was not isolated because of its instability. It is either 5-methyl-3-[5′-(4′-ureido)-imidazolyl]-1,2,4-oxidiazole or its 4′-acetyl derivative. The fact that it is closely related to the final product, the 4′-acetamido derivative, is demonstrated by hydrolyzing the solid mixture of the two imidazoles obtained from a 3-hour acetylation. After heating one hour in 1 *N* HCl, chromatographic analysis of the hydrolyzate shows it to contain only 5-methyl-3-[5′-(4′-amino)-imidazolyl]-1,2,4-ozadiazole. The 5-methyl-3-[5′-(4′-acetamido-, and 5-methyl-3-[5′-(4′-amino)imidazolyl]-1,-2,4-oxadiazoles prepared from 2,6-diaminopurine 1-N-oxide were spectrally identical with those from adenine 1-N-oxide.

Preparation of a 2-Methyladenine 1-N-Oxide.—2-Methyladenine (1 g.) was suspended in a mixture of acetic acid (100 ml.) and 30% hydrogen peroxide (10 ml.). After 4 hours at room temperature the solid dissolved. The solution was kept 6 days at room temperature, at which time chromatographic analysis showed that the material in solution was mainly 2-methyladenine N-oxide. The hydrogen peroxide was destroyed by adding 10% palladium-on-charcoal (150 mg.) and stirring the solution overnight. The palladium-on-charcoal was removed by filtration and the filtrate was evaporated to 7 ml. when pure 2-methyladenine 1-N-oxide (165 mg.) crystallized. After evaporation to 4 ml. a further 275 mg. of the oxide crystallized. Further crops (356 mg.) were not pure, and were recrystallized from water. A total of 623 mg. (56%) was obtained as white crystals, decomposing at 306° (some initial decomposition at 230°). Analysis was performed on a sample after drying at 78° for 24 hours over phosphorus pentoxide.

Anal. Calcd. for $C_6H_7N_5O\cdot H_2O$: C, 39.34; H, 4.95; N, 38.23. Found: C, 39.31; H, 5.33; N, 38.83.

Hydrolysis of 2-Methyladenine 1-N-Oxide.—2-Methyladenine 1-N-oxide (36 mg.) was dissolved in 2 *N* HCl (6.0 ml.) and the solution was refluxed for 20 minutes. At the end of this time aliquots of the solution were chromatographed in solvents A and B. The main spot observed on the chromatograms was at R_f 0.22 in A, and 0.55 in B, identical with 4-aminoimidazole-5-carboxamidoxime.[9] This hydrolysis product had the same ultraviolet spectrum as 4-aminoimidazole-5-carboxamidoxime and gave the same orange color with Pauly reagent.

Hydrogenation of 2-Methyladenine 1-N-Oxide.—2-Methyladenine 1-N-oxide (50 mg.) was dissolved in acetic acid (25 ml.). Raney nickel (10 mg.) was added and the mixture was shaken with hydrogen for 21 hours, at which time 6.0 ml. (theory 6.7 ml.) of hydrogen had been absorbed. Chromatograms run on the solution showed that it still contained 2-methyladenine 1-N-oxide but that most had been reduced to a material with R_f's in solvents A (0.39) and B (0.38), and spectra which were identical with those of 2-methyladenine.

Preparation of O-Acetyl-2-methyladenine 1-N-Oxide.—2-Methyladenine 1-N-oxide (62 mg.) was suspended in a 1:1 mixture of acetic acid and acetic anhydride (4 ml.). After 5 minutes the solid went into solution and the resulting solution was lyophilized to a yellow solid (59 mg.). Partial purification of the O-acetyl derivative could be effected by suspending the solid in ethyl acetate, adding methyl alcohol, and warming to obtain a clear solution. O-Acetyl-2-methyladenine 1-N-oxide, contaminated with minor amounts of starting material, crystallized when the solution was cooled. The O-acetyl derivative had a spectrum similar to O-acetyladenine 1-N-oxide with peaks at 234 and 287 mμ. Upon hydrolysis, the O-acetyl-2-methyladenine 1-N-oxide was reconverted to 2-methyladenine 1-N-oxide.

Further Acetylation of 2-Methyladenine 1-N-oxide.—2-Methyladenine 1-N-oxide was refluxed with an acetic anhydride–acetic acid mixture for 2 hours, then chromatographed. The main product, separated by chromatography, was a material (R_f in A of 0.61; in B of 0.67) which exhibits a yellow fluorescence in ultraviolet and is negative to Pauly's reagent. The product could be isolated from solution, but soon became tarry, and resisted purification.

Reaction of 8-Hydroxyadenine 1-N-Oxide with Acetic Anhydride.—8-Hydroxyadenine 1-N-oxide (2.1 g.) was suspended in a solution of acetic anhydride (110 ml.) and acetic acid (10 ml.). The suspension was heated and dissolution of suspended material occurred on approach to reflux temperature. The brown solution obtained was refluxed for 12 hours and contained, as determined by paper chromatography, a major product (R_f 0.83 in solvent A and R_f 0.61 in solvent B). The solution was evaporated to a viscous residue and the residue obtained was refluxed with 3 *N* HCl (25 ml.) for 2 hours. Evaporation of the hydrochloric acid solution yielded 1.1 g. of a pale brown solid. The solid was recrystallized from glacial acetic acid (60 ml.) yielding 0.2 g. of chromatographically pure 5-methyl-3-[5′-(2′-hydroxy-4′-amino)-imidazolyl]-1,2,4-oxadiazole monohydrochloride, decomposition point 205°.

Anal. Calcd. for $C_6H_7N_5O_2\cdot HCl$: N, 32.18. Found: N, 31.85.

Halogen was present, and no 2,8-dihydroxyadenine was detected by chromatography.

NEW YORK 21, N. Y.

[CONTRIBUTION NO. 1049 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Synthesis of Nitrogen-containing Ketones. IX. The Acylation of 1-(2-Pyridyl)-3-dimethylaminopropane and 1-(2-Pyridyl)-1-phenyl-3-dimethylaminopropane[1—3]

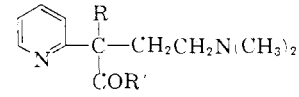
BY STUART RAYNOLDS[4] AND ROBERT LEVINE

RECEIVED JUNE 22, 1959

A study has been made of the acylation of 1-(2-pyridyl)-3-dimethylaminopropane (I) and 1-(2-pyridyl)-1-phenyl-3-dimethylaminopropane (II) using phenylsodium and/or phenyllithium as the condensing agents to give ketones of the type $2\text{-}C_5H_4NCR(COR^1)CH_2CH_2N(CH_3)_2$, where R = H and C_6H_5 and R^1 = alkyl and phenyl. Comments are made concerning the molar proportions of I and II:condensing agent:ester which are required to give maximum yields of the ketones. The acylation of 1-(2-pyridyl)-1-phenyl-3-(N-pyrrolidino)-propane is also described.

In the first paper of this series, we reported[5] the synthesis of a series of 2-picolyl ketones, $2\text{-}C_5H_4NCH_2COR$ (where R is an alkyl, aryl or heterocyclic radical) by the acylation of 2-picoline with esters using phenyllithium as the condensing agent.

The present paper is concerned with the synthesis of two series of ketones of the formula



series I: R = H and R′ = alkyl and phenyl
series II: R = C_6H_5 and R′ = alkyl and phenyl

(1) For paper VIII in this series, see S. Raynolds and R. Levine, THIS JOURNAL, **82**, 472 (1960).

(2) Part of this work was performed under Contract No. AT(30-1)-670 between the U. S. Atomic Energy Commission and the University of Pittsburgh.

(3) This paper is based on part of the thesis presented by S. Raynolds to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements for the Ph.D. degree.

(4) Monsanto Chemical Co. Research Fellow for the academic year 1958–1959.

(5) N. N. Goldberg, L. B. Barkley and R. Levine, THIS JOURNAL, **73**, 4301 (1951).

TABLE I

ACYLATION OF 2-$C_5H_4N(CH_2)_3N(CH_3)_2$ (I) TO GIVE THE KETONES 2-$C_5H_4NCH(COR)(CH_2)_2N(CH_3)_2$

Compound	R	Yield, %	B.p. or m.p. °C.	Mm.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	C_6H_5	30,[a,b] 66[b] 85[c]	132–133	0.28[d]					
2	CH_3	35,[b] 84[c]	86–87	.33	$C_{12}H_{18}N_2O$	69.87	69.62	8.80	8.55
3	C_2H_5	49[b]	90–91	.29	$C_{13}H_{20}N_2O$	70.87	70.94	9.15	9.40
4	n-C_3H_7	44[b]	95–96	.26	$C_{14}H_{22}N_2O$	71.75	71.72	9.46	9.58
5	$(CH_3)_2CH$	48,[b] 85[c]	89–90	28	$C_{14}H_{22}N_2O$	71.75	71.62	9.46	9.11
6	$(CH_3)_3C$	50[b]	90–91	.29	$C_{15}H_{24}N_2O$	72.54	72.13	9.74	9.62
			Dipicrates						
1a			179.2–179.8[e]						
2a			179.7–180.4[e]		$C_{24}H_{24}N_8O_{15}$	43.38	43.60	3.63	3.63
3a			169.0–170.0[e]		$C_{25}H_{26}N_8O_{15}$	44.25	44.21	3.86	3 98
4a			149.6–150.6[e]		$C_{26}H_{28}N_8O_{15}$	45.09	44.78	4.07	3.65
5a			155.8–156.7[e]		$C_{26}H_{28}N_8O_{15}$	45.09	44.96	4.07	3.86
6a			171.3–172.5[e]		$C_{27}H_{30}N_8O_{15}$	45.89	45.49	4.28	4.15

[a] A 1:1:1 molar ratio of I:condensing agent:ester was used. In all the other reactions a 2:2:1 molar ratio of reactants was used. [b] Phenyllithium in ether was used as the condensing agent. [c] Phenylsodium in benzene was used as the condensing agent. [d] Literature value, b.p. 140–149° at 0.3 mm. for crude material (see ref. 7). [e] Recrystallized from 95% ethanol.

These ketones were prepared by acylating 1-(2-pyridyl)-3-dimethylaminopropane (I) and 1-(2-pyridyl)-1-phenyl-3-dimethylaminopropane (II) with a series of esters using phenylsodium in benzene and/or phenyllithium in ether as the condensing agents. Compound I was synthesized in 64% yield by alkylating 2-picoline with β-dimethylaminoethyl chloride employing phenylsodium as the condensing agent. Compound II was obtained in 79% yield by a similar alkylation of 2-benzylpyridine using phenyllithium as the condensing agent.

$$\text{2-}C_5H_4NCH_2R + ClCH_2CH_2N(CH_3)_2 \xrightarrow[C_6H_5Li]{C_6H_5Na \text{ or}} HCl + \text{2-}C_5H_4NCH(R)CH_2CH_2N(CH_3)_2$$

I, R = H
II, R = C_6H_5

The yields of I and II compare favorably with those, 60 and 80%, respectively, which were obtained earlier by Sperber, et al.,[6] using potassium amide as the condensing agent.

The results of the acylation of I with ethyl benzoate and five aliphatic esters are found in Table I. In the three cases where the same compounds (1, 2 and 5) were prepared using phenyllithium and phenylsodium as the condensing agents, higher yields were obtained using phenylsodium. When Compound I was acylated with ethyl benzoate, using phenyllithium(III) as the condensing agent, the yield of 1-benzoyl-1-(2-pyridyl)-3-dimethylaminopropane (V) was 66% of theory using a 2:2:1 molar ratio of I:phenyllithium:ester and only 30% of theory using equivalents of reactants. These results can be rationalized on the basis of the previously suggested[5] mechanism for the acylation of 2-picoline. Thus, the methinyl hydrogen on the carbon atom next to the pyridine ring of the initially-formed ketone V is sufficiently acidic so that it reacts with IV, the anion of I, to form VI, the anion of the ketone. Hence a 2:2:1 molar ratio of I:III:ester is required to give maximum yields of V.

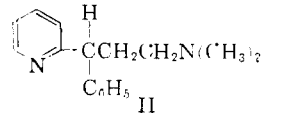
Of the six compounds in Table I, only 1-benzoyl-1-(2-pyridyl)-3-dimethylaminopropane (R = C_6H_5) has been previously reported. Thus, Sperber, *et al.*,[7] alkylated 2-phenacylpyridine (VII) with β-dimethylaminoethyl chloride using sodium amide as the condensing agent and obtained a mixture of 19% of the C-alkylated compound V and 65% of the O-alkylated isomer VIII as compared with the 85% yield of V which was isolated in the present study by acylating I with ethyl benzoate using phenylsodium as the condensing agent. More recently, Beckett and Kerridge[8] repeated the experiment described by Sperber, *et al.*,[7] and they obtained only the enol ether, VIII.

$$\text{2-}C_5H_4N(CH_2)_3N(CH_3)_2 \text{ (I)} + C_6H_5CO_2C_2H_5 \xrightarrow{C_6H_5Na} C_2H_5OH + \text{2-}C_5H_4NCH(COC_6H_5)(CH_3)_3N(CH_3)_2 \text{ (V, 85\%)}$$

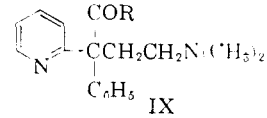
$$\text{2-}C_5H_4NCH_2COC_6H_5 \text{ (VII)} + ClCH_2CH_2N(CH_3)_2 \xrightarrow{NaNH_2} \text{V} + \text{2-}C_5H_4NCH{=}C(C_6H_5)O(CH_2)_2N(CH_3)_2 \text{ (VIII, 65\%)}$$

We next turned our attention to the acylation of 1-(2-pyridyl)-1-phenyl-3-dimethylaminopropane (II).[9] This compound has been acylated with one aromatic and six aliphatic esters and the results are found in Table II.

Compound II has only one active hydrogen atom and hence any ketone IX formed by acylating II does not have labile hydrogen on the carbon atom next to the pyridine ring. Unless the R group of IX-



II



IX

contains a hydrogen atom on the carbon atom alpha to the carbonyl group, formation of a ketone anion at the end of the reaction is not possible. In such a

(6) N. Sperber, D. Papa, E. Schwenk, M. Sherlock and R. Fricano, THIS JOURNAL, **73**, 5752 (1951).

(7) N. Sperber, R. Fricano and D. Papa, *ibid.*, **72**, 3069 (1950).

(8) A. H. Beckett and K. A. Kerridge, *J. Chem. Soc.*, 2948 (1954).

(9) This compound is called Trimeton by Schering Corporation.

TABLE II

ACYLATION OF 2-$C_5H_4NCH(C_6H_5)(CH_2CH_2N(CH_3)_2)$ (II) TO GIVE THE KETONES 2-$C_5H_4NC(COR)(C_6H_5)(CH_2CH_2N(CH_3)_2)$[a]

Compound	R	Yield, %	B.p. or m.p. °C.	Mm.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
7	CH_3	30,[b] 67[c]	151–152	0.62	$C_{18}H_{22}N_2O$	76.54	76.82	7.85	7.98
8	C_2H_5	32,[b] 75[c]	144–145[d]	.27					
9	n-C_3H_7	40,[b] 69[e]	152–153	.29	$C_{20}H_{26}N_2O$	77.37	77.14	8 84	8.48
10	$(CH_3)_2CH$	42,[b] 69[e]	145–146	.29	$C_{20}H_{26}N_2O$	77.37	76.91	8.84	8.48
11	C_6H_5	68,[b] 64[e]	200–205	1.0	$C_{23}H_{24}N_2O$	80.20	80.33	7.02	7.14
			86.0–87.4[e]						
12	$(CH_3)_3C$[e]	10,[c,f] 63,[c,g] 32[b,g]	156–158	0.25	$C_{21}H_{26}N_2O$	77.75	77.49	8.70	8 92
			65–67[e]						
13	$CH(C_2H_5)(C_4H_9$-$n)$	70,[b] 82	176–177	0.28	$C_{24}H_{34}N_2O$	78.54	78.77	9.35	9.48
			Dipicrates						
7a			159.2–160.4[h]		$C_{30}H_{28}N_8O_{15}$	48.65	48.69	3.81	3.85
8a			144.2–145.3[i]						
9a			150.5–151.4[h]		$C_{32}H_{32}N_8O_{15}$	50.00	50.06	4.19	4.19
10a			159.0–160.0[h]		$C_{32}H_{32}N_8O_{15}$	50.00	49.77	4.19	4.32
11a			199.0–200.5[h]		$C_{41}H_{33}N_{11}O_{22}$[j]	47.73	48.09	3.22	3.58
12a			156.6–157.4[h]		$C_{33}H_{34}N_8O_{15}$	50.64	50.94	4.38	4.52
13a			[k]						

[a] Except where noted, the ether solution of the lithium derivative of II, prepared by the addition of II to an equivalent of phenyllithium in ether, was refluxed for 30 minutes. Then, the ester was added and the mixture was refluxed for an additional 60 minutes prior to hydrolysis. [b] A 1:1:1 molar ratio of II:phenyllithium:ester was used. [c] A 2:2:1 molar ratio of II:phenyllithium:ester was used. [d] Literature value, b.p. 151–155° at 0.4 mm. (see ref. 10). [e] Recrystallized from 60–70° petroleum ether. [f] This reaction mixture was refluxed for 1 hour after the ester was added. [g] This reaction mixture was refluxed for 28 hours after the ester was added. [h] Recrystallized from 95% ethanol. [i] This is a maleate and was recrystallized from ethyl acetate; literature value m.p. 142–143° (see ref. 10). [j] This derivative analyzed as a tripicrate. [k] Attempts to prepare a crystalline derivative of this ketone failed.

case (*e.g.*, R = C_6H_5), a 1:1 molar ratio of the anion of II to ester should be sufficient to give maximum yields. If, however, IX contains active hydrogen atoms in R (*e.g.*, R = CH_3, CH_3CH_2, $CH_3CH_2CH_2$ or $(CH_3)_2CH$), the molar ratio of the anion of II to ester to give maximum yields of IX should be 2:1. These arguments are supported by the data on compounds 7–11 which appear in Table II.

However, when the acylating ester is ethyl pivalate, the resulting ketone (IX, R = $(CH_3)_3C$) has no enolizable hydrogen atoms, and a 1:1 molar ratio of the anion of II to ethyl pivalate should suffice to give maximum yields. The data in Table II show, however, that an excess of the anion of II is required to give an appreciable yield of product.

The ketone, 1-dimethylamino-3-(2-pyridyl)-3-phenyl-5-ethylnonanone-4, which results from the acylation of II with ethyl 2-ethylhexoate, has active hydrogen in the R group, $CH(C_2H_5)(C_4H_9$-$n)$. It might be expected, therefore, that a 2:1 molar ratio of the anion of II to ester would be required to give maximum yields. The yield (70%) obtained using a 1:1 molar ratio of anion to ester is therefore far greater than would be expected from the results of the acylation of II with other esters containing active hydrogen atoms. Furthermore, the use of a 2:1 molar ratio of anion to ester did not increase the yield (82%) of ketone appreciably. These facts suggest that the anion of II is not able to convert the ketone formed in this reaction to its anion probably because of steric reasons.

Only one of the compounds which appear in Table II, *i.e.*, 1-(dimethylamino)-3-(2-pyridyl)-3-phenylhexanone-4 (XI) (compound 8 in Table II) has been previously reported. Thus, Ehrhart and Bestim[10] obtained XI in unreported yield by first alkylating ethyl phenyl-(2-pyridyl)-acetate with β-dimethylaminoethyl chloride to give ethyl α-phenyl-α-(2-pyridyl)-γ-(dimethylamino)-butyrate (X) using sodium amide as the condensing agent. Then, X was converted to XI by reaction with ethylmagnesium bromide. Ehrhart, et al.,[11] have also obtained XI by the addition of a sodium dispersion in ether to a mixture of II and chlorobenzene[12] followed by the addition of ethyl propionate.

None of the expected ketone XI was obtained when Sperber, *et al.*,[6] treated α-phenyl-α-(2-pyridyl-γ-(dimethylamino)-butyronitrile (XII), $C(CN)(C_6H_5)(2\text{-}C_5H_4N)(CH_2CH_2N(CH_3)_2)$, with ethylmagnesium bromide or ethyllithium. From this reaction, there was obtained a mixture of recovered XII and II, which apparently arises by the removal of the nitrile group from XII (by the Grignard reagent or organolithium compound) and its replacement by a hydrogen atom.

Finally, the pyrrolidine analog of II, *viz.*, 1-(2-pyridyl)-1-phenyl-3-(N-pyrrolidino)-propane (XIII), was prepared in 68% yield by alkylating 2-benzylpyridine with N-(2-chloroethyl)-pyrrolidine using phenyllithium as the condensing agent. The acylation of the lithium derivative of XIII with ethyl propionate gave 1-(N-pyrrolidino)-3-phenyl-3-(2-pyridyl)-hexanone-4 (XIV) in yields of 30 and 57%, respectively, using a 1:1 and 2:1 molar ratio of the pyrrolidine derivative to ester.[13]

(10) G. Ehrhart and W. Bestim, U. S. Patent 2,731,462, Jan. 17, 1956.

(11) G. Ehrhart, K. Schmitt and H. Ott, U. S. Patent 2,774,768, Dec. 18, 1956.

(12) Apparently the sodium dispersion and chlorobenzene react first to give phenylsodium, which then metalates II.

(13) This ketone has been prepared previously in unreported yield (see ref. 10) by the alkylation of ethyl phenyl-(2-pyridyl)-acetate with N-(2-chloroethyl)-pyrrolidine followed by the reaction of the resulting ester with ethylmagnesium bromide.

Experimental[14]

Alkylation of Pyridine Derivatives. (a) Reaction of 2-Picoline with β-Dimethylaminoethyl Chloride Using Phenylsodium as the Condensing Agent.—The previously described procedure[1] for the alkylation of 3-picoline using sodium diisopropylamide as the condensing agent was employed except that phenylsodium was used in place of sodium diisopropylamide. Thus, from the reaction of a benzene suspension of phenylsodium (0.6 mole), 2-picoline (0.6 mole, 55.8 g.) and β-dimethylaminoethyl chloride (0.6 mole, 64.2 g.) there was obtained 62.9 g. (64%) of 1-(2-pyridyl)-3-dimethylaminopropane, b.p. 97–99° at 6.0 mm.[6]

(b) Reaction of 2-Benzylpyridine with β-Dimethylaminoethyl Chloride and N-(2-Chloroethyl)-pyrrolidine Using Phenyllithium as the Condensing Agent.—The previously described[15] procedure for alkylating 2-picoline was followed. Thus, from the reaction of an ether solution of phenyllithium (1.0 mole), 2-benzylpyridine (1.0 mole, 169 g.) and β-dimethylaminoethyl chloride (1.0 mole) there was isolated 188.9 g. (79%) of 1-(2-pyridyl)-1-phenyl-3-dimethylaminopropane, b.p. 128–129° at 0.85 mm.[6]; picrate, m.p. 201–202°[6] (from 95% ethanol).

Similarly, from the interaction of one mole each of phenyllithium, 2-benzylpyridine and N-(2-chloroethyl)-pyrrolidine there was isolated 183 g. (68%) of 1-(2-pyridyl)-1-phenyl-3-(N-pyrrolidino)-propane, b.p. 136–138° at 0.18 mm.

Anal. Calcd. for $C_{18}H_{22}N_2$: C, 81.15; H, 8.33. Found: C, 80.68; H, 8.25.

This compound formed a dipicrate, m.p. 170–171° (from 95% ethanol).

Anal. Calcd. for $C_{30}H_{28}N_8O_{14}$: C, 49.72; H, 3.89. Found: C, 50.04; H, 4.02.

Acylation of 1-(2-Pyridyl)-3-dimethylaminopropane (I), 1-(2-Pyridyl)-1-phenyl-3-(dimethylamino)-propane (II) and 1-(2-Pyridyl)-1-phenyl-3-(N-pyrrolidino)-propane (XIII).—These compounds were acylated using phenylsodium and/or phenyllithium as the condensing agents using the procedures for similar reactions which were previously described.[1,5] The properties of the ketones which were obtained by acylating I and II appear in Tables I and II, respectively. From the reaction of XIII (0.2 mole, 54.3 g.), phenyllithium (0.2 mole) and ethyl propionate (0.1 mole), there was obtained 18.3 g. (57%) of 1-(N-pyrrolidino)-3-phenyl-(2-pyridyl)-hexanone-4, b.p. 190–195° at 1 mm. (literature value[10] b.p. 165–170° at 0.15 mm.). The ketone forms a succinate salt, m.p. 149.0–149.8° (from ethyl acetate, literature value,[10] m.p. 144–146°).

PITTSBURGH 13, PENNA.

(14) The 2-picoline and 2-benzylpyridine were supplied through the courtesy of Dr. F. E. Cislak, Reilly Tar and Chemical Corp.

(15) C. Osuch and R. Levine, THIS JOURNAL, **78**, 1723 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

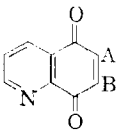
Quinolinequinones. V. 6-Chloro- and 7-Chloro-5,8-quinolinequinones[1a]

BY YOLANDA T. PRATT WITH NATHAN L. DRAKE[1b]

RECEIVED JULY 6, 1959

6-Chloro- and 7-chloro-5,8-quinolinequinone (II and III) were prepared and aryl groups were introduced at the unsubstituted positions of the quinone rings by reaction with diazonium salts; alkyl groups were introduced by peroxide alkylation. The 7-aryl-6-chloro- and 6-aryl-7-chloro-5,8-quinolinequinones were readily hydrolyzed to the corresponding hydroxyl derivatives. The parent compound, 5,8-quinolinequinone, adds hydrogen chloride at the 6,8-positions exclusively to yield 6-chloro-5,8-dihydroxyquinoline under anhydrous conditions.

Several of the derivatives of 5,8-quinolinequinone[2] described in preceding papers of this series have displayed significant amebicidal activity in preliminary tests. One of the most effective of these was 7-undecyl-6-hydroxy-5,8-quinolinequinone (I).[3] Since the well-known amebicides Vioform and Diodoquin are halogenated quinolines, it was of interest to investigate the activity of some halogenated quinolinequinones as well as certain other hydroxyquinolinequinones. In the



I, A = OH, B = n-$C_{11}H_{23}$
II, A = Cl, B = H
III, A = H, B = Cl

present work a variety of potential parasiticides have been prepared from 6-chloro- and 7-chloro-5,8-quinolinequinone (II and III) as shown in the table. The first two compounds, IV and V, are modifications of I and its isomer, 6-undecyl-7-hydroxy-5,8-quinolinequinone, in which the hydroxyl groups are replaced by chlorine. A second type of derivative is represented by the 7-aryl-6-chloro- and 6-aryl-7-chloro-5,8-quinolinequinones, VI–XIII, with various p-substituents in the aryl groups. In compounds XIV–XX the alkyl group of I and its isomer are replaced by p-substituted aryl groups.

The parent 6-chloro-5,8-quinolinequinone (II) was synthesized by oxidation of 6-chloro-5,8-diaminoquinoline obtained from 6-chloro-8-aminoquinoline[4] by diazonium coupling and subsequent reduction. The yield of the diamine (32%) was very poor in contrast to the high yield of the positively substituted 6-methoxy-5,8-diaminoquinoline previously prepared by the same procedure.[3] The over-all yield of the chloroquinone II from 6-chloro-8-aminoquinoline was 24%. The 7-chloroquinone III was readily obtained in 42% over-all yield from 5-nitro-8-hydroxyquinoline by chlorination at the 7-position followed by reduction to the 5-amino compound and oxidation of the latter. This procedure is an adaptation of Petrow and Sturgeon's synthesis of 7-bromo-5,8-quinolinequinone.[5]

The undecyl derivatives (IV and V) of the two chloroquinolinequinones were prepared by alkylation of the parent chloroquinones with dilauroyl

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(2) "Chemical Abstracts" indexes list this compound as 5,8-quinolinedione.

(3) Y. T. Pratt with N. L. Drake, THIS JOURNAL, **77**, 4664 (1955).

(4) H. Gilman, *et al.*, *ibid.*, **68**, 1577 (1946).

(5) V. Petrow and B. Sturgeon, *J. Chem. Soc.*, 570 (1954).