# A Study of the Chemistry of Pyrophthalone and Related Compounds

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The synthesis and reactions of pyrophthalone and related compounds has been investigated. Pyrophthalone, 2-(2'-pyridyl)-1,3-indanedione, and certain other 2-substituted-1,3-indanediones have been shown to exist in a chelated enol form by chemical evidence and a comparison of infrared spectra. However, the carbonyl group was reactive toward organometallic compounds to form 2-hetero-3-arylindan-1-on-3-ols from which the elements of water could be eliminated to form the corresponding 2-hetero-3-arylindenone. The indanediones and the indenones were reduced by sodium borohydride, catalytically, and in one case, by Clemmensen's method to yield a variety of hydrogenated products.

This work was undertaken to provide, for pharmacological testing, a series of new 2-substituted-1,-3-indanediones in which the substituent groups are heterocyclic residues. These structures suggested possible activity as anticonvulsants and estrogenic antagonists. Perhaps the best known of such substances is pyrophthalone itself, I.

a.   b.

I
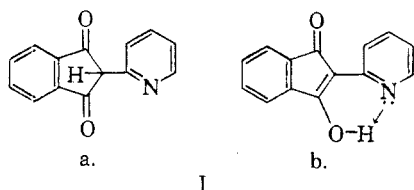
Pyrophthalone was first synthesized by Jacobsen and Reimer[1] and later by von Huber[2] by the condensation of α-picoline with phthalic anhydride. These workers correctly assumed the indanedione structure for their product, although the phthalide-type structure, LIV, was suggested by von Huber for a low-melting product he obtained at one time.

LIV
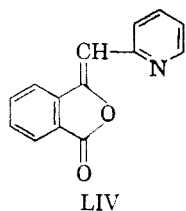
In an attempt to repeat von Huber's work, Eibner[3,4] isolated only one product, a high melting compound, I. When treated with alcoholic sodium methoxide, phthalides produce a red color and rearrange, but these phenomena were not observed with Eibner's product. On the basis of these data, Eibner assumed von Huber's low melting product to be impure pyrophthalone having the symmetrical structure shown in I above. In our work, derivatives of phthalide were not encountered. Furthermore, an infrared spectrum of pyrophthalone shows

a diminished carbonyl band at 6.04μ and a band at 8.4μ attributed to an NH stretching. In many instances, the compounds decolorized potassium permanganate solution, produced a color with ferric chloride, and failed to form picrates. These data are indicative of a chelated enolic system, Ib, for compounds analogous to pyrophthalone.

DISCUSSION

2-Substituted-1,3-indanediones. Table I lists the methods for the synthesis of 2-substituted-1,3-indanediones and the physical data pertaining to these compounds. For the most part, the 2-substituted-1,3-indanediones were synthesized by condensing phthalic anhydride with an alkyl heterocycle. The reactive hydrogens were usually restricted to those on a methyl group although, occasionally, reactive methylene groups were found to condense, as in 2-ethylpyridine and 2-benzylpyridine. Attempts to condense phthalic anhydride with either ethyl 2-pyridyl acetate or 2-[β-(N-piperidylethyl)]pyridine failed.

The most reactive methyl groups are those on carbon adjacent to a ring nitrogen. Thus, the product from 2,3- and 2,4-, and 2,5-dimethylpyridine consistently contained the 2-pyridyl nucleus. In no case was a product formed where both methyl groups had reacted. Furthermore, 2-methylquinoline condensed readily, whereas 4-methylquinoline was unreactive. It is interesting to note that though 2-methylpyridine readily condensed to form pyrophthalone, 2-methylpyrazine resembled toluene in being quite unreactive toward phthalic anhydride. An analogous situation arises in comparing 2-methylquinoline and 2-methylquinoxaline. The former was very reactive, (more so than 2-methylpyridine), while the latter was unreactive. Methyl groups at the 2-position of cyclic structures containing hetero-atoms in both the 1- and 3- positions were sufficiently reactive to form condensation products readily; thus, 2-methylbenzimidazole, 5-chloro-2-methylbenzimidazole, and 2-methylbenzothiazole formed 2-substituted-1,3-indanediones readily. Although reactive,
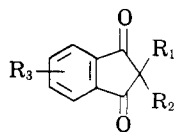
(1) E. Jacobsen and C. L. Reimer, *Ber.*, **16**, 2602 (1883).
(2) H. von Huber, *Ber.*, **36**, 1653 (1903).
(3) A. Eibner and H. Merkel, *Ber.*, **37**, 300 (1904).
(4) A. Eibner and K. Hofmann, *Ber.*, **37**, 3023 (1904).
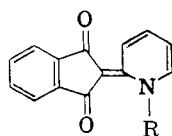
TABLE I—SUBSTITUTED 1,3-INDANEDIONES

Com-pound	R_1	R_2	R_3[j]	Method	Yield (%)	M.P. °C.	M.P. °C. (lit.)	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
I	2-Pyridyl	H-	H-	A	7.2	289–291	280[2]						
				B	39.9	290–292							
				C	43.1	285–290							
				D[a]	18	287–290							
				E	28	288–291							
II	2-(6-Methyl-pyridyl)	H-	H-	C	12	218–219	210–211[8]						
III	2-(5-Ethylpyridyl)	H-	H-	A	31	235–237		76.47	76.17	5.21	5.05		
				C	21	235–237							
IV[k]	2-Pyridyl	Br-	H-	F	—	152–154	157[8]						
V	2-(3-Methyl-pyridyl)	H-	H-	C	2.1	178–180		75.50	75.64	4.67	4.60		
VI	2-(4-Methyl-pyridyl)	H-	H-	C	11	259–260	262[5]						
VII[b]	2-Pyridyl	CH₃-	H-	D[b]	15	137–138		75.9	75.7	4.64	4.65	10.4	10.3
VIII	2-Pyridyl	H-	4-NO₂	C	3.2	315–316						10.45	10.34
IX	2-(6-Methyl-pyridyl)	H-	4-NO₂	A[c]	14	293–294						9.98	10.16
X	2-Pyridyl	H-	5-NO₂	A	17	352–355		62.7	61.4	2.95	3.15	10.4	9.87
XI[l]	2-Pyridyl	φ-	H-	D[h]	52	152–153		80.3	80.2	4.37	4.63		
				D[i]	49	152–153							
XII	2-Quinolyl	H-	H-	C[e]	42	241–242	241[6]						
XIII	2-Benzothiazoyl	H-	H-	A[d,f]	51	350–360		68.8	69.0	3.23	3.18	5.02	5.04
XIV	2-(5-Chlorobenz-imidazoyl)	H-	H-	C[e]	61	No m.p. up to 480						9.44	9.45
XV	2-Benzimidazoyl	H-	H-	G[g]	67	No m.p. up to 500	No m.p. up to 350[g]						

[a] Benzene used as a solvent. [b] Toluene used as a solvent for a reflux period of 16 hr. The product was extracted with dilute hydrochloric acid and reprecipitated by neutralization with sodium hydroxide solution. Picrate: m.p. 216–218°C; *Anal.* Calcd.: N, 12.0; found: N, 11.6. [c] Heated to reflux only until solid began to appear. [d] No catalyst employed. [e] Phosphoric acid used as a catalyst. [f] Product was insoluble in all solvents; purified by washing with boiling 95% ethyl alcohol. [g] Author[7] reports product to be slightly soluble in glacial acetic acid but insoluble in all other solvents. In this work, the product was found to be soluble in concentrated sulfuric acid from which it could be reprecipitated unchanged, upon dilution. [h] Refluxed for 63 hr. [i] Toluene used as a solvent, mixture refluxed for 10 hr. [j] Phthalones with R_3 substituents are derived from the corresponding phthalic anhydrides. [k] Hydrobromide salt: m.p. 305°C. *Anal.* Calcd. for $C_{14}H_9O_2Br_2N$: Br, 42.3. Found: Br, 41.8. [l] Picrate: m.p. 189–190°C., *Anal.* Calcd. for $C_{26}H_{16}O_9N_4$: N, 10.6. Found: N, 10.9.

2-methylbenzoxazole gave a product which could not be characterized.

Compounds which reacted with phthalic anhydride readily condensed with substituted phthalic anhydrides to form indanediones substituted in the benzene ring; thus, 2-methylpyridine condensed readily with 3-nitro-, 4-nitro-, and 4,5,6,7-tetrachlorophthalic anhydride while 2,6-dimethylpyridine condensed with 3-nitrophthalic anhydride.

LVI

Little success was had in the preparation of N-substituted pyrophthalones (structure LVI).

Using the method of Kuhn and Bär[5] for the synthesis of N-methylpyrophthalone from dimethyl sulfate and the sodium salt of pyrophthalone, there resulted, in good yield, a compound melting at 223–225° which reverted to pyrophthalone on attempted reduction with Raney nickel W-6. Kuhn and Bär[5] reported a melting point of 165°. An attempt to form N-benzylpyrophthalone from benzyl chloride and the sodium salt of pyrophthalone afforded no product at all.

Products of reaction with organometallic compounds. Table II lists the products of reaction of phthalone-type molecules with organometallic compounds. For the most part, organolithium compounds were employed but in one case, the reaction of pyrophthalone with benzylmagnesium

(5) R. Kuhn and F. Bär, *Ann.*, **516**, 155 (1935).
(6) J. Ogilvie, U. S. Patent, **1,963,374**.
(7) J. van Alphen, *Rec. trav. chim.*, **59**, 289 (1940).
(8) A. Scholze, *Ber.*, **38**, 2806 (1905).

TABLE II

A. PRODUCTS OF REACTION WITH ORGANOMETALLIC COMPOUNDS[i]

Compound	Reactant	R_1	R_2	R_3	Method	Yield (%)	M.P.	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
XVI	I	2-Pyridyl	H-	C_6H_5-	H	80	142–143	79.99	78.08	4.70	4.95		
XVII	I	2-Pyridyl	H-	p-CH$_3$O-C$_6$H$_4$-	H	70	156–157	76.12	75.88	5.17	5.35		
XVIII	I	2-Pyridyl	H-	p-CH$_3$C$_6$H$_4$-	H	92	150	79.99	79.70	5.39	5.43		
XIX	I	2-Pyridyl	H-	m-CH$_3$-C$_6$H$_4$-	H	75	130d	79.99	80.00	5.39	5.40		
XX	I	2-Pyridyl	H-	o-CH$_3$C$_6$H$_4$-	H	70	145–155	79.99	79.90	5.39	5.36		
												Cl	Cl
XXI	I	2-Pyridyl	H-	p-ClC$_6$H$_4$-	H^c	80	150–160	71.55	69.80	4.17	4.90	10.58	9.57
XXII^d	XII	2-Quinolyl	H-	C_6H_5-	H	100	164	79.78	77.80	4.71	5.01		Ash
XXIII	XIII	2-Benzo-thiazoyl	H-	C_6H_5-	H	89	No m.p. up to 360	73.95	70.60	4.20	4.22	3.88	11.00
XXIV	XIV	2-(5-Chloro-benzimid-azoyl)	H-	C_6H_5-	H	49	No m.p. up to 510					7.48	9.66^k
XXV	I	2-Pyridyl	H-	$C_6H_5CH_2$-	I	68	100–120						
XXVI	XV	2-Benzimid-azoyl	H-	C_6H_5-	J	94	235 (100d)					8.23	7.45

Compound		Name			Method	Yield (%)	M.P.	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
XXVII	^{h}	2-(2'-Pyridyl)indan-2-ol			H^c	10	119–120	79.58	79.40	6.20	6.23	6.63	6.80
XXVIII	^{j}	1-(2'-Pyridyl)indan-1-ol			H^c	33	78–80					6.63	6.49
XXIX	XXXI	1,3-Diphenyl-2-(2'-pyridyl)-1-inden-3-ol			H H^a	28 78	237–238 237–238	86.4	85.9	5.30	5.49	3.87	3.79
XXX	XI	1,2,3-Triphenyl-2-(2'-pyridyl)in-dane-1,3-diol			H	90	107					3.08	3.02

B. PRODUCTS OF DEHYDRATION OF CARBINOL INTERMEDIATES

Compound	Reactant	R_1	R_2	Method	Yield (%)	M.P.	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
XXXI^f	XVI	2-Pyridyl	C_6H_5-	J K	100 82	130–131 129–131	84.8	84.9	4.62	4.92		
XXXII	XVII	2-Pyridyl	p-CH$_3$OC$_6$H$_4$-	J	100	155–156	80.52	80.06	4.83	4.70		
XXXIII	XVIII	2-Pyridyl	p-CH$_3$C$_6$H$_4$-	J	100	155–156	84.83	84.95	5.08	5.07	4.71	4.66
XXXIV	XIX	2-Pyridyl	m-CH$_3$C$_6$H$_4$-	J^b	100	107–110	84.83	84.30	5.08	5.10	4.71	4.87
XXXV	XX	2-Pyridyl	o-CH$_3$C$_6$H$_4$-	J	100	121–122	84.83	85.20	5.08	5.51	4.71	4.59
XXXVI	XXI	2-Pyridyl	p-ClC$_6$H$_4$-	J	100	136–138	75.59	75.15	3.78	4.40	11.18	11.10
											Cl	Cl
XXXVII^g	XXII	2-Quinolyl	C_6H_5-	K	96	220(125^d)	86.5	81.6	4.50	4.95	4.20	3.94
XXXVIII	XXIII	2-Benzothiazoyl	C_6H_5-	K	100	169–170	77.9	77.4	3.83	3.91	4.13	4.14
XXXIXe	XXV	2-Pyridyl	$C_6H_5CH_2$-	K	54	65–100 (gum)						
XL	XXVI	2-Benzimidazoyl	C_6H_5-	K	100	255–257	81.95	81.75	4.38	4.33	8.74	8.81

^{a} A benzene solution of the phthalone was added to the ether solution of the phenyllithium. The mixture was then treated with dilute hydrochloric acid, and the solid was recrystallized from n-amyl alcohol. ^{b} Prepared by thermally decomposing the carbinol in boiling nitroethane. ^{c} Organolithium prepared by the method of Gilman, Langham, and Moore[9] using n-butyllithium and the corresponding halo compound. ^{d} Product decolorized KMnO$_4$, and did not form a 2,4-dinitrophenylhydrazone, but formed a picrate which melted at 205°C. ^{e} A picrate derivative of the gummy residue melted at 209–211°C, but analyzed poorly. Anal. Calcd. for C$_{27}$H$_{18}$O$_8$N$_4$: C, 61.6; H, 3.44; N, 10.64. Found: C, 61.5; H, 3.77; N, 9.50. ^{f} Picrate, m.p. 198–199°C; oxime, m.p. 185–186°C; 2,4-dinitrophenylhydrazone, m.p. 295–299°C (d). ^{g} Picrate, m.p. 205°C. ^{h} The reactant was 2-indanone. ^{i} The halide used to prepare the organometallic compound was the bromide corresponding to R$_3$ except for the compound XXXV, where the chloride was used. ^{j} Reactant was 1-indanone. ^{k} Some ash present.

(9) H. Gilman, W. Langham, and F. W. Moore, J. Am. Chem. Soc., 62, 2327 (1940).

chloride, a product was obtained which was a gum and difficult to characterize. The sequence of reactions involved may be illustrated by the reaction of pyrophthalone with phenyllithium:

Control experiments have indicated that two moles of organometallic compound are required for one mole of phthalone, and for this reason, we write the dilithiated intermediate above, LV. Hydrolysis of the reaction mixtures always resulted in the formation of an indanol, XVI, which is shown above in the enolic form for reasons previously stated. The carbinols so produced could be isolated, but since they dehydrated readily, purifications and characterizations were difficult and sometimes impossible. Dehydration of the carbinols could be done either thermally, that is by heating above the melting point of the carbinol, or by treating the carbinol with concentrated hydrochloric acid. In either case, a pure indenone, XXXI, could usually be isolated.

In a few cases, a second mole of phenyllithium added to the phthalone. In the reaction of 2-phenyl-pyrophthalone (XI) with phenyllithium, the product isolated was 1,2,3-triphenyl-2-(2'-pyridyl)-indanediol (XXX), indicating the addition of two moles of organometallic compound to the molecule. In addition, 3-phenyl-2-(2'-pyridyl)indenone (XXXI), reacted with phenyllithium to form 1,3-diphenyl-2-(2'-pyridyl)-1-inden-3-ol (XXIX).

The indenones differed markedly from their parent indanedione. They were usually more intensely colored, had lower melting points, and were more soluble in organic solvents and hydrochloric acid solutions. Since they were unable to enolize, they could not chelate, and it was usually possible to form derivatives such as picrates, oximes, and occasionally, 2,4-dinitrophenylhydrazones. They generally decolorized potassium permanganate solutions, and infrared spectra indicated the presence of a carbonyl group in the molecules.

The addition of organometallic compound to the indandione generally proceeded smoothly and the carbinol and the indenone produced by dehydration of the carbinol were solids. Occasionally, however, the indenone would form as a gum which could not be crystallized and when this occurred, characterization was virtually impossible. Such was the case, for example, in the reaction of pyro-

phthalone with n-butyllithium, benzylmagnesium chloride, or methyllithium.

Reduction products. Reductions of pyrophthalone-type compounds were done: 1. catalytically, 2. with sodium borohydride, and 3. in one instance, using Clemmensen's method. These products are listed in Table III.

The Clemmensen reduction was attempted on 2-phenylpyrophthalone and 3-phenyl-2-(2'-pyridyl)indenone (XXXI). The 2-phenyl derivative reduced nicely to give 60% yield of 2-phenyl-2-(2'-pyridyl)-indan-3-on-1-ol, XLVII. The 3-phenyl derivative (XXXI) could not be reduced by this method, although catalytically, or with sodium borohydride, it afforded a variety of products depending upon the conditions (Table III). Attempted reduction of 2-phenylpyrophthalone with lithium aluminum hydride gave 2-benzylpyridine and phthalide. A probable mechanism for the formation of these substances follows:
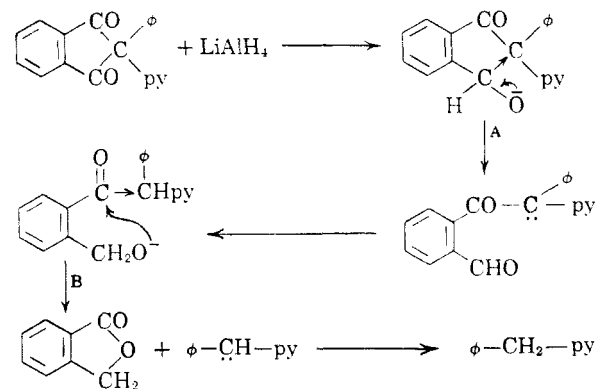
Step A is a reversal of the aldol condensation and Step B is a reversal of the Claisen ester condensation. Both of these reactions are well known to be equilibrium reactions.

A Wolff-Kishner reduction on 2-phenylpyrophthalone gave an unidentified product, melting at 252–255°.

XLVII
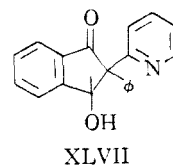
Vigorous catalytic hydrogenation not only reduced indene double bonds, but occasionally reduced part or all of the heterocyclic ring substituent. Thus, 3-phenyl-2-(2'-pyridyl)indenone, XXXI, was reduced with Raney nickel W-6 to give 3-phenyl-2-(2'-pyridyl)indanone. This compound was demonstrated to exist in a chelated enol form XLI, by
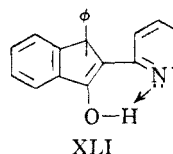

XLI

TABLE III

REDUCTION PRODUCTS

A. INDENES

Compound	Reactant	R₁	R₂	R₃	Method	Yield (%)	M.P.	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
XLI	XXXI	2-Pyridyl	H-	C₆H₅-	L^c	60	187–188	84.0	83.8	5.61	5.39		
					L^d	30	188–189						
					N	49	188–189						
XLII	XXXI	2-(3,4,5,6-Tetra-hydro-pyridyl)	H-	C₆H₅-	L^f	36	213	83.1	83.1	6.59	6.62	4.84	5.07
					L^g	46	212–213						
XLIII	XXXVII	2-(3,4-Dihydro-quinolyl)	H-	C₆H₅-	N	86	275	85.5	85.8	5.64	5.58	4.15	4.07
XLIV	XIII	2-Benzothiazoyl	H-	HO-	N	100	345–348	68.3	68.5	3.91	3.73		
XLV	XXXVIII	2-Benzothiazoyl	H-	C₆H₅-	N	50	151–152	77.4	77.6	4.37	4.55		
XLVI^i	XXXIII	2-Dihydro-pyridyl^h	H-	p-CH₃-C₆H₄-	N	43	183–184	84.0	84.2	6.00	5.95	4.67	4.64

B. INDANES

Compound	Reactant	Name	Method	Yield (%)	M.P.	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
XLVII	XI	2-Phenyl-2-(2'-pyridyl)indan-3-on-1-ol	M	60	186–187	79.6	78.3	4.98	5.11	4.65	4.70
XLVIII^b	XXXI	3-Phenyl-2-(2'-piperidyl)in-dan-1-ol	L^a	15	180–181	81.86	82.4	7.91	8.08		
XLIX	XXXI	3-Phenyl-2-(2'-piperidyl)in-dan-1-ol	L^n	39	206–208	81.86	81.94	7.91	7.84		
L	XXX	1,2,3-Triphenyl-2-(2'-piperid-yl)indane-1,3-diol	L^e	71	135–136	83.3	83.0	6.73	7.17		
LI	I	2-(2'-Piperidyl)indane-1,3-diol	L^j	11	230–232(d) as B·HCl	62.31	62.42	7.47	7.49		
LII	XI	2-Phenyl-2-(2'-piperidyl)in-dane-1,3-diol	L^l	8	184–186	77.62	77.61	7.49	7.64		
LIII	I	2-(2'-Piperidyl)hexahydroin-dane-1,3-diol	L^k	41	196–199	65.00	65.82	10.10	10.01		

^{a} Conditions: 3.3 g. phthalone in 30 ml. absolute ethanol containing three molar equivalents of dry HCl, 20 mg. platinum oxide, 2100 lbs/in², 24 hr. ^{b} Acetic anhydride reacted with the reduced compound to produce the N-acetyl-O-acetyl derivative, m.p. 166–167°. Anal. Calcd. for C₂₄H₂₇O₃N: C, 76.4; H, 7.17. Found: C, 76.2; H, 7.32. We believe XLVII and XLIX to be optical isomers. ^{c} Conditions: 5.7 g. phthalone in 250 ml. absolute ethanol, 0.2 g. Raney nickel W-6, 2 atm., 78 hr. The product did not form a 2,4-dinitrophenylhydrazone or picrate, but gave a dark green color with ferric chloride. A repeat synthesis using three molar equivalents of dry HCl in absolute ethanol gave a 46% yield. ^{d} Conditions: 10 g. phthalone in 30 ml. dioxane, 2.0 g. Raney nickel W-6, 2 atm., 16 hr. A 10% yield of an unidentified product was also obtained; this compound was insoluble in ethanol and melted at 148–149°. ^{e} Conditions: 1.5 g. phthalone in 25 ml. of dioxane, 2 g. Raney nickel W-6, 122 atm., 24 hr., 125°. ^{f} Conditions: 5.6 g. phthalone in 30 ml. of dioxane, 2 g. Raney nickel W-6, 2000 lbs/in², 42 hr. 125°. ^{g} Conditions: 28.3 g. phthalone in 300 ml. of dioxane, 10 g. Raney nickel W-6, 153 atm., 20 hours, 108°. ^{h} Exact location of the dihydropyridyl ring hydrogens is not known at present. ^{i} Picrate: m.p. 193–195°. ^{j} Conditions: 6 g. phthalone in 50 ml. of CH₃OH, 2.7 ml. concentrated HCl, 0.5 g. platinum oxide at 60 lbs/in². ^{k} Conditions: 7.5 g. phthalone in 100 ml. of glacial HOAc, 0.8 g. platinum oxide, 2 hr. ^{l} Conditions: 2 g. phthalone, 50 ml. 80% HOAc, 0.4 g. platinum oxide.

an infrared spectrum which showed -OH and -NH stretching at 2.7μ and 3.05μ respectively, a peak for -NH bending at 6.4μ, a peak for -OH at 7.5μ, and a broad peak for -OH deformation at 9.1–9.3μ.

Furthermore, the compound produced a green color with ferric chloride and did not form a picrate or a 2,4-dinitrophenylhydrazone. This same product was synthesized by a reduction of the parent compound with sodium borohydride. Under
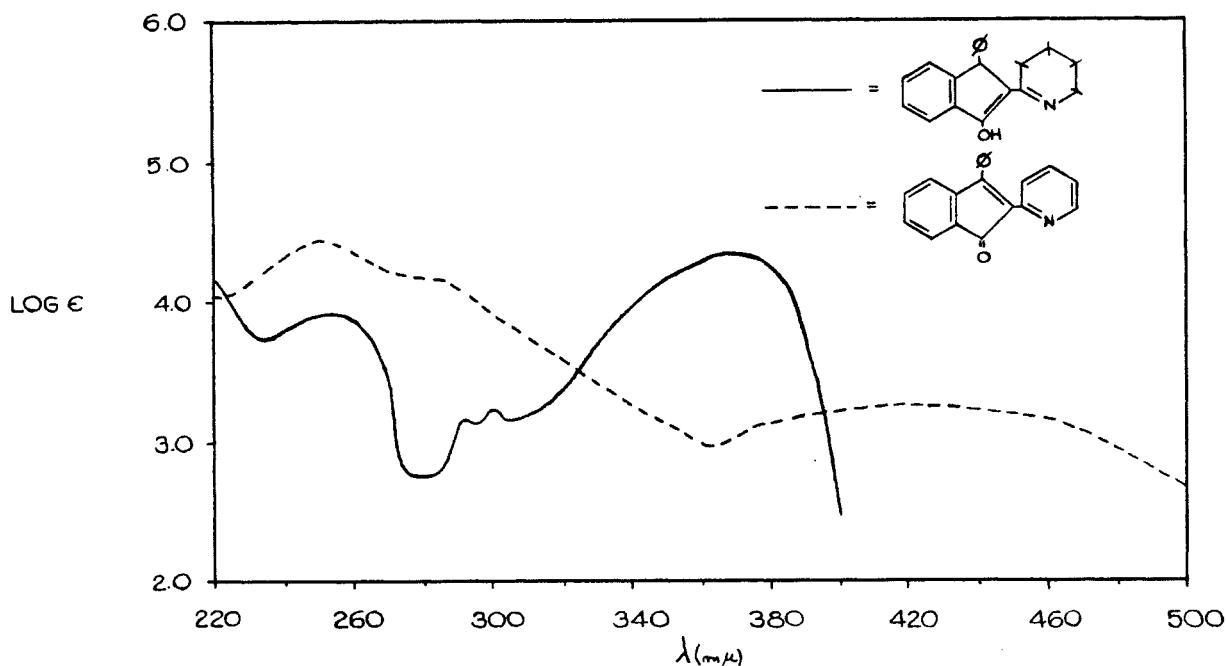
Figure 1

more vigorous conditions, 3-phenyl-2-(2'-pyridyl)indenone, XXXI, was reduced to 3-phenyl-2-[2'-(3',4',5',6'-tetrahydropyridyl)]indenone, XLII, which was also shown to have a chelated enol structure by the same methods as described above. Further evidence for the assignment of XLII as the structure of the compound was found in a comparison of the ultraviolet and visible absorption spectra (Fig. 1) of both the parent compound and the reduced product. The similarity in the curves is indicative of analogous chains of conjugation. The small hypsochromic shift at the longer wavelengths is as expected by a slight decrease in the length of the conjugated chain brought about by the partial reduction of the pyridine ring. Under still more vigorous conditions, the compound was reduced to 3-phenyl-2-(2'-piperidyl)indanol, XLVIII, which was acetylated at the piperidine nitrogen and the indanol oxygen by refluxing with acetic anhydride. A higher melting isomer (XLIX) of XLVIII was isolated under slightly different conditions and it is believed that these are optical isomers. In one instance, pyro-

XLVIII   XLII   LIII
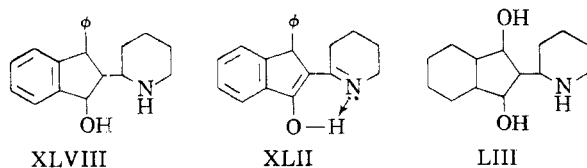
phthalone itself was completely reduced to a saturated diol (LIII).

Sodium borohydride reduced the 3-phenyl-2-substituted indenones more readily than it reduced the 2-substituted indanediones. Thus, pyrophthalone and 2-(2'-quinolyl)indanedione were not reduced by sodium borohydride while the corresponding 3-

phenyl-2-(2'-substituted)indenone was reduced readily by this reagent. The reduction product of 3-phenyl-2-(2'-pyridyl)indenone was discussed above. In the case of 3-phenyl-2-(2'-quinolyl)-indenone, analysis showed that four hydrogen atoms were added to the system. Unlike the parent compound, the reduction product did not decolorize potassium permanganate solutions, did not form a picrate, and was insoluble in hydrochloric acid solutions. Furthermore, it gave no ferric chloride test[10] and did not form a 2,4-dinitrophenylhydrazone. There was little difference in the ultraviolet and visible spectra (Fig. 2) of the starting material and the reduced product, indicating that the chain of conjugation in each is essentially the same. On this basis, the most likely structure of the reduced product is XLIII.

XLIII
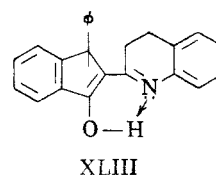
The reduction of 3-(p-tolyl)-2-(2'-pyridyl)indenone with sodium borohydride yielded a compound which contained a partially reduced pyridyl ring. The product produced a green color with ferric chloride, decolorized potassium permanganate, did not form a 2,4-dinitrophenylhydrazone, did form a picrate, and, by analysis, appeared to be a tetrahydro derivative. These data indicate an enolic system which could be weakly chelated to the ring nitrogen, thus, the compound must have

(10) The spectra (see Fig. 2) indicated the presence of an enolic system in spite of the negative ferric chloride test.
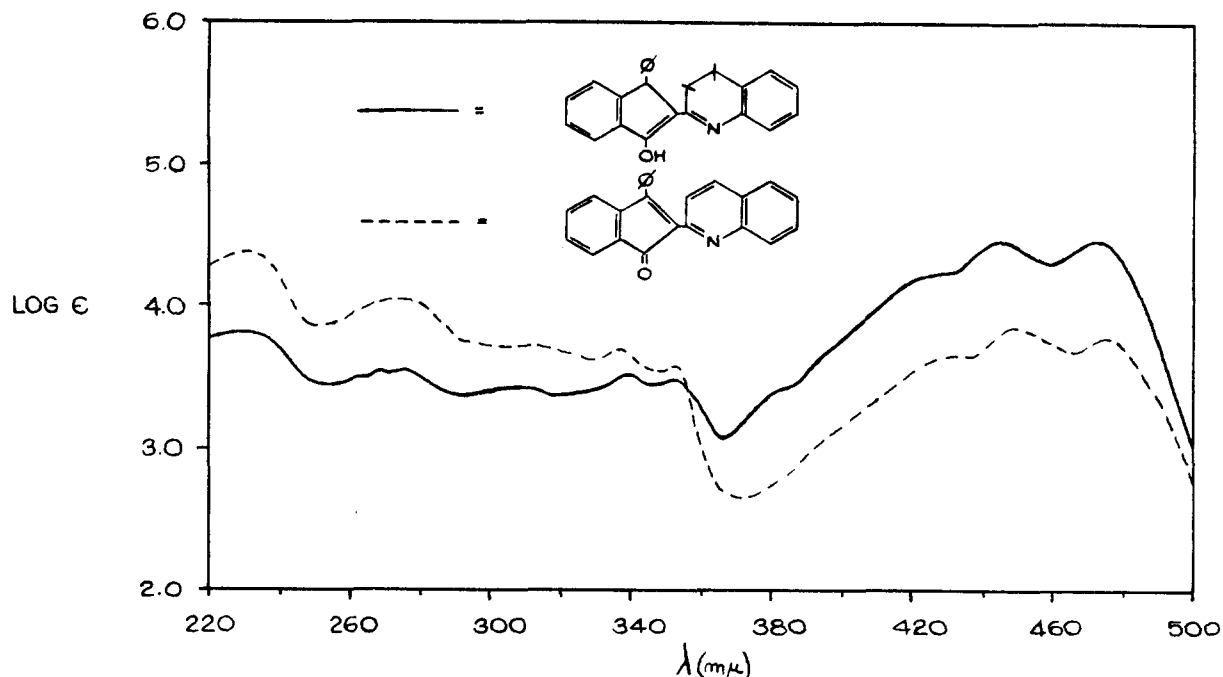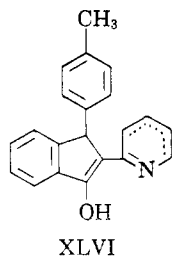
Figure 2

been partially reduced in the heterocyclic ring. The location of the ring hydrogens is as yet uncertain, but the compound can be considered as the enol form of 3-(p-tolyl)-2-(2'-dihydropyridyl)indanone, XLVI.

XLVI

The reduction of 2-(2'-benzothiazoyl)indandione with sodium borohydride gave a quantitative yield of 2-(2'-benzothiazoyl)indan-3-on-1-ol, XLIV. The product was insoluble in all solvents and could not be completely characterized; however, previous experience indicates this compound probably is in the enol form and chelated to one of the heteroatoms of the benzothiazole ring. The 3-phenyl-2-(2'-benzothiazoyl)indenone was reduced to form a compound which was soluble in most organic solvents, but did not dissolve in concentrated hydrochloric acid solutions as did the parent compound. Furthermore, it gave no color with ferric chloride, and formed no picrate. These data indicate the ring nitrogen to be chelated with the hydroxyl group on the five-membered ring, and the product has been assigned structure XLV.

Attempts to reduce 3-phenyl-2-(2'-benzimidazoyl)indenone and 2-[2'-(5'-chlorobenzimidazoyl)]-indanedione with sodium borohydride, failed.

Results of Pharmacological Testing. After ex-

XLIV   XLV
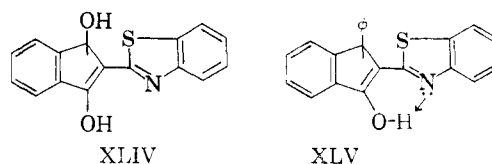
tensive screening, seven of the compounds under consideration were found to have antiarthritic activity. These are XVII, XXXI, XXXII, XXXIII, XXXIV, XXXVI, and XXXVII. It is interesting to note that six of these are indenones and that the remaining compound (XVII) is a carbinol precursor to an indenone (XXXII).

EXPERIMENTAL

Method A. H. von Huber[2] employed an equimolar mixture of phthalic anhydride and the active methyl compound and heated with a catalytic amount of zinc chloride for 5 hr. at 200°.

Method B. A modification of Method A. A two-molar quantity of active methyl compound was used and the mixture was heated in a sealed tube.

Method C. The method of J. Ogilvie[6] is a modification of Method A employing a solvent. The reactants and catalyst were dissolved in a quantity of nitrobenzene (approximately equal in weight to the phthalic anhydride employed), and the solution was refluxed for 6 hr. The mixture was cooled and the solid phthalone was filtered, washed with ether, and recrystallized from a suitable solvent such as nitroethane, nitrobenzene, or ethanol.

Method D. In this procedure, phthalyl chloride in benzene was used in place of phthalic anhydride.[2]

Method E. A modification of Method C, employing phosphoric acid as a catalyst.

Method F. The phthalone was dissolved in glacial acetic acid, and a half-molar quantity of bromine (based on the phthalone) added dropwise with stirring. Stirring was continued for 10 min. after complete addition of the bromine. The solution was filtered, the solid was slurried with cold

water, and 5% sodium hydroxide solution was added until the slurry was slightly basic. The product was then filtered, washed, and dried.

Method G. J. van Alphen[7] heated phthalic anhydride and an equimolar amount of 2-methylbenzimidazole at 200°C for 2 hr. The mixture was washed with hot water, hot ethanol, and hot glacial acetic acid until the washings were clear. The product was only slightly soluble in glacial acetic acid, but was reprecipitated from concentrated sulfuric acid by dilution with water.

Method H. The organolithium compound was prepared from the halide corresponding to R_3. The molar ratio of lithium to halide to phthalone was 4:2:1. The lithium was cut into small pieces and added to 35 times its weight of absolute ether. A 0.5M solution of the halide in absolute ether was added to the lithium-ether mixture with stirring, and at such a rate as to maintain gentle reflux of the ether. After the lithium had reacted completely, the phthalone was added as a powder at such a rate as to maintain gentle reflux. After complete addition of the phthalone, the mixture was stirred with gentle reflux until a negative Gilman test indicated complete reaction of all the organometallic compound. A solid usually precipitated during the course of the reaction. The reaction vessel was surrounded by an ice bath and an equal volume of a dilute solution of ammonium chloride was slowly added to the reaction mixture with stirring. The solid present dissolved and a new solid precipitated as more ammonium chloride solution was added. Stirring was continued for 0.5 hr. after addition of the hydrolysis solution. The solution was filtered, and the solid carbinol was washed with water and dried.

Method I. The Grignard reagent was prepared according to the method of Gilman and Meyers.[11] In this work, the molar quantity of Grignard employed was four times the molar quantity of the phthalone used. The phthalone was added as a solid to the Grignard solution and the mixture was refluxed for 1 hr. The product worked up as described in Method H.

Method J. The dried carbinol, as prepared by Method H or I was heated above its melting point until effervescence ceased, and the melt was uniform in color. It was purified by recrystallization from an ethanol-water solution.

Method K. The dried carbinol, as prepared by Method H or I, was dissolved in concentrated hydrochloric acid. A great deal of effervescence occurred and the solution became a deep red. The solution was stirred for 15 min., cooled with an ice bath, and neutralized with sodium hydroxide solution. The solid which separated was the dehydrated carbinol, which was filtered, washed with 10% sodium bicar-

bonate solution, and dried. The product was purified by recrystallization from an ethanol-water solution.

Method L. Reference to the specific reaction conditions is given in Table III. After completion of the reaction, the solution was filtered away from the catalyst, and the solvent was removed by distillation under reduced pressure. The solid residue was purified by recrystallization from a suitable solvent such as ethanol or nitroethane.

Method M. The following quantities were used for every mole of phthalone: 598 g. mossy zinc, 47.9 g. mercuric chloride, 30 ml. concentrated hydrochloric acid, and 720 ml. water. The materials were mixed and shaken vigorously for 10 min., and the liquid phase was then decanted. To the residue of amalgamated zinc was added 450 ml. water, 598 ml. concentrated hydrochloric acid, and 1 mole of the phthalone. An oil separated, and therefore, 450 ml. water, and 598 ml. concentrated hydrochloric acid were again added, and thereafter, 59.8 ml. concentrated hydrochloric acid was added every hour for 5 hr., and the solution was refluxed overnight. On cooling, a solid separated which was slurried with sodium hydroxide solution until the mixture remained basic. The product was then washed with water, and recrystallized from a suitable solvent such as ethanol or nitroethane.

Method N. The phthalone was added as a solid to a 0.2M solution of sodium borohydride in tetrahydrofuran. The molar ratio of phthalone to borohydride was 1:1. The mixture was stirred, and a volume of a 0.5M solution of lithium chloride in tetrahydrofuran was added slowly, the volume chosen was such that there was present a 1 molar equivalent of lithium chloride, based on the quantity of the phthalone used. The mixture was allowed to stir 24 hr. at room temperature, after which it was slowly added to a beaker filled with ice and a few milliliters of concentrated hydrochloric acid. The hydrolysis mixture was stirred during the addition and stirring was continued until the vigorous reaction ceased. The solid which formed was filtered, washed with 10% sodium hydroxide solution, dried, and recrystallized from a suitable solvent such as ethanol or nitroethane.

(11) H. Gilman and C. H. Meyers, *Org. Syn.*, **4**, 59, (1925).