Control experiments in which no precursor was used gave no appreciable quantities of *p*-hydroxybenzylpenicillin.

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Summary

The N-2-hydroxyethylamide and/or valine derivatives of a series of substituted phenylacetic acids have been prepared and tested as penicillin precursors. The effect of these materials on the formation of new penicillins has been indicated and discussed.

It has been demonstrated that N-2-hydroxyethyl-*p*-hydroxyphenylacetamide serves as a precursor for penicillin X.

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[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Biosynthesis of Penicillins. VI. N-2-Hydroxyethylamides of Some Polycyclic and Heterocyclic Acetic Acids as Precursors[1]

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In connection with the biosynthetic preparation of new penicillins, a wide variety of acids and their derivatives were tested as possible precursor substances. This paper describes the N-2-hydroxyethylamides of a number of polycyclic and heterocyclic analogs of phenylacetic acid. In addition several new polycyclic and heterocyclic acetic acids are reported.

Of a large number of derivatives of phenylacetic acid, the N-2-hydroxyethylamide was among the most effectively utilized by *P. notatum* NRRL 1976 for the production of benzylpenicillin.[3] On this basis the N-2-hydroxyethylamides of the present series of acids were chosen as appropriate derivatives for testing. The compounds of Table I were tested in the manner previously described[3,4] using *P. notatum* NRRL 1976 and *P. chrysogenum* Q176. Only a few of these compounds appeared to be utilized readily by the mold for the formation of new penicillins. 2-Thiopheneacetic acid and 2-thiopheneacetyl-DL-valine as well as N-(2'-hydroxyethyl)-2-thiopheneacetamide were converted by the mold to 2-thiophenemethylpenicillin, the isolation of which has been described.[5]

Several of the compounds appeared to effect some increase in penicillin yield (last column, Table I) or to change the differential assay value[3] of the crude penicillin produced in their presence. In some of these cases the crude penicillins were subjected to separation in the "Craig apparatus."[4] This analysis failed to show that significant quantities of new penicillins were formed from 2-furanacetic acid, 6-quinolineacetic acid, 1-bromo-2-naphthaleneacetic acid or N-(2'-hydroxyethyl)-1-pyrroleacetamide using *P. chrysogenum* Q176, or from N-(2'-hydroxyethyl)-2-furanacetamide using *P. notatum* NRRL 1976. On the other hand, when NRRL 1976 was grown in the presence of N-(2'-hydroxyethyl)-2-naphthaleneacetamide a new penicillin fraction was found by the Craig technique. This new penicillin has not as yet been isolated in a pure condition. Its differential assay value appears to be about 0.6.

In a number of cases efforts were made to isolate new penicillins by separations on silica gel columns.[3] From this work it has been concluded that, under the conditions of testing which were used, no significant quantities of new penicillins were formed from the N-2-hydroxyethylamides of 3-pyridineacetic acid, 5-benzimidazoleacetic acid, 7-hydroxy-4-coumarinacetic acid or 2-furanacetic acid.

In addition to the compounds listed in Table I, 3-coumarinacetic acid,[6] tryptamine and histamine were tested as possible precursor substances, In each case there was no stimulation in penicillin yield.

Polycyclic Acetic Acids.—The new acids in this group include five substituted 2-naphthaleneacetic acids and two phenanthreneacetic acids. 6-Methoxy-2-naphthaleneacetic, 5,6,7,8-tetrahydro-2-naphthaleneacetic, 2-phenanthreneacetic and 3-phenanthreneacetic acids were obtained in satisfactory yields from the corresponding methyl ketones by the modified Willgerodt method.[6a] 6-Amino-2-methylnaphthalene served as a starting point in the synthesis of 6-fluoro- and 6-bromo-2-naphthylacetic acids. The amino group was replaced with the halogens through diazonium reactions: the 6-halo-2-methylnaphthalenes were monobrominated in the side chain, and

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(3) Behrens, Corse, Jones, Mann, Soper, Van Abeele and Chiang, *J. Biol. Chem.*, **175**, 751 (1948).

(4) Behrens, Corse, Huff, Jones, Soper and Whitehead, *ibid.*, **175**, 771 (1948).

(5) Behrens, Corse, Edwards, Garrison, Jones, Soper, Van Abeele and Whitehead, *ibid.*, **175**, 793 (1948).

(6) Dey and Sankaranarayanan, *J. Indian Chem. Soc.*, **8**, 817 (1931); [*C. A.*, **26**, 3499 (1932)].

(6a) Schwenk and Bloch, THIS JOURNAL, **64**, 3051 (1942).

TABLE I

N-2-HYDROXYETHYLAMIDES OF POLYCYCLIC AND HETEROCYCLIC ACETIC ACIDS

$RCONHCH_2CH_2OH$

Parent acetic acid RCH_2COOH	Empirical formula	M. p., °C.	Analyses, % (N or C and H) Calcd.	Found	Stimulation[a]
2-Naphthalene[7]	$C_{14}H_{15}NO_2$	125–127	6.11	6.20	1.3
1-Bromo-2-naphthalene[8]	$C_{14}H_{14}BrNO_2$	155–156	4.54	4.55	0.5
6-Fluoro-2-naphthalene	$C_{14}H_{14}FNO_2$	145–146	68.00 5.71	67.88 5.60	1.2
3-Chloro-2-naphthalene	$C_{14}H_{14}ClNO_2$	150–151	5.31	5.58	0.3
6-Bromo-2-naphthalene	$C_{14}H_{14}BrNO_2$	167–168	54.56 4.58	54.55 4.58	0.9
5,6,7,8-Tetrahydro-2-naphthalene	$C_{14}H_{19}NO_2$	88–90	6.00	6.19	0.9
1-Nitro-2-naphthalene[9]	$C_{14}H_{14}N_2O_4$	154–155	10.22	10.08	0.9
6-Methoxy-2-naphthalene	$C_{15}H_{17}NO_3$	160	5.40	5.85	1.1
1-Acenaphthene[10]	$C_{16}H_{17}NO_2$	96–98	75.27 6.71	75.47 6.59	0.4
9-Fluorene[11]	$C_{17}H_{16}NO_2$	127–128	76.38 6.41	76.40 6.73	0.7
2-Phenanthrene	$C_{18}H_{17}NO_2$	135–137	5.02	4.76	0.5
3-Phenanthrene	$C_{18}H_{17}NO_2$	133–135	5.02	5.22	0.5
1-Pyrrole[12]	$C_8H_{12}N_2O_2$	85–87	16.60	16.93	0.9
2-Thiophene[13]	$C_8H_{11}NO_2S$	66–67	7.56	7.96	1.8
2-Furan[14]	$C_8H_{11}NO_3$	Oil	8.28	8.95	0.4
2,6-Dihydroxy-5-pyrimidine[15]	$C_8H_{11}N_3O_4$	271–272	45.07 5.20	44.98 5.07	1.0
2-Methyl-4-hydroxy-5-pyrimidine[16]	$C_9H_{13}N_3O_3$	184	20.09	19.97	0.9
3,4-Methylenedioxyphenyl[17]	$C_{11}H_{13}NO_4$	99–100	6.28	6.42	1.0
2-Methyl-4-thiazole[18]	$C_8H_{12}N_2O_2S$	93–94	13.99	14.04	0.85
4-Methyl-2-thiazole	$C_8H_{12}N_2O_2S$	80–82	13.99	14.23	0.9
2-Pyridine[19,20]	$C_9H_{12}N_2O_2$	93–94	15.54	15.54	1.0
3-Pyridine[21]	$C_9H_{12}N_2O_2$	94	59.98 6.71	59.90 6.54	1.0
6-Methyl-2-pyridine[20]	$C_{10}H_{14}N_2O_2$	49–50	14.42	14.40	1.0
2-Benzyl-1-imidazole	$C_{14}H_{17}N_3O_2$	177–179	16.16	16.54	1.0
3-Quinoline	$C_{13}H_{14}N_2O_2$	151–152	67.81 6.13	67.83 6.02	1.0
6-Quinoline	$C_{13}H_{14}N_2O_2$	135	12.17	12.32	1.0
8-Quinoline	$C_{13}H_{14}N_2O_2$	92–93	12.17	12.20	1.0
2-Benzimidazole[22]	$C_{11}H_{13}N_3O_2$	185–190	19.16	19.09	1.0
5-Benzimidazole	$C_{11}H_{13}N_3O_2$	160–162	19.16	19.11	1.0
2-Hydroxy-5-benzimidazole	$C_{11}H_{13}N_3O_3$	245–246	17.87	18.01	1.0
7-Hydroxy-4-coumarin[23]	$C_{13}H_{13}NO_5$	114–116	4.53	4.31	1.0
9-Xanthene[24]	$C_{17}H_{17}NO_3$	157–158	4.95	4.87	0.8
9-Thioxanthene	$C_{17}H_{17}NO_2S$	148–149	4.68	4.60	0.7
5-Hydantoin[25]	$C_7H_{11}N_3O_4$	160–162	20.89	20.50	0.9

[a] Stimulation is defined as the ratio: units of penicillin in test container/units in control container. We are happy to acknowledge the help given by Dr. J. M. McGuire in conducting the numerous assays.

the resulting α-bromomethylnaphthalenes were treated with sodium cyanide in the usual way followed by alkaline hydrolysis. 3-Chloro-2-naphthaleneacetic acid was obtained from 3-chloro-2-naphthaldehyde through the azlactone made with hippuric acid.[26,27]

Heterocyclic Acetic Acids.—In this group the new members include thiazole-, imidazole-, benzimidazole-, quinoline- and thioxantheneacetic acids. These acids were prepared in a variety of ways. The Willgerodt reaction served as a method for the preparation of the 3- and 6-quinolineacetic acids. 6-Quinolineacetic acid was also synthesized from *p*-aminophenylacetic acid through the Skraup reaction. 9-Thioxantheneacetic acid was obtained by the condensation of thioxanthydrol with malonic acid in pyridine solution, a method previously described by Ziegler[24] for the preparation of 9-xantheneacetic acid. The known 3-nitro-4-aminophenylacetic acid was reduced to 3,4-diaminophenylacetic acid, and this was converted to the 5-benzimidazole- and 2-hydroxy-5-benzimidazoleacetic acids. Ethyl bromo-

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(8) Mayer and Sieglitz, *ibid.*, **55**, 1859 (1922).
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(17) Mauthner, *Ann.*, **370**, 375 (1909).
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(19) Clemo, Morgan and Raper, *J. Chem. Soc.*, 1743 (1935).
(20) Kindly supplied by Dr. R. B. Woodward, Department of Chemistry, Harvard University.
(21) Hartman and Bosshard, *Helv. Chim. Acta*, **24**, 28E (1941).
(22) Copeland and Day, THIS JOURNAL, **65**, 1072 (1943).
(23) Dey, *J. Chem. Soc.*, **107**, 1632 (1915).
(24) Ziegler, *Ann.*, **434**, 60 (1923).
(25) Gabriel, *ibid.*, **348**, 87 (1906).
(26) "Organic Syntheses," Coll. Vol. II, 1943, p. 55.
(27) *Ibid.*, p. 333.

acetate, acting upon the silver salt of 2-benzylimidazole in boiling xylene, gave ethyl 2-benzyl-1-imidazoleacetate in a yield of 25%, but, when butanol was used as the solvent in place of xylene, the yield dropped to about 8%.

Experimental

N-2-Hydroxyethylamides.—These amides were obtained by heating the methyl or ethyl esters of the various acids with a slight excess of ethanolamine at about 100 to 150° for several hours. The resulting products were recrystallized, usually from ethyl acetate–petroleum ether mixtures or from ethylene dichloride. Occasionally other solvents were employed.

6-Fluoro-2-naphthaleneacetic Acid: 6-Fluoro-2-methylnaphthalene.—A thin paste of 78 g. (0.4 mole) of 6-amino-2-methylnaphthalene[28] in a solution of 80 ml. of concentrated hydrochloric acid and 200 ml. of water was cooled to 5° and diazotized with a solution of 35 g. (0.5 mole) of sodium nitrite in 50 ml. of water. After one-half hour at 0–5°, 130 g. of ice-cold 42% fluoroboric acid was added with stirring. The resulting crystalline precipitate was collected, washed with 100 ml. of water, 100 ml. of cold methanol and three 200-ml. portions of ether and dried in vacuum over sulfuric acid. The yield was 92 g. (90%).

One hundred grams (0.39 mole) of the dry 6-methylnaphthalene-2-diazonium fluoroborate in a 1-liter flask was decomposed in the usual way, and the product was distilled directly from the flask under vacuum to yield 43 g. (69%) of white, crystalline 6-fluoro-2-methylnaphthalene. A sample for analysis was recrystallized from petroleum ether; m. p. 77°.

Anal. Calcd. for $C_{11}H_9F$: C, 82.48; H, 5.66. Found: C, 82.53; H, 5.63.

2-Bromomethyl-6-fluoronaphthalene.—Forty grams (0.25 mole) of 6-fluoro-2-methylnaphthalene in a 1-liter 3-necked flask was heated in an oil-bath at 210° and illuminated with a 100-watt lamp while 40 g. (0.25 mole) of bromine was added with stirring during fifteen minutes. The mixture was cooled, transferred to a small flask and distilled under vacuum. The main fraction, 2-bromomethyl-6-fluoronaphthalene, boiled at 125–130° (2 mm.) and crystallized after cooling; m. p. 53°; yield 49 g. (82%).

Anal. Calcd. for $C_{11}H_8BrF$: C, 55.26; H, 3.37. Found: C, 54.63; H, 3.15.

6-Fluoro-2-naphthaleneacetic Acid.—Forty-eight grams (0.20 mole) of 2-bromomethyl-6-fluoronaphthalene was added in portions to a refluxing solution of 30 g. of potassium cyanide in 60 ml. of water and 200 ml. of ethanol. After refluxing four hours, the alcohol was evaporated under vacuum, 500 ml. of water was added and the aqueous solution was extracted with ether. The ether solution was washed with sodium bicarbonate solution, evaporated, and the residue boiled for five hours with a mixture of 40 g. of potassium hydroxide, 40 ml. of water and 200 ml. of ethanol. The alcohol was removed under vacuum, 300 ml. of water added, the aqueous solution washed with ether, clarified with carbon and acidified to yield 30 g. (74%) of 6-fluoro-2-naphthaleneacetic acid; m. p. 138–139° (from benzene–petroleum ether).

Anal. Calcd. for $C_{12}H_9FO_2$: C, 70.58; H, 4.44. Found: C, 70.68; H, 4.60.

The acid was esterified with methanol and sulfuric acid in the usual way to yield 25 g. (81%) of methyl 6-fluoro-2-naphthaleneacetate; b. p. 163–166° (2 mm.); m. p. 48–49°.

Anal. Calcd. for $C_{13}H_{11}FO_2$: C, 71.55; H, 5.08. Found: C, 71.35; H, 5.25.

6-Bromo-2-naphthaleneacetic Acid: 6-Bromo-2-methylnaphthalene.—To a slurry of 63 g. (0.4 mole) of 6-amino-2-methylnaphthalene[28] in 100 ml. of water was added 700 g. of 48% hydrobromic acid. The mixture was cooled to 5° and well-stirred while a solution of 45 g. (0.76 mole) of sodium nitrite in 75 ml. of water was introduced below the surface over a period of three or four hours. The resulting diazonium mixture was poured during ten minutes into a solution of 170 g. of cuprous bromide in 800 ml. of 48% hydrobromic acid at 70–80°. After standing overnight, the mixture was steam distilled. Thirty-five grams (40%) of 6-bromo-2-methylnaphthalene was obtained; m. p. 142° (from petroleum ether).

Anal. Calcd. for $C_{11}H_9Br$: C, 59.75; H, 4.10. Found: C, 59.75; H, 4.07.

6-Bromo-2-bromomethylnaphthalene.—From 33 g. (0.15 mole) of 6-bromo-2-methylnaphthalene was obtained 36 g. (80%) of 6-bromo-2-bromomethylnaphthalene; m. p. 124–125°.

Anal. Calcd. for $C_{11}H_8Br_2$: C, 44.04; H, 2.69. Found: C, 44.08; H, 2.64.

6-Bromo-2-naphthaleneacetic Acid.—6-Bromo-2-bromomethylnaphthalene (36 g., 0.12 mole) was converted to the nitrile. This was hydrolyzed to yield 22 g. (69%) of 6-bromo-2-naphthaleneacetic acid, m. p. 175–176° (from benzene).

Anal. Calcd. for $C_{12}H_9BrO_2$: C, 54.36; H, 3.42. Found: C, 54.45; H, 3.30.

The acid was esterified with methanol and sulfuric acid to give methyl 6-bromo-2-naphthaleneacetate (70% yield); b. p. 187–193° (2 mm.); m. p. 67–69°.

Anal. Calcd. for $C_{13}H_{11}BrO_2$: C, 55.93; H, 3.97. Found: C, 55.36; H, 3.61.

3-Chloro-2-naphthaleneacetic Acid.—A mixture of 32.5 g. (0.17 mole) of 3-chloro-2-naphthaldehyde,[29] 35 g. of dry hippuric acid, 14.5 g. of anhydrous sodium acetate and 50 ml. of acetic anhydride was stirred together and heated on a hot plate. At 60–80° an exothermic reaction set in and the mixture turned bright yellow. The pasty mass was heated on the steam-bath for one hour and then treated with 70 ml. of methanol and placed in the ice-box overnight. The bright yellow 2-phenyl-4-(3-chloro-2-naphthylmethylene)-oxazolone was collected, washed with two 20-ml. portions of methanol and three 25-ml. portions of boiling water and air dried. The yield was 42 g. (75%) and m. p. 187–188°. A sample for analysis was recrystallized from benzene; m. p. 192°.

Anal. Calcd. for $C_{20}H_{12}ClNO_2$: N, 4.20. Found: N, 4.15.

The above oxazolone (40 g., 0.12 mole) in 200 ml. of 10% sodium hydroxide solution was boiled under reflux for nine hours. The mixture was diluted to 1500 ml. with water, warmed, filtered, and the filtrate washed with ether. The aqueous solution was warmed to remove dissolved ether, cooled again to room temperature, and treated with 20 ml. of 12.5 *N* sodium hydroxide solution followed by 15 ml. of 30% hydrogen peroxide added over a period of ten minutes. After standing overnight the solution was filtered, acidified with hydrochloric acid, and extracted with 200 ml. of ether and 500 ml. of benzene. The ether–benzene solution was evaporated and the residue was treated with 250 ml. of dry methanol and 3 ml. of concentrated sulfuric acid. The ester mixture was isolated as usual and distilled to yield 12.5 g. (77%) of methyl benzoate boiling at 61° (1 mm.). The residual methyl 3-chloro-2-naphthaleneacetate was distilled at a pressure of 2 mm. It boiled at 163–165° and after cooling crystallized; m. p. 49–50°. The yield was 10.5 g. (37%).

Anal. Calcd. for $C_{13}H_{11}ClO_2$: C, 66.53; H, 4.73. Found: C, 66.70; H, 4.75.

The acid obtained by saponification of the ester and recrystallization from 50% alcohol melted at 193–194°.

Anal. Calcd. for $C_{12}H_9ClO_2$: C, 65.32; H, 4.11. Found: C, 65.25; H, 3.95.

6-Methoxy-2-naphthaleneacetic Acid.—A mixture of 100 g. (0.5 mole) of 6-methoxy-2-acetonaphthone,[30] 25.5

(28) Dziewonski, Shoenowna and Waldmann, *Ber.*, **58**, 1216 (1925).

(29) Shoesmith and Mackie, *J. Chem. Soc.*, 1586 (1930).

(30) Robinson and Rydon, *ibid.*, 1399 (1939).

g. (0.8 g. atom) of sulfur and 87 g. (1.0 mole) of morpholine was heated at 140° for eighteen hours. Part of the excess morpholine was removed under vacuum; then 250 ml. of glacial acetic acid and 350 ml. of concentrated hydrochloric acid were added. The mixture was refluxed for twenty-four hours and then evaporated to a sirup. To the residue was added 1 liter of water. The dark crystalline product was collected, washed with water and then extracted with a hot solution of 60 g. of sodium carbonate in 500 ml. of water. The green aqueous solution was filtered and acidified with hydrochloric acid. The resulting pasty mixture was extracted with one liter of ether. The ether solution was boiled with 5 g. of activated carbon, dried over magnesium sulfate and the ether evaporated, leaving 72 g. (67% yield) of 6-methoxy-2-naphthaleneacetic acid. A sample for analysis was recrystallized from benzene–ethyl acetate, m. p. 203–205°.

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.10; H, 5.60. Found: C, 71.74; H, 5.07.

A solution of 32.5 g. (0.15 mole) of the acid in 500 ml. of methanol containing 5 ml. of concentrated sulfuric acid was refluxed for two hours and then evaporated to small volume. The residue was treated with water and extracted with ether. After washing with sodium carbonate solution and drying, the ether was removed and the ester distilled under vacuum. It boiled at 192–193° (1 mm.) and very slowly crystallized after standing; m. p. 86°. The yield was 25 g. (73%).

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.72; H, 6.12.

Ethyl 5,6,7,8-Tetrahydro-2-naphthaleneacetate.—A mixture of 50 g. of 2-aceto-5,6,7,8-tetrahydronaphthone,[31] 13 g. of sulfur and 40 ml. of morpholine was heated under reflux overnight. Then 400 ml. of concentrated hydrochloric acid and 300 ml. of water were added and this mixture was refluxed overnight. The resulting acid was separated from neutral material and esterified with absolute ethanol and sulfuric acid in the usual manner. The fraction boiling at 140–143° (0.5 mm.) was collected.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.84; H, 8.62.

2-Phenanthreneacetic Acid.—A mixture of 13.2 g. (0.06 mole) of 2-acetylphenanthrene,[32] 3.2 g. (0.10 g. atom) of sulfur and 10.5 g. (0.12 mole) of morpholine was heated in an oil-bath at 160° for fifteen hours. The product was treated with 150 ml. of glacial acetic acid and 150 ml. of 36% hydrochloric acid and the mixture refluxed for twenty-four hours. After cooling and diluting with 300 ml. of water, a crystalline product separated. This was collected, washed with water and taken up in a sodium bicarbonate solution. The aqueous solution was heated to boiling with a little decolorizing carbon, filtered and acidified with hydrochloric acid to precipitate 11.6 g. (81%) of crystalline product, m. p. 186–187°. A sample for analysis was recrystallized from benzene; m. p. 187–188°.

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.40; H, 5.29.

3-Phenanthreneacetic Acid.—This was prepared from 3-acetylphenanthrene[26] in the same way as the 2-isomer. The yield was 84%; m. p. 174–175°.

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.00; H, 5.12.

The acid (19.3 g., 0.082 mole) was esterified with methanol and sulfuric acid in the usual way. The ester distilled as a viscous liquid at 203–205° (1.5 mm.) and the yield was 18.6 g. (89%).

Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.14; H, 5.49.

Ethyl 8-Quinolineacetate.—A solution of 120 g. (0.54 mole) of 8-bromomethylquinoline[33] in 250 ml. of warm ethanol was added during one-half hour to a warm solution of 50 g. (0.77 mole) of potassium cyanide in 100 ml. of water. The mixture was boiled under reflux for one and one-half hours, and then most of the alcohol was removed *in vacuo*. To the residue was added 200 ml. of water, and the mixture was cooled. The resulting crystalline product was collected, dried and extracted with petroleum ether which upon cooling deposited 8-cyanomethylquinoline as colorless needles. The yield was 70 g. (78%); m. p. 86–87°.

Anal. Calcd. for $C_{11}H_8N_2$: C, 78.55; H, 4.74; N, 16.66. Found: C, 77.86; H, 5.05; N, 17.11.

A mixture composed of 50 g. (0.30 mole) of 8-cyanomethylquinoline, 40 g. of sodium hydroxide, 100 ml. of water and 250 ml. of alcohol was refluxed for four hours. After the addition of 60 ml. of glacial acetic acid, the mixture was evaporated to dryness at reduced pressure. The residue was treated with 200 ml. of benzene, and evaporated again to dryness on the steam-bath. To the dry residue was added one liter of absolute ethanol, and the mixture was saturated with dry hydrogen chloride. After standing for sixty hours, the mixture was boiled for two hours, filtered, and the filtrate concentrated under vacuum. The resulting partially crystalline mass was treated with excess sodium carbonate solution and extracted with three 300-ml. portions of ether. The ether extract was dried, the ether removed and the residual liquid distilled *in vacuo*. The ester distilled as a colorless oil at 158–160° (3 mm.). The yield was 58 g. (91%).

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.20; H, 6.22; N, 6.41.

Ethyl 3-Quinolineacetate.—3-Acetylquinoline was prepared according to Nandi.[34] A mixture of sodium ethoxide from 12 g. (0.52 g. atom) of sodium sand and 0.52 mole of absolute ethanol in 100 cc. of dry benzene, 70 g. (0.35 mole) of ethyl 3-quinolinecarboxylate and 62 g. (0.70 mole) of ethyl acetate was refluxed for twenty hours. The resulting solution was cooled, poured on ice and diluted to five liters with water. To the aqueous solution was added 50 ml. of 12 *N* sodium hydroxide solution and the solution was washed with two 300-ml. portions of ether. The water solution was just neutralized with dilute sulfuric acid and extracted with two 500-ml. portions of ether. Evaporation of the ether left 63 g. (75% yield) of ethyl 3-quinolylacetate as a crystalline solid. A sample recrystallized from petroleum ether melted at 84°.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.92; H, 5.04; N, 5.71.

A solution of 27 g. (0.11 mole) of the keto-ester in 125 g. of 25% sulfuric acid was heated at 100° for thirty minutes, and then the solution was cooled and made basic with sodium hydroxide. The yield of 3-acetylquinoline was 18 g. (95%); m. p. 97.5–98.5°.

A mixture of 7.0 g. (0.041 mole) of 3-acetylquinoline, 5 g. of sulfur, 50 ml. of ammonium sulfide solution (made by saturating ice-cold concentrated ammonium hydroxide solution with hydrogen sulfide) and 25 ml. of water in a sealed tube was heated at 145–150° for twenty hours. The contents from three such tubes were combined and evaporated to dryness under vacuum. The residue was extracted with two 300-ml. portions of boiling 5% hydrochloric acid, and this solution was refluxed for three hours. The solution was filtered and evaporated to dryness. The residue was treated with 20 g. of sodium carbonate in 200 ml. of water and the solution was washed with four 200-ml. portions of ether. The aqueous solution was filtered, evaporated to dryness at reduced pressure, and the residue was treated with 200 ml. of benzene which was distilled off at atmospheric pressure. To the dry residue was added 200 ml. of absolute ethanol and the mixture was saturated with dry hydrogen chloride. After refluxing for two hours, the mixture was filtered and the filtrate concentrated *in vacuo* to about 50 ml. This was treated with excess aqueous sodium bicarbonate solution and

(31) Scharwin, *Ber.*, **35**, 2511 (1902).

(32) Mosettig and Van de Kamp, THIS JOURNAL, **52**, 3704 (1930).

(33) Howitz and Nöther, *Ber.*, **39**, 2705 (1906).

(34) Nandi, *Proc. Indian Acad. Sci.*, **12A**, 1 (1940) [*C. A.*, **34**, 7918 (1940)].

extracted with three 150-ml. portions of ether. The ether solution was dried over magnesium sulfate, the ether evaporated and the residual liquid distilled under vacuum. The ester boiled at 140–142° (2.5 mm.). The yield was 5.0 g. (19%).

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.27; H, 6.09; N, 6.49.

The modified Willgerodt reaction using sulfur and morpholine gave only a trace of the desired 3-quinolineacetic acid.

6-Quinolineacetic Acid.—(a) A mixture of 46 g. (0.3 mole) of *p*-aminophenylacetic acid, 10.5 g. of ferrous sulfate, 115 g. of glycerol, 23 g. of nitrobenzene, and 53 ml. of concentrated sulfuric acid was heated gently. After the first vigorous reaction the mixture was boiled for five hours under reflux and then steam distilled to remove excess nitrobenzene. The aqueous solution was treated with 220 ml. of 12 *N* sodium hydroxide solution, stirred up with filtercel, and filtered. The filtrate was acidified with glacial acetic acid, and a dark brown precipitate separated. This was collected, washed with water, taken up in 500 ml. of 0.82 *N* sodium hydroxide solution, boiled with 25 g. of carbon, and the solution filtered. The filtrate was treated with 40 ml. of glacial acetic acid and set aside for twenty-four hours, during which time 37 g. of dark-brown crystalline precipitate separated.

Since no suitable solvent was found from which to recrystallize the crude acid, it was suspended in 400 ml. of absolute ethanol, and the mixture was saturated with dry hydrogen chloride. The resulting solution was refluxed for four hours and then evaporated under vacuum to a small volume. This residue was treated with excess sodium carbonate solution and extracted with ether. The ether solution was dried, the ether removed and the remaining liquid distilled at reduced pressure. This ester distilled at 160° (3 mm.) as a colorless liquid which darkened a little after several days. The yield was 25 g. (39%).

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.52; H, 6.17; N, 6.64.

A mixture of 1.0 g. of the ester with 5 ml. of 4 *N* sodium hydroxide solution was heated at 90° for one hour. The solution was diluted, filtered and made just acid with acetic acid. The white precipitate of 6-quinolineacetic acid was collected, washed with water and air dried; yield, 0.85 g. (100%); m. p. 218–220° (dec.).

Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.54; H, 4.84; N, 7.21.

(b) **Ethyl 6-quinolinecarboxylate**[35] (m. p. 55–56°; literature gives m. p. 50°) and ethyl acetate were condensed with sodium ethylate and worked up as described above for the 3-quinoline analog to yield 87% of ethyl 6-quinolylacetate as a light brown oil. This ester was not purified, but was hydrolyzed directly with 25% sulfuric acid at 100° to give 6-acetylquinoline in 90% yield; m. p. 76°.

Anal. Calcd. for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.23; H, 5.15; N, 8.14.

A mixture of 30 g. (0.175 mole) of 6-acetylquinoline, 8.5 g. of sulfur and 30 g. of morpholine was heated at 150° for eighteen hours, then 200 ml. of concentrated hydrochloric acid was added and refluxing was continued for twenty-four hours. The solution was evaporated to a sirup. The residue was taken up in 200 ml. of water containing 40 g. of sodium carbonate. The solution was treated with carbon, filtered and acidified with acetic acid to yield 28.5 g. (87.5%) of 6-quinolineacetic acid; m.p. 218–219°, and mixed m. p. with an authentic sample 218–219°.

3,4-Diaminophenylacetic Acid.—3-Nitro-4-aminophenylacetic acid was prepared according to Gabriel[36] by nitrating a mixture of *p*-mono- and diacetylaminobenzyl cyanides and hydrolyzing the resulting acetaminonitrobenzyl cyanide with concentrated hydrochloric acid. However, the yield of 3-nitro-4-aminophenylacetic acid was poor (about 40%) and a large quantity of unidentified by-product was always obtained. Satisfactory yields of the desired acid were prepared by nitrating *p*-monoacetylaminobenzyl cyanide with fuming nitric acid at −20 to −25° and then allowing the mixture to warm up to 0° during fifteen minutes before pouring it on cracked ice. The monoacetylaminobenzyl cyanide was best prepared by acetylating *p*-aminobenzyl cyanide in pyridine with just slightly more than one equivalent of acetic anhydride. Hydrolysis of the acetaminonitrobenzyl cyanide with concentrated hydrochloric acid according to Gabriel's directions[36] then led to 3-nitro-4-aminophenylacetic acid in yields of 75 to 80%.

A suspension of 108 g. (0.55 mole) of 3-nitro-4-aminophenylacetic acid in 350 ml. of concentrated hydrochloric acid was stirred while 125 g. of mossy tin was added in portions. The temperature was maintained below 90°. When almost all of the tin had dissolved the solution was diluted to 2.5 liters and saturated with hydrogen sulfide. The mixture was filtered and the filtrate was evaporated to dryness *in vacuo*. The white crystalline residue was thoroughly washed with absolute ethanol and air dried. It weighed 64 g. The alcohol filtrate which still contained some of the product in the form of its soluble tin salts was diluted with 1.5 liters of water, saturated with hydrogen sulfide, filtered, evaporated to dryness in vacuum and the residue washed with absolute ethanol to yield another 26 g. of product. A third treatment of the alcohol filtrate gave an additional 24 g. of 3,4-diaminophenylacetic acid dihydrochloride bringing the total yield to 114 g. (87%); m. p. 222–224° (dec.).

Anal. Calcd. for $C_8H_{12}Cl_2N_2O_2$: C, 40.18; H, 5.06; N, 11.72. Found: C, 40.72; H, 4.76; N, 11.86.

A suspension of 30 g. (0.125 mole) of 3,4-diaminophenylacetic acid dihydrochloride in 300 ml. of absolute ethanol was saturated with dry hydrogen chloride. The solid gradually dissolved. After twenty-four hours at room temperature, the mixture was chilled to 0°. The white crystalline precipitate of ethyl 3,4-diaminophenylacetate dihydrochloride was collected, and washed with anhydrous ether. The yield was 25 g. (75%); m. p. 185–187° (dec.).

Anal. Calcd. for $C_{10}H_{16}Cl_2N_2O_2$: C, 44.95; H, 6.04. Found: C, 44.85; H, 6.02.

5-Benzimidazoleacetic Acid.—Three grams (0.0125 mole) of 3,4-diaminophenylacetic acid dihydrochloride was warmed on the steam-bath with 20 ml. of 98–100% formic acid. Hydrogen chloride was evolved and a clear solution formed. After several hours the solution was evaporated under vacuum, leaving 2.7 g. (100%) of pure 5-benzimidazoleacetic acid hydrochloride, m. p. 240–242°.

Anal. Calcd. for $C_9H_9ClN_2O_2$: C, 52.07; H, 4.37. Found: C, 52.08; H, 4.08.

A suspension of 10.5 g. (0.05 mole) of the hydrochloride in 250 ml. of absolute alcohol was saturated with dry hydrogen chloride. After twenty-four hours the solution was concentrated under vacuum to about 50 ml. and treated with excess, ice-cold sodium carbonate solution. The mixture was extracted with ether, the ether solution was dried, the ether was removed, and the residual sirup was heated at 100° *in vacuo* for four hours. After standing for one week the sirup crystallized. The yield of the ethyl 5-benzimidazoleacetate was 7.5 g. (75%) and the melting point 65–66°.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: N, 13.72. Found: N, 13.72.

Ethyl 2-Hydroxy-5-benzimidazoleacetate.—A solution of 14 g. (0.05 mole) of ethyl 3,4-diaminophenylacetate dihydrochloride in 200 ml. of ice-water was cooled in an ice-bath and phosgene was bubbled in until no more precipitate formed. The white solid was collected, washed with water and dried. It weighed 11 g. (95%) and after recrystallization from 50% alcohol melted at 208–209°.

(35) Einhorn and Feibelmann, *Ber.*, **42**, 4854 (1909).

(36) Gabriel, *ibid.*, **15**, 836 (1882).

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: N, 12.72. Found: N, 13.07.

Ethyl 4-Methyl-2-thiazoleacetate.—A slow stream of hydrogen sulfide was passed through a solution of 113 g. of ethyl cyanoacetate and 15 g. of triethanolamine in 100 ml. of absolute alcohol. After five days the reaction mixture was poured into ice water, and the resulting oil was extracted with ether and dried over magnesium sulfate. The solution was filtered and the solvent was evaporated, leaving a brown oil. A solution of 38 g. of this oil and 23.1 g. of chloroacetone in 300 ml. of anhydrous ether was allowed to stand four days. At this time a heavy layer had separated; it was dissolved in water. The aqueous layer was separated and made neutral with potassium bicarbonate solution. The resulting oil was extracted with ether and dried. Vacuum distillation gave 20.6 g. of ethyl 4-methyl-2-thiazoleacetate, b. p. 136–139° (17 mm.).

Anal. Calcd. for $C_8H_{11}NO_2S$: N, 7.56. Found: N, 7.23.

9-Thioxanthenacetic Acid.—A mixture of 42 g. (0.195 mole) of thioxanthydrol,[37] 30 g. (0.24 mole) of malonic acid and 80 ml. of pyridine was warmed for two hours at 60–70° then for two hours at 90–95°. The liquid was poured into 600 ml. of 2 *N* hydrochloric acid yielding an oil which soon crystallized. The product was collected, washed with water, and dissolved in excess dilute sodium bicarbonate solution. After acidification this solution yielded 45 g. (90%) of white, crystalline 9-thioxanthenacetic acid; m. p. 167–168° (from 50% alcohol).

Anal. Calcd. for $C_{15}H_{12}O_2S$: C, 70.29; H, 4.72. Found: C, 70.51; H, 5.20.

The acid was esterified with methanol and sulfuric acid and the methyl ester was obtained in 94% yield as a colorless, viscous liquid; b. p. 182–184° (2 mm.).

Anal. Calcd. for $C_{16}H_{14}O_2S$: C, 71.09; H, 5.22. Found: C, 70.92; H, 4.97.

2-Benzyl-1-imidazoleacetic Acid.—A solution of 31.6 g. (0.20 mole) of 2-benzylimidazole[38] in 200 ml. of ethanol was treated with a solution of 34 g. (0.20 mole) of silver nitrate in 100 ml. of water followed by 25 ml. of concentrated ammonium hydroxide. The resulting white precipitate was collected and washed by suspension first in water and then in alcohol. It was dried *in vacuo* over sulfuric acid. The yield was 50 g. (94%); m. p. 230° (dec.).

A suspension of 53 g. (0.20 mole) of the silver salt in 200 ml. of xylene was treated with 50 g. (0.31 mole) of ethyl bromoacetate. The mixture was refluxed for forty-eight hours. The xylene solution was decanted from the dark insoluble material and distilled. After the forerun of xylene, the residual liquid distilled at 180–190° (5–7 mm.) and crystallized after standing. It was recrystallized from 400 ml. of petroleum ether (b. p. 60–100°) to yield 14 g. (25.4%) of ethyl 2-benzyl-1-imidazoleacetate as white needles; m. p. 70–70.5°.

Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.83; H, 6.60. Found: C, 68.87; H, 6.71.

A 3.0-g. sample of the ester was saponified in 30 ml. of 2 *N* sodium hydroxide solution. The solution was neutralized to methyl red with hydrochloric acid and evaporated to dryness. The residue was extracted with hot absolute ethanol. Evaporation of the extract left a sirup which slowly crystallized. The product was recrystallized from 20 ml. of boiling *n*-butanol to yield 2.1 g. of 2-benzyl-1-imidazoleacetic acid; m. p. 173–174°.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.60. Found: C, 66.51; H, 5.78.

Methyl 1-Acenaphthenacetate.—This ester was obtained by esterification of 1-acenaphtheneacetic acid with methanol and sulfuric acid. It distilled at 176–178° (4 mm.).

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.58; H, 6.14.

2-Thiophenacetyl-DL-Valine.—DL-Valine in sodium hydroxide solution was treated with 2-thiophenacetyl chloride[13] in the usual way and the resulting 2-thiophenacetyl valine was isolated by acidification of the solution. It melted at 110–112°.

Anal. Calcd. for $C_{11}H_{15}NO_3S$: N, 5.80. Found: N, 6.10.

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Summary

The N-2-hydroxyethylamides of a variety of polycyclic and heterocyclic acetic acids have been prepared and evaluated as penicillin precursors.

A number of new polycyclic and heterocyclic acetic acids have been synthesized.

(37) Mayer, *Ber.*, **42**, 1132 (1909).

(38) Sonn and Grief, *ibid.*, **66**, 1900 (1933).

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