2-Butynylmalononitrile. To a mixture of 38 g of a sodium hydride suspension in mineral oil[45] (53.5%, 0.85 mole) and 400 ml of anhydrous THF was added 56 g (0.85 mole) of malononitrile in 200 ml of THF. The suspension was then heated to reflux and a solution of 189 g (0.85 mole) of 2-butyn-1-ol tosylate[46] in 400 ml of THF was added over a period of 1 hr. After heating to reflux for an additional 3 hr, 500 ml of benzene was added to the cooled mixture which was then filtered. The solids were washed with 1 l. of benzene and 200 ml of ethanol. The combined filtrates were washed with water and concentrated sodium chloride solution and dried. Removal of the solvents gave two layers; the lower layer was shown by gas chromatography to be a mixture of 16% of malononitrile, 21% of 2-butynylmalononitrile, and 63% of bis(2-butynyl)malononitrile; some mineral oil was also present. Repeated distillation using a spinning-band column gave pure 2-butynylmalononitrile, bp 82° (1.2 mm), $n^{24}D$ 1.4612, which solidified on standing at room temperature.

Anal. Calcd for $C_7H_6N_2$: C, 71.17; H, 5.12; N, 23.71; mol wt, 118.13. Found: C, 71.44; H, 5.26; N, 23.67; mol wt, 119, 117.

The nmr spectrum (in $CDCl_3$) shows a triplet at τ 5.96 (1 H, J = 6 cps), seven bands at 7.1 (2 H, presumably two doublets, J = 6 cps, split again with J = 2.5 cps), and a triplet centered at 8.1 (3 H, J = 2.5 cps).

(45) The mineral oil interferes seriously with the purification of the products and should be removed in any repetitions of this preparation.

(46) A. Marszak-Fleury, *Ann. Chim.* (Paris), [13] 3, 656 (1958).

Adamantyloxycarbonyl, a New Blocking Group. Preparation of 1-Adamantyl Chloroformate[1]

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Contribution from the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana. *Received December 22, 1965*

Abstract: 1-Adamantyl chloroformate was prepared from 1-adamantanol and phosgene. The chloroformate was allowed to react with amino acids to give the corresponding 1-adamantyloxycarbonyl (*t*-AdOC) derivatives. Several of them could be obtained in crystalline form while the corresponding *t*-butyloxycarbonyl derivatives have either not been reported or have been described as oils or amorphous solids. The adamantyloxycarbonylamino acids are cleaved by acid-catalyzed solvolysis with trifluoroacetic acid to yield the free amino acids. Adamantyl chloroformate forms mixed carbonic–carboxylic anhydrides with triethylamine salts of N-protected amino acids which give peptide derivatives on reaction with amino acid esters.

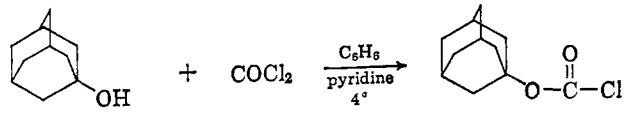
Considerable progress has been made in recent years in finding groups that can be used to block amino and hydroxy functions temporarily and can subsequently be removed under mild (solvolytic) conditions.[2]

The *t*-butyloxycarbonyl group proved to be particularly useful in peptide synthesis.[3a]

Because of the difficulty in the preparation and the lack of stability of *t*-butyl chloroformate,[3b] and because of the failure of this compound to react in even moderate yields with aniline or methyl glycinate,[3a] *t*-butyl azidoformate[4] or *t*-butyl *p*-nitrophenyl carbonate[3a] are widely used to introduce the *t*-butyloxycarbonyl group.[5]

The ease with which *t*-butylcarbamates are cleaved to yield free amino functions relates to the tendency of the *t*-butyl group to form a carbonium ion which in turn can lose a proton to yield isobutene. Adamantane forms a relatively stable carbonium ion at the bridgehead tertiary carbon[6] which can accept anions from the reaction mixture but cannot lose a proton to form an olefin.

It has been possible to prepare 1-adamantyl chloroformate (1-adamantyloxycarbonyl chloride) in crystalline form by allowing 1-hydroxyadamantane[6] to react with excess phosgene in a benzene solution in the presence of pyridine.



Crystalline 1-adamantyl chloroformate, mp 45–46°, was obtained from petroleum ether at −20°. Its structure is supported by analytical and infrared data. Further confirmation of the structure was obtained in two ways. First, reaction with hydrazine gave the crystalline carbazate, mp 142°, which was found to be identical with samples prepared from 1-adamantyl *p*-nitrophenyl carbonate[7] and from O-1-adamantyl S-methylthiolcarbonate.[8]

Secondly, reaction of the chloroformate and ammonia gave 1-adamantylcarbamate which was found to be identical with a sample prepared from 1-adamantyl phenyl carbonate.[9]

(1) Presented in part before the Division of Biological Chemistry, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965, Abstracts, p 44C.

(2) For reviews see (a) J. Rudinger, *Pure Appl. Chem.*, 7, 335 (1963); (b) R. A. Boissonnas, *Advan. Org. Chem.*, 3, 159 (1963).

(3) (a) G. W. Anderson and A. C. McGregor, *J. Am. Chem. Soc.*, 79, 6180 (1957), and numerous applications by other authors since then; (b) A. R. Choppin and J. W. Rogers, *ibid.*, 70, 2967 (1948).

(4) L. A. Carpino, C. A. Giza, and B. A. Carpino, *ibid.*, 81, 955 (1959).

(5) Recently *t*-butyl cyanoformate (L. A. Carpino, *J. Org. Chem.*, 29, 2820 (1964), and M. Leplawy and W. Stec, *Bull. Acad. Polon. Sci. Ser. Sci. Chim.*, 12, 21 (1964)) and *t*-butyl iminodicarboxylate (L. A. Carpino, *J. Org. Chem.*, 29, 2820 (1964)) have been suggested for the same purpose.

(6) R. C. Fort and P. von R. Schleyer, *Chem. Rev.*, 64, 277 (1964).

(7) Prepared from adamantyl alcohol and *p*-nitrophenyloxycarbonyl chloride by the general method of Anderson and McGregor.[3a]

(8) Prepared from adamantyl alcohol and S-methylchlorothiolformate by the general method of L. A. Carpino, *J. Org. Chem.*, 28, 1910 (1963).

(9) Prepared from adamantyl alcohol and phenyloxycarbonyl chloride by the general method of McLamore, *ibid.*, 20, 3791 (1955).

Table I

Nα-Adamantyloxycarbonyl derivatives of	Mp, °C	[α]²⁵D, deg[a]	Yield, %	Anal, % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
L-Alanine	140–142	−20.6	27	62.90	7.92	5.24	62.90	8.22	5.01
L-Asparagine	181–183	−1.5	36[b]	58.05	7.15	9.03	58.29	7.44	9.04
L-Glutamine	152–154	−3.9[g]	28	59.24	7.46	8.64	59.19	7.38	8.54
Glycine	141–143	...	44	61.64	7.56	5.33	61.81	7.77	5.52
L-Leucine	71–74	−16.2	81 oil	65.99	8.80	4.53			
			50 cryst	+1H₂O 62.35	8.87	4.28	62.70	8.60	4.36[c]
L-Leucine, dicyclohexylamine salt	133–135	...		70.98	10.27	5.71	70.96	10.46	5.49
L-Methionine	...	...	65 oil						
L-Methionine, dicyclohexylamine salt	133–135	+12.2	48	66.10	9.50	5.51	66.04	9.40	5.76
L-Phenylalanine	60–65 (amorph)	...	74	69.95	7.33	4.08	69.76	7.59	3.82
L-Phenylalanine, dicyclohexylamine salt	160–164	+27.3	50	73.26	9.22	5.34	73.04	9.27	5.28
D-Phenylglycine	92–98	−102	65	69.28	7.04	4.25	69.23	7.17	4.18
L-Proline	154–156	−43.4	65	65.51	7.90	4.78	65.61	8.20	4.67
L-Serine	66–71	...	50			4.94			5.05
D-Serine, dicyclohexylamine salt	180	−9.6	45	67.50	9.15	6.06	67.57	9.44	5.95
L-Threonine	89–93	−2.6		60.59	7.80	4.71	60.59	8.01	4.43
L-Tryptophan	150–153	−0.2	85	69.09	6.85	7.33	69.22	6.97	7.22[d]
				0.5CHCl₃ 66.20	6.75	6.87	66.77	6.74	6.95[e]
D-Tryptophan	150–154	+1.7	89	69.09	6.85	7.33	69.09	6.95	7.18
N^{imid}-Adamantyloxycarbonyl-L-histidine	138 dec	+12.5	86	65.73	7.29	8.21	65.88	7.59	7.86
N^{ϵ}-Benzyloxycarbonyl-L-lysine	56–60	−0.6	68	65.48	7.47	6.11	64.80	7.63	6.00[f]

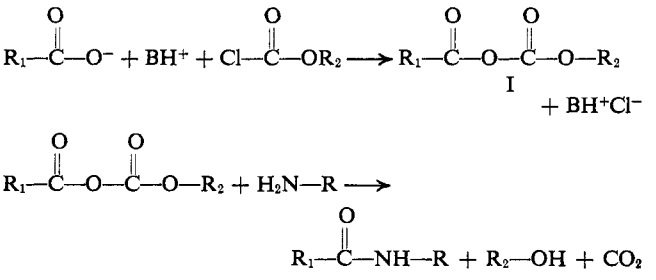
[a] *c* 2, methanol. [b] Reaction at pH 9.5. [c] Calcd: O, 24.48. Found: O, 24.23. [d] Recrystallized from ethyl acetate. [e] Recrystallized from $CHCl_3$. [f] Calcd: O, 20.94. Found: O, 21.12. [g] *c* 1, methanol.

A concentrated solution of the chloroformate in benzene obtained directly from the reaction mixture can be used as such in subsequent reactions or can be stored in a freezer compartment for several months without appreciable decomposition. The chloroformate was used to prepare crystalline 1-adamantyloxycarbonyl (*t*-AdOC) derivatives of a number of amino acids and amino acid derivatives. The reaction is readily carried out at ice-bath or room temperature in a short time at moderately high pH which should minimize racemization. The chloroformate made it possible to substitute less reactive amino functions as, for example, in the imidazole portion of histidine which will not react with *t*-butyl azidoformate. In a number of cases the *t*-AdOC derivatives are crystalline while the corresponding *t*-BOC derivatives have either been obtained as oils or amorphous solids or have not been described at all (asparagine, glutamine, N^{ϵ}-benzyloxycarbonyllysine, N^{α},N^{imid}-diamantyloxycarbonylhistidine, serine, and threonine; the latter two crystallized after longer periods of time). Table I contains data on *t*-AdOC amino acids that have been prepared. We have not tried to make the *t*-AdOC amino acids which are missing.

The *t*-AdOC group can be removed from amino nitrogen under solvolytic conditions as shown by short treatment of the derivatives of glycine, phenylglycine, and the disubstituted histidine with anhydrous trifluoroacetic acid. This acid is widely used to remove *t*-butyloxycarbonyl blocking groups[10] and has been shown not to cleave amide bonds. After 15 min or less in trifluoroacetic acid at room temperature, thin layer chromatography revealed that the *t*-AdOC derivatives had completely disappeared and glycine, phenylglycine, or histidine were the only compounds that could be detected with ninhydrin.

It might be worthy of note that the *t*-AdOC derivatives give strong ninhydrin-positive spots when the thin-layer plates are heated at 100° for a short time.

Further use of adamantyl chloroformate has been made in the mixed carboxylic–carbonic anhydride procedure[11] for the formation of amide bonds. The reaction is



There are two carbonyl groups present in the mixed carboxylic–carbonic anhydride (I) either one of which could possibly be nucleophilically attacked by an amine. The desired reaction, of course, is attack of the amino nitrogen on the carbonyl carbon adjacent to R_1. Therefore, the group R_2 should be such as to render the carbonyl adjacent to it less reactive, that is, the carbon less electron deficient. Therefore, R_2 should be an electron-releasing rather than -attracting group. 1-Adamantoic acid has been shown to be a very weak acid,

(10) A. L. Carpino, *J. Am. Chem. Soc.*, 79, 98 (1957); R. Schwyzer, W. Rittel, H. Kappeler, and B. Iselin, *Angew. Chem.*, 72, 915 (1960).

(11) T. Wieland and H. Bernhard, *Ann. Chem.*, 572, 190 (1951); R. A. Boissonnas, *Helv. Chim. Acta*, 34, 847 (1951); J. R. Vaughan, *J. Am. Chem. Soc.*, 73, 3547 (1951).

the pK being about 7.[12a] This probably means that the electronic influence of the adamantyl group is indeed such as to render adjacent atoms more negative. Furthermore, there should be a favorable steric effect in that the bulky adamantyl residue could prevent amino groups from coming close enough to the adjacent carbonyl carbon to react. Formylleucyl-O-*t*-butyl-L-threonine *t*-butyl ester was synthesized *via* a mixed anhydride of formylleucine and adamantyl chloroformate.

The same peptide was prepared using isobutyl chloroformate and also by the "Anderson method" with tetraethyl pyrophosphite.[12b] Although the yield obtained by using 1-adamantyl chloroformate was higher than in either of the other two cases, considerably more racemization was observed with this chloroformate. It should, however, be borne in mind that the reaction of activated derivatives of acylamino acids (like formyl, acetyl) with amino acid esters seems always to be accompanied by partial racemization whereas amino acids protected by groups giving a urethan-like arrangement (*i.e.*, benzyloxycarbonyl) retain their configuration. There chould be no racemization problem when these N-blocking groups are used in combination with 1-adamantyl chloroformate in a mixed anhydride synthesis.

Formylleucyl-O-*t*-butyl-L-threonine *t*-butyl ester had been chosen as a model because it crystallizes well but is quite soluble in organic solvents so that addition of petroleum ether is required in the crystallization step. If the separation of 1-hydroxyadamantane, a likely by-product of the mixed-anhydride reaction, should present any problem, it should be most evident in a case like that.

In another experiment benzyloxycarbonyl-L-asparagine was allowed to react with 1-adamantyl chloroformate under the conditions of a mixed anhydride synthesis. After addition of methyl L-phenylalaninate, a 24% yield of crystalline benzyloxycarbonyl-L-asparagine-L-phenylalanine methyl ester was obtained.[12c] Benzyloxycarbonylasparagine does not give mixed carboxylic–carbonic anhydride with the chloroformates usually employed (like ethyl, isobutyl, etc.).[12d] Only pivalyl chloride was found to form a carboxylic–carboxylic anhydride with this asparagine derivative which would react with amino acid esters to yield peptide derivatives.[12d]

Experimental Section

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Solvents were reagent grade and were used without further purification except for dioxane and tetrahydrofuran which were distilled from sodium, and pyridine which was distilled after drying over sodium hydroxide pellets. Benzene was dried over sodium–lead alloy and molecular sieve.

1-Adamantyl Chloroformate. To a solution of liquid phosgene (30 g) in anhydrous benzene (100 ml), a solution of 1-hydroxyadamantane[13] (8 g) and pyridine (7 g) in benzene (200 ml) was added dropwise and with stirring over a 1-hr period, while maintaining the reaction temperature at about 4°. When white solids precipitated, additional benzene (about 100 ml) was added.

The reaction mixture was allowed to stand at room temperature for 1 hr. The solution was filtered and the filtrate was poured into ice water and shaken in a separatory funnel. The organic layer was dried with sodium sulfate and concentrated to about one-fifth of its original volume under reduced pressure at room temperature, and the concentrated solution was stored in a freezer. The yield may be considered essentially quantitative for the purpose of synthetic use of the solution.

When a sample of the concentrate was evaporated to dryness at room temperature, the solid obtained melted at 41.5–42.5°. Recrystallization from anhydrous petroleum ether (bp 30–60°) at −20° yielded crystals melting at about 46–47°. The infrared spectrum (maxima at 4.2, 5.6 and 8.4 μ) of the product supports the proposed structure.

Anal. Calcd for $C_{11}H_{15}O_2Cl$: C, 61.54; H, 7.04; Cl, 16.52. Found: C, 61.48; H, 7.06; Cl, 16.70.

1-Adamantyl Carbazate. A. From 1-Adamantyl Chloroformate. A solution of 1-adamantyl chloroformate (2 g) in anhydrous benzene (150 ml) was added slowly to a stirred solution of anhydrous hydrazine (2.5 g) in *t*-butyl alcohol (20 ml). After stirring for about 2 hr, the solvents were removed *in vacuo*. The syrupy residue was dissolved in a mixture of ether (150 ml) and water (10 ml). The ether layer was washed with 35-ml portions of water, 5 ml of 1% sodium carbonate solution, and 5 ml of water, and dried. Anhydrous hexane (10 ml) was added and the solution was concentrated to about 10 ml. Cooling the solution at about −10° yielded shiny, white crystalline plates of 1-adamantyl carbazate (1.7 g) melting at about 141–142°. Titration in 66% DMF revealed a group with a pK_a' of 3.4 with an apparent molecular weight of 208 (theory 210). The infrared absorption spectrum (maxima at 2.5, 5.8, and 6.1 μ) was in agreement with the proposed structure of the product.

Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 63.05; H, 8.68; N, 13.39.

B. From 1-Adamantyl *p*-Nitrophenyl Carbonate. This carbonate[9] melted at 106–108° after recrystallization from ether–hexane.

Anal. Calcd for $C_{17}H_{19}O_5N$: C, 64.34; H, 6.04; N, 4.41. Found: C, 64.16; H, 5.81; N, 4.60.

The carbonate (0.5 g) was heated on a steam bath with a solution of anhydrous hydrazine (0.25 g) in *t*-butyl alcohol (5 ml). Solution occurred after about 10 min. Ether (10 ml) was added to the cooled solution and the mixture was extracted with water (10 ml) and four portions of 5% potassium carbonate solution (10 ml each). The ether was dried over anhydrous sodium sulfate and concentrated under reduced pressure to a small volume (5 ml). Anhydrous hexane (10 ml) was added and the solution was cooled at about −10°. The crystals obtained (200 mg) melted at 140–142°, and the mixture melting point with the carbazate prepared by route A was not depressed.

C. From O-1-Adamantyl S-methylthiolcarbonate. This thiolcarbonate[8] melted at 99–100° after recrystallization from methanol.

Anal. Calcd for $C_{12}H_{18}O_2S$: C, 63.68; H, 8.01; S, 14.17. Found: C, 63.62; H, 8.29; S, 14.11.

Thiolcarbonate (0.5 g) was heated on a steam bath with a solution of anhydrous hydrazine (0.25 g) in anhydrous dioxane (0.5 ml). Heating was continued until gas evolution had stopped (about 1 hr). The crystalline mass obtained after cooling the mixture to room temperature was extracted with three portions (100 ml total) of ether. The ether solution was washed, dried, and concentrated as described under B. The crystalline carbazate obtained (220 mg) melted at 141–142°, and the mixture melting point with the material prepared by route A was undepressed.

1-Adamantylcarbamate. A. From 1-Adamantyl Chloroformate. A solution of adamantyl chloroformate (0.1 g) in anhydrous benzene (25 ml) was saturated with gaseous ammonia (about 1 hr). The flask was stoppered and maintained at ambient temperature for 24 hr. The reaction mixture was filtered, and the filtrate was shaken with ice water (200 ml). Ether (200 ml) was added; the organic layer was dried and evaporated *in vacuo* to yield 500 mg of 1-adamantylcarbamate, which melted at about 170–171° after recrystallization from anhydrous ethanol. The absorption spectrum showed maxima at 2.8, 2.9, 5.8, and 6.15 μ, compatible with the proposed structure of the compound.

Anal. Calcd for $C_{11}H_{17}NO_2$: N, 7.17. Found: 7.07.

B. From 1-Adamantyl Phenyl Carbonate. This carbonate[9] melted at 88° after recrystallization from ether at −10°.

Anal. Calcd for $C_{17}H_{20}O_3$: C, 75.00; 7.36. Found: C, 75.30; H, 7.46.

(12) (a) H. Stetter and J. Mager, *Chem. Ber.*, **95**, 667 (1962); (b) G. W. Anderson, J. Blodinger, and A. D. Welcher, *J. Am. Chem. Soc.*, **74**, 5309 (1952); (c) the authors are indebted to Mr. C. S. Hollinden for running this experiment; (d) M. Zaoral, private communication by Dr. J. Tudinger, Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague.

(13) H. Stetter, M. Schwarz, and A. Hirschhorn, *Chem. Ber.*, **92**, 1629 (1959).

1-Adamantyl phenyl carbonate (1 g), methanol (1 ml), and ammonia (2 ml) were heated for 1 hr in a sealed tube at 100°. The cooled contents were added to ice water (10 ml), and the carbamate was extracted into ether (100 ml). The ether solution was washed with two portions (5 ml) of 1 *N* NaOH solution and dried over anhydrous sodium sulfate. Removal of the ether by evaporation, addition of 3 ml of petroleum ether (bp 30–36°), and cooling of the resulting solution gave crystals, mp 168–170°. The infrared absorption spectrum and the X-ray diffraction pattern of this material were found to be identical with those of the material prepared by method A.

1-Adamantyloxycarbonyl Amino Acids. General Procedure. The amino acid (5 mmoles) was suspended in water (about 20 ml). The mixture was stirred and cooled in an ice bath. Sodium hydroxide (1 *N*, 5 ml) was added whereupon the amino acid usually dissolved. To this sodium carbonate (0.8 g, 7.5 mmoles) was added. From a solution of adamantyl chloroformate, the solvent was removed *in vacuo* on a flash evaporator at a bath temperature of about 30°. (The concentration of chloroformate in the benzene solution was determined by removing the solvent from an aliquot *in vacuo* at about 30° and weighing the residue.) To the residue which may be oily or semisolid, dry petroleum ether was added and removed *in vacuo*. This was repeated once more in order to remove traces of phosgene which may be left from the preparation of the chloroformate. The residue was dissolved in anhydrous dioxane (5 ml) and added in about four portions to the solution of the amino acid over a period of about 1 hr with continued stirring and cooling. Since some solid usually precipitated, ether (5 ml each) was added after the first and last addition of chloroformate. The container of the chloroformate solution was washed twice with a little dioxane. After stirring in ice for about 2 more hr, the solution was extracted three times with ether, and the aqueous phase was cooled in ice, layered with ether or ethyl acetate (in case of tryptophan the derivative of which is not very soluble in ether), and under stirring and cooling acidified with 85% phosphoric acid or 10% sulfuric acid to a pH of about 2. About 2.5 ml of phosphoric acid was required. The precipitated adamantyloxycarbonyl amino acid was extracted into the organic layer and the aqueous phase was extracted with two more portions of fresh organic solvent. The combined extracts were dried over sodium sulfate and the solvent was removed *in vocuo*. The residue was recrystallized from a suitable solvent (ether–petroleum ether, ethyl acetate, ethyl acetate–petroleum ether).

N^{α},N^{imid}-Diadamantyloxycarbonyl-L-histidine. L-Histidine hydrochloride monohydrate (1 g, 4.78 mmoles) was dissolved in cold 1 *N* sodium hydroxide solution (9.6 ml), and sodium carbonate (1.06 g, 10 mmoles) was added. From a solution of adamantyl chloroformate (2.14 g, 10 mmoles) in benzene, the solvent was removed *in vacuo* at a bath temperature of 30°. Cyclohexane was added and evaporated *in vacuo*. This was repeated once more. The residue was dissolved in dry dioxane (3 ml) and added in five portions over a period of 45 min to the histidine solution which was stirred in an ice bath. Ether (3 ml) was added after the first addition of chloroformate. The reaction mixture was stirred at room temperature for another 75 min when it was extracted three times with ether. Some sticky precipitate formed which partially dissolved on addition of some water. The mixture was cooled in ice and layered with ether, and 85% phosphoric acid (2 ml) was added with stirring. The aqueous phase was extracted two more times with ether. The combined extracts were dried over sodium sulfate and the solvent was removed *in vacuo*. A gummy material (2.25 g) remained. It was dissolved in ether. Cyclohexane and petroleum ether were added. In a refrigerator, 0.52 g of soft crystals, mp 95° dec, separated. (At 95° gas is evolved and a popcorn-like material is formed. It may be an impure solvate of the desired material.) From the mother liquor the solvents were removed *in vacuo* and the residue was dissolved in a little ether. After addition of cyclohexane, crystallization started in a refrigerator and was completed by addition of petroleum ether. The crystals were removed by filtration and washed with petroleum ether, yield 1.58 g, mp 140–145°. A sample for analysis was obtained by extraction of a small amount with a volume of hot cyclohexane insufficient to dissolve all. The melting point was then 134–144° dec. For reactions the crude material was used without further purification.

N^{α}-Adamantyloxycarbonyl-N-benzyloxycarbonyl-L-lysine. N^{ϵ}-Benzyloxycarbonyl-L-lysine[14] (560 mg, 2 mmoles) was suspended in water (10 ml), the mixture was stirred in an ice bath, and 1 *N* sodium hydroxide solution (2 ml) was added. Sodium carbonate (530 mg, 5 mmoles) was then added to the almost clear solution. From a solution of adamantyl chloroformate in benzene (5%, 12 ml) the solvent was removed *in vacuo* at a bath temperature of 30°. The residue was dissolved in cyclohexane and the solvent was removed *in vacuo*. The residue was dissolved in dry dioxane (2 ml). This solution was added in five portions over a period of 1 hr to the solution of the lysine derivative with continued cooling and stirring. The container was washed with little dioxane. After the second and last addition of chloroformate ether was added (2 ml each time). After stirring in the cold for another 3 hr, the mixture was extracted three times with ether. Most of a precipitate in the ether layer dissolved on addition of more water. The aqueous phase was cooled in ice and acidified with 85% phosphoric acid to pH 2. The oily precipitate was extracted into three portions of ether. The combined extracts were dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was dissolved in little ether and cyclohexane was added. In a refrigerator, gelatinous material separated which was removed by filtration, washed with cyclohexane, and dried; 620 mg of a powder was obtained with a melting point of 50–55°. A sample for analysis was recrystallized once more from ether–cyclohexane. The melting point was then 56–60°.

Adamantyloxycarbonyl-L-methionine. Dicyclohexylamine Salt. L-Methionine (149 mg, 1 mmole) was suspended in water (3 ml), the mixture was stirred in ice, and sodium carbonate (265 mg, 2.5 mmoles) was added. From a solution of adamantyl chloroformate (280 mg, 1.3 mmoles) in benzene the solvent was removed *in vacuo* at 30° bath temperature. The residue was dissolved in tetrahydrofuran (1 ml) and added to the methionine solution. The flask was rinsed twice with tetrahydrofuran (0.5 ml each time). The mixture was stirred in ice for 4.5 hr. After 30 min, ether (1 ml) was added since a solid had formed on the surface. Water (5 ml) was added to the milky mixture and extracted three times with ether, the aqueous phase was cooled in ice and acidified with 85% phosphoric acid (0.5 ml), and the precipitate was extracted into three portions of ether. The extracts were dried over sodium sulfate and the solvent was removed *in vacuo;* 185 mg of an oil remained. The same yield was obtained when the reaction was run on a pH-Stat at an apparent pH (in the presence of THF) of 12. The combined oils of the two runs were dissolved in little ether and dicyclohexylamine (0.3 ml) was added. The crystals that formed in a refrigerator were removed by filtration and washed with ether, yield 485 mg, mp 133–135°.

Adamantyloxycarbonyl-D-tryptophan. D-Tryptophan (5.1 g, 25 mmoles) was suspended in water (80 ml), the mixture was stirred in an ice bath, and 1 *N* sodium hydroxide (25 ml) was added followed by sodium carbonate (4 g) which resulted in a clear solution. From a solution of adamantyl chloroformate in benzene (5%, 150 ml) the solvent was removed *in vacuo* at a bath temperature of 30°. Cyclohexane was added to the residue twice and removed *in vacuo* each time. The residue was dissolved in dry dioxane (20 ml) and added to the tryptophan solution in five portions over 90 min with continued stirring in ice. After the second addition ether (20 ml) was added. The mixture was stirred in ice for another 3 hr when it was extracted three times with ether. The aqueous phase was layered with ethyl acetate and cooled in ice, and 85% phosphoric acid (12.5 ml) was added with stirring. The ethyl acetate layer was removed and the aqueous phase was extracted two more times with ethyl acetate (250 ml total). The combined extracts were dried over sodium sulfate and the solvent removed *in vacuo*. The solid residue was dissolved in ethyl acetate (25 ml) and cooled in a refrigerator to yield 6.23 g of crystals, mp 149–151° dec. The mother liquor was concentrated *in vacuo* to dryness and the residue was dissolved in ethyl acetate (15 ml). A second crop weighing 2.05 g and melting at 147–151° was obtained.

When a sample of the L isomer was recrystallized from chloroform, a material, mp 152–154°, was obtained, the elemental analysis of which indicated it contained 0.5 mole of chloroform in the crystal.

Formylleucyl-O-*t*-butyl-L-threonine *t*-Butyl Ester. A. Mixed Anhydride with 1-Adamantyl Chloroformate. Formyl-L-leucine (318 mg, 2 mmoles) was dissolved in THF (4 ml), the solution was cooled in ice, and triethylamine (0.28 ml, 2 mmoles) was added. From a solution of 1-adamantyl chloroformate in benzene containing 2.1 mmoles of the chloroformate, the solvent was removed *in vacuo* at a bath temperature below 40°, the residue was dissolved in THF (1 ml), and this solution was added to the formylleucine while stirring in ice. The container was washed twice with 1-ml portions of THF. After stirring in ice for 30 min, a solution of

(14) Aldrich Chemical Co., Inc., Milwaukee, Wis.

O-*t*-butyl-L-threonine *t*-butyl ester, acetic acid salt, mp 54–57° (*Anal.* Calcd for $C_{14}H_{29}NO_5$: C, 57.7; H, 9.95; N, 4.81. Found: C, 56.90; H, 9.81; N, 4.86) (582 mg, 2 mmoles), was added. The container was rinsed twice with 0.5-ml portions of THF. The mixture was stirred in ice for 10 min and at room temperature for 4 hr and was kept in a refrigerator overnight.

The solvent was removed *in vacuo*, and ethyl acetate (about 40 ml) and a little water were added. The ethyl acetate layer was washed with 1 *N* citric acid (50 ml in three portions), 10% potassium bicarbonate solution (50 ml in three portions), and a little saturated sodium chloride solution. The aqueous phases were extracted twice with ethyl acetate. The combined ethyl acetate extracts were dried over sodium sulfate and the solvent removed *in vacuo;* 950 mg of a solid remained. It was recrystallized from little ether by addition of petroleum ether, yield 450 mg, mp 138–40°. To this material ether (10 ml) was added; 135 mg of crystals remained undissolved, mp 139–53°, $[\alpha]^{25}D$ −15.6° (*c* 2, methanol).

Anal. Calcd for $C_{19}H_{36}N_2O_5$: C, 61.26; H, 9.74; N, 7.52. Found: C, 61.26; H, 9.92; N, 7.42.

Most of the ether was allowed to evaporate and petroleum ether was added; 130 mg, mp 142–145°, $[\alpha]^{25}D$ +4.8° (*c* 2, methanol).

Anal. Calcd for $C_{19}H_{36}N_2O_5$: C, 61.26; H, 9.74; N, 7.52. Found: C, 61.22; H, 10.21; N, 7.33.

From the mother liquor, 65 more mg was obtained, mp 151–158°, $[\alpha]^{25}D$ −6.3° (*c* 2, methanol).

Anal. Calcd for $C_{19}H_{36}N_2O_5$: C, 61.26; H, 9.74; N, 7.52. Found: C, 61.38; H, 9.82; N, 7.54.

B. Mixed Anhydride with Isobutyl Chloroformate. The mixed anhydride was prepared exactly the same way as described under A, using 0.275 ml of isobutyl chloroformate (2.1 mmoles). The reaction mixture was stirred overnight at room temperature. After the same work-up as under A, 640 mg of an oil was obtained. It was dissolved in cyclohexane and petroleum ether was added. In a refrigerator 285 mg of crystals melting at 146–152° separated, $[\alpha]^{25}D$ −35.8° (*c* 2, methanol).

Anal. Calcd for $C_{19}H_{36}N_2O_5$: C, 61.26; H, 9.74; N, 7.52. Found: C, 61.56; H, 10.06; N, 7.55.

A small second fraction of beautiful crystals, mp 148–151°, was obtained, whereas a third fraction of 120 mg did not give a correct analysis.

C. Anderson's method with Tetraethyl Pyrophosphite. Formyl-L-leucine (318 mg, 2 mmoles) was dissolved in diethyl phosphite with warming. O-*t*-Butyl-L-threonine *t*-butyl ester, acetic acid salt (582 mg, 2 mmoles), was dissolved in this solution and triethylamine (0.28 ml, 2 mmoles) was added followed by tetraethyl pyrophosphite (0.54 ml, 2.2 mmoles). The mixture was heated on a steam bath for 30 min and stored in a refrigerator overnight. The solution was concentrated *in vacuo* at a bath temperature of up to 65°. The work-up was the same as described under A. The residue was dissolved in a little ether and a large volume of petroleum ether and seed crystals were added. Crystallization started immediately and was completed in a refrigerator, yield 190 mg, mp 154–156°, $[\alpha]^{25}D$ −45.5°. The relatively low yield may be due to the use of the acetic acid salt of the threonine derivative which may give rise to the formation of acetyl-O-*t*-butyl-L-threonine *t*-butyl ester.

Benzyloxycarbonyl-L-asparaginyl-L-phenylalanine Methyl Ester *via* Mixed Anhydride with 1-Adamantyl Chloroformate. Benzyloxycarbonyl-L-asparagine (5.32 g, 0.02 mole) was suspended in dry tetrahydrofuran (40 ml), triethylamine (2.78 ml, 0.02 moles) was added, and the mixture was stirred in an ice bath. From a solution of 1-adamantyl chloroformate (4.5 g, 0.021 moles) in benzene, the solvent was removed *in vacuo*, and the residue was dissolved in dioxane (20 ml) and added to the solution of the asparagine derivative. The mixture was stirred in ice for 20 min when a mixture of methyl phenylalaninate hydrochloride (4.31 g, 0.02 mole) in dioxane and triethylamine (2.78 ml, 0.02 mole) was added. Stirring was continued for 0.5 hr in ice and 1.5 hr at room temperature when the solvents were removed *in vacuo*. The residue was dissolved in water and ethyl acetate. The ethyl acetate layer was washed with 1 *N* citric acid, 10% potassium bicarbonate, and saturated sodium chloride solution. A flocky precipitate appeared in the ethyl acetate at the end of these operations. It was removed by filtration, washed with ethyl acetate, and dried, yield 1.18 g, mp 192–193°. The ethyl acetate was evaporated *in vacuo* and the residue was recrystallized from methanol. A second fraction, mp 191–194°, was obtained, total yield 24%. A sample was recrystallized once more from methanol. The melting point was then 195–197°, $[\alpha]^{25}D$ +16.5° (*c* 2, glacial acetic acid).

Anal. Calcd for $C_{22}H_{25}N_3O_6$: C, 61.81; H, 5.90; N, 9.83. Found: C, 61.75; H, 6.14; N, 9.66.

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The Diazapentalene System. IV. The Parent Pyrazolo[1,2-*a*]pyrazole and Derivatives[1]

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Abstract: Proton magnetic resonance evidence is presented for the preparation of pyrazolo[1,2-*a*]pyrazole and its 2-bromo, 1-phenyl, and 2-*p*-chlorophenyl derivatives. These molecules are all very easily oxidized and this property is correlated with the Hückel molecular orbital prediction of an orbital lying at or near the nonbonding level. Hydropicrates of all of these molecules have been prepared and were found to be stable.

In earlier publications[2,3] we postulated that the pentalene system[6] with nitrogen atoms at the bridgehead positions, *i.e.*, structure IIIa,[8] would be aromatic. This prediction was based on Hückel molecular orbital (HMO) calculations,[9] as well as on steric and electronic similarities between I and the pentalene dianion.[7] The

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