β-LACTAMS

PART IV. SYNTHESIS OF 3,3-DIPHENYLAZETIDINONES-2

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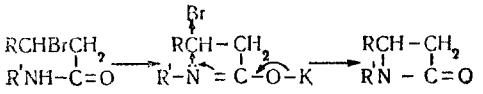
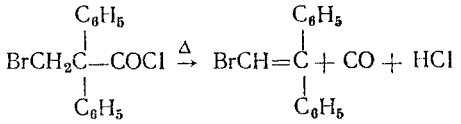
Translated from Izvestiya Akademii Nauk SSSR, Otdelenie Khimicheskikh Nauk,
No. 1, pp. 83-88, January, 1961
Original article submitted July 16, 1959

We have previously developed a method for the synthesis of β-lactams from the amides of β-bromosubstituted carboxylic acids [1, 2]

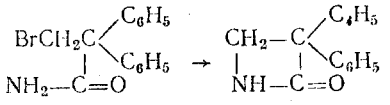


The preparation of lactams from all the amides of β-bromohydrocinnamic acid investigated was accompanied by a side reaction in which unsaturated amides were formed. Naturally it was thought that cyclization of the amides of β-bromosubstituted carboxylic acids which did not have a α-hydrogen should go in one sense only. This cyclization appeared still more interesting because 3-substituted azetidinones-2 are known to be biologically active substances which render the central nervous system passive [3, 4].

The readily accessible amides of α,α-diphenyl-β-bromopropionic acid were chosen for cyclization. They were prepared in the usual way from α,α-diphenyl-β-bromopropionyl chloride. During the preparation of the acid chloride it was observed to undergo an interesting decomposition to 1,1-diphenyl-2-bromoethylene, with the evolution of carbon monoxide and hydrogen chloride. The impure acid chloride decomposed even on prolonged heating in vaccum on the water bath. However, the recrystallized substance was considerably more stable; it had to be heated to 180-200° to bring about breakdown:

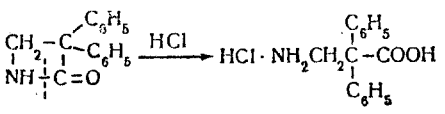


Decarbonylation reactions of acid chlorides have been observed before, but at considerably higher temperature or in the presence of such catalysts as H_2SO_4 or $AlCl_3$ [5, 6]. All the α,α-diphenyl-β-bromopropionamides synthesized by us cyclized easily into the corresponding azetidinones-2 (Table 1). In particular, 3,3-diphenylazetidinone-2 (unsubstituted at nitrogen) was obtained in quantitative yield:

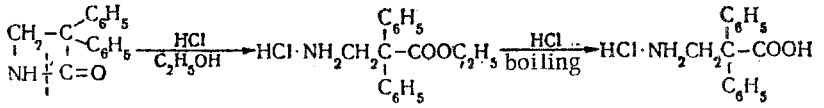


Until recently, all the methods for synthesizing β-lactams were shown to be inapplicable to the synthesis of azetidinones-2, unsubstituted at the nitrogen atom. It was not until 1958 that an azetidinone-2 substituted at position "3" was successfully prepared, starting from an ester or a hydrochloride of β-aminoacyl chloride [7, 8].

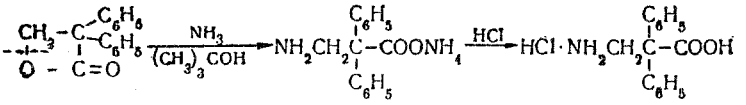
The structure of 3,3-diphenylazetidinone-2 was confirmed by acid hydrolysis when α,α-diphenyl-β-aminopropionic acid separated as its hydrochloride



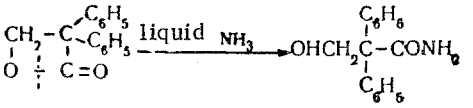
When the lactam is hydrolyzed with ethanolic hydrogen chloride, even in the presence of considerable moisture, the initial product of reaction is the hydrochloride of ethyl α,α-diphenyl-β-aminopropionate, which in its turn can be hydrolyzed with concentrated HCl to the aminoacid hydrochloride.



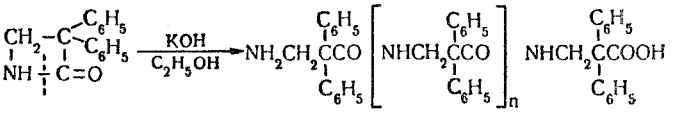
The same β-aminoacid was formed by the action of gaseous ammonia on α,α-diphenyl-β-propiolactone in anhydrous trimethylcarbinol:



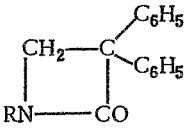
α,α-diphenyl-β-hydroxypropionamide was obtained by the aminolysis of α,α-diphenyl-β-propiolactone with liquid ammonia:



The potassium salt of the polymeric aminoacid is obtained by the action of alcoholic alkali on 3,3-diphenyl-azetidinone-2.



Apart from the indirect evidence in [9], this is the first experimental confirmation that it is possible to polymerize β-lactams with four-membered rings. We carried out pilot experiments on the polymerization of 3,3-diphenylazetidinone-2 in the presence of traces of metallic sodium and obtained a high melting polyamide which was insoluble in the usual organic solvents but soluble in phenol and cresol. The properties of this polymer are being studied.

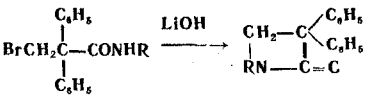
TABLE 1. Preparation and Properties of β-Lactams $BrCH_2C(C_6H_5)_2CONHR \rightarrow$ 

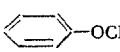
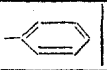
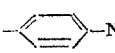
R	Reaction conditions		Yield, %	M. p., °C (from alcohol)	Found, %			Calculated, %		
	base	solvent			C	H	N	C	H	N
H	KNH_2	NH_3 liq.	95,2	168—169	80,75	5,95	6,58	80,71	5,83	6,97
	C_2H_5ONa	Abs. ethanol	94,3							
	KOH	"	95,2							
C_6H_5	KNH_2	NH_3 liq.	98,3	168—170	84,15	5,66	4,94	84,26	5,66	4,35
	KOH	Methylethyl-ketone	98,0							
n-$CH_3OC_6H_4$—	C_2H_5ONa	Abs. ethanol	94,0	148—149	80,02	5,66	4,45	80,24	5,59	4,25
n-$NO_2C_6H_4$—	C_2H_5ONa	"	90,0	177—179	73,37	4,38	8,27	73,25	4,65	8,13
$C_6H_5CH_2$—	NaSH	Alcohol		140—141	83,86	5,88		84,3	6,07	

It was shown previously [2] that the rate of cyclization of β-bromosubstituted carboxylic acid amides was determined to a noticeable degree by the acidity of the initial amide. Therefore, the rate increased on introducing a secondary substituent at the para-position on the benzene ring attached to the nitrogen atom. Measurements of the rate of cyclization of α,α-diphenyl-β-bromopropionamides showed (Table 2) that the type of influence exerted by substituents remained the same as for β-bromohydrocinnamides. However the absolute rate values were considerably

higher for α,α-diphenyl-β-bromopropionamides. Amides unsubstituted at the nitrogen atom cyclized noticeably more slowly than amides substituted at nitrogen.

TABLE 2. Rate of Cyclization of α,α-diphenyl-β-bromopropionamides*



R	H				R	H	CH_3
Time, min	Amide used up, % of initial				Time, min	Amide used up, % of initial	
	In dioxane at 0°				In ethanol at 35°		
2	—	90,0	94,0	100	5	9,0	26,5
4	—	93,2	95,2	—	15	17,5	36,5
7	—	94,5	98,0	—	30	31,5	48,5
10	0	100	100	—	60	44,5	77

*Equimolar quantities (equal to 0.01 M/liter) were taken in all experiments.

EXPERIMENTAL

Preparation of α,α-diphenyl-β-bromopropionyl chloride. To a solution of 20.9 g α,α-diphenyl-β-bromopropionic acid in absolute benzene 14.21 g PCl_5 was added. The solution was boiled for 1 hr, after which the benzene, $POCl_3$ and HCl were removed in vacuum at 30-40°. The crystalline residue was washed with a small quantity of water. α,α-Diphenyl-β-bromopropionyl chloride (I) was obtained 19.7 g (89.1%) with m. p. 90-92° (from n-octane). Found: C 55.73; H 3.83; Br + Cl 35.89%. $C_{15}H_{12}OBrCl$. Calculated: C 55.62; H 3.71; Br + Cl 35.69%.

Thermal decomposition of α,α-diphenyl-β-bromopropionyl chloride. The nonrecrystallized acid chloride decomposed with the evolution of gaseous products even on heating on a boiling water bath in vacuum. Filter paper moistened with 5% $PdCl_2$ darkened in an atmosphere of the gas evolved (qualitative test for CO). Pure (I) was stable in these conditions. 6.47 g recrystallized (I) was heated at 190-210° until no more gas was evolved. 1,1-Diphenyl-2-bromoethylene was obtained 4.25 g (82.4%) with b. p. 131-134°/7 mm and m. p. 41-42° (from ethanol). A mixed melting point determination with addition of 1,1-diphenyl-2-bromoethylene with m. p. 42-43° gave no melting point depression.

Preparation of α,α-diphenyl-β-bromopropionamides. All the amides cited in the present work were made by the method described in previous papers [1, 2], except for the p-nitrophenylamide of α,α-diphenyl-β-bromopropionic acid. In those cases in which the initial amine was gaseous, it was passed into the cooled acid chloride solution until the appearance of a weakly alkaline reaction to litmus, and the reaction products were worked up immediately. The properties of the amides are cited in Table 3.

Preparation of the p-nitrophenylamide of α,α-diphenyl-β-bromopropionic acid. A mixture of 16.2 g (0.05 M) α,α-diphenyl-β-bromopropionyl chloride, 6.9 g (0.05 M) p-nitroaniline, 4.8 g (0.05 M) triethylamine, and 200 ml absolute benzene was refluxed for some days. The benzene was then evaporated off in vacuum. The solid residue was washed with water and recrystallized from ethanol. The p-nitrophenylamide of α,α-diphenyl-β-bromopropionic acid was obtained with m. p. 118-120°. Found: C 58.91; H 4.02; N 6.47%. $C_{21}H_{17}O_3N_2Br$. Calculated: C 59.36; H 4.00; N 6.58%.

Decomposition of 3,3-diphenylazetidinone-2 with concentrated HCl. 0.5 g of the β-lactam was heated with 20 ml concentrated HCl in a sealed ampoule for 20 hr on a boiling water bath. The hydrochloride of α,α-diphenyl-β-aminopropionic acid separated from the cooled solution as large crystals with m. p. 220-230°. In its properties the substance was completely identical with the hydrochloride obtained by ammonolysis of the β-lactam in trimethylcarbinol.

Properties of the Amides $BrCH_2C(C_6H_5)_2CONHR$

R	M. p., °C (from ethanol)	Yield, %	Found, %				Calculated, %			
			C	H	N	Br	C	H	N	Br
H	171—171,5	70	58,86	4,67			59,21	4,60		
CH_3	170—171	85	60,29	4,88		25,18	60,37	5,03		25,16
C_6H_5	153—154 *	73			3,89				3,76	
p-$C_6H_4OCH_3$	108—109	91	64,20	4,75		18,84	64,37	4,87		19,51
p-$C_6H_4NO_2$	118—120	90	58,91	4,02	6,47		58,91	4,00	6,58	
$C_6H_5CH_2$	172	95,5	67,12	5,06		20,23	67,0	5,07		20,30

* From absolute ethanol.

Decomposition of 3,3-diphenylazetidinone-2 with ethanolic HCl. 0.5 g of the β-lactam, 20 ml of saturated ethanolic solution of HCl, and 0.2 ml H_2O were boiled for 4 hr. The alcohol was evaporated in vacuum. The residue – 0.54 g of a solid substance – was completely soluble in water without hydrolysis. It dissolved very well in ethanol. It was not precipitated from ethanolic solution by pyridine. The hydrochloride of ethyl α,α-diphenyl-β-aminopropionate was purified by reprecipitation with ether from a saturated ethanolic solution at room temperature; m. p. 194-196°. Found: Cl 11.85%. $C_{17}H_{20}NO_2Cl$. Calculated: Cl 11.82%.

Hydrolysis of the hydrochloride of ethyl α,α-diphenyl-β-aminopropionic acid. 0.35 g of the ester was boiled under reflux for 16 hr with 15 ml concentrated HCl. On cooling 0.2 g of large crystals, m. p. 218-226°, separated from the solution. By evaporation of the filtrate a further 0.06 g of the same crystals was obtained. A mixed melt of the substance with the hydrochloride of α,α-diphenyl-β-propionic acid from α,α-diphenyl-β-propiolactam gave no depression of the melting point.

Decomposition of α,α-diphenyl-β-propiolactone. For decomposition with liquid ammonia 1.2 g α,α-diphenyl-β-propiolactone was added to 150 ml liquid ammonia. Significant solution of the substance was not observed after prolonged shaking. The suspension was kept for 7 days and than the ammonia was evaporated. The solid residue (1.12 g), which was crystallized first from ethanol and then from nitromethane, was α,α-diphenyl-β-hydroxypropionamide, m. p. 167-168°. It was not soluble in bases or alkalies, but it dissolved well in the common organic solvents. Found: C 74.32; H 5.79%. $C_{15}H_{15}N_2O_2$. Calculated: C 74.68; H 6.12%.

For decomposition with ammonia in trimethylcarbinol 2 g of α,α-diphenyl-β-propiolactone was dissolved in 75 ml anhydrous trimethylcarbinol. Dry ammonia was passed into the solution until a precipitate appeared. The reaction mixture was left overnight. The plentiful colloidal precipitate was boiled with water to decompose the ammonium salt. The solid product for decomposition was treated with excess 2 N HCl and the solution evaporated to dryness on a water bath. The hydrochloride obtained was hydrolyzed rapidly on dissolving in water; on recrystallization from ethanol it partially lost HCl. For purification the substance was dissolved in the minimal quantity of boiling ethanol. To the solution 2-3 drops of pyridine were added. The precipitate was filtered off, washed with ethanol and then with water, and dissolved in 2N HCl. The solution was evaporated to dryness. Glistening crystals of the hydrochloride of α,α-diphenyl-β-ammopropionic acid separated, m. p. 220-230° (decomp.). Found: C 64.68; H 5.79; Cl 12.54%. $C_{15}H_{16}O_2NCl$. Calculated: C 64.80; H 5.77; Cl 12.70%.

Decomposition of 3,3-diphenylazetidinone-2 with potassium hydroxide solution. 1 g 3,3-diphenylazetidinone-2 was dissolved in 25 ml absolute ethanol. 10 ml 0.08 N ethanolic KOH was added to the solution. The mixture was boiled on a water bath for 2 hr. Ethanol was evaporated in vacuum. The solid residue (1.1 g) did not dissolve in water, acids or the common organic solvents, but it dissolved in phenol, tricresol and nitrobenzene. On ignition it left an inorganic residue which was soluble in water and turned phenolphthalein red. Found: C 79.86; H 6.04%. $C_{15}H_{13}ON$. Calculated: C 80.72; H 5.83%.

Polymerization of 3,3-diphenylazetidinone-2. 1 g of the β-lactam dried at 100° was placed in an ampoule with the smallest possible lump of metallic sodium in an atmosphere of nitrogen. The ampoule was heated at 200-210° for 20 hr. A solid substance was obtained which did not melt or darken on heating to 320°, and which did not dissolve in the common organic solvents. It dissolved in phenol, p-cresol, and, on heating to 160°, in benzyl alcohol.

Determination of the rate of reaction of α,α-diphenyl-β-bromopropionamides with lithium hydroxide solution. The rate of reaction of the amides of the β-bromosubstituted acids with 0.25 N LiOH solution was determined from the quantity of bromide ion removed. This was done by the method described in detail in a previous paper [2].

SUMMARY

1. Various amides of α,α-diphenyl-β-bromopropionic acid were prepared, and the effect of substituents on the nitrogen atom on the rate of cyclization to the corresponding azetidinone-2 was investigated.

2. 3,3-Diphenylazetidinone-2 unsaturated at nitrogen was synthesized, and it was shown to be possible to polymerize it to a polyamide.

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