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

Quinone Imides. XLVI. The Addition of Heterocyclic Active Methylene Compounds to *p*-Benzoquinone Diimides

BY ROGER ADAMS, LESLIE M. WERBEL AND M. D. NAIR

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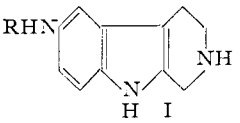
The adducts of acetylacetone, methone, benzoylacetone and dibenzoylmethane with *p*-benzoquinonedibenzimide, were readily cyclized to heterocyclic systems. Heterocyclic analogs failed to add to this imide. Both simple and heterocyclic adducts of *p*-benzoquinonedibenzenesulfonimide were prepared; however, cyclization was successful only with the simple structures.

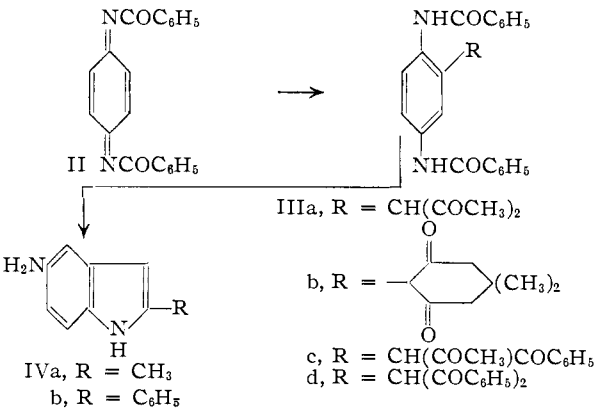
Recent work[1-3] has demonstrated the synthetic feasibility of obtaining heterocyclic substances from quinone diimides. Indole, carbazole and furan derivatives have been prepared by acid-catalyzed cyclization of the adducts formed from active methylene compounds and quinone diimides or quinone monoimides. Extension of this work to include heterocyclic active methylene compounds has now been attempted with the hope of providing a synthetic route to the more complex heterocyclic ring systems. For example, condensation of 4-carbethoxy-3-piperidone with a benzoquinone diimide followed by cyclization might be expected to yield the β-carboline I.



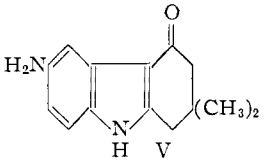
Initial studies employed *p*-benzoquinonedibenzimide (II) because complex side reactions upon adduct formation ordinarily were not noted with this diimide and since *p*-benzoquinonebis-(dimethylsulfamimide), which would be preferred as a result of the ease of hydrolysis of the resulting amide groupings, was found[1] not to form adducts with either ethyl 2-ketonipecotate or 3-carbethoxy-1-methyl-4-piperidone.

In the first investigation[4] the addition of active methylene compounds to *p*-benzoquinonedibenzimide was limited to diethyl malonate and acetylacetone. As a consequence the work has been extended to the addition of other simple active methylene compounds and to the attempted cyclization of the products to indoles. The methone, benzoylacetone and dibenzoylmethane adduct, IIIb, c, d, were prepared by the addition of the active methylene compound and a trace of sodium methoxide to a dioxane solution of the diimide.

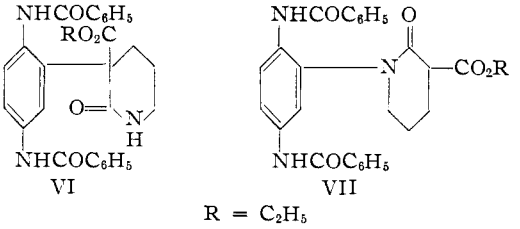
The acetylacetone adduct of *p*-benzoquinonedibenzimide[4] (IIIa) was converted to 5-amino-2-methylindole (IVa) in 91.4% yield upon treatment with constant boiling hydrochloric acid. The use of 70% sulfuric acid lowered the yield of IVa, while concentrated sulfuric acid led only to recovery of the starting material. Similarly, compound IIIc upon treatment with hydrochloric acid yielded 5-amino-2-methylindole, while compound IIId upon treatment with warm concentrated sulfuric acid gave an 86% yield of 5-amino-2-phenylindole



(IVb). The methone adduct IIIb, upon treatment with constant boiling hydrochloric acid, gave a product in 60% yield whose structure was presumed to be that of the carbazole derivative V.



Addition of ethyl 2-ketonipecotate (3-carbethoxy-2-piperidone) to the imide gave a quantitative yield of the adduct VI.

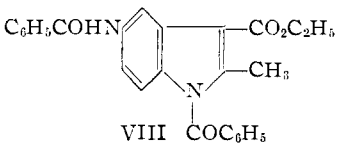


Structure VII for the adduct was eliminated on the basis of a study of the infrared absorption spectrum. Two different types of NH absorption were present. Moreover, compounds such as pyrrolidone, succinimide and phthalimide, which afford only the NH and no active methylene positions for addition, failed to add to the imide system. Attempted cyclization of VI was unsuccessful.

3-Ethoxalyl-2-pyrrolidone, 2-carbethoxy-1-ketoquinolizidine, ethyl cyanoacetate, benzoylacetonitrile and diethyl γ-chloropropylmalonate did not add to the imide but led only to reduction of the diimide with formation of *p*-phenylenedibenzamide. 1,3-Indanedione, N-ethyloxindole, ethyl acetopyruvate and ethyl acetoacetate yielded amor-

(1) R. Adams and W. P. Samuels, Jr., THIS JOURNAL, **77**, 5375 (1955).
(2) R. Adams and W. P. Samuels, Jr., *ibid.*, **77**, 5383 (1955).
(3) R. Adams and L. Whitaker, *ibid.*, **78**, 658 (1956).
(4) R. Adams and D. S. Acker, *ibid.*, **74**, 5872 (1952).

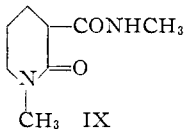
phous solids which resisted all attempts at purification. However, treatment of the crude reaction mixture of *p*-benzoquinonedibenzimide and ethyl acetoacetate with constant boiling hydrochloric acid yielded the corresponding indole VIII.



VIII

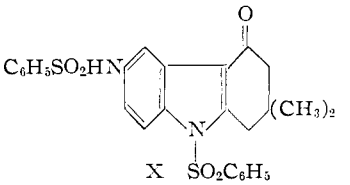
The other ring nitrogen compounds which were subjected to addition experiments were prepared as the N–CH_3 derivatives in order that no complications from the presence of NH function could arise. However, none of the additions using 4-carbethoxy-1-methyl-3-piperidone, 3-carbethoxy-1-methyl-4-piperidone, 4-carbethoxy-1-methyl-3-pyrrolidone, 3-carboxamido-1-methyl-2-piperidone[5] and 3-acetyl-1-ethyloxindole was successful.

A compound believed to be 1-methyl-3-N-methylcarboxamido-2-piperidone (IX) was prepared from diethyl γ-chloropropylmalonate and methylamine, but it did not add to the imide.

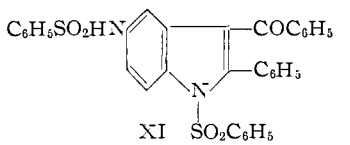


IX

Utilization of *p*-benzoquinonedibenzenesulfonimide as the diimide proved more successful. The acetylacetone adduct of this imide,[6] upon treatment with concentrated sulfuric acid, gave a product assumed to be 3-acetyl-5-benzenesulfonamido-2-methylindole. The alternate structure, 3-acetyl-5-amino-1-benzenesulfonyl-2-methylindole, cannot be excluded, but the former is preferred by analogy to the similar compound prepared in the dimethylaminosulfamamide series.[1] Cyclization of the acetylacetone adduct with constant boiling hydrochloric acid yielded 3-acetyl-5-benzenesulfonamido-1-benzenesulfonyl-2-methylindole. The methone[6] and dibenzoylmethane adducts of *p*-benzoquinonedibenzenesulfonimide were cyclized smoothly to the expected products X and XI.



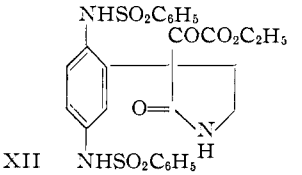
X



XI

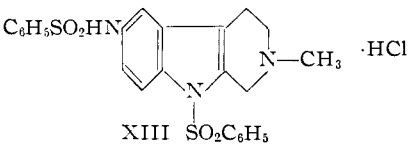
4-Carbethoxy-1-methyl-3-piperidone, 2-carbethoxytetrahydrothiapyrane-3-one, 4-carbethoxy-1-methyl-3-pyrrolidone, 4-carbomethoxy-3-oxotetrahydrothiophene and 3-acetyl-1-ethyloxindole added readily to the disulfonimide to give the desired adducts in good yield. No isolable product other than *p*-phenylenedibenzenesulfonamide was obtained upon attempted addition of 3-carbethoxy-2-piperidone or 3-carbethoxy-1-methyl-4-piperidone to the imide.

The attempted addition of 2-carbethoxy-1-ketoquinolizidine, pyrrolidone and caprolactam also failed. The addition of 3-ethoxalyl-2-pyrrolidone resulted in a product believed to be the monohydrate of the desired adduct XII.



XII

Treatment of an acetone solution of the 4-carbethoxy-1-methyl-3-piperidone adduct with constant boiling hydrochloric acid yielded a product, apparently the hydrochloride of the desired β-carboline XIII.



XIII

All cyclization attempts on the other heterocyclic adducts, including the use of sulfuric acid, polyphosphoric acid, 70% formic acid, phosphorus oxychloride and sodium hydroxide failed.

It is noteworthy that attempted cyclization of the 4-carbethoxy-1-methyl-3-pyrrolidone adduct with both constant boiling hydrochloric acid and 70% formic acid led to cleavage of the carbon–carbon bond to form *p*-phenylenedibenzenesulfonamide.

Acknowledgment.—The authors are indebted to Mr. Josef Nemeth, Mrs. Maria Stingl and Miss Claire Higham for the microanalyses and to Mr. James Brader for the determination and interpretation of the infrared spectra.

Experimental

All melting points are corrected.

Preparation of Quinone Diimide Adducts.—To a solution of the diimide in the minimum amount of dry dioxane was added an equimolar portion of the active methylene compound and a small amount of sodium methoxide. After a short period of standing the product could usually be obtained by trituration with water or petroleum ether (b.p. 80–100°).

Cyclization of the Acetylacetone Adduct of *p*-Benzoquinonedibenzimide; 5-Amino-2-methylindole.—A suspension of 1 g. of the adduct[4] and 40 ml. of constant boiling hydrochloric acid was heated under reflux for 24 hours. After cooling and filtering, 0.50 g. of crude benzoic acid resulted. The filtrate was treated with 15% aqueous sodium hydroxide, brought to a *p*H of 8 and extracted with ether. The extracts yielded 0.32 g. (91.4%) of crude 5-amino-2-methylindole. Sublimation at 160° (15 mm.) pressure yielded 0.24 g. (69%) of pure product; white crystals, m.p. 152–156°. The infrared spectrum of this material was identical to that of an authentic sample.

Anal. Calcd. for $C_9H_{10}N_2$: C, 73.94; H, 6.90; N, 19.16. Found: C, 74.26; H, 6.77; N, 19.51.

The other cyclizations were performed in a similar manner.

1-Methyl-3-N-methylcarboxamido-2-piperidone.—A mix-

(5) W. I. M. Holman and C. Wiegand, *Biochem. J.*, **43**, 423 (1948).

(6) R. Adams and D. C. Blomstrom, THIS JOURNAL, **75**, 3403 (1953).

TABLE I

ADDUCTS OF QUINONE DIIMIDES

Diimides	Addend	Yield, %	M.p., °C.	Solvent for recrystln.	Formula	Analyses, % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
p-Benzoquinonedibenzimide											
(a)	Methone	88	237–238.5	Dil. EtOH	$C_{28}H_{26}N_2O_4$	73.99	73.80	5.77	5.82	6.17	6.12
(b)	Benzoylacetone	79	215.5–217	EtOAC–pet. eth. (b.p. 80–100°)	$C_{30}H_{24}N_2O_4$	75.61	75.47	5.07	5.08	5.88	5.63
(c)	Dibenzoylmethane	94	185–186	EtOAc–pet. eth. (b.p. 80–100°)	$C_{35}H_{26}N_2O_4$	78.05	77.72	4.86	5.07		
(d)	Ethyl 2-ketonipecotate	Quant.	250–250.5	EtOH	$C_{28}H_{27}N_3O_5$	69.26	69.32	5.61	5.66	8.65	8.95
p-Benzoquinonedibenzenesulfonimide											
(e)	Dibenzoylmethane	60	196–197	EtOAc–pet. eth. (b.p. 80–100°)	$C_{33}H_{26}N_2O_6S_2$	64.90	64.84	4.29	4.33		
(f)	3-Ethoxalyl-2-pyrrolidone	..	191 dec.	EtOH	$C_{26}H_{25}N_3O_8S_2 \cdot H_2O$	52.96	52.60	4.62	4.77	7.13	6.89
(g)	4-Carbethoxy-1-methyl-3-piperidone	95	171 dec.	EtOH	$C_{27}H_{29}N_3O_6S_2$	56.73	57.03	5.11	5.20	7.35	7.41
(h)	2-Carbethoxytetrahydrothiapyrane-3-one	77	171 dec.	C_6H_6–C_6H_{12}	$C_{26}H_{26}N_2O_7S_3$	54.34	54.21	4.56	4.69	4.88	4.64
(i)	4-Carbethoxy-1-methyl-3-pyrrolidone	82	207.5–208.5	Dil. EtOH	$C_{26}H_{27}N_3O_7S_2$	56.00	56.06	4.88	5.08	7.54	7.54
(j)	4-Carbomethoxy-3-oxotetrahydrothiophene	82.5	221.5 dec.	MeOH	$C_{24}H_{22}N_2O_7S_3$	52.73	52.85	4.06	4.13	5.13	5.16
(k)	3-Acetyl-1-ethyloxindole	55.6	196.5–197.5	Dil. EtOH	$C_{30}H_{27}N_3O_6S_2$	61.10	61.19	4.62	4.59	7.13	6.93

TABLE II

CYCLIZATION OF ADDUCTS

Adduct (from Table I)	Cyclization agent	Yield, %	M.p., °C.	Solvent for recrystln.	Formula	Analyses, % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
(a)	Const. boiling HCl 17 hr., refl.	60	273.5–275.5	Sublimed	$C_{14}H_{16}N_2O$	73.65	73.97	7.07	7.27	12.27	11.98
(b)	Const. boiling HCl 20 hr., refl.	81.5	153–154[b]	Sublimed							
(c)	Concd. H_2SO_4 18 hr., steam-bath	86	229–230.5[c]	Sublimed							
Ethyl acetoacetate–*p*-benzoquinonedibenzimide	Const. boiling HCl 12 hr., refl.	63.7	181–182.5	EtOH	$C_{26}H_{22}N_2O_4$	73.22	73.18	5.20	5.22	6.57	6.52
Acetylacetone–*p*-benzoquinonedibenzenesulfonimide	Concd. H_2SO_4 24 hr., room temp.	30.4	282–283	Dil. EtOH	$C_{17}H_{16}N_2O_3S$	62.18	62.05	4.91	4.89	8.53	8.57
Acetylacetone–*p*-benzoquinonedibenzenesulfonimide	Const. boiling HCl 12 hr., refl.	80	170–171	Dil. EtOH	$C_{23}H_{20}N_2O_5S_2$	58.96	59.24	4.30	4.27	5.98	5.95
(e)	Const. boiling HCl 12 hr., refl.	94	235–236		$C_{33}H_{24}N_2O_6S_2$	66.89	66.69	4.06	4.02	4.73	4.69
Methone–*p*-benzoquinonedibenzenesulfonimide	Const. boiling HCl 6 hr., refl.	84	232–233	EtOH	$C_{26}H_{24}N_2O_6S_2$	61.39	61.39	4.75	4.95	5.29	5.29
(g)[a]	Const. boiling HCl–acetone 16 hr., refl.	56.3	255.5–258.5 d.	Dil. MeOH	$C_{24}H_{24}ClN_3O_4S_2$	55.64	56.50	4.67	4.60	8.11	7.97

[a] The product gave a positive Beilstein test for halogen, and its infrared spectrum contained a salt band at 2340 cm.$^{-1}$. [b] Lit.[8] m.p. 157–159°. [c] Lit.[8] m.p. 231.5–233°.

ture of 10 g. of diethyl (γ-chloropropylmalonate[7] and 25 ml. of 40% aqueous methylamine was heated in a pressure bottle on the steam-bath for 24 hours. The cooled reaction mixture was extracted with chloroform, and the dried extracts evaporated to dryness. The resulting yellow oil, weighing 3.2 g. (44.5%), partially solidified on standing. The pure product was obtained by recrystallization from a mixture of benzene and petroleum ether (b.p. 40–60°), m.p. 91–93°.

Anal. Calcd. for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.68; H, 8.23; N, 16.30.

3-Carboxamido-1-methyl-2-piperidone.—A solution of 0.2 g. of 3-carboxamido-1-methyl-2-pyridone[5] in 45 ml. of glacial acetic acid was hydrogenated at 29° and 743 mm. pressure over 0.10 g. of platinum oxide (1.5 hr.). The solution was filtered from the catalyst, and the solvent was removed *in vacuo*. The pink oily residue was recrystallized from a mixture of chloroform and diethyl ether; white crystals, m.p. 140.5–142.5°. The yield was 0.14 g. (69.5%).

Anal. Calcd. for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.75; N, 17.94. Found: C, 53.55; H, 7.62; N, 17.86.

3-Acetyl-1-ethyloxindole.—To a solution of 0.37 g. of sodium in 10 g. of ethanol was added 2 g. of 1-ethyloxindole and 1.3 g. of ethyl acetate. The mixture was warmed for 2 hours with intermittent shaking to reduce frothing. It was then poured into water and made acid with hydrochloric acid. The solid product weighed 1.4 g. (56%) after recrystallization from dilute ethanol, m.p. 101.5–103.5°.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 71.13; H, 6.47; N, 7.01.

See Tables I and II for constants on adducts and cyclization products.

URBANA, ILLINOIS

(7) E. Fischer and M. Bergmann, *Ann.*, **398**, 120 (1913).

(8) W. P. Samuels, Jr., Ph.D. Thesis, University of Illinois, 1955, pp. 76, 86.