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STUDIES ON HIGHLY STRAINED HETEROCYCLIC COMPOUNDS

THE REACTION OF CYCLIC IMINE AND ALKYLAZIDOFORMATE

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Abstract—The reaction of N-alkylcycloimines with alkylazidoformate was studied. With cycloimines having large angular strain, even if of low basicity, the reaction proceeded smoothly and produced stereospecific products—ring opened azidocarbamates. Whereas lesser angular strained amines or aliphatic amines required higher reaction temperature and showed an essentially different type of reaction.

Alkylaziodoformate reacts rapidly with a primary amino group to produce carbamate.[1] The reaction is a simple substitution and its mode is quite different from that of the nitrene reaction observed between azidoformate and olefins.[2] One reason for the different reactivity of azidoformate towards primary amine and olefin is thought to be the difference in nucleophilicity between a lone pair and a π-electron.

$$R{-}\underset{\displaystyle NH_2}{\underset{|}{CH}}{-}COOH + N_3COOBu \rightarrow R{-}\underset{\displaystyle NHCOOBu}{\underset{|}{CH}}{-}COOH + N_3H$$

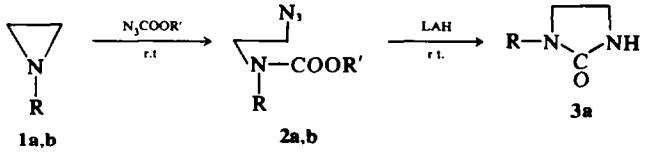
Another possible reason is that a hydrogen on the amino group accelerates the reaction by removing azidoanion through the formation of azidohydride. In our study of the reactions of highly strained heterocyclic compounds, we have been interested in the properties of the lone pair of an amino group toward azidoformate, and present here the results of a study of the reactions of N-alkylcyclic imines with alkylazidoformate.

Aliphatic tertiary amines, *e.g.* trimethyl- or triethylamine, are quite inert to azidoformate at room temperature. N-alkylaziridines, however, in spite of their lower basicity[3†] due to large angle strain, react smoothyl when mixed with azidoformate at room temperature to produce the ring opened azido carbamate **2**.

Compounds **2a,b** have characteristic absorption bands at 2100 cm^{-1} and 1698 cm^{-1} for azido and carboalkoxy groups. Their structures were confirmed by conversion to the corresponding **3a** and compared with authentic samples[4] by NMR and IR spectroscopy.

2,3-Disubstituted aziridines react similarly and the stereochemistry of the product depends on the substitute group. *trans*-Dimethylaziridine **4** gave only *erythro* carbamate **5** and *cis*-aziridine **7** gave exclusively *threo* derivative **8**.

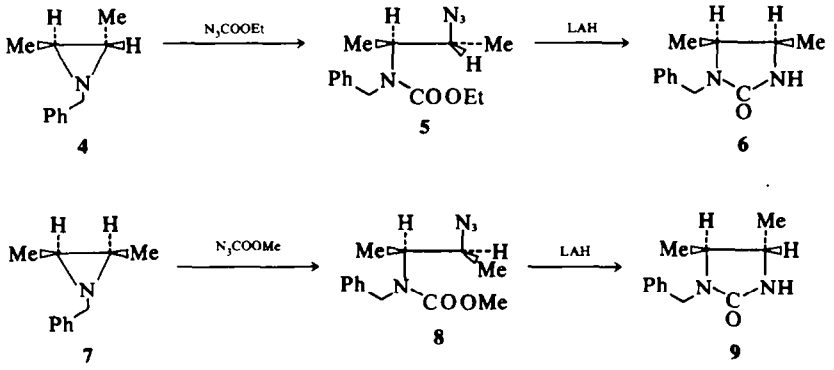
The stereochemistry of *erythro* and *threo* carbamates (**5** and **8**) was determined by a study of the conformation of the cyclic ureas derived from them. Thus, in its physical properties, *e.g.* IR, NMR or m.p., compound **6** was identical with an authentic sample prepared from *cis*-4,5-dimethyl-



1a,b **2a,b** **3a**

a: R = CH_2CH_2Ph, R' = Et
b: R = CH_2Ph, R' = Me

†p*Ka* (H_2O, 25°C) of N-methylcycloimines are aziridine 7·86, azetidine 10·40, pyrrolidine 10·40.



2(3H)-imidazolone by hydrogenation over PtO_2 followed by N-benzylation.[5,6]

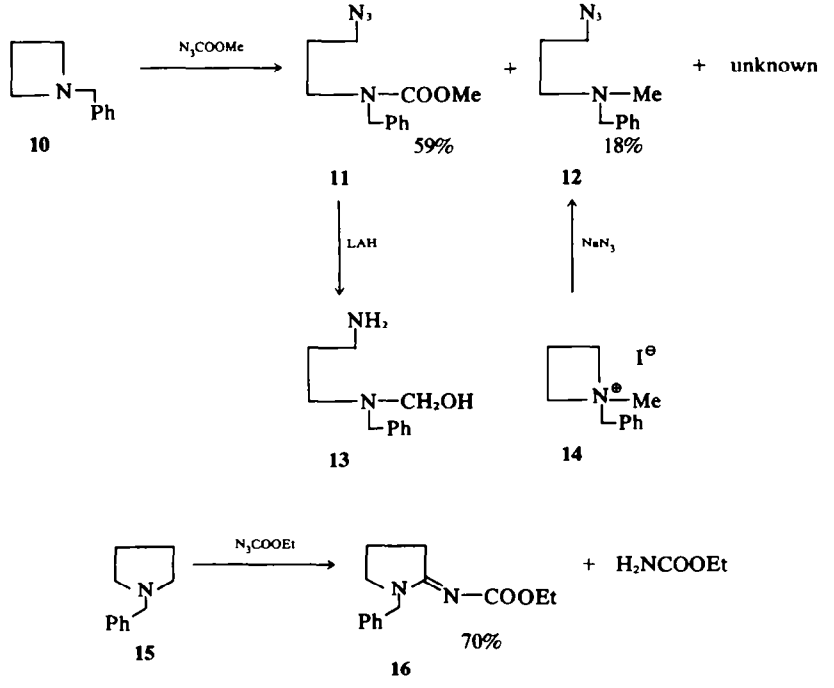
The 4-membered ring amino compounds azetidines usually have higher basicity than aziridines.[3] But reaction of azetidines with azidoformate was much slower than that of aziridine derivatives. The reaction of compound **10** required 5 days at room temperature for completion, the products being **11** and **12**.

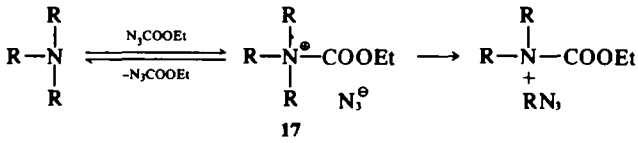
LAH reduction of azidocarbamate **11** gave only aminoalcohol **13**, and no cyclic urea as observed in the reduction of **2a**. An authentic sample of **12** was prepared by the reaction of **14** with sodium azide.

The 5-membered ring compound **15** was much less reactive to azidoformate. No reaction was observed even after the mixture had been left for one month. By heating at 70° however, N_2 gas was evolved, clearly showing that a different type of reaction was occurring. The products isolated in good yield by distillation were cyclic imine **16** and ethylcarbamate. The structure of cyclic imine **16** was identified by its characteristic IR at 1580 cm^{-1} and the fact that reduction over platinum oxide gave N-benzylpyrrolidine **15** and ethylcarbamate.

The fact that the less basic nitrogen of aziridine derivatives reacts easily with azidoformate clearly suggests that the normal tertiary amino group is also reactive to azidoformate.

It is generally known that the azido anion is a very strong nucleophile. This anion therefore rapidly attacks the quaternary ammonium intermediate **17** forcing the reaction back toward the starting materials.[7] However, tertiary amino groups having large angular strain undergo an essentially different reaction in which the release of strain has an important effect. In this reaction, azidoanion





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should be attacked to R to produce ring opened compounds.*

The reaction of azidoanion on aziridine is stereospecific and this means that the reagent must approach along the line of the C–N bond cleaved. We can see other examples of such stereospecificity in certain reactions of cyclopropanes.[9,10,11]

EXPERIMENTAL

M.ps are corrected. NMR spectra were recorded with Varian A-60 and T-60 spectrometers and IR spectra were obtained on a Hitachi Model EPI-G3 spectrophotometer. Alkylazidoformates were prepared according to the procedure of Lwowski *et al.*[12] Ethyleneimine was commercially available. 1-Benzylaziridine[13] and 1-phenethylaziridine[14] were prepared according to the literature.

Reaction of 1-*alkylaziridine* (**1a** or **1b**) *with alkylazidoformate.* An equimolar mixture of **1a** or **1b** with alkylazidoformate was kept for 4 days at room temp, then distilled to give **2a** or **2b** as a colorless liquid. Compound **2a**: b.p. 155°/0·04 mmHg yield was quantitative, (Found: C, 59·24; H, 6·95; N, 21·34, requires: C, 59·52; H, 6·92; N, 21·36%), IR ν_{max} (neat) 2100, 1698 cm^{-1}; NMR ($CDCl_3$) (δ) 7·2 (5H, s), 4·15 (2H, q), 3·5 (2H, t), 3·25 (4H, s), 2·8 (2H, t), 1·2 (3H, t). Compound **2b**: b.p. 110–115°/0·1 mmHg (71%), (Found: C, 56·98; H, 6·17; N, 22·86, requires: C, 56·40; H, 6·02; N, 23·92%), IR ν_{max} (neat) 2100, 1698, 1475, 1407 cm^{-1}; NMR ($CDCl_3$) (δ) 7·2 (5H, s), 3·8 (5H, s), 2·7 (4H, m).

1-*Phenethyl*-2-*imidazoline* (**3a**). A soln of **2a** (710 mg; 2·7 mmole) in 10 ml ether was treated with excess LAH. When the reaction ceased, water was added and the mixture was extracted with CH_2Cl_2 to obtain 520 mg of a white crystalline product.

Recrystallization from CCl_4 gave **3a** (235 mg) m.p. 145·5°, 47%. (Found: C, 69·70; H, 7·44; N, 14·70, MW 192·4 requires: C, 69·44; H, 7·42; N, 14·73%, MW 190·24). **3a** gave simple m.p. in a mixture with an authentic sample.[4]

1-*Benzyl*-2,3-trans-*dimethyl*-, *and* 1-*benzyl*-2,3-cis-*dimethylaziridine* (**4** *and* **7**). Dimethylaziridines were prepared according to the procedure of Hassner *et al.*[15] A mixture of *trans*- or *cis*-dimethylaziridine and excess of triethylamine was treated with the calculated amount of benzyl bromide in the usual manner,[13] then distilled to give **4** or **7**. Compound **4**: b.p. 66–69°/2 mmHg (42%), (Found: C, 81·81; H, 9·42; N, 8·78 requires: C, 81·94; H, 9·38; N, 8·69%), NMR ($CDCl_3$) (δ) 7·35 (5H, s), 3·7 (H, s), 3·6 (H, s), 1·9 (2H, m), 1·3 (6H, d). Compound **7**: b.p. 50–57°/1 mmHg (30%), (Found: C, 81·24; H, 9·48; N, 8·52, requires: C, 81·94; H, 9·38; N, 8·69%), NMR ($CDCl_3$) (δ) 7·35 (5H, s), 3·5 (2H, s), 1·5 (2H, m), 1·15 (6H, d).

Reaction of 1-*benzyl*-2,3-trans-*dimethylaziridine* **4** *with ethylazidoformate.* A mixture of **4** (1·61 g; 10 mmole) and ethyl azidoformate (1·3 g; 12 mmole) was heated at 60–65° for 3 days. After removal of excess ethylazidoformate by distillation under reduced pressure, the residue was chromatographed on 200 g of neutral Al_2O_3, eluting with ether-pentane (1:9). Distillation of the eluate gave the *erythro*-carbamate **5** as a colourless liquid, b.p. 120°/0·2 mmHg, 72·5% (Found: C, 61·15; H, 7·34; N, 19·77, requires: C, 60·85; H, 7·30; N, 20·28%), IR ν_{max} (neat) 2100, 2075, 1696 cm^{-1}; NMR ($CDCl_3$) (δ) 7·4 (5H, s), 4·6 (2H, s), 4·2 (2H, q), 3·7 (2H, m), 1·3 (9H, t).

Reaction of 1-*benzyl*-2,3-cis-*dimethylaziridine* **7** *with methylazidoformate.* By a procedure analogous to the above reaction, *threo*-carbamate **8** was obtained, b.p. 110°/0·04 mmHg, 92% (Found: C, 59·80; H, 7·02; N, 20·28, requires: C, 59·52; H, 6·92; N, 21·36%), IR ν_{max} (neat) 2100, 2080, 1700 cm^{-1}; NMR ($CDCl_3$) (δ) 7·3 (5H, s), 4·7 (2H, s), 3·78 (2H, m), 3·78 (3H, s), 1·25 (3H, d), 1·1 (3H, d).

1 - *Benzyl* - 4,5 - cis - *dimethyl or* 1 - *benzyl* - 4,5 - trans - *dimethyl* - 2 - *imidazolidone* (**6** *or* **9**). *Erythro*- or *threo*-carbamate **5** or **8** was hydrogenated with excess LAH in ether at room temp. When the reaction was complete, water was added to decompose excess LAH, the solvent was removed, and the residue was recrystallized from n-hexane. Compound **6**: m.p. 121–122°, 60% (Found: C, 70·41; H, 7·96; N, 13·98, requires: C, 70·56; H, 7·90; N, 13·72%), IR ν_{max} ($CHCl_3$) 3425, 1693 cm^{-1}; NMR ($CDCl_3$) (δ), 7·28 (5H, s), 4·77 (H, d), 3·89 (H, d), 3·65 (2H, m), 1·1 (3H, d), 1·04 (3H, d). **9**, m.p. 105–106°, 60% (Found: C, 70·66; H, 8·00; N, 13·58, requires: C, 70·56; H, 7·90; N, 13·72); IR ν_{max} ($CHCl_3$) 3430, 1698 cm^{-1}; NMR ($CDCl_3$) (δ) 7·27 (5H, s), 4·72 (H, d), 4·05 (H, d), 3·2 (2H, d), 1·15 (3H, d), 1·1 (3H, d).

Reaction of 1-*benzylazetidine* **10** *with methylazidoformate.* 1-Benzylazetidine **10** was prepared according to the literature.[16] A mixture of **10** (200 mg; 1·36 mmole) and of methylazidoformate (300 mg; 2·97 mmole) was kept for 5 days at room temp. When VPC showed that azetidine had completely disappeared from the mixture, it was chromatographed on 25 g of neutral Al_2O_3. From the fraction eluted by n-pentane-ether (9:1) **12**. b.p. 80°/1 mmHg, 50 mg (18%) was obtained. From the fraction eluted by n-pentane-ether (1:1) **11** b.p. 110°/0·04 mmHg, 200 mg (59%) was obtained. Compound **11** (Found: C, 57·78; H, 6·53; N, 22·30, requires: C, 58·05; H, 6·50; N, 22·57%), IR ν_{max} (neat) 2940, 2090, 1705 cm^{-1}; NMR ($CDCl_3$) (δ) 7·28 (5H, s), 4·43 (2H, s), 3·7 (3H, s), 3·2 (4H, d, t), 1·75 (2H, q). Compound **12** (Found: C, 64·00, H, 18·04; N, 27·48, requires: C, 64·68; H, 7·90; N, 27·43%), IR ν_{max} (neat) 2940, 2790, 2090 cm^{-1}; NMR ($CDCl_3$) (δ) 7·25 (5H, s), 3·40 (2H, s), 3·2 (2H, t), 2·35 (2H, t), 2·1 (3H, s), 1·65 (2H, q).

LAH *reduction of methyl* N-(3-*azidopropyl*)-N-*benzylcarbamate* **11**. Azidocarbamate **11** (120 mg; 0·45 mmole) was added to a soln of LAH (30 mg; 0·78 mmole) in 5 ml ether and the mixture was stirred for 3 h at room temp. When the reaction was complete, water was added and the soln was extracted with CH_2Cl_2. Distillation of the

*The structure of the intermediates **17** which derive from N-alkyl aziridines is the same as that of protonated N-carboalkoxy aziridines. The reactions of the latter were studied by Iwakura *et al.*[8]

CH_2Cl_2 soln gave **13** (50 mg 57%) b.p. 130°/0·04 mmHg; IR ν_{max} (neat) 3350, 3280, 2940, 2790 cm^{-1}; NMR ($CDCl_3$) (δ) 7·3 (5H, s), 3·5 (2H, s), 2·7 (2H, t), 2·4 (2H, t), 2·2 (2H, s), 1·8 (2H, t).

Reaction of 1-*benzyl*-1-*methylazetinium iodide* **14** *with sodium azide.* Compound **14**, prepared in the usual manner,[17] was treated with a soln of excess sodium azide in water. The reaction was complete after 1 h at room temp, giving **12** in good yield.

Reaction of 1-*benzylpyrrolidine* **15** *with ethylazido formate.* A mixtrue of **15**[18] (2 g; 12·4 mmole) and ethylazidoformate (2·0 g; 17·5 mmole) was heated at 70–75° under N_2. During 6 h, 320 ml (84%) of N_2 was generated. After gas evolution had ceased, the mixture was distilled to give a colorless oil (b.p. 120–125°/0·04 mmHg) which crystallized at room temp. Recrystallization from n-hexane, gave **16**, m.p. 89–90° (36%). By further distillation of the mixture, 0·4 g ethylcarbamate and 0·8 g starting material **15** were recovered. VPC, measurement showed that the yield of **16** was 52·4%; 25% of starting material was recovered.

Compound **16** (Found C, 68·43; H, 7·46; N, 11·17, requires: C, 68·27; H, 7·37; N, 11·37%), UV λ_{max} = 245 nm (20000); IR ν_{max} ($CHCl_3$) 1675, 1580, 1495, 1250 cm^{-1}; NMR ($CDCl_3$) (δ) 7·25 (5H, s), 4·65 (2H, s), 4·13 (2H, q), 3·25 (2H, t), 3·10 (2H, t), 1·9 (2H, t . t), 1·3 (3H, t).

Hydrogenolysis of ethyl N-(1-*benzyl*-2-*pyrrolidinyl*-*idene*) *carbamate* **16**. A soln of **16** (246 mg; 1 mmole) in a suspension of PtO_2 (10 mg) in 10 ml EtOH was stirred under 4 atmospheres of H_2 at room temp for 12 h. After removal of the catalyst, distillation gave a 1:1 mixture of **15** (b.p. 70–80°/15 mmHg), and ethylcarbamate. The yield was 90%.

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