2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ). A New Preparation

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The first synthesis of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) was described by Thiele and Günther[1] in 1906. However, no interest was shown in the compound until Linstead and co-workers[2] discovered its extraordinary potency as a dehydrogenating agent. Its oxidation potential is greater than that of any other known quinone.[2,3]

The broad utility of DDQ in the steroid field was first demonstrated by the British Drug Houses group. Since that time a number of drug companies, notably Syntex S.A. and E. Merck A.G., have studied its reactions in the steroid field. It now appears to be a reagent *par excellence* for converting Δ^4- and $\Delta^{4,6}$-steroidal 3-ketones into the corresponding $\Delta^{1,4}$ and $\Delta^{1,4,6}$ ketones, though this reaction by no means defines the scope of its usefulness. Recent reviews[4,5] clearly indicate that its unique properties are encouraging wider interest.

Thiele's original preparation of DDQ from 2,3-dicyanohydroquinone involved five steps.[1] Oxidation of 2,3-dicyanohydroquinone with nitric acid fumes gave 2,3-dicyanobenzoquinone which, with anhydrous hydrogen chloride, gave 2-chloro-5,6-dicyanohydroquinone. Repetition of these two steps yielded 2,3-dichloro-5,6-dicyanohydroquinone which was oxidized with nitric acid fumes to DDQ. This procedure was improved by Brook[6] who employed nitrogen tetroxide instead of nitric acid fumes. Later Mitchell[7] eliminated four steps of the original procedure when he found that chlorination of 2,3-dicyanohydroquinone in acetic acid gave 2,3-dichloro-5,6-dicyanohydroquinone. This compound was then oxidized to DDQ with lead dioxide in aqueous ethanol containing hydrochloric acid. However, while a more convenient synthesis, the over-all yield reported by Mitchell was only 36.5%, compared with the 70% yield obtained by Linstead, *et al.*,[2] using the five-step procedure.

We now wish to report a simple one-step procedure for converting 2,3-dicyanohydroquinone into DDQ in 90% yield. It is reported[4,8] that DDQ decomposes in water, and, while true, these statements have tended to obscure the fact that DDQ is stable in aqueous mineral acid. Herein lies one basis of the present process. We also found that 2,3-dicyanobenzoquinone and 2-chloro-5,6-dicyanobenzoquinone would rapidly add hydrogen chloride from aqueous solution. Thus, when 2,3-dicyanohydroquinone was suspended in 1:1 hydrochloric acid and the mixture was treated with a suitable oxidizing agent, pure DDQ was obtained in 90% yield.

Attempts to extend this procedure to other strong acid systems have failed. Hydrogen bromide adds only slowly to 2,3-dicyanobenzoquinone, and several other acids, among them hydrogen fluoride and trifluoroacetic acid, failed to add under the conditions employed. A large number of oxidizing agents have been used successfully, for example, nitric acid, nitric acid and air or oxygen, nitrogen tetroxide, bromic acid, chromic acid, and permanganic acid. Finally, since the 2,3-dichloro-5,6-dicyanohydroquinone recovered from DDQ oxidations can be readily reconverted to the quinone using the new process, it is obvious that DDQ now becomes a relatively economical dehydrogenating agent.

Experimental

A slurry of 2,3-dicyanohydroquinone (5 g., 0.031 mole) in water (35 g.) and concentrated hydrochloric acid (35 ml.) was treated over 45 min. with concentrated nitric acid (9.4 g. of 70%, 0.15 mole) at a temperature of 35 ± 3°. The mixture, which foamed initially, turned yellow. After all the nitric acid had been added, the yellow suspension was stirred for 1 hr., filtered, washed with carbon tetrachloride, and dried, yield 6.4 g. (90%), m.p. 212–213° (lit.[7] m.p. 213–215°). The infrared spectrum and elemental analysis were consistent with expectation. Reduction of DDQ with aqueous sodium bisulfite gave 2,3-dichloro-5,6-dicyanohydroquinone, mol. wt. 229.3 (calcd. 229).

(1) J. Thiele and F. Günther, *Ann.* **349**, 45 (1906).
(2) E. A. Braude, A. G. Brook, and R. P. Linstead, *J. Chem. Soc.*, 3569 (1954).
(3) M. E. Peover, *ibid.*, 4540 (1962).
(4) L. M. Jackman, *Advan. Org. Chem.*, **2**, 329 (1960).
(5) "DDQ— Its Reactions and Uses," Arapahoe Chemicals, Inc., Boulder, Colo., 1964.
(6) A. G. Brook, *J. Chem. Soc.*, 5040 (1952).
(7) P. W. D. Mitchell, *Can. J. Chem.*, **41**, 550 (1963).
(8) L. Anderseh, *Finska Kemistsamfundets Medd.*, **70**, 31 (1961); *Chem. Abstr.*, **56**, 5383 (1962).

Carbon–Carbon Alkylations of Enamines with Mannich Bases

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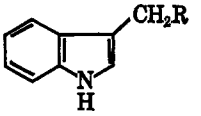
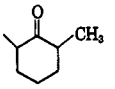
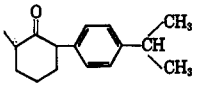
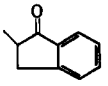
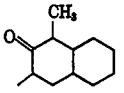
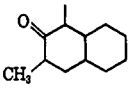
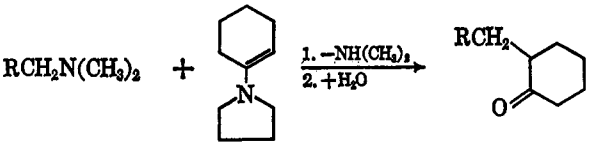
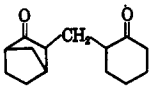
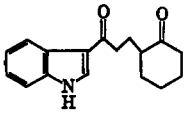
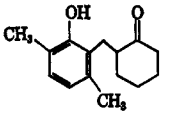
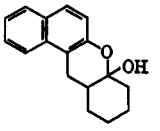
Carbon–carbon bond formation by amine replacement has been the subject of extensive studies.[1] In comparison to the large number of reports on alkylation of substances which readily form anions, such as nitroalkanes, β-dicarbonyl compounds, etc., relatively few examples of the application of this method to the alkylations of simple ketones have been described. These have been carried out in the presence of a strong base, usually with a quaternary Mannich amine as the alkylating agent.[2] A useful modification has been reported by Gill, *et al.*,[3] who have effected β-acylethylations by thermal decomposition of a Mannich base in an excess of a suitable ketone.

(1) For pertinent reviews, see (a) J. H. Brewster and E. L. Eliel, *Org. Reactions*, **7**, 99 (1953); (b) H. Hellmann and G. Opitz, "α-Aminoalkylierung," Verlag Chemie, Weinheim, 1960; (c) F. Möller (Houben–Weyl), "Methoden der Organischen Chemie," 4th Ed., Vol. 11, part 1, Georg Thieme Verlag, Stuttgart, 1957, p. 259; part 2, 1958, p. 207.
(2) (a) E. C. du Feu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, **53** (1937); (b) R. Robinson and F. Weygand, *ibid.*, 386 (1941); (c) F. D. Gunstone and R. M. Heggie, *ibid.*, 1437 (1952).
(3) N. S. Gill, K. B. James, F. Lions, and K. T. Potts, *J. Am. Chem. Soc.*, **74**, 4923 (1952).

TABLE I

No.	R	M.p. or b.p. (mm.), °C.	Yield,[a] %	Calcd. (found), % C	H	N
A. Compounds Prepared by Alkylation of Enamines of Ketones with Gramine						
						
1		62–65 183–192 (0.075)	50	79.26 (79.42)	7.54 (7.45)	6.16 (6.13)
2		176–178 (0.05)	45	79.63 (79.65)	7.94 (7.95)	5.80 (6.00)
3		144–145.5	46	83.44 (83.19)	7.88 (7.86)	4.05 (4.28)
4		152–153	84	82.73 (82.86)	5.79 (5.64)	5.36 (5.25)
5		230 (0.2)	30	81.31 (81.36)	8.53 (8.65)	4.74 (4.70)
6		212–218 (0.1)	30	81.31 (81.55)	8.53 (8.36)	4.74 (4.86)
B. Compounds Prepared by β-Acylethylation and o-Hydroxybenzylation of Cyclohexanone Enamine						
						
7		119–124 (0.05)	38	76.32 (76.18)	9.15 (9.17)	
8		179–184	37	75.81 (75.93)	7.11 (7.25)	5.20 (5.17)
9		182–225 (0.05)	30	77.55 (77.76)	8.68 (8.74)	
10		143.5–145	35	80.28 (80.01)	7.13 (7.05)	

[a] The yields stated in the table represent materials of analytical purity. They reflect losses incurred by purification processes which in most cases involved small-scale distillations of high-boiling liquids.

It has now been found that the enamine of a ketone is easily alkylated by the Mannich base[4] when equivalent amounts of the two reactants are heated for *ca.* 24 hr. in a solvent such as dioxane or xylene. Compounds prepared by this method are listed in Table I.

Investigation of the crude reaction product by thin layer chromatography has shown that conversion is usually quantitative and only rarely was there indication of small amounts of byproducts. The reaction is limited to monoalkylation on the unsubstituted carbon of the enamine. This point was confirmed by the n.m.r. spectrum of 2-(indol-3-ylmethyl)-6-methylcyclohexanone (**2**) which displayed the signal of the methyl group as a doublet at 1.03 p.p.m. and by that of 2-(indol-3-ylmethyl)-6-(*p*-cumenyl)cyclohexanone (**3**) which showed the benzylic hydrogen adjacent to the ketone at 3.58 p.p.m. The latter chemical shift was found to be identical with that of the corresponding proton in 2-(*p*-cumenyl)cyclohexanone.

There appears to be no advantage in replacing the tertiary amine with its quaternary salt. When gramine methiodide was heated with cyclohexanone

(4) In accordance with the generally accepted mechanism of alkylation with tertiary amines (see ref. 1a, p. 126) this reaction most likely involves elimination of dialkylamine, followed by Michael addition of the resulting unsaturated species to the enamine.

pyrrolidine enamine the time required for conversion, as well as the yield of the product, was the same as with gramine. In order to compare the utility of the enamine with that of the ketone, cyclohexanone and 2-methylcyclohexanone were refluxed with gramine under conditions identical with those of the enamine reaction. The endpoint was determined by cessation of the evolution of basic fumes as well as by the use of thin layer chromatography. It was found that this reaction required 5 days for completion and was less selective with respect to the site of alkylation as shown by the presence of several spots in the thin layer chromatograms of the crude product derived from 2-methylcyclohexanone.

Compound **10** (7a,8,10,11,11a,12-hexahydro-9H-benzo[*a*]xanthen-7a-ol) resulted from a spontaneous intramolecular hemiketalization of the primary product of the alkylation of the cyclohexanone pyrrolidine enamine with 1-dimethylaminomethyl-β-naphthol. That this conversion of the naphthol ketone to a hemiketal had taken place was indicated by the negative $FeCl_3$ color test for a phenolic hydroxyl, the insolubility of the compound in aqueous alkali, and the absence of a carbonyl band in the infrared spectrum.

Experimental[5]

General Procedure.—The reactions were carried out by refluxing 0.1 mole of pyrrolidine enamine of a ketone[6] with 0.1 mole of a Mannich base in 100 ml. of dioxane until, after *ca.* 24 hr., the evolution of basic fumes had subsided. After addition of 30 ml. of water, the reaction mixture was refluxed for 1 hr. and evaporated *in vacuo*. The residue was purified for analyses by distillation (compounds **1**, **2**, **5**, **6**, **7**, and **9**), by crystallization from ethanol (**4** and **10**) or ethyl acetate (**8**), and by chromatography on activated magnesium silicate (Florisil) 25 g./g. using ethyl acetate as eluent (**3**).

(5) Melting points were determined with the Thomas–Hoover capillary melting point apparatus which was calibrated against known standards. N.m.r. spectra were recorded in deuterated chloroform with tetramethylsilane as an internal reference using a Varian A-60 spectrometer. The thin layer chromatography was performed using silica gel G according to Stahl (Merck, Darmstadt) as the absorbent and ethanol as the eluent. Chromatograms were developed by spraying with aqueous $KMnO_4$. The authors are indebted to the Analytical and Physical Chemistry Department under the supervision of Mr. A. D. Lewis. In particular we wish to thank Mr. R. DeSimone and Mr. R. Puchalski for the spectral data and Mrs. U. Zeek for analytical determinations.

(6) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrel, *J. Am. Chem. Soc.*, **85**, 207 (1963).

The Pyrolysis of Acetylazo Compounds[1]

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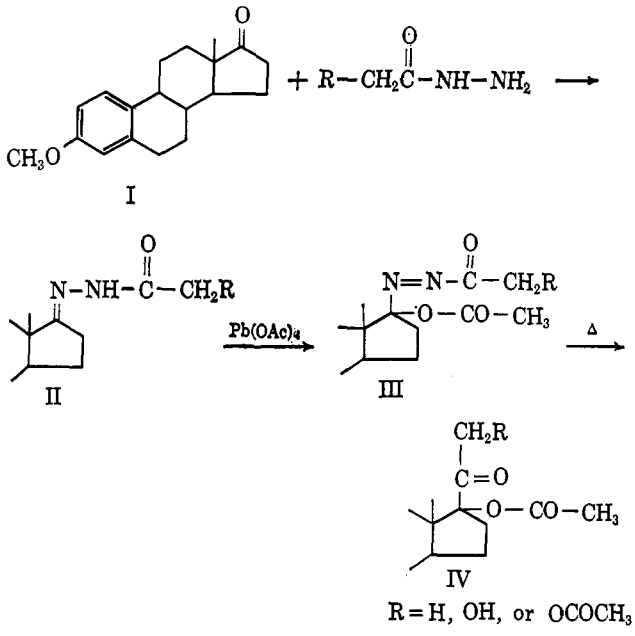
Aliphatic azo compounds are generally thought to decompose thermally by the simultaneous rupture of both carbon–nitrogen bonds, to form molecular nitrogen and two carbon radicals.[2,3] The subsequent behavior of the two radicals depends primarily on their structures and may be recombination, disproportionation, or abstraction of a proton from the solvent.[3] Wieland[4] has shown that, in the case of acetylazotriarylmethanes, radical recombination is dominant, and the major product of pyrolysis is the acetyltriarylmethane. More recently Freeman[5] has demonstrated that 3-acetoxy-Δ^1-pyrazoline, an α-acetoxyazoalkane, behaves similarly affording acetoxycyclopropane in good yield. We have sought to combine these two observations in attempting a simple synthesis of the cortical side chain from steroidal 17-ketones. While



this synthesis proved unsuccessful, our results do illustrate some interesting aspects of the behavior of radicals derived from the pyrolysis of azo compounds.

As a model for the proposed synthesis, we chose to study the conversion of estrone 3-methyl ether (I) into the corresponding 17-acetoxy-17-acetyl derivative IV (R = H). Accordingly, estrone 3-methyl ether was treated with acetylhydrazine, to form the acetylhydrazone II (R = H). This was converted to the 17-acetoxy-17-acetylazo steroid III (R = H) by reaction with lead tetraacetate, following the procedure developed by Iffland.[6] Elemental analysis, nuclear magnetic resonance (n.m.r.), and infrared spectral analysis showed the introduction of an acetoxy group, and were consistent with the formulation of our product as III (R = H). The stereochemistry of the substituents at C-17 is not known, although by analogy with other additions to 17-ketones, introduction of an α-acetoxy group would seem most probable. The spectral properties of the parent $-N{=}N-\underset{|}{C}{=}O$ group [λ_{max} 223 mμ (ε 1560), 317 mμ (ε 162)[7]] do not appear to have been reported previously; it is interesting to note the resemblance to the $-\underset{|}{C}{=}\underset{|}{C}-\underset{|}{C}{=}O$ chromophore.

(1) This work was carried out under Contract SA-43-ph-4351 of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health.

(2) S. Seltzer, *J. Am. Chem. Soc.*, **85**, 14 (1963); **83**, 2625 (1961).

(3) H. Zollinger, "Azo and Diazo Chemistry," Interscience Publishers, Inc., New York, N. Y., 1961.

(4) H. Wieland, T. Ploetz, and H. Indest, *Ann.*, **532**, 166 (1937).

(5) J. P. Freeman, *J. Org. Chem.*, **29**, 1379 (1964).

(6) Iffland has shown that lead tetraacetate will convert alkylhydrazones into the corresponding α-acetoxyazoalkanes: D. C. Iffland, L. Salisbury, and W. R. Schafer, *J. Am. Chem. Soc.*, **83**, 747 (1961).

(7) The ultraviolet spectrum of III is complicated by the aromatic A ring absorption. These figures refer to the androstane VIII.