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The Synthesis of Cyclic α-Amino Acids. II

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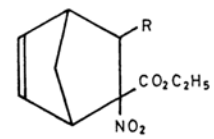
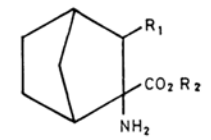
The reaction of substituted derivatives of α-nitrocinnamates bearing a nitro group or a chlorine atom at the *p*- or *m*-position with cyclopentadiene produced corresponding cyclic α-nitro esters (adducts) in a good yields. The reaction of ethyl α-nitrocrotonate with cyclohexadiene gave ethyl 3-methyl-2-nitrobicyclo[2.2.2]-5-octene-2-carboxylate. In the case of an adduct, ethyl 2-nitro-3-(*p*-nitrophenyl)bicyclo[2.2.1]-5-heptene-2-carboxylate, there could be isolated four diastereoisomers as crystalline forms by column chromatography and fractional recrystallization. The stereochemistry of the four isomeric adducts were established by NMR spectroscopy. The readily available three of those isomers were converted to corresponding pure isomers of amino acids by reduction followed by hydrolysis. From the other adducts the major amino acid isomers or the amino acid mixtures were obtained in an analogous route.

A recent publication[1] from this laboratory described the synthesis of cyclic α-amino acids from α,β-unsaturated α-nitro esters, which were used as dienophiles in the Diels-Alder reaction. The present paper is concerned with an extension of this work and presents the syntheses of 2-amino-3-(*p*- or *m*-substituted phenyl)bicyclo[2.2.1]heptane-2-carboxylic acids (IV, XI, XII) and 2-amino-3-methylbicyclo-[2.2.2]octane-2-carboxylic acid (XV) (Fig. 1).

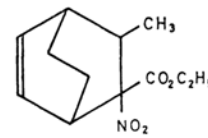
The Diels-Alder reaction of ethyl α,*p*-dinitrocinnamate[2] (I) which was confirmed to be a single isomer by NMR, with excess cyclopentadiene in benzene at 120°C for 1.5 hr gave ethyl 2-nitro-3-(*p*-nitrophenyl) bicyclo [2.2.1] - 5-heptene-2-carboxylate (II) in quantitative yield. The semicrystalline adduct II was shown to be a mixture of two fractions, II_1 (R_f, 0.5) and II_2 (R_f, 0.4), by thin layer chromatography. These fractions were effectively separated from each other by silica gel column chromatography. The ratios of II_1 to II_2 observed in several batches of II fell in a range of 1 : 9—1 : 10 by weight. The NMR spectra of II_1 and II_2 showed that both of them were mixtures of diastereoisomers. The fractional recrystallization of II_1 and II_2 resulted in the separation of the diastereoisomers. The components IIA and IID separated from II_1, and the other components IIB and IIC from II_2 were characterized as the pure diastereoisomers of the adduct II (Table 1). The ratios of IIA to IID and of IIB to IIC were estimated to be about 3.5 : 1 and 4 : 1 on the basis of NMR analysis, respectively.



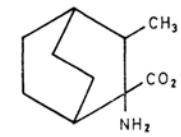
II: R=$C_6H_4NO_2$ (*p*)
VII: R=$C_6H_4NO_2$ (*m*)
VIII: R=C_6H_4Cl (*p*)



III: R_1=$C_6H_4NH_2$ (*p*), R_2=C_2H_5
IX: R_1=$C_6H_4NH_2$ (*m*), R_2=C_2H_5
X: R_1=C_6H_4Cl (*p*), R_2=C_2H_5
IV: R_1=$C_6H_4NH_2$ (*p*), R_2=H
XI: R_1=$C_6H_4NH_2$ (*m*) R_2=H
XII: R_1=C_6H_4Cl (*p*), R_2=H



XIII



XIV: R=C_2H_5
XV: R=H

Fig. 1.

The stereochemistry of the four diastereoisomers was established by NMR as shown in Fig. 2. Spectral features were assigned on the basis of chemical shifts, integrated area, magnitudess of plittings, and decoupled splitting patterns.[3] The assigned chemical shifts and coupling constants are listed in Tables 2 and 3, respectively.

1) S. Umezawa, M. Kinoshita and H. Yanagisawa, This Bulletin, **40**, 209 (1967).
2) A. Dornow and H. Menzel, *Ann.*, **588**, 40 (1954).
3) J. C. Davis, Jr., and T. V. Van Auken, *J. Am. Chem. Soc.*, **87**, 3900 (1965).

Table 1. Adducts

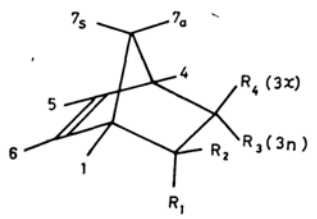
Compound	Reaction condition °C	hr	Mol ratio*	Mp °C or Bp °C (mmHg)	n_D^{21}	Formula	Calcd, % C	H	N	Found, % C	H	N
IIA	120	1.5	8.1	119—120		$C_{16}H_{16}O_6N_2$	57.83	4.82	8.43	57.58	5.09	8.24
IIB				107—108						57.93	5.12	8.34
IIC				79—80						57.87	5.05	8.13
IID				81—81.5						57.81	4.72	8.30
VIIA	120	2.0	8.1	101—102						58.05	4.64	8.26
VIII	110	6.0	8.1	130—140 (0.5)		$C_{16}H_{16}O_4NCl$	59.73	5.01	4.37	59.19	4.64	4.42
XIII	130	12.0	5.9	89—97 (1.0)	1.4830	$C_{12}H_{17}O_4N$	60.24	7.16	5.85	60.47	7.11	5.77

* Diene/dienophile

Table 2. Chemical shift (τ) of adduct II and VII

Compound \ H	5 (q)*	6 (q)	3x (d)*	3n (d)	1 (s)*	4 (s)	7a	7s	CH_2 (q)	CH_3 (t)*
IIA	3.27	3.83	—	5.83	6.20	6.72	7.23(d)	8.00(d)	6.28	9.14
IIB	3.48	3.27	5.27	—	6.28	6.80	8.28(s)		5.66	8.70
IIC	3.29	3.84	—	5.83	6.35	6.77	7.20(d)	7.92(d)	5.69	8.70
IID	3.47	3.27	5.13	—	6.12	6.76	8.27(s)		6.23	9.24
VIIA	3.25	3.83	—	5.84	6.22	6.75	7.15(d)	7.92(d)	6.28	9.17
VIIB	3.45	3.27	5.28	—	6.28	6.78	8.27(s)		5.65	8.70

* s=singlet; d=doublet; t=triplet; q=quartet.



IIA: $R_1=NO_2$, $R_2=CO_2C_2H_5$, $R_3=3n$, $R_4=C_6H_4NO_2(p)$
IIB: $R_1=NO_2$, $R_2=CO_2C_2H_5$, $R_3=C_6H_4NO_2(p)$, $R_4=3x$
IIC: $R_1=CO_2C_2H_5$, $R_2=NO_2$, $R_3=3n$, $R_4=C_6H_4NO_2(p)$
IID: $R_1=CO_2C_2H_5$, $R_2=NO_2$, $R_3=C_6H_4NO_2(p)$, $R_4=3x$
VIIA: $R_1=NO_2$, $R_2=CO_2C_2H_5$, $R_3=3n$, $R_4=C_6H_4NO_2(m)$
VIIB: $R_1=NO_2$, $R_2=CO_2C_2H_5$, $R_3=C_6H_4NO_2(m)$, $R_4=3x$

A letter *n* is added to the number of a hydrogen to denote an *endo* hydrogen and *x* is used to denote an *exo* hydrogen. For the 7-hydrogens the letter *s* specifies the hydrogen *syn* to the double bond and theletter *a* designates the *anti* hydrogen.

Fig. 2.

The bridgehead protons (1,4) are assigned by their broad patterns resulting from several coupling interactions. The bridgehead peak (6.80—6.76τ) at higher field in the isomer IIB and IID can be ascribed to the 4-proton by its coupling constant ($J_{3x,4}=3.3$ cps). It is ascertained that there is no coupling between the bridgehead protons (6.28—6.12τ) in lower field and the 3*x*-protons (doublet centered at 5.27—5.13τ). The olefinic protons (5, 6) in IIB and IID can be assigned by an existence of a remarkable coupling with the bridgehead protons (4, 1). Decoupling shows that the upfield-half of the eight-line pattern of the olefinic protons is coupled ($J_{4,5}=3.0$ cps) with the peak assigned as 4-proton.

In IIA and IIC, both of bridgehead protons show no detectable coupling with 3*n*-proton (doublet centered at 5.83τ). The zero coupling constant ($J_{3n,4}$) can be explained by the deformation of the vicinal dihedral angle[4,5] between 3*n*- and 4-proton. On the other hand, the bridgehead peak at lower field can be assinged to 1-proton as well as in the cases of IIB and IID on the basis of the electronegativity effect[5] of the nearby substituents R_1 and R_2. Decoupling shows that the upfield-half

4) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).
5) P. Laszlo and P. von R. Schleyer, *J. Am. Chem. Soc.*, **85**, 2709 (1963); W. E. Noland, B. A. Langarger, J. W. Manthey, A. G. Zacchei, D. L. Petrak and K. L. Fian, *Can. J. Chem.*, **45**, 2969 (1967).

TABLE 3. COUPLING CONSTANTS (cps) OF ADDUCT II

Compound	$J_{5,6}$	$J_{4,5}$	$J_{1,6}$	$J_{3n,4}$	$J_{3x,4}$	$J_{7s,3n}$	$J_{7s,7a}$
IIA	5.8	3.0	3.0	0	—	3.0	10.0
IIB	6.0	3.0	3.0	—	3.3	—	?
IIC	5.5	3.1	3.1	0	—	3.0	10.0
IID	6.0	3.0	3.4	—	3.3	—	?

of the eight-line pattern of the olefinic protons in IIA and IIC is coupled ($J_{1,6}=3.0$—3.1 cps) with the peak assigned as 1-proton.

It is interesting that the methylene bridge (7-protons) appear as the characteristic four-line pattern for the spin-spin coupling of two nonequivalent protons in the isomer IIA and IIC, and the geminal coupling constants are equal in both isomers ($J_{7s,7a}=10.0$ cps). However in both IIB and IID, the methylene bridge protons appear as a single peak (8.27—8.28τ) with barely detectable fine structure. In the adduct IIA and IIC, the upfield-doublet (7.92—8.00τ) of this pattern is further split into discernible features, while the downfield-doublet (7.20—7.23τ) is relatively unsplit. Decoupling shows that the upfield-pattern is coupled with the peak assigned as 3*n*-proton, and is attributed to 7*s*-proton. The long-range coupling constant ($J_{7s,3n}=3.0$ cps) falls in the range reported.[3,6,7] The downfield-doublet is then assigned to 7*a*-proton. A downfield shift for hydrogens *syn* to an *exo* substituent has been noted previously by Davis and Van Auken[3] in some *exo*-norbornene derivatives. The downfield shift for 7*a*-proton in IIA and IIC may be attributed to anisotropic effect of the *exo*-substituted *p*-nitrophenyl ring.

The above-mentioned NMR studies for the bridgehead protons, methylene bridge protons and 3-protons of the four isomeric adducts establish the following configurations of 3-*p*-nitrophenyl groups in the addcuts; *exo* in IIA and IIC, while *endo* in IIB and IID. The configurations of 2-carbethoxy groups in the addcuts are deduced on the basis of the chemical shifts of their methyl and methylene protons. Recently, Kleinfelter[8] reported that some phenylnorbornyl *p*-nitrobenzoates in which the *p*-nitrobenzoyl group is in a *cis* relationship with the phenyl group shows a great shielding of one proton pair of *p*-nitrobenzoyl group which is held close to the center of benzene ring. Kleinfelter also reported[9] that a 3-*exo*-phenyl group in 3-phenyl-2-nitrobornanols and their derivatives diamagnetically shields an eclipsed 2-*exo*-proton. A similar effect was observed in *trans*-1,2-diphenylcyclopentane in which the 1- and 2-hydrogens are shielded 0.40 ppm relative to the *cis* isomer.[10] As shown in Table 2, the carbethoxy proton absorptions of the adduct IIA and IID apparently occurred upfield from those of the adduct IIB and IIC. The "*cis*" relationship between the *p*-nitrophenyl and carbethoxy group may exist here in the addcut IIA and IID.

The catalytic hydrogenation of isomers IIA, IIB, IIC and the mixture adduct II with Raney Ni T-4[11] gave three isomers of ethyl 2-amino-3-(*p*-aminophenyl)bicyclo[2.2.1]heptane-2-carboxylate, *i. e.* IIIA, IIIB, IIIC and III, respectively. On hydrolysis with 6 N hydrochloric acid, IIIA, IIIB and IIIC afforded diastereoisomeric 2-amino-3-(*p*-aminophenyl)bicyclo[2.2.1]heptane-2-carboxylic acid, *i. e.* IVA, IVB and IVC, respectively (Table 5). It was interesting that the amino ester IIIA strongly resisted against hydrolysis and, especially, it suffered no hydrolysis in methanolic barium hydroxide solution at 37°C for eighty hours, while the other amino esters IIIB and IIIC were smoothly hydrolyzed. This fact supported the structure of the adduct IIA in which the 2-carbethoxy group undergoes more steric interference owing to the *cis*-3-*p*-nitrophenyl group. The dihydrochloride of major amino acid IVB was sparingly soluble in a cold 6 N hydrochloric acid as compared with its isomeric amino acid dihydrochlorides. On this basis, a convenient preparation of major amino acid IVB was accomplished with 40% overall yield by starting from the mixture adduct II.

In addition, two other amino acids 2-amino-3-(*m*-aminophenyl)bicyclo[2.2.1]heptane-2-carboxylic acid (XIB) and 2-amino-3-(*p*-chlorophenyl)bicyclo-[2.2.1]heptane-2-carboxylic acid (XII) of the above-mentioned type have been synthesized by a similar route. The reaction of cyclopentadiene with ethyl *α*,*m*-dinitrocinnamate (V) and ethyl *α*-nitro-*p*-chlorocinnamate[2] (VI) gave ethyl 2-nitro-3-(*m*-nitrophenyl)bicyclo[2.2.1]-5-heptene-2-carboxylate (VII) and ethyl 2-nitro-3-(*p*-chlorophenyl)bicyclo-[2.2.1]-5-heptene-2-carboxylate (VIII) in a good yield, respectively (Table 1).

6) D. Laszlo and P. von R. Schleyer, *J. Am. Chem. Soc.*, **86**, 1171 (1964).
7) J. Meinwald and Y. Meinwald, *ibid.*, **85**, 2514 (1963).
8) D. C. Kleinfelter, *J. Org. Chem.*, **32**, 3526 (1967).
9) D. C. Kleinfelter, *ibid.*, **32**, 1734 (1967).
10) D. Y. Curtin, H. Gruen and B. A. Shoulders, *Chem. Ind. (London)*, **1958**, 1250; D. Y. Curtin, H. Gruen, Y. G. Hendrickson and H. E. Knipmeyer, *J. Am. Chem. Soc.*, **83**, 4838 (1961).
11) S. Nishimura, This Bulletin, **32**, 61 (1959).

TABLE 4. CYCLIC α-AMINO ESTERS AND THEIR HYDROCHLORIDES

Compound	Mp °C or Bp °C/mmHg	Solvent for Recrystallization (or n_D^{21})	Formula	Calcd, %				Found, %			
				C	H	N	Cl	C	H	N	Cl
IIIA·2HCl	228 (decomp.)	a	$C_{16}H_{24}O_2N_2Cl_2$	55.34	6.97	8.07	20.42	55.51	7.06	7.93	20.25
IIIB·2HCl	250—252 (decomp.)	b						55.66	6.98	8.12	20.20
IXB·2HCl	224—226 (decomp.)	b						54.87	6.90	7.70	20.06
IIIC	94—95.5	c	$C_{16}H_{22}O_2N_2$	70.04	8.08	10.21		70.36	8.32	9.88	
IXB	83—84	c						69.93	8.08	10.37	
X′	95.5—96	d	$C_{16}H_{20}O_2NCl$	65.41	6.86	4.77		65.53	6.75	4.74	
X′·HCl	207—208 (decomp.)	b	$C_{16}H_{21}O_2NCl_2$	58.19	6.41	4.24	21.47	58.44	6.58	4.20	21.41
XIV	74—81/1	(1.4915)	$C_{12}H_{21}O_2N$	68.21	10.02	6.63		68.70	9.72	6.54	
XIV·HCl	177—178	e	$C_{12}H_{22}O_2NCl$	58.17	8.95	5.65		58.05	8.79	5.77	

a=ethanol/diisopropyl ether; b=ethanol/ether; c=petroleum ether (bp 40—60°C); d=*n*-hexane; e=butanone

TABLE 5. HYDROCHLORIDE OF CYCLIC α-AMINO ACIDS

Compound	Mp °C (decomp.)	pK_a	Formula	Calcd, %				Found, %			
				C	H	N	Cl	C	H	N	Cl
IVA·2HCl	275	2.3, 5.0, 9.9	$C_{14}H_{20}O_2N_2Cl_2$	52.67	6.32	8.77	22.21	52.67	6.71	8.39	21.96
IVB·2HCl	270	2.3, 4.4, 9.5						52.51	6.73	8.29	22.44
IVC·2HCl	296	2.4, 4.4, 9.1						52.80	6.59	8.42	22.26
XIB·2HCl	238	2.3, 4.3, 9.5						52.76	6.20	8.55	22.23
XII·HCl	242—245		$C_{14}H_{17}O_2NCl_2$	55.64	5.67	4.63	23.46	55.88	5.72	4.59	23.35
XV·HCl	258—260		$C_{10}H_{18}O_2NCl$	54.67	8.26	6.37	16.14	54.49	8.17	6.67	16.41

The NMR analysis showed that the dienophile V is a single isomer. The NMR spectrum of the adduct VII which was very similar to the pattern of the adduct mixture II, showed the presence of two pairs of isomeric adducts, *i. e.*, VIIB—VIIC (major) and VIIA—VIID (minor) corresponding to the adduct pairs IIB—IIC and IIA—IID, respectively. The presence of about 70% of the main isomer VIIB in VII was also suggested on the basis of the relative intensity of the 3*x*-proton. The separation of the main isomer VIIB by chromatography and recrystallization was unsuccessful, however, sometimes, spontaneous partial separation of VIIA in pure crystalline state was observed. Its NMR spectrum was found to be closely similar to that of the adduct IIA with exception of pattern due to aromatic protons (Tables 1 and 2). The structures of VIIA and VIIB were assigned as shown in Fig. 2.

The hydrogenations of VII and VIII with Raney Ni T-4 gave ethyl 2-amino-3-(*m*-aminophenyl)-bicyclo[2.2.1]heptane-2-carboxylate (IX) and ethyl 2-amino-3-(*p*-chlorophenyl) bicyclo[2.2.1]heptane-2-carboxylate (X), from which crystalline amino esters, IXB and X′ were obtained respectively. The hydrolysis of IXB and X with 6 N hydrochloric acid or barium hydroxide afforded hydrochlorides of corresponding amino acids XIB and XII, respectively (Table 5).

The Diels-Alder reaction of ethyl α-nitrocrotonate[1,12] with 1,3-cyclohexadiene gave an adduct, ethyl 3-methyl-2-nitrobicyclo[2.2.2]-5-octene-2-carboxylate (XIII) in 25% yield. The gas chromatogram of XIII showed three peaks. Hydrogenation of XIII with Raney Ni T-4 gave ethyl 2-amino-3-methylbicyclo[2.2.2]octane-2-carboxylate (XIV), which, on hydrolysis with barium hydroxide, afforded 2-amino-3-methylbicyclo[2.2.2]octane-2-carboxylic acid(XV).

Experimental

Thin layer chromatography (TLC) was conducted by the use of silica gel (Daiichi Pure Chemicals Co., Inc.). The prepared plates were activated at 110°C. The spray reagent used was concentrated sulfuric acid and 0.25% pyridine solution of ninhydrin. Silica

12) S. Umezawa and S. Zen, This Bulletin, **36**, 1143 (1963).

gel column chromatography was carried out by the use of silica gel (Kanto Chemicals Co., Inc.) activated at 110°C before use. The pK_a values were determined by the method of Parks and Davis.[13] Gas-liquid chromatographic analysis was carried out with a Shimadzu-Kotaki Gas Chromatograph, Model GU-21. The NMR spectra were taken with a Japan Electron Optics JNM-H-60 spectrometer at a frequency of 60 Mc by using about 10—20% solution of the sample in deuteriochloroform with tetramethylsilane as an internal standard. Spin decoupling experiments were carried out by using Japan Electron Optics JNM-4H-100 spectrometer and JNM-SD-30 spin decoupler.

Ethyl 2-Nitro-3-(*p*-nitrophenyl)bicyclo[2.2.1]-5-heptene-2-carboxylate (II) (A typical example of the general procedure). A mixture of ethyl α,*p*-dinitrocinnamate (mp 108—109°C from ether) (1.0 g, 3.76 mmol), freshly distilled cyclopentadiene (2.0 g, 30.3 mmol) and dry benzene (2 m*l*) was heated for 1.5 hr at 120°C in a sealed tube. Unchanged cyclopentadiene and benzene were removed in a vacuum. The resulting red-brown oil was placed on a silica gel column (20 g, 2×15 cm) and eluted with 25% petroleum ether in benzene. The first effluent (*ca.* 90 m*l*) containing dicyclopentadiene was discarded. The second effluent (180 m*l*) gave the adduct II (1.26 g, 100%) as a pale-yellow crystalline solid. TLC (6 : 1 *n*-hexane/ethyl acetate) of II showed two spots having R_f-values of 0.5 and 0.4.

The other adducts VII, VIII and XIII were prepared by the general procedure (Table 1). The preparations of VIII and XIII, however, were carried out without solvent and purification was done by distillation. The gas chromatographic analysis of XIII on polyester-succinate column (1-m long) at 180°C with helium (40 m*l*/min) showed three peaks with elution times of 20.0, 22.0 and 26.4 min.

The Separation of Diastereoisomers of the Adduct II and VII. Separation of the Fraction II_1 and II_2. A sample of 1.04 g of II in a small amount of ethyl acetate was placed on a silica gel column (100 g, 3×38 cm) and eluted with 6 : 1 *n*-hexane/ethyl acetate in the flow rate of 12 m*l*/hr. Fractions (*ca.* 4 m*l*) were collected and examined by TLC with the same solvent system as the column chromatography. Fractions 80—118 (150 m*l*) gave II_1 (R_f 0.5; 70 mg, mp 74—114°C). Fractions 124—190 (270 m*l*) gave II_2 (R_f 0.4; 676 mg, mp 71—79°C) and fractions 119—123 (20 m*l*) gave a II_1-II_2 mixture (15 mg). Total yield was 73.2% based on the original adduct II.

Adduct IIA: Recrystallization of the fraction II_1 (230 mg) from methanol gave IIA (115 mg), colorless needles, mp 119—120°C.

Adduct IID: The separation of the adduct IID from its isomer IIA was a laborious work. The mother liquor separated from the first crop of IIA was evaporated to give a yellow crystalline mass melting at 64—70°C. A sample (30 mg) of the material was dissolved in hot methanol (0.6 m*l*). After inoculation of pure IID as a seed, the solution was allowed to stand overnight in a refrigerator to afford colorless large plates of IID (9 mg) which was partly contaminated by the needles of IIA. The plates (4 mg) of IID were picked out with a tweezer from the mixture; mp 79—80°C. The products from similar twelve batches were pooled (50 mg) and recrystallized from methanol to yield 33 mg of an analytical sample, mp 81—81.5°C.

Adduct IIB: A sample (656 mg) of the above-mentioned fraction II_2 was recrystallized from hot methanol (12 m*l*) by inoculation of pure crystals of IIB to give granular crystals (425 mg) of IIB melting at 104.5—106.2°C. Recrystallization afforded an analytical sample, mp 107—108°C. An additional crop (64 mg) of IIB was obtained from the mother liquor; total yield, 489 mg (74.5%).

Adduct IIC: The mother liquor separated from the second crop of IIB was evaporated to give a crystalline mass, which was recrystallized from methanol by inoculation of seed crystals of IIC to afford granular crystals (105 mg) melting at 78.5—80.0°C. An analytical sample of IIC was obtained by one recrystallization from methanol, mp 79—80°C.

Adduct VIIA: (A rare example of the separation of of VIIA). When a mixture adduct VII (1.20 g) prepared by above-mentioned general procedure was triturated with 3 m*l* of ethanol and the triturated mixture was allowed to stand for several hours in a cold place, there separated the crystals of VIIA; yield, 470 mg, mp 82—92°C. Two recrystallizations from ethanol afforded an analytical sample, mp 101—102°C.

Ethyl 2-Amino-3-(*p*-aminophenyl)bicyclo[2.2.1]-heptane-2-carboxylate (IIIB) (A typical example of the general procedure). A solution of ethyl 2-nitro-3-(*p*-nitrophenyl)bicyclo[2.2.1]-5-heptene-2-carboxylate (IIB) (1.5 g) in ether (25 m*l*) was shaken with Raney Ni T-4 (7 m*l*) at 20—25°C and 120 kg/cm² for 5 hr in an autoclave. The contents were then filtered to remove the catalyst and the solution was evaporated in a vacuum. A solution of the resulting oil (1.08 g) in ether (30 m*l*) was extracted with 1 N hydrochloric acid (9 m*l*), and the ethereal solution was washed with water (10 m*l*×4). The aqeuous layer and washings were combined, washed with ether (10 m*l*) and made alkaline by addition of a 50% potassium carbonate solution (2.5 m*l*). The liberated oil was extracted with ether (10 m*l*×4), and the ethereal extract was dried over potassium carbonate. After evaporation of the solvent, the amino ester IIIB was obtained as a pale-yellow viscous oil; yield, 967 mg (77.8%).

The other amino esters, III (isomeric mixture), IIIA, IIIC, IX, X and XIV were prepared by the general procedure. The hydrogenations of X and XIV were carried out in ethanol instead of in ether. The crystalline amino esters IXB and X′ were isolated from the corresponding mixed ester IX and X in a yield of 46.4% and 15%, respectively (Table 4).

The hydrochlorides of IIIA, IIIB, IIIC, IXB, X′, and XIV were obtained from their ethanolic hydrogen chloride solution by dilution with absolute ether (Table 4).

2-Amino-3-(*p*-aminophenyl)bicyclo[2.2.1]heptane-2-carboxylic Acid Dihydrochloride (IVB·2HCl) (A typical example of the general procedure). A solution of IIIB (220 mg) in 6 N hydrochloric acid (5.5 m*l*) was heated in a sealed tube at 110—120°C for 8 hr. After refrigeration of the reaction mixture, the precipitated dihydrochloride of IVB was collected and washed with acetone to afford colorless fine crytals; yield, 218 mg (85.2%). By concentration of the mother

13) T. V. Parke and W. W. Davis, *Anal. Chem.*, **26**, 642 (1954).

liquor the second crop of IVB·2HCl (42 mg) was obtained. Tow recrystallizations from methanol-diisopropyl ether gave an analytical sample, granular crystals; mp 270°C (decomp.).

The dihydrochlorides, IVC·2HCl and XIB·2HCl were prepared by the general procedure, but the isolation of IVC·2HCl was accomplished by evaporation of the reaction mixture, because of its high solubility in cold hydrochloric acid. An analytical sample of IVC·2HCl was obtained by recrystallization from absolute methanolic hydrogen chloride-diisopropyl ether.

2-Amino-3-(*p*-aminophenyl)bicyclo[2.2.1]heptane-2-carboxylic Acid Dihydrochloride (IVA·2HCl). A solution of IIIA (220 mg) in 6 N hydrochloric acid (5.0 m*l*) was heated in a sealed tube at 110—120°C for 16 hr. The resulting mixture was evaporated in a vacuum to give a solid mass, which was washed with ether and acetone. The yellow powdery product (180 mg) was placed on a silica gel column (1.5×30 cm) and developed with a solvent system of ethyl acetate-pyridine-methanol (3 : 1 : 1) until the yellow band of amino acid was separated completely from the orange band of unchanged amino ester on the column. The silica gel containing amino acid band in a upper portion of the column was scraped out and extracted out with methanol. The methanol extract was evaporated to give an oil which crystallized by trituration with absolute ether; yield, 130 mg (64%). Recrystallization from absolute ethanolic hydrogen chloride-diisopropyl ether afforded an analytical sample of IV·2HCl, mp 232°C(colored)—275°C(decomp.).

2-Amino-3-(*p*-chlorophenyl)bicyclo[2.2.1]heptane-2-carboxylic Acid (XII) and 2-Amino-3-methylbicyclo[2.2.2]octane-2-carboxylic Acid (XV). XII and XV were prepared from X and XIV, respectively by hydrolysis with 0.45 N barium hydroxide in aqueous methanol at 36—37°C for 20 hr, by the similar method as reported previously.[1] The hydrochlorides of XII and XV were obtained from their ethanolic hydrogen chloride solution by dilution with absolute ether.

Ethyl *α*,*p*-Dinitrocinnamate[2] (I). The NMR signals were observed at $\tau(CDCl_3)$: 2.04 (center of A_2B_2 pattern, aromatic protons); 2.35 (a singlet, *β*-proton); 5.53 (a quartet, ester methylene protons); and 8.62 (a triplet, ester methyl protons).

Ethyl *α*,*m*-Dinitrocinnamate (III). Prepared from *m*-nitrobenzylidene-*n*-butylamine[14] and ethyl nitroacetate by the same method as reported by Dornow and Menzel[2]; yield, 61%, mp 101—102°C (from ether). The NMR signals were observed at $\tau(CDCl_3)$: 2.28 (a singlet, *β*-proton); 5.54 (a quartet, ester methylene protons); and 8.59 (a triplet, ester methyl protons).

Found: C, 49.85; H, 3.95; N, 10.43%. Calcd for $C_{11}H_{10}O_6N_2$: C, 49.63; H, 3.79; N, 10.52%.

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14) S. Zen, Ph. D. Thesis, Keio University, 1963.