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

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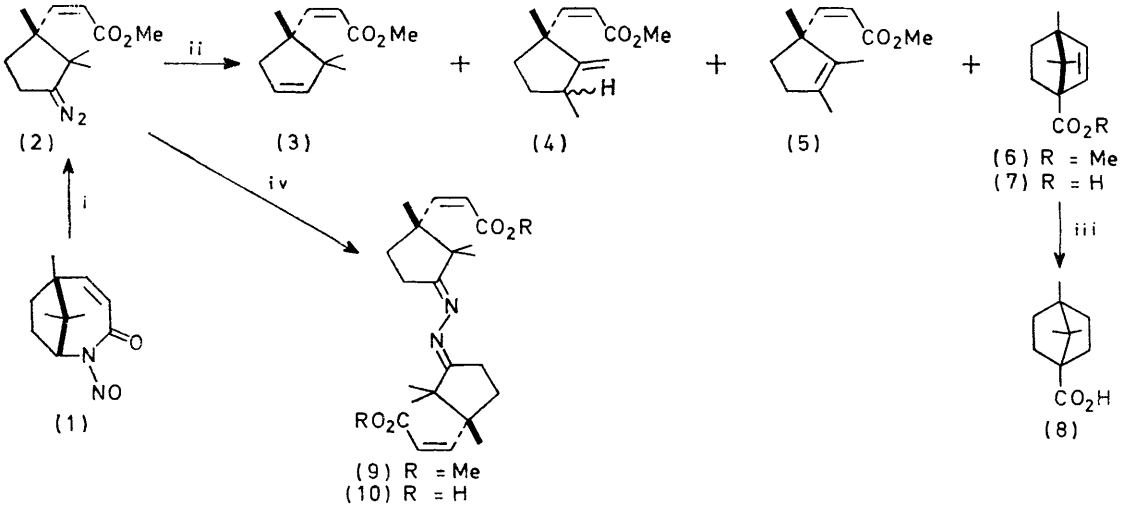
Methyl *cis*-β-(3-diazo-1,2,2-trimethylcyclopentyl)acrylate (2) decomposed in alcoholic solvents to give an insertion product, methyl 4,7,7-trimethylbicyclo[2.2.1]hept-2-ene-1-carboxylate (6), in addition to the solvolysis products arising from protonation of the diazoalkane and described in the preceding paper. This is the first example of a reaction between a diazoalkane group and an ester group, and is similar to the well-known reaction of diazomethane with ketones. A study of the effect of solvent on the reaction led to an isolated yield of 89% of the bicyclic product. The less acidic the alcohol solvent, the slower the reaction and the more bicyclic product there is. In polar aprotic solvents such as acetonitrile the azine corresponding to the diazoalkane (2) is the major product.

In the preceding paper [1] we described how the diazoalkane (2) was prepared, and how it was decomposed by mineral acid to the solvolysis products (3)—(5). We also mentioned that a small amount of a bicyclic isomer of (3)—(5) was produced. This isomer did not result from the treatment with mineral acid, but was being produced as the diazoalkane slowly decomposed in the methanol. Indeed, if the diazoalkane solution was not poured into acid, but instead simply left to decompose, the bicyclic ester was the major product. On the other hand, if the diazoalkane solution was prepared rapidly on a small scale and rapidly treated with acid, virtually none of the bicyclic ester was produced. We now describe the identification of this product and our search for the optimum conditions for its formation.



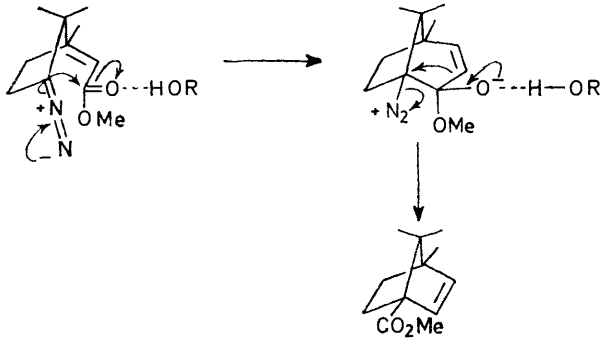
Reagents: i, NaOMe; ii, ROH; iii, H_2–Pt; iv, MeCN, or Me_2CO, or Et_3N

The diazoalkane solution could be kept for many hours when it was prepared with a concentrated solution of sodium methoxide in methanol. If, instead, the preparation of the diazoalkane was attempted with a dilute solution of sodium methoxide in methanol, the pink colour was transitory and the major product (*ca.* 50% yield) was the bicyclic ester, accompanied by the solvolysis products (3)—(5). Saponification of the mixture readily allowed the separation of the corresponding acid (7) in crystalline form in 40% yield. This acid was not αβ-unsaturated ($\nu_{max.}$ of the ester 1735 cm^{-1}, and of the acid 1700 cm^{-1}, and no maximum and only weak end-absorption in the u.v. spectrum above 210 nm), but it did contain a double bond, as shown in the n.m.r. spectrum by a clean AB system between τ 3·9 and 4·2 (J 6·1 Hz). Hydrogenation gave a dihydro-acid, m.p. 199—200°, which was optically inactive and identical with a sample of the acid (8) prepared by Winstein and Traylor.[2] Thus the bicyclic ester, produced from the diazoalkane (2), must have the structure (6), the only point of doubt being the absolute configuration. This was settled by oxidation of the acid (7) with alkaline permanganate followed by thermal decarboxylation. The product was a mixture of camphoric and isocamphoric acids, the optical rotations of both of which showed that the absolute configuration of the ester (6) was that depicted.

This product is probably formed by a sequence (Scheme) similar to that of the well-known reaction [3] of a diazoalkane with a ketone, but the combination of a diazoalkane group with an ester group in this way is new. In this example there are several factors which make such a reaction favourable, in spite of the fact that esters are generally less electrophilic than ketones. First, the reaction is intramolecular; ketones can react with diazoalkanes intermolecularly as well as intra-

[1] I. Fleming and R. B. Woodward, preceding paper.
[2] S. Winstein and T. G. Traylor, *J. Amer. Chem. Soc.*, 1956, **78**, 2597.
[3] C. D. Gutsche, *Org. Reactions*, 1954, **8**, 364.

molecularly, but no intermolecular reactions of esters with diazoalkanes of this type have ever been observed.* Secondly, the ester group will quite often be close to the diazoalkane group, having only one of the intervening σ bonds relatively free to rotate. Finally, the *gem*-dimethyl group flanking the diazoalkane group hinders



SCHEME

protonation of the diazoalkane and in consequence may make the intramolecular reaction relatively more favourable. Like the well-known reaction of diazoalkanes with ketones,[3] this intramolecular reaction also required an alcoholic solvent. When the diazoalkane (2) decomposed in any other kind of solvent, no bicyclic ester (6) was produced. Thus in benzene, for example, only the solvolysis products (3)—(5) were produced, though not in a ratio which was advantageous for the synthesis of (5).[5] We sought reaction conditions which might improve the yield. Temperature, concentration, and the concentration of the base were without effect on the yield, as was the addition of weak Lewis acids, such as aluminium isopropoxide and sodium borohydride, which merely increased the rate of reaction. Stronger Lewis acids,[6] such as boron trifluoride, gave only the solvolysis products. Solvent polarity, however, had a marked effect on product distribution. In benzene, toluene, and dioxan, the only products were the solvolysis products. The more thoroughly these solvents were dried, the slower the reaction (in benzene, over metallic sodium, decolorisation took over two weeks at room temperature), but there was no change in product distribution. Irradiation of these relatively stable solutions also caused no change in product distribution, but did speed up the decomposition. In slightly more polar solvents, such as acetone, acetonitrile, and triethylamine, decomposition was still slow but a new product was found in addition to small amounts of the solvolysis products. This was the azine (9), which we invariably hydrolysed with alkali and isolated as the corresponding acid (10). Azines are commonly observed in the decomposition of diazoalkanes.[7] What is surprising is that none of this product was detected in the benzene and dioxan runs; and yet it is the major product in the slightly more polar aprotic solvents. Little, if any, bicyclic ester (6) was formed in the aprotic solvents. Only when alcohols were used as the solvent was the bicyclic ester formed. To test the effect of different alcohols on the yield of the bicyclic ester, the diazoalkane (2) was prepared in benzene, and the solution added to a large excess of the alcohols trifluoroethanol, ethylene glycol, methanol, propan-1-ol, propan-2-ol, and t-butyl alcohol. The proportion of the bicyclic ester increased along this series in a range from 12% of the volatile products in trifluoroethanol, through 52% in methanol, to 98% in t-butyl alcohol. Only in the last case was there any azine (9) evident, in this case to the extent of *ca.* 8% of the total product. When t-butyl alcohol was used as the solvent for a larger-scale run, the tricyclic acid (7) was isolated pure in 89% yield from the nitroso-lactam (1).

The effect of the various alcohols on the yield of the bicyclic ester correlates with the acidity of the alcohols rather than with their polarity. Thus a plot of the yield of bicyclic ester against dielectric constant shows a random arrangement of points, but a plot against pK_a [8] is a reasonable straight line. Thus the alcoholic solvent is acting as an acid. There are two productive sites of protonation: the diazoalkane carbon and the oxygen of the carbonyl group. Protonation at the former site, which is probably not reversible,[9] leads to the solvolysis products (3)—(5), whereas protonation at the latter site, which is probably reversible, can lead to the bicyclic ester (6). Evidently, the less acidic the solvent, the more the protonation at the kinetically more basic site, the carbonyl group, is responsible for product formation. In other words, the least acidic solvent, t-butyl alcohol, is effectively the most selective protonator. This is reasonable if the protonation on carbon is rate-determining in the reaction leading to the solvolysis products, whereas protonation of the carbonyl group is part of a pre-equilibrium process in the reaction leading to the bicyclic ester. Thus although the reaction is much slower in t-butyl alcohol than in trifluoroethanol (about 1 day is required for complete decomposition in t-butyl alcohol, compared to a virtually instantaneous reaction in trifluoroethanol), it is much more selective for the formation of the bicyclic ester relative to the solvolysis products. In t-butyl alcohol the reaction is so slow that the by-product azine has time to appear (the azine having presumably been formed without any need for protons, as shown by its formation in aprotic solvents as well). Nevertheless, t-butyl alcohol is the optimum solvent for the production of a bicyclic ester in this example. In other molecules, however,

* Ester exchange (with solvent alcohol) *catalysed* by diazoalkanes is the only known reaction of diazoalkanes and esters; in this reaction, the diazoalkane is merely acting as a base.[4]

[4] H. Bredereck, R. Sieber, and L. Kamphenkel, *Chem. Ber.*, 1965, **89**, 1169 and references therein.

[5] See Experimental section of ref. 1.

[6] For the effect of Lewis acids on ketone–diazoalkane reactions, see H. O. House, E. J. Grubbs, and W. F. Gannon, *J. Amer. Chem. Soc.*, 1960, **82**, 4099; E. Müller, H. Kessler, and B. Zeeh, *Fortschr. Chem. Forsch.*, 1966, **7**, 128.

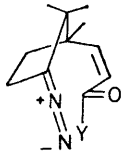
[7] G. W. Cowell and A. Ledwith, *Quart. Rev.*, 1970, **24**, 119.

[8] P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, 1959, **81**, 1050; and estimated from J. Hine and M. Hine, *ibid.*, 1952, **74**, 5266; and W. K. McEwan, *ibid.*, 1936, **58**, 1124.

[9] R. A. More O'Ferrall, *Adv. Phys. Org. Chem.*, 1967, **5**, 331.

the balance between losses due to azine formation and those due to solvolysis might favour a more acidic alcohol such as propan-2-ol.

Finally, we tried to extend the reaction by using nucleophiles other than methoxide ion. The hope was that the intermediate diazoalkane (11) would have a more electrophilic carbonyl group when a suitable group (Y) was used in place of the methoxy-group. Organometallic nucleophiles (methylmagnesium iodide, methyllithium, and sodium acetylide) attacked at the nitroso-group and gave back the lactam we had started with. Iodide and azide ion were without effect on the nitroso-lactam, and cyanide ion reacted only in methanol solu-



(11)

tion. The products in the latter case were the usual methyl esters, (3)—(6), in the usual proportions; apparently the cyanide ion acted as a base and not as a nucleophile.

EXPERIMENTAL

4,7,7-Trimethylbicyclo[2.2.1]*hept-2-ene-1-carboxylic Acid* (7).—*Optimum conditions.* The nitroso-lactam (1) [1] (250 mg) in dry tetrahydrofuran (15 ml) was added dropwise and with stirring to a solution of sodium methoxide (250 mg) in methanol (3 ml) and dry tetrahydrofuran (5 ml) cooled in ice. The result was added to t-butyl alcohol (100 ml) and kept at room temperature until the colour had disappeared (usually about 1 day). Water (100 ml) and *NNN*-trimethylanilinium hydroxide (2 ml of a 50% solution in water) were added. The mixture was heated under reflux for 24 h, cooled, washed with pentane (4 × 50 ml), acidified (dil. HCl), and extracted with ether (4 × 20 ml). The extract was dried (Na_2SO_4) and evaporated, and the residue triturated with pentane (50 ml) to leave a residue of the azine (10) (4 mg, 7%) (see later). The pentane was evaporated off and the residue recrystallised to give the *acid* (7) (191 mg, 89%), m.p. 180° (from methanol–water) (Found: C, 72·7; H, 9·2. $C_{11}H_{16}O_2$ requires C, 72·8; H, 8·9%), u.v. (EtOH) weak end-absorption with no max. above 210 nm, $\nu_{max.}$ (KBr) 1700 cm^{-1}, τ (CCl_4) −2·5 (1H, s), 3·9 (1H, d, *J* 6·1 Hz), 4·2 (1H, d, *J* 6·1 Hz), 7·7—8·8 (4H, m), and 8·85, 9·05, and 9·06 (each 3H, s). The pure *methyl ester* (6) was prepared with diazomethane (Found: C, 74·9; H, 9·2. $C_{12}H_{18}O_2$ requires C, 74·3; H, 9·3%), u.v. (EtOH) weak end-absorption, $\nu_{max.}$ (CCl_4) 1735 cm^{-1}, τ 3·9 (1H, d, *J* 6·1 Hz), 4·2 (1H, d, 6·1 Hz), 6·3 (3H, s), 7·8—8·9 (4H, m), and 8·85, 9·02, and 9·03 (each 3H, s), M^+ 179, *m/e* 166, 151, 107, 102, 93, and 91. On g.l.c. (25 ft × 1/4 in column, 15% LAC on 60—80 Celite at 150°) this ester had a retention time of 12·5 min; the esters (3)—(5) had retention times of 18, 20, and 22 min, respectively.

4,7,7-Trimethylbicyclo[2.2.1]*heptane-1-carboxylic Acid* (8).—The bicyclic acid (7) (70 mg) in methanol (20 ml) was hydrogenated over Adams catalyst (70 mg) for 45 min; hydrogen uptake had then ceased (9·5 ml, 1·02 equiv.). The product was recrystallised from methanol–water and had m.p. 199—200° (lit.,[2] 199—200°), mixed m.p., with a sample of acid (8) provided by Winstein, 199—200°. The two samples were identical in t.l.c. behaviour and in i.r. spectra.

Oxidation of the Acid (7) *to Camphoric and Isocamphoric Acids.*—The bicyclic acid [derived from (+)-camphor and therefore the mirror image of (7)] (1 g) in sodium hydroxide solution (25 ml; 10% in water) was stirred, and a solution of potassium permanganate (2·7 g) in water (25 ml) was added. The temperature spontaneously rose to 60°, and was then maintained between 60 and 80° for a further 30 min. The excess of permanganate was destroyed with methanol, and the mixture was filtered, acidified, and extracted with ether to give *2,2,3-trimethylcyclopentane-1,1,3-tricarboxylic acid* (825 mg, 61%), m.p. 220° (from water) (Found: C, 53·8; H, 6·3. $C_{11}H_{16}O_6$ requires C, 54·1; H, 6·6%), $\nu_{max.}$ (KBr) 1740 (sharp) and 1700 (broad) cm^{-1}. This acid (100 mg) was heated at 220° for 10 min. The product was separated [10] to give camphoric acid (33 mg), m.p. 186—187°, $[\alpha]_D$ (MeOH) +44·2° (lit.,[11] +47·8°), and isocamphoric acid (15 mg), m.p. 170°, $[\alpha]_D$ (MeOH) −50° (lit.,[11] −47·1°), both of which were identical in mixed m.p. and i.r. spectra with authentic samples obtained from (+)-camphor. For this experiment, the acid (7) had been prepared from (+)-camphor, and therefore had the configuration enantiomeric to that illustrated. The fact that this experiment was done in the enantiomeric series does not affect the argument in the text: the absolute configuration drawn here is used for consistency with the preceding paper, where the absolute configuration was important.

cis-β-(*1,2,2-Trimethyl-3-oxocyclopentyl*)*acrylic Acid Azine* (10).—The optimum conditions for the formation of this derivative were not investigated. It was isolated, after hydrolysis, from several different sets of reaction conditions, including the one already described. It could readily be separated from the bicyclic acid (7) and from the solvolysis product acids corresponding to (3)—(5) because of its in-

Approximate yields of the products from the decomposition of the diazoalkane (2) under various conditions

Solvent	Time for complete reaction [a]	Azine (9) (%) [b]	Bicyclic ester (6) (%)	Solvolysis products (3)—(5) (%)
Benzene	Several days	—	5	95
Dioxan	Several days	—	3	97
Triethylamine	3 days	+	2 [c]	98 [c]
Acetone	3 days	+	6 [c]	94 [c]
Acetonitrile	Several days	+	20 [c]	80 [c]
t-Butyl alcohol	2 days	8	90	2
Propan-2-ol	Several h	—	80	20
Propan-1-ol	10 min	—	63	37
Methanol	10 min	—	52	48
Ethylene glycol	0	—	50	50
Trifluoroethanol	0	—	12	88
Acetamide	2 h	—	48	52

[a] Very dependent on temperature and, for the aprotic solvents, on the extent to which the solvent is anhydrous. [b] The symbol + means that azine is at least the major product. The symbol — means that the azine was not detectable. [c] Note that these are merely percentages of the *volatile* products.

[10] O. Aschan, *Annalen*, 1901, **316**, 209.

[11] J. L. Simonsen and L. N. Owen, 'The Terpenes,' Cambridge University Press, Cambridge, 2nd edn., 1949, vol. II, p. 479.

solubility in hexane or pentane. Thus when the nitroso-lactam (1) (100 mg) in pyridine (10 ml) was treated with sodium methoxide (0·1 g), the pink colour was allowed to fade over 1 day, and the mixture was then hydrolysed with alkali, the *azine* was obtained (0·6 g crude, 0·4 g pure, 43%) as prisms, m.p. 243—246° (decomp.) (from methanol–water) (Found: C, 67·8; H, 8·5; N, 6·9. $C_{22}H_{32}O_4N_2$ requires C, 68·0; H, 8·25; N, 7·1%), $\lambda_{max.}$ (EtOH) 213 nm (ε 38,000), $\nu_{max.}$ (KBr) 1700 and 1650 cm^{-1}, τ −1·7 (2H, s), 4·8 (2H, d, *J* 13 Hz), 5·2 (2H, d, *J* 13 Hz), 7·4—8·6 (8H, m), 8·8 (6H, s), and 9·0 (12H, s), M^+ (of the methyl ester) 416, with peaks corresponding to ester fragmentation, and cleavage of the two halves, with and without loss of nitrogen. The formation of this product could also be detected and roughly assayed by t.l.c. (silica gel; elution with ether). The volatile esters moved just behind the solvent front and the azine ester moved only *ca.* 1/20th of this distance.

Effect of the Reaction Conditions on Products.—The diazoalkane was typically generated in the aprotic solvents by treatment of the nitroso-lactam (1) (200 mg) in the solvent (10 ml) with freshly prepared solid sodium methoxide (200 mg; freshly prepared and dried at 200° and 0·2 mmHg). The red solution was then allowed to decompose. The azine was assayed by t.l.c. (see before) and the volatile products were estimated by g.l.c. (see before). For the protic solvents a solution of the diazoalkane was prepared in benzene, as already described, and a sample of this solution was added to the alcohol to make the final solution 10% in benzene. The results are given in the Table.

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