2-Benzylimino-4-(acetylbenzyl)-aminofuran-5-one (X^x).—VII (4 g.) was heated with 20 ml. of acetic anhydride until it dissolved completely. After cooling and on addition of ether and petroleum ether, a white substance was precipitated; m.p. after recrystallization from ethyl acetate–petroleum ether 118°, yield 3 g. (70%).

Anal. Calcd. for $C_{20}H_{20}O_3N_2$: C, 71.4; H, 6.0; N, 8.3. Found: C, 70.6; H, 6.2; N, 8.5.

N,N^2-Dibenzyl-*dl*-asparagine Hydrochloride (VIII).—VII (4 g.) was suspended in 20 ml. of glacial acetic acid and 20 ml. of acetyl chloride added. The substance dissolved at once and after a short time, the hydrochloride precipitated. This was filtered off five minutes after the start of the reaction and washed with acetyl chloride and ether; yield 2.7 g. (60%), m.p. 170–171°; on recrystallization from ethanol (hexagonal plates) the m.p. was raised to 172°.

Anal. Calcd. for $C_{18}H_{21}O_3N_2Cl$: C, 62.0; H, 6.1; N, 8.0; Cl, 10.2. Found: C, 61.6; H, 6.0; N, 8.0; Cl, 10.2.

N^2-Acetyl-N^2-benzyl-*dl*-aspartimide (IX).—VI (2.5 g.) was suspended in 15 ml. of acetyl chloride and on addition of 10 ml. of glacial acetic acid it dissolved completely. The reaction mixture was left for 6 hr. and finally petroleum ether was added which precipitated an oil. This solidified on recrystallization from water (rhombs), m.p. 144–145°. On mixing IX with IX^x the m.p. was considerably lowered; yield 1.6 g. (58%).

Anal. Calcd. for $C_{13}H_{14}O_3N_2$: C, 63.3; H, 5.7; N, 11.4. Found: C, 63.2; H, 5.7; N, 11.2.

N^2-Acetyl-N,N^2-dibenzyl-*dl*-aspartimide (X). (A) From VII.—VII (2 g.) was suspended in 10 ml. of glacial acetic acid and 10 ml. of acetyl chloride added. The hydrochloride which precipitated almost immediately was not separated and it dissolved in the reaction mixture after having been left for some hours at room temperature. On addition of ether, X was obtained; m.p. 140° on recrystallization from ethanol (triangular prisms), yield 1.3 g. (60%).

Anal. Calcd. for $C_{20}H_{20}O_3N_2$: C, 71.4; H, 6.0; N, 8.3. Found: C, 72.1; H, 5.9; N, 8.3.

(B) From XII.—XII (4 g.) dissolved in acetyl chloride (100 ml.) was refluxed for 0.5 hr. After cooling, ether and petroleum ether was added and an oil obtained. This on trituration with ethanol gave a solid which, when crystallized from the same solvent, melted at 140°.

(C) From III.—III (1 g.) suspended in 10 ml. of acetyl chloride was refluxed for 90 minutes, when it dissolved completely. After cooling, the solution was poured into 50 ml. of water. A white oil separated which solidified on scratching with a glass rod; m.p. after recrystallization from ethanol, 140°.

Hydrolysis of X.—X (1 g.) suspended in 20 ml. of 10% sodium carbonate solution was refluxed for 2 hr. After filtration from undissolved residue, the solution was acidified with hydrochloric acid. The precipitated substance melted at 172–173°. On recrystallization from ethanol the typical irregular octahedra of III, m.p. 174°, were obtained.

N,N^2-Dibenzyl-*dl*-aspartimide Hydrochloride (XIII). (A) From XII.—XII (4 g.) was dissolved in 110 ml. of acetyl chloride and left for 6 hr., when precipitation of white crystals commenced. After an additional 30 minutes, the substance was filtered and washed with acetyl chloride; yield 2.6 g. (59%), m.p. 191°, m.p. after recrystallization from ethanol (short needles), 195°.

Anal. Calcd. for $C_{18}H_{19}O_2N_2Cl$: C, 65.2; H, 5.7; N, 8.5; Cl, 10.7. Found: C, 64.9; H, 5.9; N, 8.7; Cl, 10.7.

(B) From X^x or X.—X^x or X (4 g.) suspended in 30 ml. of 5 *N* hydrochloric acid was heated at 130° (oil-bath) for 1 hr.; on cooling, crystals of XIII separated.

Anal. (for substance obtained from X) Found: C, 65.2; H, 5.8; N, 8.4; Cl, 10.7.

(C) From III.—As in B.

(D) From VII.—VII (2 g.) in 25 ml. of 2 *N* hydrochloric acid was refluxed for 30 minutes; on cooling, XIII crystallized; yield 1.5 g. (73%), m.p. 194°.

N-Benzyl-*dl*-aspartimide Hydrochloride (XIV).—XIII (2 g.) was dissolved in glacial acetic acid (25 ml.) and 0.2 g. of $PdCl_2$-on-charcoal (30%) added. Hydrogenolysis was carried out for 4 hr. at 70°. After separation of the catalyst by filtration the solvent was evaporated *in vacuo;* yield almost quantitative. The residue was recrystallized from ethanol (needles), m.p. 210°.

Anal. Calcd. for $C_{11}H_{13}O_2N_2Cl$: C, 54.9; H, 5.4; N, 11.6; Cl, 14.7. Found: C, 54.8; H, 5.3; N, 11.6; Cl, 14.6.

N-Benzyl-*dl*-asparagine (XV).—XIV was dissolved in 2 *N* sodium hydroxide and the solution was neutralized by addition of 2 *N* hydrochloric acid. XV precipitated and was recrystallized from water (hexagonal plates); m.p. 265° was not depressed by mixing with an authentic sample.[4]

Anal. Calcd. for $C_{11}H_{14}O_3N_2$: C, 59.4; H, 6.3; N, 12.6. Found: C, 59.4; H, 6.3; N, 12.2.

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[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, THE HEBREW UNIVERSITY]

Syntheses of Aspartic Acid Derivatives. II. N-Alkylated α- and β-Asparagines

BY Y. LIWSCHITZ, YOLAN EDLITZ-PFEFFERMANN AND Y. LAPIDOTH

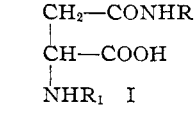
RECEIVED NOVEMBER 22, 1955

N-Alkylated-β-asparagines have been prepared by reaction of N-alkyl-maleamic acids with benzylamine and hydrogenolysis of the intermediate N^2-benzyl derivatives. In this last step, which had to be carried out in acid medium, partial ring closure to the aspartimide derivative occurred, depending on the nature of the alkyl group. N^2-Alkylated-β-asparagines were obtained when maleamic acid reacted with alkyl amines. N-Alkylated-α-asparagines have been synthesized by the reaction of the mixed anhydride of N-benzyl-*dl*-aspartic acid and chloroformic acid with primary amines.

The synthesis of derivatives of α- or β-asparagines in which either the α-amino, the amido or both groups are alkylated presents difficulties and only relatively few substances of this class have been recorded in the literature.[1]

We, therefore, sought to exploit the methods communicated in our previous papers for the preparation of such compounds.

The method, permitting the synthesis of aspartyl peptides,[2] has now been extended to the preparation of aspartyl amides, treated in the present paper. It has also been demonstrated that by variations of this method any asparagine derivative of type I (R and R_1 being either alkyl groups or one of them hydrogen), may be prepared.[3]



(1) (a) G. Piutti, *Gazz. chim. ital.*, **18**, 480 (1888); (b) O. Lutz, *Ber.*, **62B**, 1879 (1929); (c) D. C. Carpenter, *et al.*, THIS JOURNAL, **64**, 2899 (1942); (d) F. E. King and D. A. A. Kidd, *J. Chem. Soc.*, 2976 (1951); (e) P. Desnuelle and G. Bonjour, *Biochim. Biophys. Acta*, **9**, 356 (1952).

(2) Y. Liwschitz and A. Zilkha, THIS JOURNAL, **77**, 1265 (1955).

(3) Substances for which R = H and R_1 = alkyl are dealt with in this paper, those for which R = R_1 = alkyl in a forthcoming one.

N-Alkyl-asparagines were synthesized by opening maleic anhydride in ethereal solution with various alkyl amines and reaction of N-alkylmaleamic acids thus produced with benzylamine[4] in dioxane. The last step consisted in the hydrogenolysis of the N^2-benzyl amides. As regards this latter reaction, it was found that on performing it in acid medium (acetic acid), part of the amide apparently underwent ring closure to yield a derivative of aspartimide, since analyses of some amides showed according deviations. The tendency for ring closure was most pronounced for small alkyl groups (*i.e.*, ethyl), less for *n*-propyl and *n*-butyl and negligible for *n*-hexyl, the same holding for the isopropyl group. On omission of acetic acid, however, hydrogenolysis could not be effected.

N-Alkyl-maleamic acids were mostly obtained quantitatively, N^2-benzyl-N-alkyl-asparagines in 60–80% yields and the hydrogenolysis step was also quantitative, as a rule. N^2-Benzyl-N-allylasparagine yielded N-*n*-propylasparagine on hydrogenolysis with a $PdCl_2$-on-charcoal catalyst (30%); this was identical with the product obtained from N^2-benzyl-N-*n*-propylasparagine. Analyses, however, seem to indicate that ring closure occurred to a lesser extent on hydrogenolysis of the unsaturated substance, than was the case with the *n*-propyl derivative.

Those amides which are sufficiently water soluble give a deep blue coloration when their aqueous solution, heated to boiling, is treated with copper carbonate.[1e] This behavior contrasts with that of α-asparagine derivatives in which the α-carboxyl group is not available. The color reaction is given by amino acids possessing a free α-carboxyl group whose α-amino nitrogen is not acylated. Alkylation of the latter group, however, does not interfere and N^2-benzyl derivatives reacted positively. This reaction, combined with the biuret test[5] may, therefore, be used to determine the purity of either α- or β-aspartyl derivatives which should only give one positive reaction, whereas for mixtures both tests are generally positive.

All free amides gave a positive ninhydrin reaction and produced bluish spots with this reagent in paper partition chromatography.[6]

N-Alkyl-asparagines prepared are listed in Table III.

N^2-Arylated-asparagines have been produced by reaction between bromosuccinamide and aryl amines.[1b] A general method which allows the synthesis of any alkyl derivative of this type consists in heating maleamic acid with the appropriate amine in pyridine at reflux. The aspartyl amides are precipitated during the reaction which is conducted for comparatively short periods. Yields are high, nearly quantitative with methyl- and ethylamine and never below 50% with other bases. The yield of N^2-benzylasparagine was improved by conducting the reaction in pyridine, thus avoiding isolation of the benzylamine salt of maleamic acid which was necessary according to our former method.[4]

The color reaction with copper carbonate was positive and the biuret test negative for each substance.

N^2-Alkyl-asparagines prepared are listed in Table IV.

The synthesis of N-alkyl-α-asparagines by existing methods is especially troublesome and, as far as we are aware, no fully characterized substances have been reported in the literature.[1e] Since it has already been shown that α-asparagine is obtained in good yield by means of a mixed anhydride of chloroformic and N-benzyl-*dl*-aspartic acid,[5] we undertook the preparation of such derivatives by the same route. The previous finding that the α-isomer is produced almost exclusively when strong bases react with the mixed anhydride, but the β-derivative in the case of less reactive amines, has been confirmed. All aliphatic amines, as well as cyclohexylamine, yielded derivatives of α-asparagine, the weaker aromatic amines, on the other hand, gave N-alkylated-β-asparagines. When both α- and β-amides were produced, they could be separated quantitatively, since the β-isomer, being insoluble in dioxane, was precipitated during the reaction, whereas the α-amide remained in solution. But if a sufficient excess of the amine was taken in order to bind any free hydrochloric acid, no β-product was obtained, since the formation of the inner anhydride probably did not then take place.[5]

Yields were generally 50–70% in the coupling reaction and nearly quantitative in the second step, leading to the removal of the benzyl group.

In contrast to the behavior of the corresponding β-isomers, no ring closure to the aspartimide was observed when the N^2-benzyl derivatives were hydrogenolyzed in acetic acid solution.

The biuret reaction was strongly positive in all cases where the alkyl substituent contained a methylene group attached to the amido nitrogen. A methine group, however, (*e.g.*, isopropyl, cyclohexyl) shifted the adsorption to a more bluish region. The N^2-benzyl derivatives likewise gave a positive biuret test, but of less intensive color than the free amides.

The copper carbonate test was negative in all cases, indicating the purity of the preparations. The free α-amides gave purple spots with ninhydrin on paper chromatograms.[6]

N-Alkyl-α-asparagines prepared are listed in Table VI.

Experimental[7]

Preparation of N-Alkyl-maleamic Acids.—To an ice-cooled solution of 0.1 mole of maleic anhydride in 150 ml. of anhydrous ether was added 0.1 mole of the amine in 20 ml. of ether. The N-alkylmaleamic acid settled immediately. The crystals were filtered off and washed with ether.

Preparation of N^2-Benzyl-N-alkyl-*dl*-asparagines.—To 0.035 mole of the N-alkyl maleamic acid in 50 ml. of dry dioxane, was added 0.035 mole of benzylamine and the mixture heated under reflux for 75 minutes. The precipitate which formed was filtered after cooling and washed with acetone.

Preparation of N-Alkyl-*dl*-asparagines.—Two to three grams of the N^2-benzyl-N-alkyl-*dl*-asparagine was dissolved in 75 ml. of glacial acetic acid and 0.2 g. of catalyst (palladium chloride-on-charcoal (30%)) added. Hydrogenolysis was carried out for about 5 hr. (*cf.* ref. 5). Finally, the catalyst was separated by filtration and the solvent removed *in vacuo*.

(4) Max Frankel, Y. Liwschitz and Y. Amiel, THIS JOURNAL, **75**, 330 (1953).

(5) Y. Liwschitz and A. Zilkha, *ibid.*, **76**, 3698 (1954).

(6) W. J. Le Quesne and G. T. Young, *J. Chem. Soc.*, 24 (1952).

(7) Micro-combustion analyses were made by Drs. Weiler and Strauss. Melting points were determined in a Fisher–Johns apparatus.

TABLE I

PREPARATION OF N-ALKYL-MALEAMIC ACIDS

Substances were recrystallized from benzene if not indicated otherwise

Substance, N-alkyl-maleamic acid	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Ethyl	88	123	$C_6H_9O_3N$	50.3	50.3	6.2	6.2	9.8	9.8
n-Propyl	Quant.	102	$C_7H_{11}O_3N$	53.5	53.3	7.0	6.7	8.9	8.8
Allyl	93	106	$C_7H_9O_3N$	53.9	54.3	6.4	6.0	9.0	8.7
Isopropyl	Quant.	103	$C_7H_{11}O_3N$	53.5	53.1	7.0	6.7	8.9	9.1
n-Butyl	Quant.	79	$C_8H_{13}O_3N$	56.1	56.1	7.7	7.7	8.2	7.7
n-Hexyl	Quant.	76	$C_{10}H_{17}O_3N$	60.2	60.2	8.5	8.5	7.0	6.9
Cyclohexyl[a]	Quant.	150	$C_{10}H_{15}O_3N$	60.8	61.0	7.6	7.6	7.1	6.7
p-Tolyl[b]	85	193	$C_{11}H_{11}O_3N$	64.3	64.4	5.3	5.4	6.8	6.8
α-Naphthyl	Quant.	134	$C_{14}H_{11}O_3N$	69.7	69.8	4.6	4.6	5.8	5.6

[a] Recrystallized from chloroform–ether. [b] Recrystallized from ethanol.

TABLE II

PREPARATION OF N^2-BENZYL-N-ALKYL-*dl*-ASPARAGINES

Substances were recrystallized from ethanol if not indicated otherwise

Substance N^2-benzyl-N-alkylasparagine	Yield, %	M.p., °C.	Reflux time, min.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Ethyl	65	208	60	$C_{13}H_{18}O_3N_2$	62.4	63.0	7.2	7.4	11.2	10.7
n-Propyl	88	218	60	$C_{14}H_{20}O_3N_2$	63.6	64.1	7.6	7.2	10.6	10.7
Allyl	50	211	60	$C_{14}H_{18}O_3N_2$	64.1	64.1	6.9	7.0	10.7	11.0
Isopropyl	78	229	75	$C_{14}H_{20}O_3N_2$	63.6	63.3	7.6	7.3	10.6	10.6
n-Butyl	78	212	75	$C_{15}H_{22}O_3N_2$	64.7	65.2	7.9	7.8	10.0	9.8
n-Hexyl	75	209	75	$C_{17}H_{26}O_3N_2$	66.6	66.0	8.5	7.9	9.1	9.1
Cyclohexyl[a]	50	240	60	$C_{17}H_{24}O_3N_2$	67.0	67.1	7.9	7.8	9.2	9.1
p-Tolyl[b]	75	224	60	$C_{18}H_{20}O_3N_2$	69.2	68.4	6.4	6.3	8.9	8.7
α-Naphthyl[b]	62	199	60	$C_{21}H_{20}O_3N_2$	72.2	71.5	5.7	5.9	8.0	7.2

[a] Owing to insolubility in solvents, the substance was purified by dissolving in alkali, precipitation with hydrochloric acid and washing with water and hot ethanol. [b] Recrystallized from water.

TABLE III

PREPARATION OF N-ALKYL-*dl*-ASPARAGINES[e]

Substances were recrystallized from water if not indicated otherwise

Substance, N-alkylasparagine	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Ethyl[a,b]	257	$C_6H_{12}O_3N_2$	45.0	50.6	7.5	7.0	17.5	16.6
n-Propyl[b]	263	$C_7H_{14}O_3N_2$	48.3	49.8	8.1	8.0	16.1	16.0
n-Propyl[b] (*via* allyl)	264	$C_7H_{14}O_3N_2$	48.3	49.2	8.1	7.7	16.1	16.3
Isopropyl	245	$C_7H_{14}O_3N_2$	48.3	48.7	8.1	8.0	16.1	15.6
n-Butyl[b]	265	$C_8H_{16}O_3N_2$	51.0	52.6	8.6	8.4	14.9	14.8
n-Hexyl	257	$C_{10}H_{20}O_3N_2$	55.5	56.0	9.3	8.8	12.9	13.0
Cyclohexyl	247	$C_{10}H_{18}O_3N_2$	56.0	55.8	8.5	8.4	13.1	13.0
p-Tolyl[c]	270	$C_{11}H_{14}O_3N_2$	59.4	59.4	6.3	6.1	12.6	12.5
α-Naphthyl[d]	239	$C_{14}H_{14}O_3N_2$	65.1	64.1	5.4	5.7	10.8	10.6

[a] Hydrogenolysis was carried out in aqueous methanol to which a small quantity of acetic acid had been added. [b] Analytical values indicate partial closure to imide. [c] Part of the substance which adhered to the catalyst was dissolved in cold formic acid, separated by filtration and recovered on evaporation of the solvent. [d] Purified by trituration with hot ethanol. [e] Yield almost quantitative in all cases.

TABLE IV

PREPARATION OF N^2-ALKYL-*dl*-ASPARAGINES

All substances were recrystallized from ethanol

Substance, N-alkyl-asparagine	Yield, %	M.p., °C.	Reflux time, min.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl	Quant.	208	180	$C_5H_{10}O_3N_2$	41.1	40.5	6.9	7.0	19.1	18.6
Ethyl	Quant.	203	45	$C_6H_{12}O_3N_2$	45.0	44.8	7.5	7.1	17.5	17.2
Allyl	58	199	60	$C_7H_{12}O_3N_2$	48.8	48.5	7.0	6.7	16.3	16.3
n-Propyl	72	211	60	$C_7H_{14}O_3N_2$	48.3	48.6	8.1	8.1	16.1	16.1
Isopropyl	66	223	60	$C_7H_{14}O_3N_2$	48.3	48.4	8.1	8.0	16.1	16.0
1-Hydroxy-*n*-propyl	60	225	60	$C_7H_{14}O_4N_2$	44.2	44.2	7.4	7.3	14.7	14.7
n-Butyl	70	219	45	$C_8H_{16}O_3N_2$	51.0	51.0	8.5	8.1	14.9	15.0
n-Amyl	53	221	45	$C_9H_{18}O_3N_2$	53.4	53.9	8.9	8.3	13.9	13.9
n-Hexyl	68	223	45	$C_{10}H_{20}O_3N_2$	55.5	55.3	9.3	9.3	12.9	12.8
Cyclohexyl	63	221	150	$C_{10}H_{18}O_3N_2$	56.0	55.6	8.4	8.0	13.1	13.0
Benzyl[a]	80	216	60							

[a] Identical with substance prepared by different method (*cf.* ref. 5).

TABLE V

PREPARATION OF N^2-BENZYL-N-ALKYL-*dl*-α-ASPARAGINES

All substances were recrystallized from ethanol.

Substance, N^2-benzyl-N-alkyl-*dl*-α-asparagine	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Ethyl	72	159	$C_{13}H_{18}O_3N_2$	62.4	62.2	7.2	7.4	11.2	11.0
n-Propyl	50	163	$C_{14}H_{20}O_3N_2$	63.6	63.2	7.6	7.6	10.6	10.3
Isopropyl	70	182	$C_{14}H_{20}O_3N_2$	63.6	63.3	7.6	7.0	10.6	10.2
Allyl	55	153	$C_{14}H_{18}O_3N_2$	64.1	64.2	6.9	6.9	10.7	10.7
n-Butyl	60	161	$C_{15}H_{22}O_3N_2$	64.7	64.2	7.9	7.9	10.0	9.8
n-Hexyl	55	167	$C_{17}H_{26}O_3N_2$	66.6	67.0	8.5	8.6	9.1	9.0
Cyclohexyl	70	188	$C_{17}H_{24}O_3N_2$	67.0	66.2	7.9	7.9	9.2	9.0

TABLE VI

PREPARATION OF N-ALKYL-*dl*-α-ASPARAGINES

Yields were almost quantitative in all cases

Substance, N-alkyl-*dl*-α-asparagine	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Ethyl[a]	197	$C_6H_{12}O_3N_2$	45.0	45.0	7.5	7.5	17.5	16.9
n-Propyl[b]	222	$C_7H_{14}O_3N_2$	48.3	47.6	8.1	8.1	16.1	16.1
n-Propyl[b] (*via* allyl)	221	$C_7H_{14}O_3N_2$	48.3	48.2	8.1	8.4	16.1	16.0
Isopropyl[b]	233	$C_7H_{14}O_3N_2$	48.3	48.1	8.1	8.0	16.1	16.0
n-Butyl[b]	226	$C_8H_{16}O_3N_2$	51.0	51.0	8.5	8.4	14.9	14.7
n-Hexyl[c]	223	$C_{10}H_{20}O_3N_2$	55.5	55.5	9.3	9.0	12.9	13.2
Cyclohexyl[c]	247	$C_{10}H_{18}O_3N_2$	56.0	56.2	8.4	8.3	13.1	12.7

[a] Purified by trituration with hot ethanol. [b] Recrystallized from aqueous ethanol. [c] Recrystallized from water.

Preparation of N^2-Alkyl-*dl*-asparagines.—Maleamic acid (0.025 mole) and the alkylamine (0.025 mole) in 15 ml. of pyridine was heated under reflux (for reaction times see Table IV). After cooling, the precipitate was filtered off and washed with acetone.

Preparation of N^2-Benzyl-N-alkyl-*dl*-α-asparagines.—To a cooled solution of the mixed anhydride of N-benzyl-*dl*-aspartic acid and chlorocarbonic acid,[5] freshly prepared from 9 g. of N-benzyl-*dl*-aspartic acid in 150 ml. of dry dioxane, was added 0.1 mole of the amine.[8] After having stood overnight at room temperature, the formed precipitate which contained various amounts of the amide in addition to amine-hydrochloride, was filtered off, washed with ether and dried. Separation of the amine-salt was then effected by trituration with acetone. The dioxane solution was evaporated *in vacuo* to dryness and the residue redissolved in acetone and left in a refrigerator overnight (or sometimes longer) until the amide crystallized out. Both fractions of the substance were finally recrystallized as indicated in Table I.

Preparation of N-Alkyl-*dl*-α-asparagines.—These substances were obtained in the same way as their corresponding β-isomers.

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(8) An excess of the amine must be taken to bind any free hydrochloric acid already present in the reaction mixture. This depends on the purity of the phosgene which besides greatly influences the formation of the mixed anhydride and consequently the yield of the amide. Therefore, only first grade quality phosgene should be used.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, "PLIVA" PHARMACEUTICAL AND CHEMICAL WORKS, ZAGREB, YUGOSLAVIA]

The Correlation of Configurations of Chloroamphenicol and D-Serine

BY DRAGUTIN FLEŠ AND BRANKO BALENOVIĆ

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Chloroamphenicol (D-*threo*-1-*p*-nitrophenyl-2-dichloroacetamido-1,3-propanediol) (I) was prepared from O-methyl-N-phthaloyl-D-serine (III) through the intermediate α-phthalimido-β-methoxy-D-propiophenone (V). The configurational correlation between I and D-serine was thus established.

The configurational correlation between chloramphenicol (D-*threo*-1-*p*-nitrophenyl-2-dichloroacetamido-1,3-propanediol) and (−)-nor-*pseudo*-ephedrine, based on optical rotation data of chloramphenicol and its derivatives, was first suggested by Rebstock, *et al.*[1] The correctness of this assumption was later confirmed by several investigators. Fodor, *et al.*,[2] established the configurational relation of chloramphenicol to nor-*pseudo*-ephedrine by means of chemical interconversion. Miyamoto[3] showed that DL-*erythro*-1-phenyl-1-methoxy-2-benzamido-3-hydroxypropane was related to nor-ephedrine, through appropriate transformations. Honjo[4] synthesized the L-*threo*-1-*p*-nitrophenyl-2-amino-1,3-propanediol from D-*threo*-phenylserine, correlating in this way the configuration of chloramphenicol with the L-*threo*-phenylserine.

In the course of our studies on the configuration

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(4) M. Honjo, *J. Pharm. Soc. Japan*, **73**, 368 (1953); *C. A.*, **48**, 2642 (1954).