TABLE II

COUPLING CONSTANTS FOR THE 1-X-2,4-DINITRONAPHTHALENES IN DIOXANE

J	X = Cl	X = Br	X = I
3,5	0	0	0
5,6	8.64 ± 0.04	8.49 ± 0.03	8.56 ± 0.04
5,7	1.17 ± 0.04	1.29 ± 0.03	1.05 ± 0.04
5,8	0.75 ± 0.03	0.57 ± 0.02	0.58 ± 0.03
6,7	7.16 ± 0.03	6.91 ± 0.02	6.93 ± 0.03
6,8	1.20 ± 0.04	1.12 ± 0.04	0.98 ± 0.04
7,8	8.59 ± 0.04	8.66 ± 0.04	8.56 ± 0.04

TABLE III

CHEMICAL SHIFTS AND COUPLING CONSTANTS FOR 1-X-2,4-DINITROBENZENES IN ACETONE

Substituent	Chemical shift			Coupling constant		
	ν_3	ν_5	ν_6	$J_{3,5}$	$J_{3,6}$	$J_{5,6}$
F[a]	530.2	515.7	466.1	3.0	0.2	9.3
Cl	530.8	512.6	483.4	2.49	0.10	8.85
Cl[b]	529.8	512.3	483.2	2.70	0.36	8.81
Br	527.9	506.6	494.0	2.63	0.26	8.76
I	523.5	495.4	510.7	2.54	0.02	8.80

[a] T. Schaefer, *Can. J. Chem.*, **40**, 431 (1962). [b] S. L. Smith and A. M. Ihrig, *J. Mol. Spectrosc.*, **22**, 241 (1967).

With the data of Spiesecki and Schneider,[8] a plot was made of the chemical shift of the halobenzene protons *vs.* the Pauling electronegativity of the halogen. The same type plot for the chemical shifts of the 2,4-dinitrohalobenzenes shows striking similarities. The H_3 and H_5 in the 2,4-dinitrohalobenzenes series are qualitatively similar to the meta protons of the halobenzene series; H_6 corresponds to the ortho protons in the halobenzenes. The two nitro groups affect the magnitude of the chemical shift, but the nature of the halogen still controls the relative chemical shift within the series.

The 2,4-dinitrohalonaphthalenes gave a much more complex spectra than the benzene series. H_3 appears as an intense singlet with a complex ABCD spectrum for the other protons, H_5, H_6, H_7, and H_8. Since the α protons of naphthalene have a greater chemical shift than β, the assignment of H_5 and H_8 to the downfield portion of the spectra is obvious. Since there is *no* coupling between the substituted and unsubstituted rings, the correct assignment of *one* of the protons (H_5 or H_8) is essential. From this one correct assignment, all other shifts and coupling constants are calculated *via* LAOCN3. The assignment of H_8 to the lower field is based on the data of Wells.[9] The effect of the nitro groups on H_5, H_6, H_7, and H_8 can be calculated.[9] These calculations indicate that $\nu_8 = 510$, $\nu_5 = 503$, $\nu_6 = 499$, and $\nu_7 = 437$ Hz. In other words, the order is $H_8 > H_5 > H_6 > H_7$. The data of Table I follow this pattern. If one draws resonance structures of the 1-halo-2,4-dinitronaphthalenes, both the 2- and the 4-nitro groups show resonance forms with + charges on the 6 and 8 positions. If electronegativity is the major factor in chemical shifts, these two protons should be downfield with respect to protons 5 and 7. The above argument has the implicit assumption that the halogens do not greatly affect the shift, and that their effect is a perturbation on the major effect of the nitro groups. Is this assumption correct or can we arrive at a satisfactory assignment on other bases? An alternative method is to apply the chemical shift changes of halogens in the ortho, meta, and para positions in benzene to the naphthalene series. If H_8 is regarded as meta to the halogen and H_5 as para, we arrive at the following qualitative result:

1-chloro	ν_8 = 510 (for NO_2 groups)	(−2)	(*m*-Cl)	= 508 Hz
	ν_5 = 503 (for NO_2 groups)	(−8)	(*p*-Cl)	= 495 Hz
1-bromo	ν_8 = 510	(−6)	(*m*-Br)	= 504 Hz
	ν_5 = 503	(−2)	(*p*-Br)	= 501 Hz
1-iodo	ν_8 = 510	(−15)	(*m*-I)	= 495 Hz
	ν_5 = 503	(−3)	(*p*-I)	= 500 Hz

These assumptions give the same qualitative order as the previous assumptions for the chloro and bromo compounds, but not for iodo. The iodine atom is large, and the peri positions of naphthalene are closer than the meta positions of the benzene. It is probable that the contributions of both the *m*-Br (−6) and the *m*-I (−15) are too negative; their real contribution would be more toward the ortho halogens, which are positive. This approach, though somewhat argumentative, supports the first. The peri effect has been discussed by Zweig, Lancaster, and Neglia.[10] The effect of a peri substituent is to shift that proton downfield; the low-field proton is always at the α position peri to the substituent. In our compounds, H_8 is the α and peri position and should be the low-field proton. Hence, the assignments $\nu_8 > \nu_5$ and $\nu_6 > \nu_7$ were accepted.

Comparison of the 2,4-dinitrohalonaphthalene series with the benzene series shows the meta pattern is followed. In each case, the chemical shift of the chloro compound is slightly greater than the bromo, which, in turn, is considerably greater than the iodo compounds.

Coupling constants do not vary much with respect to change in halogen. The ortho coupling constants, $J_{5,6}$ and $J_{7,8}$, are about equal (8.5 Hz) and greater than $J_{6,7}$ (7.0 Hz). The meta coupling constants, $J_{5,7}$ and $J_{6,7}$, show no pronounced trends and have the value of (1.0–1.3) Hz. The para coupling constants range from 0.75 to 0.6 Hz.

Registry No.—1-Cl-2,4-Dinitronaphthalene, 2401-85-6; 1-Br-2,4-dinitronaphthalene, 2401-86-7; 1-I-2,4-dinitronaphthalene, 4112-02-1; 1-Cl-2,4-dinitrobenzene, 97-00-7; 1-Br-2,4-dinitrobenzene, 584-48-5; 1-I-2,4-dinitrobenzene, 709-49-9.

(8) H. Spiesecki and W. G. Schneider, *J. Chem. Phys.*, **35**, 731 (1961).
(9) R. P. Wells, *J. Chem. Soc.*, 1967 (1963).
(10) A. Zweig, J. E. Lancaster, and M. T. Neglia, *Tetrahedron*, **23**, 2577 (1967).

Stepwise Synthesis of Oligopeptides with *N*-Carboxy-α-Amino Acid Anhydrides. IV. Glycine NCA

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Received July 6, 1971

A successful procedure for peptide synthesis using the controlled reaction of *N*-carboxy α-amino acid anhydrides (NCA's) in an aqueous system has been

TABLE I
RESULTS OF SYNTHESES OF N-GLYCYL PEPTIDES

Peptide	Yield, %	[α]D, deg	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Gly-Gly	90		36.36	6.11	21.20	36.55	6.20	21.50
Gly-L-Ala	87	−59.0 (c 2.5, 0.5 N HCl)[a]	41.08	6.91	19.17	40.75	7.12	19.34
Gly-L-Val	91	−19.5 (c 2.0. water)[b]	48.25	8.12	16.08	48.33	8.25	16.26
Gly-L-Leu	92	−36.4 (c 2.5, water)[c]	51.04	8.58	14.88	51.12	8.61	14.80
Gly-L-Phe	89	41.0 (c 2.5, water)[d]	59.45	6.35	12.60	59.60	6.46	12.55
Gly-L-Leu-L-Ala	86	−59.2 (c 2.4, water)[e]	50.94	8.18	16.21	51.05	8.20	16.14

[a] −59.3° (c 2, 0.5 N HCl): B. F. Erlanger and E. Brand, *J. Amer. Chem. Soc.*, **73**, 3508 (1951). [b] −19.9° (c 2, water): K. R. Rao, S. M. Birnbaum, R. B. Kingsley, and J. P. Greenstein, *J. Biol. Chem.*, **198**, 507 (1952). [c] −36.3° (c 2, water): F. H. Carpenter and D. T. Gish, *J. Amer. Chem. Soc.*, **74**, 3818 (1952). [d] 40.8° (c 2.5, water): ref 2. [e] −59.0° (c 2.5 water): E. Abderhalden and A. Fodor, *Z. Phys. Chem.*, **81**, 1 (1912).

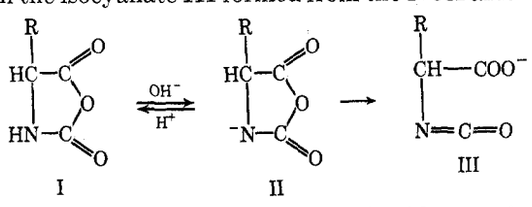
developed by the Merck group.[1,2] The procedure was satisfactorily used by Koppel and coworkers[3] to prepare some oligopeptides. The usefulness of this synthetic method was demonstrated by the total synthesis of the S protein of RNase A.[4-8] In the aqueous system, however, glycine NCA reacted with an amino acid as a nucleophile to give hydantoic acid as a side product to the extent of more than 20% even at the optimal pH of 10.2. 2,5-Thiazolidinedione (glycine NTA), therefore, was used to avoid the formation of the hydantoic acid.[9,10]

Another NCA method for peptide synthesis using the heterogeneous system acetonitrile–water has been reported by us.[11,12] With ordinary stirring and addition of sodium carbonate, the method permitted the synthesis of peptides without such side reactions as polymerization and hydrolysis of the NCA.

A distinct difference in the formation of the hydantoic acid was found between the NCA method in the aqueous system and that in the heterogeneous system. In the reaction of NCA with an amino acid or a peptide in our previous synthesis,[11] attention was not paid to the formation of the hydantoic acid because the desired peptide was obtained in high yield[12,13] and the by-product, if it had been formed, could not react with NCA. In the reaction of glycine NCA with glycine in heterogeneous system, glycylglycine was obtained in 90% yield. Such a yield could not be expected from the results in the aqueous system reported by the Merck group. Glycyl-L-leucine was also obtained in 92% yield by the reaction of L-leucine in the heterogeneous system acetonitrile–water containing sodium carbonate with glycine NCA in acetonitrile. A tripeptide with N-terminal glycine, glycyl-L-leucyl-L-alanine, was also synthesized by the NCA method in the heterogeneous system. The sodium salt of L-alanine was treated with L-leucine NCA and the dipeptide formed was treated with glycine NCA. The resulting tripeptide was recrystallized from aqueous ethanol to give pure tripeptide (86% overall yield). Some *N*-glycyl dipeptides were also prepared in high yields in the heterogeneous system and these results are summarized in Table I.

These results strongly suggest that few side reactions occurred in the heterogeneous system. This was demonstrated by the synthesis of glycyl-L-tryptophan. After the reaction of glycine NCA with L-tryptophan in the heterogeneous system, the aqueous layer of the system was analyzed by thin layer chromatography. All of the Ehrlich positive components detected on silica gel were ninhydrin positive. No component that was Ehrlich positive and ninhydrin negative could be detected by tlc. These components were quantitatively determined as unreacted L-tryptophan (1%), glycyl-L-tryptophan (96.5%), and glycylglycyl-L-tryptophan (2.5%).

The formation of N-terminal glycyl peptides in high yields without formation of hydantoic acid is consistent with our previous suggestion[11] that the NCA in the heterogeneous system may be protected from side reactions by the acetonitrile layer. The hydantoic acid formed in the homogeneous system may be derived from the isocyanate III formed from the NCA anion II.[2]



I II III

The rapid polymerization of NCA (a side reaction in the peptide synthesis by the NCA method) *via* the NCA anion[2,14] does not occur in acetonitrile[15] or in the heter-

(1) R. G. Denkewalter, H. Schwam, R. G. Strachan, T. E. Beesley, D. F. Veber, E. F. Schoenewaldt, H. Barkemeyer, W. J. Paleveda, Jr., T. A. Jacob, and R. Hirschmann, *J. Amer. Chem. Soc.*, **88**, 3163 (1966).

(2) R. Hirschmann, R. G. Strachan, H. Schwam, E F. Schoenewaldt, H. Joshua, B. Barkemeyer, D. F. Veber, W. J. Paleveda, Jr., T. A. Jacob, T. E. Beesley, and R. G. Denkewalter, *J. Org. Chem.*, **32**, 3415 (1967).

(3) K. D. Kopple, T. Saito, and M. Ohnishi, *ibid.*, **34**, 1631 (1969).

(4) R. G. Denkewalter, D. F. Veber, F. W. Holly, and R. Hirschmann, *J. Amer. Chem. Soc.*, **91**, 502 (1969).

(5) R. G. Strachan, W. J. Paleveda, Jr., R. F. Nutt, R. A. Vitali, D. F. Veber, M. J. Dickinson, V. Garsky, J. E. Deak, E. Walton, S. R. Jenkins, F. W. Holly, and R. Hirschmann, *ibid.*, **91**, 503 (1969).

(6) S. R. Jenkins, R. F. Nutt, R. S. Dewey, D. F. Veber, F. W. Holly, W. J. Paleveda, Jr., T. Lanza, Jr., R. G. Strachan, E. F. Schoenewaldt, H. Barkemeyer, M. J. Dickinson, J. Sondey, R. Hirschmann, and E. Walton, *ibid.*, **91**, 505 (1969).

(7) D. F. Veber, S. L. Varga, J. D. Milkowski, H. Joshua, J. B. Conn, R. Hirschmann, and R. G. Denkewalter, *ibid.*, **91**, 506 (1969).

(8) R. Hirschmann, R. F. Nutt, D. F. Veber, R. A. Vitali, S. L. Varga, T. A. Jacob, F. W. Holly, and R. G. Denkewalter, *ibid.*, **91**, 507 (1969).

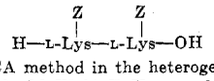
(9) R. S. Dewey, E. F. Schoenewaldt, H. Joshua, W. J. Paleveda, Jr., H. Schwam, H. Barkemeyer, B. H. Arison, D. F. Veber, R. G. Denkewalter, and R. Hirschmann, *ibid.*, **90**, 3254 (1968).

(10) D. F. Veber, R. Hirschmann, and R. G. Denkewalter, *J. Org. Chem.*, **34**, 753 (1969).

(11) Y. Iwakura, K. Uno, M. Oya, and R. Katakai, *Biopolymers*, **9**, 1419 (1970).

(12) R. Katakai, M. Oya, K. Uno, and Y. Iwakura, *ibid.*, in press.

(13) Izumiya, *et al.*, synthesized



in 87% yield by the NCA method in the heterogeneous system: N. Mitsuyasu, S. Terada, K. Noda, M. Waki, T. Kato, and N. Izumiya, Proceedings of the 8th Symposium on Peptide Chemistry, Osaka, Japan, 1970, p 5.

(14) M. Goodman and J. Hutchison, *J. Amer. Chem. Soc.*, **88**, 3627 (1966).

(15) Y. Iwakura, K. Uno, and M. Oya, *J. Polym. Sci., Part A-1*, **6**, 2165 (1968).

ogeneous system of acetonitrile–water. Since glycine NCA cannot be transformed to the isocyanate through the NCA anion in the heterogeneous system, hydantoic acid is not formed in this system.

Experimental Section

Glycine NCA.[16]—Into a suspension of 10 g of finely powdered glycine in 400 ml of dry tetrahydrofuran, dry phosgene was bubbled at 45° with magnetical stirring. A clear solution was obtained after 2 hr. The solution was concentrated at reduced pressure at 30°, then glycine NCA crystallized out. To the residue was added 200 ml of *n*-hexane in order to crystallize out the NCA completely. The crystals of the product were filtered off and dried over P_2O_5 in a vacuum desiccator. The crude product was recrystallized twice from ethyl acetate to yield 9.8 g (73%) of the chlorine-free NCA,[17] mp 100° (lit.[18] 100°).

General Procedure for Synthesis of Glycyl Dipeptides.—To a solution of 0.01 mol of α-amino acid and 1 g of sodium carbonate in 10 ml of 1 *N* sodium hydroxide and 40 ml of water was added 40 ml of acetonitrile and the system was cooled to −10°. A solution of 1.2 g (0.012 mol) of glycine NCA in 24 ml of acetonitrile was added to the system and allowed to react for 3 hr at −10° with stirring. The aqueous layer of the system was washed with 50 ml of acetonitrile under cooling and neutralized with concentrated sulfuric acid. Sodium sulfate was removed by addition of 200 ml of ethanol followed by filtration and the alcoholic solution was concentrated *in vacuo* at 35°. Addition of 50 ml of ethanol and 100 ml of diethyl ether to the residue gave a crystalline product. The crude product was recrystallized from aqueous methanol to yield a crystalline dipeptide.

Glycyl-L-leucyl-L-alanine.—To a heterogeneous system of 50 ml of acetonitrile and 50 ml of 0.2 *N* sodium hydroxide containing 0.89 g (0.01 mol) of L-alanine and 1 g of sodium carbonate was added a solution of 1.73 g (0.011 mol) of L-leucine NCA in 17.3 ml of acetonitrile. The condensation reaction was allowed for 2 hr at −10° with stirring. After the reaction the acetonitrile layer of the system was separated off and the aqueous layer was washed with 100 ml of acetonitrile under cooling. The solution was warmed to 40° for 5 min. Then 50 ml of acetonitrile and 20 ml of 0.2 *N* sodium hydroxide were added to the solution and the system was cooled again to −10°. After the addition of 1.2 g (0.012 mol) of glycine NCA in 24 ml of acetonitrile, the system was kept at −10° for 3 hr with stirring. The aqueous layer of the system was treated by the same manner as above, washing, neutralization, and condensation. The crude product was recrystallized from aqueous ethanol.

Reaction of Glycine NCA with L-Tryptophan.—To a solution of 2.05 g (0.01 mol) of L-tryptophan and 1 g of sodium carbonate in 10 ml of 1 *N* sodium hydroxide and 40 ml of water, 40 ml of acetonitrile was added and the system was cooled to −10°. After the addition of 1.2 g of glycine NCA in 24 ml of acetonitrile the system was allowed to stand for 3 hr with stirring. The aqueous layer of the system was washed with 50 ml of acetonitrile and diluted with water to a volume of 50 ml. A 40-μl sample of the solution was analyzed by tlc on silica gel in pyridine–water (4:1). A strip showed three ninhydrin-positive spots, unreacted L-tryptophan (R_f 0.57), glycyl-L-tryptophan (R_f 0.39), and glycylglycyl-L-tryptophan (R_f 0.18). Three Ehrlich-positive spots were detected on another strip, L-tryptophan (R_f 0.57), glycyl-L-tryptophan (R_f 0.39), and glycylglycyl-L-tryptophan (R_f 0.18). Then the pertinent areas of the tlc developed anew were scraped off and extracted with 100 ml of water. The transmittancy of the extracts was measured at 280 mμ.[19] The residual sample was treated as above to isolate the dipeptide. The crude product was recrystallized from methanol to yield 2.33 g (89%) of a pure dipeptide: $[\alpha]_D$ 33.5° (*c* 2.5, 5 *N* HCl) [lit.[20] $[\alpha]_D$ 34.3° (*c* 2, 5 *N* HCl)]. *Anal.* Calcd for $C_{13}H_{15}N_3O_3$: C, 59.75; H, 5.80; N, 16.08. Found: C, 59.94; H, 6.06; N, 16.15.

Registry No.—Glycine NCA, 2185-00-4; Gly-Gly, 556-50-3; Gly-L-Ala, 3695-73-6; Gly-L-Val, 1963-21-9; Gly-L-Leu, 869-19-2; Gly-L-Phe, 3321-03-7; Gly-L-Leu-L-Ala, 32557-24-7; Gly-L-tryptophan, 2390-74-1.

(16) Y. Iwakura K. Uno, and S. Kang, *J. Org. Chem.*, **30**, 1158 (1965). We synthesized glycine NCA by the reaction of glycine with phosgene in tetrahydrofuran. The reaction time needed in phosgenation of the amino acid was shorter in this solvent than in any other solvents. High yield and high purity of the product were obtained in this solvent.

(17) M. Oya, K. Uno, and Y. Iwakura, *Kogyo Kagaku Zasshi*, **69**, 741 (1966).

(18) H. Leuchs, *Ber.*, **39**, 857 (1906).

(19) Uv spectra of peptides were measured with Shimazu MPS-50 L and Hitachi Perkin-Elmer 139 spectrophotometers.

(20) K. R. Rao, S. M. Birnbaum, R. B. Kingsley, and J. P. Greenstein, *J. Biol. Chem.*, **198**, 507 (1952).

A Convenient Synthesis of 5-Fluorouracil

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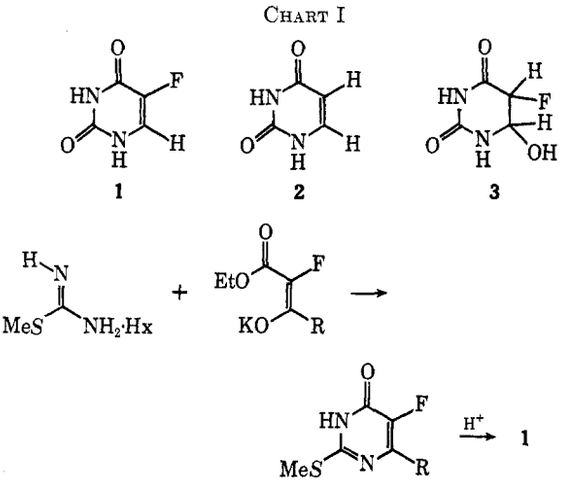
Communication No. 54[1] from the Research Institute for Medicine and Chemistry, Cambridge, Massachusetts 02142

Received August 13, 1971

5-Fluorouracil (**1**) is a cytotoxic analog of uracil of use in biochemical research and also of a certain value in medicine.[2] This derivative of uracil is typically prepared by a total synthesis as expressed in Chart I[3]

CHART I



which requires the use of a persistent and insidious toxin, fluoroacetic acid. The discovery that fluoroxytrifluoromethane (CF_3OF) is a useful reagent for the heretofore difficult direct electrophilic fluorination of aromatic compounds[4] led us to consider that the reaction of CF_3OF with uracil (**2**) (or an appropriate derivative thereof) might lead directly to 5-fluorouracil (or a derivative thereof) and thus constitute a convenient synthesis of such compounds. We now report that the direct conversion of uracil to 5-fluorouracil may be accomplished in high yield by electrophilic fluorination.

Electrophilic substitution at the 5 position of the pyrimidine ring is well known.[5] Uracil itself undergoes nitration at position 5 without complication,[6] and

(1) For no. 53, see D. H. R. Barton, T. J. Bentley, R. H. Hesse, F. Mutterer, and M. M. Pechet, *Chem. Commun.*, 912 (1971).

(2) G. Ramirez, *et al.*, *Amer. J. Surg.*, **120**, 400 (1970); J. Dule, *Bull. Soc. Fr. Dermatol. Syphiligr.*, **77**, 218 (1970); L. Y. Deemarsky, *et al.*, *Cancer*, **26**, 771 (1970); M. S. Mitchell, *et al.*, *ibid.*, **26**, 884 (1970); M. Hursthouse, *Brit. J. Dermatol.*, **82**, 218 (1970).

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(4) D. H. R. Barton, *et al.*, *Chem. Commun.*, 806 (1968).

(5) C. W. Kenner and A. Todd in "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1957, pp 235 ff.

(6) T. B. Johnson, *J. Amer. Chem. Soc.*, **30**, 19 (1908); *Chem. Abstr.*, **2**, 2792 (1909).