The Intramolecular Reaction between a Diazoalkane Group and an Ester Group: the Second Example

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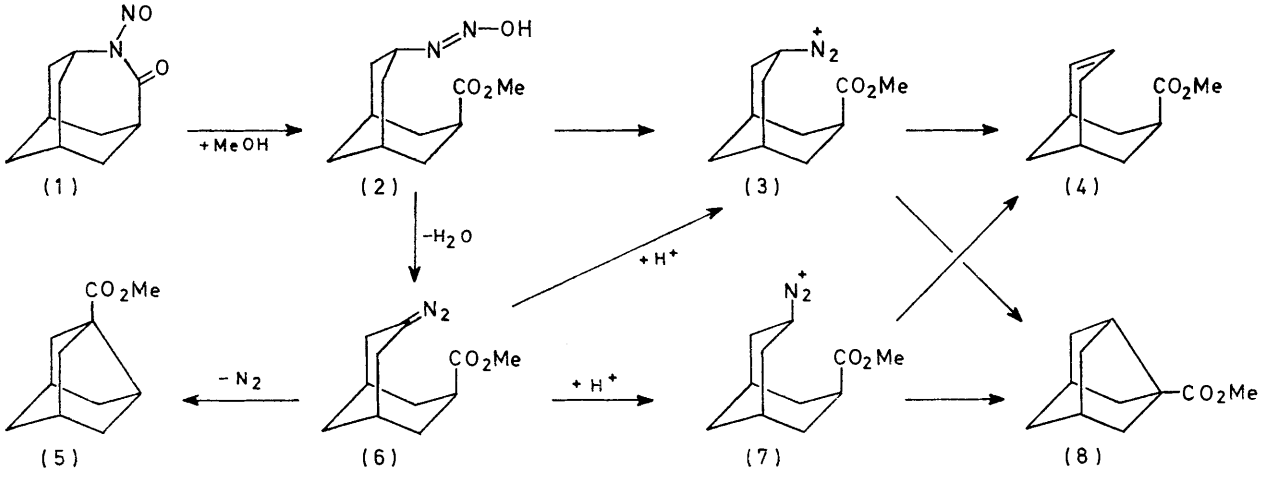
The isomeric nitroso-lactams, *cis*- and *trans*-9-hydroxy-4-nitroso-4-azahomoadamantan-5-ones (11) and (13), have been synthesised and treated with sodium methoxide. The major products were the unexceptionable solvolysis products, the methyl *cis*- and *trans*-9-hydroxybicyclo[3.3.1]non-7-ene-3-*endo*-carboxylates, which were actually isolated as their dihydro-derivatives (27) and (29). In the latter case, methyl 9-oxatricyclo[5.2.1.$0^{3,8}$]decane-5-*endo*-carboxylate (28) was also formed. The minor products, the methyl *trans*- and *cis*-9-hydroxynoradamantane-3-carboxylates (12) and (14), respectively, were the result of a diazoalkane ester insertion reaction. The configurations of the nitroso-lactams were determined directly from n.m.r. spectra, and the configurations of the products were determined from the trisdipivaloylmethanatoeuropium(III)-shifted n.m.r. spectra.

The low yield of these products is evidently a consequence of the low yield of the diazoalkane. The diazoalkane ester insertion reaction, however, is so favoured that all the diazoalkane formed is converted into the noradamantane, even in the absence of a protic solvent.

In the preceding paper [1] we described how the nitroso-lactam (1), on treatment with sodium methoxide, gave a mixture of the solvolysis product (4) (86%) and the product expected of a diazoalkane ester insertion reaction,[2] the noradamantanecarboxylic ester (5) (14%). However, the diazoalkane ester insertion reaction is not the only pathway by which this product could have been obtained. For example, the diazonium ions (3) and (7) may be intermediates in the formation of both products, the former product (4) being formed by β-elimination of a proton and the latter (8) by transannular elimination of a proton [structures (8) and (5) are identical]. There are several similar schemes which could be considered: the free carbonium ion may be invoked; even the possibility of inversion of configuration of the ester group before transannular deprotonation cannot be ruled out; and the intermediate enolate involved in that inversion would be likely [3] to yield a noradamantane.



Scheme

However, the simple Scheme illustrated makes it clear that the diazoalkane (6) may not be involved at all in the decomposition of the nitroso-lactam (1). We mentioned in the preceding paper the significant observation that this was one of the few nitroso-lactams we have studied which did not give rise even to a transitory colour during the reaction. We therefore had no evidence of the involvement of a diazoalkane. Further, we observed that the proportion of 'insertion' product (5) in the product mixture was not greatly affected by changing the solvent. Only a small increase (to 18%) in the proportion of (5) was observed when the solvent was changed from methanol to t-butyl alcohol but more significantly there was a further small increase (to 25%) when the decomposition took place in benzene. This was strikingly at odds with our earlier observation [2] with our camphor-derived diazoalkane, namely that the diazoalkane ester insertion reaction was essentially suppressed in benzene.

Our first experiment to test for the intermediacy of the diazoalkane was a reaction in methan[^{2}H]ol. If we had been observing the same partitioning of the diazoalkane (6) between solvolysis product (4) and insertion product (5) as we had been with our camphor-derived diazoalkane, then we should, in this case, have observed the incorporation of deuterium at least into the solvolysis product (4). In the event, neither product contained deuterium. This result, however, did not rule

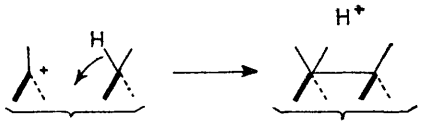
[1] E. H. Billett, I. Fleming, and S. W. Hanson, preceding paper.

[2] E. H. Billett and I. Fleming, *J.C.S. Perkin I*, 1973, 1658.

[3] R. M. Black and G. B. Gill, *Chem. Comm.*, 1970, 972.

out the intermediacy of the diazoalkane (6) in the insertion reaction, but it did rule out some of the possible pathways such as (6) ⟶ (7) ⟶ (4) and (6) ⟶ (7) ⟶ (8).

The possibility that the reaction involved a transannular deprotonation interested us. Only those reactions of the general type (9) ⟶ (10) when a three-

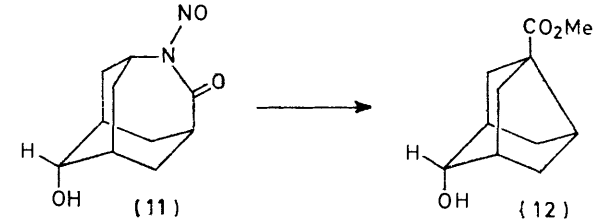


(9) (10)

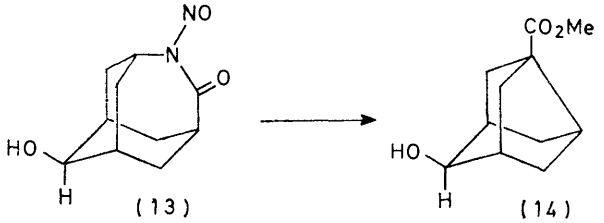
membered ring is being formed are well known: there are many examples of such reactions in terpene chemistry and elsewhere; the process is often called 1,3-elimination.[4,5] Of the formation of larger rings, however, there are few examples: for a cyclobutane there is the example of one of Winstein's cage compounds;[6] for a cyclopentane there is the observation[7] that 2,2-dimethylindane is one of the products of the diazotisation of *o*-neopentylaniline; and for a cyclohexane there is the observation[8] that *cis*- and *trans*-decalin are formed when cyclodecene is protonated.

In view of the paucity of examples of this type of reaction and in view of the possibility that we had another, in the reaction (3) ⟶ (8), we decided to do a more elaborate experiment to decide whether the formation of the 'insertion product' [(5) ≡ (8)] was the result of transannular elimination or of a diazoalkane ester reaction. The key to this experiment would be to provide a way of distinguishing between the products (5) and (8). The difference is that, in the former, the methoxycarbonyl group has been transferred from the carbon atom to which it was originally bonded to a different carbon atom, but in the latter, the methoxycarbonyl group has remained on the same carbon atom throughout. The former product (5) could most reasonably be accounted for by the diazoalkane ester insertion reaction, and the latter (8) by the route involving a transannular elimination of a proton. The compounds we made, the nitroso-lactams (11) and (13), were designed with a configurational label, the hydroxy-group, to distinguish the two sides of the molecule. This group was chosen, first because it was potentially a versatile one for the critical and unpredictable business of determining the configuration both of the starting materials, (11) and (13), and of the products, (12) and (14); secondly, because the synthesis of such a compound was likely to be straightforward (though not short); and thirdly, because, situated as it was, remote from the site of reaction, it was not likely to interfere seriously in any of the steps we contemplated. Our choice was vindicated by the ease with which the configurations were assigned, and by the clear answer we got: the methoxycarbonyl group had changed sides. Thus the nitroso-lactam (11) gave the ester (12) and the nitroso-lactam (13) gave the ester (14). The reaction was therefore of the diazoalkane ester insertion type.

Synthesis, Proof of Configuration, and Decomposition of the Nitroso-lactams (11) *and* (13).—Our starting material was the known diester (15).[9] Careful saponification gave the diacid (16), which was converted into its bis-t-butyl peroxyester (18) and a by-product, the anhydride (19). On heating the bis-peroxyester (18) in cumene, the monoacetal (20) of adamantane-2,6-dione (21) was



(11) (12)



(13) (14)

obtained. After this work was done, adamantane-2,6-dione (21) became more readily available,[10] and it may be simpler to prepare the monoacetal (20) from the diketone. In any event, we have, in the monoacetal (20), an adamantane derivative separately functionalised at each end. The oxime (22) of the monoacetal in polyphosphoric acid at 100° underwent a Beckmann rearrangement, with concomitant hydrolysis of the acetal, to give the keto-lactam (23). With sodium borohydride, this gave a mixture of two alcohols, (24) and (25), which were separated by fractional crystallisation. Nitrosation, under carefully controlled conditions, to prevent nitrosation of the hydroxy-groups, gave in turn the nitroso-lactams (11) and (13).

The lactams were not easily distinguished by their inconveniently high m.p.s, but the 'first-crop' lactam had an i.r. band at 960 cm^{-1}, and the 'second-crop'

[4] C. J. Collins, *Chem. Rev.*, 1969, **69**, 543.

[5] For some preparatively interesting examples, see W. G. Dauben, T. L. Westman, and F. T. Bond, Abstracts of 141st meeting of the American Chemical Society, Washington, 1962, 29-0; M. L. Poutsma, *J. Amer. Chem. Soc.*, 1965, **87**, 4293; R. H. Shapiro, J. H. Duncan, and J. C. Clopton, *ibid.*, 1967, **89**, 471; S. Ranganathan, A. Goel, and B. B. Singh, *Tetrahedron Letters*, 1968, 3299.

[6] P. Bruck, D. Thompson, and S. Winstein, *Chem. and Ind.*, 1960, 590, 405; see also R. Howe and S. Winstein, *J. Amer. Chem. Soc.*, 1965, **87**, 915; T. Fukunaga, *ibid.*, p. 917.

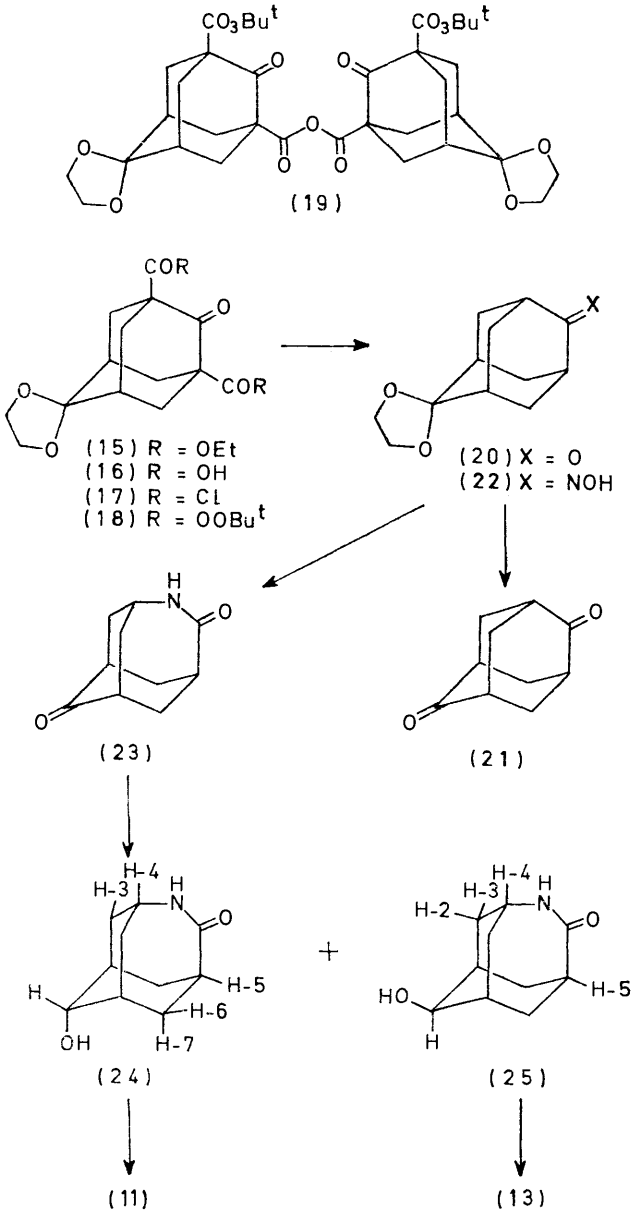
[7] P. Martinson, *Acta Chem. Scand.*, 1968, **22**, 1357.

[8] A. C. Cope, D. C. McLean, and N. A. Nelson, *J. Amer. Chem. Soc.*, 1955, **77**, 1628; V. Prelog, W. Küng, and T. Tomljenovic, *Helv. Chim. Acta*, 1962, **45**, 1352; G. A. Olah, D. P. Kelly, and R. G. Johanson, *J. Amer. Chem. Soc.*, 1970, **92**, 4137.

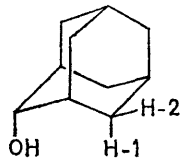
[9] H. Stetter and H. G. Thomas, *Chem. Ber.*, 1968, **101**, 1115.

[10] H. W. Geluk and J. L. M. A. Schlatmann, *Rec. Trav. chim.*, 1971, **90**, 516.

lactam had a similar band at 970 cm^{-1}, so we shall, for the purposes of this discussion, call them the 960-lactam and the 970-lactam. We were able to assign the configurations (24) and (25) respectively to these lactams entirely on the basis of their n.m.r. spectra and those of the corresponding nitroso-lactams (11) and (13). We were able to do this because of the following useful phenomenon. It is well known that a downfield shift occurs in the position of resonance of a crowded hydrogen nucleus. It is less well known that, if that hydrogen is one of a geminal pair, the resonance of the uncrowded geminal hydrogen nucleus often suffers an upfield shift.



Thus in adamantan-2-ol (26), the H-1 signal is 0·31 p.p.m. downfield from the corresponding resonance in adamantane, and the H-2 signal is 0·22 p.p.m. upfield.[11] Because the lactams (24) and (25) had suffered only a small change in the geometry from that of an adamantane, the same phenomenon was observed with them. It was clearer in the 960-lactam (24), where the



(26)

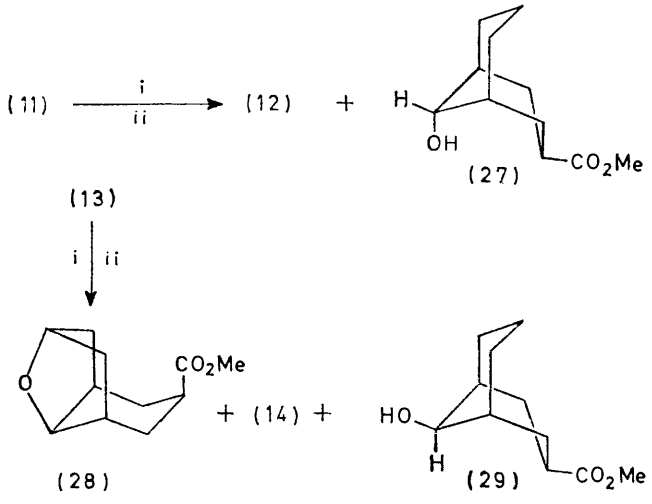
signals of H-4, H-5, H-6, and H-7 could be seen clearly. The signal from H-7 was an eight-line pattern (J 14, 6, and 4 Hz) at τ 7·59, and the signal from H-6 was a doublet (J 14 Hz) at τ 8·24. These two signals had been shifted to just below and just above the adamantane envelope between τ 7·75 and 8·00. Double irradiation established that the 14 Hz coupling was indeed between these two nuclei, and it also established that the 6 Hz coupling was to H-5, which gave rise to a triplet (J 6 Hz) at τ 7·32. Since this latter signal could clearly be distinguished from that of H-4 (a multiplet at τ 6·62), it was now obvious that in the 960-lactam the hydroxy-group, which had caused the shifts of the signals of H-6 and H-7, was on the same ' side ' of the molecule as H-5 and hence as the carbonyl group. This assignment was supported by the n.m.r. spectrum of the nitroso-derivative (11). One of the effects of a nitroso-group is to cause the signal of the hydrogens (H-3) (*cis* to the N–NO) to move upfield by about 0·3 p.p.m.; this effect was first observed in the parent nitroso-lactam (1).[1] In the case of the 960-lactam, the result of nitrosation was a second signal in the region upfield of the envelope: the nitroso-derivative of the 960-lactam had two doublets in this region—one at τ 8·22 which was probably the signal from H-6, unaffected by the nitroso-group, and the other at τ 8·42, which was probably the signal from H-3. Incidentally, the signals from H-4 and H-5 were shifted well downfield by nitrosation, the former more than the latter, as expected. This evidence of discrete shielding and deshielding regions for the NO group shows that the rotation of the N–N bond in nitroso-lactams is probably slow on the n.m.r. time scale.

The spectrum of the 970-lactam (25) was not so clear-cut: the upfield doublet of H-3 was evident at τ 8·32 (J 13 Hz), well clear of the envelope between τ 7·8 and 8·1; but the signals of H-2, probably at about τ 7·57 were not clearly enough separated from those of H-5 and the envelope for first-order analysis. But in this case, nitrosation was unambiguous: the signal from H-3 was shifted even further upfield of the envelope, to τ 8·83, and no other signal appeared in this region. Thus, with the hydroxy-group and the nitroso-group influencing the same hydrogen atom, these two groups must be on the same ' side ' of the molecule, as they are in the nitroso-lactam (13). As it happens these assignments were

[11] F. W. van Deursen and P. K. Korver, *Tetrahedron Letters*, 1967, 3923; see also S. Winstein, P. Carter, F. A. L. Anet, and A. J. R. Bourn, *J. Amer. Chem. Soc.*, 1965, **87**, 5247.

further confirmed by the results of treating the nitroso-lactams with sodium methoxide.

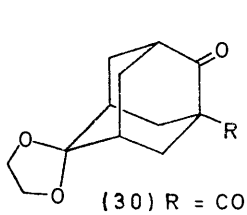
The decomposition of the nitroso-lactam (11) was straightforward: it gave with sodium methoxide the expected two products, a noradamantane ester (25%) and a bicyclo[3.3.1]nonene ester (75%). These were more conveniently separated by g.l.c. when the latter had been hydrogenated, so the products actually isolated were the noradamantane ester (12) and the bicyclo[3.3.1]nonane (27). The other nitroso-lactam (13) however, gave three products, although this was only evident on the g.l.c. trace when, as before, the first-formed product mixture had been hydrogenated. The



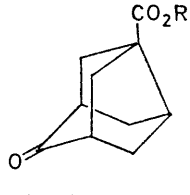
Reagents: i, NaOMe–$[CH_2]_4O$; ii, H_2–Pd

major product (67%) was assigned the structure (28), and the other products were the noradamantane ester (14) (7%) and the bicyclo[3.3.1]nonane (29) (26%). Although the ratio of (14) to (29) was about that expected, the intervention of the hydroxy-group had made the yield of (14) inconveniently low. It had, however, confirmed our assignment of configuration, as did also the n.m.r. spectra of the bicyclo[3.3.1]nonanes (27) and (29), which we have reported on separately.[12] We could limit this pathway to a minor role by silylating the hydroxy-group of the nitroso-lactam (13) before the treatment with sodium methoxide. The products were then the corresponding silyl ethers, which were hydrolysed, and the mixture was hydrogenated as before. The three products (28), (14), and (29) were then found in 13, 20, and 67% yields, respectively, and were separated by preparative g.l.c.

That the noradamantane esters (12) and (14) had the expected gross structures was confirmed by oxidation of a mixture of the esters (12) and (14) to the keto-ester (33), which was hydrolysed to the keto-acid (32). The same acid was independently synthesised, from our by-product in the synthesis, the anhydride (19). When this anhydride was heated in cumene it gave the decarboxylated anhydride, which was hydrolysed to the acid (30). Use of the modified Hunsdiecker reaction with this acid gave the bromo-ketone (31), which, on treatment with potassium hydroxide, gave the acetal



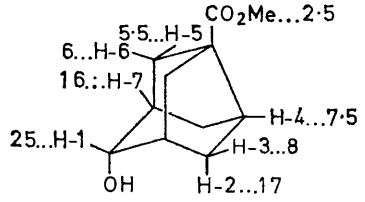
(30) R = CO_2H
(31) R = Br



(32) R = H
(33) R = Me

of the keto-acid (32). Hydrolysis of the acetal group gave the keto-acid itself (32), identical with the previous sample. Except for the presence of the acetal group in the sequence from the acid (30), this route is the same as that of Stetter and his co-workers [13] for the synthesis of the same acid (32).

The configuration of the two alcohols (12) and (14) was readily established by use of the trisdipivaloylmethanatoeuropium(III) shift reagent.[14] With this reagent it was possible to identify the signals from each hydrogen atom, both from the initial chemical shift in deuteriochloroform and pentadeuteriopyridine, and by double irradiation experiments. The gradient of a plot of shift against molar equivalents of $Eu(dpm)_3$ was then measured for each signal. This gradient is a measure of the distance of the hydrogen atom from the europium nucleus, which, at the concentrations used (up to 0·3 mol. equiv.), is forming a complex almost exclusively on the hydroxy-group. The gradients are shown on the structures (34) and (35), where it should be



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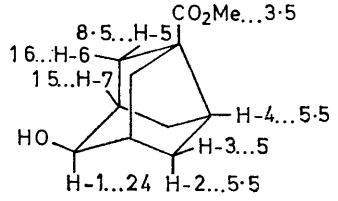

(35)

noted in particular that the most readily identified hydrogen atoms, H-2, H-3, and H-4 in the hydroxy-ester [(34) ≡ (12)] give rise to larger slopes than the hydrogen atoms, H-2, H-3, and H-4 in the other hydroxy-ester

[12] I. Fleming, S. W. Hanson, and J. K. M. Sanders, *Tetrahedron Letters*, 1971, 3733.

[13] H. Stetter, H. G. Thomas, and K. Meyer, *Chem. Ber.*, 1970, **103**, 863.

[14] J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, 1971, **93**, 641, and references cited therein.

[(35) ≡ (14)]. The slopes of all the other signals are also in accord with this assignment.

Mechanism of the Reaction.—We have shown that that portion of the reaction giving the noradamantanes must involve a transfer of the methoxycarbonyl group from one carbon atom to another. We are still left with the anomalous observations which caused us to investigate this point in such detail. Why did the change of solvent actually increase the proportion of diazoalkane insertion product, the ester (5) as we now know it to be, relative to the solvolysis product (4), especially when, in our other example of the reaction, the use of benzene had caused virtually the complete suppression of the diazoalkane ester insertion reaction? The answer must be that, whereas in that earlier reaction we had been getting a high yield of the diazoalkane, and were examining the partitioning of that intermediate between insertion and solvolysis reactions, we were now seeing an earlier partitioning, namely that of the diazotic acid (2) between solvolysis [perhaps by way of the diazonium ion (3) or perhaps directly] to the olefin (4) and dehydration to the diazoalkane (6). It follows that all of the reaction that gets as far as the diazoalkane (6) is going on to the insertion product (5) regardless of solvent. Furthermore, we have support for this contention: there is no deuterium in the solvolysis product (4) when the reaction is carried out in methan[^{2}H]ol.

Thus we have shown that the adamantane case is indeed an example of a diazoalkane ester insertion reaction. Although it is only the second example of our reaction, the diazoalkane and ester groups of the intermediate (6) are evidently so well arranged that their reaction together does not even need the assistance of an alcoholic solvent.

EXPERIMENTAL

6,6-Ethylenedioxy-2-oxoadamantane-1,3-dicarboxylic Acid (16).—The ethylenedioxy-diester (15) [9] (60 g) was dissolved in ethanol (600 ml) and added to a solution of sodium carbonate (60 g) in water (600 ml). After heating under reflux for 6 h, the mixture was cooled, and water (200 ml) and ether (400 ml) were added. The ether layer was separated and discarded. The aqueous layer was acidified with dilute hydrochloric acid and extracted with ether (2 × 800 ml). The two ether layers were combined, dried ($MgSO_4$), and evaporated. The *diacid* was recrystallised from ethyl acetate (4 l) and dried *in vacuo* at 120° for 6 h (to remove solvent of crystallisation) to give prisms (40·5 g, 80%), m.p. 294·5—297·5° (Found: C, 56·6; H, 5·5. $C_{14}H_{16}O_7$ requires C, 56·75; H, 5·45%), $\nu_{max.}$ (mull) 3390, 3200—2500, 1760, and 1720 cm^{-1}, τ [$(CD_3)_2SO$] 6·06 (4H, s, CH_2·O), 7·74 (8H, d, CH_2), and 7·98br (2H, s, CH).

6,6-Ethylenedioxy-2-oxoadamantane-1,3-dicarbonyl Dichloride (17).—The diacid (17·5 g), thionyl chloride (37 ml), and dioxan (37 ml) were heated under reflux for 2 h. The dioxan and thionyl chloride were distilled off *in vacuo* to give the *acid chloride* (19·7 g, 100%), prisms, m.p. 103—105° (Found: C, 50·55; H, 4·3. $C_{14}H_{14}Cl_2O_5$ requires C, 50·45; H, 4·25%), $\nu_{max.}$ (mull) 1770 and 1715 cm^{-1}, τ (C_6D_6) 6·75 (4H, s, CH_2·O), 7·95 (8H, d, CH_2), and 8·63br (2H, s, CH).

Di-t-butyl 6,6-Ethylenedioxy-2-oxoadamantane-1,3-bisperoxycarboxylate (18).—The diacid dichloride (53·6 g) and t-butyl hydroperoxide (150 ml) in benzene (2 l) were stirred while pyridine (250 ml) was slowly added, with the temperature kept below 10°. The mixture was stirred at 0° for 1 h, water (500 ml) was added, and the benzene layer was separated. The aqueous layer was extracted with benzene (500 ml). The combined organic layers were extracted with dilute sulphuric acid (2 × 400 ml), water (400 ml), aqueous sodium carbonate (400 ml; 10%), and water (2 × 400 ml), dried ($MgSO_4$), and evaporated *in vacuo* at 30°. The oily residue was dissolved in ethyl acetate (500 ml) at room temperature and light petroleum (b.p. 40—60°) (2 l) was slowly added with stirring. *Bis-(6,6-ethylenedioxy-2-oxo-3-t-butylperoxycarbonyladamantane-1-carboxylic) anhydride* (19) precipitated and was filtered off, washed with light petroleum (b.p. 40—60°; 200 ml) and dried *in vacuo* at room temperature (9 g, 16%), m.p. 141—143° (from cyclohexane–benzene) (Found: C, 59·8; H, 6·45. $C_{36}H_{46}O_{15}$ requires C, 60·15; H, 6·45%), $\nu_{max.}$ 1815, 1770, and 1720 cm^{-1}, τ (C_6D_6) 6·66 (8H, s, CH_2·O), 7·72 (16H, m, CH_2), 8·46 (4H, m, CH), and 8·82 (18H, s, CH_3). The filtrates were combined, dried ($MgSO_4$), and evaporated *in vacuo* at room temperature to give the *bisperoxyester* (18) (51·5 g, 73%), m.p. 119—121° (from cyclohexane) (Found: C, 60·15; H, 7·35. $C_{22}H_{32}O_9$ requires C, 60·0; H, 7·3%), $\nu_{max.}$ 1780 and 1715 cm^{-1}, τ (C_6D_6) 6·70 (4H, s, CH_2·O), 7·66br (4H, d, HCH), 7·84br (4H, d, HCH), 8·50 (2H, m, CH), and 8·81 (18H, s, CH_3).

6,6-Ethylenedioxyadamantan-2-one (20).—The bisperoxyester (18) (12·75 g) was dissolved in cumene (80 ml) and heated under reflux for 1 h. This solution was used directly in the next stage. In an earlier run, the cumene was evaporated *in vacuo* and, by removing the 2,3-dimethyl-2,3-diphenylbutane and other impurities on a silica column, a sample of the *ethylenedioxy-ketone* (20) was obtained, m.p. 97—99° (sublimation) (Found: C, 69·25; H, 7·6. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·75%), $\nu_{max.}$ (mull) 1720 cm^{-1}, τ (C_6D_6) 6·58 (4H, s, CH_2·O), 7·63br (2H, s, CH–C=O), 7·86br (4H, d, methylene protons 1,3-diaxial to the O–CH_2–), 8·40br (4H, d, methylene protons 1-axial, 3-equatorial to the O–CH_2–), and 8·45br (2H, s, CH·CO_2), *m/e* 208 (M^+, 57%), 180 (M − CO, m^* 156, 17%), and 99 ($O{-}CH_2{\cdot}CH_2{-}\overset{+}{O}{=}C{-}CH{=}CH_2$, m^* 47·2, 100%).

Adamantane-2,6-dione (21).—The ethylenedioxy-ketone (20) (20 mg) was added to ethanol (2 ml), water (0·5 ml), and concentrated hydrochloric acid (1 ml). The mixture was stirred at room temperature for 24 h and extracted with ether (3 × 2 ml). The combined ether layers were extracted with saturated sodium hydrogen carbonate solution (2 ml), dried ($MgSO_4$), and evaporated *in vacuo* to give the diketone (11 mg, 70%), prisms, m.p. 323—325° (sublimation) (lit.,[15] 313—314·5°; lit.,[16] 323—323·4°; lit.,[10] 308—312°), $\nu_{max.}$ (mull) 1715 cm^{-1}, τ (CCl_4) 7·42 (4H, m, CH) and 7·75br (8H, s, CH_2).

6,6-Ethylenedioxyadamantan-2-one Oxime (22).—The cumene solution of ethylenedioxy-ketone (20) (80 ml of solution obtained from 12·75 g of the bisperoxy-ester) was added to pyridine (240 ml). Hydroxylamine hydrochloride (3 g) was added and the mixture was stirred at room

[15] O. W. Webster and L. H. Sommer, *J. Org. Chem.*, 1964, **29**, 3103.

[16] J. Janku and S. Landa, *Coll. Czech. Chem. Comm.*, 1970, **35**, 375.

temperature for 12 h. The pyridine was removed *in vacuo* at 40° and ethanol (80 ml), water (80 ml), and light petroleum (b.p. 60—80°; 160 ml) were added. The light petroleum layer was separated and extracted with aqueous ethanol (160 ml; 50% v/v). The combined aqueous ethanol layers were extracted with light petroleum (b.p. 60—80°; 80 ml) and after addition of water (160 ml) were then extracted with ether (5 × 160 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated under vacuum. The residue was sublimed (150—180° at 2 × 10^{-3} Torr) to give the *oxime* (4·5 g, 70%), prisms, m.p. 239—243° (from cyclohexane–benzene) (Found: C, 64·45; H, 7·55; N, 6·45. $C_{12}H_{17}NO_3$ requires C, 64·55; H, 7·65; N, 6·25%), $\nu_{max.}$ 3200, 3100, and 1670 cm^{-1}, τ ($CDCl_3$) 6·07 (4H, s, CH_2·O), 6·5br (1H, s, *syn*-C*H*C=NOH), 7·52br (1H, s, *anti*-C*H*C=NOH), 7·83br (4H, d, methylene protons 1,3-diaxial to O–CH_2–), 8·16br (2H, s, C*H*·CO_2), and 8·23br (4H, d, methylene protons 1-axial, 3-equatorial to the O–CH_2–).

4-Azahomoadamantane-5,9-dione (23).—The oxime (22) (4·5 g) was finely powdered and added to polyphosphoric acid (40 g) held at 100—105°. The mixture was stirred for 15 min at 100—105° and ice and water (150 g) were added. After extraction with ether (40 ml) the mixture was made slightly alkaline (pH 8·9) with sodium carbonate and extracted with dichloromethane (8 × 60 ml). The combined organic layers were dried ($MgSO_4$) and the dichloromethane was removed *in vacuo*. The residue was recrystallised from benzene (5 ml) to give the *keto-lactam* (2·0 g, 55%), prisms, m.p. 356—359° (from cyclohexane–benzene) (Found: C, 67·0; H, 7·2; N, 8·05. $C_{10}H_{13}NO_2$ requires C, 67·0; H, 7·3; N, 7·8%), $\nu_{max.}$ (mull) 3280, 3200, 3060, 1730, and 1660 cm^{-1}, τ ($CDCl_3$) 2·0br (1H, s, NH), 6·8br (1H, quintet, C*H*·NH), 7·38 (3H, m, CH–C=O), and 7·5—8·0 (8H, m).

cis- *and* trans-9-*Hydroxy*-4-*azahomoadamantan*-5-*one* [(24) *and* (25)].—The keto-lactam (23) (1 g) was dissolved in methanol (25 ml), a solution of sodium borohydride (1 g) in methanol (25 ml) was slowly added, and the mixture was stirred at room temperature for 30 min. After addition of chloroform (250 ml) and slow addition of silica (100 g; 60—120 mesh), the mixture was stirred for 5 min and filtered. The residue was washed with a mixture of methanol (100 ml) and chloroform (400 ml). The combined filtrates were dried ($MgSO_4$) and evaporated. The residue was recrystallised from chloroform–benzene to give a mixture of the *cis*- and *trans*-hydroxy-lactams (0·98 g, 97%). These were separated by several fractional crystallisations from chloroform and from chloroform–benzene to give the 960-*lactam* (24), prisms, m.p. 367—370° (from chloroform) (Found: C, 66·2; H, 8·1; N, 7·65. $C_{10}H_{15}NO_2$ requires C, 66·25; H, 8·35; N, 7·75%), $\nu_{max.}$ (mull) 3280 and 1640 cm^{-1}, $\nu_{max.}$ (CH_2Cl_2) 3400, 1645, and 960s cm^{-1}, τ (CD_3·OD) 6·02 (1H, t, C*H*·OH), 6·62 (1H, m, CH·N), 7·32 (1H, t, *J* 6 Hz, C*H*–C=O), 7·59 (2H, octet, *J* 14, 6, and 4 Hz, methylene protons 1,3-diaxial to the OH), 7·75—8·0 (6H, m), and 8·24 (2H, d, *J* 14 Hz, methylene protons 1-axial, 3-equatorial to the OH); and the 970-*lactam* (25), prisms, m.p. 379—384° (from chloroform–benzene) (Found: C, 66·05; H, 8·1; N, 7·95%), $\nu_{max.}$ (mull) 3390, 3200, and 1650 cm^{-1}, $\nu_{max.}$ (CH_2Cl_2) 3400, 1650, and 970s cm^{-1}, τ (CD_3·OD) 6·06 (1H, t, C*H*·OH), 6·64 (1H, m, CH·N), 7·37 (1H, m, CH–C=O), 7·57 (2H, m, methylene protons 1,3-diaxial to the OH), 7·8—8·1 (6H, m), and 8·32 (2H, d, *J* 13 Hz, methylene protons 1-axial, 3-equatorial to the OH).

cis-9-*Hydroxy*-4-*nitroso*-4-*azahomoadamantan*-5-*one* (11).—A solution of nitrogen tetroxide (0·6 ml of nitrogen tetroxide in 9·4 ml of glacial acetic acid at 5°) was added to the *cis*-hydroxy-lactam (24) (200 mg) and the mixture was stirred for 30 min, the temperature being allowed to rise to room temperature. Ice and water (30 g) were added, the mixture was extracted with chloroform (3 × 30 ml), and the chloroform layers were extracted with saturated sodium hydrogen carbonate solution (3 × 20 ml) and water (1 × 20 ml), and dried ($MgSO_4$). The chloroform was removed *in vacuo* to give the *nitroso-lactam*, which was not purified further owing to its instability (232 mg, '100%') (Found: N, 13·05. $C_{10}H_{14}N_2O_3$ requires N, 13·35%), $\nu_{max.}$ 1720 and 1520 cm^{-1}, $\lambda_{max.}$ (EtOH) 256 nm (ε 5700), τ ($CDCl_3$) 4·9 (1H, m, CH·N), 6·1 (1H, m, C*H*·OH), 6·82 (1H, m, CH–C=O), 7·3—8·1 (6H, m), 8·22br (2H, d, methylene protons 1-axial, 3-equatorial to the OH group), and 8·42br (2H, d, methylene protons *cis*-vicinal to the –NNO group).

Decomposition of cis-9-*Hydroxy*-4-*nitroso*-4-*azahomoadamantan*-5-*one* (11).—A solution of sodium methoxide (35 mg) in tetrahydrofuran (4·2 ml) and methanol (0·8 ml) at 0° was added with stirring to a solution of the nitroso-lactam (100 mg) in tetrahydrofuran (5 ml) at 0°. The mixture was stirred for a further 10 min at 0°, neutralised with dilute hydrochloric acid, and extracted with chloroform (3 × 20 ml). The extract was dried ($MgSO_4$) and evaporated to a small volume. [This residue, on analysis by g.l.c. on a 10% poly(diethylene glycol succinate) column (6 ft), at 150°, gave two peaks with retention times of 4·4 and 5·5 min.] The residue was dissolved in methanol (5 ml) and hydrogenated over 5% Pd–C (20 mg). The mixture was filtered and evaporated. The residue on analysis by g.l.c. (conditions as above) gave two peaks with retention times of 4·4 (25% of the total product) and 6·3 min (75%). The product which corresponded to the first peak, *methyl* trans-9-*hydroxynoradamantane*-3-*carboxylate* (12) was collected by preparative g.l.c., m.p. 58—62° (sublimation) (Found: C, 67·6; H, 7·9. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%), $\nu_{max.}$ (mull) 3480 and 1705 cm^{-1}, τ (CD_3·OD) 6·25 (1H, m, C*H*·OH), 6·38 (3H, s, CH_3), 7·5 (1H, t, CH), and 7·79 (2H, m, CH).

The product which corresponded to the second peak, *methyl* cis-9-*hydroxybicyclo*[3.3.1]*nonane*-endo-3-*carboxylate* (27) was collected by preparative g.l.c., m.p. 68—70° (sublimation) (Found: C, 66·95; H, 8·85. $C_{11}H_{18}O_3$ requires C, 66·65; H, 9·15%), $\nu_{max.}$ (mull) 3300 and 1725 cm^{-1}, τ (CCl_4) 6·41 (3H, s, CH_3), 6·51 (1H, m, C*H*·OH), and 6·85 (1H, m, C*H*·CO_2·CH_3).

trans-9-*Hydroxy*-4-*nitroso*-4-*azahomadamantan*-5-*one* (13).—The trans-*nitroso-lactam* (13) was prepared from the *trans*-hydroxy-lactam (25) by the same procedure that was used to prepare the *cis*-nitroso-lactam (11) (232 mg, '100%') (Found: N, 14·8. $C_{10}H_{14}N_2O_3$ requires N, 13·35%), $\nu_{max.}$ (mull) 1720 and 1515 cm^{-1}, $\lambda_{max.}$ (EtOH) 255 nm (ε 5800), τ ($CDCl_3$) 4·96br (1H, t, CH·N), 6·12 (1H, m, C*H*·OH), 6·9 (1H, m, CH–C=O), 7·4—8·1 (8H, m), and 8·83 (2H, d, methylene protons 1-axial, 3-equatorial to the OH group).

Decomposition of trans-9-*Hydroxy*-4-*nitroso*-4-*azahomoadamantan*-5-*one* (13).—This was carried out as described for the isomer (11). The product, on analysis by g.l.c. on the same column as used before, gave two peaks with retention times of 2·4 and 4·7 min. After hydrogenation, the product gave three peaks with retention times of 2·4 (67% of the total product), 4·7 (7%), and 6·3 min (26%). The product which corresponded to the first peak, *methyl*

9-*oxatricyclo*[5.2.1.$0^{3,8}$]*decane*-endo-5-*carboxylate* (28) was collected by preparative g.l.c., m.p. 51—52° (sublimation) (Found: C, 67·35; H, 8·1. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%), $\nu_{max.}$ (mull) 1730 cm^{-1}, τ (CCl_4) 5·8 (1H, t, CH–C–O), 6·14 (1H, t, CH–C–O), and 6·41 (3H, s, CH_3).

4-*Nitroso*-trans-9-(*trimethylsilyloxy*)-4-*azahomoadamantan*-5-*one*.—The nitroso-lactam (13) (200 mg) was dissolved in pyridine (4 ml) and a silylating solution (0·6 ml of hexamethyldisilazane and 0·3 ml of trimethylchlorosilane in 3·1 ml of pyridine) was added. The mixture was stirred at room temperature for 5 min, and evaporated to dryness *in vacuo* at room temperature. The residue was taken up in dichloromethane (40 ml); the solution was filtered and evaporated to give the *trimethylsilyloxy-nitroso-lactam*, which was not purified further owing to its instability (268 mg, ' 100% ') (Found: N, 9·2. $C_{13}H_{22}N_2O_3Si$ requires N, 9·9%), $\nu_{max.}$ 1720 and 1520 cm^{-1}, $\lambda_{max.}$ (EtOH) 256 nm (ε 5700), τ ($CDCl_3$) 4·82 (1H, m, CH·N), 6·1 (1H, m, CH·O), 6·76br (1H, t, CH–C=O), 7·51 (2H, dt, methylene protons 1,3-diaxial to the SiO), 7·80br (4H, s, other methylene protons), 7·4br (2H, s, other methine protons), and 8·73br (2H, d, methylene protons 1-axial, 3-equatorial to the SiO).

Decomposition of 4-*Nitroso*-trans-9-(*trimethylsilyloxy*)-4-*azahomoadamantan*-5-*one*.—This was carried out as described above. When the reaction was over, water (5 ml) was added to the mixture and the whole was heated under reflux for 15 min. The mixture was worked up as described before. The residue (after hydrogenation) on analysis by g.l.c. gave three peaks with retention times of 2·4 (13% of the total product), 4·7 (20%), and 6·3 min (67%). The product which corresponded to the second peak, *methyl* cis-9-*hydroxynoradamantane*-3-*carboxylate* (14), was collected by preparative g.l.c., m.p. 54—58° (sublimation) (Found: C, 67·3; H, 8·2%), $\nu_{max.}$ (mull) 3280 and 1720 cm^{-1}, τ ($CDCl_3$) 6·25 (1H, m, C*H*·OH), 6·36 (3H, s, CH_3), 7·43 (1H, t, CH), and 7·76 (2H, m, CH).

The product which corresponded to the third peak, *methyl* trans-9-*hydroxybicyclo*[3.3.1]*nonane*-endo-3-*carboxylate* (29), was collected by preparative g.l.c., m.p. 92—94° (sublimation) (Found: C, 66·55; H, 9·0%), $\nu_{max.}$ (mull) 3250 and 1725 cm^{-1}, τ (CCl_4) 6·17 (1H, m, C*H*·OH), 6·40 (3H, s, CH_3), and 7·40 (1H, m, C*H*·CO_2·CH_3).

9-*Oxonoradamantane*-3-*carboxylic Acid* (32).—A mixture of the *cis*-noradamantane ester (14) (5 mg) and the *trans*-noradamantane ester (12) (5 mg) was added to benzene (0·2 ml), and an acidic solution of sodium dichromate [0·2 ml; made up from sodium dichromate (0·7 g), glacial acetic acid (0·53 ml), sulphuric acid (0·95 ml), and water (3·1 ml)] was added slowly with stirring. After stirring for a further 30 min, water (2 ml) and benzene (2 ml) were added and the aqueous layer was extracted with benzene (2 ml). The combined benzene layers were washed with a saturated sodium hydrogen carbonate solution (2 ml), dried ($MgSO_4$), and evaporated to give the keto-ester (33), which was saponified in aqueous methanol to give the acid (32) (8 mg, 76%), m.p. 132—134° (from benzene–cyclohexane) (lit.,[13] 133—137°), $\nu_{max.}$ (mull) 1720 cm^{-1}, τ (CCl_4) 6·99 (1H, t, C*H*–C–CO_2H) and 7·29br (2H, s, other bridgehead protons).

6,6-*Ethylenedioxy*-2-*oxoadamantane*-1-*carboxylic Acid* (30).—A solution of the anhydride (19) (4 g) in cumene (80 ml) was heated under reflux for 1 h and the solvent was removed under vacuum. The residual mixture of anhydride and bicumyl was added to aqueous sodium carbonate (40 ml; 10% w/v), ethanol (40 ml), and benzene (40 ml). The mixture was heated under reflux for 30 min. The aqueous layer was extracted with benzene (40 ml), acidified with dilute hydrochloric acid, and extracted with dichloromethane (4 × 40 ml). The latter extract was dried ($MgSO_4$) and evaporated. The residue was taken up in benzene (150 ml); the solution was heated until boiling, cooled to room temperature, and filtered. The insoluble material had spectroscopic data and m.p. identical with those of the diacid (16) (290 mg, 8%). The benzene was evaporated off leaving the *acid* (30) (2·1 g, 75%), m.p. 214—217° (from benzene–cyclohexane) (Found: C, 61·9; H, 6·25. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4%), $\nu_{max.}$ (mull) 3200—2500, 1715, and 1700 cm^{-1}, τ (CD_3·OD) 6·08 (4H, s, CH_2·O) and 7·5—8·3 (11H, m).

1-*Bromo*-6,6-*ethylenedioxyadamantan*-2-*one* (31).—The acid (30) (2·9 g), red mercuric oxide (2 g), and 1,2-dibromoethane (40 ml) were heated under reflux while a solution of bromine (0·65 ml) in 1,2-dibromoethane (6 ml) was slowly added. The mixture was heated under reflux for a further 2 h, cooled, and filtered. The residue was washed with 1,2-dibromoethane (15 ml). The combined filtrates were extracted with sodium hydroxide (15 ml; 5% w/v aqueous solution) and water (15 ml), dried ($MgSO_4$), and evaporated to give the *bromo-ketone* (31) (1·75 g, 53%), m.p. 136—139° (sublimation) (Found: C, 50·4; H, 5·05; Br, 28·2. $C_{12}H_{15}BrO_3$ requires C, 50·2; H, 5·25; Br, 27·85%), $\nu_{max.}$ (mull) 1730 cm^{-1}, τ ($CDCl_3$) 5·98 (4H, s, CH_2·O), 7·06 (2H, d, *H*CH·CBr), 7·13 (1H, s, C*H*–C=O), 7·64 (2H, d, HC*H*·CBr), 7·66br (2H, d, *H*CH–CH–C=O), 8·0br (2H, s, CH·CO_2), and 8·06br (2H, d, HC*H*–CH–C=O).

9,9-*Ethylenedioxynoradamantane*-3-*carboxylic Acid*.—The bromo-ketone (1·6 g) was added to a solution of potassium hydroxide (1·6 g) in water (16 ml) and ethanol (16 ml). The mixture was heated under reflux for 5 h, cooled, and extracted with chloroform (32 ml). The aqueous layer was acidified with dilute hydrochloric acid and extracted with chloroform (2 × 40 ml). The combined chloroform layers were dried ($MgSO_4$) and evaporated. The residue was recrystallised from aqueous methanol to give the *ethylenedioxy-acid* (0·9 g, 78%), platelets, m.p. 146—149° (from aqueous methanol) (Found: C, 64·05; H, 7·2. $C_{12}H_{16}O_3$ requires C, 64·25; H, 7·2%), $\nu_{max.}$ (mull) 3200—2500 and 1695 cm^{-1}, τ ($CDCl_3$) 6·01 (4H, s, CH_2·O), 7·23 (1H, m, C*H*·C·CO_2H), 7·78br (2H, s, CH·CO_2), 7·96br (4H, s, CH_2), and 8·18br (4H, s, CH_2).

9-*Oxonoradamantane*-3-*carboxylic Acid* (32).—The ethylenedioxy-acid (300 mg) was added to ethanol (2 ml), water (15 ml), and hydrochloric acid (15 ml; 10% w/v in water). The mixture was heated under reflux for 30 min, cooled, and extracted with chloroform (2 × 30 ml). The chloroform was dried ($MgSO_4$) and evaporated to give the acid (250 mg, 96%). This sample had spectroscopic data and m.p. identical with those of the sample obtained before.

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