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Decarboxylation Reactions. III.¹⁾ Reaction of N,N'- and N,O-Linked
Methylene Compounds with Carboxylic Acids

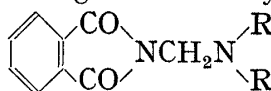
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The present paper describes a new reaction of N,N'- and N,O-linked methylene compounds with carboxylic acids such as cyanoacetic acid, malonic acid, acetoacetic acid, trichloroacetic acid and phenylpropionic acid. By the reaction substitution of one of the linking heteroatoms of the substrates by the decarboxylated residues of the carboxylic acids is effected to proceed. The reaction presented here provides an effective means of introducing mono- and/or bis-dialkylaminomethyl grouping into the decarboxylated residue of the carboxylic acids.

The methylene compounds, in which two nitrogens and both nitrogen and oxygen are bound to the methylene carbon, have been known³⁾ to suffer substitution of one of the linking heteroatoms when attacked by nucleophiles. The present paper deals with a new reaction of this type affected by reacting with certain carboxylic acids, where substitution by the decarboxylated residues of the carboxylic acids is brought about. By the use of the methylene

compounds linking dialkylamino group, such as  (I), $C_4H_9OCH_2N\begin{smallmatrix} R \\ R' \end{smallmatrix}$ (II)

and $\begin{smallmatrix} R \\ R' \end{smallmatrix}NCH_2N\begin{smallmatrix} R \\ R' \end{smallmatrix}$ (III), dialkylaminomethylation of the decarboxylated residue of cyanoacetic acid, trichloroacetic acid, malonic acid, acetoacetic acid and phenylpropionic acid has been achieved. It is toward this subject that the present paper is described.

Examination was initiated by carrying out the reaction of the above methylene compounds possessing piperidino group as NRR', Ia, IIa, IIIa, with cyanoacetic acid. The reactions were found to proceed with considerable emission of carbon dioxide by means of heating in dioxane. By treatment of the reaction mixture a liquid, bp 118—120° (0.3 mmHg), was obtained, which was identified as 3-piperidino-2-(piperidinomethyl)propionitrile (IVa) (see runs 1, 5 and 8 in Table I). Since the observed nuclear magnetic resonance (NMR) spectrum of IVa for determination of the structure was complex, an analog possessing dimethylamino in place of piperidino group was prepared similarly and sampled in view from generality of this reaction as described later. To this compound, bp 99° (11 mmHg), which forms dihydrochloride, mp 142—143°, the structure, 3-dimethylamino-2-[(dimethylamino)methyl]propionitrile (IVb), was clearly assigned by noting the presence of two symmetrical dimethylamino groups (NMR: the singlet at δ 2.28) and of a nitrile group (infrared (IR): ν 2240 cm^{-1}) and from these data the structure IVa was assigned by analogy. Recently this type of the compound has been reported⁴⁾ to be produced as a minor product together with 2-[(dialkylamino)-methyl]acrylonitrile from the reaction among dialkylamine, cyanoacetic acid and formaldehyde.

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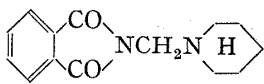
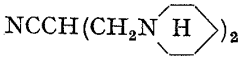
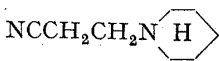
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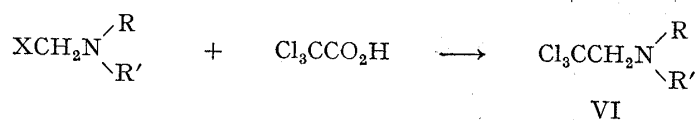
$$\text{XCH}_2\text{N} \begin{array}{c} \diagup \text{R} \\ \diagdown \text{R}' \end{array} + \text{NCCH}_2\text{CO}_2\text{H} \longrightarrow \text{NCCH}(\text{CH}_2\text{N} \begin{array}{c} \diagup \text{R} \\ \diagdown \text{R}' \end{array})_2 + \text{NCCH}_2\text{CH}_2\text{N} \begin{array}{c} \diagup \text{R} \\ \diagdown \text{R}' \end{array}$$

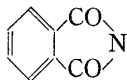

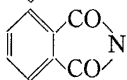

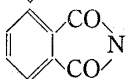
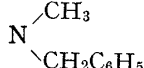
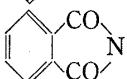



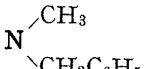




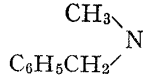
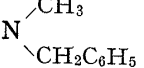
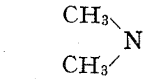

IV
V

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TABLE II. Effect of Triethylamine on the Reaction^{a)} of N-(Piperidinomethyl)phthalimide with Cyanoacetic Acid

							
	Ia			IVa		Va	
Run No.	Molar proportion			Reaction temp (°C)	Reaction period (hr)	Yield (%)	
	Ia	NCCH ₂ CO ₂ H	Et ₃ N			IVa	Va
1	1	1.2	0	45—50	1.5	39	0
2	1	0.5	0	45—50	1.5	29	4
3	1	1.2	0.6	45—50	3.0	29	19
4	1	1.2	1.2	65—70	4.0	0	26

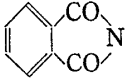

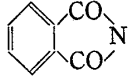

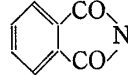

^{a)} solvent: dioxaneTABLE III. Reaction^{a)} with Trichloroacetic Acid

Run No.	X	N $\begin{array}{l} \text{R} \\ \diagup \\ \diagdown \\ \text{R}' \end{array}$	Reaction temp (°C)	Reaction period (hr)	Yield (%)
1		N 	68—70	3.5	19
2		N 	80—84	4.5	26
3		N 	74—76	6.5	43
4		N 	70—73	3.0	19
5	C ₄ H ₉ O	N 	60—65	5.7	64
6	C ₄ H ₉ O	N 	74—76	3.5	64
7	C ₄ H ₉ O	N 	63—64	4.0	64
8		N 	40—42	3.0	59
9		N 	43—45	3.0	58
10		N 	46—47	4.0	61
11		N 	36—38	2.0	50

^{a)} substrate: trichloroacetic acid=1:3 in molar proportion, solvent: dioxane

also allowed to react similarly with Ia, IIa and IIIa, whereupon 3-piperidino-2-(piperidino-methyl)propionic acid (VIIa), 4-piperidino-2-butanone (VIIIa) and N-(3-phenyl-2-propynyl)-piperidine (IXa) were obtained respectively. Reaction conditions and yields of the products are summarized in Table IV.

TABLE IV. Reaction^{a)} with Various Carboxylic Acids

Run No.	X	Reaction temp (°C)	Reaction period (hr)	Yield (%)
A. $\text{XCH}_2\text{N} \begin{array}{c} \diagup \text{H} \diagdown \\ \text{H} \end{array} + \text{CH}_2(\text{CO}_2\text{H})_2 \xrightarrow{b)} \text{HOOCCH}(\text{CH}_2\text{N} \begin{array}{c} \diagup \text{H} \diagdown \\ \text{H} \end{array})_2$ VIIa				
1		32—34	2.0	21
2	$\text{C}_4\text{H}_9\text{O}$	16—17	1.3	23
3		15—16 99—101	0.5 3.0	46
B. $\text{XCH}_2\text{N} \begin{array}{c} \diagup \text{H} \diagdown \\ \text{H} \end{array} + \text{CH}_3\text{COCH}_2\text{CO}_2\text{H} \xrightarrow{b)} \text{CH}_3\text{COCH}_2\text{CH}_2\text{N} \begin{array}{c} \diagup \text{H} \diagdown \\ \text{H} \end{array}$ VIIIa				
4		27—30	7.0	36
5	$\text{C}_4\text{H}_9\text{O}$	24—25	1.0	70
6		20—25 99—101	2.0 3.0	40
C. $\text{XCH}_2\text{N} \begin{array}{c} \diagup \text{H} \diagdown \\ \text{H} \end{array} + \text{C}_6\text{H}_5\text{C}\equiv\text{CCO}_2\text{H} \xrightarrow{c)} \text{C}_6\text{H}_5\text{C}\equiv\text{CCH}_2\text{N} \begin{array}{c} \diagup \text{H} \diagdown \\ \text{H} \end{array}$ IXa				
7		75—80	14.0	30
8	$\text{C}_4\text{H}_9\text{O}$	58—61	7.0	72
9		99—101	2.0	21

a) solvent: dioxane

b) substrate: malonic acid or acetoacetic acid=1: 1.2 in molar proportion

c) substrate: phenylpropionic acid=1: 2 in molar proportion

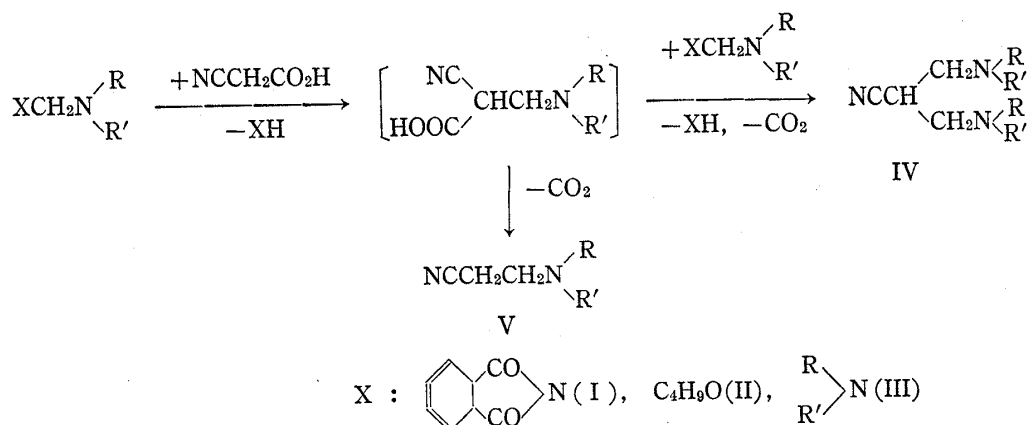


Chart 1

When we speculate on mechanism, there seems to be two paths for the above reactions. In the cases of trichloroacetic acid and phenylpropionic acid their carboxylate anions can afford VIa and IXa, respectively, through decarboxylation as a result of nucleophilic substitu-

tion. On the other hand the others possessing methylene, such as cyanoacetic acid, malonic acid and acetoacetic acid, appear to undergo a different reaction path. It is because that possibility of participation of Va as an intermediate for the formation of IVa is ruled out by noting no reaction of Va with Ia under the same condition as that for the original reaction. Therefore cyanoacetic acid, anyway in this case, appears to behave as a carbanion nucleophile as shown in Chart 1.

Experimental⁶⁾

Reaction of N-(Dialkylaminomethyl)phthalimides (I), N-(Butoxymethyl)dialkylamines (II) and N,N'-Methylenebis(dialkylamines) (III) with Carboxylic Acids—General Procedure: The following eleven N,N'- and N,O-linked methylene compounds shown with their melting and boiling points were used as substrates: N-(piperidinomethyl)phthalimide,⁷⁾ mp 117—118°; N-(dimethylaminomethyl)phthalimide,⁸⁾ mp 77—78°; N-(morpholinomethyl)phthalimide,⁸⁾ mp 118°; N-(N-methylbenzylaminomethyl)phthalimide, mp 105°. *Anal.* Calcd. for C₁₇H₁₆O₂N₂: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.96; H, 5.62; N, 10.02; N-(butoxymethyl)piperidine,⁹⁾ bp 98—99° (19 mmHg); N-(butoxymethyl)morpholine,¹⁰⁾ bp 105—108° (14 mmHg); N-(butoxymethyl)-N-methylbenzylamine,^{3b)} bp 132—137° (18 mmHg); N,N'-methylenebispiperidine,¹¹⁾ bp 110° (15 mmHg); N,N'-methylenebis(dimethylamine),¹²⁾ bp 82—84°; N,N'-methylenebismorpholine,¹³⁾ bp 127—129° (18 mmHg); N,N'-methylenebis(N-methylbenzylamine),¹⁴⁾ bp 153—154° (2 mmHg). As can be seen in Tables I, II, III and IV the reactions of these with the carboxylic acids, *i.e.*, cyanoacetic acid, trichloroacetic acid, malonic acid, acetoacetic acid and phenylpropionic acid, were carried out by the following general procedure.

A solution of I, II or III (0.05 mole) and the carboxylic acid in the molar proportion shown in Tables I—IV in 60 ml of dry dioxane was heated with stirring at the temperature causing considerable CO₂ emission, which was checked by Ba(OH)₂ solution by passing a stream of dry air free from CO₂. In some runs it was necessary to raise the temperature for completion. The reaction temperature and period for each run are recorded in Tables I—IV.

The reaction solution was concentrated under reduced pressure. In the runs with I this procedure resulted in deposition of phthalimide which was removed by filtration. The concentration residue was strongly basified with NaOH on cool, and an oily layer liberated was extracted with ether. The ethereal solution was dried over K₂CO₃. Evaporation of ether followed by distillation of the residue under reduced pressure gave the corresponding product as a liquid or solid distillate in the yield recorded in Tables I—IV. Only in the runs 1, 2 and 3 in Table IV by means of treating the concentration residue with HCl in EtOH the product VIIa was obtained as dihydrochloride. Physical, spectral and analytical data of the products are described in the following.

3-Piperidino-2-(piperidinomethyl)propionitrile (IVa)—Liquid, bp 118—120° (0.3 mmHg) [lit.⁴⁾ bp 117° (0.5 mmHg)], n_D^{20} 1.4874. IR $\nu_{\max}^{\text{liquid}}$ cm⁻¹: 2240 (CN). NMR δ : 2.33—2.88 (13H, m, -CH[CH₂N(CH₂)₂]₂), 1.30—1.75 (12H, m, (CH₂)₈). Mass Spectrum m/e : 235 (M⁺). *Anal.* Calcd. for C₁₄H₂₅N₃: C, 71.44; H, 10.71; N, 17.85. Found: C, 71.03; H, 10.33; N, 18.11. Dipercarbonate, needles from EtOH, mp 150—151°. *Anal.* Calcd. for C₁₄H₂₇O₈N₃Cl₂: C, 38.54; H, 6.23; N, 9.63. Found: C, 38.62; H, 6.32; N, 9.46. Dihydrochloride, plates from EtOH, mp 213—214°.

3-Dimethylamino-2-[(dimethylamino)methyl]propionitrile (IVb)—Liquid, bp 99° (11 mmHg) [lit.⁴⁾ bp 97° (10 mmHg)], n_D^{19} 1.4427. IR $\nu_{\max}^{\text{liquid}}$ cm⁻¹: 2240 (CN). NMR δ : 2.46—2.76 (5H, m, -CH(CH₂N<)₂), 2.28 (12H, s, CH₃). Mass Spectrum m/e : 155 (M⁺). *Anal.* Calcd. for C₈H₁₇N₃: C, 61.89; H, 11.04; N, 27.07. Found: C, 61.77; H, 10.94; N, 27.09. Dihydrochloride, needles from EtOH, mp 142—143°. *Anal.* Calcd.

- 6) All melting and boiling points are uncorrected. IR and ultraviolet (UV) spectra were determined with a Hitachi EPI-G2 spectrophotometer and a Hitachi EPS-3T spectrophotometer, respectively. Mass spectra were recorded with a Hitachi RMS-4 spectrometer. NMR spectra were taken at 60 MHz in CDCl₃ solution with a JEOL-C-60-H spectrometer and a Hitachi R-24 spectrometer using tetramethylsilane as internal standard. The following abbreviations are used: s=singlet, m=multiplet, t=triplet.
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for $C_8H_{19}N_3Cl_2$: C, 42.11; H, 8.39; N, 18.41. Found: C, 42.14; H, 8.88; N, 18.46. Hydrolysis by refluxing with 35% HCl gave 3-dimethylamino-2-[(dimethylamino)methyl]propionic acid dihydrochloride, prisms from MeOH, mp 166—167° (lit.¹⁵) mp 169—171°, undepressed by admixture with an authentic sample prepared from malonic acid, dimethylamine and formaldehyde. IR ν_{\max}^{KBr} cm^{-1} : 1709 (CO).

3-Morpholino-2-(morpholinomethyl)propionitrile—Plates from ether-petr. ether, mp 31—32°, bp 170—172° (3 mmHg) [lit.⁴] bp 153° (0.8 mmHg), n_D^{25} 1.4890. IR ν_{\max}^{liquid} cm^{-1} : 2240 (CN). NMR δ : 3.62—3.88 (8H, m, $-CH_2OCH_2-$), 2.43—2.93 (13H, m, $-CH[CH_2N(CH_2)_2]_2$). Anal. Calcd. for $C_{12}H_{21}O_2N_3$: C, 60.22; H, 8.85; N, 17.56. Found: C, 60.61; H, 8.82; N, 17.41.

3-N-Methylbenzylamino-2-[(N-methylbenzylamino)methyl]propionitrile—Needles from EtOH, mp 52—53°, bp 171—173° (1 mmHg). IR ν_{\max}^{KBr} cm^{-1} : 2238 (CN). NMR δ : 7.23—7.45 (10H, s, aromatic protons), 3.55 (4H, s, $CH_2C_6H_5$), 2.52—2.80 (5H, m, $-CH(CH_2NCH_3)_2$), 2.26 (6H, s, CH_3). Anal. Calcd. for $C_{20}H_{25}N_3$: C, 78.13; H, 8.20; N, 13.67. Found: C, 78.05; H, 8.00; N, 13.96.

3-Piperidinopropionitrile (Va)—Liquid, bp 114—115° (18 mmHg) [lit.¹⁶] bp 128—130° (30 mmHg), n_D^{19} 1.4699. IR ν_{\max}^{liquid} cm^{-1} : 2246 (CN). Anal. Calcd. for $C_8H_{14}N_2$: C, 69.52; H, 10.21; N, 20.27. Found: C, 69.57; H, 9.99; N, 20.43. Hydrochloride, plates from EtOH, mp 180—181° (lit.¹⁷) mp 181—182°. Picrate, yellow plates from EtOH, mp 159—160° (lit.¹⁶) mp 160°.

3-(Dimethylamino)propionitrile—Liquid, bp 76—77° (24 mmHg) [lit.¹⁸] bp 71.8—72° (20 mmHg), n_D^{18} 1.4259. IR ν_{\max}^{liquid} cm^{-1} : 2248 (CN). NMR δ : 2.56 (4H, t, $J=3.6$ Hz, CH_2CH_2), 2.29 (6H, s, CH_3). Anal. Calcd. for $C_5H_{10}N_2$: C, 61.18; H, 10.27; N, 28.55. Found: C, 61.14; H, 10.37; N, 28.65. Hydrochloride, needles from EtOH, mp 201—202° (lit.¹⁹) mp 203°. Picrate, yellow plates from EtOH, mp 153—154° (lit.²⁰) mp 155°.

3-Morpholinopropionitrile—Liquid, bp 134—135° (15 mmHg), [lit.¹⁶] bp 149° (20 mmHg), n_D^{22} 1.4750. IR ν_{\max}^{liquid} cm^{-1} : 2223 (CN). Anal. Calcd. for $C_7H_{12}ON_2$: C, 59.97; H, 8.63; N, 19.99. Found: C, 59.72; H, 8.38; N, 20.14. Hydrochloride, needles from EtOH, mp 209—210° (lit.¹⁷) mp 210—211°.

3-N-Methylbenzylaminopropionitrile—Liquid, bp 110—112° (2 mmHg) [lit. bp 163—164° (14 mmHg),²¹] bp 112—115° (3 mmHg)²², n_D^{22} 1.5190. IR ν_{\max}^{liquid} cm^{-1} : 2248 (CN). Anal. Calcd. for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.95; H, 8.15; N, 16.10.

N-(2,2,2-Trichloroethyl)piperidine (VIa)—Liquid,⁵ bp 102—103° (16 mmHg), n_D^{18} 1.4950. NMR δ : 3.27 (2H, s, CH_2), 2.73—3.08 (4H, m, $-CH_2NCH_2-$), 1.33—1.93 (6H, m, $(CH_2)_3$). Anal. Calcd. for $C_7H_{12}NCl_3$: C, 38.81; H, 5.58; N, 6.49. Found: C, 38.80; H, 5.80; N, 6.57.

N-(2,2,2-Trichloroethyl)dimethylamine—Liquid,⁵ bp 49—50° (17 mmHg), n_D^{25} 1.4590. NMR δ : 3.32 (2H, s, CH_2), 2.63 (6H, s, CH_3). Anal. Calcd. for $C_4H_8NCl_3$: C, 27.22; H, 4.56; N, 7.93. Found: C, 27.53; H, 4.86; N, 7.71.

N-(2,2,2-Trichloroethyl)morpholine—Plates from ether, mp 56—57° (lit.⁵) mp 62°, bp 73—74° (1 mmHg). NMR δ : 3.65—3.90 (4H, m, $-CH_2OCH_2-$), 3.32 (2H, s, CH_2), 2.80—3.04 (4H, m, $-CH_2NCH_2-$). Anal. Calcd. for $C_6H_{10}ONCl_3$: C, 32.97; H, 4.61; N, 6.41. Found: C, 33.16; H, 4.63; N, 6.67.

N-Methyl-N-(2,2,2-trichloroethyl)benzylamine—Liquid, bp 110—111° (1 mmHg), n_D^{22} 1.5340. NMR δ : 7.20—7.60 (5H, m, aromatic protons), 3.98 (2H, s, $>NCH_2C_6H_5$), 3.53 (2H, s, $>CCH_2N<$), 2.53 (3H, s, CH_3). Anal. Calcd. for $C_{10}H_{12}NCl_3$: C, 47.55; H, 4.78; N, 5.54. Found: C, 48.06; H, 4.87; N, 5.34.

3-Piperidino-2-(piperidinomethyl)propionic Acid (VIIa)—Dihydrochloride, prisms from acetone-EtOH (2:3), mp 160—161°. IR ν_{\max}^{KBr} cm^{-1} : 1724 (CO). Anal. Calcd. for $C_{14}H_{28}O_2N_2Cl_2$: C, 51.37; H, 8.62; N, 8.55. Found: C, 51.18; H, 8.90; N, 7.96. Picrate, yellow needles from EtOH, mp 167—170°.

4-Piperidino-2-butanone (VIIIa)—Liquid, bp 117—118° (30 mmHg) [lit.²³] bp 100—101° (11 mmHg), n_D^{18} 1.4648. IR ν_{\max}^{liquid} cm^{-1} : 1710 (CO). Anal. Calcd. for $C_9H_{17}ON$: C, 69.63; H, 11.03; N, 9.02. Found: C, 69.57; H, 10.97; N, 9.18. Picrate, yellow needles from EtOH, mp 106° (lit.²³) mp 107°. Anal. Calcd. for $C_{15}H_{20}O_8N_4$: C, 46.87; H, 5.24; N, 14.52. Found: C, 47.08; H, 5.29; N, 14.53.

N-(3-Phenyl-2-propynyl)piperidine (IXa)—Liquid, bp 126—127° (2 mmHg) [lit.²⁴] bp 90—95° (0.025 mmHg), n_D^{18} 1.5595. UV λ_{\max}^{EtOH} $m\mu$ (log ϵ): 240 (4.20), 251 (4.16) [lit.²⁴] UV λ_{\max}^{EtOH} $m\mu$ (log ϵ): 239.5 (4.32), 250

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(4.25)]. NMR δ : 7.15—7.60 (5H, m, aromatic protons), 3.46 (2H, s, CH₂), 2.40—2.75 (4H, m, —CH₂NCH₂—), 1.20—1.85 (6H, m, (CH₂)₃). *Anal.* Calcd. for C₁₄H₁₇N: C, 84.37; H, 8.60; N, 7.30. Found: C, 84.24; H, 8.69; N, 6.99. Picrate, yellow needles from EtOH, mp 160—161° (lit.^{3a}) mp 161—162°).

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