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Decarboxylation Reaction. X.[1] Introduction of a Carbon Unit at the α-Position of Amines by Reaction of Hexahydro-1,3,5-triazines with Carboxylic Acids

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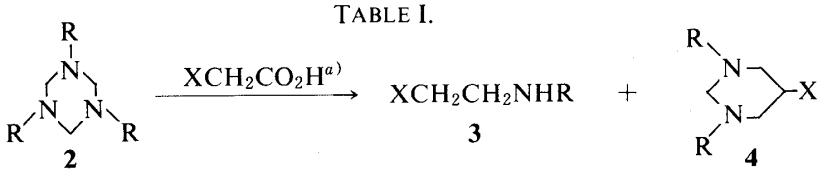
An efficient method for introducing a carbon unit at the α-position of alicyclic amines is described. The method involves the reaction of monocyclic or tetracyclic hexahydro-1,3,5-triazines with trichloroacetic acid, cyanoacetic acid, malonic acid and their derivatives, which are introduced into the α-position of amines in the decarboxylated form.

Keywords——1,3,5-trialkylhexahydro-1,3,5-triazine; trimer of alicyclic imine; decarboxylation; β-amino acid; carboxylic acid

Introduction of a carbon unit at the α-position of alicyclic amines is of current interest because of its potential applications in organic synthesis, especially of a number of pharmaceuticals such as biologically important bicyclic β-lactams. The activation of the α-position of alicyclic amines in advance by converting them to imines[2] or *N*-chlorinated,[3] *N*-nitrosoated[4] or α-methoxylated[5] amines is necessary for this purpose. However, the formation of these intermediates is not necessarily easy, and the subsequent introduction of the carbon unit sometimes has limited selectivity. Our recent communication[6] briefly reported a new, efficient method based on the reaction of tetracyclic hexahydro-1,3,5-triazines (THTA) (**1**) with malonic acid derivatives, which are introduced into the α-position of alicyclic amines in the decarboxylated form. THTA is readily available synthetically by *N*-chlorination of alicyclic amines by treatment with sodium hypochlorite[7] or *N*-chlorosuccinimide,[8] follwed by dehydrochlorination with base. The present paper describes details of the work together with some extended experimental data.

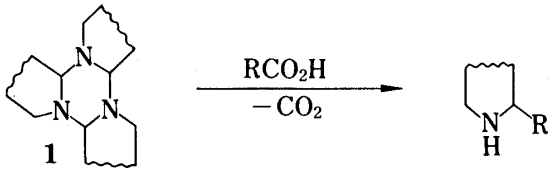
The reaction of 1,3,5-trialkylhexahydro-1,3,5-triazines (**2**) with carboxylic acids, *i.e.*, cyanoacetic acid and monoethyl malonate, proceeded in the presence of triethylamine in acetonitrile to give secondary cyano- and carboethoxyethylamines (**3**) with formation of hexahydropyrimidine derivatives (**4**) as by-products. The results are summarized in Table I. The product **3a**, obtained by the reaction of **2a** [R=$(CH_3)_2CH$–] with cyanoacetic acid, was exceptional, and was assigned as 1-(*N*-isopropylamino)-2-cyano-2-propene. The products

TABLE I.



R	X	Product **3**	Yield[b)] (%)	Product **4**	Yield[b)] (%)
$(CH_3)_7CH$ (**2a**)	CN	**3a**[c)]	54	**4a**	26
$(CH_3)_2CH$ (**2a**)	CO_2Et	**3b**	23	**4b**	42
$C_6H_5CH_2$ (**2b**)	CN	**3c**	42	**4c**	24
$C_6H_5CH_2$ (**2b**)	CO_2Et	**3d**	63	**4d**	1

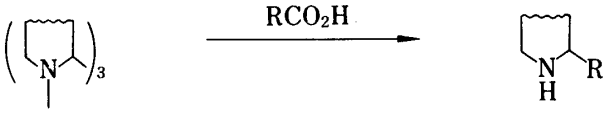
a) **2**/XCH_2CO_2H/NEt_3=1/6/6 (molar proportion).
b) Based on the product isolated.
c) The structure of **3a** is assigned as $NC-\underset{\underset{CH_2}{\|}}{C}-CH_2NHCH(CH_3)_2$.

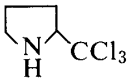
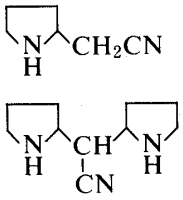
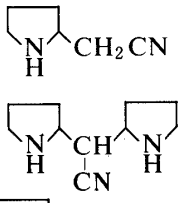
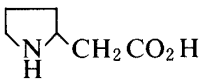
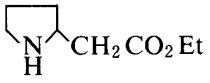
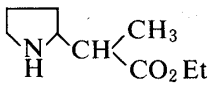
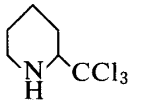
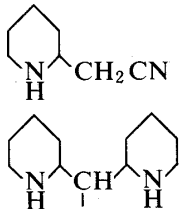


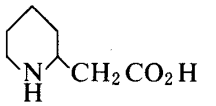
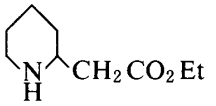
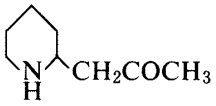
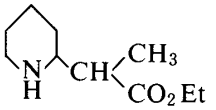
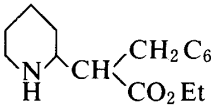
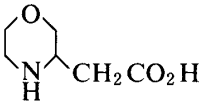
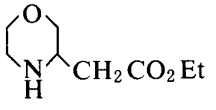
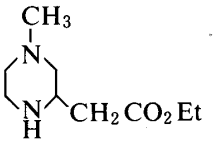
4a—**d**, unknown previously, were identified on the basis of their infrared (IR), proton magnetic resonance (^{1}H-NMR), and mass spectral (MS) data. Triethylamine is an efficient catalyst for this reactions. For example, when reacted with cyanoacetic acid in the absence of triethylamine, **2b** (R=$C_6H_5CH_2$) gave **4c** (R=$C_6H_5CH_2$, X=CN) in 62% yield with a trace amount of **3c**.

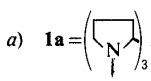
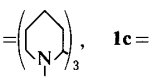
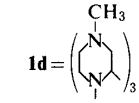
Since the reaction can be applied to the introduction of the decarboxylated residues of carboxylic acids at the α-position of alicyclic amines, its scope was extended to include tetracyclic hexahydro-1,3,5-triazines, trimers of alicyclic imines.

TABLE II.



Trimer[a]	RCO_2H	Reaction conditions Method[b]	(℃)	(h)	Product	No.	bp ℃ (mmHg) or mp ℃	Yield[c] (%)
1a	CCl_3CO_2H	A	30—35	2		**5a**	109—110 (25)	15
1a	$H_2C(CN)CO_2H$	A	34—40	3.5		**5b**	110—111 (17)	7
						5c	131—132 (1)	41
		B	50—55	3		**5b**		47
						5c		35
1a	$H_2C(CO_2H)CO_2H$	C	55—60	2.5		**5d**	170—171 (HCl salt)	57
1a	$H_2C(CO_2Et)CO_2H$	B	35—40	2		**5e**	58—60 (0.4)	63
1a	$CH_3CH(CO_2Et)CO_2H$	B	65—70	2		**5f**	68—69 (0.7)	59
1b	CCl_3CO_2H	A	55—60	3		**6a**	64—65 (0.2)	35
1b	$H_2C(CN)CO_2H$	B	50—55	3		**6b**	105—106 (1)	71
						6c	141—142 (1)	3

Trimer[a]	RCO_2H	Reaction conditions Method[b]	(℃)	(h)	Product	No.	bp ℃ (mmHg) or mp ℃	Yield[c] (%)
1b	$H_2C(CO_2H)_2$	C	55—60	2.5		**6d**	178—179 (HCl salt)	51
1b	$H_2C(CO_2Et)CO_2H$	B	30—35	3		**6e**	65—67 (0.7)	61
1b	$O{=}C(CH_2CO_2H)_2$	C	−10—−5	4		**6f**	93—94 (15)	75
1b	$CH_3CH(CO_2Et)CO_2H$	B	65—70	2		**6g**	64—65 (0.2)	42
1b	$C_6H_5CH_2CH(CO_2Et)CO_2H$	B	60—65	5		**6h**	149—151 (1)	41
1c	$H_2C(CO_2H)_2$	C	55—60	7		**7a**	159—160 (HCl salt)	26
1c	$H_2C(CO_2Et)CO_2H$	B	55—60	5.5		**7b**	85—86 (0.2)	51
1d	$H_2C(CO_2Et)CO_2H$	B	50—55	1.5		**8**	85—87 (0.4)	45

a) **1a**=  , **1b**=  , **1c**=  , **1d**=.

b) A:trimer/RCO_2H=1/6 (molar proportion), B:trimer/RCO_2H/NEt_3=1/6/6 (molar proportion), C:trimer/RCO_2H/NEt_3=1/6/12 (molar proportion).

c) Based on the product isolated.

Trimers of 1,2-didehydropyrrolidine (**1a**), 1,2-didehydropiperidine (**1b**), 3,4-didehydromorpholine (**1c**), and 1,2-didehydro-4-methylpiperazine (**1d**) were used as tetracyclic hexahydro-1,3,5-triazines, the latter two being newly prepared in the present work. As carboxylic acid reactants, trichloroacetic acid, cyanoacetic acid, malonic acid, monoethyl malonate, monoethyl methylmalonate, monoethyl benzylmalonate, and acetonedicarboxylic acid were selected. The results are summarized in Table II. Though trichloroacetic acid did not react with **2a** or **2b** in the presence or in the absence of triethylamine, it reacted with **1a** and **1b** in the presence of triethylamine to give 2-trichloromethylated pyrrolidine and piperidine. On the other hand, as can be seen in the reaction of cyanoacetic acid with **1a**, the presence of triethylamine considerably increases the yield of the desired 2-substituted product, 2-cyanomethylpyrrolidine, the formation of 2,2′-cyanomethylenebispyrrolidine being depressed.

Since a similar effect of triethylamine was observed in the reaction of various carboxylic acids possessing active methylene, most of the results shown in Table II are for experiments

carried out in the presence of triethylamine. By this procedure, a variety of 2-substituted alicyclic amines, including several previously unknown compounds, were obtained in considerable yields. Among them, derivatives of alicyclic β-amino acids obtained by the use of malonic acid derivatives are expected to be transformable, by known methods, into bicyclic β-lactams, one of the most biologically important groups.

TABLE III. Spectral and Analytical Data for the α-Substituted Alicyclic Amines

Compd. No.	IR ν_{max}^{neat} cm^{-1}	MS m/z (M^+)	^{1}H-NMR[a] δ (in $CDCl_3$)[b]	Formula	Analysis (%) Calcd (Found) C	H	N
5a	3325(NH)	187	1.25—2.35(4H, m, $-CH_2CH_2-$), 2.69(1H, s, NH), 3.11(2H, t, J=5.0 Hz, NCH_2), 4.05(1H, t, J=5.0 Hz, CH)	$C_5H_8Cl_3N$	31.86 (32.08	4.28 4.26	7.43 7.87)
5b	3354(NH) 2240(CN)	110	1.40—2.20(4H, m, $-CH_2CH_2-$), 2.40(1H, s, NH), 2.45(2H, d, J=6.0 Hz, CH_2CN), 2.48(2H, m, CH_2N), 3.44(1H, m, CH)	$C_6H_{10}N_2$	65.42 (65.48	9.15 9.15	25.43 25.04)
5c	3354(NH) 2240(CN)	179	1.33—2.05(8H, m, 2×$-CH_2CH_2$), 2.01(2H, s, NH), 2.26—2.71(1H, m, CHCN), 2.71—3.15(4H, m, 2×CH_2N), 3.15—3.53(2H, m, 2×CHN)	$C_{10}H_{17}N_3$	67.00 (66.69	9.56 9.59	23.44 23.83)
5f	3358(NH)		1.16(3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 1.20(3H, t, J=6.6 Hz, $CH_2C\underline{H}_3$), 1.50—2.00(4H, m, $-CH_2CH_2-$), 1.85(1H, s, NH), 2.05—3.40(4H, m, CH_2NCH, CHCO), 4.08(2H, q, J=6.6 Hz, OCH_2),	$C_9H_{17}NO_2$	63.12 (62.82	10.01 10.00	8.18 7.95)
6a	3350(NH)	201	1.20—1.80(6H, m, $-CH_2CH_2CH_2-$), 2.23(1H, s, NH), 2.50—3.00(1H, m, CH), 3.10—3.50(2H, m, NCH_2)	$C_6H_{10}Cl_3N$	35.59 (35.49	4.98 4.91	6.92 7.05)
6b	3340(NH)	124	1.00—2.00(6H, m, $-CH_2CH_2CH_2-$), 1.80(1H, s, NH), 2.41(2H, d, J=6.0 Hz, CH_2CN), 2.55—3.30(3H, m, CH_2NCH)	$C_7H_{12}N_2$	67.70 (67.23	9.74 9.79	22.56 22.18)
6c	3345(NH)	207	1.00—2.00(12H, m, 2×$-CH_2CH_2CH_2-$), 2.0(2H, s, NH), 2.10—3.00(7H, m, other protons)	$C_{12}H_{21}N_3$	69.52 (69.23	10.21 10.34	20.27 19.96)
7a	1740(CO)[c]		2.75(2H, d, J=5.8 Hz, CH_2CO), 3.15—3.45(3H, m, CH_2NCH), 3.46—4.06(4H, m, CH_2OCH_2)	$C_6H_{12}ClNO_3$	39.68 (39.98	6.66 6.73	7.71 7.68)
7b	3332(NH) 1715(CO)		1.24(3H, t, J=6.6 Hz, CH_3), 2.21(1H, s, NH), 2.26 (2H, d, J=6.0 Hz, CH_2CO), 2.90—3.30(3H, m, CH_2NCH), 3.30—3.90(4H, m, CH_2OCH) 4.12(2H, q, J=6.6 Hz, $COOCH_2$)	$C_8H_{15}NO_2$	55.47 (55.27	8.73 8.60	8.09 8.09)
8	3362(NH) 1735(CO)		1.27(3H, t, J=6.8 Hz, $CH_2C\underline{H}_3$), 2.35(3H, s, NCH_3), 2.20—3.10(9H, m, CH_2CO, CH_2NCH, CH_2NCH_2), 3.35(1H, s, NH), 4.11(2H, q, J=6.8 Hz, OCH_2)	$C_9H_{18}N_2O_2$	58.04 (57.76	9.74 9.73	15.04 14.75)

a) The following abbreviations are used; s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet.
b) As an exception, the ^{1}H-NMR spectrum of **7a** was measured in D_2O.
c) KBr tablet.

Hexahydro-1,3,5-triazines are regarded as functionally equivalent to imines, so that their ring carbons are susceptible to the attack of nucleophiles. In the present reaction, synchronous decarboxylation may be initiated by nucleophilic attack of carboxylate anions in the case of trichloroacetic acid or by that of the carbanion at the α-carbon of carboxylates in the cases of carboxylic acids possessing active methylene.

It should be noted that this new decarboxylation reaction is admirably suitable for the introduction of decarboxylated residues of carboxylic acids at the α-position of alicyclic amines by a simple procedure.

Experimental

All melting points and boiling points are uncorrected. IR spectra were taken with a Hitachi EPI-G2 spectrophotometer. NMR spectra were recorded on a Hitachi R-24B spectrometer, and all chemical shifts are given in ppm downfield from tetramethylsilane. Mass spectra were measured with a JEOL JMS-D100 machine.

Preparation of 1,3,5-Trialkylhexahydro-1,3,5-triazines (2) and Trimers of Alicyclic Imines (1)——Preparation of 1,3,5-triisopropyl- and 1,3,5-tribenzylhexahydro-1,3,5-triazines (**2a, b**) were done according to the method described by Reynolds.[9]

Trimers of 1,2-didehydropyrrolidine (**1a**), and 1,2-didehydropiperidine (**1b**) were prepared according to the method described in the literature.[7] In a similar manner the trimer of 3,4-didehydromorpholine (**1c**) was newly prepared from morpholine and sodium hypochlorite followed by treatment with alkali. **1c**: mp 99—101°C (from acetone). MS *m/z* 255 (M^+). *Anal.* Calcd for $C_{12}H_{21}N_3O_3$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.67; H, 8.29; N, 16.15.

Trimer of 4-methyl-1,2-didehydropiperazine (**1d**) was prepared from 1-methylpiperazine and *N*-chlorosuccinimide followed by treatment with alkali. **1d**: bp 86—88°C (0.5 mmHg), MS *m/z* 294 (M^+). *Anal.* Calcd for $C_{15}H_{30}N_8$: C, 61.19; H, 10.27; N, 28.54. Found: C, 60.97; H, 10.56; N, 28.34.

Reaction of 1,3,5-Tribenzylhexahydro-1,3,5-triazine (2b) with Cyanoacetic Acid——A mixture of **2b** (7.2 g, 0.02 mol) and cyanoacetic acid (10.2 g, 0.12 mol) in 40 ml of acetonitrile was heated at 45—48°C with stirring. The reaction proceeded with evolution of CO_2 gas. After the evolution of CO_2 gas had ceased (1 h), the solution was concentrated under reduced pressure. The residue was treated with 30% aq. K_2CO_3, then extracted with ether, and the ethereal solution was dried over $MgSO_4$. After removal of the ether, the resulting residue was subjected to distillation under reduced pressure to give 3.6 g (62%) of 5-cyano-1,3-dibenzylhexahydropyrimidine (**4b**), bp 176—178°C (0.4 mmHg). A trace amount of *N*-(cyanoethyl)-benzylamine was also detected by gas chromatography of a forerun. **4b**: IR ν_{max}^{neat} cm^{-1}: 2258 (CN). ^{1}H-NMR (in $CDCl_3$): 2.58—3.28 [5H, m, $CH_2CH(CN)CH_2$], 3.60 (4H, s, $2\times C\underline{H}_2C_6H_5$), 3.74 (2H, s, NCH_2N), 7.22 (10H, s, $2\times C_6H_5$). *Anal.* Calcd for $C_{19}H_{21}N_3$: C, 78.32; H, 7.26; N, 14.42. Found: C, 78.59; H, 7.26; N, 14.31.

Reaction of 1,3,5-Trialkylhexahydro-1,3,5-triazine (2) with Carboxylic Acid in the Presence of Triethylamine——General Procedure: To a solution of carboxylic acid (cyanoacetic acid or monoethyl malonate) (0.12 mol) and triethylamine (0.12 mol) in 40 ml of acetonitrile was added 1,3,5-trialkylhexahydro-1,3,5-triazine (**2a, b**) (0.02 mol). The mixture was heated with stirring at a sufficient temperature to cause considerable evolution of CO_2 gas. After the evolution of CO_2 gas had ceased (2—5 h), the reaction solution was concentrated under reduced pressure. The residue was treated with 30% aq. K_2CO_3 and extracted with ether. The ethereal solution was dried over $MgSO_4$. After removal of the ether, the resulting residue was subjected to distillation under reduced pressure. Yields of the products are shown in Table I. Boiling points of all products, and the spectral and analytical data of the previously unknown products are as follows. **3a**: bp 74—76°C (16 mmHg). IR ν_{max}^{neat} cm^{-1}: 2241 (CN). ^{1}H-NMR δ (in $CDCl_3$): 1.05 (6H, d, J=6.0 Hz, $2\times CH_3$), 1.11 (1H, s, NH), 2.53—3.14 (1H, m, NCH), 3.38 (2H, s, NCH_2), 5.88 (2H, br s, $=CH_2$), *Anal.* Calcd for $C_7H_{12}N_2$: C, 67.70; H, 9.74; N, 22.56. Found: C, 67.60; H, 9.82; N, 22.25. **3b**: bp 129—130°C (3 mmHg). **3c**: bp 78—79°C (15 mmHg). **3d**: bp 112—113°C (0.2 mmHg). **4a**: bp 139—141°C (16 mmHg). IR ν_{max}^{neat} cm^{-1}: 2250 (CN). ^{1}H-NMR δ (in $CDCl_3$): 1.07 (12H, d, J=6.2 Hz, $4\times CH_3$), 2.46—3.22 (7H, m, NCH_2N, CH_2CHCH_2). MS *m/z* 195 (M^+). *Anal.* Calcd for $C_{11}H_{12}N_2$: C, 67.65; H, 10.84; N, 21.51. Found: C, 67.70; H, 10.95; N, 21.87. **4c**: bp 104—106°C (2 mmHg). IR ν_{max}^{neat} cm^{-1}: 1734 (CO). ^{1}H-NMR δ (in $CDCl_3$): 1.09 (12H, d, J=6.0 Hz, $4\times CH_3$), 1.28 (3H, t, J=6.2 Hz, $CH_2C\underline{H}_3$), 2.10 (1H, m, CHCO), 4.11 (2H, q, J=6.2 Hz, OCH_2). **4d**: bp 173—174°C (0.1 mmHg). IR ν_{max}^{neat} cm^{-1}: 1735 (CO). MS *m/z* 338 (M^+).

Reaction of Tetracyclic Hexahydro-1,3,5-triazine (1) with Carboxylic Acid——Method A: A mixture of **1** (0.02 mol) and carboxylic acid (0.06 mol) in 40 ml of acetonitrile was heated with stirring at a sufficient temperature to cause considerable evolution of CO_2 gas. The reaction temperature and period for each run are recorded in Table II. The reaction solution was concentrated under reduced pressure. The residue was treated with 30% aq. K_2CO_3, then extracted with ether, and the ethereal solution was dried over $MgSO_4$. After removal of ether, the residue was subjected to distillation under reduced pressure.

Method B: Tetracyclic hexahydro-1,3,5-triazine (**1**) (0.02 mol) was added to a solution of carboxylic acid (0.12 mol) and triethylamine (0.12 mol) in 40 ml of acetonitrile. The solution was worked up by a procedure similar to that described in Method A.

Method C: Tetracyclic hexahydro-1,3,5-triazine (**1**) (0.02 mol) was added to a solution of carboxylic acid (0.12 mol) and triethylamine (0.24 mol) in 40 ml of acetonitrile. The solution was worked up by a procedure similar to that described in method A. The products (**5d, 6d, 7a**) were isolated as their hydrochlorides. Boiling points and yields of the products are recorded in Table II. Spectral data of the previously unknown products are shown in Table III.

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References and Notes

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