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Isoindoline 誘導體의 合成硏究 III*

二塩基酸無水物 또는 Imide에 對한 有機酸의 Gabriel 縮合反應에 關한 硏究

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Nam Soon Lee, Choong Ki Lim, Tae Soon Cho, Chung Hi Won, Dow Won Moon, In Suk Park, Moo Gon Kim, Yun Sik Min, Jin Soo Chung, Yung Bong Cho, Yung Soo No : Studies on Isoindoline Derivatives. III. Studies on the Anhydrides and Imides of Dibasic Acids for the Organic Acids in the Gabriel Condensation.

Abstract— Fifteen derivatives of phthalide were synthesized from *m*-hemipinic, hydrastic and 4,5-benzophthalic anhydride with acetic, phenylacetic, *p*-methoxyphenylacetic, *p*-nitrophenylacetic, α-naphthylacetic and succinic acid by the Gabriel condensation. In the same way, 13 derivatives of phthalimidine and 4 derivatives of α,β-benzisothiazoline-1, 1-dioxide were synthesized from diphenylmaleimide, phthalimide, saccharine and 4,5-benzo-phthalimide with previous 6 acids. 3-Substituted derivatives of *m*-hemipinic anhydride, hydrastic anhydride and 4,5-benzophthalic anhydride were treated with formamide and seven 3-substituted imidines could be synthesized. In case of 4,5-benzophtha lide, two isomers,4,5-benzophthalidene-3-acetic acid and 4,5-benzophthalidene-1-acetic acid, can be obtained theoretically, but only one product we got, and the chemical structure of it was identified by the following way.

It was hydrolyzed and then decarboxylated, and this decomposed product was identical with 1-acetyl-2-naphthoic acid which was synthesized from β-naphthylamine. This indicates that by the Gabriel condensation 4,5-benzophthalide only produces 4,5-benzophthlidene-3-acetic acid, that is α-carbonyl substitute.

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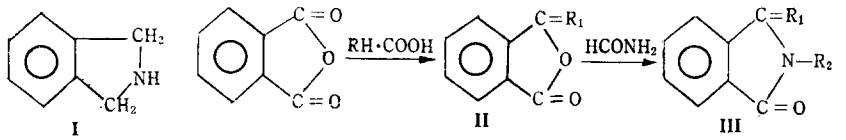
* 第一報, S. Sugasawa and Nam Soon Lee, *J. Pharm. Soc. Japan*, **63**, 98 (1943)
第二報, Nam Soon Lee, *ibid.*, 64, 9 (1944)

The Gabriel condensation was also achieved from heterocyclic monocarboxylic acids, 3-indole acetic acid and 6-quinoline acetic acid, with phthalic anhydride, then produced indole-3-methinyl-3′-phthalide and quinoline-6-methinyl-3′-phthalide.

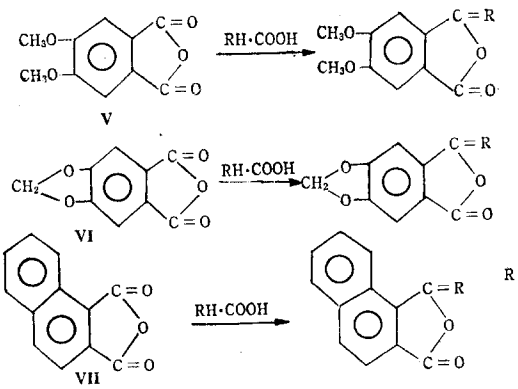
窒素環式化合物中 isoindole 및 isoindoline 〔I〕 系化合物에 關한 文獻記載가 稀少하기 때문에 著者는 이미 이 硏究의 第1報와 第2報에서 phthalic anhydride에 無水錯酸나트륨存在下에 數種의 有機酸을 Gabriel 縮合反應시키어 phthalide 誘導體 (II)를 合成하여 가지고 이것을 formamide 또는 methylformamide와 加熱하여 phthalimidine 誘導體(III)로 한다음 Tafel 氏 電解還元法에 依하여 容易하게 數種의 置換 isoindoline 誘導體(IV)를 合成할 수 있었음을 報告하였다.



R_1: $CH{\cdot}C_6H_5$, $CH{\cdot}C_6H_4{\cdot}OCH_3$, $CH{\cdot}C_6H_3{\cdot}(OCH_3)_2$, $CH{\cdot}C_6H_3{\cdot}(O_2CH_2)$, $CH{\cdot}C_{10}H_7$

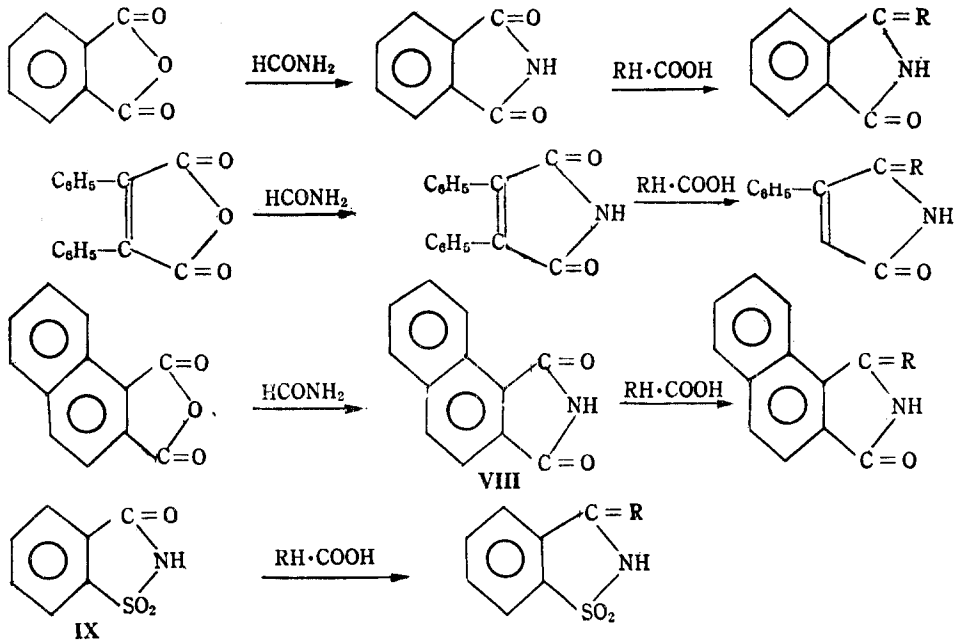
R_2: H, CH_3

著者等은 이 系列의 化合物을 廣範圍하게 繼續 合成할 意圖로 于先 phthalic anhydride 대신에 *m*-hemipinic anhydride (**V**), hydrastic anhydride (**VI**), 4,5-benzophthalic anhydride[1] (**VII**)를 使用하고 活性一鹽基酸으로서는 acetic, phenylacetic, *p*-methoxyphenylacetic, *p*-nitrophenylacetic, α-naphthylacetic acid 等의 各酸과 二鹽基酸中의 succinic acid 를 使用하여 Gabriel 縮合段階를 檢討한 結果, 이들에서도 良好한 所期의 目的을 達하였다.

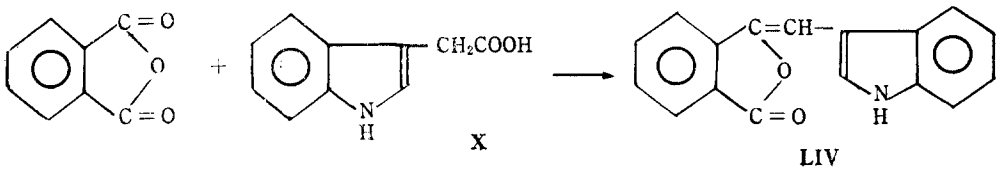


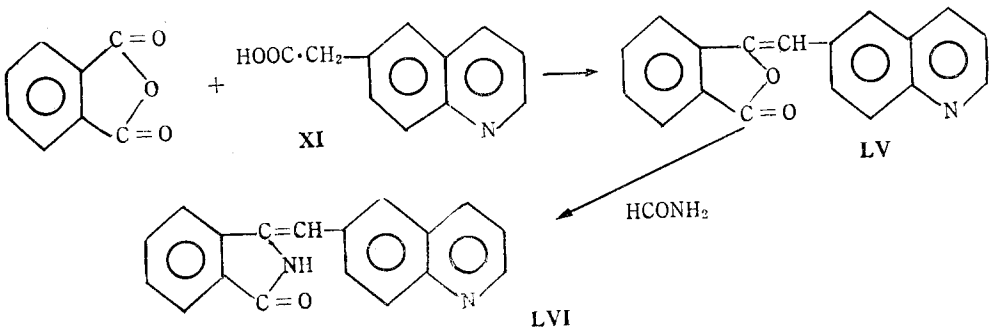
R : $CH{\cdot}COOH$, $CH{\cdot}C_6H_5$, $CH{\cdot}C_6H_4{\cdot}OCH_3$, $CH{\cdot}C_6H_4{\cdot}NO_2$, $CH{\cdot}C_{10}H_7$, $=CH-CH=$

또 著者等은 過去에 formamide를 使用하여 有機酸을 酸 amide로 만드는 反應[2]을 硏究하던때에 二鹽基酸 및 二鹽基酸無水物이 거의 定量的으로 二鹽基酸 imide로 되는것을 알았다. 그리고 Gabriel 縮合反應이 過去에 二鹽基酸無水物에만 適用되었고, 二鹽基酸 imide에 對한 縮合反應例는 文獻에 볼 수 없었으므로, 著者들은 이 硏究에 使用된 二鹽基酸들을 formamide로써 得量좋게 二鹽基酸 imide (**VIII**)로 만들어 Gabriel 縮合反應을 實施한 結果, 大體로 좋은 得量으로 phthalimidine 誘導體를 얻을 수 있었으며 sulfonimide인 saccharin (**IX**)에서 成果가 至極히 良好하였다는 것은 興味있는 事實이다.



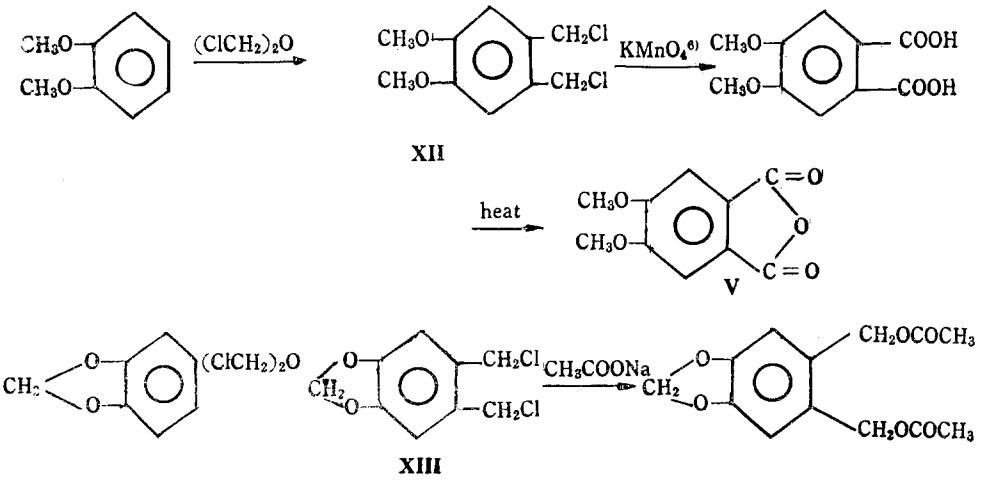
또 이 縮合反應에서 活性一鹽基酸으로서 複素環式化合物의 一鹽基酸이 適用된 例가 文獻에 보이지 않았기 때문에, 著者들은 phthalic anhydride에 對하여 4-pyridylacetic acid, 3-indoleacetic acid (**X**), 6-quinolineacetic acid[3] (**XI**) 等의 窒素環式一鹽基酸의 Gabriel 縮合反應을 試圖한 結果 4-pyridylacetic acid에서는 反應途中 分解되어 目的物을 얻지 못하였으나 나머지 兩化合物에서는 順調로이 各各 目的物을 얻을 수 있었다.

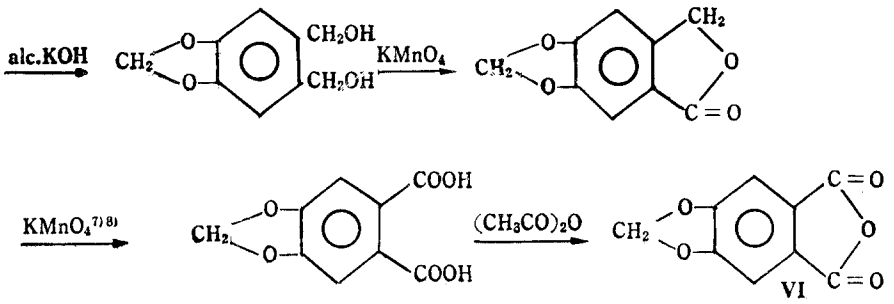




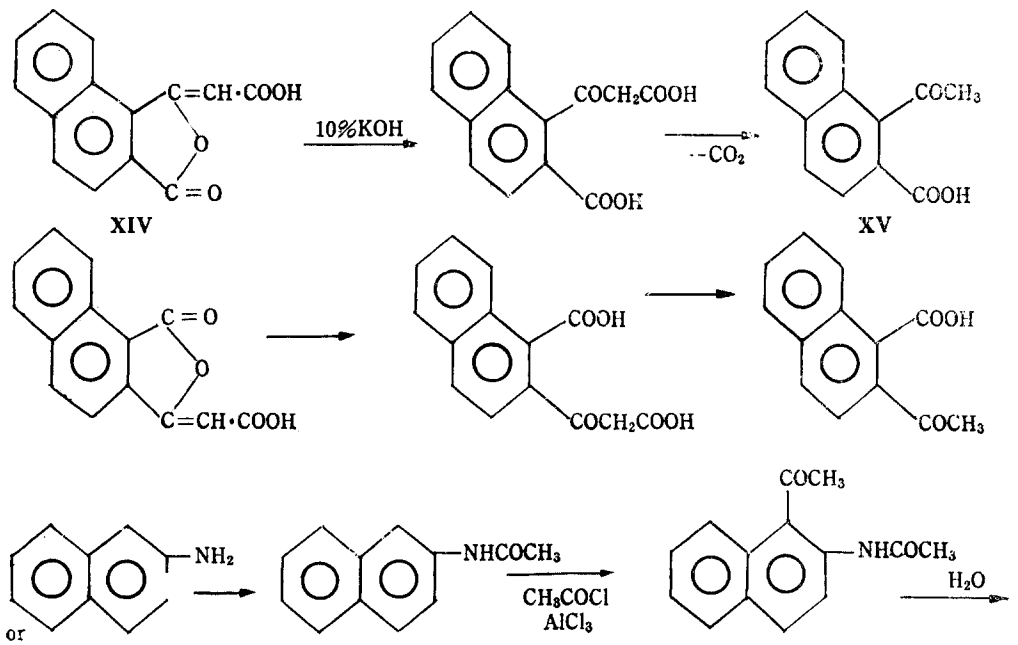
縮合劑로서 大部分의 경우 無水醋酸나트륨으로서 잘 進行되었지만 高分子量의 生成物을 形成하는 몇 경우에는 無水醋酸칼륨이 더욱 有効하였다.

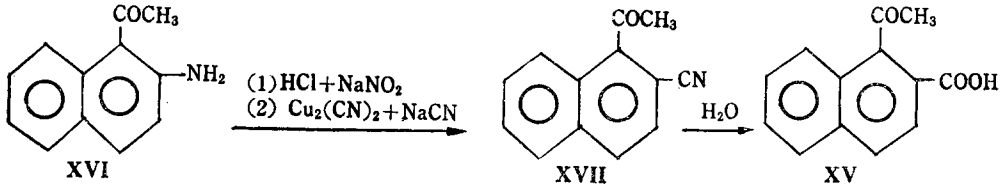
原料物質中 *m*-hemipinic anhydride (**V**)와 hydrastic anhydride (**VI**)의 製造에 있어서는 *s*-dichloromethyl ether[4] 에 依한 chloromethylation 法[5]을 veratrole 과 methylenedioxybenzene 에 各各 適用하여 chloromethyl 基 2個씩을 導入시킨 4,5-bischloromethylveratrole (**XII**)과 4,5-bischloromethyl-1,2-methylenedioxybenzene (**XIII**)을 合成한 다음에 Perkin[6], Wood[7] 및 藤澤法[8]에 依하여 다음과 같이 二鹽基酸으로 酸化시켜가지고 加熱脫水시키어 各各 酸無水物을 얻었다.





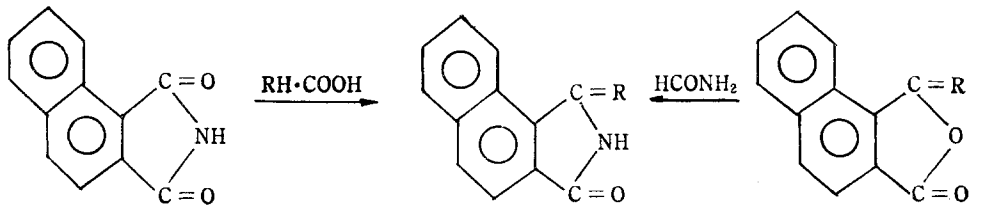
그런데 이들 二鹽基酸無水物中 4,5-benzo-phthalic anhydride (**VII**)에서 Gabriel 縮合反應에 依하여 生成되는 誘導體들에는 4,5-benzophthalic anhydride의 α-와 β-의 2個의 CO基가 不對稱이기 때문에 α-와 β-의 2가지의 異性體가 形成될 可能性이 있다. 그러나 本實驗에서는 한가지의 生成物만이 單離되었으므로 이 生成物에 導入된 導入基의 結合位置를 究明하기 위하여 이 生成物中 4,5-benzophthalidene-3-acetic acid (**XIV**)를 다음式과 같이 加水分解한후 脫炭酸시켜서 얻은 1-acetyl-2-naphthoic acid (**XV**)를 別途로 β-naphthylamine에서 부터 다음式에 따라 合成하여 比較確認하였다.





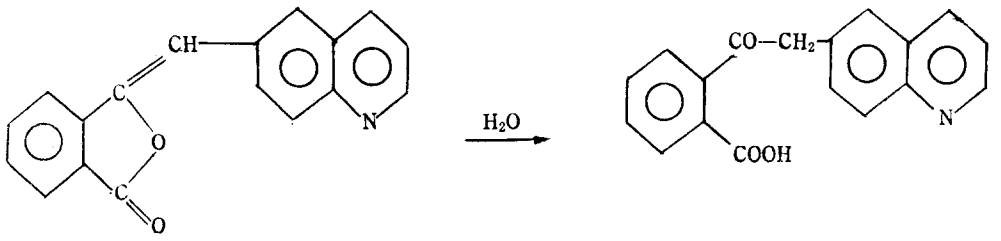
XVI XVII XV

또 4,5-benzophthalimide (**VIII**)에 對한 Gabriel 縮合反應에서도 마찬가지로 α,β- 2가지 異性體의 形成이 可能하지만 이 경우에도 實際의 生成物은 한가지뿐이었고 이것의 縮合位置는 앞에서 位置決定한 該當 phthalide 誘導體 **XXVII** 및 **XXX**에 各各 formamide를 反應시켜서 만든 phthalimidine 誘導體 **XLVI** 및 **XLVIII**과 各各 合致되었으므로 亦是 α-位置에 縮合되었음을 알았다.



VIII XLVI, XLVII XXVII, XXX

Quinoline-6-methinyl-3′-phthalide (**LV**), quinoline-6-methinyl-3′-phthalimidine (**LVI**), indole-3-methinyl-3′-phthalide (**LIV**) 및 **LV**를 10% KOH 용액으로 加水分解한 生成物인 2-carboxyphenacylquinoline-6′ (**LVII**)에 對하여 Beckman model IR-4 및 Perkin-Elmer model-421을 使用하여 赤外線吸收 spectra (IR)를 測定한 結果로써 이들의 構造를 確認하였다.



LV LVII

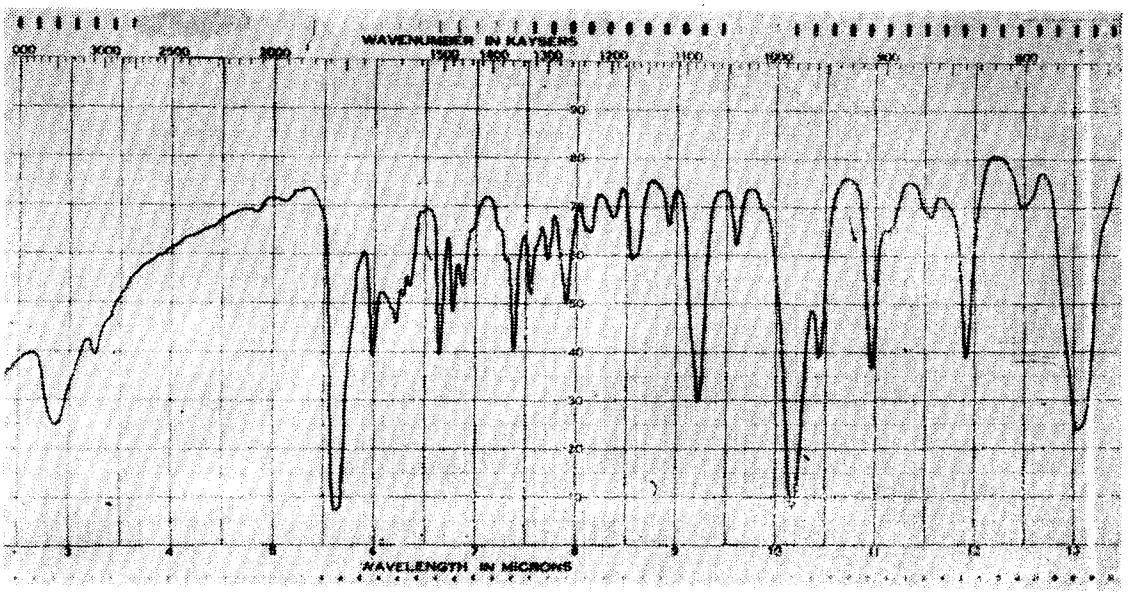


Fig. 1— Infrared spectrum of quinoline-6-methinyl-3′-phthalide (**LV**)
$IR\nu_{max}^{KBr}$ cm^{-1}: 1670 (C=C), 1770 (C=O), 3050 (C−H), 1520 (C=N).

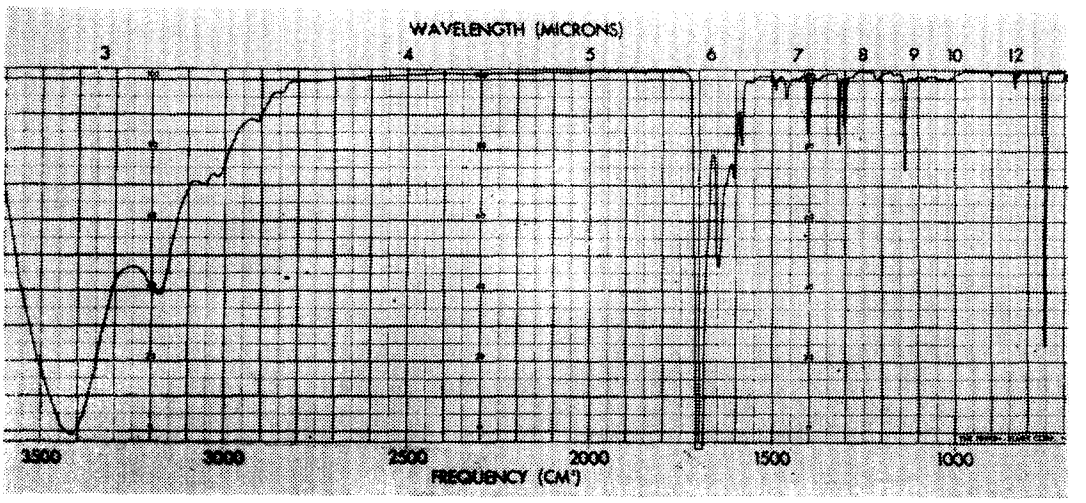


Fig. 2— Infrared spectrum of quinoline-6-methinyl-3′-phthalimidine (**LVI**).
$IR\nu_{max}^{KBr}$ cm^{-1}: 1650(C=C), 3400(N—H) 3180(C—H), 1700 (C=O), 1580 (C=N).

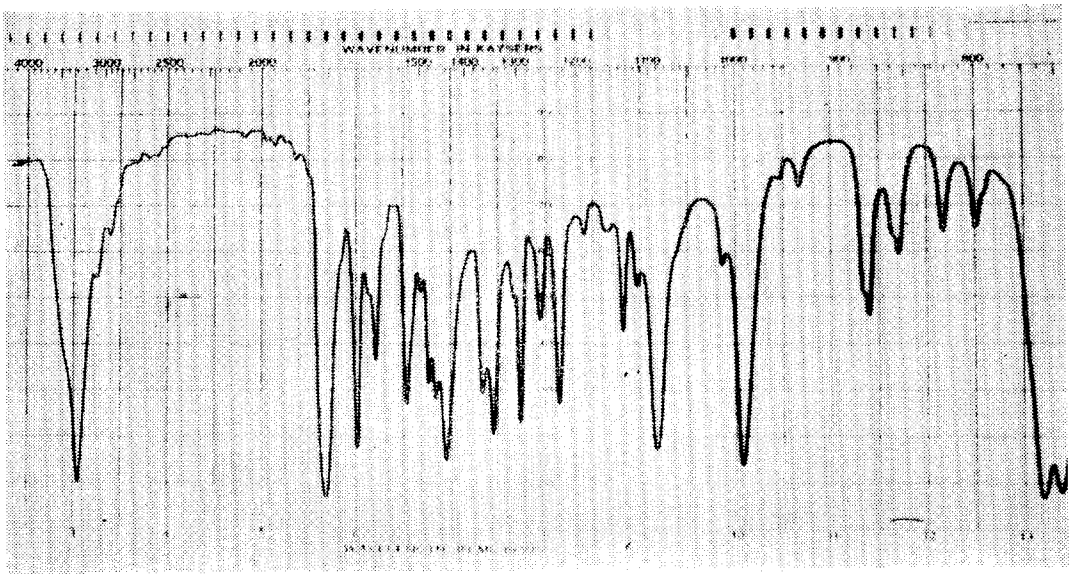


Fig 3— Infrared spectrum of Indole-3-methinyl-3′-phthalide (**LIV**).
IRν_{max}^{KBr} cm^{-1}; 3300(N-H), 3100(C-H), 1770(C=O), 1670(C=C).

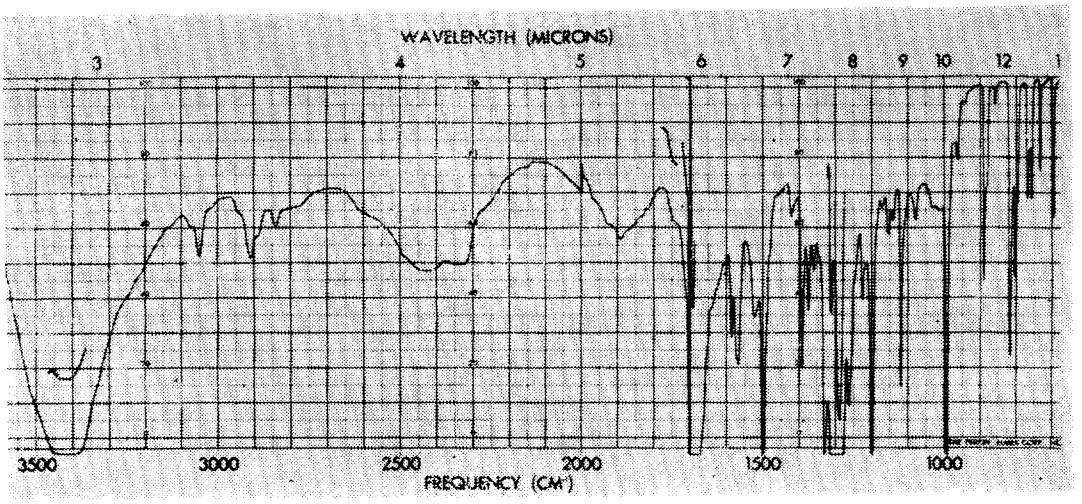


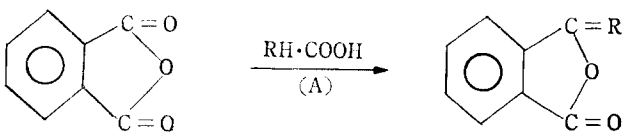
Fig. 4— Infrared spectrum of 2-Carboxy phenacyl quinoline-6′ (**LVII**)
IRν_{max}^{KBr} cm^{-1}; 3400(O—H), 3050(C—H), 2910(—CH_2), 1700(C=O), 1500, 1570(C=N), 1390(—CH_2CO—).

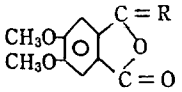
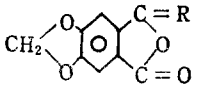
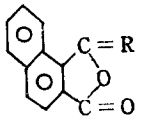
實 驗

4, 5-Bischloromethylveratrole (XII)— 溫度計, Hg-sealed 攪拌器, $CaCl_2$ 管을 달은 分液깔때기를 장치한 three necked flask 에 빙초산 60g 과 dichloromethyl ether[2] 140g 을 넣고 교반하면서 初期反應溫度를 45° 로 유지하고 veratrole 50g 을 1 時間에 걸쳐 滴加한다음 反應混合物을 9 時間동안 50°로 유지시킨다. 오록색의 反應混合物을 200g 의 얼음조각과 100ml 의 $CHCl_3$ 에 교반하면서 붓고 $CHCl_3$ 층을 분리하고 水층을 다시 $CHCl_3$ 30ml 로 두번 抽出한다. $CHCl_3$ 용액을 합하여 20ml 의 물로 씻고, 無水 Na_2SO_4 로 건조시킨다음 $CHCl_3$ 를 溜去시키고 殘留物을 감압증류한다. bp 155~165/1mmHg, mp 85~86° (Me_2CO 에서), 得量 30g (35.8%), 文獻[5] (HCl-formaline 法)과 부합되고 酸化物質인 *m*-hemipinic anhydride (**V**, mp 175°)로서 確認하였다.

4, 5-Bischloromethyl-1, 2-methylenedioxybenzene (XIII)— **XII** 의 제조에서와 같은 反應器에 빙초산 40g 과 dichloromethyl ether 30g 을 넣고 교반하면서 반응온도를 80~85° 로 유지하고 methylene-dioxybenzene 4 g 을 서서히 滴加한 다음 이 반응온도에서 10時間동안 가온교반한다. 冷後 反應混合液을 약 10倍量의 얼음물에 교반하면서 붓고 油층을 C_6H_6 로

Table I— Numbers of 3-substituted phthalides by the procedure-A.



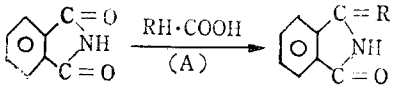
Anhydride \ R	=CH·COOH	=CH-⟨⟩	=CH-⟨⟩-OCH₃	=CH-⟨⟩-NO₂	=CH-⟨⟩	=CH·HC=
		XVIII	XIX	XX	XXI	XXII
		XXIII	XXIV	XXV	XXVI	
	XIV	XXVII	XXVIII	XXIX	XXX	XXXI

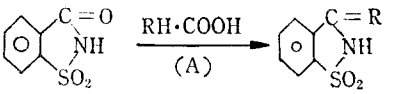
抽出한다. 이 추출액을 $NaHCO_3$ 수용액으로 씻고 $CaCl_2$로 건조한 다음 감압증류한다. bp 153~155°/3mmHg, mp 76° (ligroin 에서), 得量 5.5g(75%), 文獻[9] (HCl-formaline 法)과 부합되고 Wood[5], 藤澤[6]의 方法에 따라 hydrastic anhydride[10] (**VI**, mp 178~179°)로 酸化시키어 確認하였다.

縮合反應 一般處理法(A)— 1 mole의 二鹽基酸無水物 또는 imide와 1.5mole의 活性一鹽基酸 또는 2 mole의 一鹽基酸無水物(醋酸만은 醋酸無水物로서 使用하였다)을 加熱熔融시킨 다음에 微細粉末로 한 0.5 mole의 脫水초산나트륨 또는 초산칼륨을 加하고 $CaCl_2$管을 달은 유리管을 달고 反應溫度에서 一定時間 加熱한다. 冷後 反應物質을 粉粹하여 溫水와 Na_2CO_3 용액으로 씻고, 얻은 生成物을 適當한 溶媒에서 再結晶한다.

Imide化 一般處理法(B)— 文獻[2]과 같다.

Table II— Numbers of 3-substituted imidines by the procedure-A.





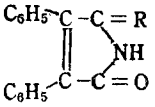
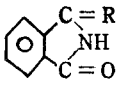
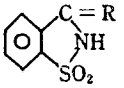
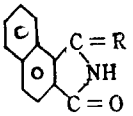
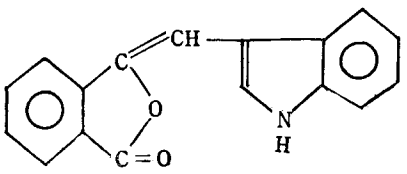
Imide \ R	=CH·COOH	=CH-C6H5	=CH-C6H4-OCH3	=CH-C6H4-NO2	=CH-C10H7	=CH.HC=
	XXXII	XXXIII	XXXIV	XXXV	XXXVI	
		XXXVII	XXXVIII	XXXIX		XL
	XLI	XLII		XLIII		XLIV
	XLV	XLVI	XLVII		XLV	

Table III— Isoindoline derivatives produced by the procedure-A.

Product No.	Formula	Conden. agent	React. temp.	React. time (hrs)	Recryst. solvent	Color	mp	yield (%)	Analysis(%) Calcd. C	Calcd. H	Found C	Found H
XVIII	$C_{17}H_{14}O_4$	NaAc	195～200	2	AcOH	white	204	40	72.27	4.98	71.88	4.77
XIX	$C_{18}H_{16}O_4$	NaAc	210～215	4	AcOH	yellow	238	51	69.20	5.10	68.75	5.13
XX	$C_{17}H_{13}O_6N$	NaAc	180～185	1	AcOH	yellow	245	56	62.39	4.02	62.44	4.37
XXI	$C_{21}H_{16}O_4$	NaAc	195～200	2	C_6H_6	yellow	270	49	75.89	4.85	75.97	49.3
XXII	$C_{22}H_{18}O_8$	NaAc	205～210	2	AcOH	yellow	300over	52	64.37	4.43	64.13	4.53
XXIII	$C_{16}H_{1}{}^{0}O_4$	NaAc	190～195	1.5	C_6H_6	white	206～207	27	72.17	3.78	71.88	4.00
XXIV	$C_{17}H_{12}O_5$	NaAc	210～215	4.5	C_6H_6	yellow	219～220	18	68.90	4.00	69.30	4.04
XXV	$C_{16}H_9O_6N$	NaAc	170～175	1	AcOH	yellow	290～291	34	61.74	2.91	61.32	2.78
XXVI	$C_{2}{}^{0}H_{12}O_4$	NaAc	190～195	2	C_6H_6	yellowish green	229～230	22	75.90	3.80	75.26	3.84
XIV	$C_{18}H_8O_4$	KAc	135～140	0.5	AcOH	yellow	236～238	49	70.01	3.36	70.28	3.08
XXVII	$C_{19}H_{12}O_2$	NaAc	180～190	3	AcOH	yellow	207～209	51	83.81	4.44	83.47	4.34
XXVIII	$C_{19}H_{12}O_2$	NaAc	220～230	8	AcOH	yellowish green	161～163	32	79.46	4.76	79.09	4.35
XXIX	$C_{19}H_{11}O_4N$	NaAc	155～165	2	AcOH	yellow	158～160	56	71.09	3.46	70.64	3.12
XXX	$C_{23}H_{14}O_2$	NaAc	210～220	3	C_6H_6	yellow	197～199	36	85.08	4.38	84.71	4.06
XXI	$C_{26}H_{14}O_4$	KAc	190～200	3	$C_6H_5NO_2$	yellow	300 over	45	79.99	3.61	79.54	3.43
XXXII	$C_{18}H_{13}O_3N$	NaAc	160～170	0.5	AcOH	yellow	159～161	44	74.20	4.51	74.81	4.82
XXXIII	$C_{23}H_{17}ON$	NaAc	220～230	3	EtOH	yellow	236～237	38	85.44	5.23	85.22	5.62
XXXIV	$C_{24}H_{19}O_2N$	NaAc	230～240	4	EtOH	yellow	252～253	25	81.04	5.38	81.01	5.36
XXXV	$C_{23}H_{16}O_3N_2$	NaAc	190～200	2	AcOH	yellow	177～178	45	75.01	4.32	75.04	3.96
XXXVI	$C_{27}H_{19}ON$	NaAc	220～230	4	C_6H_6		273～274	40	86.86	5.09	86.59	5.15
XXXVII	$C_{15}H_{11}ON$	NaAc	230～240	3	EtOH	orange	181～183	57	81.43	5.06	81.28	4.84
XXXVIII	$C_{16}H_{13}ON$	NaAc	220～230	1	EtOH	yellow	196～198	47	76.47	5.21	76.38	5.17

Product No.	Formula	Conden. agent	Recat. temp.	React. time (hrs)	Recryst. solvent	Color	mp	Yield (%)	Analysis(%) Calcd. C	Calcd. H	Found C	Found H
XXXIX	$C_{15}H_{10}O_3N_2$	NaAC	200~210	1	$C_6H_5NO_2$	yellow	230~232	55	66.69	3.79	66.03	3.63
XL	$C_{18}H_{12}O_2N_2$	KAc	200~210	2	$C_6H_5NO_2$	yellowish green	338~340	13	74.98	4.20	74.38	4.08
XLI	$C_9H_7O_4NS$	NaAc	160~165	2	EtOH	white	196~198	63	47.95	3.13	47.70	3.13
XLII	$C_{14}H_{12}O_2NS$	NaAc	205~210	2	EtOH	yellowish brown	225~226	60	65.3	4.3	65.0	4.1
XLIII	$C_{14}H_{10}O_4N_2S$	NaAc	170~175	1.5	EtOH	yellowish brown	153~154	61	55.6	3.3	55.3	3.2
XLIV	$C_{16}H_{12}O_4N_2S_2$	NaAc	205~210	4.5	EtOH	brawn	226~227	26	53.3	3.3	53.2	3.2
XLV	$C_{14}H_9O_3N$	NaAc	135	0.1	EtOH	yellow	153~154	67	70.29	3.79	70.25	3.59
XLVI	$C_{19}H_{13}ON$	NaAc	230~235	3	AcOH	yellow	247~248	15	84.11	4.83	83.92	4.71
XLVII	$C_{20}H_{15}O_2N$	NaAc	220~225	6	AcOH	yellow	274	13	79.72	5.02	79.66	5.09
XLVIII	$C_{23}H_{15}ON$	NaAc	230~235	3	AcOH	yellow	266~267	11	85.65	4.71	85.07	5.01
LIV	$C_{17}H_{11}O_2N$	NaAc	160~180	0.5	MeOH	yellowish green	245~250	58	78.15	4.24	78.14	4.18
LV	$C_{18}H_{11}O_2N$	NaAc	190~220	3	MeOH	yellow	191~192	65	78.82	4.04	79.05	4.50

LIV :



LV :

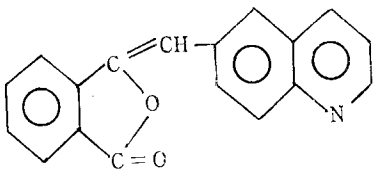
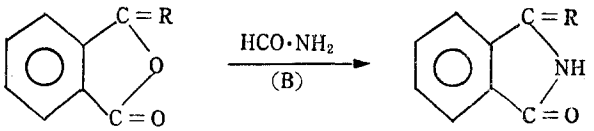


Table IV— Numbers of 3-substituted imidines by the procedure-B.



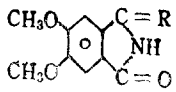
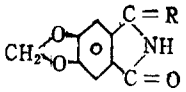
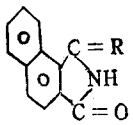
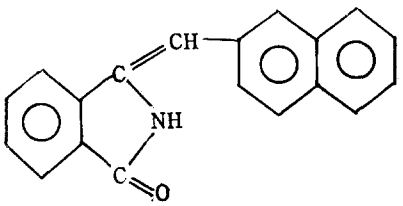
Phthalimidine \ R	=CH-C6H5	=CH-C6H4-OCH3	=CH-C6H4-NO2	=CH-C10H7	=CH·HC=
	XLIX	L			LI
	LII	LIII			
	XLVI			XLVIII	

Table V— Isoindoline derivatives produced by the procedure-B.

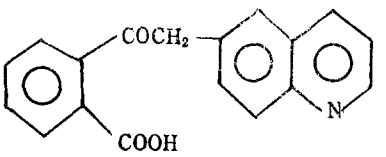
Product No.	Formula	Start material	React. temp.	React. time (hrs)	Recryst. solvent
VIII	$C_{12}H_7O_2N$	VII	160～170	3	AcOH
XLVI	$C_{19}H_{13}ON$	XXVII	160～170	3	AcOH
XLVIII	$C_{23}H_{15}ON$	XXX	160～170	3	AcOH
XLIX	$C_{18}H_{17}O_4N$	XIX	175～180	3	AcOH
L	$C_{17}H_{14}O_5N_2$	XX	175～180	3	AcOH
LI	$C_{22}H_{20}O_6N_2$	XXII	180～190	3	AcOH
LII	$C_{17}H_{13}O_4N$	XXIV	170～180	4	AcOH
LIII	$C_{16}H_{10}O_5N_2$	XXV	180～190	4	AcOH
LVI	$C_{18}H_{12}ON_2$	LV	180～190	3	EtOH
LVII	$C_{18}H_{12}O_3N$				

LVI :



Product No.	Color	Mp	Yield (%)	Analysis(%) Calcd. C	Calcd. H	Found C	Found H
VIII	yellow	228~229	85	72.59	3.57	72.82	3.80
XLVI	yellow	247~248					
XLVIII	yellow	266~267					
XLIX	yellow	272~273					
L	yellow	300 over					
LI	yellow	300 over					
LII	yellow	261~262					
LIII	yellow	300 over					
LVI	yellowish brown	247~249	90			IR	
LVII		225	98	74.22	4.49	74.85	4.27

LVII :



4,5-Benzophthalidene-3-acetic acid(XIV)의 加水分解 (1-Acetyl-2-naphthoic acid(XV)의 生成)- XIV 1 g에 10%-KOH 수용액 6 ml를 加하고 2時間 加熱後 10%-HCl 용액으로 중화시킨다. 이 溶液을 잠시 加熱한후 放冷시켜 浮遊되는 油分을 除去하고 溫時濾過한 濾液을 放置하면 微黃色粉末이 析出되므로 이것을 濾取하여 물에서 再結晶한다. mp 221~222°, 得量 0.2g. *Anal.* Calcd for $C_{13}H_{10}O_3$: C, 72.89; H. 4.66. Found: C, 72.99; H, 4.21.

1-Acetyl-2-cyanonaphthalene (XVII)— 2-Aminonaphthalene에서 Brown[12]의 方法에 依하여 2-amino-1-acetonaphthone (**XVI**)을 合成하여 가지고 **XVI** 6 g을 써서 Sandmeyer 反應에 依하여 黃色結晶體인 nitrile (**XVII**) 1.4g을 얻었다. mp 117° (ligroin에서).

1-Acetyl-2-naphthoic acid (XV)— 위에서 얻은 nitrile (**XVII**) 2 g에 KOH 1.7g 및 물 1ml를 加하여 2時間 加熱하고 冷後 10%-HCl 용액으로 중화하여 放置하면 結晶性粉末이 析出된다. 이것을 濾取하여 물에서 再結晶하여 mp 221~222° 의 淡黃色結晶 1.2g을 얻었다. *Anal* Calcd for $C_{12}H_{10}O_3$:C, 72.89; H, 4.66 Found: C, 73.04; H, 4.89.

XIV의 加水分解生成物인 1-acetyl-2-naphthoic acid (**XV**)와 2-naphthylamine에서 부터 前記方法에 依하여 合成한 **XV** 化合物을 混融試驗한 結果 融點降下가 없었다.

끝으로 IR 測定을 도와주신 서울大學校 生藥硏究所 禹麟根博士에게 感謝를 드리며 元素分析을 擔當하여 주신 林順子 藥學士에게 謝意를 표한다.

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