pellets. After the addition was complete, the reaction mixture was stirred at reflux for an additional 10 hr. and then cooled to 25°. The mixture was poured very slowly into a beaker containing 420 g. of concd. hydrochloric acid and 600 g. of ice. The resulting solution was extracted three times with 200 ml. of benzene, the combined benzene extracts dried over magnesium sulfate, and the solvent removed. The product was then fractionated.

*Preparation of chlorodithioformates.* Method F. A solution of the alkylthiol (0.5 mole) in 75 ml. of benzene at 10° was added dropwise to a stirred solution of thiophosgene (62.1 g., 0.54 mole) in 75 ml. of benzene maintaining the temperature at 10°. After all of the thiol solution was added, the reaction mixture was stirred 16 hr. in an ice bath. The solvent was removed and the product fractionated.

*Ethyl chlorodithioformate:* b.p., 63° (5.8 mm.), yield, 65%. Lit.,[12] b.p. 74–75° (15 mm.)

*Methyl chlorodithioformate:* b.p., 156–159°, yield, 66%. Lit.,[11] b.p. 50–52° (15 min.)

Method G. The substituted arylthiol (0.8 mole) was added to a stirred solution of 32 g. (0.8 mole) of sodium hydroxide in 32 ml. of water. Thiophosgene (94.9 g., 0.84 mol.) was dissolved in 200 ml. of benzene. The sodium thiophenolate slurry was slowly added to the thiophosgene solution which was stirred and maintained at 10–15°. After the addition was complete, the reaction mixture was allowed to rise to 25° and stirred for 3 hr. The salt was filtered and the benzene filtrate was washed twice with 150 ml. of water and then dried over magnesium sulfate. The solvent was removed and the product fractionated.

*m-Tolyl chlorodithioformate:* b.p. 93° (0.5 mm.), yield, 74%.

*Anal.* Calcd. for $C_8H_7ClS_2$: Cl, 17.5. Found: Cl, 18.4.

*p-Tolyl chlorodithioformate:* b.p. 102–104° (1.0 mm.), yield, 62%.

*Anal.* Calcd. for $C_8H_7ClS_2$: Cl, 17.5. Found: 18.2.

*Acknowledgment.* We wish to thank Dr. B. Katlafsky, Mr. O. E. Kinast, Mr. J. L. O'Sullivan, and Mr. O. S. Kring for their assistance with the numerous infrared analyses and other analytical data.

ST. LOUIS, MO.

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[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

# The Rearrangement and Cyclization of Ethyl *N*-(Methylaminoalkyl)carbanilates and 1,1-Dimethyl-3-methylaminoalkyl-3-phenylureas[1]

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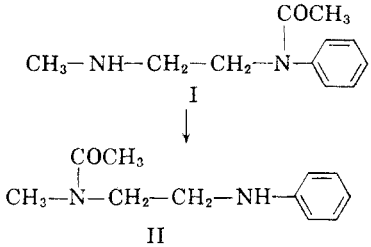
When ethyl *N*-(2-methylaminoethyl)carbanilates and 1,1-dimethyl-3-(2-methylaminoethyl)-3-phenylureas are heated, 1-methyl-3-phenyl-2-imidazolidinones are obtained as the major product. Molecular rearrangement also occurs, and ethyl *N*-methyl-*N*-(2-anilinoethyl)carbamates and 1-anilinoethyl-1,3,3-trimethylureas may be isolated in low yield. Related reactions are discussed.

We have recently described[2] intramolecular *N* → *N'* acyl migrations within a series of *N*-[2-(and 3) *sec*-aminoalkyl]anilides. For example, *N*-(2-methylaminoethyl)acetanilide (I) rearranges slowly on standing at room temperature and rapidly on heating to *N*-(2-anilinoethyl)-*N*-methylacetamide (II).




These observations prompted us to determine if the carbethoxy and dimethylcarbamoyl moieties in a series of related compounds would also migrate.

Ethyl *N*-(methylaminoalkyl)carbanilates and 1,1-dimethyl-3-(methylaminoalkyl)-3-phenylureas were prepared by the catalytic debenzylation of the appropriate *tert*-benzylamines. Samples of these bases were heated and the course of the reaction was followed by frequent determinations of the refractive indices and infrared absorption spectra, and by isolation of the products.

When ethyl *N*-(2-methylaminoethyl)carbanilate (IIIa) was heated for eight hours at 160–165°, both rearrangement and cyclization occurred. Crystalline 1-methyl-3-phenyl-2-imidazolidinone (IV) was isolated in 59% yield and ethyl *N*-(2-anilinoethyl)-*N*-methylcarbamate (Va) was obtained in 25% yield. A second sample heated at 130–135° for two and a half hours resulted in a 39% yield of IV, and examination of the mother liquor indicated that the reaction was incomplete. The index of refraction and infrared spectrum of Va were identical to those of the product prepared by the reaction of ethyl chloroformate with *N*-methyl-*N'*-phenylethylenediamine (VI).

Other carbanilates having a two carbon chain between the nitrogen atoms behaved similarly. When ethyl *m*-methoxy-*N*-(2-methylaminoethyl)-carbanilate was heated for five hours at 200–205°, 1-

(1) Presented in part at the Frederick F. Blicke Symposium of the Division of Medicinal Chemistry at the 138th National Meeting of the American Chemical Society, New York, N. Y., September, 1960.

(2) W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., *J. Org. Chem.*, **26**, 2120 (1961).

TABLE I. ALKYLENEDIAMINE DERIVATIVES[a] $CH_3-NH-\underset{A}{CH}-\underset{B}{CH}-N(R_2)-C_6H_4-R_1$

| A | B | $R_1$ | $R_2$ | Yield, % | $n_D^{25}$[b] | Hydrochloride M.P. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Chlorine, % Calcd. | Chlorine, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | H | H | 75 | | 167–169[c] | $C_9H_{15}ClN_2$ | 57.9 | 58.0 | 8.1 | 8.4 | 19.0 | 19.2 | 15.0 | 15.3 |
| H | H | H | $CON(CH_3)_2$ | 75 | 1.535 | 131–132[d] | $C_{12}H_{20}ClN_3O$ | 55.9 | 55.7 | 7.8 | 7.9 | 13.0 | 14.0 | 16.3 | 16.0 |
| H | H | H | $COOC_2H_5$ | 75 | 1.513 | 187–189[c] | $C_{12}H_{19}ClN_2O_2$ | 55.7 | 55.5 | 7.4 | 7.7 | 13.7 | 13.7 | 10.8 | 10.7 |
| H | H | *m*-$CH_3$ | $CON(CH_3)_2$ | 41 | 1.529 | 108–110[e] | $C_{13}H_{23}ClN_3O_{1.5}$[f] | 55.5 | 56.0 | 8.2 | 8.5 | 12.6 | 12.7 | 15.0 | 15.0 |
| H | H | *m*-$OCH_3$ | $COOC_2H_5$ | 69 | 1.521 | 109–111[e] | $C_{13}H_{21}ClN_2O_3$ | 54.1 | 54.2 | 7.3 | 7.5 | 12.3 | 12.4 | 9.7 | 9.8 |
| H | H | *p*-$OCH_3$ | H | 49 | | 204–206[c] | $C_{10}H_{17}ClN_2O$ | 55.4 | 55.2 | 7.9 | 8.1 | 16.4 | 16.2 | 12.9 | 13.3 |
| H | H | *p*-$OCH_3$ | $CON(CH_3)_2$ | 30 | 1.537 | 130–132[d] | $C_{13}H_{22}ClN_3O_2$ | 54.3 | 54.1 | 7.7 | 7.9 | 12.3 | 12.3 | 14.6 | 14.5 |
| H | $CH_3$ | H | $CON(CH_3)_2$ | 94[g] | | 132–133[d] | $C_{13}H_{22}ClN_3O$ | 57.5 | 57.3 | 8.2 | 8.2 | 13.0 | 13.0 | 15.5 | 15.4 |
| $CH_3$ | H | H | $COOC_2H_5$ | 66 | 1.509 | 119–121[d] | $C_{13}H_{21}ClN_2O_2$ | 57.2 | 57.0 | 7.8 | 7.9 | 13.0 | 12.9 | 10.3 | 10.4 |
| $CH_3$ | H | H | $CON(CH_3)_2$ | 90 | 1.525 | | [h] | | | | | | | | |
| [i] | | H | $COOC_2H_5$ | 81 | 1.509 | 134–136[c] | $C_{13}H_{21}ClN_2O_2$ | 57.2 | 57.0 | 7.8 | 8.0 | 13.0 | 13.0 | 10.3 | 10.4 |
| [j] | | H | $CON(CH_3)_2$ | 58 | 1.532 | 133–134[d] | $C_{13}H_{22}ClN_3O$ | 57.4 | 57.3 | 8.2 | 8.3 | 13.1 | 13.0 | 15.5 | 15.5 |

[a] All compounds were prepared by the catalytic reduction of the corresponding benzyl analog as described in a previous publication.[5] [b] Refractive index was measured on the crude base prepared from the purified hydrochloride. [c] Recrystallized from ethanol. [d] Recrystallized from acetone. [e] Recrystallized from ethyl acetate. [f] Calcd. for hemihydrate: $H_2O$, 3.2. Found: 4.3. [g] Crude yield, m.p. 130–132°. [h] Used without analysis. [i] Ethyl *N*-(3-methylaminopropyl)carbanilate hydrochloride. [j] 1,1-Dimethyl-3-(3-methylaminopropyl)-3-phenylurea hydrochloride.

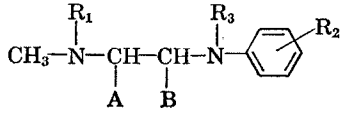
TABLE II. 1-ANILINOALKYL-1-METHYLUREAS $CH_3-N(CONRR)-\underset{A}{CH}-CH_2-NH-C_6H_4-R_1$

| A | R | $R_1$ | Method | Yield, % | B.p. Mm. | $n_D^{25}$ | M.P. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Halogen, % Calcd. | Halogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | H | C | 76 | | | 144–145 | $C_{10}H_{15}N_3O$ | 62.2 | 61.8 | 7.8 | 7.9 | | | 21.8 | 22.1 |
| H | H | *m*-Cl | C | 56 | | | 124–125 | $C_{10}H_{14}ClN_3O$ | 52.8 | 52.4 | 6.2 | 6.5 | 15.6 | 15.8 | 18.5 | 18.5 |
| H | H | *p*-Cl | C | 58 | | | 125–127 | $C_{10}H_{14}ClN_3O$ | 52.8 | 52.9 | 6.2 | 6.5 | 15.6 | 15.9 | 18.5 | 18.4 |
| H | H | *m*-Br | C | 40 | | | 126–127 | $C_{10}H_{14}BrN_3O$ | 44.1 | 44.4 | 5.2 | 5.5 | 29.4 | 29.0 | 15.4 | 15.5 |
| H | H | *p*-$OCH_3$ | C | 68 | | | 157–158 | $C_{11}H_{17}N_3O_2$ | 59.2 | 58.9 | 7.7 | 7.9 | | | 18.8 | 18.9 |
| H | $CH_3$ | H | D | 61[a] | | | 68–70 | $C_{12}H_{19}N_3O$ | 65.1 | 64.7 | 8.6 | 8.6 | | | 19.0 | 18.8 |
| | | | F | <5[b] | | | 127–128[b] | $C_{18}H_{22}N_6O_8$ | 48.0 | 47.6 | 4.9 | 5.2 | | | 18.7 | 18.7 |
| H | $CH_3$ | *m*-Cl | D | 52 | 158–162/0.1 | 1.567 | | $C_{12}H_{18}ClN_3O$ | 56.3 | 56.2 | 7.1 | 7.0 | 13.9 | 14.2 | 16.4 | 16.4 |
| H | $CH_3$ | *p*-Cl | D | 67 | | | 63–64 | $C_{12}H_{18}ClN_3O$ | 56.3 | 56.0 | 7.1 | 7.1 | 13.9 | 14.1 | 16.4 | 16.7 |
| H | $CH_3$ | *m*-Br | D | 50 | 165–167/0.07 | 1.584 | | $C_{12}H_{18}BrN_3O$ | 48.0 | 47.6 | 6.0 | 6.2 | 26.6 | 26.9 | 14.0 | 13.8 |
| H | $CH_3$ | *p*-$OCH_3$ | D | 65 | 160–165/0.08 | 1.555 | | $C_{13}H_{21}N_3O_2$ | 62.1 | 61.8 | 8.4 | 8.6 | | | 16.7 | 17.1 |
| $CH_3$ | $CH_3$ | H | D | 23 | | | 100–102 | $C_{13}H_{21}N_3O$ | 66.4 | 66.2 | 9.0 | 8.9 | | | 17.9 | 17.7 |
| [c] | $CH_3$ | H | F | 60[d] | 144–154/0.5 | 1.551 | | $C_{13}H_{21}N_3O$ | 66.4 | 66.1 | 9.0 | 9.3 | | | 17.9 | 16.9 |
| | | | | | | | 128–130[e] | $C_{19}H_{24}N_6O_8$ | 49.1 | 48.9 | 5.2 | 5.4 | | | 18.1 | 17.9 |

[a] Does not cyclize at 185°. [b] Product of the rearrangement of 1,1-dimethyl-3-(3-methylaminoethyl)-3-phenylurea after 4.5 hr. at 155–160°, isolated as the picrate. [c] 1-(3-Anilinopropyl)-1,3,3-trimethylurea. [d] Prepared by heating 1,1-dimethyl-3-(3-methylaminopropyl)-3-phenylurea at 200° for 3 hr. [e] Picrate.

## TABLE III

### MISCELLANEOUS ALKYLENEDIAMINE DERIVATIVES

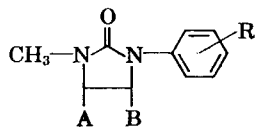


| A | B | $R_1$ | $R_2$ | $R_3$ | Method | Yield, % | B.p./Mm. | $n_D^{25}$ | M.P. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Halogen, % Calcd. | Halogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | $C_7H_7$[a] | H | $CON(CH_3)_2$ | B | 72[b] | | | 150–152[b] | $C_{19}H_{26}ClN_3O$ | 65.6 | 65.6 | 7.5 | 7.7 | 10.2 | 10.4 | 12.1 | 12.0 |
| H | H | $C_7H_7$ | *m*-$CH_3$ | $CON(CH_3)_2$ | B | 56 | 178–184/0.3 | 1.556 | | $C_{20}H_{27}N_3O$ | 73.8 | 73.9 | 8.4 | 8.4 | | | 12.9 | 12.8 |
| H | H | $C_7H_7$ | *p*-$OCH_3$ | $CON(CH_3)_2$ | B | 69 | 182–186/0.3 | 1.561 | 124–125[b,c] | $C_{20}H_{29}Cl$-$N_3O_{2.5}$ | 62.1 | 62.4 | 7.3 | 7.6 | 9.2 | 9.2 | 10.9 | 10.8 |
| H | $CH_3$ | $C_7H_7$ | H | $CON(CH_3)_2$ | B | 74[d] | 160–165/0.4 | 1.551 | 127–129[b] | $C_{20}H_{28}ClN_3O$ | 66.4 | 65.9 | 7.8 | 8.1 | 9.8 | 9.6 | 11.6 | 11.3 |
| $CH_3$ | H | $C_7H_7$ | H | $COOC_2H_5$ | A | 90[e] | | 1.537 | 125–127[f] | $C_{20}H_{27}ClN_2O_2$ | 66.2 | 66.3 | 7.5 | 7.8 | 9.8 | 9.9 | 7.7 | 7.9 |
| $CH_3$ | H | $C_7H_7$ | H | $CON(CH_3)_2$ | B | 78 | 170–174/0.2 | 1.557 | | $C_{20}H_{27}N_3O$ | 73.8 | 73.8 | 8.4 | 8.7 | | | 12.9 | 12.8 |
| [g] | | $C_7H_7$ | H | $CON(CH_3)_2$ | B | 79 | 173–177/0.2 | 1.554 | | $C_{20}H_{27}N_3O$ | 73.8 | 73.5 | 8.4 | 8.5 | | | 12.9 | 12.8 |
| H | H | $COOC_2H_5$ | H | H | D | 77[h] | | 1.535 | 153–155[i] | $C_{18}H_{21}N_5O_9$ | 47.9 | 48.3 | 4.7 | 5.1 | | | 15.5 | 15.3 |
| | | | | | E | 25[j] | | 1.536 | | | | | | | | | | |
| H | H | $COOC_2H_5$ | *m*-$OCH_3$ | H | E | 15[k] | 164–168/0.2 | 1.536 | | $C_{13}H_{20}N_2O_3$ | 61.9 | 61.7 | 8.0 | 8.2 | | | 11.1 | 11.1 |
| $CH_3$ | H | $COOC_2H_5$ | H | H | D | 83[l] | 122–126/0.1 | 1.529 | | $C_{13}H_{20}N_2O_2$ | 66.1 | 65.5 | 8.5 | 8.5 | | | 11.9 | 11.6 |
| | | $COOC_2H_5$ | H | H | E | 20 | 160–165/0.07 | 1.532 | | $C_{13}H_{20}N_2O_2$ | 66.1 | 66.0 | 8.5 | 8.6 | | | 11.9 | 11.6 |

[a] $C_7H_7$ signifies benzyl. [b] Hydrochloride. [c] Hemihydrate. [d] 42-hr. reflux in toluene. Normal procedure gave very low yield. [e] Crude base. [f] 1-(3-Benzylmethylaminopropyl)-1-phenyl-3,3-dimethylurea. [g] Not distilled. Does not cyclize on heating for 5 hr. at 230–255°. [h] Picrate. [i] By heating ethyl *N*-(2-methylaminoethyl)carbanilate for 8 hr. at 160–165°. [j] By heating ethyl *m*-methoxy-*N*-(2-methylaminoethyl)carbanilate for 5 hr. at 200–205°. [k] Infrared spectra indicated that this was also formed when ethyl *N*-(2-methylaminopropyl)-carbanilate was heated. [l] Ethyl *N*-(3-anilinopropyl)-*N*-methylcarbamate, prepared by the rearrangement of ethyl *N*-(3-methylaminopropyl)carbanilate at 220–230° for 6 hr.

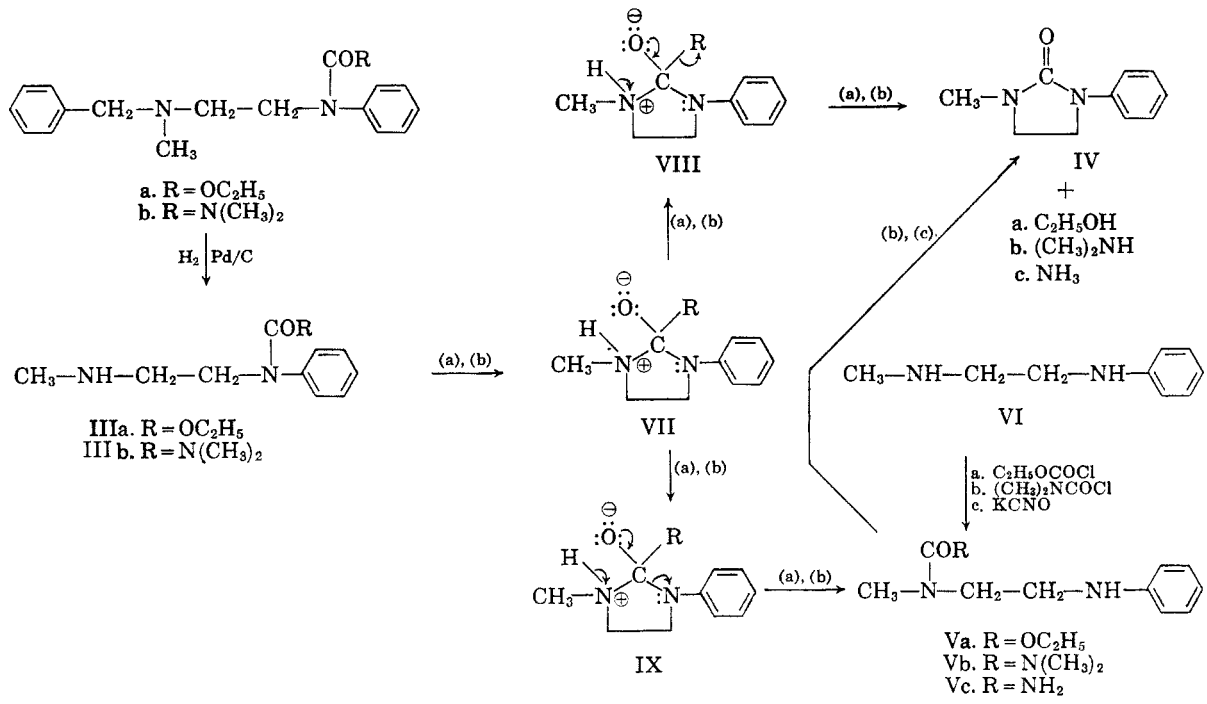
TABLE IV

2-IMIDAZOLIDINONES




| A | B | R | Method[a] | Time,[b] Hours | Temp.[b] | Yield,[c] % | M.P. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Halogen, % Calcd. | Halogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | H | E | 2.5 | 130–135 | 39 | 110–111 | $C_{10}H_{12}N_2O$ | 68.2 | 67.9 | 6.9 | 6.8 | | | 15.9 | 15.9 |
| | | | E | 8 | 160–165 | 59 | 110–111 | | | | | | | | | |
| | | | F | 4.5 | 155–160 | 55 | 110–111 | | | | | | | | | |
| | | | H | 8 | 200–235[d] | 45[e] | 103–106 | | | | | | | | | |
| | | | G | 8.5 | 200–225[d] | 23[e] | 104–108 | | | | | | | | | |
| | | | I | 3 | 77 | 96 | 108–109 | | | | | | | | | |
| $CH_3$ | H | H | F | 3 | 165–210 | 89 | 48–49 | $C_{11}H_{14}N_2O$ | 69.4 | 69.6 | 7.4 | 7.4 | | | 14.7 | 14.5 |
| | | | E | 2 | 135–140 | [f] | 43–44 | | | | | | | | | |
| | | | H | 6 | 215–230 | 26 | 44–45 | | | | | | | | | |
| H | $CH_3$ | H | I | 3 | 77 | 93–100[g] | [h] | $C_{11}H_{14}N_2O$ | 69.4 | 68.9 | 7.4 | 7.4 | | | 14.7 | 14.8 |
| H | H | *m*-Cl | G | 8 | 225–235 | 48 | 93–95 | $C_{10}H_{11}ClN_2O$ | 57.0 | 56.7 | 5.3 | 5.0 | 16.8 | 16.8 | 13.3 | 13.2 |
| H | H | *p*-Cl | G | 8 | 230–235 | 35 | 148–150 | $C_{10}H_{11}ClN_2O$ | 57.0 | 57.4 | 5.3 | 5.5 | 16.8 | 16.9 | 13.3 | 13.5 |
| H | H | *m*-$OCH_3$ | E | 5 | 200–205 | 39 | 97–99 | $C_{11}H_{14}N_2O_2$ | 64.0 | 64.1 | 6.8 | 7.2 | | | 13.6 | 13.3 |
| H | H | *p*-$OCH_3$ | F | 7 | 200–225 | 47 | 100–110 | $C_{11}H_{14}N_2O_2$ | 64.0 | 64.0 | 6.8 | 7.2 | | | 13.6 | 13.7 |
| H | H | *m*-$CH_3$ | F | 3 | 200–205 | 54 | 81–83 | $C_{11}H_{14}N_2O$ | 69.4 | 69.8 | 7.4 | 7.6 | | | 14.7 | 14.6 |
| H | H | *m*-Br | G | 8 | 225–235 | 55 | 113–115 | $C_{10}H_{11}BrN_2O$ | 47.1 | 46.8 | 4.3 | 4.3 | 31.3 | 31.2 | 11.0 | 11.1 |

[a] Refer to Experimental. [b] Time and temperature of heating period before workup. [c] Yield of recrystallized product unless otherwise noted. [d] Starting material was relatively stable at 180–185°. [e] Infrared spectra suggested that the yield was nearly quantitative. However, the reaction mixture was very dark and difficult to purify. [f] Yield not determined. Infrared spectra indicated complete conversion to cyclic and rearranged products. [g] As determined by Infrared spectra and precipitated dimethylamine hydrochloride. [h] B.p. 134–140°/0.2 mm.




(*m*-methoxyphenyl)-3-methyl-2-imidazolidinone and ethyl *N*-(2-*m*-anisidinoethyl)-*N*-methylcarbamate were isolated in purified yields of 39% and 15%, respectively. Infrared absorption spectra indicated that ethyl *N*-(2-methylaminopropyl)carbanilate reacted similarly and completely in less than two hours at 135–140°.

Ethyl *N*-(3-methylaminopropyl)carbanilate, which has a three carbon chain between the nitrogen atoms, was much more stable and little change occurred at temperatures below 200°. When this compound was heated for six hours at 220–230°, a reaction mixture was obtained which was difficult to purify by distillation, although a 20% yield of ethyl *N*-(3-anilinopropyl)-*N*-methylcarbamate was obtained. A cyclic product was not isolated in this experiment.

The rearranged compounds (Va and homologues) are stable and do not cyclize when heated at 200–230°. This may be considered as evidence that cyclization occurs before rather than after rearrangement.

When 1,1-dimethyl-3-(2-methylaminoethyl)-3-phenylurea (IIIb) was heated for four and a half hours at 155–160°, 1-methyl-3-phenyl-2-imidazolidinone (IV) was isolated in 55% yield. An infrared absorption spectrum on the mother liquor indicated that the rearranged product, 1-(2-anilinoethyl)-1,3,3-trimethylurea (Vb) was also present, but in very low yield. This compound was isolated as the picrate and was shown by mixture melting point and infrared spectra to be identical to the picrate obtained from the product (Vb) of the reaction of dimethylcarbamoyl chloride with *N*-methyl-*N'*-phenylethylenediamine (VI). Vb was less stable than the carbethoxy analog (Va) and cyclized to IV on heating above 200°.

1,1-Dimethyl-3-(3-methylaminopropyl)-3-phenylurea, which has a three carbon chain between the nitrogen atoms, required temperatures above 200° for rapid rearrangement. 1-(3-Anilinopropyl)-1,3,3-trimethylurea was isolated in 60% yield after heating the above compound at 200° for three hours.

1-(2-Benzylmethylamino-1-methylethyl)-3,3-dimethyl-1-phenylurea hydrochloride was catalytically debenzylated and an attempt was made to recrystallize the crude product from ethyl acetate. Instead of the expected product, dimethylamine hydrochloride, insoluble in ethyl acetate, was obtained in almost quantitative yield. Workup of the mother liquor resulted in an excellent yield of 1,4-dimethyl-3-phenyl-2-imidazolidinone. A further study of this reaction showed that the desired 1,1-dimethyl-3-(1-methyl-2-methylaminoethyl)-3-phenylurea hydrochloride could be obtained in nearly quantitative yield if heat was avoided throughout the workup. This product was, however, unstable to heat and completely cyclized in less than one hour of heating under reflux in ethyl acetate. Analogous compounds with a two carbon chain between the nitrogen atoms could be similarly cyclized. On the other hand, 1,1-dimethyl-3-(3-methylaminopropyl)-3-phenylurea hydrochloride was recovered unchanged after eighteen hours at reflux temperature.

This procedure appears satisfactory, therefore, for the preparation of 2-imidazolidinones, but is of no value, at the temperature of refluxing ethyl acetate, for the cyclization of compounds having a three carbon chain between the nitrogens. This method

avoids the dark colors often found in compounds prepared at high temperatures, and the products are essentially pure and obtained in excellent yield.

Attempts were made to rearrange *N*-(2-methylaminopropyl)propionanilide hydrochloride[2] and *N*-(2-methylaminopropyl)benzanilide hydrochloride[2] and to cyclize ethyl *N*-(2-methylaminoethyl)carbanilate hydrochloride by heating at reflux in ethyl acetate for eighteen hours. Starting material was recovered in each case.

1-Methyl-3-phenyl-2-imidazolidinone (IV) was also prepared by heating 1-(2-anilinoethyl)-1-methylurea (Vc) for eight hours at 200–235°. The infrared absorption spectrum indicated that IV was obtained in good yield, but purification was difficult because of the dark color of the reaction mixture.

Additional evidence for the structure of the rearranged and cyclic compounds was afforded by examination of the infrared absorption spectra of these compounds. The N—H stretching band in the 3 $\mu$ region was much more intense in the rearranged compounds, as would be expected in a change from an aliphatic to an aromatic secondary amine. The C—H stretching band at 3.58–3.59 $\mu$, a characteristic of secondary and tertiary alkylamines,[3] was absent in both the rearranged and cyclic compounds. The carbonyl band at 5.87–5.88 $\mu$ in the ethyl *N*-(methylaminoalkyl)carbanilates and at 6.05–6.06 $\mu$ in the 1,1-dimethyl-3-(methylaminoalkyl)-3-phenylureas was found at slightly higher wave length in the rearranged compounds and at 5.90–5.92 $\mu$ in the 2-imidazolidinones.

These reactions appear to take place through a cyclic transition state (VII) similar to that proposed for intramolecular acyl migrations.[2,4] The unshared pair of electrons of the methylamino moiety takes part in a nucleophilic attack on the carbonyl carbon leading to VII, which cleaves either externally (VIII) to give a cyclic product (IV) or internally (IX) to give the rearranged product (V). The reaction in which Vb and Vc are converted to IV most likely occurs through a similar cyclic transition state.

Other compounds, analogous to those described above, were prepared by these procedures and submitted for pharmacological testing. These compounds are described and characterized in the tables.

## EXPERIMENTAL

Intermediates required for this research which are not described in this paper have been reported in our previous publications.[2,5] The compounds recorded in Table I were prepared by the catalytic debenzylation of the tertiary benzylamine analog.[5] General procedures are given below for the preparation of the other compounds. Critical variations in the procedure are noted in the table footnotes.

(3) W. B. Wright, Jr., *J. Org. Chem.*, 24, 1362 (1959).
(4) C. J. M. Stirling, *J. Chem. Soc.*, 4531 (1958).
(5) W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., *J. Org. Chem.*, 26, 485 (1961).

Analyses, yields, and physical properties of the compounds prepared are recorded in the tables. Temperatures are uncorrected.

*Ethyl N-(2-benzylmethylaminopropyl)carbanilate hydrochloride* Method A. A solution of 11.4 g. (0.105 mole) of ethyl chloroformate in 25 ml. of benzene was added dropwise with stirring to a cooled solution of 25.4 g. (0.10 mole) of $N^2$-benzyl-$N^2$-methyl-$N^1$-phenyl-1,2-propanediamine in 75 ml. of benzene. The reaction mixture was heated under reflux for five hours, cooled and then stirred with 100 ml. of 2.5*N* hydrochloric acid. The benzene layer was separated and the aqueous layer was extracted with ether. The aqueous phase was cooled and made alkaline by the addition of 5*N* sodium hydroxide. The organic base was extracted into ether. Concentration of this ether layer afforded 29.5 g (90%), $n_D^{25}$ 1.537, of ethyl *N*-(2-benzylmethylaminopropyl)carbanilate. When the base was treated with ethanolic hydrogen chloride and the insoluble product was recrystallized from acetone, the analytically pure hydrochloride, m.p. 125–127°, was obtained.

*1-(Benzylmethylaminoalkyl)-3,3-dimethyl-1-phenylureas.* Method B. A solution of 0.2 mole of dimethylcarbamoyl chloride in benzene was added dropwise with cooling to a solution of 0.1 mole of the *N*-benzyl-*N*-methyl-*N'*-phenylalkylenediamine and 0.2 mole of triethylamine in 100 ml. of benzene. The mixture was heated under reflux for 3–4 hr., cooled and filtered to remove the insoluble triethylamine hydrochloride. The benzene solution was stirred for 1 hr. with 0.3 mole of 2*N* hydrochloric acid and the layers were then separated. The aqueous layer was treated with 80 ml. of 5*N* sodium hydroxide and the organic base was extracted into ether. The ether layer was dried over magnesium sulfate and distilled. The hydrochlorides were prepared by treating an ether solution of the base with ethanolic hydrogen chloride. Recrystallization was from acetone or ethyl acetate.

*1-(2-Anilinoethyl)-1-methylureas.* Method C. A mixture of 0.02 mole of the *N*-methyl-*N'*-phenylalkylenediamine hydrochloride, 0.02 mole of potassium cyanate, and 20 ml. of water was stirred at room temperature for 3 hr. and then heated under reflux for 3 hr. The product was extracted into chloroform. The chloroform layer was concentrated to remove the solvent and the residue was recrystallized from ethyl acetate.

*Ethyl N-anilinoalkyl-N-methylcarbamates and 1-anilinoalkyl-1,3,3-trimethylureas.* Method D. A solution of 0.036 mole of ethyl chloroformate or dimethylcarbamoyl chloride in 15 ml. of ether was added dropwise to a rapidly stirred mixture of 0.04 mole of the *N*-methyl-*N'*-phenylalkylenediamine hydrochloride, 17.6 ml. of 5*N* sodium hydroxide, 20 ml. of water, and 40 ml. of ether. The reaction temperature was kept below 10° during this addition, and stirring was then continued for 1–2 hr. while the reaction mixture was allowed to come to room temperature. The ether layer was separated and washed with 5 ml. of water, 8 ml. of 1*N* hydrochloric acid, and finally with 10 ml. of water. The ether layer was dried over magnesium sulfate and concentrated. Crystalline products were recrystallized from benzene by addition of hexane. Noncrystalline products were distilled.

*Preparation of the 2-imidazolidinones.* Method E–H. The compound to be cyclized was placed in a distilling flask and immersed in a Woods metal bath regulated to a predetermined temperature. The course of the reaction was followed by removing samples at intervals and measuring changes in the index of refraction and infrared absorption spectrum. If necessary, the temperature was raised until the reaction proceeded at a satisfactory rate. When the reaction appeared to be over, the reaction mixture was cooled and triturated with petroleum ether or hexane. The crystalline 2-imidazolidinone was filtered off and further purified by recrystallization from benzene by addition of hexane.

In some reactions the mother liquors from the filtration of the crude product were concentrated to remove solvent and were examined by infrared absorption spectra to determine if rearranged products, ethyl *N*-anilinoalkyl-*N*-methylcar-

bamates or 1-anilinoalkyl-1,3,3-trimethylureas, were present. These were then characterized by distillation or preparation of the picrate salt.

For the sake of clarity in reading Table IV, the following assignments have been made based on type of compound cyclized:

Method E. Ethyl *N*-(Methylaminoalkyl)carbanilates.

Method F. 1-(Methylaminoalkyl)-3,3-dimethyl-1-phenylureas.

Method G. 1-(2-Anilinoethyl)-1-methylureas.

Method H. 1-(Anilinoalkyl)-1,3,3-trimethylureas.

*Cyclization of 1,1 - dimethyl - 3 - (1 - methyl - 2 - methylaminoethyl)-3-phenylurea hydrochloride.* Method I. A mixture of 1.0 g. of 1,1-dimethyl-3-(1-methyl-2-methylaminoethyl)-3-phenylurea hydrochloride and 50 ml. of ethyl acetate was heated under reflux for 3 hr., cooled, and filtered. The insoluble material was dimethylamine hydrochloride, 278 mg. (93%). The mother liquor was concentrated to remove volatile material. The residue was an oil, 700 mg. (100%), $n_D^{25}$ 1.565, which gave an infrared absorption spectrum essentially identical to that of analytically pure, distilled 1,4-dimethyl-3-phenyl-2-imidazolidinone. Other experiments indicated that cyclization was complete in 50–60 min.

1,1 - Dimethyl - 3 - (2-methylaminoethyl)-3-phenylurea hydrochloride was cyclized as described above. The cyclization was complete in 3 hr. but incomplete in 2 hr. 1,1-Dimethyl-3-(3-methylaminopropyl)-3-phenylurea hydrochloride and ethyl *N*-(2-methylaminoethyl)carbanilate hydrochloride were recovered (91–97%) unchanged after 18 hr. under reflux in ethyl acetate.

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[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

# Debenzylation of Tertiary Benzylamines with Ethyl Chloroformate[1]

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When ethyl *N*-(2-benzylmethylaminoethyl)carbanilate (I) (which was desired for testing in our analgesic program[2]) was prepared by the reaction of *N*-benzyl-*N*-methyl-*N'*-phenylethylenediamine (II) with excess ethyl chloroformate under reflux in benzene, a crude product was obtained which distilled over a wide temperature range. Purification by an acid/ether extraction procedure afforded two products. Examination of the infrared absorption spectra showed that both of these compounds had the expected carbonyl band at 5.87 $\mu$, but only one (I) had a band in the 3.6 $\mu$ region (3.58 $\mu$). This latter band is a characteristic of secondary and tertiary alkylamines[3] and is generally strong with dialkylbenzylamines. The conclusion that debenzylation had occurred and diethyl *N*-[2-(*N*-carboxy-*N*-methylamino)ethyl]carbanilate (IIIa) had been formed was confirmed by microanalysis. IIIa was also prepared by the reaction of I with ethyl chloroformate. Additional evidence for this structure was obtained by the hydrobromic acid-acetic acid hydrolysis of the analogous diethyl *N*-[2-(*N*-carboxy-*N*-methylamino)ethyl]-*m*-chlorocarbanilate (IIIb) to *N*-(*m*-chlorophenyl)-*N'*-methylethylenediamine (IV) identical to the compound prepared by the reaction of *m*-chloroaniline with 2-chloro-*N*-methylethylamine hydrochloride.

Other compounds, analogous to those described above, have been prepared by these procedures and are characterized in Tables I and II.

The cleavage of tertiary amines by chloroformates has been described in the literature as a means of preparing carbamates,[4] for the opening of tetrahydroisoquinoline ring systems,[5] and in the preparation of derivatives of des-*N*-methylerythromycin.[6] We were unaware of any reference to chloroformates as specific reagents for the debenzylation of tertiary benzylamines, and two additional experiments designed to further study the scope of this reaction, therefore, seemed worthwhile.

Dimethylbenzylamine and 1-benzylpiperidine were each heated under reflux in benzene with 1.5 moles of ethyl chloroformate. After removal of the solvent, the crude reaction mixtures were found to have infrared curves and refractive indices almost identical to those of synthetic mixtures of equal molar quantities of benzyl chloride and the expected carbamate. Gas phase chromatography gave similar results. These data indicated that the benzyl group was preferentially removed as benzyl chloride and that very little cleavage of the methyl groups or the piperidine ring occurred under these conditions.

The debenzylation of tertiary benzylamines can be explained by the intermediate formation of a quaternary urethane salt (V) followed by the loss of the benzyl carbonium ion. Similar mechanisms have been postulated for the cleavage of tertiary amines by carbamates,[4] acids, acid chlorides, acid

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(2) W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., *J. Org. Chem.*, 26, 485 (1961).

(3) W. B. Wright, Jr., *J. Org. Chem.*, 24, 1362 (1959).

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