CAUTION: Prolonged skin contact with ketone **6** and its derivatives may be fatal.

Registry No.—**2**, 5144-46-7; **3**, 26932-22-9; **4**, 26932-23-0; **5**, 26913-18-8; **7**, 26932-24-1.

Acknowledgments—The authors are grateful to L. Shadoff for the mass spectral data, to R. Nyquist for the infrared spectra, to J. Heeschen and T. Evans for the nmr data, and to L. Swim and P. North for the elemental analyses.

Synthesis and Certain Reactions of 1-Aryl-4-(2-quinolyl)-1,3-butanediones, a New Class of β-Diketones[1]

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In connection with the synthesis of potential new antimalarial agents, a series of 1-aryl-4-(2-quinolyl)-1,3-butanediones (**4**) were required as key intermediates. In spite of their seemingly simple array of functionality, β-diketones of type **4** have not been reported. Moreover, their preparation *via* standard Claisen condensations of a 2-quinolineacetic acid ester with substituted acetophenones appeared to hold little promise of success, owing to the probability that the basic reagents commonly employed in such reactions would preferentially abstract one of the highly acidic methylene hydrogens of the ester.

We now wish to describe a general method for the preparation of this new class of β-diketones as exemplified by the synthesis of five such compounds from readily available starting materials (see Scheme I). The present sequence involved metalation of quinaldine (**1**) with *n*-butyllithium in tetrahydrofuran–hexane at room temperature to afford lithio derivative **2**, which was then acylated with ethyl acetate to give 2-acetonylquinoline (**3**).[3] Completion of the β-dicarbonyl side chain was then accomplished by selective aroylation at the methyl position of **3** using the appropriate aromatic ester and excess sodium hydride in refluxing 1,2-dimethoxyethane as the condensing agent (see Table I). The rather unusual tendency for ketone **3** to undergo preferential aroylation at the less acidic methyl site may be due to the fact that the azomethine function imparts

SCHEME I

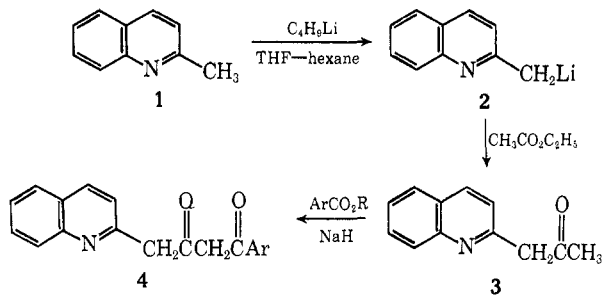


TABLE I[a]

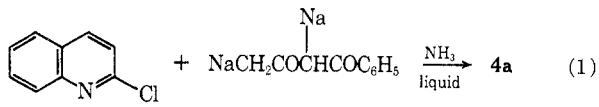
AROYLATIONS OF 2-ACETONYLQUINOLINE (**3**) TO PRODUCE β-DIKETONES **4**

β-Diketone Ar	No.	Reaction period, hr	Yield, %	Mp, °C
C_6H_5	**4a**	24	56	138–139.5[b]
C_6H_4Cl-*p*	**4b**	12	62	158–160[c]
3,4-$C_6H_3(Cl)_2$	**4c**	4	64	186–188[c]
p-$C_6H_4OCH_3$	**4d**	22	45	145–147[c]
3,4,5-$C_6H_2(OCH_3)_3$	**4e**	24	30	158–160[c]

[a] Satisfactory analytical data (±0.3 for C, H, N, and when present Cl) were found for all compounds: Ed. [b] Recrystallized from methanol. [c] Recrystallized from 95% ethanol.

to **3** chemical characteristics similar to those of a β-diketone. Consequently, these condensations may then proceed by one of the possible mechanistic pathways recently proposed to account for the conversion of β-diketones to 1,3,5-triketones under similar reaction conditions.[4] Incidentally, alkali amides, which have also been used to effect terminal aroylations of β-diketones,[5] were found to be much less satisfactory than sodium hydride for the conversion of **3** to **4a**.

Structural assignments for new β-diketones **4a–e** were confirmed by analyses (Table I), spectral data, and, in the case of **4a**, independent synthesis from 2-chloroquinoline and disodiobenzoylacetone (eq 1).[6] The nmr



(1)

spectra of **4a–e** (Table II), which had multiple peaks in the vinyl proton region, were consistent with the presence of several enolic forms for each of these compounds in solution. Comparison of the integrated intensity of the methylene proton absorption to that of the aromatic resonance in the spectrum of **4a** indicated the total enol content of this ketone to be approximately 75% in $CDCl_3$.

In order to test the feasibility of utilizing the β-dicarbonyl function of the above ketones for the construction of a second heterocyclic moiety, we examined the cyclization of several of these compounds with hydrazine and urea. Treatment of β-diketones **4a–c** and **4e** with the

* To whom correspondence should be addressed.

(1) (a) This is Contribution No. 807 from the Army Research Program on Malaria and was supported by Contract No. DA-49-193-MD-3024 from the U. S. Army Research and Development Command. (b) Presented before the Medicinal Chemistry Division of the American Chemical Society, New York, N. Y., Sept 1969.

(2) Abstracted from the Ph.D. Dissertation of T. P. M., Virginia Polytechnic Institute, Oct 1969.

(3) This procedure utilizing commercial *n*-butyllithium and ethyl acetate for the synthesis of **3** was found to be much more satisfactory than the method of M. J. Weiss and C. R. Hauser [*J. Amer. Chem. Soc.*, **71**, 2023 (1949)], in which alkali amides and acetic anhydride are employed as the metalating and acylating agents, respectively. It also gives a comparable yield and is less tedious than the procedure of N. N. Goldberg and R. Levine [*ibid.*, **74**, 5217 (1952)], which involves the preparation of phenyllithium as the metalating agent.

(4) See M. L. Miles, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 1007 (1965).

(5) R. J. Light and C. R. Hauser, *ibid.*, **25**, 538 (1960).

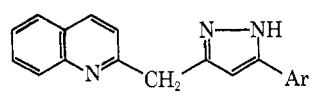
(6) The possibility of utilizing 1,3-dialkali salts of other β-diketones in a one-step route to quinolyl β-diketones of type **4** did not pass unnoticed. However, numerous unsuccessful attempts to increase the low yield of **4a** obtained in the above reaction forced us to abandon this approach.

TABLE II
NMR DATA FOR β-DIKETONES 4 AND 3-QUINALDYLPYRAZOLES 5

Compd	Types of hydrogen, δ values (multiplicities)			
	ArH	Vinyl	Methylene	Other
4a[a]	7.9 (m)	6.66 (s), 6.24 (s) 5.72 (s), 5.44 (s)	4.38 (s), 4.36 (s)	16.76 (s),[c] 14.76 (s)[c]
4b[a]	7.87 (m)	6.66 (s), 6.24 (s) 5.78 (s), 5.48 (s)	4.3 (s), 4.44 (s)	16.76 (s),[c] 14.82 (s)[c]
4c[a]	7.49 (m)	6.45 (s), 6.21 (s) 5.92 (s), 5.47 (s)	4.42 (s), 4.3 (s)	16.7 (s),[c] 15.82 (s)[c]
4d[b]	8.32 (m)	6.68 (s), 6.08 (s) 5.88 (s)	4.64 (s), 4.46 (s)	14.9 (s),[c] 4.26 (s)[d]
4e[b]	8.34 (m)	6.95 (s), 6.2 (s) 5.94 (s)	4.76 (s), 4.58 (s)	15.56 (s),[c] 14.12 (s)[c] 4.3 (s),[d] 4.2 (s)[d]
5a[b]	8.23 (m)		4.72 (s)	13.88 (s),[e] 7.0 (s)[f]
5b[b]	7.67 (m)		4.3 (s)	13.16 (s),[e] 6.44 (s)[f]
5d[b]	7.42 (m)		4.3 (s)	12.8 (s),[e] 6.44 (s)[f] 3.8 (s),[d] 3.69 (s)[d]

[a] $CDCl_3$ was used as the nmr solvent. [b] DMSO-d_6 was used as the nmr solvent. [c] Enolic NH or OH. [d] CH_3O. [e] Pyrazole NH. [f] Pyrazole CH.

former reagent in refluxing ethanol resulted in their smooth conversion to 3-quinaldylpyrazoles **5a–d**, the



5a, Ar = C_6H_5
b, Ar = *p*-C_6H_4Cl
c, Ar = 3,4-$C_6H_3(Cl)_2$
d, Ar = 3,4,5-$C_6H_2(OCH_3)_3$

analyses (Table III) and nmr spectra (Table II) of

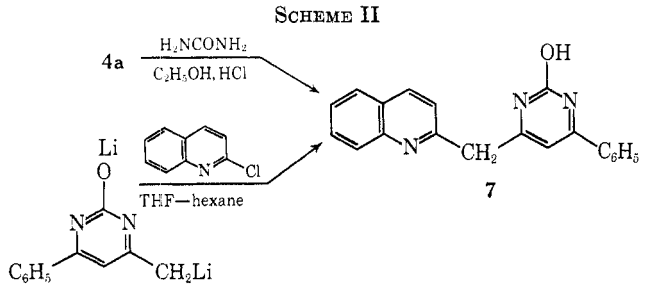
TABLE III[a]
CYCLIZATIONS OF β-DIKETONES 4 TO 3-QUINALDYLPYRAZOLES 5

β-Diketone	Pyrazole	Yield, %	Mp, °C	Recrystn solvent
4a	5a	59	168.5–170	Acetone–heptane
4b	5b	90	175–179	Ethanol–water
4c	5c	59	166–168	Benzene
4e	5d	72	165–167	Benzene

[a] Satisfactory analytical data (±0.25 for C, H, and N) were found for all compounds: Ed.

which were in accord with the proposed structures. Acid-catalyzed cyclization of diketone **4a** with urea afforded 6-quinaldylpyrimidinol **7**, which was also prepared independently, albeit in low yield, by allowing 2-chloroquinoline to react with dilithio derivative **6**[7] (see Scheme II).

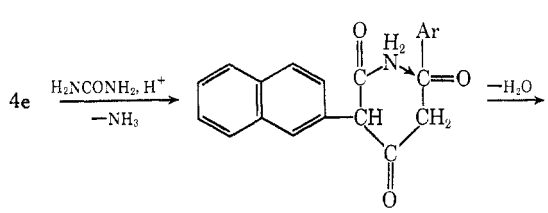
SCHEME II



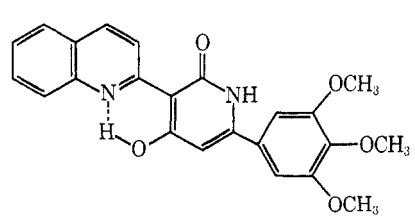
6 7

In contrast to **4a**, β-diketone **4e** was not transformed into the expected quinaldylpyrimidinol on treatment with urea. Instead a single product, to which we have assigned pyridone structure **8**,[8] was isolated. This formulation was based on the molecular formula, $C_{23}H_{20}N_2O_5$, derived from mass spectral analyses. In addition, the ir spectrum (KBr), which had principal bands at 3400 and 1650–1580 cm^{-1}, was also compatible with the assigned structure. The nmr spectrum of **8** (CF_3COOH) had singlets at 4.14 (9 H), 7.14 (1 H), and 7.26 ppm (2 H), attributable to methoxy protons, the C-5 proton of pyridone ring, and the two equivalent protons of the trimethoxyphenyl residue, respectively. In addition, there was a multiplet centered at 8.16 (4 H), which was assigned to the benzenoid protons of the quinoline nucleus, and an AB group at 9.04 ppm (2 H), which was attributed to the C-3 and C-4 protons of the quinoline ring.

It is conceivable that transformation of β-diketone **4e** into pyridone **8** by urea may involve initial formation of carbamoyl derivative **9**, which then undergoes cyclization to afford **8** (eq 2). Although attempts to further define the course of this reaction by isolation of possible acyclic intermediates such as **9** were unsuccessful, carbamoylation at an active methylene position by urea, or



9



8 (2)

(7) J. F. Wolfe and T. P. Murray, *Chem. Commun.*, 336 (1970).

(8) For convenience we have chosen the above structural representation, although other tautomers are possible. An intramolecularly hydrogen-bonded structure such as **8** would have the carbonyl group of the pyridone ring fixed in such a position to cause deshielding of the C-3 hydrogen of the quinoline nucleus, thereby accounting for the downfield position of this proton in the nmr spectrum of **8**. The alternative 2-hydroxy-4(1)-pyridone tautomer could assume a similar hydrogen-bonded configuration with the C-4 carbonyl function of the pyridone ring exerting a similar deshielding effect.

a urea derivative, is not without precedent.[9] However, reactions of this type appear to have been limited previously to β-dicarbonyl compounds which are sterically prohibited from undergoing cyclization to form pyrimidine or pyridone derivatives.[9c]

Experimental Section[10]

Preparation of 2-Acetonylquinoline (3).—To a stirred solution of 14.32 g (0.10 mol) of quinaldine (1) in 100 ml of dry tetrahydrofuran (THF) at 25° under nitrogen, was added 70 ml (0.11 mol) of a 1.6 *M* solution of *n*-butyllithium in hexane. The resulting dark red solution of lithio derivative **2** was stirred for 10 min before addition of 13.2 g (0.015 mol) of ethyl acetate as a 50% v/v solution in dry THF. After 1 hr the reaction mixture was quenched with 75 ml of water and the original organic layer combined with an ethereal extract (100 ml) of the aqueous layer. The extracts were dried (Na_2SO_4), the solvent removed, and the resulting oil distilled to afford 8.2 g (44%) of 2-acetonylquinoline (**3**), bp 140–145° (4.0 mm) [lit.[3] bp 145–147° (2.5 mm)]. The distillate, which solidified on standing, was recrystallized from hexane to give the desired ketone as yellow needles, mp 73–75° (lit.[3] mp 76–77°).

Aroylations of 3 by Means of Sodium Hydride to Form β-Diketones 4a–e.—The aroylation of **3** with methyl benzoate is described in detail. Other aroylations were conducted in a similar manner and the results of these reactions are summarized in Table I.

In a 2-l., three-necked flask equipped with a pressure-equalizing addition funnel, a mechanical stirrer, and a reflux condenser, connected at its upper end through a cold trap (Dry Ice–acetone) to a Precision Scientific wet-test meter filled with water, were placed 1000 ml of 1,2-dimethoxyethane (DME) and 2.6 mol of sodium hydride dispersion. A solution of methyl benzoate (54.4 g, 0.4 mol) and **3** (46.4 g, 0.26 mol) in 250 ml of DME was placed in the addition funnel. The system was purged with dry nitrogen, then closed to the atmosphere. The solvent in the reaction flask was heated to reflux, and when thermal equilibrium had been established, an initial reading was taken on the gas meter. The solution of ester and ketone was then added over a period of 20 min, and the resulting suspension was refluxed until hydrogen evolution had ceased.[11] The solvent was removed under reduced pressure, and the remaining pasty residue was cooled to 0°. Addition of ether (250 ml) was followed by the cautious addition of 150 ml of water. The sodio salt of the product, which separated between the layers, was collected and stirred with 500 ml of water, then acidified (pH 6) with dilute HCl. The resulting solid was collected by filtration, washed with 5% aqueous $NaHCO_3$, and crystallized from methanol to give 41.0 g of 1-phenyl-4-(2-quinolyl)-1,3-butanedione (**4a**).

The nmr spectra of β-diketones **4a–c** (Table II) were consistent with the assigned structures. Each of the ir spectra had several strong bands in the 1670–1550 cm^{-1} region. The mass spectra of **4a–d** had molecular ion peaks at *m/e* 289, 324, 358, and 319, respectively.

Benzoylation of 3 by Means of Sodium Amide.—To a stirred solution of sodium amide,[12] prepared from 0.375 g-atom of sodium in 300 ml of anhydrous liquid ammonia, was added a solution of 2.32 g (0.0125 mol) of **3** in 10 ml of dry ether. The resulting deep red solution was allowed to stir for 30 min before a solution of 2.72 g (0.02 mol) of methyl benzoate in 10 ml of ether was added. After 1 hr the reaction mixture was neutralized with 10 g of solid NH_4Cl and the ammonia was removed on a steam bath as an equal volume of ether was added. Water (100 ml) was added, the resulting layers were separated, and the aqueous layer was extracted with two 100-ml portions of ether. The original ethereal layer and extracts were combined, dried (Na_2SO_4), and concentrated to yield a red oil which slowly crystallized. Recrystallization of this crude product from methanol afforded 0.5 g (14%) of β-diketone **4a**.

Independent Synthesis of 4a from 2-Chloroquinoline and Disodiobenzoylacetone.—To a stirred suspension of 0.025 mol of disodiobenzoylacetone[13] in 300 ml of liquid ammonia was added 4.07 g (0.025 mol) of 2-chloroquinoline as a 20% w/v solution in dry ether. The reaction mixture was stirred for 2.5 hr, quenched with excess solid NH_4Cl, and processed as in the reaction of **3** with methyl benzoate and sodium amide. The semisolid crude product thus obtained was crystallized from 95% ethanol to give 1.19 g (17%) of diketone **4a**, mp 138–140°, which was identical in all respects with a sample of **4a** prepared from ketone **3**.

Cyclization of β-Diketones 4a–c and 4e with Hydrazine to Form Pyrazoles 5a–d.—A 0.01-mol sample of the appropriate β-diketone was treated with hydrazine [3.80 g (0.10 mol) of an 85% aqueous solution] in 40 ml of refluxing ethanol for 2 hr. Removal of the ethanol under reduced pressure and recrystallization of the resulting solid gave the respective pyrazole.

Yields and analytical data for these products are given in Table III. Principle nmr absorptions for **5a**, **5b**, and **5d** are listed in Table II. All pyrazoles had major ir bands at 3350–3300 (NH) and 1620–1550 cm^{-1}. The mass spectrum of **5a** had a molecular ion peak at *m/e* 285.

Cyclization of β-Diketone 4a with Urea to Form 2-Hydroxy-4-phenyl-6-quinaldylpyrimidine (7).—To a hot, stirred solution of 2.89 g (0.01 mol) of **4a** in 75 ml of absolute ethanol were added urea (3.60 g, 0.06 mol) and concentrated HCl (1 ml, 0.01 mol). After refluxing for 17 hr, the mixture was cooled and the resulting solid filtered, washed with ether, and recrystallized from 95% ethanol to give 1.81 g (59%) of **7**: mp 265–267° (sealed tube); ir (KBr) 3400–3180, 1700–1640, and 1545 cm^{-1}; nmr (CF_3CO_2H) δ 9.08 (m, 12, aromatic) and 5.70 ppm (s, 2, CH_2); mass spectrum, molecular ion peak at *m/e* 313, with abundant fragment peaks at *m/e* 128 and 77.

Anal. Calcd for $C_{20}H_{15}N_3O$: C, 76.65; H, 4.82; N, 13.41. Found: C, 76.77; H, 4.61; N, 13.55.

Independent Synthesis of 7 Using Dilithio Derivative 6.—To a stirred solution of 4.62 g (0.025 mol) of 2-hydroxy-4-methyl-6-phenylpyrimidine[14] in 250 ml of dry THF at 0° under nitrogen was added dropwise, 35 ml (0.56 mol) of a 1.6 *M* solution of *n*-butyllithium in hexane. The soluble, red pyrimidine dianion **6** was stirred for 30 min, and 4.07 g (0.025 mol) of 2-chloroquinoline, in 10 ml of dry THF was then added dropwise. The reaction mixture was allowed to stir for 1.5 hr before being quenched with 100 ml of water. The THF–hexane was removed on a rotary evaporator and the resulting solution was acidified with 10 ml of concentrated HCl. The precipitate which formed was filtered, washed with dilute aqueous NH_4OH, dried, and recrystallized from 95% ethanol to give 0.6 g (7%) of **7**, mp 263–265° (sealed tube). The ir spectrum of this product was identical with that of a sample of **7** prepared by urea cyclization of β-diketone **4a**.

Urea Cyclization of β-Diketone 4e to Form Pyridone 8.—To a stirred solution of 3.79 g (0.01 mol) of **4e** in absolute ethanol (80 ml) was added 1 ml of concentrated HCl and 3.60 g (0.06 mol) of urea. The mixture was allowed to reflux for 48 hr before being cooled to precipitate the crude product, which was collected by filtration and crystallized from ethanol to afford 3.0 g (75%) of 3-(2-quinolyl)-4-hydroxy-6-(3,4,5-trimethoxyphenyl)-2(1)-pyridone (**8**): mp 286–288° (sealed tube); mass spectrum (50 eV), molecular ion peak at *m/e* 404.

Anal. Calcd for $C_{23}H_{20}N_2O_5$: C, 68.25; H, 4.98; N, 6.94. Found: C, 68.53; H, 5.18; N, 6.71.

Several attempts to isolate possible acyclic intermediates by decreasing both reaction time and the molar quantity of urea afforded only unreacted β-diketone **4e** and pyridone **8**.[15]

(9) For examples, see (a) H. C. Scarborough, *J. Org. Chem.*, **26**, 2579 (1961); (b) H. C. Scarborough, *ibid.*, **26**, 3717 (1961); (c) H. C. Scarborough and W. A. Gould, *ibid.*, **26**, 3720 (1961).

(10) Infrared spectra were taken on a Beckman IR-5A infrared spectrophotometer. Nmr spectra were determined on an A-60 spectrometer with tetramethylsilane as internal standard. Mass spectra were obtained on a Perkin-Elmer Hitachi RMU-6E mass spectrometer at 50 eV. The sodium hydride used was an approximately 50% dispersion in mineral oil, obtained from Metal Hydrides, Inc. *n*-Butyllithium, as a 1.6 *M* solution in hexane, was obtained from Foote Mineral Co. 1,2-Dimethoxyethane and tetrahydrofuran were distilled from sodium ribbon immediately before use.

(11) A total of 3 mol equiv of hydrogen was evolved in this and subsequent aroylations of ketone **3**.

(12) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. React.*, **8**, 122 (1954).

(13) K. G. Hampton, R. J. Light, and C. R. Hauser, *J. Org. Chem.*, **30**, 1413 (1965).

(14) C. R. Hauser and R. M. Manyik, *ibid.*, **18**, 588 (1953).

(15) We wish to thank Mr. J. C. Greene for carrying out these experiments.

Registry No.—**4a**, 26958-30-5; **4b**, 26958-31-6; **4c**, 26958-32-7; **4d**, 26958-33-8; **4e**, 27039-92-5; **5a**, 26958-34-9; **5b**, 26958-35-0; **5c**, 27006-05-9; **5d**, 26958-36-1; **7**, 26958-37-2; **8**, 26958-38-3.

Viologen Radical from Di(4-pyridyl) Ketone Methiodides in Hydroxide[1]

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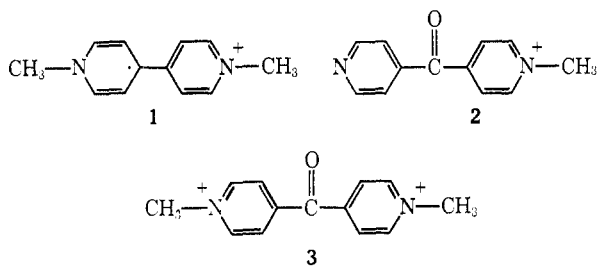
Received August 10, 1970

The stability of pyridinyl radical cations has made them subject to intense investigations.[3-8] Kosower and Cotter reported an interesting formation of dimethylviologen radical **1** from 4-cyanopyridinium methiodide and sodium dithionite, presumably *via* dimerization of the neutral 4-cyanopyridinyl radical intermediate.[6] We report here on the unusual formation of the same viologen radical from di(4-pyridyl) ketone mono- and dimethiodides (**2** and **3**) in aqueous hydroxide solution.

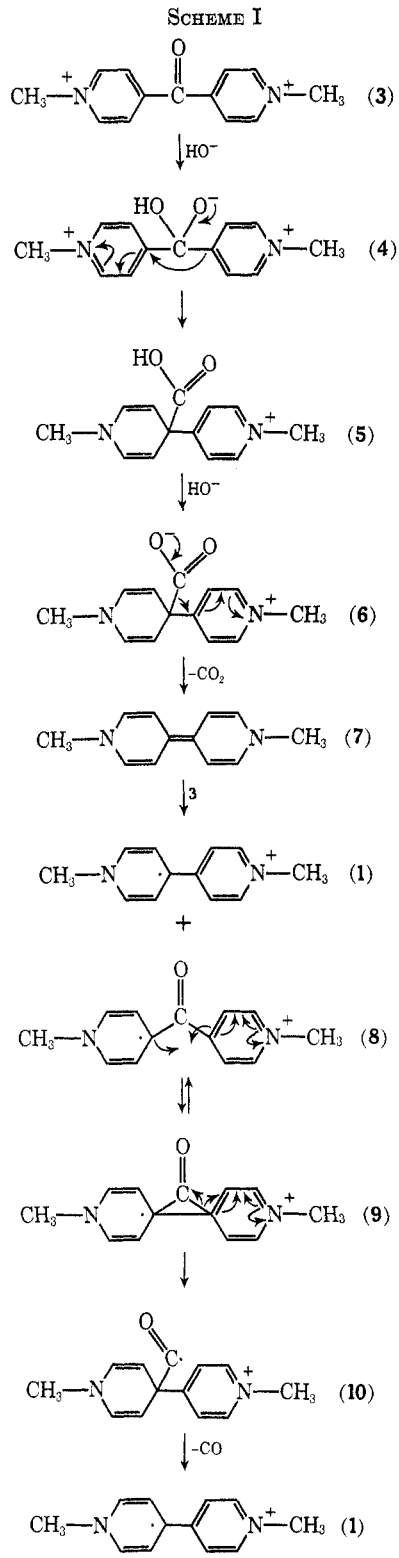


1 **2**

3

When 1 *M* NaOH solutions, thoroughly degassed by numerous freeze–thaw cycles, were mixed under vacuum with crystals of either **2** or **3**, the resulting mixture turned deep blue immediately and remained so indefinitely (months). As the color developed, the near-uv–visible absorption showed a parallel increase in the two structured bands characteristic[6] of **1**, namely, in the visible at λ_{max} (ϵ) 560 (7450), 602 (10,400), 660 (5500), and 730 nm [1650l./(mol cm)] and in the uv at 367 (12,300), 384 (22,300), and 395 nm [34,200 l./(mol cm)]. The blue solutions gave strong esr signals whose presence or absence paralleled that of the color. Examination of high-resolution esr spectra clearly indicated that the blue paramagnetic species formed from both **2** and **3** was dimethylviologen cation radical.[6,9,10] The experimental splitting constants for **1** in water, which differ only slightly from those in ethanol,[9] are 1.33 and 1.59 Oe for the ring protons, 3.99 Oe for the methyl hydrogens, and 4.25 Oe for the nitrogens; a spectrum simulated by computer,[11] with Lorentzian line shape and with a line width of 140 mOe, verified the constants. Radical **1** was generated in a similar manner in nondeaerated samples. Eventually, after months in open sample tubes or much more rapidly upon oxygenation, the blue alkaline solutions turned pale yellow or reddish brown, depending on concentration, and lost their para-

SCHEME I



(1) Taken in part from work done by C. L. T. in partial fulfillment of the Ph.D. requirements at The George Washington University.

(2) To whom correspondence should be directed at The George Washington University.

(3) P. Borger and A. San Pietro, *Arch. Biochem. Biophys.*, **120**, 279 (1967).

(4) P. Borger, C. C. Black, and A. San Pietro, *Biochemistry*, **6**, 80 (1967).

(5) O. Rogne, *Biochem. Pharmacol.*, **16**, 1853 (1967).

(6) E. M. Kosower and J. L. Cotter, *J. Amer. Chem. Soc.*, **86**, 5524 (1964).

(7) E. M. Kosower and E. J. Poziomek, *ibid.*, **86**, 5515 (1964).

(8) E. M. Kosower and I. Schwager, *ibid.*, **86**, 5528 (1964).

(9) C. S. Johnson and H. S. Gutowsky, *J. Chem. Phys.*, **39**, 58 (1963).

(10) A. H. Corwin, R. R. Arellano, and A. B. Chivvis, *Biochim. Biophys. Acta*, **162**, 533 (1968).

(11) Modifications to a program by A. Inzaghi and L. Mongini, European Atomic Energy Commission-Euratom, Report EUR-4064e.