amalgam, Baeyer[1] obtained a product melting at 190°, which he called phenolphthalol. He reported that this compound is oxidized to phenolphthalein by potassium ferricyanide. He also described a red, water-insoluble condensation product formed by treatment of phenolphthalol with concentrated sulfuric acid.

By reduction of phenolphthalin with lithium aluminum hydride, in this Laboratory, a compound which melted at 201° was obtained. This substance neither produced Baeyer's red product, nor did it yield phenolphthalein on oxidation. This phenolphthalol, 2-(4′,4″-dihydroxybenzhydryl)-benzyl alcohol (I), gave a mono- as well as a triacetyl derivative, as would be expected from its formula.

Experimental

Phenolphthalol (I).—A three-necked flask fitted with a rubber-sleeved stirrer, an inlet tube for nitrogen, and a glass tube holding a 25 × 85 mm. glass thimble topped by a reflux condenser, was charged with 500 ml. of absol. ether and 3.0 g. of $LiAlH_4$. Into the thimble was placed 6.40 g. (0.02 mole) of phenolphthalin (m.p. 233–236°). After two hours of refluxing, the latter had dissolved. Stirring was continued for 16 hours at 36°. Then a mixture of 50 ml. of water and 35 ml. of concd. hydrochloric acid was carefully added and the ether layer extracted with 2 *N* sodium carbonate. Phenolphthalin (0.81–0.97 g.) was recovered from the extract. After evaporation of the ether, the solid was recrystallized from either water (1 g. in 750 ml.) or from 20% ethanol (1 g. in 110 ml.). The yield was 4.65–4.96 g. (76–81%); m.p. 201–202°.

The pure I, colorless needles, melts at 201.5–201.9° cor. It can be sublimed at 180° and 8 microns pressure.[2] It is very soluble in acetone or ethanol, soluble in ether, and insoluble in chloroform or benzene. Its solution in dilute alkali is colorless; a 0.001 molar solution in concd. sulfuric acid is of moderate orange color.

Anal. Calcd. for $C_{20}H_{18}O_3$: C, 78.42; H, 5.92; mol. wt., 306. Found: C, 78.59; H, 6.25; mol. wt., 292.[3]

When a solution of phenolphthalein in dilute acetic acid was treated with sodium amalgam according to Baeyer's procedure,[1] a crude product which melted at about 190° was obtained in very low yield. After several crystallizations from water it melted at 198–199° and proved to be identical with I.

Monoacetyl Derivative of I.—A mixture of 1.0 g. of I and 10 ml. of acetic acid was refluxed for one hour. The crude product was treated with 50 ml. of hot benzene and then filtered; the insoluble portion was I. Yellow crystals separated from the cooled filtrate. After further crystallizations from either benzene or chloroform, the pure monoacetate was obtained in the form of colorless crystals, m.p. 171.5–173.6° cor. It is soluble in dilute sodium hydroxide.

Anal. Calcd. for $C_{22}H_{20}O_4$: C, 75.84; H, 5.78; CH_3CO–, 12.3; mol. wt., 348. Found: C, 75.68; H, 5.75; CH_3CO–, 12.2; mol. wt., 329.[3]

Triacetyl Derivative of I.—A mixture of 1.0 g. of I, 2 ml. of acetic anhydride and a trace of sulfuric acid was heated for 30 minutes at 100°. The crude material was crystallized from 5 ml. of ethanol (1.29 g., 91%). The pure compound, obtained from methanol (1 g. in 3 ml.) or from ethanol (1 g. in 4 ml.) forms colorless crystals which melted at 104.8–105.6° cor.; it is insoluble in dilute alkali.

Anal. Calcd. for $C_{26}H_{24}O_6$: C, 72.21; H, 5.59; mol. wt., 432. Found: C, 71.88; H, 5.76; mol. wt., 410.[3]

RESEARCH LABORATORY
EX-LAX, INC.
BROOKLYN 17, N. Y.

(1) A. Baeyer, *Ann.*, **202**, 87 (1880).
(2) M. H. Hubacher, *Ind. Eng. Chem., Anal. Ed.*, **15**, 448 (1943).
(3) Signer method, as described by E. P. Clark, *ibid.*, **13**, 820 (1941).

The Synthesis of Nitrogen-containing Ketones. II. Ketones Derived from 2-Picoline, Quinaldine and 2,6-Lutidine

BY NEWTON N. GOLDBERG AND ROBERT LEVINE

RECEIVED MAY 21, 1952

In connection with an extensive program which is in progress in this Laboratory on the synthesis of potential chelating agents[1–5] containing heterocyclic nuclei, we have been interested in developing general methods for the synthesis of heterocyclic ketones. To date progress has been made in the thiophene, furan and 2-picoline series.[6–10]

The present report is concerned with further acylations of 2-picoline and the extension of the method recently described[10] to the condensation of quinaldine and 2,6-lutidine with a number of esters. Of the three ketones described in this paper which were obtained by acylating 2-picoline, 2-pyridyl 2-picolyl ketone was previously prepared by Wibaut and de Jong[11] in 13% yield by the interaction of 2-lithiopicolyl with benzonitrile and hydrolyzing the resulting ketimine. Five of the quinaldyl ketones, prepared in our study, have also been synthesized earlier. The methods employed by the earlier workers involved the interaction of the sodium or potassium derivative of quinaldine (prepared from the tar base and either sodium or potassium amide) with the appropriate esters. Thus, the methyl, ethyl and isopropyl ketones were prepared in 17–36% yields by Weiss and Hauser[12]; while the phenyl and 2-furyl ketones have been reported by Bergstrom and Moffat[13] in yields of 60–65% and 28%, respectively. Apparently only one acylated derivative of 2,6-lutidine has been reported. Thus, de Jong and Wibaut[14] have prepared 2-methyl-6-phenacylpyridine in 30% yield by the ketimine synthesis.

The method employed in our syntheses may be summarized by the following general equations where CH_3R represents 2-picoline, quinaldine or 2,6-lutidine.

$$C_6H_5Li + CH_3R \longrightarrow C_6H_6 + RCH_2L$$

$$RCH_2Li + R'CO_2R'' \longrightarrow R''OLi + RCH_2COR'$$

$$RCH_2COR' + RCH_2Li \longrightarrow (RCHCOR')Li \text{ and } R'C(OH)(CH_2R)_2$$

Our results are summarized in Table I. It may be seen that good to high yields of condensation products were obtained in all cases. While the present acylations of 2-picoline and quinaldine gave only ketonic products, the acylation of 2,6-

(1) S. R. Harris and R. Levine, THIS JOURNAL, **70**, 3360 (1948).
(2) S. R. Harris and R. Levine, *ibid.*, **71**, 1120 (1949).
(3) J. K. Sneed and R. Levine, *ibid.*, **72**, 5219 (1950).
(4) R. Levine and J. K. Sneed, *ibid.*, **73**, 4478 (1951).
(5) L. B. Barkley and R. Levine, *ibid.*, **73**, 4625 (1951).
(6) J. V. Heid and R. Levine, *J. Org. Chem.*, **13**, 409 (1948).
(7) R. Levine, J. V. Heid and M. W. Farrar, THIS JOURNAL, **71** 1207 (1949).
(8) M. W. Farrar and R. Levine, *ibid.*, **72**, 3695 (1950).
(9) M. W. Farrar and R. Levine, *ibid.*, **72**, 4433 (1950).
(10) N. N. Goldberg, L. B. Barkley and R. Levine, *ibid.*, **73**, 4301 (1951).
(11) J. P. Wibaut and A. P. de Jong, *Rec. trav. chim.*, **68**, 485 (1949).
(12) M. J. Weiss and C. R. Hauser, THIS JOURNAL, **71**, 2023 (1949).
(13) F. W. Bergstrom and A. Moffat, *ibid.*, **59**, 1494 (1937).
(14) A. P. de Jong and J. P. Wibaut, *Rec. trav. chim.*, **70**, 962 (1951).

TABLE I

SYNTHESIS OF PYRIDYL AND QUINOLYL KETONES OF THE TYPE RCH_2COR'

R	R'	Acylating ester methyl	Yield,[a] %	M.p. or b.p., °C. (mm.)	Analyses,[b] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Picrate	M.p.,[c] °C.	Analyses,[b] % Nitrogen Calcd.	Nitrogen Found
2-Pyridyl	2-Pyridyl	Picolinate	55.0[d]	149–150 (1.2)[e] M. 86–87[f]					14.14	14.23	Di	154–155[g,s]	17.07	16.77
2-Pyridyl	3-Pyridyl	Nicotinate	50.3	158.5–160.0 (1.3) M. 69–70[f]					14.14	14.37	Di	187.3–187.8[g,q]	17.07	16.76
2-Pyridyl	4-Pyridyl	Isonicotinate	75.7	M. 114.7–115.2[f]					14.14	14.25	Di	200.5–201.0[g,r]	17.07	17.14
2-Quinolyl	Methyl	Acetate	87.6	145–147 (2.5)[h] M. 76–77[i]							Mono	182–183[g,q]	13.52	13.26
2-Quinolyl	Ethyl	Propionate	94.0	142–143 (1.4)[h]							Mono	181–182[g,h,q]		
2-Quinolyl	Isopropyl	Isobutyrate[j]	89.2	152–154 (2.0)[h]					6.57	6.49	Mono	145–146[g,q]	12.67	12.50
2-Quinolyl	Phenyl	Benzoate	85.5	M. 115–116[h,k]							Mono	172–173[g,q]	11.76	11.79
2-Quinolyl	2-Furyl	2-Furoate	68.6	185–190 (1.2)[k] M. 103.0–103.3[f]					5.91	5.91	Mono	172–173[g,q]	12.01	12.19
2-Quinolyl	2-Thienyl	2-Thenoate	75.5	220–223 (2.2) M. 125.5–126.5[f]					5.53	5.76	Mono	159.5–160.0[g,r]	11.61	11.42
2-Quinolyl	2-Pyridyl	Picolinate	58.4	M. 152.5–154[f]					11.29	11.46	Di	171.5–172.0[g,r]	15.86	15.66
2-Quinolyl	3-Pyridyl	Nicotinate	53.2	M. 121–122[f]					11.29	11.17	Di	215.0–215.5[g,r]	15.86	15.83
2-Quinolyl	4-Pyridyl	Isonicotinate	77.1	M. 147.3–147.8[f]					11.29	11.20	Di	218.5–219.5[g,s]	15.86	15.92
6-Methyl-2-pyridyl	Methyl	Acetate	41.6[l,m]	105–106 (9.9)	72.45	72.43	7.43	7.24	9.39	9.61	Mono	137.7–138.3[r]	14.81	15.08
6-Methyl-2-pyridyl	Ethyl	Propionate	46.0[n]	114–115 (9.5)	73.59	73.43	8.03	7.88	8.58	8.66	Mono	121.5–122.2[r]	14.28	14.19
6-Methyl-2-pyridyl	*n*-Propyl	*n*-Butyrate[j]	55.6[o]	126–127 (10.3)	74.54	74.66	8.53	8.58	7.90	8.14	Mono	124.4–124.9[r]	13.79	13.85
6-Methyl-2-pyridyl	Isopropyl	Isobutyrate[j]	61.9[p]	119.5–120.5 (9.5)	74.54	74.68	8.53	8.67	7.90	8.00	Mono	124.0–124.5[r]	13.79	13.65
6-Methyl-2-pyridyl	Phenyl	Benzoate	94.5	150–151 (1.7) M. 77.3–77.7[f]	79.59	79.65	6.20	6.38	6.63	6.51	Mono	180–181[g,q]	12.72	12.75
6-Methyl-2-pyridyl	2-Furyl	2-Furoate	78.6	136–137 (1.4)	71.62	71.67	5.51	5.46	6.96	6.97	Mono	160.5–161.5[g,q]	13.02	13.11
6-Methyl-2-pyridyl	2-Thienyl	2-Thenoate	82.9	156–157 (1.6)	66.33	66.55	5.10	5.40	6.45	6.28	Mono	173–174[g,q]	12.55	12.57
6-Methyl-2-pyridyl	2-Pyridyl	Picolinate	66.4	156–157 (1.2) M. 48–49					13.20	13.22	Di	218.5–219.5[g,r]	16.71	16.84
6-Methyl-2-pyridyl	3-Pyridyl	Nicotinate	62.3	160–161 (1.2)					13.20	13.06	Di	198.2–198.8[g,r]	16.71	16.91
6-Methyl-2-pyridyl	4-Pyridyl	Isonicotinate	90.5	M. 111.0–111.7[f]					13.20	13.21	Di	200.0–200.5[g,s]	16.71	16.82

[a] All yields based on molar quantity of ester. [b] All analyses were performed by Mr. George Stragand of the Microanalytical Laboratory of the University of Pittsburgh. [c] Recrystallized from 95% ethanol. [d] This ketone and all those derived from 2-picoline give a blue-green color test with alcoholic iron(III) chloride solution. [e] See ref. 11. [f] Recrystallized from 60–70° petroleum ether. [g] Melts with decomposition. [h] See ref. 12. [i] Recrystallized from 60–70° petroleum ether cooled in a Dry Ice–acetone mixture. [j] Ethyl ester. [k] See ref. 13. [l] This ketone and all those derived from 2,6-lutidine give a weak red color test with alcoholic iron(III) chloride solution. [m] There was also obtained 35.3% of methyl bis-(2,6-lutidyl)-carbinol, b.p. 152–153° (1.3 mm.). *Anal.* Calcd. for $C_{16}H_{20}ON_2$: C, 74.96; H, 7.86; N, 10.93. Found: C, 75.11; H, 7.62; N, 11.01. Dipicrate recrystallized from 95% ethanol; m.p. 206.5–207.5° (dec.). *Anal.* Calcd. for $C_{28}H_{26}O_{15}N_8$: N, 15.86. Found: N, 15.42. [n] There was also obtained 31.8% of ethyl bis-(2,6-lutidyl)-carbinol, b.p. 164–165° (1.7 mm.). *Anal.* Calcd. for $C_{17}H_{22}ON_2$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.54; H, 8.14; N, 10.25. Dipicrate recrystallized from 95% ethanol; m.p. 190–190.7° (dec.). *Anal.* Calcd. for $C_{29}H_{28}O_{15}N_8$: N, 15.38. Found: N, 15.56. [o] There was also obtained 27.3% of *n*-propyl bis-(2,6-lutidyl)-carbinol, b.p. 150–152° (0.9 mm.). *Anal.* Calcd. for $C_{18}H_{24}ON_2$: C, 76.02; H, 8.51; N, 9.85. Found: C, 76.33; H, 8.71; N, 9.59. Dipicrate recrystallized from 95% ethanol; m.p. 185.8–186.6° (dec.). *Anal.* Calcd. for $C_{30}H_{30}O_{15}N_8$: N, 15.09. Found: N, 15.21. [p] There was also obtained 23.8% of isopropyl bis-(2,6-lutidyl)-carbinol, b.p. 154–155° (1.0 mm.). *Anal.* Calcd. for $C_{18}H_{24}ON_2$: C, 76.02; H, 8.51; N, 9.85. Found: C, 76.15; H, 8.58; N, 9.79. Dipicrate recrystallized from 95% ethanol; m.p. 180.8–181.4° (dec.). *Anal.* Calcd. for $C_{30}H_{30}O_{15}N_8$: N, 15.09. Found: N, 15.18. [q] Picrate colored yellow. [r] Picrate colored orange. [s] Picrate colored red.

lutidine with aliphatic esters gave rise to both ketones and carbinols as had been observed earlier[10] when 2-picoline was acylated with aliphatic esters. It should be noted that while those ketones derived from 2-picoline and 2,6-lutidine appeared to give copper salts when treated with copper(II) acetate solution, the salts could not be obtained in crystalline form. Furthermore, the ketones derived from quinaldine did not exhibit a visible reaction when treated similarly.[15]

Experimental

Starting Materials.—The tar bases and the methyl esters were obtained from commercial sources with the exception of the methyl pyridinecarboxylates which were prepared by the method of Levine and Sneed.[16]

Operating Procedure for Conducting Condensations.—The syntheses were carried out by the interaction of the lithium derivatives of the tar bases with the appropriate esters as described earlier.[10]

Acknowledgment.—The authors gratefully acknowledge the support of the U. S. Atomic Energy Commission during the course of the investigation.

(15) The reaction between divalent cations and these ketones is being studied by Dr. W. C. Fernelius and his co-workers at the Pennsylvania State College. Their results will be reported at a later date.

(16) R. Levine and J. K. Sneed, THIS JOURNAL, **73**, 5614 (1951).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF PITTSBURGH
PITTSBURGH, PA.

An Agent from *E. Coli* Causing Hemorrhage and Regression of an Experimental Mouse Tumor. II. The Component Monosaccharides[1]

BY MIYOSHI IKAWA, J. B. KOEPFLI, S. G. MUDD AND CARL NIEMANN[2]

RECEIVED MAY 19, 1952

It has been shown previously[3] that the agent, isolated from cultures of *E. coli*, which produces a hemorrhagic response in and causes the regression of the experimental mouse sarcoma 180 is a complex polysaccharide which contains both a peptide and a phospholipide component. An acid hydrolysate of the above polysaccharide was found to possess a reducing power of 52–55 equivalent % glucose and a hexosamine content of 15–17 equivalent % glucosamine.

Ultraviolet absorption spectra of solutions of the experimental mouse tumor hemorrhagic agent in 79% sulfuric acid[4,5] are given in Fig. 1. The lack of any appreciable absorption at 25° is indicative of the absence of ketoses and nucleic acids. The character of the spectrum of the heated solution suggests the probable absence of 6-desoxyaldehexoses (no maximum in the 327 mμ region), aldopentoses (low extinction value at 300 mμ), aldohexuronic acids (low extinction values at 220 and 294 mμ), and mannose (no maximum in the 250 mμ region). Paper chromatography, with phenol and collidine as solvents,[6] of an acid hydrolysate of the hemorrhagic agent gave evidence of the presence of glucosamine and of either or both glucose and galactose. Of the qualitative carbohydrate tests applied directly to the agent, the Scherer test for inositol[7] was negative, the mucic acid test for galactose, or galacturonic acid, positive, and the Morgan–Elson test for apparent N-acetylhexosamine,[8] negative. The phenylhydrazone test for mannose, performed on a hydrolysate of the agent, was negative. The presence of hexosamine has been commented upon previously.[3] By drastic hydrolysis of the hemorrhagic agent D-glucosamine was isolated and identified as the hydrochloride and the N-carbobenzoxy derivative. With milder conditions of hydrolysis D-glucose and D-galactose were isolated and identified as the diethyl mercaptals,[9] the substituted benzimidazoles[10] and the picrates thereof.[10] The properties of the above derivatives are summarized in Table I.

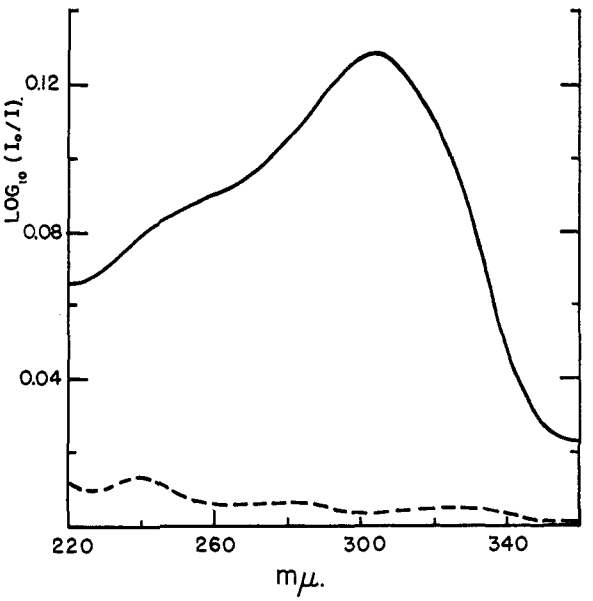

Fig. 1.—Ultraviolet absorption spectra of solutions of the mouse tumor hemorrhagic agent from *E. coli* in 79% sulfuric acid; solid line, after 15 min. at 100°; dotted line, after 2 hours at 25°.

The observation that the component monosaccharides of the experimental mouse tumor hemorrhagic agent from *E. coli* are D-glucosamine, D-glucose and D-galactose serves to differentiate this substance from the corresponding agent obtained from *B. prodigiosus* which was reported to contain hexosamine, a methylpentose, and presumably an aldehexose.[11]

Experimental

Hemorrhagic Agent.—All experiments were conducted on the ethanol-fractionated material designated in our previous communication[3] as fraction B_1.

(1) Supported from 1938 to 1943 by grants from the Argonaut Foundation and from 1948 onwards by grants from the National Cancer Institute of the U. S. Public Health Service.

(2) To whom inquiries regarding this article should be sent.

(3) M. Ikawa, J. B. Koepfli, S. G. Mudd and C. Niemann, *J. Nat. Cancer Inst.*, **13**, 157 (1952).

(4) M. Ikawa and C. Niemann, *J. Biol. Chem.*, **180**, 923 (1949).

(5) M. Ikawa and C. Niemann, *Arch. Biochem. Biophys.*, **31**, 62 (1951).

(6) S. M. Partridge, *Biochem. J.*, **42**, 238 (1948).

(7) J. Scherer, *Ann.*, **81**, 375 (1852).

(8) W. T. J. Morgan and L. A. Elson, *Biochem. J.*, **28**, 988 (1934).

(9) M. L. Wolfrom and J. V. Karabinos, THIS JOURNAL, **67**, 500 (1945).

(10) S. Moore and K. P. Link, *J. Biol. Chem.*, **133**, 297, 303 (1940).

(11) J. L. Hartwell, M. J. Shear, J. R. Adams, Jr., and A. Perrault, *J. Nat. Cancer Inst.*, **4**, 107 (1943).