In a more recent experiment by Dr. F. Gadient, hydrogenation of 243 mg. of bromoöxazine XI in 15 ml. of methanol over palladium on charcoal at atmospheric pressure gave rise to 117 mg. (60.5%) of oxazine XII, m.p. 102–103°, m.p. of picrate 178–179°, and 65 mg. of N-cyclohexylbenzamide, m.p. 150–151°, mixed m.p. with an authentic specimen, 150–151°.

Reaction of Bromoöxazine Hydrochloride with Zinc.—The bromoöxazine XI, 0.50 g., was dissolved in 10 ml. of ether, and an excess of ethereal hydrogen chloride solution was added dropwise. The ether was decanted from the precipitate and 10 ml. of glacial acetic acid and 1.0 g. of zinc dust were added. The mixture was shaken until the white solid dissolved, and then it was allowed to stand at room temperature for 1.5 hours. The zinc was removed by filtration and the filtrate was evaporated *in vacuo*. Water was added to the residue which readily crystallized, yielding 0.25 g. (70%) of 3-benzamidocyclohexene (I), m.p. 91–92°, mixed m.p. with authentic I 99–101°, m.p. 94–95° after one recrystallization.

Attempted Hydrolysis of Bromoöxazine XI.—To 0.25 g. of bromoöxazine was added 2 ml. of water and 4 ml. of 60% perchloric acid. The solution was boiled 15 minutes and allowed to stand overnight. The solution was heated on the steam-bath for 2 hours and neutralized with excess sodium bicarbonate solution, yielding 0.20 g. of a solid, m.p. 90–110°. This material was dissolved in 5 ml. of absolute ethanol and to it was added a solution of 0.1 g. of potassium hydroxide in 6 ml. of absolute ethanol. The alcohol was removed *in vacuo* and ether was added to the residue. The ethereal solution was filtered, and the filtrate was divided into two equal parts. To one part was added ethereal picric acid solution, yielding 0.10 g. of bromoöxazine XI picrate, m.p. and mixed m.p. 204–205°. The other portion of the ether filtrate was evaporated to yield 0.09 g. of material, m.p. 118–119°, m.p. 120–121° when mixed with the starting material. The recovery of starting material was 56%.

To 0.61 g. of bromoöxazine XI was added 6 ml. of 60% perchloric acid and 3 ml. of water. The solution was sealed in a bomb tube and was heated at 160–170° for 1.25 hours. The tube was cooled, opened, and the contents filtered from a small amount of tar. To the nearly colorless filtrate was added excess sodium bicarbonate solution, 0.21 g. (34%) of a white solid precipitating, m.p. and mixed m.p. with starting material, 118–120°.

Acknowledgment.—The authors are grateful to Dr. Fulvio Gadient for very recent experiments which clarified the nature of the solvolysis product from dibromides A and B.

LOS ANGELES 24, CALIF.

[CONTRIBUTION FROM ABBOTT LABORATORIES]

The Amidomethylation Reaction. Preparation of *m*- and *p*-Aminomethylphenylacetic Acids

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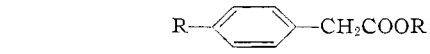
Condensation of phenylacetic acid with N-hydroxymethylphthalimide in concentrated sulfuric acid gives a mixture of *m*-(X) and *p*-(I)-phthalimidomethylphenylacetic acids, the latter in preponderant quantity. The *p*-isomer I can also be isolated from the zinc chloride-catalyzed reaction of phenylacetic acid with N-bromomethylphthalimide. The reaction of phenylacetic acid with N-hydroxymethylchloroacetamide in concentrated sulfuric acid likewise gives *p*-chloroacetylaminomethylphenylacetic acid (II) in 35–40% yields. *p*-Aminomethylphenylacetic acid hydrochloride (III) and the corresponding *m*-isomer XI are obtained readily from these condensation products. Their structures have been established by conversion to *p*-tolyl(V)- and *m*-tolyl(XII)-acetic acids, respectively.

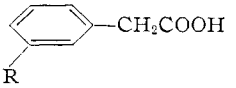
In connection with the study of basically substituted phenylacetic acids for use as penicillin precursors, the aminomethyl derivatives seemed to offer appropriate possibilities. However, *o*-aminomethylphenylacetic acid, prepared by a circuitous route,[1] appeared to be the sole isomer of this series described in the literature.

A direct aromatic substitution reaction by certain N-hydroxymethylamides, originally reported by Tscherniac[2] and later extended by Einhorn, seemed to offer the most direct route to the desired compounds. Thus Einhorn and co-workers[3] found that both benzoic and cinnamic acids, with N-hydroxymethylchloroacetamide in concentrated sulfuric acid, yielded the ring substituted chloroacetylaminomethyl derivatives, the former giving only the *m*-isomer, but the latter, both *m*- and *p*-substituted cinnamic acids. This paper reports the extension of this amidomethylation reaction to the direct substitution of phenylacetic acid.

Treatment of phenylacetic acid with N-hydroxymethylphthalimide in concentrated sulfuric acid led to a mixture of the *m*-(X) and *p*-(I) phthalimidomethylphenylacetic acids with the latter predominating. Removal of the phthaloyl groups by means of hydrazine and hydrochloric acid gave, respectively, the hydrochlorides of *m*-aminomethylphenylacetic acid (XI), m.p. 193–195°, and *p*-aminomethylphenylacetic acid (III), m.p. 232–233°. The third isomer, *o*-aminomethylphenylacetic acid hydrochloride, reportedly[1] melts at 154°. Orientations of the two isomers were established by catalytic reductive methylation ($CH_2O + H_2 + Pd$) to the corresponding dimethylamino derivatives



I, R = *o*-$C_6H_4(CO)_2NCH_2$–, R′ = H (phthalimidomethyl)
II, R = $ClCH_2CONHCH_2$–, R′ = H
III, R = $-CH_2NH_2 \cdot HCl$, R′ = H
IV, R = $-CH_2N(CH_3)_2 \cdot HCl$, R′ = H
V, R = CH_3, R′ = H
VI, R = $ClCH_2CONHCH_2$–, R′ = C_2H_5
VII, R = $ClCH_2CONHCH_2$–, R′ = CH
VIII, R = $(C_2H_5)_2NCH_2CONHCH_2$–, R′ = C_2H_5
IX, R = $-CH_2NH_2 \cdot HCl$, R′ = CH_3



X, R = *o*-$C_6H_4(CO)_2NCH_2$–, (phthalimidomethyl)
XI, R = $-CH_2NH_2 \cdot HCl$
XII, R = CH_3

(1) J. v. Braun and H. Reich, *Ann.*, **445**, 243 (1925).

(2) J. Tscherniac, German Patent 134,979 (1902); P. Friedlaender, *Fortschr. Teerfarb.*, **6**, 143 (1900–1902).

(3) (a) A. Einhorn and T. Mauermayer, *Ann.*, **343**, 295 (1905). (b) A. Einhorn and M. Göttler, *Ber.*, **42**, 4837 (1909).

which, without isolation, were catalytically hydrogenolyzed to *m*-(XII) and *p*-(V)-tolylacetic acids. Comparison with authentic specimens of XII and V confirmed their identity.

Heating phenylacetic acid with N-bromomethylphthalimide in the presence of anhydrous zinc chloride, according to the method of Herzberg and Lange,[4] likewise led to a mixture from which the *p*-isomer I could be isolated in preponderant amounts. There was also isolated only a trace of another isomer of nearly the same melting point as that of X, but yet which gave a large depression of melting point when mixed with X. It was not investigated further.

When phenylacetic acid was treated with N-hydroxymethylchloroacetamide in concentrated sulfuric acid solution, *p*-chloroacetylaminomethylphenylacetic acid (II) was formed and readily isolated in 35–40% yields. No other isomer could be obtained from this reaction. Hydrolysis of II with concentrated hydrochloric acid gave III in nearly quantitative yields. Indeed, III could be obtained in 32% over-all yield by direct hydrolysis of the crude product obtained from the sulfuric acid condensation reaction. Although many other condensing agents and reaction conditions were tried in efforts to improve the yield, anhydrous hydrofluoric acid was the only other agent used which approached concentrated sulfuric acid in efficiency.

Further synthetic work reported in the Experimental section includes methylation of III to IV, preparation of the methyl (VII) and ethyl (VI) esters of II and replacement of the chlorine atom in VI by diethylamine to give VIII. Direct methanol esterification of III gave a good yield of the amino ester hydrochloride IX, the free base of which polymerized readily on heating.

None of the compounds (I, II, III, IV, X and XI) tested as penicillin precursors seemed to serve readily in that capacity. Compound VIII exhibited local anesthetic activity. Both its potency and toxicity were one fourth to one third that of procaine and 1% solutions produced no irritation on injection.

Discussion.—These results, taken together with previous work,[2–4] give evidence that these acid-catalyzed substitution reactions of methylol- and halomethylamides occur with little selectivity. It follows,[5] therefore, that the reaction involves a relatively low free energy of activation and a high degree of carbonium ion contribution to the transition state. In addition, it might be expected that the incipient carbonium ion, $-\overset{\|}{\underset{O}{C}}-\underset{H}{N}-CH_2^{\oplus}$, could function as a polarizer of a nucleophilic center more effectively than the simple alkyl carbonium ion, or even the acyl carbonium ion of the Friedel–Crafts reaction.

Acknowledgments.—Mr. E. F. Shelberg and the staff of the Abbott Microanalytical Department carried out the elementary analysis. Mr. Morris Freifelder and Mr. George Stone performed the hydrogenations and the autoclave reaction.

Experimental

All melting points are uncorrected.

Condensation of Phenylacetic Acid with N-Bromomethylphthalimide. Method A.—A mixture of 13.6 g. (0.1 mole) of phenylacetic acid, 12 g. (0.05 mole) of N-bromomethylphthalimide (Aldrich Chemical Co., Inc., Milwaukee, Wis.) and 1 g. of powdered, anhydrous zinc chloride was heated at 110–120° for 15 minutes while stirring manually with a thermometer. After adding 0.5 g. more zinc chloride, heating was continued for another 45 minutes after which evolution of hydrogen bromide practically ceased. The hot mixture was then poured into ice-water in a separatory funnel, benzene was added and after shaking, the two layers were filtered. Three recrystallizations from 95% ethanol of the insoluble material (5.3 g.) thus obtained gave 1.5 g. of *p*-(N-phthalimidomethyl)-phenylacetic acid (I), m.p. 196–198°.

Anal. Calcd. for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74; O, 21.67. Found: C, 69.20; H, 4.41; N, 4.72; O, 21.47.

The benzene extract was concentrated to a volume of about 150 ml. and then diluted with hexane (Skellysolve B) to a volume of about 500 ml. The precipitated oil (8.3 g.) slowly solidified, m.p. 120–140°. It was dissolved in 200 ml. of a saturated solution of sodium bicarbonate, clarified with charcoal and reprecipitated with concentrated hydrochloric acid. The 3.6 g. of solid thus obtained was recrystallized twice from 95% ethanol (5 ml.) and three times from benzene (60 ml.) to give 0.3 g. of shiny white needles, m.p. 171–172°, probably *o*-(N-phthalimidomethyl)-phenylacetic acid.

Anal. Calcd. for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74. Found: C, 69.23; H, 4.46; N, 4.62.

Condensation of Phenylacetic Acid with N-Hydroxymethylphthalimide. Method B.—A well-pulverized mixture of 102 g. (0.75 mole) of phenylacetic acid and 88.5 g. (0.5 mole) of N-hydroxymethylphthalimide[6] was added in portions over a period of 30 minutes to 180 ml. of concentrated sulfuric acid stirred in an ice-bath. The temperature of the reaction was not allowed to rise above 20° during the addition. After stirring at room temperature overnight, the solution was allowed to stand for one week. It was then poured onto ice and stirred vigorously for several hours. After standing in water overnight, the solid (142 g., m.p. 120–140°) was removed, dried and allowed to stand in ether overnight. Filtration and drying gave 126 g., m.p. 125–145°. After rather laborious fractional crystallization of this crude product using 95% ethanol and benzene separately as solvents, 13.6 g. (9.2%) of *p*-(N-phthalimidomethyl)-phenylacetic acid (I), m.p. 195–197°, was obtained together with 9.0 g. (6%) of *m*-(N-phthalimidomethyl)-phenylacetic acid (X), m.p. 170–172°. When mixed with a sample of the isomer, m.p. 171–172°, obtained by method A, the melting point was depressed to 145–155°.

Anal. Calcd. for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44. Found: C, 69.25; H, 4.55.

Condensation of Phenylacetic Acid with N-Hydroxymethylchloroacetamide. Method C.—A well-pulverized mixture of 102 g. (0.75 mole) of phenylacetic acid and 62 g. (0.5 mole) of N-hydroxymethylchloroacetamide, m.p. 100–102°,[7] was treated according to the conditions specified in method B. The ether-insoluble fraction (65 g., m.p. 115–140°) was recrystallized once from 100 ml. of 95% ethanol to give 42 g. (35%) of *p*-chloroacetylaminomethylphenylacetic acid (II), m.p. 147–151°. One more recrystallization gave analytically pure material, m.p. 152–153°.

Anal. Calcd. for $C_{11}H_{12}ClNO_3$: C, 54.66; H, 5.01; N, 5.80. Found: C, 54.77; H, 5.09; N, 5.72.

Numerous attempts were made to increase the yield by varying time, temperature and environmental conditions, but optimal yields always varied between 35 and 40%. Dilution of the sulfuric acid with ether led to no improvement of yield. Milder conditions including use of catalytic amounts of anhydrous zinc chloride in phosphorus oxychloride, or catalytic proportions of sulfuric or *p*-toluenesulfonic

(4) W. Herzberg and H. Lange, German Patent 442,774 (1927); P. Friedlaender, *Fortschr. Teerfarb.*, **15**, 1700 (1925–1927).

(5) K. L. Nelson, *J. Org. Chem.*, **21**, 145 (1956).

(6) E. Sakellarios, THIS JOURNAL, **70**, 2822 (1948).

(7) A. Einhorn and T. Mauermayer, *Ann.*, **343**, 282 (1905).

acids in benzene or ethylene dichloride with azeotropic removal of water formed, led only to self-condensation of the hydroxymethylamide to give $(ClCH_2CONH)_2CH_2$, m.p. 176–178°, as the only identifiable product other than starting material. However, anhydrous hydrofluoric acid brought about the desired condensation in yields comparable to those obtained by method C.

p-Aminomethylphenylacetic Acid Hydrochloride (III). Method D. From the p-Phthaloyl Derivative I.—A solution of 13.4 g. (0.0454 mole) of *p*-(N-phthalimidomethyl)-phenylacetic acid (I) and 1.52 ml. (0.0454 mole) of 95% hydrazine in 150 ml. of 95% ethanol was refluxed for 6 hours. The insoluble precipitate was removed by filtration, the filtrate was concentrated to dryness and the combined residue and filter cake were warmed several minutes at 55° with a solution of 20 ml. of concentrated hydrochloric acid in 100 ml. of water. After cooling to room temperature, the insoluble phthalhydrazide (7.8 g.) was removed by filtration, the filtrate was concentrated to dryness and the residue was washed with ether and dried to give 8.4 g. (92%) of *p*-aminomethylphenylacetic acid hydrochloride (III), m.p. 230°. Recrystallization from glacial acetic acid gave product of m.p. 232–233° dec. identical with the material obtained by method E.

Method E. From p-Chloroacetylaminomethylphenylacetic Acid (II).—A mixture of 10 g. of II and 50 ml. of concentrated hydrochloric acid was refluxed for 90 minutes. After refrigerating overnight, the crystallized product was removed by filtration and washed with successive portions of dry ethanol and ether. The *p*-aminomethylphenylacetic acid hydrochloride (III) (7.80 g., 93%) thus obtained melted with decomposition at 232–233° and was analytically pure.

Anal. Calcd. for $C_9H_{12}ClNO_2$: C, 53.60; H, 6.00. Found: C, 53.77; H, 6.21.

This product also could be obtained readily without isolation of the intermediate chloroamide II. In one run, 116 g. of crude solid obtained from method C, which had been washed with water, but not with ether, was hydrolyzed with 500 ml. of concentrated hydrochloric acid according to method E. The hot reaction mixture was filtered through a layer of charcoal. The pure amino acid hydrochloride III (32 g., 32%, based on $ClCH_2CONHCH_2OH$), m.p. 232–234° dec., crystallized from the cooled filtrate.

***m*-Aminomethylphenylacetic Acid Hydrochloride (XI) from the *m*-Phthalimido Derivative X.**—The 9.0 g. of *m*-(N-phthalimidomethyl)-phenylacetic acid (X), m.p. 170–172°, obtained by method B was treated with 1.05 ml. of 95% hydrazine according to the procedure specified in method D. The *m*-amino acid hydrochloride XI was obtained in 76% yield, m.p. 193–195°.

Anal. Calcd. for $C_9H_{12}ClNO_2$: C, 53.60; H, 6.00. Found: C, 53.27; H, 6.05.

p-Dimethylaminomethylphenylacetic Acid Hydrochloride (IV).—A mixture of 4.04 g. (0.02 mole) of III, m.p. 232–233°, 1.36 g. (0.02 mole) of sodium formate, 10 ml. of 40% aqueous formaldehyde and 15 ml. of formic acid was refluxed for five hours. After standing overnight, the solution was concentrated *in vacuo* to a colorless sirup and treated with 5 ml. of concentrated hydrochloric acid. After refrigerating overnight, the precipitated sodium chloride (1.1 g.) was removed by filtration and the filtrate was concentrated to dryness *in vacuo*. The solid residue was recrystallized from 15 ml. of glacial acetic acid to give 3.5 g. (76%) of IV, m.p. 219–221°.

Anal. Calcd. for $C_{11}H_{16}ClNO_2$: C, 57.51; H, 7.02. Found: C, 57.32; H, 7.05.

Proof of Structure of p-Aminomethylphenylacetic Acid (III).—A mixture of 2.02 g. (0.01 mole) of the amino acid hydrochloride III, m.p. 232–233°, 0.84 g. (0.01 mole) of sodium bicarbonate, 4 ml. of 40% aqueous formaldehyde and 50 ml. of 95% ethanol was allowed to stand for 30 minutes. Then 1 g. of 5% palladium–charcoal catalyst was added and the solution was hydrogenated at room temperature and 35 pounds pressure. One equivalent of hydrogen was absorbed in less than an hour but the second one required somewhere between 6 and 15 hours. The third equivalent required for hydrogenolysis was not absorbed. The catalyst was then removed by filtration, the filtrate was concentrated to dryness *in vacuo* and the residue was taken up in 25 ml. of 90% acetic acid. Addition of 1 g. of 5% palladium–charcoal catalyst and then hydrogenation at 50° and 25 pounds pressure led to absorption of the third equivalent of hydrogen in three more hours.

The catalyst was removed by filtration and the filtrate was concentrated to dryness under reduced pressure. The residue was taken up in 25 ml. of dilute (5%) sodium hydroxide solution, filtered from insoluble material and reprecipitated with concentrated hydrochloric acid. Filtration gave 0.75 g. (50%) of product which after one recrystallization each from water and hexane (Skellysolve B), produced shiny leaflets, m.p. 91–92°, of *p*-tolylacetic acid (V).

Anal. Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71; O, 21.31. Found: C, 72.24; H, 6.95; O, 21.51.

A mixture with an authentic sample of *p*-tolylacetic acid, m.p. 90–91°, melted at 90–92°, whereas a mixture with a specimen of *o*-tolylacetic acid, m.p. 87–88°, melted at 60–75°.

Proof of Structure of *m*-Aminomethylphenylacetic Acid (XI).—The amino acid hydrochloride XI, m.p. 193–195°, 2.02 g., was submitted to exactly the same procedure as detailed above for the *p*-isomer. There was obtained a 36% yield of XII as shiny leaflets, m.p. 63–64°. A mixture with an authentic sample of *m*-tolylacetic acid, m.p. 62–64°, melted at 63–64°.

Anal. Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71; O, 21.31. Found: C, 72.53; H, 6.64; O, 21.26.

Methyl p-Aminomethylphenylacetate Hydrochloride (IX).—A suspension of 20.15 g. (0.1 mole) of *p*-aminomethylphenylacetic acid hydrochloride (III) in 250 ml. of dry methanol was saturated with dry hydrogen chloride during a period of about 90 minutes. The clear solution was then refluxed for another 90 minutes and refrigerated overnight. The methyl *p*-aminomethylphenylacetate hydrochloride (IX) (16 g. 75%) crystallized in the form of long colorless blades, m.p. 215–217°. It was analytically pure.

Anal. Calcd. for $C_{10}H_{14}ClNO_2$: C, 55.68; H, 6.54; N, 6.49; O, 14.84. Found: C, 55.75; H, 6.71; N, 6.58; O, 14.84.

Ethyl p-Chloroacetylaminomethylphenylacetate (VI).—This esterification was carried out using the method of Clinton[8] employing 10 g. (0.0415 mole) of *p*-chloroacetylaminomethylphenylacetic acid (II), 6.9 g. (0.15 mole) of dry ethanol, 15 ml. of ethylene chloride and 0.05 ml. of ethanesulfonic acid as catalyst. The ethyl ester VI (9.3 g., 83%) was obtained in the form of a nearly white solid, m.p. 79–81°. For analysis, a sample was recrystallized from aqueous ethanol to give long white needles, m.p. 81–82°.

Anal. Calcd. for $C_{13}H_{16}ClNO_3$: C, 57.81; H, 5.97; N, 5.19. Found: C, 58.10; H, 6.13; N, 5.01.

Methyl p-chloroacetylaminomethylphenylacetate (VII) also was obtained in 85% yield using the above procedure but substituting 4.8 g. (0.15 mole) of dry methanol for the ethanol. It gave colorless leaflets, m.p. 79–80°, from aqueous methanol.

Anal. Calcd. for $C_{12}H_{14}ClNO_3$: C, 56.36; H, 5.51; N, 5.48. Found: C, 56.66; H, 5.46; N, 5.33.

Ethyl p-Diethylaminoacetylaminomethylphenylacetate (VIII).—A mixture of 8.07 g. (0.03 mole) of ethyl *p*-chloroacetylaminomethylphenylacetate (VI), 6.2 ml. (0.06 mole) of diethylamine and 50 ml. of dry benzene was heated in a stainless steel autoclave for 7 hours at 100°. After cooling, the precipitated diethylamine hydrochloride (2.9 g.) was removed by filtration, and the filtrate was concentrated to dryness *in vacuo*. The residual oil was taken up in ether, washed with water, and dried over anhydrous magnesium sulfate. Removal of the drying agent by filtration followed by evaporation of the ether gave an oil which was distilled *in vacuo* to yield 8.3 g. (90%) of the ester VIII, b.p. 183–185° (0.3 mm.), m.p. 46–48°.

Anal. Calcd. for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14; O, 15.67. Found: C, 66.36; H, 8.06; N, 9.17; O, 15.95.

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(8) R. Clinton and S. Laskowski, THIS JOURNAL, **70**, 3135 (1948).