

SYNTHESIS OF MONOCYCLIC ANALOGUES OF A POTENT  
 THROMBOXANE RECEPTOR ANTAGONIST, (±)-(5Z)-7-[3-*ENDO*-  
 [(PHENYLSULFONYL)AMINO]BICYCLO[2.2.1]HEPT-2-*EXO*-  
 YL]HEPTENOIC ACID (S-145)<sup>1</sup>

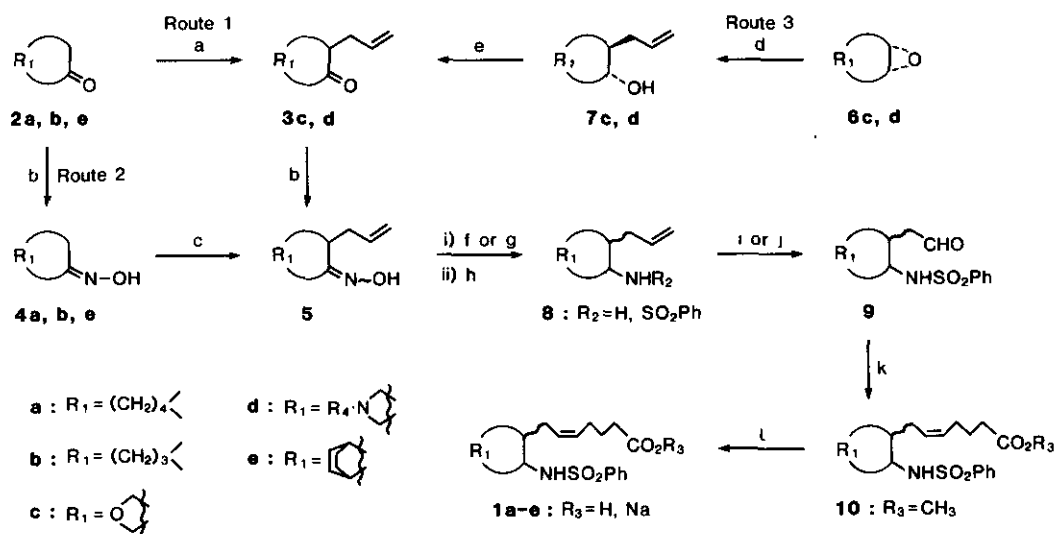
Kenji Kawada and Tadahiko Tsushima\*

Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku,  
 Osaka 553, Japan

**Abstract** — Several monocyclic analogues of the potent thromboxane-A<sub>2</sub> receptor antagonist S-145, i.e. cyclohexane, cyclopentane, tetrahydrofuran, and pyrrolidine, as well as the bicyclo[2.2.2]octane one were synthesized using allylation via oxime dianion and the Barton's method for oxime reduction in the key steps.

A thromboxane receptor antagonist, (±)-(5Z)-7-[3-*endo*-[(phenylsulfonyl)amino]bicyclo[2.2.1]hept-2-*exo*-yl]heptenoic acid (S-145), recently synthesized by Narisada et al. has attracted much attention because of its remarkably high potency.<sup>2,3</sup> This compound effectively suppresses both *in vitro* and *in vivo* the platelet aggregation and the vascular and respiratory smooth muscle constriction elicited by several kinds of thromboxane A<sub>2</sub> (TxA<sub>2</sub>) mimics.<sup>4</sup> The compound is presently under development for use in the chemotherapy of various TxA<sub>2</sub>- and/or PGH<sub>2</sub>-mediated disorders<sup>5</sup> such as angina pectoris, thrombotic ischemia, myocardial infarction, or asthma. The diversity of the structures and activities of hitherto known TxA<sub>2</sub> antagonists<sup>6</sup> suggests that the TxA<sub>2</sub> receptor has considerable tolerance for structural changes in substrates. This has led to extensive study in these laboratories of the structural modification of S-145 in order to design more useful antagonists.<sup>7</sup> Efforts have also been made to find structure-activity relationships on the partial agonist activity frequently accompanying TxA<sub>2</sub> antagonists.<sup>8</sup> As a part of these studies<sup>7</sup>, we synthesized monocyclic analogs, cyclohexane **1a**, cyclopentane **1b**, tetrahydrofuran **1c**, and pyrrolidine **1d**, as well as the bicyclo[2.2.2]octane derivative **1e**, in order to examine the effects of ring size, heteroatom substitution, and the configurations of the side-chains, as shown in Scheme 1.

The synthetic procedure of S-145 which involves allylation of a ketone-enolate (Route 1 in Scheme 1) and oxime reduction with LiAlH<sub>4</sub> has recently been reported<sup>2b</sup> but its straightforward application to the present case, particularly to five-membered compounds, was not suitable at two key stages, allylation and oxime reduction, because these enolates are quite unstable due to rapid aldol condensation or β-elimination



Scheme 1. (a) LDA,  $\text{CH}_2=\text{CHBr}$ , r.t. (b)  $\text{H}_2\text{N}\cdot\text{NH}_2\cdot\text{HCl}$ , Py/EtOH, refl. (c) BuLi,  $\text{CH}_2=\text{CHBr}$ ,  $-30^\circ\text{C}$ -r.t. (d)  $\text{CH}_2=\text{CHMgBr}/\text{Et}_2\text{O}$ ,  $0^\circ\text{C}$ . (e) PCC/ $\text{CH}_2\text{Cl}_2$ , r.t. (f)  $\text{LiAlH}_4/\text{THF}$ , r.t.- $45^\circ\text{C}$ . (g)  $\text{Bu}_3\text{P}\cdot\text{PhSSPh}$ ,  $\text{NaBH}_3\text{CN}/\text{THF}$ . (h)  $\text{PhSO}_2\text{Cl}\cdot\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ -r.t. (i) m-CPBA/ $\text{CH}_2\text{Cl}_2\text{-HIO}_4\cdot 2\text{H}_2\text{O}/\text{THF}$ . (j)  $\text{OsO}_4\text{-NaIO}_4/\text{THF}\text{-H}_2\text{O}$  (10 : 3), r.t. (k)  $\text{Ph}_3\text{P}^+(\text{CH}_2)_4\text{CO}_2\text{H Br}^-$  -NaH/DMSO,  $10\text{-}15^\circ\text{C}$ ;  $\text{H}_2\text{CN}_2/\text{CH}_2\text{Cl}_2$ , r.t. (l) MeOH-1N-NaOH,  $0^\circ\text{C}$ .

and also because cyclopentanone oxime strongly resists reduction. To overcome these problems, we chose two recently reported procedures, namely allylation via oxime dianion<sup>9</sup> and oxime reduction, which was developed by Barton et al.<sup>10</sup>

Treatment of the oximes of cyclohexanone, cyclopentanone, and bicyclo[2.2.2]octanone (**4a**, **4b**, and **4e**) with *n*-butyllithium followed by the addition of allyl bromide smoothly afforded the desired monoallylated oximes (**5a**, **5b**, and **5e**) in 50%, 58%, and 90% yields, respectively, particularly in an enhanced yield with the cyclopentanone case (**5b**) as previously reported<sup>9b</sup>. Surprisingly however, in contrast to the earlier study<sup>9b</sup>, both *Z*- and *E*-allyl oximes were produced despite our careful work-up avoiding equilibration; for cyclohexanone oxime **5a**, *Z/E* = 1/1.6 and for cyclopentanone oxime **5b**, *Z/E* = 2/1. Both isomers were separated and their structures unambiguously identified.<sup>11</sup> These results raised some questions as to the *syn* regioselectivity of the reaction, which has been attributed to chelate formation in dilithium enolate intermediates. With other heterocyclic cases (**4c** and **4d**), this allylation was not successful, giving complex mixtures of products because of the facile ring opening due to  $\beta$ -elimination. In these cases, Grignard reaction of the epoxides (**6c** and **6d**) with allylmagnesium bromide gave the allylated alcohols (**7c** and **7d**) in 79% and 85% yields, respectively. They were subsequently converted into the oximes (**5c** and **5d**) *via* ketone in a usual manner.

As for the subsequent oxime reduction step, treatment of the 6-membered ring oximes (**5a** and **5e**) and also the tetrahydrofuranone **5c** with  $\text{LiAlH}_4$  in THF smoothly afforded the desired amines in the following isolation yields: **8a** (75%, *t/c* = 1/5.0), **8e** (52%, all *trans*) and **8c** (76%, *t/c* = 5.1/1). Here, both *Z*- and *E*-oximes

were confirmed to give the corresponding amines in a similar way. The resulting amines were isolated as sulfonamides which were directly used for the subsequent reaction.<sup>12</sup> The resulting *cis* and *trans* sulfonamides were separated and their configurations unambiguously determined on the basis of their nmr spectroscopic data<sup>12</sup>. Unlike these oximes (**5a**, **5e**, and **5c**), the reduction of the cyclopentanone oxime **5b** with either LiAlH<sub>4</sub> or Vitride afforded the desired product **8b** only in 11% yield (exclusively *trans*) together with a large amount of byproducts. Here, application of the Barton's procedure<sup>10</sup>, namely a tandem reduction via an imine intermediate by successively using tri-*n*-butylphosphine-diphenyl disulfide and sodium cyanoborohydride, smoothly afforded **8b** in a greatly improved isolation yield of 65% (*t/c* = 2.3/1), although the yield was not fully optimized. The stereochemical result obtained suggested a somewhat decreased stereoselectivity of the products compared to the reduction with LiAlH<sub>4</sub>, which gave the *trans* isomer exclusively. Therefore, the reaction was used with the cyclohexanone oxime **5a** to obtain the minor product *trans*-**8a** in a higher yield. As expected, the reaction gave *trans*-**8a** in an enhanced yield [the isolation yield of both isomers (*trans*- and *cis*-**8a**) was 62%, *t/c* = 1/1.4]. Reduction of the pyrrolidone oxime **5d**, being somewhat bothersome in these cases, was also achieved by this Barton's method in 39% yield. These results clearly showed the versatility of the reaction.<sup>7c</sup>

All the *trans* sulfonamides (*trans*-**8b** to *trans*-**8e**) thus far obtained, except *trans*-**8a**, were then converted into the aldehydes **9** in good yields by treatment with *m*-CPBA followed by oxidative carbon-carbon bond cleavage by periodate, whereas the *cis* isomers (*cis*-**8a** and *cis*-**8b**) as well as *trans*-**8a** were treated with osmium tetroxide - sodium periodate to afford the desired aldehydes **9**.<sup>12</sup> Here, the aldehydes (*cis*- and *trans*-**9a** and *cis*-**9b**) existed in a cyclic aminal form but the aldehydes (*trans*-**9b**, *trans*-**9c**, *trans*-**9d**, and *trans*-**9e**) were in a free form. Next, all of these aldehydes were subjected to the Wittig reaction, without purification, as done by Corey et al.<sup>13</sup> and the corresponding free acids (**1a**-**1e**) were obtained as crude product mixtures. After esterification with diazomethane, the desired esters with the *Z*-olefin configuration (*cis*- and *trans*-**10a**, *cis*- and *trans*-**10b**, and *trans*-**10c** to *trans*-**10e**) were isolated from the mixtures in the following combined yields from the starting sulfonamides (**8a**-**8e**) and fully characterized: for **10a** (44.8% for *trans* and 21% for *cis*), **10b** (48.1% for *trans* and 43.2% for *cis*), **10c** (41.4% for *trans*), **10d** (45% for *trans*), and **10e** (58%).<sup>14</sup> These esters were hydrolyzed under mild conditions to afford the analytically pure free acids (**1a**-**1e**). They were converted to sodium salts which were subjected to primary screening. With the pyrrolidine derivative, the nitrogen deprotection was done at the very last stage before metalation of free acid **1d** and some *N*-substituted derivatives were prepared. The fluorinated derivative of **S-145** at the C-7 position was also prepared but the details will be reported elsewhere.

All the compounds prepared were tested for TxA<sub>2</sub> receptor antagonist activity in our primary screening system<sup>4</sup> which involves evaluation of inhibitory activities against aggregation of both rabbit platelet-rich plasma and rat washed platelets induced by arachidonic acid and collagen, respectively, and also against

arachidonic acid induced sudden death of mouse. Although some compounds, e.g., 1e, 1a, N-Me-1d, showed comparable activities to those of S-145 in some of the screening tests, all of these compounds were 1/2 to 1/800 as effective as S-145. The biological assay results obtained will be reported elsewhere from the viewpoint of structure-activity relationships.

#### ACKNOWLEDGEMENT

We would like to thank Dr. Narisada, the head of Organic Chemistry Division, for his encouragement and valuable suggestions throughout this work. The authors are also very grateful to Drs. Uchida, Kurosawa, Doteuchi, Arita, and their collaborators for the biological activity evaluation. T. T would like to express his most heartfelt thanks to Dr. K. Takeda, ex-director of these laboratories, for his encouragement to contribute this paper to this special issue.

#### REFERENCES AND NOTES

1. Dedicated to Professor Sir Derek Barton on the occasion of his 70th birthday.
2. (a) British patent-2184118A (Nov.18, 1985). (b) M. Narisada, M. Otani, F. Watanabe, K. Uchida, H. Arita, M. Doteuchi, M. Ueda, K. Kawasaki, H. Kakushi, K. Otani, S. Hara, and M. Nakajima, J. Med. Chem., 1988, 31, 0000. (c) See also, Abstracts of Taipei Conference on Prostaglandines and Leukotrienes, 1988, 10 (W 9). Following this patent, the synthesis of the same compounds, in either a chiral or achiral manner, have been reported by other groups<sup>3</sup>.
3. (a) K. Furuta, S. Hayashi, Y. Miwa, and H. Yamamoto, Tetrahedron Letts., 1987, 28, 5841. (b) N. Hamanaka, ref. 2c, 10 (W 10).
4. (a) K. Hanasaki and H. Arita, Thrombosis Res., 1988, 50, 365. (b) K. Hanasaki, K. Nakano, H. Kasai, H. Kurihara, and H. Arita, Biochem. Biophys. Res. Commun., 1988, 151, 1352. (c) S. Narumiya, M. Okuma, and F. Ushikubi, Br. J. Pharmacol., 1986, 88, 323. (d) N. Nakajima, K. Otani, M. Doteuchi, and M. Ueda, ref. 2c, 173 (P 85). (e) A. Kurosawa, H. Jyoyama, H. Hatakeyama, F. Asanuma, Y. Hori, H. Umehara, K. Otani, and M. Doteuchi, ibid., 172 (P 83).
5. For general review articles, (a) E. Granstrom, U. Diczfalusy, M. Hamberg, G. Hansson, and B. Samuelsson, 'Adv. in Prostaglandins Thromboxane Research,' Vol.10, ed. by J. A. Oates, Raven Press, New York, 1982, pp. 15-58. (b) A. M. Lefer, Drugs Today, 1985, 21, 283-291. (c) References cited in ref. 3(a) and 3(b).
6. (a) See references cited in ref. 4b. and for other recently developed antagonists, see (b) P. P. A. Humphrey, E. W. Collington, P. Hallett, E. J. Hornby, P. Lumley, and C. J. Wallis, Abstracts of 10th Int. Congress Pharmacol: Sydney, 1987, O 137. (c) J. F. Evans, C. Leveille, J. Gillard, R. Fortin, Y. Guindon, A. W. Ford-Hutchinson, and J. Rokach, ibid., P 370. (d) S. Lee, Chem. and Ind., 1987, 223.

7. (a) M. Otani and M. Narisada, J. Med. Chem., submitted for publication. (b) S. Hagishita and K. Seno, Chem. Pharm. Bull., submitted for publication. (c) Some other interesting examples of the application of the Barton's method will be reported elsewhere by S. Kamata, et al. of these laboratories. (d) M. Kishi, to be submitted for publication.
8. T. Nakano, K. Hanasaki, and H. Arita, FEBS Letts., 1988, in press.
9. (a) F. E. Henock, K. G. Hampton, and C. R. Hauser, J. Am. Chem. Soc., 1969, **91**, 676. (b) W. G. Kofron and M.-K. Yeh, J. Org. Chem., 1970, **35**, 1806.
10. D. H. R. Barton, W. B. Motherwell, E. S. Simon, and S. Z. Zard, J. Chem. Soc., Chem. Commun., 1984, 337.
11. Both (*E*)- and (*Z*)-2-allylcyclohexanone oximes were characterized as follows. For *E*-isomer: mp 71-2 °C; <sup>1</sup>H-nmr (CDCl<sub>3</sub>) δ 1.20-2.67 (m, 10H, CH<sub>2</sub>), 2.83 (m, 1H, CH), 4.83-5.17 (m, 2H, =CH<sub>2</sub>), 5.78 (m, 1H, CH=), 9.30 (br. s, 1H, OH); <sup>13</sup>C-nmr (CDCl<sub>3</sub>) δ 162.4 (C-1), 41.8 (C-2), 23.5 (C-3), 32.2 (C-4), 23.8 (C-5), 26.1 (C-6), 35.3 (CH<sub>2</sub>), 116.2 (=CH<sub>2</sub>), 136.7 (=CH); For *Z*-isomer: mp 46-47.5 °C; <sup>1</sup>H-nmr (CDCl<sub>3</sub>) δ 1.20-2.47 (m, 10H, CH<sub>2</sub>), 3.53 (m, 1H, CH), 4.88-5.18 (m, 2H, =CH<sub>2</sub>), 5.78 (m, 1H, =CH), 9.28 (br. s, 1H, OH); <sup>13</sup>C-nmr δ 162.9 (C-1), 32.0 (C-2), 20.4 (C-3), 28.7 (C-4), 26.8 (C-5), 34.7 (C-6), 28.7 (CH<sub>2</sub>), 116.2 (=CH<sub>2</sub>), 136.2 (=CH). Both mass and analytical data support these structures. Although ir spectroscopic measurement showed the complete absence of the intramolecular π hydrogen bonding in both isomers, their structural assignment could be clearly made by these nmr data based on the general rule of nmr spectroscopic assignment of oximes. The *Z*-isomer shows considerable upfield-shifted <sup>13</sup>C-nmr signals of sterically hindered β-carbon as well as lowfield-shifted β-methine proton signals compared to those of the *E*-isomer. For cyclopentane derivatives also, structural elucidation was unambiguously done in the same way.
12. Experimental details will be reported elsewhere.
13. E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, J. Amer. Chem. Soc., 1969, **91**, 5675.
14. All the esters obtained were characterized as follows. For *trans*-10a: <sup>1</sup>H-nmr δ 0.73-2.17 (m, 15H, CH<sub>2</sub> and CH), 2.29 (t, 2H, CH<sub>2</sub>CO<sub>2</sub>Me, J = 7.0 Hz), 2.92 (m, 1H, CHN), 3.70 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 4.92 (d, 1H, NH, J = 9.0 Hz), 5.10-5.53 (m, 2H, CH=CH), 7.42-8.03 (m, 5H, arom. H); ir (CHCl<sub>3</sub>) 3370, 2925, 2850, 1725, 1445, 1325, and 1155, 1090, 1065, 945, and 910 cm<sup>-1</sup>; mass m/z 379 (M<sup>+</sup>), 347, 238 (M<sup>+</sup> - C<sub>6</sub>H<sub>5</sub>SO<sub>2</sub>), 77 (C<sub>6</sub>H<sub>5</sub>). For *cis*-10a: <sup>1</sup>H-nmr (CDCl<sub>3</sub>) δ 1.00-2.15 (m, 15H, CH<sub>2</sub> and CH), 2.29 (t, 2H, CH<sub>2</sub>CO<sub>2</sub>Me, J = 7.0 Hz), 3.47 (m, 1H, CHN), 3.67 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 5.03-5.50 (m, 2H, CH=CH), 5.50 (d, 1H, NH, J = 9.0 Hz), 7.33-8.03 (m, 5H, arom. H); ir 3375, 2925, 2850, 1725, 1445, 1330, 1155, 1090, 1000, 990 cm<sup>-1</sup>; mass m/z 379 (M<sup>+</sup>), 347, 238 (M<sup>+</sup> - C<sub>6</sub>H<sub>5</sub>SO<sub>2</sub>), 77 (C<sub>6</sub>H<sub>5</sub>). For *trans*-10b: <sup>1</sup>H-nmr δ 1.00-2.40 (m, 13H, CH<sub>2</sub> and CH), 2.28 (t, 2H, CH<sub>2</sub>CO<sub>2</sub>Me, J = 7.0 Hz), 3.17 (m, 1H, CHN), 3.67 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 4.93 (d, 1H, NH, J = 9.0 Hz), 5.07-5.50 (m, 2H, CH=CH), 7.40-8.03 (m, 5H, arom. H); ir

3360, 2925, 1720, 1440, 1325, 1155, 1090  $\text{cm}^{-1}$ ; mass  $m/z$  366 ( $\text{MH}^+$ ), 334 ( $\text{M}^+ - \text{OCH}_3$ ), 224 ( $\text{M}^+ - \text{C}_6\text{H}_5\text{SO}_2$ ), 77 ( $\text{C}_6\text{H}_5$ ). For *cis*-10b:  $^1\text{H}$ -nmr  $\delta$  1.00-2.30 (m, 13H,  $\text{CH}_2$  and  $\text{CH}$ ), 2.28 (t, 2H,  $\text{CH}_2\text{CO}_2\text{Me}$ ,  $J = 7.0$  Hz), 3.60 (m, 1H,  $\text{CHN}$ ), 3.66 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 4.74 (d, 1H,  $\text{NH}$ ,  $J = 9.0$  Hz), 5.10-5.50 (m, 2H,  $\text{CH}=\text{CH}$ ), 7.38-8.03 (m, 5H, arom. H); ir 3370, 2940, 1725, 1445, 1345, 1325, 1160, 1090  $\text{cm}^{-1}$ ; mass  $m/z$  366 ( $\text{MH}^+$ ), 334 ( $\text{M}^+ - \text{OCH}_3$ ), 224 ( $\text{M}^+ - \text{C}_6\text{H}_5\text{SO}_2$ ), 77 ( $\text{C}_6\text{H}_5$ ). For *trans*-10c:  $^1\text{H}$ -nmr  $\delta$  1.42-2.27 (m, 7H,  $\text{CH}_2$  and  $\text{CH}$ ), 2.27 (t, 2H,  $\text{CH}_2\text{CO}_2\text{Me}$ ,  $J = 7.0$  Hz), 3.24-4.07 (m, 5H,  $\text{CH}_2\text{O}$  and  $\text{CHN}$ ), 3.66 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 4.97-5.50 (m, 2H,  $\text{CH}=\text{CH}$ ), 5.89 (d, 1H,  $\text{NH}$ ,  $J = 6.5$  Hz), 7.37-8.02 (m, 5H, arom. H); ir 3350, 2900, 1720, 1580, 1430, 1330, 1155, 1090, 1060, 905  $\text{cm}^{-1}$ ; mass  $m/z$  367 ( $\text{M}^+$ ), 335, 226 ( $\text{M}^+ - \text{SO}_2\text{C}_6\text{H}_5$ ), 200, 77 ( $\text{C}_6\text{H}_5$ ). For *trans*-N-Boc-10d:  $^1\text{H}$ -nmr  $\delta$  1.39 (s, 9H, t-Bu), 1.45-2.35 (m, 7H,  $\text{CH}_2$  and  $\text{CH}$ ), 2.29 (t, 2H,  $\text{CH}_2\text{CO}_2\text{Me}$ ,  $J = 7.0$  Hz), 2.73-3.73 (m, 5H,  $\text{CH}_2\text{N}$  and  $\text{CHN}$ ), 3.68 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 4.97-5.58 (m, 2H,  $\text{CH}=\text{CH}$ ), 5.99 (d, 1H,  $\text{NH}$ ,  $J = 7.5$  Hz), 7.32-8.03 (m, 5H, arom. H); ir 3350, 2900, 1720, 1680, 1580, 1405, 1365, 1325, 1160, 1090  $\text{cm}^{-1}$ ; mass  $m/z$  466 ( $\text{M}^+$ ), 410, 393 ( $\text{M}^+ - \text{CH}_2\text{CO}_2\text{Me}$ ), 365 ( $\text{M}^+ - \text{C}_3\text{H}_6\text{CO}_2\text{Me}$ ), 57 ( $\text{C}_4\text{H}_9$ ). For *trans*-10e:  $^1\text{H}$ -nmr  $\delta$  1.00-2.10 (m, 17H,  $\text{CH}_2$  and  $\text{CH}$ ), 2.27 (t, 2H,  $\text{CH}_2\text{CO}_2\text{Me}$ ,  $J = 7.5$  Hz), 2.83 (m, 1H,  $\text{CHN}$ ), 3.66 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 4.93-5.40 (m, 3H,  $\text{CH}=\text{CH}$  and  $\text{NH}$ ), 7.40-8.03 (m, 5H, arom. H); ir 3370, 2925, 2850, 1720, 1440, 1320, 1150, 1090, 960, 905  $\text{cm}^{-1}$ . All these compounds and the final sodium salts gave satisfactory results on elementary analysis.

Received, 24th August, 1988