The Intramolecular Reaction between a Diazoalkane Group and an Ester Group: a Search for Other Examples

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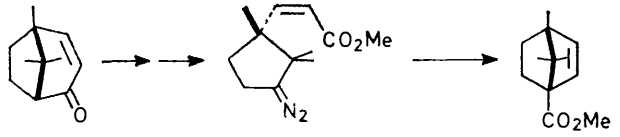
The reactions of eight *N*-nitroso-lactams with sodium methoxide are described. In most cases the intermediate diazoalkane ester does not give an insertion product of the kind described in the preceding paper, but gives instead the solvolysis products—ethers and/or olefins. The intramolecular reaction between a diazoalkane and an ester group is not therefore a promising one for synthesis. One other example of the diazoalkane ester reaction was, however, observed: 4-nitroso-4-azahomoadamantan-5-one (24) gave a 14% yield of methyl noradamantane-3-carboxylate (27). One other nitroso-lactam, 3-nitroso-3-aza-A-homocholest-4a-en-4-one (32), failed even to give a diazoalkane, but instead rearranged to an isomer, methyl (3-nitroso-3-aza-A-nor-5ξ-cholestan-5-yl)-acetate (34).

The partitioning of the intermediate diazotic acids between diazoalkane and solvolysis products indicates that substantial yields of diazoalkanes were realised in most cases. The synthesis of the *N*-nitroso-lactams is described.

In the preceding paper [1] we described the first observation of a reaction [(2) ⟶ (3)] between a diazoalkane group and an ester group similar to the well-known reaction of diazoalkanes with ketones. Because both diazoalkane and ester groups are readily set up by an alkoxide-induced opening of a nitroso-lactam, and because we had, in that one example, been able to raise the yield to 89%, we thought that this new reaction might be generally useful in synthesis, especially since we were able to do the six-stage sequence (1) ⟶ (3)



(1) (2) (3)

in 63% yield. Accordingly we have examined the reaction of several nitroso-lactams with sodium methoxide in methanol or t-butyl alchohol, and have found only one other example of the reaction.

RESULTS AND DISCUSSION

We first studied the nitroso-lactam (4), in the hope that we would get the bicyclo[2.1.1]hexene (6). (At that time, no bicyclo[2.1.1]hexenes had been prepared.) The major products from the reaction with sodium methoxide quenched the fluorescence of t.l.c. plates; these were probably the usual solvolysis products, in which the αβ-unsaturated ester group would still be present. But a minor product did not quench this fluorescence. This product was difficult to isolate, since it was present only in small quantities, but the n.m.r. spectrum of a partially purified sample was not in agreement with structure (6) (there were only two *C*-methyl groups). Also, there was no evidence in this case that the diazoalkane (5) was involved: at −30° there was no development of even a transitory pink colour. Several syntheses of bicyclo[2.1.1]hexenes had been reported by this time,[2] so we turned our attention to other systems, where we met, almost uniformly, even less encouraging results.

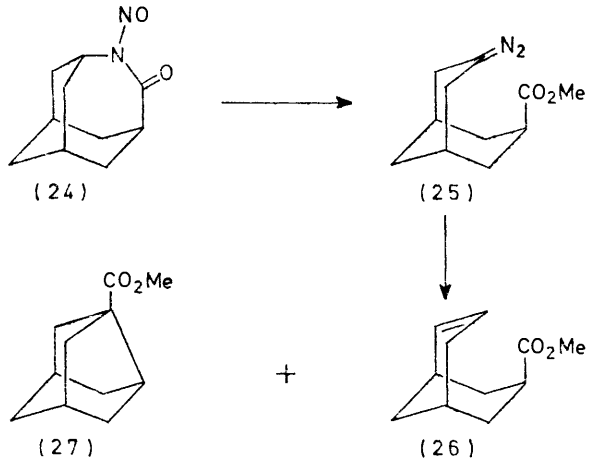
[1] E. H. Billett and I. Fleming, preceding paper.

[2] J. Meinwald and B. E. Kaplan, *J. Amer. Chem. Soc.*, 1967, **89**, 2611; J. Meinwald and F. Uno, *ibid.*, 1968, **90**, 800; K. B. Wiberg and R. W. Ubersax, *Tetrahedron Letters*, 1968, **3063**; F. T. Bond and L. Scerbo, *ibid.*, p. 2789; see also, W. R. Roth and A. Friedrich, *ibid.*, 1969, 2607; J. Meinwald and H. Tsuruta, *J. Amer. Chem. Soc.*, 1969, **91**, 5877; and H. E. Zimmerman, J. D. Robbins, and J. Schantl, *ibid.*, p. 5878; S. Masamune, E. N. Cain, R. Vukov, S. Takoda, and N. Nakatsuka, *Chem. Comm.*, 1969, 243.

The nitroso-lactams (7), (11), (15), and (18) did give appropriately coloured solutions which slowly lost their colour, indicating that the diazoalkanes [(8), (12), (16) and (19)] had been produced. But the hoped-for products (10), (14), (17), and (20), were not detected by g.l.c., although we had available a sample of each for direct comparison. In the first two cases, (7) and (11), the n.m.r. spectra showed that the major products were the ethers (9) and (13), respectively. In the latter cases, (15) and (18), the n.m.r. spectra indicated that the several products were the ethers and olefins expected of the solvolytic route.[1] The latter cases were disappointing because they involved such small changes in structure from that of the first, successful case (2); thus the *gem*-dimethyl group and the conjugated double bond are necessary features for the reaction in that particular compound.

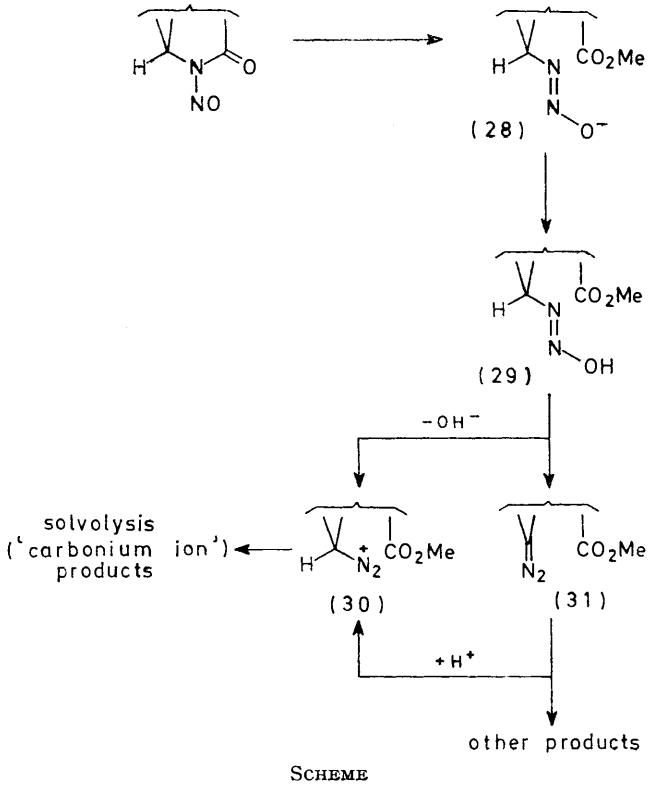
It seemed likely that the chief effect of the conjugation was in reducing the rotational freedom of the acrylic ester side chain rather than in the conjugation as such. If this were the case, the new reaction might take place with an acetic ester side chain, as in (22), which would both be saturated and have a comparable freedom to rotate away from the diazoalkane group to that of the acrylic ester side chain of (2). This time, we did not have the product (23), of such a reaction, but we were able to show that there was none of this compound present. In particular, the solution of the diazoalkane (22) was decomposed in dilute aqueous sulphuric acid (optimum conditions for the formation of solvolysis products [1]) and also in t-butyl alcohol (optimum conditions for the insertion reaction [1]). The g.l.c. traces from these two runs were identical, and the products with shortest retention time were clearly (n.m.r.) the olefinic esters corresponding to those numbered (3)—(5) in the preceding paper.[1] Also, the bicyclic product (23), had it been formed, would almost certainly have had a shorter retention time than that of these monocyclic products. The failure of this diazoalkane (22) to undergo the new reaction does not *prove* that the conjugated double bond of the original diazoalkane (2) was essential in a mechanistic sense: the loss of this feature in (22) is accompanied by other changes, such as the distance between the diazoalkane and ester groups, and it may be these changes which operate against the new reaction. Certainly its failure demonstrates the main conclusion of the work described in this paper, namely that the intramolecular reaction between diazoalkane and ester groups is only likely to be useful in rare situations.

One of these rare situations, however, was that involving the nitroso-lactam (24). Treatment of this with sodium methoxide gave two products, (26) and



(27), but without the development of any transitory pink colour. The first of these (26) is the usual solvolysis kind of product; the second, (27) a minor product, present to the extent of about 14%, is that expected of our diazoalkane ester reaction. In the following paper [3] we describe our evidence that this product is indeed the result of such a diazoalkane ester reaction. Here, we only note that the ester group in the diazoalkane (25) is not conjugated, and that therefore this feature need not always be present for the reaction to take place. Of course, the structural features of the diazoalkane (25) are also well suited for the diazoalkane ester reaction.

The synthesis of diazoalkanes from nitroso-amides is not usually very efficient. The sequence by which this change is accomplished [4-8] is shown in the Scheme, where the first step, the formation of the diazotate (28), is highly efficient.[9] We find, for example, that the diazotate, if it is wanted free of subsequent reaction, can be obtained in suspension in benzene by treating a benzene solution of such nitroso-lactams as (1) with a suspension of potassium t-butoxide. The diazotate (28) is converted into the diazoalkane (31) only when a proton source is available.[9] Thus the colour of a diazoalkane only develops in a hydroxylic solvent, or when an alcohol or water is added to the benzene suspension of the diazotate. This process is always [6,7] accompanied by some loss of nitrogen and the formation of what, in these papers, we have been calling the solvolysis products. The diazotic acid (29) is thought to partition itself between the diazonium ion (30) and the diazoalkane (31), by way of a diazonium hydroxide ion-pair.[6-8] The factors affecting this partition are not well known, but primary diazoalkanes are got in higher yields than secondary diazoalkanes,[6] and the presence of electron-donating groups or bulky alkyl groups is known [7] to lower the proportion of diazoalkane. Because, in our work, we had observed in most cases only the solvolysis products, it was important for us to know just how much diazoalkane has been produced. The pink or orange colours observed could have represented only a small fraction of the total reaction. The partition of the diazoalkane (31) between the new reaction and solvolysis could have been in favour of the former and yet have escaped detection if the partitioning of the diazotic acid (29) had been greatly in favour of the solvolysis products at the expense of the diazoalkane (31). We tested this by measuring the nitrogen evolved when the diazoalkanes (31) were generated in tetrahydrofuran and by measuring the nitrogen evolved when acid was subsequently added.[5,10] The results (Table) show that a substantial amount of the products must have been produced from the diazoalkanes in the cases of the



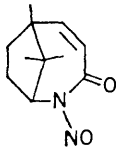
SCHEME

nitroso-lactams (1), (7), (11), (15), and (21). The only one of these cases which leads to the new reaction, namely that of the nitroso-lactam (1), coincidentally

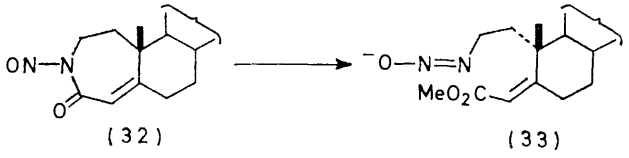
[3] I. Fleming and S. W. Hanson, following paper.
[4] H. von Pechmann, *Ber.*, 1894, **27**, 1888; F. W. Bollinger, F. N. Hayes, and S. Siegel, *J. Amer. Chem. Soc.*, 1950, **72**, 5592; M. S. Newman and W. M. Edwards, *ibid.*, 1954, **76**, 1840; D. E. Applequist and D. E. McGreer, *ibid.*, 1960, **82**, 1965.
[5] C. D. Gutsche and H. E. Johnson, *J. Amer. Chem. Soc.*, 1955, **77**, 109.
[6] R. A. Moss, *J. Org. Chem.*, 1966, **31**, 1082; R. A. Moss, D. W. Reger, and E. M. Emery, *J. Amer. Chem. Soc.*, 1970, **92**, 1366.
[7] H. Hart and J. L. Brewbaker, *J. Amer. Chem. Soc.*, 1969, **91**, 716.
[8] W. Kirmse and H. A. Rinkler, *Annalen*, 1967, **707**, 57; W. Kirmse and H. Arold, *Chem. Ber.*, 1970, **103**, 3722.
[9] A. Hantzch and M. Lehmann, *Ber.*, 1902, **35**, 897; R. Huisgen and J. Reinertshofer, *Annalen*, 1952, **575**, 174 and 197; C. D. Gutsche and I. Y. C. Tao, *J. Org. Chem.*, 1967, **32**, 1778.
[10] K. Heyns and A. Heins, *Annalen*, 1957, **604**, 133.

gives the best yield of the diazoalkane (2); indeed this is the best yield yet recorded for a secondary diazoalkane. Only two cases in the Table give, within experimental error, no detectable amount of diazoalkane: one of these (24) is the one which provides the second example of our reaction and the other (32) we have not yet discussed. It was the failure to detect diazoalkane in the former case which led us to examine that reaction in more detail.[3] The latter case gave little nitrogen evolution, and is a special case.

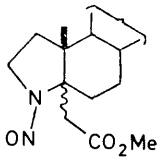
Yields of diazoalkanes derived from nitroso-lactams

Nitroso-lactam	% N_2 evolved [a] on addition of NaOMe	% N_2 evolved [a,b] on subsequent addition of dilute sulphuric acid	% Total N_2 evolved [a]
	20	85	105
(7)	25	65	90
(11)	25	60	85
(15)	45	65	110
(21)	30	75	105
(24)	90	5	95
(32)	15	0	15

[a] Expressed as a percentage of the theoretical maximum; accuracy *ca.* ±10%. [b] This column is an estimate of the yield of the diazoalkane.



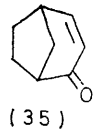
(32) (33)



(34)

When the nitroso-lactam (32) (derived from cholestenone) was treated with sodium methoxide, no new colour (orange would have been appropriate) was developed and little nitrogen was evolved. The product in this case was the nitroso-amine (34). The sequence by which this is formed probably begins as usual with the formation of the diazotate (33); this intermediate evidently collapses by nucleophilic attack of the nitrogen at the conjugate position of the αβ-unsaturated ester. The reverse of this kind of reaction is known[11] in one of the many syntheses of diazomethane: the one from 4-methyl-4-[methyl(nitroso)amino]pentan-2-one in which diazomethane and mesityl oxide are produced. The nitroso-amine (34) was stable to base, so the potential reversibility of the reaction could not, in this case, be used to generate the diazoalkane. We have not investigated this reaction further, but the versatility of the functional sites produced, and the ready formation of a pyrrolidine ring, could make it a useful one.

Synthetic Work.—The three nitroso-lactams with a conjugated double bond [(4), (15), and (32)] were made from the corresponding αβ-unsaturated ketones, bicyclo[3.2.1]oct-3-en-2-one (35), pin-2-en-4-one, and cholestenone, respectively, by use of the sequence previously outlined[12] for the conversion of the ketone (1) into the corresponding lactam. In each case, the Beckmann rearrangement step was carried out with the oxime sulphonate in a hot mixture of hydrochloric and acetic acids, which catalysed the interconversion of the geometric isomers of the oxime sulphonate. Bicyclo[3.2.1]oct-3-en-2-one (35) is a known compound,[13] but



(35)

we prepared it by a different method. Since this compound is the trisnor equivalent of compound (1), we first tried a route along the lines we had used[12] for the synthesis of that compound, but with norbornanone in place of camphor: this route was not promising. Instead, we used the route of Sauers[14] to prepare *exo*-bicyclo[3,2,1]oct-3-en-2-ol and then oxidised this alcohol to the desired ketone (35).

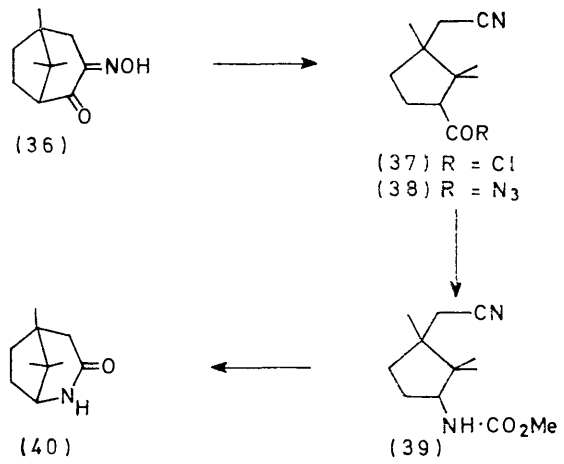
Of the saturated nitroso-lactams, two [(18) and (24)] were prepared by trivial routes, the first by hydrogenation followed by nitrosation of the lactam already described[1,12] and the second from the lactam obtained by Beckmann rearrangement of adamantanone oxime. Three accounts[15] of this Beckmann rearrangement have appeared since we first did it. It is characterised by giving, as Beckmann rearrangements go, a poor yield and, under some conditions, an unusually high proportion, for a reaction leading to a secondary lactam, of the 'second-order Beckmann' product, the nitrile corresponding to the ester (26).[16]

For the synthesis of the nitroso-lactam (21), we first tried the Beckmann rearrangement of bornan-3-one

[11] C. E. Redemann, F. O. Rice, R. Roberts, and H. P. Ward, *Org. Synth.*, Coll. Vol. III, p. 244.
[12] I. Fleming and R. B. Woodward, *J.C.S. Perkin II*, 1973, 1653.
[13] H. L. Goering, R. W. Greiner, and M. F. Sloan, *J. Amer. Chem. Soc.*, 1961, **83**, 1391.
[14] R. R. Sauers, *Tetrahedron Letters*, 1961, 146.
[15] J. G. Korsloot and V. G. Keizer, *Tetrahedron Letters*, 1969, 3517; *Rec. Trav. chim.*, 1969, **88**, 447; V. L. Narayanan and L. Setescak, *J. Heterocyclic Chem.*, 1969, **6**, 445, 1970, **7**, 841; R. M. Black and G. B. Gill, *J. Chem. Soc.* (*C*), 1970, 671; and also M. A. McKervery, personal communication; see also T. Sasaki, S. Eguchi, and T. Toru, *J. Org. Chem.*, 1970, **35**, 4109.
[16] L. G. Donaruma and W. Z. Heldt, *Org. Reactions*, 1960, **11**, 1; compare, B. L. Fox and J. E. Reboulet, *J. Org. Chem.*, 1968, **33**, 3639; G. H. Schmid, P. H. Fitzgerald, *Canad. J. Chem.*, 1968, **46**, 3758; A. Hassner and E. G. Nash, *Tetrahedron Letters*, 1965, 525; R. C. Elderfield and E. T. Losin, *J. Org. Chem.*, 1961, **26**, 1703; and ref. 17, all of whom also observe fragmentation as well as secondary lactam.

oxime, because bornan-3-one was readily available to us by zinc–acid reduction of *exo*-2-hydroxybornan-3-one. Indeed this is one of the best methods of making bornan-3-one, giving 55% overall yield from camphor.

We were unable, in this case, to direct the Beckmann rearrangement step to give only the lactam we wanted



and, like Erdtman and Thorén,[17] found ourselves with a mixture of lactams to separate. Because these authors were interested in both products, they chose to separate them. We, on the other hand, decided to develop an alternative route, specific for the lactam we wanted. 5,8,8-Trimethylbicyclo[3.2.1]octane-2,3-dione 3-oxime (36) with thionyl chloride gave the acid chloride (37),[18] which was converted into the azide (38). The azide was heated in methanol to give the urethane (39), which, in hot water, gave the lactam (40), from which the nitroso-derivative (21) was readily prepared.

EXPERIMENTAL

The Esters (10), (14), (17), *and* (20).—The esters (10) and (14) were obtained by methylation of commercial samples of the corresponding acids with diazomethane. The esters (17) and (20) were also obtained by methylation of the corresponding acids, samples of which were sent to us by Professors J. W. Wilt [19] and S. Winstein,[20] respectively.

Decomposition of the N-*Nitroso-lactams*.—Typical reaction conditions were to take the nitroso-lactam (50 mg) in dry tetrahydrofuran (3 ml) and to add to it a solution of sodium methoxide (50 mg) in a mixture of tetrahydrofuran (2 ml) and methanol (0·5 ml), usually with cooling in ice; the coloured solution (pink for the secondary diazoalkanes and orange for the primary) was then diluted with t-butyl alcohol (20 ml) and kept until the colour had faded. Ether and water were added, and the ether layer was dried ($MgSO_4$) and concentrated. The product was examined by g.l.c., which showed the absence (<0·5%) of the esters (10), (14), (17), and (20) in the reactions with the nitroso-lactams (7), (11), (15), and (18), respectively. T.l.c. (silica gel–benzene) was used to separate the u.v.-inactive product (1 mg) from the nitroso-lactam (4), but we are only able to say that (6) was not its structure and that there were many other products.

In the monocyclic cases, (7) and (11), the diazoalkanes were also generated, and allowed to decompose in methanol. With the latter, the two products were separated by g.l.c. (LAC; 4 ft); the major product (95%), τ (CCl_4) 6·4 and 6·8 (each 3H, s, OMe), 6·8 (2H, t, CH_2·OMe), 7·3 (2H, t, CH_2·CO), and an envelope centred at 8·0 (6H), was the ether (13), and the minor product (5%), τ (CCl_4) 6·4 and 6·8 (each 3H, s) 6·8 (1H, m, >CH·OMe), 7·3 (2H, t), an envelope centred at 8 (4H), and 8·5 (3H, d, >CH·CH_3), was the result of a hydride shift: methyl 5-methoxyhexanoate. The products from the former (7) showed a similar g.l.c. trace, with only two products and no cyclobutanecarboxylic ester. The decomposition of these two nitroso-lactams has been described before.[9,21]

In the bicyclic cases (15) and (21), the diazoalkane solution was also decomposed in dilute aqueous sulphuric acid and in methanol. The t-butyl alcohol and the aqueous acid runs gave, in each case, identical g.l.c. traces. From (15) there were peaks [10% poly(diethylene glycol adipate); 6 ft; 150°] with retention times of 1·7, 4·2, 5·2, and 6·2 min (methyl norbornene-1-carboxylate had a retention time of 1·3 min). The peak with a retention time of 1·7 min was the major product; it was collected, τ (CCl_4) 3·7—4·5 (4H, m, olefinic) and 6·36 (3H, s, OMe), and was probably the mixture of olefins. The peak with a retention time of 6·2 min was also collected and was one of the possible methyl ethers, τ (CCl_4) 4·01 (1H, dd, –CH–C*H*=CH), 4·39 (1H, d, –CH=C*H*·CO), and 6·36 and 6·8 (each 3H, s, OMe). From (21) there were peaks (10% Carbowax 20M; 6 ft; 125°) with retention times of 5, 6, 6·5, 14, 18, and 21 min. The first of these was the major product, τ (CCl_4) 5·25 (0·7H, m, olefinic) and 6·45 (3H, s, OMe), and was probably a mixture of olefinic solvolysis products. In both cases, the decomposition in methanol caused an increase in the proportion of the ether products—the three peaks at 4·2, 5·2, and 6·2 min from (15), and the three peaks at 14, 18, and 21 min from (21). In two cases [(24) and (32)], no coloured solution developed but definite products were obtained. These are described separately later.

Decomposition of 4-*Nitroso*-4-*azahomoadamantan*-5-*one* (24).—The nitroso-lactam (24) (100 mg) in dry methanol (1 ml) was added to a stirred solution of sodium methoxide (100 mg) in methanol (2 ml). G.l.c. analysis [10% poly-(diethyleneglycol adipate); 6 ft; 150°] showed two peaks with retention times of 3·2 (14%) and 4·3 min (86%). Aqueous sodium hydroxide solution (3 ml; 10%) was added and the mixture was heated under reflux for 2 h. The solution was acidified and extracted with ether; the ether layer was dried ($MgSO_4$) and evaporated. Fractional crystallisation from hexane gave one of the products, exo-*bicyclo*[3.3.1]*non*-2-*ene*-7-*carboxylic acid* (50 mg), plates, m.p. 212—213° (from hexane) (Found: C, 72·3; H, 8·6. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·4%), $\nu_{max.}$ (KBr) 3200—2500 and 1680 cm^{-1}, τ (CCl_4) 4·5 (2H, m, olefinic C*H*) and 7·5—8·5 (11H, m). The known *endo*-isomer [22] has m.p. 195—198°. Remethylation of this acid, with diazomethane, gave an ester which had a slightly longer retention time than the major product (26) of the reaction.

[17] H. Erdtman and S. Thorén, *Acta Chem. Scand.*, 1970, **24**, 87.
[18] F. Salmon-Legagneur, *Bull. Soc. chim. France*, 1932, **51**, 807.
[19] J. W. Wilt, C. T. Parsons, C. A. Schneider, D. G. Schultenover, and W. J. Wagner, *J. Org. Chem.*, 1968, **33**, 694.
[20] S. Winstein and T. G. Traylor, *J. Amer. Chem. Soc.*, 1956, **78**, 2597.
[21] W. Pritzkow and P. Dietrich, *Annalen*, 1963, **665**, 88.
[22] A. C. Udding, H. Wynberg, and J. Strating, *Tetrahedron Letters*, 1968, 5719.

Presumably the first-formed *endo*-ester had isomerised to the *exo*-ester under the saponification conditions. Hydrogenation of the crystalline acid with Adams catalyst gave *exo*-bicyclo[3.3.1]nonane-3-carboxylic acid, m.p. 122—126° (lit.,[23] 122—126°).

The mother liquors from the crystallisation of the major product were re-esterified with diazomethane and the product with shorter retention time isolated by preparative g.l.c. Alternatively, the nitroso-lactam (24) (100 mg) could be decomposed with sodium methoxide as before, the crude mixture of esters isolated by extraction with pentane, and this mixture warmed to 60° with potassium permanganate (3 ml; saturated solution in water) for 2 h. Extraction with ether, evaporation, and saponification gave a single acid, the olefinic product having been destroyed. The acid was noradamantanecarboxylic acid (10 mg), m.p. 103—104° (lit.,[24] 106—107°). This acid was identical (mixed m.p., i.r., and g.l.c. of the methyl ester) with an authentic sample sent to us by Dr. Hoover.

Decomposition of 3-*Nitroso*-3-*aza*-A-*homocholest*-4a-*en*-4-*one* (32).—The nitroso-lactam (32) (360 mg) in tetrahydrofuran (3 ml) was added to a stirred solution of sodium methoxide (195 mg) in a mixture of tetrahydrofuran (4·2 ml) and methanol (1·8 ml). After 5 min, the mixture was poured on ice and water (100 ml); *methyl* (3-*nitroso*-3-*aza*-A-*nor*-5ξ-*cholestan*-5-*yl*)*acetate* (34) (335 mg, 86%) precipitated, prisms, m.p. 146—148° (from aqueous methanol) (Found: C, 73·15; H, 10·8; N, 5·95. $C_{28}H_{48}N_2O_3$ requires C, 73·00; H, 10·5; N, 6·05%), $\nu_{max.}$ (mull) 1735 cm^{-1}, τ ($CDCl_3$) 6·40 (1H, m, *H*CH·N), 6·48 (3H, s, OMe), 7·04 (1H, dt, HC*H*·N), 7·37 (1H, d, *J* 12 Hz, *H*CH·CO), and 7·55 (1H, d, *J* 12 Hz, HC*H*·CO), $\lambda_{max.}$ (EtOH) 232 and 348 nm (ε 7300 and 90) [compare *N*-nitrosopiperidine,[25] $\lambda_{max.}$ (EtOH) 235 and 351 nm (ε 8100 and 95)]. The ester group of this compound (100 mg) was hydrolysed at 90° for 1 h in a mixture of acetic acid (4 ml), urea (28 mg), water (1 ml), and sulphuric acid (1 ml). On pouring into ice and water, 3-*nitroso*-3-*aza*-A-*nor*-5ξ-*cholestan*-5-*ylacetic acid* (80 mg, 82%) precipitated. The acid was hygroscopic; a fresh anhydrous sample has m.p. 226—229° (from aqueous methanol followed by heating *in vacuo* at 120°), $\nu_{max.}$ 3300—2500 and 1720 cm^{-1}, $\lambda_{max.}$ (EtOH) 232 nm (ε 6500), τ (CH_2Cl_2) 6·4 (1H, m), 7·02 (1H, dt), 7·36 (1H, d), and 7·54 (1H, d), M^+ 446, *m/e* 416·3517 (M^+ − NO requires 416·3527, 36%), 387·3405 (M^+ − $CH_2{\cdot}CO_2H$ requires 387·3375, 8%), 357·3378 (M^+ − NO − $CH_2{\cdot}CO_2H$ requires 357·3395, 100%). Microanalysis gave variable results. The same acid could also be obtained by alkaline hydrolysis.

Quantitative Estimation of the Yield of Diazoalkane.—The results given in the Table were obtained by treatment of the nitroso-lactams (100 mg) in tetrahydrofuran (6 ml) with a solution of sodium methoxide (100 mg) in tetrahydrofuran (4 ml) and methanol (1 ml). The nitrogen evolved at this stage, and after the addition of dilute sulphuric acid from a pressure-equalised separating funnel, was measured by weighing mercury displaced. The results are expressed as percentages of the theoretical amount of nitrogen and are only accurate to ±10%. We also investigated the possibility that the direct solvolysis of the diazotic acid took place on the surface of the solid sodium methoxide. By using dicyclohexyl-18-crown-6,[26] we were able to do the foregoing experiment in homogeneous solution: there was no significant change in the figures in the cases that we tried.

Preparation of the Nitroso-lactams.—Two of the nitroso-lactams [(7) [9] and (11) [9]] were known compounds. The others were prepared by long or short routes, as follows.

5,7,7-*Trimethyl*-2-*nitroso*-2-*azabicyclo*[4.1.1]*oct*-4-*en*-3-*one* (4).—Pin-2-en-4-one oxime, m.p. 119—120° (lit.,[27] 119—120°) (3·6 g) (obtained in 44% yield from pin-2-en-4-one [28] by the method described for 5,8,8-trimethylbicyclo[3.2.1]-oct-3-en-2-one oxime [12]) in pyridine (50 ml) was mixed with a solution of toluene-*p*-sulphonyl chloride (3·6 g) in pyridine (25 ml) at 0°. After 2 h at 0° the mixture was poured into water and ice (250 ml), and the mixture of oxime sulphonates (6 g) separated. This mixture was dissolved and kept in a mixture of acetic acid (20 ml) and concentrated hydrochloric acid (20 ml) at 100° for 1 h. The solution was cooled, neutralised, and extracted with ether to give 5,7,7-*trimethyl*-2-*azabicyclo*[4.1.1]*oct*-4-*en*-3-*one* (2·9 g, 72%), cubes, m.p. 143—144° (from hexane) (Found: C, 72·7; H, 9·2; N, 8·2. $C_{10}H_{15}NO$ requires C, 72·7; H, 9·1; N, 8·5%), $\nu_{max.}$ (KBr) 3200, 1670, and 1612 cm^{-1}, $\lambda_{max.}$ (EtOH) 236 nm (ε 12,450), τ (CCl_4) 4·5 (1H, d, *J* 1 Hz), 7—9 (5H, m), 8·1 (3H, d, *J* 1 Hz), and 8·6 and 9·1 (each 3H, s). This lactam (1 g) was nitrosated by passing nitrogen trioxide into a solution of it in acetic acid (5 ml) and acetic anhydride (0·25 ml) at 0° until the solution was green. After 2 h at room temperature the solution was added to ice and water (200 ml) and the product separated. Recrystallisation gave *nitroso-lactam* (4) (0·95 g, 85%), yellow plates, m.p. 73—74° (from hexane) (Found: C, 61·7; H, 7·2; N, 14·5. $C_{10}H_{14}N_2O_2$ requires C, 61·8; H, 7·2; N, 14·4%), $\nu_{max.}$ (KBr) 1690 and 1620 cm^{-1}, $\lambda_{max.}$ (EtOH) 275 nm (ε 8900). The starting oxime and the oxime sulphonates were approximately (n.m.r., t.l.c.) a 50 : 50 mixture of the geometrical isomers in this case; we also observed that the less reactive oxime sulphonate had about half-rearranged after 24 h under reflux in ethanol, giving a lactam different (t.l.c.) from that isolated before.

2-*Nitroso*-2-*azabicyclo*[4.2.1]*non*-4-*en*-3-*one* (15).—(i) *The ketone* (35). We give here the experimental details for this sequence because the earlier report [14] of most of it is only in preliminary form. Commercial (bicyclo[2.2.1]hept-5-en-yl)methanol (50 g) in pyridine (200 ml) was stirred at 0° while toluene-*p*-sulphonyl chloride (84 g) was added. The mixture was kept at 0° for 40 h and then poured into ice–water (2 l). The crude product slowly solidified and was collected, and the mother liquors were extracted with ether. The combined crops were recrystallised to give (*bicyclo*[2.2.1]*hept*-5-*en*-2-*yl*)*methyl toluene*-p-*sulphonate* (87·5 g, 78%), m.p. 45—47·5° (from ethanol) (Found: C, 64·5; H, 6·65. $C_{15}H_{18}O_3S$ requires C, 64·75; H, 6·5%), $\nu_{max.}$ (KBr) 1600, 1360, and 1180 cm^{-1}, τ (CCl_4) 2·3 and 2·7 (each 2H, d), 3·96 and 4·34 (each 1H, dd), and 7·60 (3H, s). The toluene-*p*-sulphonate (91·8 g) was heated under reflux in acetic acid (1·3 l) containing acetic anhydride (1 ml) and anhydrous sodium acetate (32·8 g) for 70 h. The mixture was cooled and mixed with ether (1 l) and water

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[24] B. R. Vogt and J. R. E. Hoover, *Tetrahedron Letters*, 1967, 2841.
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[28] G. Dupont, R. Dulou, and O. Mondou, *Bull. Soc. chim. France*, 1953, **60**; for other preparations see, G. H. Whitham, *J. Chem. Soc.*, 1961, 2232; J. J. Hurst and G. H. Whitham, *ibid.*, 1960, 2864; and A. F. Regan, *Tetrahedron*, 1969, **25**, 3801.

(2 l). The ether layer was washed with sodium hydrogen carbonate solution, dried ($MgSO_4$), and combined with two further extracts with ether (500 ml) which had also been washed with the same carbonate solution. The ether was evaporated off and the residue fractionally distilled to give bicyclo[3.2.1]oct-3-en-*exo*-2-yl acetate (38 g, 69%), b.p. 100—103° at 19 Torr, $\nu_{max.}$ (film) 1730 cm^{-1}, τ (CCl_4) 3·95 (1H, m, C*H*=CH), 4·60 (1H, m, CH=C*H*), 5·30 (1H, t, C*H*·OAc), 7·55br (2H, m, bridgehead), and 8·04 (3H, s, OAc). The acetate (38 g) in ether (500 ml) was added to a stirred suspension of lithium aluminium hydride (10 g) in ether (500 ml) with ice-cooling. The mixture was heated under reflux for 2 h, water was added, and the ether layer was separated and evaporated to give the crude alcohol (27 g, 95%), $\nu_{max.}$ (mull) 3350 and 1640 cm^{-1}. The alcohol (6 g) in dry light petroleum (b.p. 40—60°; 600 ml) was stirred with manganese dioxide (60 g; freshly prepared by pyrolysis of the oxalate [29]) for 24 h. The mixture was filtered, the residue washed with more light petroleum, the solvent evaporated, and the residue distilled to give the ketone (35) (4·8 g, 81%), b.p. 73—79° at 7 Torr. (lit.,[13,14] 76° at 7 Torr, 98·5° at 20 Torr), $\nu_{max.}$ (film) 1675 and 1600 cm^{-1}, $\lambda_{max.}$ (EtOH) 228 nm (ε 7800), τ (CCl_4) 2·86 (1H, dd, C*H*=CHCO), 4·33 (1H, d, CH=C*H*CO), and 7·20br (2H, t, bridgehead).

(ii) *Oximation, Beckmann rearrangement, and nitrosation.* The ketone (35) (8 g) in pyridine (80 ml) and hydroxylamine hydrochloride (5·35 g) in pyridine (40 ml) were mixed at 0° and stirred for 15 h. Water and ether were added, the ether and some of the pyridine were evaporated off, and the residue of oxime in pyridine was used directly. This solution was cooled to 0°, stirred with toluene-*p*-sulphonyl chloride (12 g) for 24 h, and then added to ice–water (400 ml). *Bicyclo*[3.2.1]*oct-3-en-2-one* anti-p-*tolylsulphonyloxime* (7·6 g, 40%) crystallised slowly, prisms, m.p. 97—99° (from methanol) (Found: C, 61·9; H, 6·15; N, 4·65. $C_{15}H_{17}NO_3S$ requires C, 61·85; H, 5·85; N, 4·8%), $\nu_{max.}$ (KBr) 1620, 1600, 1370, and 1190 cm^{-1}, $\lambda_{max.}$ (MeOH) 230 and 274 nm (ε 25,200 and 700), τ (CCl_4) 2·2 and 2·75 (each 2H, d), 3·4 (1H, t), 4·2 (1H, d), 6·15 (1H, m), 7·28 (1H, m), and 7·6 (3H, s). Chromatography of the residue obtained by evaporating the mother liquors gave only a little of the desired lactam (0·2 g, 2%). The lactam therefore had to be obtained by isomerising the 'wrong', *anti*-oxime sulphonate. The *anti*-oxime sulphonate (1 g) in acetic acid (30 ml) at 100° was mixed with concentrated hydrochloric acid (20 ml) and acetic acid (40 ml) at 100°, and kept at 100° for 1·5 min and then added directly to a mixture of sodium hydroxide solution (500 ml; 10%) and ice (200 g). The mixture was extracted with chloroform (5 × 100 ml). The extract was dried ($MgSO_4$) and evaporated. The residue crystallised from cyclohexane to give 2-*azabicyclo*[4.2.1]*non-4-en-3-one* (0·44 g, 93%), needles, m.p. 124—125·5° (from cyclohexane) (Found: C, 69·85; H, 7·95; N, 10·0. $C_8H_{11}NO$ requires C, 70·0; H, 8·1; N, 10·2%), $\nu_{max.}$ (KBr) 3350—3250, 1655, and 1605 cm^{-1}, $\lambda_{max.}$ (MeOH) 215 nm (ε 11,700), τ (CD_3OD) 3·4 (1H, dd), 4·3 (1H, d), 6·22br (1H, t), and 7·15 (1H, m). This lactam (400 mg) was nitrosated by passing nitrogen trioxide through a solution in acetic acid (100 ml) for 4 h at room temperature. The mixture was poured on ice and extracted with chloroform; the extract was washed with sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated to give the *nitroso-lactam* (15) (300 mg, 62%), yellow needles, m.p. 89—90·5° (from hexane) (Found: C, 58·05; H, 6·1; N, 17·05. $C_8H_{10}N_2O_2$ requires C, 57·8; H, 6·05; N, 16·85%), $\nu_{max.}$ (mull) 1680 and 1540 cm^{-1}, $\lambda_{max.}$ (MeOH) 245 and 269 nm (ε 6900 and 6700), τ (CCl_4) 3·31 (1H, dd, C*H*=CHCO), 3·90 (1H, d, CH=C*H*CO), 4·70 (1H, dt, C*H*·NNO), and 7·05 (1H, m, C*H*–CH=CH).

3-*Aza*-A-*homocholest*-4a-*en*-4-*one*.—Cholestenone (6·64 g), hydroxylamine hydrochloride (17·6 g), and sodium acetate trihydrate (26·4 g) were heated under reflux in methanol for 0·5 h. The mixture in water was extracted with ether; the ether layers were washed with water, dried (Na_2SO_4), and evaporated. The residue was dissolved in benzene and the solution evaporated. The residue in pyridine (50 ml) was mixed at 0° with a solution of toluene-*p*-sulphonyl chloride (3·95 g) in pyridine (10 ml) and kept overnight at 0°. It was then poured into dichloromethane and washed with dilute hydrochloric acid solution to remove the pyridine. The dichloromethane was evaporated off; the residue was dissolved in acetic acid (125 ml), heated to 100°, and added to a mixture of concentrated hydrochloric acid (50 ml) and acetic acid (50 ml), which had been preheated to 95°. The mixture was kept at 95° for 2 min and then poured into ice-cooled 30% sodium hydroxide. The mixture was extracted with dichloromethane; the extracts were washed with water and evaporated. The residue was recrystallised from ethanol to give the lactam (4·2 g, 61%), m.p. 254—256° (lit.,[30] 255—260°). On one occasion the mixture of oxime sulphonates was chromatographed on silica gel (elution with dichloromethane) to give anti-*cholest*-4-*en*-3-*one* p-*tolylsulphonyloxime*, m.p. 132—133° (Found: C, 73·8; H, 9·1; N, 2·5. $C_{34}H_{51}NO_3S$ requires C, 73·8; H, 9·3; N, 2·5%), followed by the lactam.

3-*Nitroso*-3-*aza*-A-*homocholest*-4a-*en*-4-*one* (32).—Nitrogen trioxide was passed through a solution of the lactam (570 mg) in acetic acid (100 ml) for 10 h at room temperature. The mixture was added to ice–water and the *nitroso-lactam* (32) was collected (450 mg, 74%), plates, m.p. 158—160° (from hexane) (Found: C, 75·8; H, 10·2; N, 6·3. $C_{27}H_{44}N_2O_2$ requires C, 75·7; H, 10·4; N, 6·6%), $\nu_{max.}$ (mull) 1680, 1620, and 1530 cm^{-1}, $\lambda_{max.}$ (EtOH) 264 and 424 nm (ε 12,700 and 100), τ (CCl_4) 4·05 (1H, s), 5·95 (1H, dd, *J* 15 and 9 Hz), and 6·73 (1H, dd, *J* 15 and 9 Hz).

6,9,9-*Trimethyl*-2-*nitroso*-2-*azabicyclo*[4.2.1]*nonan*-3-*one* (18).— 6,9,9-Trimethyl-2-azabicyclo[4.2.1]non-4-en-3-one [12] (1 g) was hydrogenated at room temperature and atmospheric pressure over Adams catalyst (100 mg) in methanol (5 ml) until hydrogen was no longer absorbed; 6,9,9-*trimethyl*-2-*azabicyclo*[4.2.1]*nonan*-3-*one* was crystallised from hexane (0·8 g, 79%), plates, m.p. 218—220° (from cyclohexane) (Found: C, 73·1; H, 10·4; N, 7·8. $C_{11}H_{19}NO$ requires C, 72·9; H, 10·6; N, 7·7%), $\nu_{max.}$ (CCl_4) 3280 and 1660 $cm.^{-1}$ The lactam (0·8 g) was nitrosated in acetic acid (5 ml) containing acetic anhydride (0·25 ml) with nitrogen trioxide at room temperature. The solution was added to ice–water (250 ml) to give the *nitroso-lactam* (18), m.p. 69° (decomp.) (from hexane). This nitroso-lactam was much less stable than its conjugated relative (1); it could not be obtained analytically pure and was used freshly prepared.

4-*Nitroso*-4-*azahomoadamantan*-5-*one* (24).—The lactam,[15] obtained originally in 60% yield by the oxime sulphonate method from adamantanone oxime. was nitrosated by passing nitrogen trioxide through a solution of it (533 mg)

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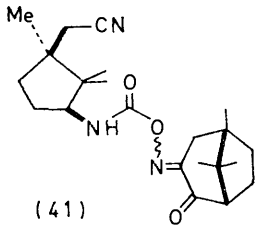
in acetic acid (70 ml) for 15 h at room temperature. The mixture was added to ice–water and the nitroso-lactam collected (408 mg, 65%), yellow needles, m.p. 145° (from hexane) (Found: C, 62·0; H, 7·5; N, 14·2. $C_{10}H_{14}N_2O_2$ requires C, 61·8; H, 7·3; N, 14·4%), $\nu_{max.}$ (mull) 1730 and 1520 cm^{-1}, $\lambda_{max.}$ (EtOH) 258 nm (ε 5470), τ ($CDCl_3$) 4·88br (1H, s, C*H*·N), 6·82br (1H, s, C*H*·CO), and 8·59 (2H, d, *J* 13 Hz, C*H*–CHN *cis* to N).

Bornan-3-one.—*exo*-2-Hydroxybornan-3-one [31] (1·68 g) was heated under reflux (wide-mouth condenser) in concentrated hydrochloric acid (25 ml), while powdered zinc (10 g) was added in portions over 45 min. The bornan-3-one produced was deposited in the condenser, and was purified by sublimation (1·03 g, 68%). G.l.c. analysis indicated that it was essentially free of camphor. The yield is the same as that reported by Baker and Davis; [32] it is slightly lower than that of the two-stage sequence used by Thorén [33] (60% from camphor). Other routes [34] appear to be less satisfactory.

Methyl (cis-3-*Cyanomethyl*-2,2,3-*trimethylcyclopentyl*)*carbamate* (39).—5,8,8-Trimethylbicyclo[3.2.1]octan-2-one was obtained in 90% yield by hydrogenation of 5,8,8-trimethylbicyclo[3.2.1]oct-3-en-2-one [12] over 5% Pd–C in ethanol, and was converted into its isonitroso-derivative (36) in 71% yield.[18] The oxime (36) (1 g) was added in small amounts to a stirred mixture of thionyl chloride (1 g) and dioxan (10 ml) at 0°. After a further 5 min, aqueous sodium azide (3 g in 12 ml) was added and stirring was continued at 0° for 15 min. Extraction with ether, washing with sodium hydrogen carbonate solution and water, drying ($MgSO_4$), and evaporation of most of the ether and dioxan gave crude azide (38), $\nu_{max.}$ 2260, 2140, and 1705 cm^{-1}. This azide was heated under reflux in methanol (250 ml) for 2 h. This reaction was troublesome (see later); it worked well with ordinary grades of methanol and with A.R. methanol containing a little potassium hydroxide. Evaporation of the methanol gave the *urethane* (39) (0·8 g, 70%), plates, m.p. 117·5—118·5° (from aqueous ethanol) (Found: C, 64·5; H, 9·0; N, 12·25. $C_{12}H_{20}N_2O_2$ requires C, 64·25; H, 9·0; N, 12·5%), $\nu_{max.}$ (mull) 3370, 3340, 2240, 1720, 1700, and 1540 cm^{-1}, τ ($CDCl_3$) 6·3 (3H, s, OMe), 7·7 (2H, s, CH_2·CN), and 8·82, 9·08, and 9·20 (each 3H, s, CMe).

When the Curtius rearrangement was done in A.R. methanol, or in benzene, a different product, 3-[(cis-3-*cyanomethyl*-2,2,3-*trimethylcyclopentyl*)*carbamoyloxyimino*]-5,8,8-*trimethylbicyclo*[3.2.1]*octan*-2-*one* (41), was obtained by evaporating the solvent and adding water. The water was necessary for the crystallisation of this compound, which tenaciously held a molecule of water of crystallisation. An analytical sample had m.p. 160—162° (plates from ethanol) (Found: C, 65·5; H, 8·5; N, 10·7. $C_{22}H_{33}N_3O_3,H_2O$ requires C, 65·2; H, 8·7; N, 10·4%), $\nu_{max.}$ (mull) 3540, 3460 (H_2O), 3210 (NH), 2250 (CN), 1740 (carbamoyl CO),[35] 1710, 1650, and 1570 cm^{-1}, $\lambda_{max.}$ (MeOH) 229 nm (ε 9300), τ ($CDCl_3$) 3·5 (1H, d, NH), 5·78 (1H, q, C*H*·NH), 7·08 (1H, d, *J* 19 Hz, *H*CH–C=NO–), 7·52 (1H, d, *J* 19 Hz, HC*H*–C=NO–), 7·72 (2H, s, CH_2·CN), and 8·81, 8·96, 9·00, 9·02, 9·05, and 9·14 (each 3H, s, CMe); there was no molecular ion, but peaks at *m/e* 195·1265 ($C_{11}H_{17}NO_2$ requires 195·1259, 95%) (corresponds to a fragment breaking at the C–O single bond with a hydrogen transfer to the O), 178 (100%, 195 − OH), and 109 (92%) helped us to assign a structure to this compound. The structure



(41)

was proved by synthesis: the azide (38) [from 300 mg of the oxime (36)] was heated under reflux in dry benzene for 1 h, and the mixture evaporated to leave the isocyanate (300 mg), $\nu_{max.}$ 2260 cm^{-1}. The oxime (36) (300 mg) and this isocyanate were heated under reflux in benzene (30 ml) for 30 min; the benzene was evaporated off to leave an oil which did not crystallise. On addition of water to an ethanolic solution the product (41) precipitated, identical in m.p. and i.r. spectrum with the sample obtained before.

5,8,8-*Trimethyl*-2-*azabicyclo*[3.2.1]*octan*-3-*one* (40).—The urethane (39) (200 mg) was heated at 200° for 24 h with water (2 ml) in a sealed tube. The tube was washed out with ethyl acetate; the solution was dried ($MgSO_4$) and evaporated to give the lactam (130 mg, 87%), needles, m.p. 242—245° [from light petroleum (b.p. 40—60°)] (lit.,[17] 232—234°) (Found: C, 72·0; H, 10·15; N, 8·4. Calc. for $C_{10}H_{17}NO$: C, 71·8; H, 10·25; N, 8·4%), $\nu_{max.}$ (mull) 3240 and 1650 cm^{-1}, τ (CCl_4) 1·25br (1H, s, NH), 6·87 (1H, t, C*H*·NH), 7·77 (1H, d, *J* 18 Hz, *H*CH–CO), 8·93 (3H, s), and 9·04 (6H, s). A sample of this lactam, sent to Dr. Thorén, was found (i.r., o.r.d., mass spectrum, and n.m.r.) to be the same as his compound.

5,8,8-*Trimethyl*-2-*nitroso*-2-*azabicyclo*[3.2.1]*octan*-3-*one* (21).—The lactam (100 mg) in ether (5 ml) and acetic acid (1 ml) was nitrosated with nitrogen trioxide for 4 h at room temperature. The mixture was added to ice–water (50 ml.) to give the *nitroso-lactam* (21) (90 mg, 84%), yellow prisms, m.p. 183—186° [from light petroleum (b.p. 40—60°)] (Found: C, 61·15; H, 8·25; N, 14·1. $C_{10}H_{16}N_2O_2$ requires C, 61·2; H, 8·2; N, 14·25%), $\nu_{max.}$ (mull) 1730 and 1500 cm^{-1}, $\lambda_{max.}$ (EtOH) 259 nm (ε 6300), τ (CCl_4) 5·49 (1H, d, CH·N), 7·28 (1H, dd, *J* 19 and 2 Hz, *exo*-CH·CO), 7·58 (1H, d, *J* 19 Hz, *endo*-CH·CO), and 8·98, 9·01, and 9·10 (each 3H, s).

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