A STUDY OF LACTAMS.

XIV. ALKYLATION PRODUCTS OF 3-SUBSTITUTED LACTIM ESTERS WITH PIPERIDONE-2 DIMETHYL SULFATE AND WITH TRIETHYLOXONIUM BORON FLUORIDE AND THEIR REACTIONS

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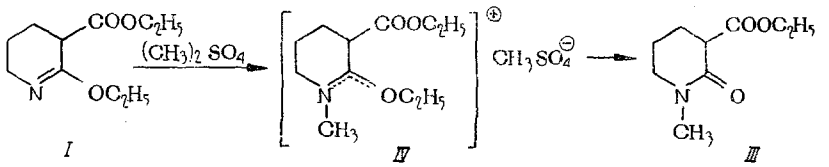
Here we have investigated the alkylation of 2-ethoxy-3-carbethoxy-3,4,5,6-tetrahydropyridine (I) and its 3-ethyl derivatives (II) with dimethyl sulfate and triethyloxonium fluoroborate; we have also investigated the possibility of utilizing intermediate complexes of these reactions in order to obtain new heterocyclic compounds.

In a previous communication [1] we described the transformation of I into N-methyl-3-carbethoxy-piperidone-2 (III) under the influence of dimethyl sulfate. As a result of this reaction we were able to distinguish the steps in the reaction, separate the intermediate complex (IV) of I with dimethyl sulfate, and study its transformation into III:



Benson and Cairns, who first proposed such a scheme for the transformation of lactim esters into N-alkyl-lactams [2], gave as an example the isomerization of O-methyl caprolactim into N-methyl caprolactam. Later it was shown that similar complexes may be obtained by the interaction of N-alkyl-lactams or of N-disubstituted amides of acids with dimethyl sulfate [3, 4], and with triethyloxonium fluoroborate [5-7], however, no description has been given of this type of complex being obtained from lactim esters.

In the alkylation of I and II with triethyloxonium fluoroborate, compounds V and VII were obtained—the fluoroborates of 1-ethyl- and of 1,3-diethyl-2-ethoxy-3-carbethoxy-3,4,5,6-tetrahydropyridine. However, in the interaction of II with dimethyl sulfate, 1-methyl-3-ethyl-3-carbethoxy-piperidone-2 (VIII) and methyl-ethyl sulfate were obtained. As a result of this reaction the intermediate complex could not be isolated. (See scheme A on top of next page.)

To explain the reduced yields of IV in comparison with the fluoroborate complexes V-VII, we made a study of their thermal stability.

It was shown that the fluoroborate complex V has a higher thermal stability than the methyl sulfate (IV); substitution of an alkyl group in position 3 increases the lability of both the fluoroborate and of the methyl sulfate complexes.

From the results obtained on the interaction of I and II with dimethyl sulfate it may be concluded that the transformation of I-II into III and VIII takes place through intermediate methyl sulfate complexes which, like the complex of dimethylformamide with dimethyl sulfate [3] break up into the corresponding N-methyl lactams and methylethyl sulfate. (See scheme B on next page).

Here the temperature and the nature of the R group have an important influence on the position of the equilibrium, which is a critical factor for the production of compounds IV-VII. A considerable difference in

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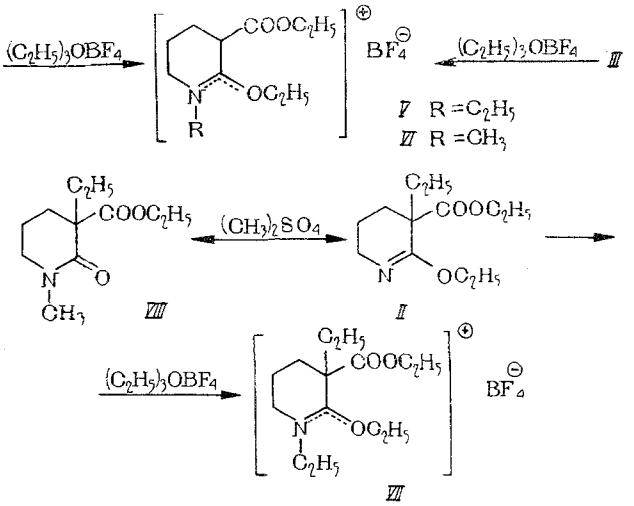
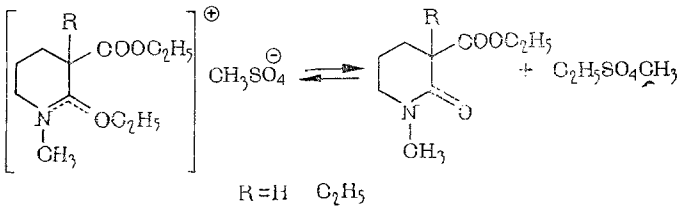


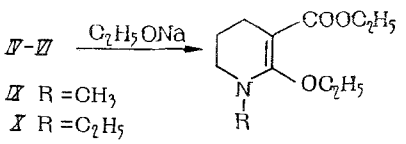
Scheme A.



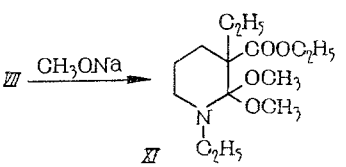
Scheme B.

the properties was found also in the interaction of the fluoroborate and the methyl sulfate complexes (IV-VI) with sodium ethoxide. Previously it was shown that the breakdown of the methyl sulfate and fluoroborate complexes of N-methyl pyrrolidone-2 with sodium ethoxide occurs with the formation of the acetal of the lactam—2,2-diethoxy-N-methyl pyrrolidone, the yield of which from the methyl sulfate complex was higher than that obtained from the fluoroborate complex [5, 8].

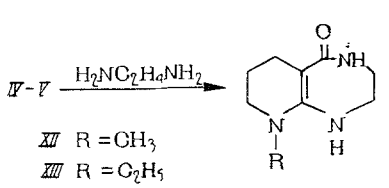
When compounds IV-VI were broken down by sodium ethoxide the action took place with the formation not of acetals, but of enamines (IX, X); in the case of the fluoroborate complexes yield of the latter was greater:



In the interaction of VII with sodium methoxide, dimethylacetal 1,3-diethyl-3-carbethoxypiperidone-2 (XI) was obtained:



The methyl sulfate [8, 9] and fluoroborate [7] complexes react actively with nucleophilic reagents. We have made use of this property in complexes IV-V, as well as of the presence in them of a secondary reaction center ($COOC_2H_5$-groups) for building up the system: pyrido (2,3-e) (1,4)-diazepine by condensation of IV-V with ethylenediamine:



EXPERIMENTAL

Methylsulfate of 1-methyl-2-ethoxy-3-carbethoxy-3,4,5,6-tetrahydropyridine (IV). A. A mixture of 15 g 2-ethoxy-3-carbethoxy-3,4,5,6-tetrahydropyridine [10] (I) and 9.5 g of dimethylsulfate were agitated for 17 h at 20-22°. The agitation was discontinued when the index of refraction n_D^{22} reached 1.4622 and showed no further change for one hour. The mixture was washed 3 times with 20 ml of anhydrous ether, which was then evaporated off, the last remains being extracted in vacuum. We obtained 20.4 g (83%) of IV, $n_D^{22} = 1.4670$. Found, %: C 43.71; H 7.19; N 4.23; S 10.12. Formula $C_{12}H_{23}NO_7S$. Calculated, %: C 44.31; H 7.08; N 4.31; S 9.85. $\nu_{COOC_2H_5}$ 1740 cm^{-1}, $\nu_{C=N}$ 1680 cm^{-1}, $\nu_{S=O}$ 1015 and 1205 cm^{-1} [4].

B. A mixture of 10 g I and 6.3 g dimethyl sulfate were heated for 2 h at 70-72°. After cooling, by similar treatment (see method A) we separated 11.6 g (71%) IV, $n_D^{26} = 1.4700$. From the ethereal solution we obtained 1.1 g (6.8%) of ethylmethyl sulfate by distillation: bp 60-61° (4-5 mm); $n_D^{27} = 1.3990$; and 1.65 g (10%) of III, bp 132-134° (4-5 mm); $n_D^{25} = 1.4740$ [1].

C. A mixture of 10 g I and 6.3 g dimethyl sulfate was heated for 16 h at 100-105°. A strong exothermic reaction started at 70°. After cooling, by a similar procedure (see method A) we obtained 6.55 g (40%) of IV, and from the ethereal extract we obtained 3.9 g (24%) of methylethyl sulfate, bp 90-95° (18-20 mm); $n_D^{25} = 1.3982$; and 4 g (24.5%) of III, bp 140-145° (5 mm), $n_D^{25} = 1.4728$.

1-Ethyl-2-ethoxy-3-carbethoxy-3,4,5,6-tetrahydropyridine Fluoroborate (V). A mixture of 10 g I and 9.6 g triethyloxonium fluoroborate was agitated for 2 h at 22°. For the first hour the temperature was held at 36°, and two layers were formed. The upper ethereal layer was separated, and the lower was washed three times in ahydrous ether; the ether was evaporated in vacuum, and 15 g (95%) of V was obtained. After prolonged standing in a refrigerator, complex V crystallized out as colorless flakes which rapidly deliquesced in air. Found, %: C 43.28; H 6.73. Formula $C_{12}H_{22}F_4NO_3B$. Calculated, %: C 45.71; H 6.63. $\nu_{COOC_2H_5}$ 1732-1752 cm^{-1}, $\nu_{C=N}$ 1670 cm^{-1}; $\nu_{BF_4^-}$ 1060 cm^{-1} [8].

N-Methyl-3-ethyl-3-carbethoxypiperidone-2 (VIII). A. A mixture of 4.55 g 2-ethoxy-3-ethyl-3-carbethoxy-3,4,5,6-tetrahydropyridine [1] (II) and 2.52 g dimethyl sulfate were heated for 2 h at 90°, when a weak exothermic reaction occurred; the mixture was cooled, 20 ml of ether was added, and the mixture was treated with 10 ml 50% potash solution at 5°. The aqueous layer was separated and extracted three times with 10 ml ether. The combined ethereal solution was dried, the ether evaporated off, and the remainder of the ether distilled off in vacuum. We obtained 3.52 g (83%) of VIII, bp 150-158° (11-12 mm). For analysis the substance was redistilled, bp 117-118° (3 mm), $n_D^{24} = 1.4730$. Found, %: C 61.48; H 9.25; N 6.41. Formula $C_{11}H_{19}NO_3$. Calculated, %: C 61.97; H 8.92; N 6.57. $\nu_{COOC_2H_5}$ 1740 cm^{-1}, $\nu_{CO\text{-amide}}$ 1650 cm^{-1}.

B. A mixture of 10 g II and 5.5 g dimethyl sulfate were agitated at 25° for 40 h. The process was controlled by thin-layer chromatography on SiO_2 (ethylacetate–hexane, 2:3; development with iodine vapor). At the end of the run the spot of VIII appeared on the chromatogram together with a small amount of the original substance. The reaction mixture was distilled in vacuum. We obtained 6 g methylethyl sulfate, bp 60-65° (4-5 mm), $n_D^{25} = 1.4039$ [1], 2 g of the original complex II, bp 95-100° (4-5 mm), $n_D^{25} = 1.4565$ [1], and 6.75 g VIII (90% of the amount reacting with II), bp 131-134° (4-5 mm), $n_D^{25} = 1.4718$.

1,3-Diethyl-2-ethoxy-3-carbethoxy-3,4,5,6-tetrahydropyridine Fluoroborate (VII). A mixture of 10 g II and 9.5 g triethyloxonium fluoroborate was agitated for 12 h at 24°; after 5 h two layers formed. The upper ethereal layer was separated, and the lower was washed three times with 15 ml of anhydrous ether; the ether was evaporated in vacuum; yield 13.25 g VII. Found, %: C 48.37; H 7.40. Formula $C_{14}H_{26}F_{24}NO_3B$. Calculated, %: C 48.98; H 7.55. $\nu_{COOC_2H_5}$ 1750 cm^{-1}, $\nu_{C=N}$ 1647 cm^{-1}, $\nu_{BF_4^-}$ 1060 cm^{-1}. From the ethereal solution we obtained 2 g of the original II, bp 95-100° (4-5 mm), $n_D^{24} = 1.4511$ [1].

Thermal Disintegration of IV, V, and VII. A. After distillation of 3.25 g IV at 5 mm pressure we obtained 1.05 g (75%) of methylethyl sulfate, bp 67-70° (5 mm), $n_D^{27} = 1.3975$ and 1.3 g (70%) of III, bp 137-140° (5 mm), $n_D^{27} = 1.4695$.

B. Compound V (3.3 g) heated to 200° for 10 min at a pressure reduced to 1 mm. After cooling and washing the residue with 5 ml of anhydrous ether the ethereal layer was separated, and the ether evaporated in vacuum; we obtained a yield of 3.1 g (94%) of the original V. Similarly from 3.3 g VII, 2.65 g (80%) remained unchanged.

N-Ethyl-2-ethoxy-3-carbethoxy-1,4,5,6-tetrahydropyridine (X). A. To a solution of sodium ethoxide (from 0.95 g Na and 30 ml absolute alcohol) was added 12.6 g V over a period of 30 min at 0-2°; the mixture

was maintained at this temperature for 1 h, filtered, and the precipitated $NaBF_4$ was washed in cooled alcohol, the alcohol evaporated, and by distillation we obtained 7.5 g (82%) X, bp 133-139° (5-6 mm). For analysis we redistilled, obtaining a compound with bp 119-120° (2 mm), $n_D^{24} = 1.5101$, λ_{max} (in alcohol) 293 nm, log $\varepsilon = 4.23$, $\nu_{COOC_2H_5} = 1690$ cm^{-1}, $\nu_{C=C}$ 1575 cm^{-1}. Found, %: C 62.92; H 9.24; N 6.56. Formula $C_{12}H_{21}NO_3$. Calculated, %: C 63.44; H 9.25; N 6.17.

From 5 g IV by treatment with 5 ml 50% potash solution, after separation of the KBF_4, by extraction with ether and redistillation we obtained 2.75 g of a mixture of X and N-ethyl-3-carbethoxypiperidone-2, bp 135-136° (5 mm), $n_D^{21} = 1.4995$. The absorption bands characteristic of X were: $\nu_{COOC_2H_5} = 1690$ cm^{-1}, $\nu_{C=C}$ 1570 cm^{-1}; the bands characteristic of the lactam were: $\nu_{COOC_2H_5} = 1740$ cm^{-1}; $\nu_{CO\text{-amide}} = 1660$ cm^{-1}.

1,3-Diethyl-2,2-dimethoxy-3-carbethoxypiperidone (XI). To a solution of sodium methoxide (obtained from 0.8 g Na and 20 ml absolute methanol) was added 7.1 g VII over a period of 15 min at −10°, and the mixture was maintained at this temperature for 30 min. By the treatment described for the separation of X we obtained 3 g (56%) of XI, bp 115-116° (4-5 mm), $n_D^{24} = 1.4631$, $\nu_{COOC_2H_5} = 1730$ cm^{-1}. Found, %: C 61.90 H 10.24; N 5.25. Formula $C_{14}H_{27}NO_4$. Calculated, %: C 61.54; H 9.89; N 5.13.

9-Alkyl-5-oxa-1H,2,3,4,5,6,7,8,9-octahydropyrido (2,3-e) (1,4)-diazepine (XII). To 6 g of ethylenediamine was added 3.25 g of complex III in drops. The mixture was heated for one hour at 110-120° when the alcohol which separated off was evaporated; the mixture was cooled in a refrigerator overnight, the precipitate filtered, carefully centrifuged, and washed with ether; yield 1.1 g (61%) of XII (R = CH_3). The product was soluble in water, alcohol, and chloroform, but insoluble in ether and in hexane. For analysis the product was crystallized from ethylacetate (1:25), mp 151-152°. Found, %: C 59.87; H 8.35; N 23.54. Formula $C_9H_{15}N_3O$. Calculated, %: C 59.67; H 8.29; N 23.20. $\nu_{CO\text{-amide}}$ 1625 cm^{-1}. Similarly, starting from 3.15 g of III and 1.8 g of ethylenediamine, we obtained 1.56 g of XIII (R = C_2H_5), mp 149-150° (from ethylacetate, 1:15). Found, %: C 61.73; H 8.72; N 21.37. Formula $C_{10}H_{17}N_3O$. Calculated, %: C 61.54; H 8.72; N 21.54. $\nu_{CO\text{-amide}}$ 1630 cm^{-1}.

CONCLUSIONS

By alkylation of 2-ethoxy-3-carbethoxy-3,4,5,6-tetrahydropyridine and its 3-ethyl derivative with dimethyl sulfate and triethyloxonium fluoroborate we synthesized the methyl sulfate of 1-methyl-2-ethoxy-3-carbethoxy-3,4,5,6-tetrahydropyridine, and also the fluoroborate of 1-ethyl and 1,3-diethyl-2-ethoxy-3-carbethoxy-3,4,5,6-tetrahydropyridine. In the interaction of these complexes with sodium alkoxides we obtained N-methyl-N-ethyl-2-ethoxy-3-carbethoxy-1,4,5,6-tetrahydropyridine and 1,3-diethyl-2,2-dimethoxy-3-carbethoxypiperidine. By condensation of the complexes with ethylenediamine we synthesized 9-alkyl-5-oxa-1H,2,3,4,5,6,7,8,9-octahydropyrido (2,3-e) (1,4) diazepines.

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