tolyl)-6*H*-cycloheptoxazole (Ib) and 6-dimethylamino-2-(*p*-nitrophenyl)-6*H*-cycloheptoxazole (Ic) were prepared by the method similar to that for Ia and the rearrangement of their dimethylamino groups was examined. The NMR spectra of Ib and Ic, which are indicative of the 6-substituted 6*H*-cycloheptoxazole structure (see Experimental), showed similar transformation as that observed in Ia on being stood at room temperatures; a singlet at 7.93 τ and two doublets at 5.46 and 5.22 τ (J=7.5 cps each) appeared in the spectrum of Ib, and a singlet at 7.81 τ and two doublets at 5.30 and 5.10 τ (J=7.5 cps each) in Ic. Therefore, rearrangement of the dimethylamino group apparently takes place in these compounds. In their equilibrium mixtures, ratios of the three isomers, Ib:IIb:IIIb and Ic:IIc:IIIc, were nearly equal to that in the case of Ia. Comparison of the rates of the rearrangement of dimethylamino group among Ia, Ib, and Ic is an interesting problem, and a preliminary examination indicated a tendency that the introduction of a nitro group into the phenyl group inhibits the rearrangement, while a methyl group, conversely, accelerates the rearrangement. However, the quantitative comparison remains to be investigated.

In contrast with the above easy rearrangement of the dimethylamino group, toluidino group in 6-(*p*-toluidino)-2-phenyl-6*H*-cycloheptoxazole (VI), obtained by the reaction of 2-phenyloxazolotropylium monomethylsulfate (V) with *p*-toluidine in the presence of triethyl-

8) Methyl signal of IIIa was presumed to appear at 7.91 τ overlapping that of IIa, and actually, the fine splitting of the signal was observed in a chloroform solution.

amine,[9] did not undergo the rearrangement on standing in carbon tetrachloride solution. Thus, the NMR spectrum of VI, in which a triplet of triplets corresponding to one proton at 6.20 τ is assignable to the methyne proton at C-6, did not show any change on standing for three days. The less facility of the toluidino group in VI to undergo rearrangement seems to be explainable by the lower dissociation constant of *p*-toluidine than that of dimethylamine. 5-Dimethylamino-5*H*-benzocycloheptene (VIII) prepared from benzotropylium ion (VII) and dimethylamine also did not show rearrangement of the amino group. The NMR

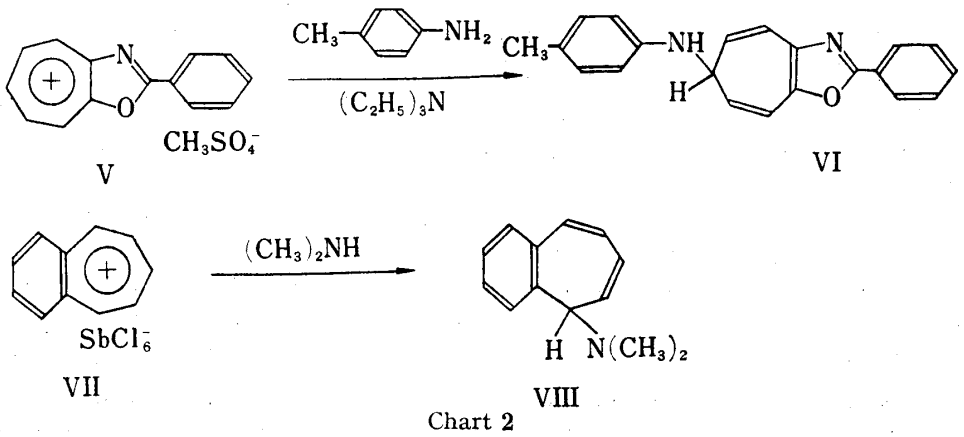
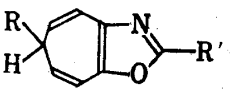


Chart 2

spectrum of VIII, in which a doublet at 7.25 τ (J=6.0 cps) shows the position of the dimethylamino group, did not suffer any change on standing for one week. Therefore, the rearrangement observed in Ia seems to be facilitated by a rather high electron density due to its fused oxazole ring.

Further investigation on the rearrangement of Ia was made using dimethylamine-^{15}N. When Ia was treated with a benzene solution of dimethylamine-^{15}N, its mass spectrum in the region of its molecular weight ($C_{16}H_{16}ON_2$, mol. wt. 252) showed an increase in the intensity of the peak at *m/e* 253 as shown in Fig. 3. This is interpretable as the result of an exchange of the dimethylamino group in Ia with dimethylamino-^{15}N. Next, 6-dimethylamino-2-phenyl-6*H*-cycloheptoxazole-amino-^{15}N (I-^{15}N) and 6-dimethylamino-2-(2-naphthyl)-6*H*-cycloheptoxazole (IX) (including 40% of a mixture of 4- and 8-isomers) were prepared, respectively by the reaction of V with dimethylamine-^{15}N and by that of 2-(2-naphthyl)oxazolotropylium monomethylsulfate with dimethylamine, and both compounds were mixed in methanol. After evaporation of the solvent, the mass spectrum of the residue was examined comparing with that of IX (M^+ at *m/e* 302) and a remarkable increase in the peak at *m/e* 303 was observed, as shown in Fig. 4. This increase is consistent with the formation of 6-dimethylamino-2-(2-naphthyl)-6*H*-cycloheptoxazole-amino-^{15}N (IX-^{15}N) by the interchange of dimethylamino group in IX with dimethylamino-^{15}N group in I-^{15}N. A comparative experiment in which Ia (without ^{15}N) was mixed, instead of I-^{15}N, with IX did not show any increase in the peak at *m/e* 303. From these results, it may be deduced that the rearrangement of the dimethylamino group observed in the present work takes place intermolecularly.



I-^{15}N: R=^{15}N(CH$_3$)$_2$; R'=C$_6$H$_5$
IX: R=N(CH$_3$)$_2$: R'=C$_{10}$H$_7$(β)
Mol. wt. 302
IX-^{15}N: R=^{15}N(CH$_3$)$_2$; R'=C$_{10}$H$_7$(β)
Mol. wt. 303

Chart 3

9) Compound VI had been assumed, in a previous paper of this series,[7] as an intermediate in the reaction between V and *p*-toluidine to afford a cycloheptimidazole derivative and was predicted to resolve into an imidazolotropylium ion by proton. In the present work, the isolation of VI was achieved by carrying out the same reaction in the presence of triethylamine, and the treatment of VI with hydrochloric acid actually afforded the previously predicted 2-phenyl-1-(*p*-tolyl)imidazolotropylium chloride. The details thereof and some reactions of VI will be reported in a later paper.

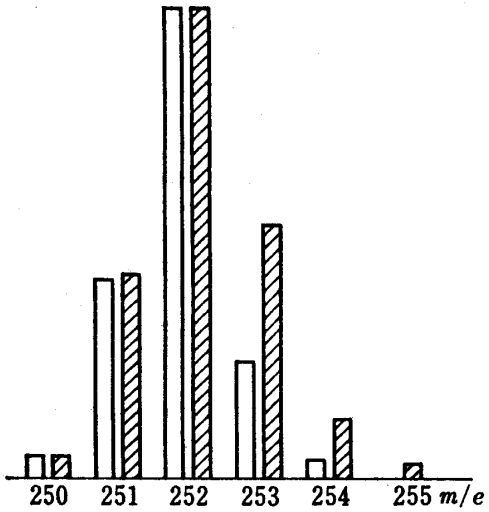


Fig. 3. Mass Spectra of Ia before (Blank) and after (Shaded) Treatment with Dimethylamine-^{15}N

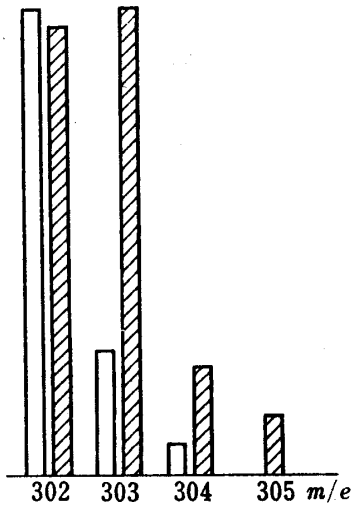


Fig. 4. Mass Spectra of IX brefore (Blank) and after (Shaded) mixing with I-^{15}N

Experimental

4-Dimethylamino-2-phenyl-4*H*-cycloheptoxazole (IIa) and Its Deuteration Products——A solution of 5.0 g of Ia in 100 ml of CCl_4 was allowed to stand for 3 days at room temperatures. The solution was evaporated to dryness and the residue was recrystallized from cyclohexane. The unchanged Ia (1.2 g) separated and was filtered. The filtrate was concentrated, the separated crystals were collected by filtration and recrystallized rapidly from cyclohexane to 0.8 g of white prisms melting at 62°. *Anal.* Calcd. for $C_{16}H_{16}ON_2$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.01; H, 6.21; N, 11.11. UV $\lambda_{max}^{CCl_4}$ mμ (log ε): 322 (4.18). NMR (CCl_4) τ: 7.91 (6H, singlet), 5.42 (1H, doublet, J=7.5 cps), 3.0—4.8 (4H, multiplet), 2.5—2.8 (3H, multiplet), 1.8—2.1 (2H, multiplet). This spectrum changed to an absorption identical with that shown in Fig. 2 after 3 days at room temperatures.

4-Deuterio-(IId), 6-deuterio- (IIe), and 8-deuterio-4-dimethylamino-2-phenyl-4*H*-cycloheptoxazoles (IIf) were respectively prepared from Id, Ie, and If by a similar procedure as above-described isolation of IIa. NMR of IId (CCl_4) τ: 7.91 (6H, singlet), 3.0—4.8 (4H, multiplet), 2.5—2.8 (3H, multiplet), 1.8—2.1 (2H, multiplet). NMR of IIe (CCl_4) τ: 7.91 (6H, singlet), 5.42 (1H, doublet, J=7.5 cps), 4.20 (1H, doublet, J=7.5 cps), 3.88 (1H, doublet, J=11.5 cps), 3.30 (1H, doublet, J=11.5 cps), 2.5—2.8 (3H, multiplet), 1.8—2.1 (2H, multiplet). NMR of IIe (CCl_4) τ: 7.91 (6H, singlet), 5.42 (1H, doublet, J=7.5 cps), 3.0—4.8 (3H, multiplet), 2.5—2.8 (3H, multiplet), 1.8—2.1 (2H, multiplet).

6-Dimethylamino-2-(*p*-tolyl)-6*H*-cycloheptoxazole (Ib)——To a suspension of 4.0 g of 2-(*p*-tolyl)oxazolotropylium monomethylsulfate in 40 ml of benzene, 6.0 ml of 20% benzene solution of Me_2NH was added at 10—15° and the mixture was stirred at room temperature for 30 min. The benzene solution was separated from the resultant heavy oily product by decantation and concentrated below 50° under reduced pressure. The residue was recrystallized from cyclohexane to 0.8 g of white crystals, mp 120°. *Anal.* Calcd. for $C_{17}H_{18}ON_2$: C, 76.66; H, 6.81, N, 10.52. Found: C, 76.60; H, 6.93; N, 10.17. IR ν_{max}^{Nujol}: no absorption in 1650—4000 cm^{-1} region. NMR (CCl_4) τ: 7.63 (6H, singlet), 7.61 (3H, singlet), 7.55 (1H, triplet of triplets, J=5.5 and 1.1 cps), 4.57 (2H, doublet of doublets, J=10.0 and 5.5 cps), 3.32 (1H, doublet of doublets, J=10.0 and 1.1 cps), 3.35 (1H, doublet of doublets, J=10.0 and 1.1 cps), 2.79 (2H, doublet, J=8.0 cps), 2.02 (2H, doublet, J=8.0 cps).

6-Dimethylamino-2-(*p*-nitrophenyl)-6*H*-cycloheptoxazole (Ic)——By a procedure similar to that described for the preparation of Ib, 2-(*p*-nitrophenyl)oxazolotropylium monomethylsulfate was allowed to react with Me_2NH and the obtained Ic was recrystallized from cyclohexane as pale yellow crystals, mp 158° (decomp.). *Anal.* Calcd. for $C_{16}H_{15}O_3N_3$: C, 64.63; H, 5.09; N, 14.14. Found: C, 64.30; H, 5.29; N, 13.96. IR ν_{max}^{Nujol}: no absorption in 3500—1650 cm^{-1} region. NMR ($CDCl_3$) τ: 7.57 (6H, singlet), 7.36 (1H, triplet of triplets, J=5.5 and 1.3 cps), 4.15—4.55 (2H, multiplet), 3.18 (2H, doublet of doublets, J=10.0 and 1.3 cps), 1.68 (4H, singlet).

2-Phenyl-6-(*p*-toluidino)-6*H*-cycloheptoxazole (VI)——To a suspension of 3.2 g of 2-phenyloxazolotropylium monomethylsulfate (V) in 20 ml of benzene, 20 ml of Et_3N and then 1.1 g of *p*-toluidine were added. The mixture was stirred at room temperature for 1 hr. After addition of water, the benzene solution was

separated and evaporated to dryness under reduced pressure below 40°. The residue was washed with hot cyclohexane giving 2.4 g of white crystals, mp 117°. *Anal.* Clacd. for $C_{21}H_{18}ON$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.45; H, 6.06; N, 8.91. UV λ_{max}^{EtOH} mμ (log ε): 237 (4.29), 314 (4.24). IR ν_{max}^{Nujol} cm^{-1}: 3300 (NH). NMR ($CDCl_3$) τ: 7.77 (3H, singlet), 6.20 (1H, triplet of triplets, J=5.5 and 1.1 cps), 4.3—4.8 (2H, multiplet), 2.7—4.0 (6H, multiplet), 2.4—2.7 (3H, multiplet), 1.8—2.1 (2H, multiplet).

6-Dimethylamino-2-(2-naphthyl)-6*H*-cycloheptoxazole (IX)——By a method similar to that described for the preparation of Ib, 3.0 g of 2-(2-naphthyl)oxazolotropylium monomethylsulfate was allowed to react with 1.0 g of Me_2NH. After repeated recrystallization from benzene and cyclohexane, IX was obtained as white crystals, mp 104—124°, containing 4- and 8-dimethylamino isomers. *Anal.* Calcd. for $C_{20}H_{18}ON_2$: C, 79.44; N, 6.00; N, 9.27. Found: C, 79.75; H, 6.10; N, 8.93. IR ν_{max}^{Nujol}: no absorption in the 2000—3500 cm^{-1} region. NMR ($CDCl_3$) τ: 7.60 (singlet, CH_3 of IX), 7.79 (singlet, CH_3 of 4-dimethylamino-isomer of IX), 7.81 (singlet, CH_3 of 8-dimethylamino isomer of IX). Five mg of this crystalline product was mixed with 10 mgof I-^{15}N in 0.5 ml of MeOH, and, after 5 min, MeOH was evaporated *in vacuo* below 40°. The MS spectrum of the residue is shown in Fig. 4.

Treatment of 6-Dimethylamino-2-phenyl-6*H*-cycloheptoxazole (Ia) with Dimethylamine-^{15}N——To a solution of 89 mg of Na in 25 ml of EtOH, 315 mg of Me_2NH-^{15}N·HCl and then 970 mg of Ia were added. After 6 hr, EtOH was evaporated *in vacuo*, and the residue was treated with cyclohexane and filtered. The crystals obtained (200 mg) were recrystallized from benzene to 10 mg of white plates, mp 112°. The MS spectrum is shown in Fig. 3.

5-Dimethylamino-5*H*-benzocycloheptene (VIII)——To a suspension of 1.9 g of benzotropylium hexachloroantimonate (VII) in 50 ml of tetrahydrofuran, 20 ml of 10% solution of Me_2NH in the same solvent was added dropwise at 10° with stirring. After stirring for 0.5 hr at room temperature, the mixture was filtered and the filtrate was concentrated to a brown syrup. Purification by alumina chromatography with benzene as a solvent gave 410 mg of VIII as a colorless syrup. NMR ($CDCl_3$) τ: 7.82 (6H, singlet), 7.25 (1H, doublet, J=6.0 cps), 3.54 (1H, triple doublet, J=6.0, 11.0 and 2.0 cps), 3.8—4.4 (2H, multiplet), 2.6—3.0 (5H, multiplet). This spectrum did not show any change after standing for 6 days at room temperature.

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