Condensation of 1,2-Dibenzoylcyclohexa-1,4-dienes. Synthesis of 1,3-Diphenyl-Substituted Isoindoles, Isobenzofurans, and Isobenzothiophenes

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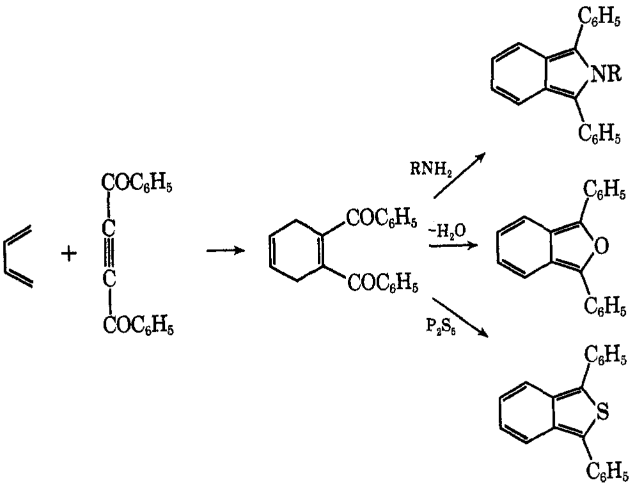
Diels–Alder addition of dibenzoylacetylene to butadiene, isoprene, 2,3-dimethylbutadiene, piperylene, *trans,-trans*-hexa-2,4-diene, and *trans,trans*-hexa-2,4-dien-1-ol gives the corresponding 1,2-dibenzoylcyclohexa-1,4-dienes. These undergo condensation with methylamine to yield *N*-methylisoindoles, with aniline to yield *N*-phenylisoindoles, and with ammonium acetate to yield a N-unsubstituted isoindole. Condensation of 1,2-dibenzoylcyclohexa-1,4-dienes in the presence of *p*-toluenesulfonic acid affords isobenzofurans and, with phosphorus pentasulfide or elemental sulfur, isobenzothiophenes are produced. The ultraviolet and nmr spectra of isoindoles are discussed, the latter indicating a substantial degree of bond delocalization within the isoindole nucleus.

Since the preparation of the first authentic isoindole derivative by Wittig[1] in 1951, a number of approaches to this system have been described.[2] These include syntheses from isoindolines,[3] phthalimidines,[3a,c,4] ortho-disubstituted benzenes,[3f,5] and 1,4-diketones,[6] as well as several unusual rearrangements which result in the formation of a stable isoindole moiety.[3a,7] The parent isoindole has thus far eluded isolation, but its presence has been inferred from trapping experiments with dienophiles.[3h]

Limitations inherent in the synthetic methods enumerated above seriously restrict their scope, and we have sought a more general approach which would be amenable to maximum structural modification of the isoindole product. Described herein are the results of an investigation which has led to the development of a new synthesis of 1,3-diphenylisoindoles,[8] capable of extension to include synthesis of 1,3-diphenylisobenzofurans and 1,3-diphenylisobenzothiophenes as well. Specifically, the condensation of a 1,2-diacylcyclohexa-1,4-diene, preparable by Diels–Alder addition of a diacylacetylene to a 1,3-diene, with ammonia or a primary amine was expected to lead to an isoindole in analogy to the well-known synthesis of pyrroles developed by Paal[9] and Knorr.[10] The anticipated aromaticity of the isoindole nucleus (*vide infra*) provides thermodynamic advantage for the reaction. Extrapolation of the method to include synthesis of isobenzofurans, by dehydration of the diacylcyclohexadiene, and isobenzothiophenes, by condensation with phosphorus pentasulfide, was envisaged as shown in Scheme I.

SCHEME I



Results and Discussion

It was judged expedient to use dibenzoylacetylene (**1**) to test the feasibility of this approach, since aryl substitution at positions 1 and 3 is known to provide stabilization of the isoindole nucleus. Dibenzoylacetylene was prepared by triethylamine-promoted dehydrobromination[11] of *meso*-2,3-dibromo-1,4-diphenylbutane-1,4-dione,[12] and underwent smooth cycloaddition to isoprene,[13] 2,3-dimethylbutadiene,[13] *trans*-penta-1,3-diene, *trans,trans*-hexa-2,4-diene,[14] and *trans,trans*-hexa-2,4-dien-1-ol to give the corresponding cyclohexa-1,4-dienes **3–7**. The reactions were carried out in hot benzene solution or a benzene–methanol mixture except with isoprene, where no solvent was used. Diels–Alder addition of **1** to *trans,trans*-hexa-2,4-diene was considerably slower than with other dienes, and the reaction mixture was seriously contaminated with rearranged and aromatized products. The addition of **1** to butadiene, which has not been previously reported, was effected in a sealed tube at 150–160° and gave **2** in

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[1] G. Wittig, H. Tenhaeff, W. Schoch, and G. Koenig, *Justus Liebigs Ann. Chem.*, **572**, 1 (1951).

[2] The chemistry of isoindoles has been reviewed: J. D. White and M. E. Mann, *Advan. Heterocycl. Chem.*, **10**, 113 (1969).

[3] (a) G. Wittig and H. Streib, *Justus Liebigs Ann. Chem.*, **584**, 1 (1953); (b) J. Thesing, W. Schaefer, and D. Melchior, *ibid.*, **671**, 119 (1964); (c) G. Wittig, G. Closs, and F. Mindermann, *ibid.*, **594**, 89 (1955); (d) R. Kreher and J. Seubert, *Angew. Chem., Int. Ed. Engl.*, **3**, 639 (1964); (e) R. Kreher and J. Seubert, *ibid.*, **5**, 967 (1966); (f) J. C. Emmett, D. F. Veber, and W. Lwowski, *Chem. Commun.*, 272 (1965); (g) G. Cignarella and G. G. Gallo, *Gazz. Chim. Ital.*, **99**, 1115 (1969); (h) R. Kreher and J. Seubert, *Z. Naturforsch.*, *B*, **20**, 75 (1966).

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[5] (a) D. F. Veber and W. Lwowski, *J. Amer. Chem. Soc.*, **86**, 4152 (1964); D. F. Veber and W. Lwowski, *ibid.*, **85**, 646 (1963); (b) J. C. Emmett and W. Lwowski, *Tetrahedron*, **22**, 1011 (1966); (c) R. Kreher and J. Seubert, *Tetrahedron Lett.*, 3015 (1966).

[6] (a) F. H. Norton, U. S. Patent 3,007,939 (1961); *Chem. Abstr.*, **56**, 7281 (1962); H. Fletcher, *Tetrahedron*, **22**, 2481 (1966); (b) C. O. Bender and R. Bonnett, *Chem. Commun.*, 198 (1966).

[7] (a) W. Theilacker, H. J. Bluhm, W. Heitmann, H. Kalenda, and H. J. Meyer, *Justus Liebigs Ann. Chem.*, **673**, 96 (1964); (b) M. P. Cava and R. H. Schlessinger, *J. Org. Chem.*, **28**, 2464 (1963); R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Amer. Chem. Soc.*, **88**, 3173 (1966); (c) R. I. Fryer, B. Brust, J. V. Earley, and L. H. Sternbach, *J. Chem. Soc. C*, 366 (1967).

[8] Preliminary communication: M. E. Mann and J. D. White, *Chem. Commun.*, 420 (1969).

[9] C. Paal, *Ber.*, **17**, 2757 (1884).

[10] L. Knorr, *ibid.*, **17**, 2863 (1884).

[11] R. T. Lutz and W. R. Smithey, *J. Org. Chem.*, **16**, 51 (1951).

[12] C. Paal, *Ber.*, **33**, 3799 (1900).

[13] G. Dupont and C. Paquot, *C. R. Acad. Sci., Paris*, **205**, 805 (1937).

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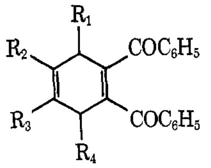
TABLE I

1,2-DIBENZOYLCYCLOHEXA-1,4-DIENES

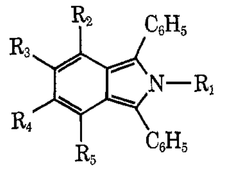


Compd[d]	R_1	R_2	R_3	R_4	Mp, °C	Yield, %	Chemical shift, ppm (multiplicity, J in Hz)			
							CH_3	CH_2	CH	=/H
2	H	H	H	H	112–114	56		3.20 (s)		5.91 (s)
3	H	CH_3	H	H	73.5–74.5[a]	74	1.79 (s)	3.14 (s)		5.57 (m)
4	H	CH_3	CH_3	H	109–111[b]	66	1.74 (s)	3.15 (s)		
5	CH_3	H	H	H		54	1.12 (d, $J = 7$)	*Ca.* 3.1 (m)	3.62 (m)	5.84 (s)
6	CH_3	H	H	CH_3	106–111[c]	37	1.15 (d, $J = 7$)		3.30 (m)	5.9 (m)
7	CH_3	H	H	CH_2OH	155–156.5	49	1.27 (d, $J = 7$)	3.81 (m)	3.39 (m)	5.91 (d, $J = 6$) 5.97 (d, $J = 6$)

[a] Lit.[13] mp 58–59°. [b] Lit.[13] mp 106–107°. [c] Decomposition. [d] Satisfactory analytical data (±0.4% for C and H) were reported for all compounds in the table.

TABLE II

1,3-DIPHENYLISOINDOLES



Compd[c]	R_1	R_2	R_3	R_4	R_5	Mp, °C	Yield, %	λ_{max}, mμ (ε)	
								Neutral solution	Acidic solution
8	CH_3	H	H	H	H	148–150[a]	68		
9	CH_3	H	CH_3	H	H	171.5–172.5	92	230 (26,200), 274[b] (10,400), 280 (12,300), 334 (10,140), 374 (15,400)	230 (15,900), 282 (14,350), 298 (13,600), 374 (6080)
10	CH_3	H	CH_3	CH_3	H	254–255	87	226 (19,000), 275 (6260), 282 (6800), 339 (4160), 377 (7300)	236 (11,870), 303 (15,300)
11	CH_3	CH_3	H	H	H	144–145.5	74	211 (19,900), 227 (26,200), 270[b] (5860), 276 (6150), 362 (13,700)	211 (20,600), 291 (14,250)
12	CH_3	CH_3	H	H	CH_3	210–213	46	221 (25,900), 357 (6000)	
13	CH_3	CH_3	H	H	CH_2OH	181–184.5	43	225 (36,100) 268 (5910), 355 (12,900)	211 (29,400), 292 (12,400)
14	C_6H_5	H	CH_3	H	H	179–180	57	237 (30,050), 281 (17,000), 318[b] (8620), 330 (9240), 374 (13,880)	237 (27,250), 282 (15,920), 322 (10,280), 374 (12,660)
15	C_6H_5	H	CH_3	CH_3	H	193–194.5	65	233 (31,750), 285 (18,570), 322[b] (8090), 332 (8990), 376 (14,500)	234 (25,800), 285 (16,470), 318 (11,620), 328 (11,490), 374 (12,350)
16	C_6H_5	CH_3	H	H	H	191.5–192.5	58	234 (34,200), 276 (11,820), 335[b] (8740), 363 (14,830)	234 (25,950), 279 (11,460), 311 (10,500), 361 (10,850)
17	H	H	CH_3	H	H	125–127	48	229 (19,100), 270[b] (15,100), 277 (16,500), 322 (13,100), 338[b] (11,600), 394 (14,900)	

[a] Lit.[5b] 149.5–150°. [b] Shoulder or inflection. [c] Satisfactory analytical data (±0.3% for C and H) were reported for all compounds in the table except **13** (Calcd: C, 84.37. Found: C, 84.86.) and **16** (Calcd: C, 90.22. Found: C, 89.73.).

satisfactory yield. Cyclohexadienes prepared by the Diels–Alder route are listed in Table I, together with nmr data which confirm the structural assignments. With methyl pentadienoate, **1** failed to give a Diels–Alder adduct and was recovered largely unchanged.

When a mixture of **2** and 40% aqueous methylamine in methanol was heated under reflux and the solution allowed to cool, a yellow crystalline product was deposited which was readily identified as 1,3-diphenyl-2-methylisoindole (**8**).[5b] A single recrystallization gave analytically pure material in 68% yield. The generality of the process was assured by conversion of cyclohexadienes **3–7** to the corresponding *N*-methylisoindoles **9–13**, as shown in Table II. The yields in these cases are noticeably dependent on the pattern of alkyl substitution; thus, whereas methyl groups at positions 5 and 6 appear to enhance isoindole formation, alkyl substitution at positions 4 and 7 diminishes yields (suggesting a destabilizing, peri interaction with the 1,3-diphenyl groups). Extension of the scheme to preparation of *N*-phenylisoindoles was realized by condensation of cyclohexadienes **3–5** with aniline in glacial acetic

TABLE III

NMR SPECTRAL DATA FOR ISOINDOLES

Compd	Chemical shifts, ppm (multiplicity, *J* in Hz)					
	CH_3C	CH_3N	H_4	H_5	H_6	H_7
8		3.86 (s)	7.4 (m)	7.05 (m)	7.05 (m)	7.4 (m)
9	2.35 (s)	3.83 (s)	7.2 (m)		6.83 (d of d, J = 2, 9)	7.2 (m)
10	2.31 (s)	3.89 (s)	7.28 (s)			7.28 (s)
11	2.09 (s)	3.63 (s)		6.96 (d, J = 7)	6.75 (m)	*a*
12	2.02 (s)	3.40 (s)		6.57 (s)	6.57 (s)	
13	2.05 (s)	3.39 (s)		6.75 (m)	6.75 (m)	
14	2.40 (s)		7.5 (m)		6.93 (d, J = 9)	7.5 (m)
15	2.31 (s)		7.46 (s)			7.46 (s)
16	2.12 (s)			6.75 (m)	6.75 (m)	7.60 (d, J = 8)
17	2.40 (s)		*a*		6.91 (d, J = 9)	*a*
18[b]	2.60, 2.70			6.34	6.34	
19	2.56 (s), 2.69 (s)	3.61 (s)		6.35 (s)	6.35 (s)	
20[c]	2.38 (s), 2.48 (s)			6.24 (s)	6.24 (s)	

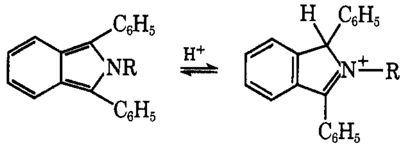
[a] Obscured by phenyl resonances. [b] Containing isoindolenine tautomer;[21] see C. O. Bender, R. Bonnett, and R. G. Smith, *J. Chem. Soc. C*, 1251 (1970). [c] Data from ref 21.

acid. Reaction was complete within 15 min at 100° and, again, the corresponding isoindoles **14–16** crystallized from the reaction mixture in a virtually pure state.

The synthesis of isoindoles possessing a free NH group has frequently encountered difficulties which appear to be associated with facile tautomerization to the isoindolenine form, a process which can be attended by both autoxidation[7c,15] and polymerization.[5b] Veber and Lwowski circumvented this problem by effecting condensation of an *o*-phthalimidobenzophenone with hydrazine and thereby accomplished the first successful preparation of an N-unsubstituted isoindole.[5a] The efficacy of the present approach in synthesis of an isoindole of this type was demonstrated by condensation of **3** with ammonium acetate in ethanol which gave 1,3-diphenyl-5-methylisoindole (**17**) in 48% yield.

The presence of an isoindole nucleus in each of the products was readily ascertained from the ultraviolet spectrum. The characteristic features of the 1,3-diphenylisoindole chromophore include a strong absorption in the region 390 mμ (ϵ >10,000) for N-unsubstituted derivatives,[4b,5b,7a] shifted to 375 mμ for N-substituted compounds.[5b] This transition is slightly perturbed in the case of 4-alkyl derivatives (**11**, **16**), more seriously so when both positions 4 and 7 are substituted (**12**, **13**). Thus, in the latter, the longest wavelength band has undergone a hypsochromic shift of *ca.* 20 mμ and, in addition, there is loss of the fine structure present in the spectra of the other isoindole derivatives. This is ascribed to a steric peri interaction between the C-3 phenyl and C-4 alkyl substituent, which causes a rotation of the phenyl ring out of coplanarity with the isoindole nucleus. Spectral changes resulting from interactions of this type are well documented in the naphthalene series.[16] In addition to the diagnostic ultraviolet spectra, each isoindole derivative gave a mass spectrum exhibiting an intense peak for the molecular ion. These observations, together with nmr data (Table III) and elemental analysis, were sufficient to establish conclusively the structures of the products. In the case of **17**, no detectable contribution from either of the possible isoindolenine tatuomers was observed.

Also of interest in connection with the ultraviolet spectra of isoindoles **9–16** is the effect of adding 0.1 *N* hydrochloric acid to an ethanol solution. Electron density calculations[17] as well as thermodynamic considerations indicate that the primary site of protonation of the isoindole nucleus should be position 1. Thus, an equilibrium of the type in eq 1 may be anticipated in



(1)

which the position of equilibrium is a function of the basicity of the isoindole. Nmr has provided convincing evidence in support of this equilibrium for 1,2,4,7-tetramethylisoindole.[6b] It is clear that, under the conditions, 1,2,3-triphenylisoindoles **14–16** are not converted to their salts, whereas the *N*-methylisoindoles are extensively or completely protonated. Comparison with the ultraviolet spectra of 1,1-diphenylmethylenimine hydrochloride [λ_{max} 275.5 mμ (ϵ 16,650)] and its 4-methyl derivative [λ_{max} 285.5 mμ (ϵ 15,700)][18] implies that **11** and **13** exist entirely as protonated isoindolenines in acidic solution. The transformation of C-1 from trigonal to tetrahedral configuration, which allows displacement of one phenyl ring out of the plane containing the C-4 substituent, undoubtedly relieves steric compression in these two cases and probably favors one of the two isoindolenine forms. The spectrum of **9** in acid is a composite of absorption bands arising from the isoindole (374 mμ) and protonated isoindolenine (298 mμ), but addition of another methyl group, as in **10**, shifts the equilibrium further toward the salt form. The inductive effect of the methyl substituent would clearly be expected to stabilize the protonated structure to a greater extent than the isoindole. The diminished basicity of *N*-phenylisoindoles is best

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(15) J. K. Kochi and E. A. Singleton, *Tetrahedron*, **24**, 4649 (1968).

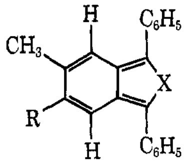
(16) V. Balasubramaniyan, *Chem. Rev.*, **66**, 567 (1966).

(17) (a) M. J. S. Dewar, *Trans. Faraday Soc.*, **42**, 764 (1946); (b) H. C. Longuet-Higgins and C. A. Coulson, *ibid.*, **43**, 87 (1947); K. Fukui, T. Yonezawa, C. Nagata, and H. Shingu, *J. Chem. Phys.*, **22**, 1433 (1954); (c) O. E. Polansky and G. Derflinger, *Monatsh. Chem.*, **92**, 1114 (1961); (d) M. J. S. Dewar, A. J. Harget, N. Trinajstic, and S. D. Worley, *Tetrahedron*, **26**, 4505 (1970).

(18) I. R. Kaplan, H. N. Parton, and J. Vaughan, *J. Amer. Chem. Soc.*, **75**, 4341 (1953).

TABLE IV

1,3-DIPHENYL-SUBSTITUTED ISOBENZOFURANS AND ISOBENZOTHIOPHENES

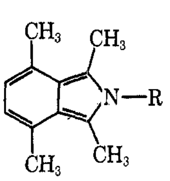


Compd[b]	R	X	Mp, °C	Yield, %	λ_{max} mμ (ε)
21	H	O	106–108	67	255 (6850), 269 (39,700), 409 (13,400)
22	CH_3	O	194–195[a]	65	258 (6300), 276 (25,800), 410 (19,500)
24	H	S	116–118	61	222 (14,200), 270 (12,900), 388 (8900)
25	CH_3	S	182.5–183	78	224 (28,800), 273 (22,000), 394 (25,000)

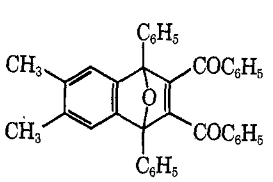
[a] Lit.[14] mp 193–195°. [b] Satisfactory analytical data (±0.25% for C and H) were reported for all compounds in the table.

understood in terms of decreased delocalization of the nitrogen nonbonding pair within the isoindole ring as a result of phenyl conjugation and is in accord with substituent basicity trends in other heteroaromatic systems.[19]

Aromatic stabilization of the isoindole nucleus was invoked above as a source of thermodynamic impetus in the condensation of dibenzoylcyclohexadienes with amines, and it is appropriate at this point to examine more critically the validity of this concept. Although calculations accord isoindole a significant degree of resonance stabilization,[17d] the experimental evidence bearing on this question is scant. We suggest, however, that data presented in Table III lend support to a structure in which there is considerable bond delocalization within the isoindole ring and in which the diamagnetic anisotropy of the nucleus exerts a significant effect on the peripheral hydrogens. Thus, proton pairs $H_{4,7}$ and $H_{5,6}$ are shifted downfield from corresponding protons in cyclohexa-1,3-diene (H_1 δ 5.68, H_2 δ 5.83),[20] and although secondary shift effects on $H_{4,7}$ may result from the presence of phenyl substituents at C-1 and C-3, it is clear from comparison with the nmr spectra of 1,3,4,7-tetramethylisoindole (**18**)[6a] and its *N*-methyl (**19**)[21] and *N*-phenyl (**20**)[21] derivatives that the downfield shift of $H_{5,6}$ is real. Furthermore, the magnitude of coupling constants $J_{4,5}$ (8–9 Hz) and $J_{5,6}$ (7 Hz), as compared with corresponding coupling in cyclohexa-1,3-diene ($J_{1,2}$ = 9.64 Hz, $J_{2,3}$ = 5.04 Hz)[20] is indicative of a more even distribution of π-bond order (p) in the six-membered ring of isoindole ($p_{4,5}$ 0.7–0.8, $p_{5,6}$ *ca.* 0.6) than is found in cyclohexadiene ($p_{1,2}$ 0.894, $p_{2,3}$ 0.447).[20] Indeed, chemical shifts, coupling constants, and π-bond orders correlate rather well with those for naphthalene (H_1 δ 7.67, H_2 δ 7.32, $J_{1,2}$ = 8.3 Hz, $p_{1,2}$ 0.724, $J_{2,3}$ = 6.83 Hz, $p_{2,3}$ 0.603); the predicted delocalization energy for 1,3-diphenylisoindole seems not unreasonable in this light.[17d] In any case, the nmr data imply that isoindole contains greater bond delocalization than would be inferred from the fusion of a pyrrole and 1,3-diene unit and, in this respect, reveals an aspect of structure which is not readily apparent in the dynamic chemistry of isoindoles.



18, R = H
19, R = CH_3
20, R = C_6H_5



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The utility of 1,2-dibenzoylcyclohexa-1,4-dienes for synthesis of isobenzofurans was already presaged in the work of Ried and Bönnighausen[14] who prepared 1,3,4,7-tetraphenylisobenzofuran from the cyclohexadiene precursor by treatment with acetic anhydride in acetic acid. In our studies it was found that this dehydration could be effected more smoothly for the 5-methyl- and 5,6-dimethylisobenzofurans, **21** and **22** (Table IV), with *p*-toluenesulfonic acid in benzene under reflux. However, neither method was successful in producing 1,3-diphenyl-4,7-dimethylisobenzofuran from **6**, the major product in each case being 1,2-dibenzoyl-3,6-dimethylbenzene.[22] Formation of **22** from **4** could also be brought about by purely thermal means; thus, when contact of **1** with 2,3-dimethylbutadiene was extended beyond 8 hr, the reaction mixture was found to contain **22** and the product (**23**) of its Diels–Alder addition to **1**. The isobenzofurans were obtained as yellow crystalline substances from solutions which exhibited strong blue fluorescence and were readily identified by their ultraviolet spectra, which showed the intense absorption band at *ca.* 410 mμ characteristic of other 1,3-diarylisobenzofurans.[23]

Isobenzothiophenes have not previously been prepared by this method but, when **4** was allowed to react with phosphorus pentasulfide in hot tetralin containing sand, the solution took on a green fluorescence and 1,3-diphenyl-5,6-dimethylisobenzothiophene (**25**) was isolated in good yield (Table IV). The same procedure was less satisfactory with **3** and gave **24** admixed with the corresponding isobenzofuran **21**. Resort was therefore made to the method of Allen and Gates[24] in which the diketone is heated in a sulfur melt. This protocol afforded 1,3-diphenyl-5-methylisobenzothiophene (**24**). The ultraviolet spectra of isobenzothiophenes **24** and **25** show a close resemblance to their isobenzofuran counterparts, **21** and **22**, with the longest wavelength absorption shifted hypsochromically 21 and 16 mμ,

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[19] A. Albert, *Phys. Methods Heterocycl. Chem.*, **1**, 1 (1963).

[20] M. A. Cooper and S. L. Manatt, *J. Amer. Chem. Soc.*, **91**, 6325 (1969).

[21] C. O. Bender and R. Bonnett, *J. Chem. Soc. C*, 3036 (1968).

[22] R. Adams and M. H. Gold, *J. Amer. Chem. Soc.*, **62**, 56 (1940).

[23] R. Adams and M. H. Gold, *ibid.*, **62**, 2038 (1940).

[24] C. F. H. Allen and J. W. Gates, *ibid.*, **65**, 1283 (1943).

respectively. Analytical, mass spectral, and nmr data confirmed the structural assignment in each case.

The lack of experimental evidence relating to the mechanism of the Paal–Knorr synthesis makes inappropriate any detailed discussion of the mode of formation of isoindoles, isobenzofurans, and isobenzothiophenes as described here.[25] However, the utility of the approach as a method of synthesis of these heterocyclic systems seems established.

Experimental Section

General.—Melting points were measured on a Kofler hot-stage microscope and are corrected. Infrared spectra were measured on a Perkin-Elmer 137 spectrophotometer. Ultraviolet spectra were measured in ethanol solution, except where otherwise indicated, on a Perkin-Elmer 202 spectrophotometer. Nmr measurements were made on Varian A-60 or T-60 spectrometers using CDCl$_3$ solutions, except where otherwise indicated, with TMS as internal standard. Mass spectra were obtained using an AEI MS-9 spectrometer at 70 eV, with direct insertion. Elemental analyses were carried out by Micro-Tech Laboratories, Skokie, Ill. All reactions were carried out under a nitrogen atmosphere.

Dibenzoylacetylene (1).—Prepared as previously described, this material after crystallization from ethanol had mp 114–116° (lit.[11] 110–111°); ir (Nujol) 1645, 1595, 1255, 710, and 695 cm^{-1}; uv max 273 mμ (ϵ 21,900).

1,2-Dibenzoylcyclohexa-1,4-diene (2).—A chilled Carius tube was charged with a solution of 6.50 g (0.028 mol) of **1** and 5 ml of butadiene (cooled to $-20°$) in 120 ml of toluene. The tube was sealed, placed in a shielded oven, and heated at 150–160° for 1 hr. The solvent was removed *in vacuo* leaving a yellow residue which was taken up into hot ethanol. On cooling, a small amount of unreacted **1** crystallized initially and was filtered off. Further cooling of the filtrate yielded **2** as pale yellow prisms: ir (Nujol) 1660, 1600, 1575, 1440, 1305, 1255, 942, 901, 800, 722, and 695 cm^{-1}; m/e 288 (parent).

1,2-Dibenzoyl-4-methylcyclohexa-1,4-diene (3).—A solution of 2.50 g (11 mmol) of **1** in 25 ml of isoprene was heated under reflux for 19 hr. Removal of excess isoprene *in vacuo* left a partially crystalline residue which was recrystallized from ethanol to give **3**: ir (Nujol) 1660, 1600, 1450, 1312, 1265, 1170, 992, 895, and 707 cm^{-1}.

1,2-Dibenzoyl-4,5-dimethylcyclohexa-1,4-diene (4).—A solution of 2.81 g (12 mmol) of **1** and 1.15 g (14 mmol) of 2,3-dimethylbutadiene in a mixture of 10 ml of benzene and 20 ml of methanol was heated under reflux for 8 hr. The solvent was removed *in vacuo* and the residue was taken up into ethanol. Crystallization was induced by addition of ether and the product was recrystallized from ethanol to yield **4**, obtained in two crops: ir (Nujol) 1665, 1622, 1595, 1310, 1292, 1260, 1222, 1174, 1048, 1025, 903, 852, 801, 792, 743, 733, and 704 cm^{-1}.

1,2-Dibenzoyl-3-methylcyclohexa-1,4-diene (5).—A solution of 2.50 g (11 mmol) of **1** in a mixture of 10 ml of piperylene and 5 ml of benzene was heated under reflux for 17 hr. Benzene and unreacted piperylene were removed *in vacuo* leaving a pale yellow, oily residue. Spectroscopic criteria established this material as virtually pure **5**, but attempted crystallization resulted in appreciable loss of material due, it is believed, to facile double bond rearrangement to the more highly substituted cyclohexa-1,3-diene. Consequently, **5** was used for subsequent operations without purification: ir (neat) 1670, 1615, 1585, 1450, 1313, 1265, 897, 747, and 710 cm^{-1}.

***cis*-1,2-Dibenzoyl-3,6-dimethylcyclohexa-1,4-diene (6).**—A solution of 0.51 g (2.2 mmol) of **1** and 2.0 ml (18 mmol) of *trans,-trans*-hexa-2,4-diene in 10 ml of benzene was heated under reflux for 43 hr. The solvent was removed *in vacuo* and the partly crystalline residue was recrystallized from ethanol to give **6** as pale yellow prisms: ir (Nujol) 1650, 1600, 1585, 1560, 1300, 1240, 902, 750, 741, 717, and 699 cm^{-1}.

***cis*-1,2-Dibenzoyl-3-methyl-6-hydroxymethylcyclohexa-1,4-diene (7).**—A solution of 2.30 g (23.5 mmol) of *trans,trans*-hexa-2,4-dien-1-ol and 5.00 g (21.4 mmol) of **1** in 30 ml of benzene was heated under reflux for 32 hr. At this point a further 1.5 g (15.3 mmol) of the dienol was added, and heating was continued for 8 hr. The mixture was then warmed on the water bath under vacuum (0.07 mm), and excess dienol and solvent were removed by distillation. The solid residue was taken up into hot benzene from which **7** crystallized upon addition of ligroin: ir (Nujol) 3620, 3480, 1650, 1600, 1580, 1570, 1437, 1300, 1245, 1163, 1058, 1020, 954, 855, 755, 726, and 705 cm^{-1}.

Condensation of 1,2-Dibenzoylcyclohexa-1,4-dienes with Methylamine.—Typically, a 40% aqueous solution of methylamine (20 ml) was added to a solution of the dibenzoylcyclohexadiene (1 g) in 30 ml of methanol. A color developed immediately and the mixture was heated under reflux for 0.3–1 hr. After cooling the mixture in ice, the precipitated material was collected by suction filtration and recrystallized once to yield the *N*-methylisoindole.

8 (from ethanol): ir (Nujol) 1600, 1530, 1510, 1495, 1239, 1079, 930, 760, 751, and 705 cm^{-1}; m/e 283 (parent).

9 (from ethanol): ir (Nujol) 1600, 1515, 1495, 1246, 1160, 1080, 1019, 934, 797, 759, and 707 cm^{-1}; m/e 297 (parent).

10 (from benzene–ethanol): ir (Nujol) 1600, 1530, 1570, 1079, 1013, 1008, 860, 761, and 708 cm^{-1}; m/e 311 (parent).

11 (from ethanol): ir (Nujol) 1600, 1510, 1485, 1080, 1026, 1012, 784, 756, 749, and 700 cm^{-1}; m/e 297 (parent).

12 (from methanol): ir (Nujol) 1580, 1220, 1105, 1065, 1030, 1020, 1010, 920, 855, 816, 753, 747, 720, and 700 cm^{-1}; m/e 311 (parent).

13 (from methanol): ir (Nujol) 3670, 1600, 1515, 1492, 1232, 1105, 1072, 1025, 1015, 996, 947, 833, 755, and 704 cm^{-1}; m/e 327 (parent).

Condensation of 1,2-Dibenzoylcyclohexa-1,4-dienes with Aniline.—A solution of the dibenzoylcyclohexadiene (1 g) and aniline (1 ml) in glacial acetic acid (50 ml) was heated at 120° for 10 min. The mixture was cooled in ice and the precipitated material was collected by suction filtration. The solid was washed with cold methanol and recrystallized to give the *N*-phenylisoindole.

14 (from benzene–ethanol and then benzene–ligroin): ir (Nujol) 1599, 1488, 1227, 1030, 920, 799, 768, 744, 719, and 700 cm^{-1}; m/e 359 (parent).

15 (from benzene–ethanol): ir (Nujol) 1600, 1525, 1495, 1233, 1112, 1075, 1029, 920, 847, 800, 768, 747, 717, 708, and 699 cm^{-1}; m/e 373 (parent).

16 (from benzene–ethanol): ir (Nujol) 1600, 1510, 1495, 1235, 1075, 1027, 781, 768, 758, 749, 737, 703, and 687 cm^{-1}; m/e 359 (parent).

1,3-Diphenyl-5-methylisoindole (17).—A solution of 0.70 g (2.32 mmol) of **3** and 0.27 g (3.50 mmol) of ammonium acetate in 10 ml of ethanol was heated under reflux for 0.5 hr. Ethanol was removed *in vacuo* and the residue was taken up into benzene. The benzene solution was washed with water and dried over anhydrous sodium sulfate. Removal of the benzene *in vacuo* left a yellow solid which was crystallized twice from ethanol, yielding **17** as yellow needles: ir (Nujol) 3520, 1600, 1545, 1500, 1485, 1285, 1220, 1072, 973, 787, 758, and 690 cm^{-1}; m/e 283 (parent).

1,3-Diphenyl-5-methylisobenzofuran (21).—A solution of 0.51 g (1.18 mmol) of **3** in 40 ml of benzene containing 50 mg of *p*-toluenesulfonic acid was heated under reflux for 1.5 hr. The mixture was washed with a saturated solution of sodium bicarbonate and dried over anhydrous magnesium sulfate. Removal of the solvent *in vacuo* left an orange-colored oil which crystallized from ethanol to give **21**: ir (Nujol) 1595, 1200, 1170, 1065, 1025, 970, 905, 785, 758, 720, and 683 cm^{-1}; nmr δ 2.28 (3 H, s), 6.79 (1 H, d of d, J = 1.5, 9 Hz), and *ca.* 7.5 (12 H, m); m/e 284 (parent).

1,3-Diphenyl-5,6-dimethylisobenzofuran (22). A. From 4.—This compound was obtained by a procedure analogous to that described for **21**: ir (Nujol) 1600, 1550, 1200, 1180, 1155, 1093, 1065, 1030, 997, 975, 900, 833, 820, 759, 720, and 682 cm^{-1}; nmr (dimethyl-d_6 sulfoxide) δ 2.11 (6 H, s) and 7.18 (12 H, m); m/e 298 (parent).

B. From 2,3-Dimethylbutadiene and 1.—A mixture of 0.80 g (9.8 mmol) of 2,3-dimethylbutadiene and 1.58 g (6.8 mmol) of **1** in 15 ml of benzene was heated under reflux for 16 hr. Upon cooling in ice, crystalline material was deposited which was recrystallized from benzene–methanol to give 0.18 g (9%, based on **1**) of **22**. Concentration of the mother liquor produced a colorless solid which was collected by filtration and recrystallized from benzene–methanol to yield 0.23 g (6%, based on **1**) of **23**: mp 203–204.5°; ir (Nujol) 1655, 1600, 1295, 1250, 1005, 829,

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[25] L. A. Paquette, "Principles of Modern Heterocyclic Chemistry," W. A. Benjamin, New York, N. Y., 1968, p 109.

760, 740, 729, 709, 698, and 692 cm^{-1}; nmr δ 2.26 (6 H, s) and 6.9–7.8 (*ca.* 22 H, m); *m/e* 532 (parent).

Attempted Condensation of 6. 1,2-Dibenzoyl-3,6-dimethylbenzene.—A solution of 0.067 g (0.22 mmol) of **6** in 10 ml of benzene containing 5 mg of *p*-toluenesulfonic acid was heated under reflux for 24 hr. Shorter reflux periods resulted in isolation of substantial quantities of unreacted **6**. The mixture was washed with a saturated solution of sodium bicarbonate and dried over sodium sulfate. Removal of the solvent *in vacuo* left a nearly colorless residue which was recrystallized from ethanol to give 0.042 g (65%) of 1,2-dibenzoyl-3,6-dimethylbenzene: mp 138–142°; ir (Nujol) 1660, 1305, 1265, 1150, 1000, 976, 959, 930, 870, 849, 828, 805, 770, 760, 729, 700, and 689 cm^{-1}; nmr δ 2.3 (6 H, s) and *ca.* 7.4 (12 H, m); *m/e* 314 (parent).

1,3-Diphenyl-5-methylisobenzothiophene (24).—A mixture of 0.24 g (0.56 mmol) of **3** and 0.05 g of elemental sulfur was heated at 220° for 20 min using an air-cooled condenser. The dark brown mixture was triturated with acetone and the solids were filtered off. The filtrate was concentrated *in vacuo* and the residue was chromatographed on 20 × 20 cm preparative layer plates coated with silica gel PF-254. Elution with 3% methanol in benzene and removal of the yellow band gave a viscous oil upon extraction of the silica with acetone. This material crystallized from hexane–acetone and was recrystallized from ethanol to give **24**, *m/e* 300 (parent).

1,3-Diphenyl-5,6-dimethylisobenzothiophene (25).—To a stirred mixture of 0.50 g (2 mmol) of phosphorus pentasulfide and 0.5 g of sand in 40 ml of tetralin at 150° was added a solution of 1.01 g (3.2 mmol) of **4** in 20 ml of tetralin during 5 min. The mixture was maintained at 150° for a further 15 min and filtered while hot. The dark red filtrate was washed with 5% sodium hydroxide solution and water and dried over magnesium sulfate. The tetralin solution was diluted with an equal volume of petroleum ether and passed through a short column of alumina (activity II). The eluate, exhibiting green fluorescence, was concentrated to a small volume *in vacuo* and, upon cooling in ice, a yellow, crystalline solid was deposited. This material was recrystallized from acetone to yield **25**: ir (Nujol) 1600, 1240, 1190, 1165, 1120, 1080, 1025, 966, 907, 855, 837, 755, 731, and 694 cm^{-1}; nmr δ 2.14 (6 H, s) and 7.6 (12 H, m); *m/e* 314 (parent).

Registry No.—**2**, 27720-52-1; **3**, 27720-53-2; **4**, 27720-54-3; **5**, 27720-55-4; **6**, 27720-56-5; **7**, 27720-57-6; **8**, 4276-24-8; **9**, 22948-71-6; **10**, 22948-72-7; **11**, 22948-70-5; **12**, 27720-38-3; **13**, 27720-39-4; **14**, 22948-74-9; **15**, 22948-75-0; **16**, 22948-73-8; **17**, 22942-68-3; **18**, 20944-65-4; **19**, 10287-38-4; **20**, 20944-69-8; **21**, 27720-46-3; **22**, 27720-47-4; **23**, 27720-48-5; **24**, 27720-49-6; **25**, 27720-50-9; 1,2-dibenzoyl-3,6-dimethylbenzene, 6807-35-8.

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The Chemistry of Indenothiophenes. III. The Metalation of 3-Benzylthiophene and an Alternative Synthesis of 4*H*-Indeno[1,2-*b*]thiophene-4-carboxylic Acid[1]

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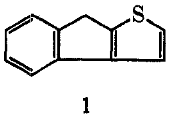
The metalation of 3-benzylthiophene (**6**) has been shown to yield 88% 4-benzylthiophene-2-carboxylic acid (**8**) and 12% 3-benzylthiophene-2-carboxylic acid (**9**). No 3-thienylphenylacetic acid (**10**) was formed. Both **9** and **10** were synthesized independently. These results are discussed in terms of single-bond bridging between the benzene and thiophene rings which is present in indenothiophenes **1**, **2**, and **3** but absent in **6**. This alters the sites of metalation of **6** when compared to **1**, **2**, and **3**. The cyclization of 3-thienylmandelic acid (**13**) gives 4*H*-indeno[1,2-*b*]thiophene-4-carboxylic acid (**5**).

Previous studies in our laboratories[3] have determined the metalative properties of the three parent indenothiophenes **1**, **2**, and **3**. Compounds **1** and **2** underwent metalation–carbonation at their respective methylene bridges to yield 8*H*-indeno[2,1-*b*]thiophene-8-carboxylic acid (**4**) and 4*H*-indeno[1,2-*b*]thiophene-4-carboxylic acid (**5**). However, metalation of 8*H*-indeno[1,2-*c*]thiophene (**3**) gave a mixture of three products: 8*H*-indeno[1,2-*c*]thiophene-3-carboxylic acid (48%), 8*H*-indeno[1,2-*c*]thiophene-8-carboxylic acid (38%), and 8*H*-indeno[1,2-*c*]thiophene-1-carboxylic acid (14%).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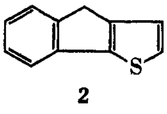
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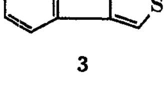
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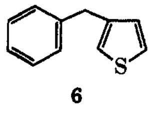
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In order to determine if direct bridging between the benzene and thiophene rings influences the position of metalation of **2** and **3**, a study of the metalative properties of 3-benzylthiophene (**6**), the open-chain analog of **2** and **3**, was undertaken.

Metalation of **6** could reasonably be expected to take place at the two α positions on the thiophene ring and on the methylene bridge.

Synthesis.—The synthesis of **6** was accomplished as shown below in Scheme I. Hydrolysis of the mixture obtained in the reaction of benzonitrile with 3-thienyllithium at −70° produced 3-benzoylthiophene (**7**) in 69% yield.[4] Reduction to **6** was achieved in 90% yield following the procedure of Nystrom and Burger.[5] Wolff–Kishner reduction gave **6** in 70% yield.

Metalation Experiments. Metalation of **6**, which produced acidic material in 80% yield, was accomplished by reaction with 1 equiv of ethereal *n*-butyllithium followed by carbonation and work-up (Scheme

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[1] Part of this work was presented at the 2nd Central Regional Meeting of the American Chemical Society, Columbus, Ohio, June 1970.

[2] NDEA Fellow, 1967–1970.

[3] D. W. H. MacDowell and T. B. Patrick, *J. Org. Chem.*, **32**, 2441 (1967); D. W. H. MacDowell and A. T. Jeffries, *ibid.*, **35**, 871 (1970).

[4] S. Gronowitz, *Ark. Kemi*, **12**, 533 (1958).

[5] R. F. Nystrom and C. R. A. Burger, *J. Amer. Chem. Soc.*, **80**, 2896 (1958).