# STUDIES ON THE SYNTHESIS OF BISINDOLE ALKALOIDS. VI.[1] NOVEL LACTAM DERIVATIVES IN THE VINBLASTINE SERIES.

James P. Kutney*, John Balsevich and Gordon H. Bokelman

Department of Chemistry

University of British Columbia

2075 Wesbrook Place

Vancouver, B.C., Canada V6T 1W5

The utilization of osmium tetroxide as an oxidant can provide a synthetic entry into lactam derivatives in the bisindole area. In complimentary investigations it was shown that iodine and air oxidation of a series of bisindole alkaloids can also provide some novel lactam derivatives. These substances are important for the purpose of biological evaluation as potential anti-tumor agents and, in particular, for information relating to structure-activity relationships in the clinically important vinblastine family of alkaloids.

In our research program on the synthesis of bisindole alkaloids in the vinblastine family, we have already described several approaches for the introduction of oxygen functionality at the $C_3$ and $C_4$ positions in the cleavamine series and, in turn, at these sites in the bisindole series. Such studies provided the first laboratory synthesis of leurosine and 3'-hydroxyvinblastine[2]. We would now like to present an attractive synthetic entry into a series of novel lactam derivatives in this clinically important alkaloid family.

In our previous work[2] we had shown that the N-oxide intermediate I (R = $COOCH_3$) (Figure 1) could under appropriate conditions, be converted to 3'-hydroxyvinblastine (II, R = $COOCH_3$, $R_1$ = OH). We would now like to discuss in more detail our studies in this area and to indicate that the nature of the products isolated from the osmylation of I depend markedly on reaction conditions employed. Thus when I (R = $COOCH_3$) is reacted with one equivalent of osmium tetroxide at low temperature (-3°C) in tetrahydrofuran as solvent, two products are isolated. One of these is the previously described[2] 3'-hydroxyvinblastine (II, R = $COOCH_3$; $R_1$ = OH; 10% yield), while the major component (53% yield) obtained is 3',4'-dehydro-19'-oxovinblastine (III, R = $COOCH_3$; $R_2$ = O) as evidenced from the following spectroscopic data, [MS: m/e 806 ($M^+$, $C_{46}H_{54}N_4O_9$ requires: 806.389; Found: 806.387), 748, 670, 136, 135 (base peak), 122, 121, 107, 106; NMR ($CDCl_3$, $\delta$): 8.10 (s, 1H, NH), 7.60 (m, 1H, $C_{14}$'H), 7.21 (m, 3H, $C_{11}$'H-$C_{13}$'H), 6.69 (s, 1H, $C_{14}$H), 6.19 (s, 1H, $C_{17}$H), 6.15 (m, 1H, $C_3$'H), 5.90 (m, 1H, $C_7$H), 5.34 (d, 1H, $C_6$H), 4.92 (m, 1H, $C_2$'H), 3.84 (bs, 6H, 2 x $OCH_3$), 3.62 (s, 3H, $OCH_3$), 2.75 (s, 3H, $NCH_3$), 2.13 (s, 3H, $OCOCH_3$), 1.01 (t, 3H, $CH_2\underline{CH_3}$), 0.85 (t, 3H, $CH_2\underline{CH_3}$); IR ($CHCl_3$): 3460, 2950, 1735, 1655, 1610 $cm^{-1}$.]

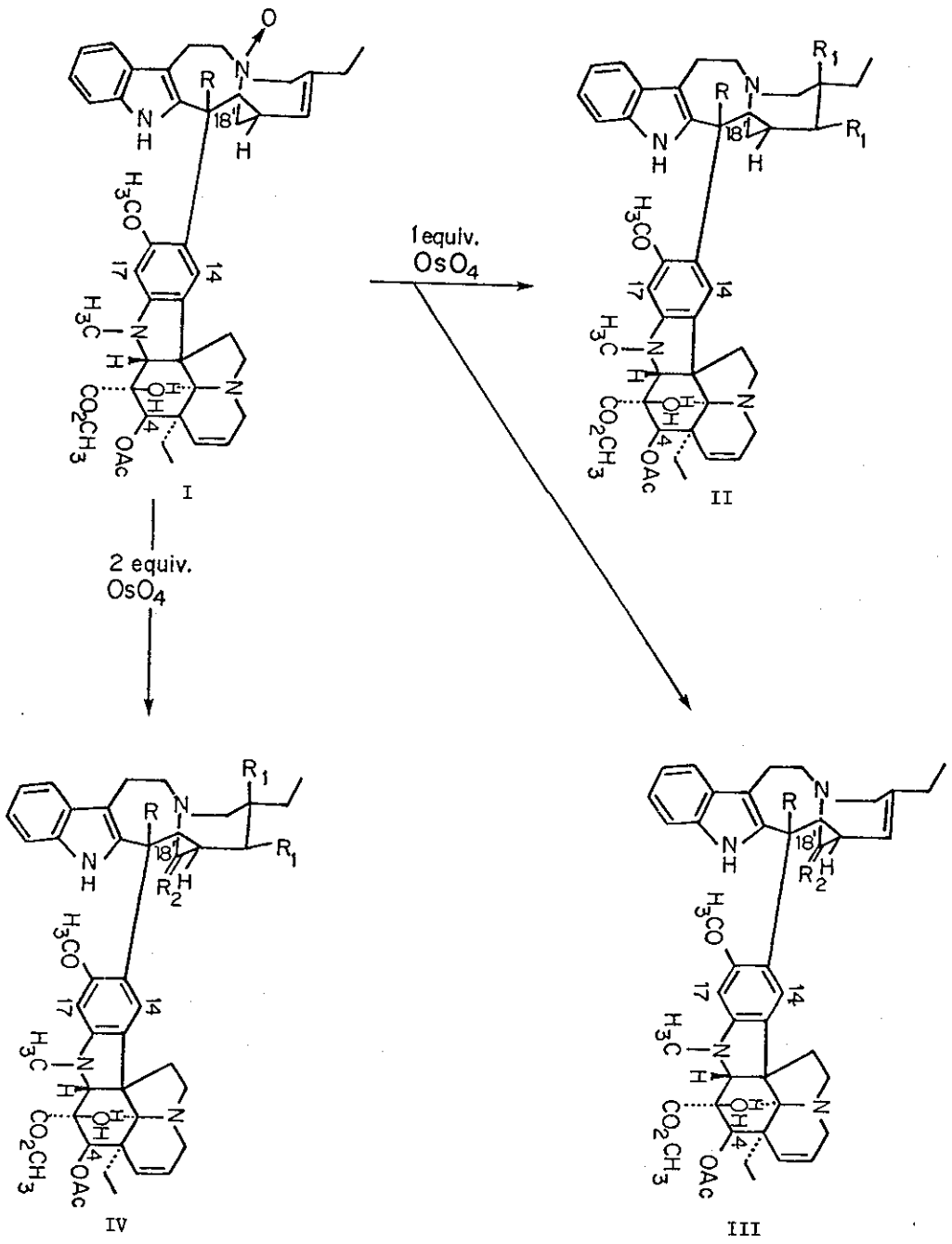


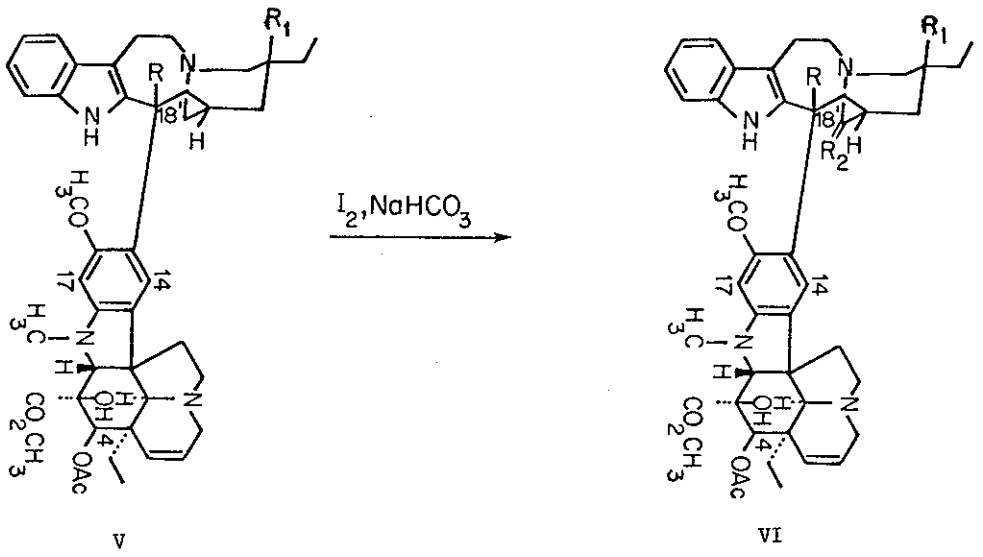

Figure 1. The reaction of the N-oxide intermediate I (R = $CO_2CH_3$) with osmium tetroxide under various conditions.

On the other hand, when I (R = $COOCH_3$) is reacted with two equivalents of osmium tetroxide at 0°C, 3'-hydroxy-19'-oxovinblastine (IV, R = $CO_2CH_3$; $R_1$ = OH; $R_2$ = O) is obtained as the major product (64% yield) [MS: m/e 840 ($M^+$, $C_{46}H_{56}N_4O_{11}$ requires: 840.394; Found: 840.390), 423, 282, 149, 135 (base peak), 122, 121, 107; NMR ($CDCl_3$, δ): 8.04 (s, 1H, NH), 7.54 (m, 1H, $C_{14'}H$), 7.18 (m, 3H, $C_{11'}H$-$C_{13'}H$), 6.66 (s, 1H, $C_{14}H$), 6.17 (s, 1H, $C_{17}H$), 5.89 (m, 1H, $C_7H$), 5.33 (d, 1H, $C_6H$), 4.65 (m, 1H, $C_{2'}H$), 3.83 (bs, 6H, 2 x $OCH_3$), 3.60 (s, 3H, $OCH_3$), 2.76 (s, 3H, $NCH_3$), 2.12 (s, 3H, $OCOCH_3$), 1.04 (t, 3H, $CH_2\underline{CH_3}$), 0.85 (t, 3H, $CH_2\underline{CH_3}$); IR ($CHCl_3$): 3600-3500, 3460, 2960, 1735, 1645, 1615 $cm^{-1}$.]

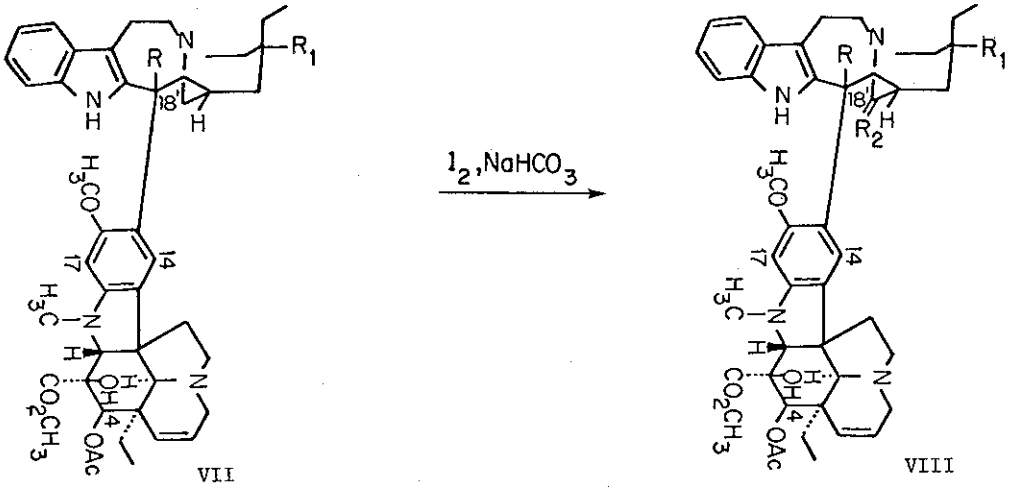
It should be emphasized that as in the previous publication[2], the assignment of stereochemistry at the $C_{3'}$ and $C_{4'}$ positions in II and IV ($R_1$ = OH) is made on a tentative basis. Further correlations with the natural vinblastine and/or leurosidine series must be made before a more definitive conclusion can be drawn.

Two other approaches to a series of novel lactam derivatives in the bisindole family were investigated and the results obtained are now presented.

Iodine oxidation under basic conditions[3,4] provides a reasonably efficient procedure for the synthesis of lactam derivatives in the vinblastine, leurosidine and leurosine series. Figure 2 summarizes the results obtained with vinblastine (V, R = $CO_2CH_3$; $R_1$ = OH) and leurosidine (VII, R = $CO_2CH_3$; $R_1$ = OH) while Figure 3 indicates the conversions with leurosine (IX, R = $CO_2CH_3$).




V VI




VII VIII

Figure 2. The conversion of vinblastine (V, R = $CO_2CH_3$; $R_1$ = OH) and leurosidine (VII, R = $CO_2CH_3$; $R_1$ = OH) to lactam derivatives VI (R = $CO_2CH_3$; $R_1$ = OH, $R_2$ = O) and VIII (R = $CO_2CH_3$; $R_1$ = OH, $R_2$ = O) by means of iodine under basic conditions.

When vinblastine (V, R = $CO_2CH_3$; $R_1$ = OH) is reacted with iodine and sodium bicarbonate in a tetrahydrofuran solution at room temperature, the major product isolated (32%) is 19'-oxovinblastine (VI, R = $CO_2CH_3$; $R_1$ = OH; $R_2$ = O), [MS: m/e 824 ($M^+$, $C_{46}H_{56}N_4O_{10}$ requires: 824.399; Found: 824.397), 765, 665, 135 (base peak); NMR ($CDCl_3$, δ): 8.06 (bs, 1H, NH), 7.54 (m, 1H, $C_{14}$'H), 7.20 (m, 3H, $C_{11}$'H-$C_{13}$'H), 6.68 (s, 1H, $C_{14}$H), 6.18 (s, 1H, $C_{17}$H), 5.91 (m, 1H, $C_7$H), 5.34 (d, 1H, $C_6$H), 4.70 (m, 1H, $C_2$'H), 3.82 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 3.60 (s, 3H, $OCH_3$), 2.75 (s, 3H, $NCH_3$), 2.12 (s, 3H, $OCOCH_3$), 0.87 (m, 6H, 2 x $CH_2\underline{CH_3}$); IR ($CHCl_3$): 3475, 1740, 1644 $cm^{-1}$.]

A similar oxidation reaction with leurosidine (VII, R = $CO_2CH_3$; $R_1$ = OH) provides the desired lactam derivative, 19'-oxoleurosidine (VIII, R = $CO_2CH_3$; $R_1$ = OH; $R_2$ = O) in much better yield (62%), [MS: m/e 824 ($M^+$, $C_{46}H_{56}N_4O_{10}$ requires: 824.399; Found: 824.395), 765, 282, 135 (base peak); NMR ($CDCl_3$, δ): 8.07 (bs, 1H, NH), 7.51 (m, 1H, $C_{14}$'H), 7.16 (m, 3H, $C_{11}$'H-$C_{13}$'H), 6.63 (s, 1H, $C_{14}$H), 6.16 (s, 1H, $C_{17}$H), 5.88 (m, 1H, $C_7$H), 5.32 (d, 1H, $C_6$H), 4.73 (m, 1H, $C_2$'H), 3.82 (s, 6H, 2 x $OCH_3$), 3.60 (s, 3H, $OCH_3$), 2.74 (s, 3H, $NCH_3$), 2.11 (s, 3H, $OCOCH_3$), 1.17 (t, 3H, $CH_2\underline{CH_3}$), 0.96 (t, 3H, $CH_2\underline{CH_3}$); IR ($CHCl_3$): 3477, 1738, 1644 $cm^{-1}$.]

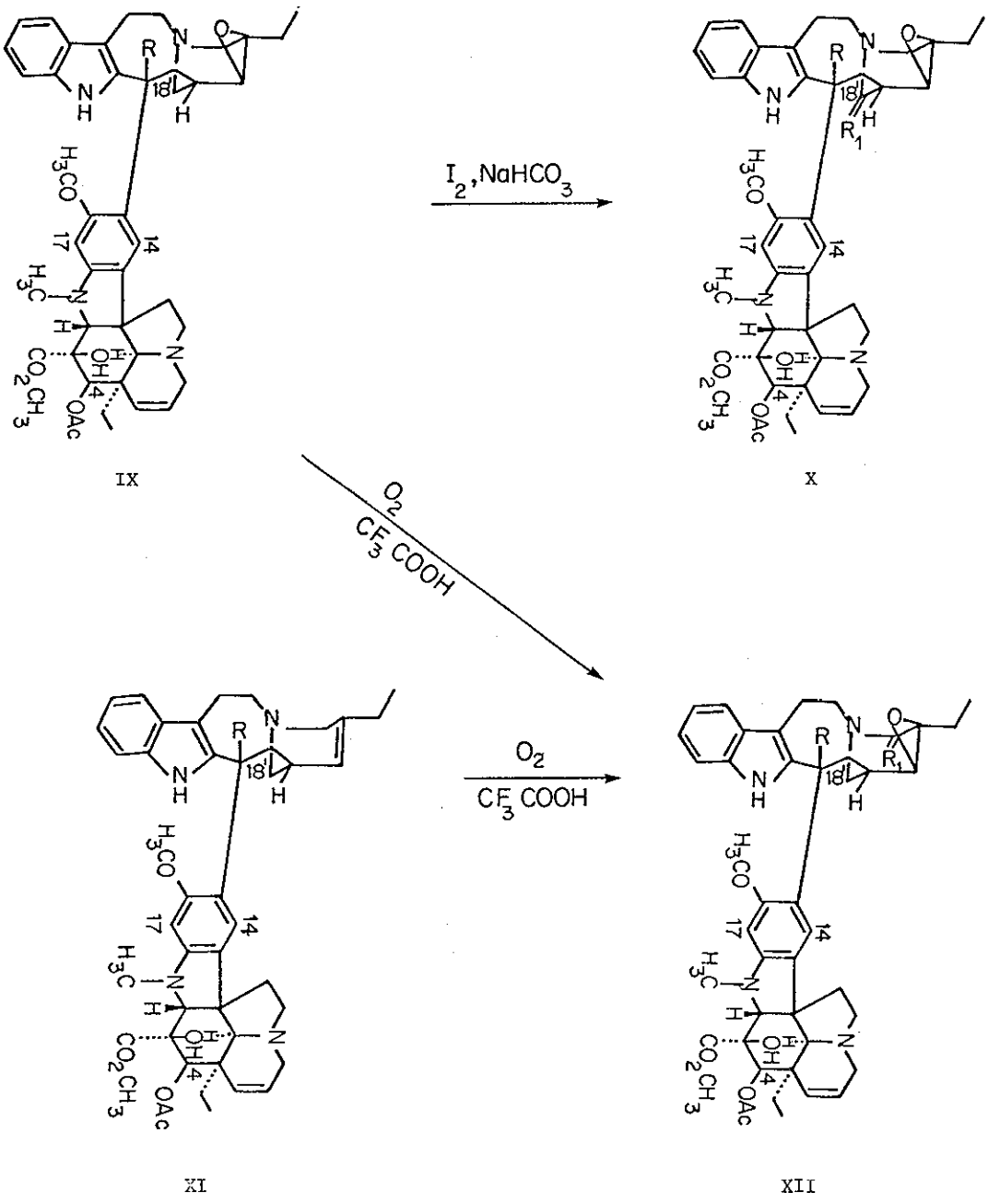
The alkaloid leurosine (IX, R = $CO_2CH_3$) can be converted to 19'-oxoleurosine (X, R = $CO_2CH_3$; $R_1$ = O) in 56% yield by means of the iodine oxidation procedure. [MS: m/e 822 ($M^+$, $C_{46}H_{54}N_4O_{10}$ requires: 822.384; Found: 822.381), 763, 282, 135 (base peak); NMR ($CDCl_3$, δ): 8.06 (bs, 1H, NH), 7.57 (m, 1H, $C_{14}$'H), 7.18 (m, 3H, $C_{11}$'H-$C_{13}$'H), 6.65 (s, 1H, $C_{14}$H), 6.19 (s, 1H, $C_{17}$H), 5.90 (dd, 1H, $C_7$H), 5.33 (m, 1H, $C_6$H), 4.76 (m, 1H, $C_2$'H), 3.85 (s, 3H, $OCH_3$), 3.83 (s, 3H, $OCH_3$), 3.63 (s, 3H, $OCH_3$), 2.76 (s, 3H, $NCH_3$), 2.12 (s, 3H, $OCOCH_3$), 1.01 (t, 3H, $CH_2\underline{CH_3}$), 0.84 (t, 3H, $CH_2\underline{CH_3}$); IR ($CHCl_3$): 3470, 1738, 1644 $cm^{-1}$.]

An interesting entry into another series of lactams is provided by the trifluoroacetic acid catalyzed oxygenation procedure developed earlier in the cleavamine series[2]. Under these conditions leurosine is converted to 5'-oxoleurosine (XII, R = $CO_2CH_3$; $R_1$ = 0; 15% yield), [MS: m/e 822 ($M^+$, $C_{46}H_{54}N_4O_{10}$ requires: 822.384; Found: 822.391), 662, 149, 135 (base peak); NMR ($CDCl_3$,δ ): 8.18 (bs, 1H, NH), 6.88 (s, 1H, $C_{14}H$), 5.99 (s, 1H, $C_{17}H$), 5.32 (d, 1H, $C_6H$), 3.80 (s, 6H, 2 x $OCH_3$), 3.70 (s, 3H, $OCH_3$), 2.68 (s, 3H, $NCH_3$), 2.10 (s, 3H, $OCOCH_3$), 0.70 (t, 3H, $CH_2\underline{CH_3}$), 0.40 (t, 3H, $CH_2\underline{CH_3}$); IR ($CHCl_3$): 3425, 1738, 1681, 1652 $cm^{-1}$.]

The lactam derivative, 5'-oxoleurosine (XII, R = $CO_2CH_3$; $R_1$ = 0) is also available more directly from 3',4'-dehydrovinblastine (XI, R = $CO_2CH_3$), by the oxygenation procedure. In this latter instance the yield is 34%.

It must be emphasized again that the β-orientation assigned to the epoxide functionality in leurosine, and the lactams X and XII (Figure 3) is <u>tentative</u> since, as already mentioned earlier[2], direct evidence relating to this aspect is lacking. Further chemical interrelationships in this series or an appropriate X-ray analysis must be performed to settle this question.

In conclusion, various novel lactam derivatives of the natural and synthetic bisindole series have been made available by appropriate control of oxidative procedures employing osmium tetroxide, iodine or oxygen as reactants. Various studies to determine the importance of such derivatives in this clinically interesting area are now underway.




IX X XI XII

Figure 3. The conversion of leurosine (IX, R = $CO_2CH_3$) and 3',4'-dehydro-vinblastine (XI, R = $CO_2CH_3$) to lactam derivatives X(R = $CO_2CH_3$; $R_1$ = O) and XII (R = $CO_2CH_3$; $R_1$ = O).

Acknowledgement: Financial aid from the National Research Council of Canada and from Contract NO1-CM-23223, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, is gratefully acknowledged.

References

1. For Part V, see J. P. Kutney, E. Jahngen and T.Okutani, Heterocycles, 1976, 4, 1267.

2. J. P. Kutney, J. Balsevich, G. H. Bokelman, T. Hibino, I. Itoh and A. H. Ratcliffe, ibid., 1976, 4, 997.

3. V. C. Agwada, Y. Morita, U. Renner, M. Hesse and H. Schmid, Helv. Chim. Acta, 1975, 58, 1001.

4. J. P. Kutney, G. H. Bokelman, M. Ichikawa, E. Jahngen, A. V. Joshua, P. Liao and B. R. Worth, Heterocycles, 1976, 4, in press.

Received, 28th June, 1976