mide pellets often afford a degree of resolution comparable to that of solution spectra, in the present study such pellets were employed. It was found, as hoped, that gross effects of intermolecular interaction would be the same or regular and that the comparative study could be made. However, in the solid state different infrared spectra may be observed due to polymorphism, and, indeed, two such cases were found in the present study, namely, ethyl indole 3-glyoxalate and indole-2-carboxylic acid.

In conclusion it is hoped that the correlation of the greater shift for substituents in the 3- as compared to those for the 2-position will prove useful in assigning structure among indole compounds.

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BROOKLYN 1, N. Y.

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Synthesis of 2-Azetidinones (β-Lactams)

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Eight *N*-substituted α-phenyl-β-amino acids, obtained by the addition of an amine to atropic acid, as well as a number of substituted β-amino acids, prepared by other procedures, were converted into 2-azetidinones. In some cases, esters of the acids were also employed. A useful method for the synthesis of certain 2-azetidinones was found to consist in the interaction of a β-amino acid chloride hydrochloride with dimethylaniline.

Hitherto, only one example of the addition of an amine, hydroxylamine, to atropic acid (α-phenylacrylic acid) has been reported; the reaction product was α-phenyl-β-aminopropionic acid.[3] Atropic acid can be obtained easily from tropic acid by a simple dehydration process.[4] Since tropic acid can now be synthesized readily,[5] it was feasible to prepare atropic acid in relatively large amounts and to study the addition of the following amines to this unsaturated acid: methyl-, allyl-, isopropyl-, cyclohexyl-, hexahydrobenzyl-, benzyl and β-phenylethylamine and aniline.[6] It was of interest to determine the extent to which the β-amino acids obtained (compounds 2, 4, 6, 8, 9, 10, 12, and 14, Table I) and their esters, as well as a number of additional β-amino acids and esters (Tables I and II) prepared by other procedures, could be employed for the synthesis of 2-azetidinones.

The β-amino acids, not obtained by the use of atropic acid, were synthesized in the following manner. Three β-amino acids were obtained by the addition of benzylamine to ethyl acrylate, methyl methacrylate and ethyl crotonate, respectively, and subsequent hydrolysis.

α - Methyl - β - phenyl - β - (benzylamino)-propionic and α,α-dimethyl-β-phenyl-β-(benzylamino)propionic acid were prepared by the alkaline hydrolysis of 1-benzyl-3-methyl-4-phenyl-2-azetidinone[7] and 1-benzyl-3,3-dimethyl-4-phenyl-2-azetidinone,[8] respectively.

β-Phenyl-β-aminopropionic acid was synthesized by interaction of benzaldehyde, malonic acid, and ammonium acetate.[9] This acid was converted into ethyl β-phenyl-β-aminopropionate which was then benzylated and hydrolyzed to yield β-phenyl-β-(benzylamino)propionic acid.[10] When ethyl β-phenyl-β-aminopropionate was hydrogenated and then benzylated, subsequent hydrolysis produced β-cyclohexyl-β-(benzylamino)propionic acid.

Ethyl cyclohexylcyanoacetate[11] was hydrogenated to form ethyl α-cyclohexyl-β-aminopropionate. The latter ester was converted into ethyl α-cyclohexyl - β - (benzylamino)propionate by treatment with benzyl chloride and also by interaction of the ester with benzaldehyde and hydrogenation of the resulting Schiff base. Hydrolysis of ethyl α-cyclohexyl-β-(benzylamino)propionate yielded the corresponding acid.

(1) Abstracted from the Ph.D. dissertation of W. A. Gould, University of Michigan, 1958.

(2) Lilly Endowment Incorporated Fellow.

(3) A. McKenzie and R. C. Strathern, *J. Chem. Soc.*, 82 (1925).

(4) H. S. Raper, *J. Chem. Soc.*, 2557 (1923).

(5) F. F. Blicke, H. Raffelson, and B. Barna, *J. Am. Chem. Soc.*, **74**, 253 (1953).

(6) In addition, α-phenyl-β-dimethylaminopropionic acid was prepared by the addition of dimethylamine to atropic acid.

(7) H. T. Clarke, J. R. Johnson, and R. Robinson, *The Chemistry of Penicillin*, Princeton University Press, Princeton, N. J., 1949, p. 973.

(8) H. Staudinger, H. W. Klever, and P. Kober, *Ann.*, **374**, 1 (1910).

(9) T. B. Johnson and J. E. Lovak, *J. Am. Chem. Soc.*, **58**, 299 (1936).

(10) R. W. Holley and A. D. Holley, *J. Am. Chem. Soc.*, **71**, 2124 (1949).

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TABLE I

SUBSTITUTED β-AMINO ACIDS AND THEIR HYDROCHLORIDES

$$\begin{array}{l} R'R''CCOOH \\ \quad\quad | \\ \quad R'''CNHR \end{array}$$

	R	R′	R″	R‴	Yield, %	M.P., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1.	H	C_6H_5	H	H	25	222–224[a]					
2.	CH_3	C_6H_5	H	H	78	198–200	$C_{10}H_{13}O_2N$	67.00	66.93	7.31	7.37
3.	HCl of 2					183–184	$C_{10}H_{14}O_2NCl$[b]				
4.	CH_2=$CHCH_2$	C_6H_5	H	H	80	164–165	$C_{12}H_{15}O_2N$	70.22	70.05	7.37	7.30
5.	HCl of 4					168–169	$C_{12}H_{16}O_2NCl$[c]				
6.	$(CH_3)_2CH$	C_6H_5	H	H	65	182–183	$C_{12}H_{17}O_2N$	69.54	69.30	8.27	8.19
7.	HCl of 6					190–191	$C_{12}H_{18}O_2NCl$[d]				
8.	C_6H_5	C_6H_5	H	H	70	128–130	$C_{15}H_{15}O_2N$	74.66	74.69	6.27[e]	6.31
9.	C_6H_{11}	C_6H_5	H	H	95	192–193	$C_{15}H_{21}O_2N$	72.84	72.69	8.56	8.32
10.	$C_6H_{11}CH_2$	C_6H_5	H	H	95	200–202	$C_{16}H_{23}O_2N$	73.53	73.22	8.86	9.05
11.	HCl of 10					160–162	$C_{16}H_{24}O_2NCl$[e]	64.52	64.41	8.12	7.77
12.	$C_6H_5CH_2$	C_6H_5	H	H	97	193–195[f]	$C_{16}H_{17}O_2N$[g]	75.28	75.32	6.71	6.68
13.	HCl of 12					174–176[h]	$C_{16}H_{18}O_2NCl$[i]	65.86	65.92	6.21	6.20
14.	$C_6H_5CH_2CH_2$	C_6H_5	H	H	97	193–194	$C_{17}H_{19}O_2N$	75.81	75.71	7.11	7.10
15.	HCl of 14					180–181	$C_{17}H_{20}O_2NCl$	66.77	66.82	6.59	6.70
16.	$C_6H_5CH_2$	H	H	C_6H_5	78	185–187[j]					
17.	$C_6H_5CH_2$	CH_3	H	C_6H_5	67	170–173[k]					
18.	$C_6H_5CH_2$	CH_3	CH_3	C_6H_5	85	143–145[l]					
19.	$C_6H_5CH_2$	H	H	H	75	182–184[m]					
20.	$C_6H_5CH_2$	CH_3	H	H	81	150–152	$C_{11}H_{15}O_2N$[n]	68.37	68.44	7.82	7.83
21.	HCl of 20					131–133	$C_{11}H_{16}O_2NCl$[o]	57.50	57.62	7.02	7.02
22.	$C_6H_5CH_2$	H	H	CH_3	88	179–181[p]					
23.	$C_6H_5CH_2$	C_6H_{11}	H	H	78	213–214	$C_{16}H_{23}O_2N$[q]	73.53	73.39	8.87	8.76
24.	HCl of 23					230–232	$C_{16}H_{24}O_2NCl$[r]	64.52	64.37	8.12	8.03
25.	$C_6H_5CH_2$	H	H	C_6H_{11}	74	165–167	$C_{16}H_{23}O_2N$	73.53	73.59	8.87	8.97
26.	HCl of 25					138–140	$C_{16}H_{24}O_2NCl$	64.52	64.43	8.12	8.24

[a] A. MacKenzie and R. C. Strathern [*J. Chem. Soc.*, 82 (1925)], m.p. 222–224°. [b] Calcd.: N, 6.50; Cl, 16.44. Found: N, 6.66, Cl, 16.56. [c] Calcd.: N, 5.80; Cl, 14.64. Found: N, 5.91; Cl, 14.87. [d] Calcd.: N, 5.75; Cl, 14.55. Found: N, 5.89; Cl, 14.80. [e] Calcd.: Cl, 11.90; Found: Cl, 12.05. [f] J. Decombe [*Ann. chim. (Paris)*, **18**, 81 (1932)], m.p. 190–195°. [g] Calcd.: N, 5.48. Found: N, 5.78. [h] J. M. Stewart and C. H. Chang [*J. Org. Chem.*, **21**, 635 (1956)], m.p. 171–173°. [i] Calcd.: Cl, 12.14. Found: Cl, 12.23. [j] Ref. 10, m.p. 187–188°. [k] Ref. 7, m.p. 169–173°. [l] Ref. 8, m.p. 145–148°. [m] Ref. 10, m.p. 184–184.5°. [n] Calcd.: N, 7.25. Found: N, 7.23. [o] Calcd.: N, 6.10. Found: N, 6.08. [p] Ref. f, m.p. about 191°. [q] Calcd.: N, 5.36. Found: 5.54. [r] Calcd.: Cl, 11.91. Found, Cl, 12.17.

Compounds 1 and 24 were recrystallized from water; 8 from aqueous methanol; 6, 19, 20, and 22 from ethanol; 15 from ethanol-ether; 3 and 7 from isopropyl alcohol; 11 and 26 from isopropyl alcohol–ether; 5 and 21 from methyl ethyl ketone; 13 from dimethoxyethane; 18 from chloroform; 2, 4, 9, 10, 12, 14, 16, 17, 23, and 25 from dimethylformamide.

TABLE II

ESTERS OF α-PHENYL-β-(BENZYLAMINO)PROPIONIC ACID AND THEIR HYDROHALIDE SALTS

$$\begin{array}{l} C_6H_5CHCOOR \\ \quad\quad | \\ \quad CH_2NHCH_2C_6H_5 \end{array}$$

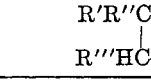
	R	M.P., °C. or B.P., °C.[a]	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Halogen Calcd.	Halogen Found
1.	CH_3	110 (20 mm.)	$C_{17}H_{19}O_2N$	75.80	75.75	7.10	7.25		
2.	HCl of 1	172–173	$C_{17}H_{20}O_2NCl$	66.78	66.74	6.59	6.77	11.60	11.90
3.	C_2H_5	116 (20 mm.)	$C_{18}H_{21}O_2N$	76.28	76.27	7.48	7.36		
4.	HCl of 3	169–170	$C_{18}H_{22}O_2NCl$	67.60	67.68	6.94	6.90	11.09	11.34
5.	HBr of 3	129–130	$C_{18}H_{22}O_2NBr$	59.34	59.76	6.09	6.35	21.94	22.14
6.	$(CH_3)_2CH$	46–48 124 (23 mm.)	$C_{19}H_{23}O_2N$	76.73	76.69	7.80	7.97		
7.	HCl of 6	163–164	$C_{19}H_{24}O_2NCl$	68.36	68.01	7.24	7.05	10.63	10.79
8.	$C_6H_5CH_2$[b]								
9.	HCl of 8	173–174	$C_{23}H_{24}O_2NCl$	72.35	72.29	6.33	6.28	9.28	9.33

[a] When distilled, the esters decomposed to a considerable extent even under more reduced pressure than that reported in the table. The yields before distillation ranged from 89–97%. [b] Decomposed extensively upon attempted distillation.

Compound 2 was recrystallized from dimethoxyethane; 4 and 5 from methyl ethyl ketone; 6 from aqueous ethanol; 7 and 9 from isopropyl alcohol.

TABLE III

SUBSTITUTED 2-AZETIDINONES



	R	R′	R″	R‴	Method	Yield, %	M.P. or B.P., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1.	$C_6H_5CH_2$	H	H	H	D	40	106–108					
					C	0[a]	(1 mm.)[a]					
2.	H	C_6H_5	H	H	A	28	114–116	C_9H_9ON[b]	73.45	73.64	6.16	6.18
3.	CH_3	C_6H_5	H	H	C	25	86–87 (0.1 mm.)	$C_{10}H_{11}ON$	74.51	74.51	6.88	6.96
4.	CH_2=$CHCH_2$	C_6H_5	H	H	C	48	103–104 (0.1 mm.)	$C_{12}H_{13}ON$	76.97	76.92	7.00	7.05
5.	$(CH_3)_2CH$	C_6H_5	H	H	C	84	90–92	$C_{12}H_{15}ON$	76.15	76.31	7.99	8.11
					B	54	(0.05 min.)					
6.	C_6H_{11}	C_6H_5	H	H	C	44	59–61	$C_{15}H_{19}ON$	78.56	78.70	8.34	8.42
7.	$C_6H_{11}CH_2$	C_6H_5	H	H	C	80	50–51	$C_{16}H_{21}ON$[c]	78.97	79.08	8.70	8.74
					B	31						
8.	$C_6H_5CH_2$	C_6H_5	H	H	C	72	70–72	$C_{16}H_{15}ON$[d]	80.99	81.14	6.37	6.44
					B	43						
					A	40						
9.	$C_6H_5CH_2CH_2$	C_6H_5	H	H	C	67	145–146	$C_{17}H_{17}ON$	81.24	81.01	6.82	6.79
					B	40	(0.05 mm.)					
10.	$C_6H_5CH_2$	CH_3	H	H	C	61	83–84 (0.1 mm.)	$C_{11}H_{13}ON$	75.40	75.16	7.48	7.33
11.	$C_6H_5CH_2$	C_6H_{11}	H	H	C	84	131–132 (0.05 mm.)	$C_{16}H_{21}ON$	78.99	78.69	8.69	8.75
12.	CH_3	H	H	C_6H_5	E	52	90–92 (0.6 mm.)	$C_{10}H_{11}ON$	74.51	74.55	6.88	6.91
13.	$C_6H_5CH_2$	H	H	C_6H_5	C	80	138–139 (0.1 mm.)[e]					
14.	$C_6H_5CH_2$	H	H	CH_3	C	76	85–86 (0.1 mm.)	$C_{11}H_{13}ON$[f]	75.40	75.46	7.48	7.59
15.	$C_6H_5CH_2$	H	H	C_6H_{11}	C	81	136–137 (0.1 mm.)	$C_{16}H_{21}ON$	78.99	79.09	8.69	8.62
16.	C_6H_5	C_6H_5	H	C_6H_5	E	7	132–133[g]	$C_{21}H_{17}ON$	84.25	84.15	5.72	5.83
17.	CH_3	CH_3	H	C_6H_5	E	81	105–106 (0.6 mm.)	$C_{11}H_{13}ON$	75.40	75.41	7.48	7.55
18.	$C_6H_5CH_2$	CH_3	H	C_6H_5	C	92	141–142					
					E	76	(0.1 mm.)[h]					
19.	$C_6H_5CH_2$	CH_3	CH_3	C_6H_5	C	92	153–155					
					E	84	(0.5 mm.)[i]					

[a] Ref. 10, b.p. 98–112° (2 mm.); yield 5%. [b] Calcd.: N, 9.52. Found: N, 9.46. [c] Calcd.: N, 5.76. Found: N, 5.88. [d] Calcd.: N, 5.90; mol. wt. 2.37. Found: N, 6.17; Mol. wt. (Rast) 235. [e] Ref.[a], b.p. 145–150° (2 mm.); yield 45%. [f] Calcd.: mol. wt. 175. Found: mol. wt. (Rast) 175. [g] A. Spasov, S. Robev, and B. Panaiotova [*Godishnik Sofiiskiya Univ. Fiz.-Mat. Fak.-Kniga 2—Khim.*, **49**, 109 (1956); *Chem. Abstr.*, **51**, 12031 (1957)], m.p. 134–135°. [h] Ref. 7, b.p. 142–145° (0.1 mm.); the yield was not reported. [i] Ref. 8, b.p. 200° (15 mm.); yields 10%, 60%, and 70%.

Compounds 2 and 16 were recrystallized from ethanol; 7 from petroleum ether (30–40°); 6 and 8 from petroleum ether (60–75°).

The methyl, ethyl, isopropyl, and benzyl esters of α-phenyl-β-(benzylamino)propionic acid (Table II) were allowed to react with methylmagnesium iodide and ethylmagnesium bromide, respectively, to form 1-benzyl-3-phenyl-2-azetidinone. This type of synthesis of 2-azetidinones was introduced by Breckpot[12] and was used later by other investigators.[7,10,13] The highest yield of the azetidinone obtained by us by this process was 40%.

Incidentally, in an attempt to convert α-phenyl-β-(benzylamino)propionyl chloride hydrochloride into α-phenyl-β-(benzylamino)ethyl diazomethyl ketone by the use of diazomethane, it was discovered that the reaction product was not the diazomethyl ketone but was 1-benzyl-3-phenyl-2-azetidinone; the azetidinone was formed in 43% yield. α-Phenyl-β-(isopropylamino)-, α-phenyl-β-(hexahydrobenzylamino)- and α-phenyl-β-(β-phenylethylamino)propionyl chloride hydrochloride, when treated with diazomethane, yielded 1-isopropyl-3-phenyl- (54%), 1-hexahydrobenzyl-3-phenyl- (31%) and 1-(β-phenylethyl)-3-phenyl-2-azetidinone (40%), respectively. Since it seemed that diazomethane may have served merely in the removal of hydrogen chloride, it was replaced, successfully, by dimethylaniline in a series of experiments. Fourteen 2-azetidinones (Table III), eleven

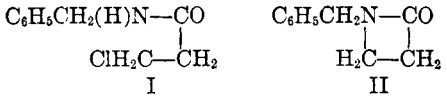
(12) R. Breckpot, *Bull. soc. chim. Belges*, **32**, 412 (1923).

(13) R. W. Holley and A. D. Holley, *J. Am. Chem. Soc.*, **71**, 2129 (1949).

of which are new compounds, were prepared by the interaction of a β-amino acid chloride hydrochloride and dimethylaniline. In all except three instances, the yields ranged from 61–92%.

We were unable to obtain 1-benzyl-2-azetidinone by the β-amino acid chloride hydrochloride–dimethylaniline process but it was found that the azetidinone could be prepared in 40% yield by the interaction of *N*-benzyl-β-bromopropionamide and sodium hydride.[14] This azetidinone was isolated by Holley and Holley,[10] in 5% yield, from the interaction of ethyl β-(benzylamino)propionate and ethylmagnesium bromide.

Certain N-benzylamides, such as Hibicon (N-benzyl-β-chloropropionamide) (I), have been shown



I II

to be effective anticonvulsants.[15,16] It can be seen that 1-benzyl-2-azetidinone (II), except for the absence of the chlorine atom, is a cyclic analog of I. As far as we are aware, anticonvulsant action of compounds of type II has not been reported.

In addition to the 2-azetidinones obtained by procedures which have been described, three azetidinones (compounds 12, 16, and 17, Table III) were synthesized by a Reformatsky-type reaction.

Two azetidinones (9 and 16, Table III) were hydrolyzed with alkali to known β-amino acids. One azetidinone (9, Table III) yielded ethyl α-phenyl-β-(benzylamino)propionate hydrobromide when it was refluxed with ethanol and hydrogen bromide. When treated with lithium aluminum hydride, 1-benzyl-3-phenyl-2-azetidinone was converted into 2-phenyl-3-(benzylamino)-propanol; the latter compound was also obtained by treatment of ethyl α-phenyl-β-(benzylamino)propionate with lithium aluminum hydride.

The carbonyl absorption of each of the 2-azetidinones prepared was found to be within the 1750–1730 cm.$^{-1}$ range.

EXPERIMENTAL

β-Amino acids obtained from atropic acid. Compounds 2, 4, 6, 9, 10, 12, and 14 (Table I) were synthesized by the following method.

A solution of 0.1 mole of the required amine in 50 ml. of absolute ethanol was added to a solution of 7.4 g. (0.05 mole) of atropic acid[4,17] in 60 ml. of absolute ethanol. After 4 days,[18] the solvent was removed and the residue was recrystallized from a suitable solvent.

α-Phenyl-β-(dimethylamino)propionic acid. This acid was obtained in 80% yield by the method described above; m.p. 143–145°[19] after recrystallization from 95% ethanol.

α-Phenyl-β-anilinopropionic acid (compound 8, Table I). This acid was prepared by heating, for 4 hr. on a steam bath, a mixture of 7.4 g. of atropic acid, 9.3 g. of aniline, and 2 ml. of acetic acid. The precipitate was filtered and recrystallized from aqueous methanol. The acid is insoluble in water, soluble in dilute acid and alkali.

Esters of α-phenyl-β-(benzylamino)propionic acid. The ester hydrochlorides (compounds 2, 4, 7, and 9, Table II) were obtained by a general method previously described.[10] The ester bases (compounds 1, 3, 6, and 8) were liberated from the salts and distilled. The ester hydrobromide (compound 5) was obtained by addition of hydrogen bromide to the ester base dissolved in ether.

Ethyl α-phenyl-β-aminopropionate hydrochloride. From 2.0 g. of α-phenyl-β-aminopropionic acid[3], by the general process mentioned above, there was obtained 2.3 g. (82%) of product; m.p. 160–162° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{11}H_{16}O_2NCl$: N, 6.10; Cl, 15.44. Found: N, 6.09; Cl, 15.69.

Methyl α-phenyl-β-anilinopropionate. Diazomethane,[20] which had been obtained from 43.0 g. of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide,[21] dissolved in 500 ml. of ether, and 16.5 g. of α-phenyl-β-anilinopropionic acid yielded 11.5 g. (65%) of ester; b.p. 154–155° (0.5 mm.).

Anal. Calcd. for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.34; H, 6.85; N, 5.36.

β-(Benzylamino)propionic acid (compound 19, Table I). This acid was obtained when a suspension of 0.2 mole of ethyl β-(benzylamino)propionate[22] in 500 ml. of water was refluxed for 6 hr. The water was removed under reduced pressure and the residue was recrystallized from ethanol; yield 75%.

β-(Benzylamino)butyric acid (compound 22, Table I). Ethyl β-(benzylamino)butyrate[23] was hydrolyzed in the manner described above.

Ethyl α-methyl-β-(benzylamino)propionate. A mixture of 98.1 g. of methyl methacrylate, 107.0 g. of benzylamine, and 500 ml. of methanol was allowed to remain at room temperature for 7 days. The solvent was removed and the residue was distilled; b.p. 97–100° (0.3 mm.); yield 123.7 g. (60%).

Anal. Calcd. for $C_{12}H_{17}O_2N$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.39; H, 8.22; N, 6.66.

The *hydrochloride* was prepared by the use of ethereal hydrogen chloride; m.p. 101–103°.

Anal. Calcd. for $C_{12}H_{18}O_2NCl$: N, 5.74; Cl, 14.55. Found: N, 5.90; Cl, 14.70.

α-Methyl-β-(benzylamino)propionic acid (compound 20, Table I). Ethyl α-methyl-β-(benzylamino)propionate was hydrolyzed in the manner described above in order to obtain this acid.

Ethyl β-cyclohexyl-β-aminopropionate. Ethyl β-phenyl-β-

(14) Several 2-azetidinones have been obtained by I. L. Knunyant and N. P. Gambaryan [*Izvest. Akad. Nauk S. S. S. R., Otdel. Khim. Nauk* **1955**, 1037; *Chem. Abstr.* **50**, 11277 (1956)] by reaction between a β-halo amide and potassium or sodium amide in liquid ammonia.

(15) S. Kushner, R. I. Cassel, J. Morton, and J. H. Williams, *J. Org. Chem.*, **16**, 1283 (1951).

(16) B. K. Harned, R. W. Cunningham, M. C. Clark, C. H. Hine, M. M. Kane, F. H. Smith, Jr., R. E. Vessey, N. N. Yuda, and F. W. Zabransky, *J. Pharmacol. Exptl. Therap.*, **107**, 403 (1953).

(17) In the preparation of tropic acid,[5] it was found necessary to stir the reaction mixture, after the addition of formaldehyde, for 12 hrs. in order to obtain the reported yield.

(18) In some instances the amino acid had partially precipitated.

(19) C. Mannich and E. Ganz [*Ber.*, **55**, 3486 (1922)], m.p. 143°.

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aminopropionate[10] (19.3 g.), dissolved in 150 ml. of acetic acid, was hydrogenated at 50° in the presence of 0.5 g. of platinum dioxide under an initial pressure of 50 pounds until the calculated amount of hydrogen had been absorbed. After filtration and removal of the solvent from the filtrate under reduced pressure, the residue was dissolved in water, the solution was made alkaline and extracted with ether. The solvent was removed from the dried extract and the residue was distilled; b.p. 81–82° (0.4 mm.); yield 13.8 g. (70%).

Anal. Calcd. for $C_{11}H_{21}O_2N$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.21; H, 10.44; N, 7.00.

The *hydrochloride*, prepared by the use of ethereal hydrogen chloride, melted at 108–110° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{11}H_{22}O_2NCl$: Cl, 15.04; N, 5.94. Found: Cl, 15.37; N, 6.01.

Ethyl β-cyclohexyl-β-(benzylamino)propionate. (a) Ethyl β-cyclohexyl-β-aminopropionate (39.8 g.) and 12.6 g. of benzyl chloride were heated at 70° for 5 hr. After the addition of 500 ml. of anhydrous ether, the mixture was cooled in a refrigerator for 12 hr., filtered, and the solvent was removed from the filtrate. The residue was distilled; b.p. 150–152° (0.1 mm.); yield 16.0 g. (55%).

Anal. Calcd. for $C_{18}H_{27}O_2N$: C, 74.70; H, 9.40. Found: C, 74.68; H, 9.49.

(b) Ethyl β-cyclohexyl-β-aminopropionate (19.9 g.), 10.6 g. of benzaldehyde, a catalytic amount of zinc chloride, and 200 ml. of benzene were refluxed for 12 hr. in a 500-ml. flask to which a Dean-Stark trap was attached. The benzene was removed from the filtered mixture under reduced pressure and the product, ethyl β-cyclohexyl-β-(benzylideneamino)propionate, was distilled; b.p. 170° (1 mm.); yield 23.0 g. (80%).

Anal. Calcd. for $C_{18}H_{25}O_2N$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.23; H, 8.81; N, 4.73.

The ester (23.0 g.), dissolved in 150 ml. of absolute ethanol, was hydrogenated in the presence of 0.5 g. of platinum dioxide under an initial pressure of 50 pounds until the calculated amount of hydrogen had been absorbed. The solvent was removed from the filtered mixture and the residue was distilled; b.p. 170–172° (0.7 mm.); yield 17.3 g. (75%).

A mixture of 0.5 g. of the propionate and 5 ml. of hydrochloric acid was evaporated to dryness and the *hydrochloride* was recrystallized from isopropyl alcohol; m.p. 179–180°.

Anal. Calcd. for $C_{18}H_{23}O_2NCl$: C, 66.33; H, 8.66; Cl, 10.88. Found: C, 66.24; H, 8.60; Cl, 11.01.

β-Cyclohexyl-β-(benzylamino)propionic acid (compound 25, Table I). Ethyl β-cyclohexyl-β-(benzylamino)propionate (16.0 g.), 4.0 g. of sodium hydroxide, and 100 ml. of 95% ethanol were refluxed for 12 hr., the solvent was removed and the residue was dissolved in 100 ml. of water. Upon careful neutralization of the solution with 10% hydrochloric acid, the product precipitated.

Ethyl α-cyclohexyl-β-aminopropionate. Ethyl cyclohexylcyanoacetate[11] (19.5 g.), dissolved in 150 ml. of acetic acid, was hydrogenated for 4 hr. in the presence of 5 ml. of concentrated sulfuric acid and 0.2 g. of platinum oxide under an initial pressure of 50 pounds. After removal of the solvent from the filtered mixture, the residue was dissolved in water, the solution was made alkaline and extracted with ether. The ether was removed from the dried extract and the residue was distilled; b.p. 76–77° (0.3 mm.); yield 17.5 g. (90%).

Anal. Calcd. for $C_{11}H_{21}O_2N$: C, 66.29; H, 10.62; N, 7.02. Found: C, 66.23; H, 10.57; N, 7.00.

The *hydrochloride* was prepared with ethereal hydrogen chloride; m.p. 143–145° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{11}H_{22}O_2NCl$: N, 5.94; Cl, 15.04. Found: N, 6.02; Cl, 15.26.

Ethyl α-cyclohexyl-β-(benzylamino)propionate. Ethyl α-cyclohexyl-β-aminopropionate (19.9 g.) was benzylated with 6.3 g. of benzyl chloride in the manner described above; b.p. 143–145° (0.2 mm.); yield 10.0 g. (70%).

Anal. Calcd. for $C_{18}H_{27}O_2N$: C, 74.70; H, 9.40. Found: C, 74.71; H, 9.44.

The *hydrochloride* was obtained by the use of ethereal hydrogen chloride; m.p. 171–173°.

Anal. Calcd. for $C_{18}H_{28}O_2NCl$: C, 66.33; H, 8.66; Cl, 10.88. Found: C, 66.23; H, 8.66; Cl, 11.08.

α-Cyclohexyl-β-(benzylamino)propionic acid (compound 23, Table I). This acid was prepared in the same manner as the corresponding β-cyclohexyl compound from ethyl α-cyclohexyl-β-(benzylamino)propionate.

Hydrochlorides of β-amino acids (Table I). These compounds were obtained by dissolving the amino acid in 10% hydrochloric acid and evaporation of the solution to dryness. The salts were then recrystallized from a suitable solvent.

2-Azetidinones (Table III). Method A. The interaction of the methyl, ethyl, isopropyl, and benzyl esters of α-phenyl-β-(benzylamino)propionic acid with methylmagnesium iodide and ethylmagnesium bromide, respectively, was studied. In some experiments, the molar ratio of the ester and Grignard reagent was 1:1, in others 1:2. The best yield of 1-benzyl-3-phenyl-2-azetidinone was obtained in the manner described below.

1-Benzyl-3-phenyl-2-azetidinone (compound 8). A solution of ethylmagnesium bromide (approximately 0.06 mole), prepared from 1.5 g. of magnesium, 8 ml. of ethyl bromide and 150 ml. of ether, was added, dropwise, to 8.9 g. (0.03 mole) of isopropyl α-phenyl-β-(benzylamino)propionate in 100 ml. of ether. After about one half of the Grignard reagent had been added, the white precipitate turned into a grey ball. The mixture was stirred for 2 hr. at room temperature. Aqueous 10% ammonium chloride (100 ml.) was added and the material was stirred until the two layers became clear. The aqueous layer was separated and extracted with ether. The combined ether solutions were dried and the solvent was removed. The semisolid residue was placed on a porous plate; 1.8 g. of crystalline material was obtained.

3-Phenyl-2-azetidinone (compound 2). Ethyl α-phenyl-β-aminopropionate (0.05 mole), prepared from the ester hydrochloride, was allowed to react with approximately 0.15 mole of ethylmagnesium bromide in the manner described above.

We were unable to obtain 1,3-diphenyl-2-azetidinone from methyl α-phenyl-β-anilinopropionate and ethylmagnesium bromide.

Method B. The required β-amino acid (compound 6, 10, 12, or 14, Table I) (0.02 mole) was treated with 10 ml. of pure thionyl chloride. The acid chloride hydrochloride obtained was suspended in 250 ml. of ether and the suspension was added slowly from a large-bore dropping funnel to a stirred solution of approximately 4.0 g. (0.1 mole) of diazomethane, prepared from 28.4 g. of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide,[20] in 500 ml. of ether which was cooled in an ice-salt bath. The mixture was stirred for 1 hr. and then allowed to remain at room temperature for 12 hr. The solution was filtered and the ether and excess diazomethane were removed. The residue was either recrystallized or distilled.

Method C. The acid chloride hydrochloride obtained from 0.05 mole of the required acid (compound 2, 4, 6, 9, 10, 12, 14, 16, 17, 18, 20, 22, 23, or 25, Table I) and 25 ml. of pure thionyl chloride was suspended in 250 ml. of dry benzene and the suspension was added slowly through a wide-bore dropping funnel to a refluxing solution of 18.2 g. (0.15 mole) of dry dimethylaniline dissolved in 250 ml. of benzene. The mixture was refluxed for 4 hr., cooled and extracted thoroughly with water. The unreacted dimethylaniline was then extracted with 10% hydrochloric acid. After the benzene layer had been extracted with water again, it was dried over magnesium sulfate, the solvent was removed, and the residue was distilled or recrystallized.

Method D. 1-benzyl-2-azetidinone (compound 1). *N*-Benzyl-β-bromopropionamide[15] (24.2 g., 0.1 mole) was added, in small amounts, to a stirred mixture of 3.0 g. (0.12 mole) of sodium hydride and 150 ml. of dry toluene. The mixture was

refluxed for 12 hr., cooled, and 150 ml. of water was added. The mixture was stirred until both layers became clear, the aqueous layer was separated and extracted with 100 ml. of toluene. The combined toluene solutions were dried over magnesium sulfate, the solvent was removed, and the residue was distilled.

Method E. By the use of a described method,[24] products were obtained from the interaction of benzylidenebenzylamine and ethyl α-bromopropionate (compound 18) or ethyl α-bromoisobutyrate (compound 19); from benzylidenemethylamine and ethyl bromoacetate (compound 12) or ethyl α-bromopropionate (compound 17); from benzylideneaniline and ethyl α-bromophenylacetate (compound 16).

2-Phenyl-3-(benzylamino)propanol. (*a*) 1-Benzyl-3-phenyl-2-azetidinone (1.2 g., 0.005 mole), dissolved in 50 ml. of ether, was added, dropwise, to a stirred suspension of 0.19 g. (0.01 mole) of lithium aluminum hydride in 30 ml. of ether, and the mixture was refluxed for 24 hr. Water (0.5 ml.) was added to the cooled mixture and it was stirred for 4 hr., filtered, the filtrate was dried with magnesium sulfate and the solvent was removed. The residue was recrystallized from ether–petroleum ether (30–40°); m.p. 52–54°[25]; yield 0.9 g. (75%).

Anal. Calcd. for $C_{16}H_{19}ON$: C, 79.64; H, 7.93. Found: C, 79.52; H, 7.79.

The *hydrochloride*, prepared by the use of ethereal hydrogen chloride, melted at 131–133°[26] after recrystallization from 2-butanone.

Anal. Calcd. for $C_{16}H_{20}ONCl$: C, 69.18; H, 7.26; Cl, 12.76. Found: C, 69.23; H, 7.13; Cl, 12.65.

(*b*) Ethyl α-phenyl-β-(benzylamino)propionate (27.4 g.), dissolved in 200 ml. of ether, was added, dropwise, to a stirred suspension of 2.3 g. of lithium aluminum hydride in 300 ml. of ether. The mixture was stirred for 3 days at room temperature; 6 ml. of water was added, dropwise, and the stirring was continued for 24 hr. The mixture was filtered, the filtrate was dried, and the solvent was removed. The oily residue, after it had crystallized, was recrystallized from ether–petroleum ether (30–40°); m.p. and mixed m.p. 52–54°; yield 21.8 g. (94%). The hydrochloride melted at 132–133° after recrystallization from 2-butanone.

ANN ARBOR, MICH.

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(25) Ref. 22, m.p. 64°.

(26) Ref. 22, m.p. 135–136°.

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Reaction of Alkyl Isocyanides with Ozone. A New Isocyanate Synthesis[1]

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The reactions of alkyl isocyanides with ozone have been shown to give exclusively the corresponding isocyanates. The formation of the isocyanates varied from 7–73%, based upon the conversion of the isocyanates with ammonia to the urea. It appears that increasing concentrations of ozone will result in excellent yields of isocyanates.

The reactions of isocyanides have been studied since their discovery in 1867.[3,4] The only reference in which the oxidation of isocyanides has been investigated dates back to the work of Gautier who found that methyl isocyanide and ethyl isocyanide were oxidized by mercuric oxide[5]; he obtained a complex mixture from which he was able to isolate a small amount of isocyanate.

The purpose of this research was to study the course and the products of the oxidation of isocyanides. Ozone was chosen because it was thought best to employ a very strong oxidizing agent which would also make the separation of products, reactants and starting material fairly easy.

The first isocyanide to be ozonized was isopropyl isocyanide. The materials obtained upon distillation of the reaction mixture were isopropyl isocyanate (identified as the diisopropylurea), unreacted isocyanide, and some residual tars. It became apparent after two preliminary runs that much of the isopropyl isocyanide was being lost through entrainment (*i.e.*, evaporation), and that the separation of the isocyanate from any unreacted isocyanide by distillation was unfeasible because extensive tar formation took place during the distillation.

To avoid these losses, the reaction vessel was provided with a Dry Ice condenser, and the isocyanate was derivatized. It is well known that isocyanates react with amines to give excellent yields of the urea.[6,7] Thus, in all the ozonolysis experiments, the isocyanate was reacted with ammonia and the yield of isocyanate was based upon the amount of urea formed. As a check upon the validity of this method, hexyl isocyanate, prepared by the phosgenation of hexylamine hydrochloride, was reacted with ammonia to give the urea. This was found to proceed in yields of 95–97% in each of four determinations.

The reaction of ethyl, isopropyl, *n*-butyl, *n*-hexyl, and *n*-octyl isocyanides with ozone was studied and the results are shown in Table I.

From the data in the table it may be noted that

(1) Abstracted in part from the Ph.D. thesis of Harry Rubinstein, (February 1958).

(2) Purdue Research Foundation Fellow, 1956–58.

(3) A. W. Hofman, *Compt. rend.*, **65**, 484 (1867).

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(6) W. Siefken, *Ann.*, **562**, 99 (1949).

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