at 35–38° was continued for 30 min. The reaction mixture was kept overnight at room temperature, after which 25 ml. of 6 *N* HCl was added. The mixture was stirred at 35–42° for 30 min. The chloroform layer was separated and washed with water, and the solvent was distilled *in vacuo*. The residue was crystallized from ether–petroleum ether; yield 8.5 g., m.p. 193–203°. A sample was recrystallized from ethylene dichloride–ether–petroleum ether.

5-(β-9-Triptycylpropionyl)valeric Acid (51).—A solution of the diketone **50** (7.85 g.) and 0.95 g. of NaOH in 100 ml. of 50% ethanol was refluxed for 4 hr. Concentrated HCl (2.5 ml.) was added, and most of the ethanol was distilled *in vacuo*. The product was filtered and washed with water; yield 7.5 g., m.p. 193–197°. A sample was recrystallized from toluene for analysis.

8-(9-Triptycyl)octanoic Acid (52).—A mixture of 7.3 g. of the keto acid **51**, 1.05 g. of KOH, 7.5 ml. of 85% hydrazine hydrate, and 20 ml. of diethylene glycol was stirred and refluxed for 6 hr. Diethylene glycol (20 ml.) and 5.5 g. of KOH were added, and the mixture was heated for 17 hr. in an open flask in an oil bath kept at 195°. The reaction mixture was poured into several volumes of water. Then 12 *N* HCl (20 ml.) was added, and the mixture was heated, then cooled, and the product was filtered and washed well with water; yield 6.7 g., m.p. 160–168°. It was recrystallized from methanol–ether. The acid chloride was prepared using oxalyl chloride according to the procedure given above for the acid chloride **34**. This was converted to the amide **53** using excess dry NH_3 in ether solution, and the amide was reduced with $LiAlH_4$ by the general procedure above to yield the amine hydrochloride **54**.

13-(9-Triptycyl)-6-ketotridecanoic Acid (55).—The acid chloride of 8-(9-triptycyl)octanoic acid (**52**) was used to acylate the morpholine enamine of cyclopentanone by the procedure used above. The crude β-diketone on alkaline hydrolysis afforded the keto acid **55**.

13-(9-Triptycyl)tridecanoic Acid Amide (56).—Wolff–Kischner reduction of the keto acid **55** by the procedure used for **52** gave the tridecanoic acid, which was converted to the amide **56** in the usual way. Reduction of the amide afforded the amine hydrochloride **57**.

12-(9-Triptycyl)dodecylamine Hydrochloride (58).—Hofmann degradation of the amide **56** was carried out using the procedure employed with **35**. The crude carbamate so formed was hydrolyzed by the method used for conversion **27** → **29** above.

Acknowledgments.—The authors thank Mr. W. L. Brown and associates for the microanalyses, and Dr. H. Boaz and co-workers for physical data. The mouse behavior studies were carried out by Mr. R. W. Kattau, and the antiinflammatory assays by Dr. R. Kraay and his associates.

Derivatives of Fluorene. XIX.[1,2] 9-*o*-Chlorocinnamylidenefluorene and Related Compounds

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In screening sponsored by the National Service Center of the National Cancer Institute, activity against an animal tumor was discovered with a compound presumed (and first reported in 1919) to be 9-*o*-chlorobenzylidenefluorene. Upon examination, the compound has been found to be 9-*o*-chlorocinnamylidenefluorene which was produced in small yield as the only recognizable product in an attempted sodium ethoxide–ethanol condensation of *o*-chlorobenzaldehyde and fluorene, presumably after formation of acetaldehyde and then *o*-chlorocinnamaldehyde or 9-ethylidenefluorene or both. A number of analogs have been made for antitumor screening, particularly by the phosphonium–ylide route which, in general, is much superior to the alkaline condensation method. Spectral properties were recorded and some new triphenylphosphonium fluorenylides were made as intermediates.

Included in the preparation of a number of derivatives of fluorene and aminofluorenes, with extended conjugation from the 9-position, we repeated the reaction reported by Sieglitz between fluorene and *o*-chlorobenzaldehyde in the presence of sodium ethoxide. We, too, obtained a small yield of the yellow product (m.p. 177–178°, lit. 176°) which had been named *o*-chlorobenzalfluorene,[3] and observed the same distressing facts that analyses were not good, and that further attempted purification did not result in better analyses. About this time we were notified that the compound was showing slight antitumor activity against S180 in tests sponsored by the Cancer Chemotherapy National Service Center, and that a relatively large amount was wanted for further testing. In view of the poor analyses and low yields of this substance (which also seemed to be a deeper yellow than expected from comparison with similar 9-benzylidenefluorenes), it appeared necessary both to prepare the *o*-chlorobenzylidenefluorene by an alternate route and to examine more critically the structure of the compound melting at 178°. It was then observed that analyses were consistent with an empirical formula C_2H_2 greater than that for the alleged compound. Thus we were led to feel that the compound wanted in further amounts by the CCNSC was probably 9-*o*-chlorocinnamylidenefluorene.

Badger and Spotswood described and confirmed the synthesis of 9-*o*-chlorobenzylidenefluorene[4] (m.p. 69–70°), essentially by Sieglitz's method, with no reference to Sieglitz's data or to the fact that there was a difference of over 100° in the melting points of the reported compounds. Reaction of *o*-chlorobenzaldehyde and 9-triphenylphosphine fluorenylide gives authentic 9-*o*-chlorobenzylidenefluorene. The melting point, al-

(1) Paper XVIII in this series: H.-L. Pan and T. L. Fletcher, *J. Med. Chem.*, **7**, 31 (1964).

(2) This research was supported in part by Research Grant No. CA-01744 from the National Cancer Institute, by Career Development Award No. 5-K3-GM-14, 991 (T. L. F.) from the National Institutes of Health, and by Contract SA-43-ph-4320, Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health. The advice of Drs. Howard W. Bond, Ronald B. Ross, Harry B. Wood, Jr., and C. Verne Bowen of the Cancer Chemotherapy National Service Center is also gratefully acknowledged.

(3) A. Sieglitz, *Chem. Ber.*, **52**, 1513 (1919).

(4) G. M. Badger and T. M. Spotswood, *J. Chem. Soc.*, 1635 (1959).

though sharp, is 10° below that reported[4]; analyses are correct. 9-Ethylidenefluorene, condensed (Sieglitz's method) with *o*-chlorobenzaldehyde, gave our original compound, now clearly the *o*-chlorocinnamylidene derivative (m.p. 177–178°). We also made the same compound from triphenylphosphonium fluorenylide and *o*-chlorocinnamaldehyde.

The ultraviolet spectrum[5] of this compound is very similar to that of 9-cinnamylidenefluorene and different from that of 9-benzylidenefluorene. The infrared spectrum[5] of this compound (and of several other substituted 9-cinnamylidenefluorenes) has a strong band between 960–950 cm.$^{-1}$, usually assigned to a *trans* ethylenic double bond, due to out-of-plane vibration of the two vinyl hydrogen atoms[6a,7a]; and also a sharp band at 1625 cm.$^{-1}$, assigned to conjugated double bonds.[7a] Neither of these absorptions is found in the spectra of 9-benzylidenefluorene derivatives.

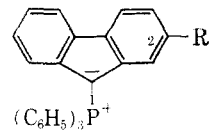
The n.m.r. spectrum[5] of 9-*o*-chlorocinnamylidenefluorene shows only a complex pattern in the aromatic region (7–8 p.p.m.) which is of no diagnostic value. It is interesting that the spectrum of 9-*o*-chlorocinnamylidenefluorene has a doublet centered at 6.88 p.p.m. (J = 16 c.p.s.) assigned to the single proton α to the phenyl group. A similar downfield shift (approximately 0.45 p.p.m.) of the signal assigned to this proton is also seen in a comparison of the spectra of *o*-chlorocinnamaldehyde and cinnamaldehyde. *o*-Chlorocinnamaldehyde gives a doublet centered at 7.82 p.p.m. (J = 16 c.p.s.), whereas for cinnamaldehyde this doublet is seen at 7.37 p.p.m. (J = 16 c.p.s.). In other respects the spectra are essentially the same. With 9-benzylidenefluorene there is only a complicated pattern at 7–8 p.p.m.

Gas–liquid chromatography confirmed our belief that the commercial *o*-chlorobenzaldehyde was free of any vinylog. The only reasonable alternative is that acetaldehyde is formed in the sodium ethoxide–ethanol–air reaction mixture and that either benzaldehyde or fluorene reacts to give a vinylog which then condenses with the other reactant. The relatively high melting point of the small amount of cinnamylidene product leads to relatively easy recovery from the heavy oil of the reaction mixture. Here and there, in the literature,[8] similar instances of such vinylogous by-products are found, with speculation (but no proof) about acetaldehyde. Several variations of the reaction were tried including initial addition of acetaldehyde. No recognizable product is recovered in the latter, but the mixture is darker and gummier than in the usual reaction.

We obtained essentially quantitative yields of pure N,N′-di-*o*-chlorobenzylidene derivatives of 2,5- and 2,7-diaminofluorene indicating the high purity of the aldehyde. Novelli,[9] using unsubstituted benzaldehyde, reported a similar compound to be "9-benzal-2-benzalamino-7-aminofluorene." We repeated the latter preparation undoubtedly obtaining the same product with a slightly higher melting point.[9] However, the infrared spectra of all three of these diarylidene compounds show no free amine band. They do show a split band in the —C=N— region (1523–1518 cm.$^{-1}$),[10] and a band at 1405–1395 cm.$^{-1}$, indicating the —CH_2— group between two (aromatic) double bonds,[11] which is, in these, the 9-methylene of the fluorene nucleus.

Table I summarizes the information about most of the compounds made in this study.

The new phosphonium ylides described in the Experimental section are of interest as intermediates, particularly the 2-dimethylamino derivative, because 9-arylidene-2-dimethylaminofluorenes are tedious to make by other methods. Examples of such condensations are included.



R = NO_2, $N(CH_3)_2$

Infrared absorption bands of the new ylides are recorded. In addition, we should like to note that the ylides show three bands at approximately 740, 720, and ~690 cm.$^{-1}$. The first and last are undoubtedly related to out-of-plane vibration of the groups of 4 and 5 adjacent hydrogen atoms.[6b] The band at 720 cm.$^{-1}$, however, seems beyond the limits (~730 cm.$^{-1}$) for 4 adjacent hydrogen atoms in the fluorene spectra we have examined, and we tentatively suggest that this band may arise from P–C stretching with the 9-carbon of the fluorene nucleus. Bellamy[6c] and Nakanishi[7b] list 750–650 cm.$^{-1}$ as a region of P–C stretching, but the former warns that no useful correlations have been developed.

9-Triphenylphosphonium 2-N,N-dimethylaminofluorenylide is bright yellow; 2-dimethylamino-9-oxofluorene is deep purple; 9-triphenylphosphonium 2-nitrofluorenylide is deep purple; 2-nitro-9-oxofluorene is bright yellow. Consideration of the P^+–C^- and P=C limiting structures and the foregoing color contrast indicates that the electron-donating or -withdrawing power of the 2-substituent on the fluorene nucleus markedly influences the relative contributions of these two structures. Further conclusions await a spectral study (ultraviolet and visible) of a more comprehensive series of 2-substituted phosphonium fluorenylides. It is of interest in the meantime, that the phosphonium 2-dimethylamino-, 2-nitro-, and unsubstituted fluorenylides all react in 30 min. or less to give high yields of the 9-*p*-nitrobenzylidene derivative. The 2-dimethylamino product is homogeneous and sharp melting. The 2-nitro product, however, is a *cis–trans* mixture in quantitative crude yield. Included in the spectral study mentioned above, we plan to report later on the influence of variously substituted fluorene nuclei in phosphonium ylides, with respect to the relative contributions in each of the P^+–(9)C^- and P=(9)C forms.

(5) Ultraviolet spectra were run on a Beckman DK-1; infrared spectra were run on a Beckman IR-5 with KBr pellets, at a concentration of 1.5–2 mg. of substance/300 mg. of KBr. N.m.r. spectra were run in deuteriochloroform solution using tetramethylsilane as an internal standard on a Varian A-60 spectrometer. We wish to thank Dr. J. M. Vandenbelt and Mr. R. B. Scott for the n.m.r. determinations.

(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958: (a) p. 45; (b) pp. 76–78; (c) p. 321.

(7) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962: (a) p. 24; (b) p. 56.

(8) E. Bergmann, *Chem. Ber.*, **63**, 1617, 2598 (1930); W. Schlenk and E. Bergmann, *Ann.*, **479**, 42 (1930).

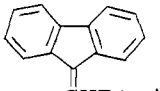
(9) A. Novelli, *Anales Asoc. Quim. Arg.*, **17**, 25 (1929); *Chem. Abstr.*, **24**, 99 (1930).

(10) L. J. Bellamy, ref. 6, p. 263 ff.

(11) K. Nakanishi, ref. 7, p. 21.

TABLE I

9-YLIDENE FLUORENES



CHR(or Ar)

9-Substituent	M.p.,[a] °C.	Yield, %	Method	Formula	% C[a] Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found	% Halogen Calcd.	% Halogen Found
Ethylidene[b]	101–103[b]		A									
Benzylidene	76–77[c]		C									
o-Chlorobenzylidene	59.5–60[d]	69	A	$C_{20}H_{13}Cl$	83.18	83.01	4.54	4.73			12.28	12.08
o-Bromobenzylidene	83.5–84.5	70.5	A	$C_{20}H_{13}Br$	72.08	72.30	3.93	3.97			23.99	24.25
o-Nitrobenzylidene[e]	126–127	100	A	$C_{20}H_{13}NO_2$	80.25	80.21	4.38	4.20	4.68	4.80		
o-Aminobenzylidene	90.5–91	91.5	D	$C_{20}H_{15}N$	89.18	89.01	5.61	5.88	5.20	4.90		
o-Acetamidobenzylidene	226–227	96	E	$C_{22}H_{17}NO$	84.86	85.18	5.50	5.92	4.50	4.38		
Cinnamylidene	157–159[f]	22	C									
o-Chlorocinnamylidene	177–178	3.5[g]	C									
o-Chlorocinnamylidene	177–178	15.3	B	$C_{22}H_{15}Cl$							11.26	11.08
o-Chlorocinnamylidene	175–176	77.0	A	$C_{22}H_{15}Cl$	83.93	83.64	4.80	4.99			11.27	11.33
o-Bromocinnamylidene[e]	187–188	26.2	B	$C_{22}H_{15}Br$	73.54	73.77	4.21	4.38			22.25	22.49
o-Fluorocinnamylidene[e]	158–159	31.6	B	$C_{22}H_{15}F$	88.56	88.92	5.07	5.15			6.37	6.10
o-Nitrocinnamylidene[e]	185–186[f]	88	A									
o-Aminocinnamylidene	172–173	97	D	$C_{22}H_{17}N$	89.46	89.43	5.80	5.86	4.74	4.91		
o-Acetamidocinnamylidene	248–249	91	E	$C_{24}H_{19}NO$					4.15	4.22		
m-Chlorocinnamylidene	164–165	32	B	$C_{22}H_{15}Cl$	83.93	83.68	4.80	4.83			11.26	11.20
p-Chlorocinnamylidene	150–151	35	B	$C_{22}H_{15}Cl$	83.93	83.88	4.80	4.78			11.26	11.38

[a] Ref. 12. [b] F. Mayer [*Ber.*, 2579 (1913)] gave m.p. 104°; A. W. Johnson [*J. Org. Chem.*, **25**, 183 (1960)] gave m.p. 102–104°. The latter started with the triphenylarsonium ylide. [c] J. Thiele and F. Henle [*Ann.*, **347**, 290 (1906)] gave m.p. 76°. [d] Lit. m.p. 176°,[3] and 69–70°[4]; the former (see text) has now been shown to be *o*-chlorocinnamylidenefluorene. [e] *o*-Nitro-, *o*-bromo-, *o*-chloro-, and *o*-fluorobenzaldehydes and *o*-nitrocinnamaldehyde were purchased from the Aldrich Chemical Co. [f] R. Kuhn and A. Winterstein [*Helv. Chim. Acta*, **11**, 116 (1928)] report for 9-cinnamylidenefluorene, m.p. 155°, and for 9-*o*-nitrocinnamylidenefluorene, m.p. 186°. [g] Higher yields, up to 15%, were obtained at one-tenth the described level (method C).

and on the production of an isomer mixture or of single products in reactions with arylaldehydes.

Experimental[12]

Triphenylphosphonium Fluorenylide.—Triphenylfluorenylphosphonium bromide was made in 1-mole batches (92.5%), then filtered, and dried. The entire product was suspended in 3 l. of boiling ethanol, and 1 l. of concentrated NH_4OH was added with stirring. The product was filtered, washed, and dried (97%, based on the bromide), m.p. 275–278° (lit. 268–270°[13] and 258–260°[14]; the latter is reported as analytically pure).

For some of the condensations we followed the procedure of Johnson[14] (method A, Table I), with slight changes. Sirupy products were digested in ethanol or methanol, filtered, and cooled, and the product was recrystallized from a suitable solvent.

9-*o*-Chlorobenzylidenefluorene (Method A).—Triphenylphosphonium fluorenylide (85.2 g., 0.2 mole) and 28.1 g. (0.2 mole) of *o*-chlorobenzaldehyde were refluxed together in 1 l. of chloroform for 60 hr. The solvent was distilled, and the residual sirup was mixed thoroughly with 300 ml. of boiling methanol and allowed to cool. After a few hours yellow needles which had precipitated were filtered off (20.5 g., m.p. 58–60°). Chromatography of 1.7 g. of the first crop in 4 ml. of benzene followed by elution with petroleum ether (b.p. 30–60°) gave a main fraction which was recrystallized from methanol (1.2 g., m.p. 59.5–60°). We are not able to explain the discrepancy between this melting point and that of Badger and Spotswood[4] (69–70°).

9-*o*-Chlorocinnamylidenefluorene. Method A.—A solution of 32.4 g. of triphenylphosphonium fluorenylide and 12.7 g. of *p*-chlorocinnamaldehyde[15] in 1 l. of chloroform was refluxed for 96 hr. The solvent was then removed on a rotary evaporator and the yellow solid residue was digested with 950 ml. of anhydrous ethyl alcohol. Very little solid dissolved. The mixture was filtered, and the collected solid was dried *in vacuo* at 50° for 24 hr.; 17.7 g. (77%), m.p. 175–176°. Thin layer chromatography on silica gel HF (E. Merck, Darmstadt) using acetone as the developing solvent gave only one spot (R_f 0.91).

Method B.—To a sodium ethoxide solution (2 g. of sodium in 100 ml. of absolute ethanol), 9.6 g. (0.05 mole) of 9-ethylidenefluorene (method A) was added, the mixture was heated to 65°, and 0.05 mole of benzaldehyde, or a substituted benzaldehyde, was added with thorough mixing. The reaction mixture became darker and was allowed to stand at room temperature overnight. The precipitate was filtered off, dried, and recrystallized from alcohol.

Method C.—To 166 g. (1 mole) of fluorene (Aldrich Chemical Co.) in a sodium ethoxide solution (20 g. of sodium in 3 l. of absolute ethanol), 140 g. (1 mole) of *o*-chlorobenzaldehyde (Eastman) was added. The mixture was heated to 65° with thorough mixing for 20 min. and allowed to cool to room temperature. The oil which separated out was triturated with 500 ml. of ethanol and this mixture then stood for several days. The solvent was decanted and 200 ml. of ligroin (*d* 0.67–0.69) was added with trituration. After 2 days the resulting yellow crystalline mass was filtered off and recrystallized from ethanol giving 10.2 g., m.p. 176–178°. The analytical sample was prepared by crystallization from methanol.

The ultraviolet spectra showed for 9-*o*-chlorocinnamylidenefluorene: λ_{max}^{EtOH} mμ (log ε) 240 (4.54), 253 (4.43), 262.5 (4.49), 273 (4.37). This is almost identical with the spectrum of 9-cinnamylidenefluorene. Both compounds have a strong band at 375 mμ. For 9-benzylidenefluorene, the band with the longest wave length is at 325 mμ (log ε 4.15); lit.[14] 325 mμ (log ε 4.1), 256 (4.4), 248 (4.3), 227 (4.6).

Method D.[16]—To a solution of 15 g. of the nitro compound in 300 ml. of alcohol, 15 ml. of 100% hydrazine hydrate and 0.5 g. of 5% palladium on powdered charcoal (Matheson Coleman and Bell) were added,[17] and the mixture was boiled gently for 30 min. with solvent replacement. The excess hydrazine was

(12) Melting points are corrected to standards and were taken on a Fisher-Johns block. Analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

(13) L. A. Pinck and G. A. Hilbert, *J. Am. Chem. Soc.*, **69**, 723 (1947).

(14) A. W. Johnson, *J. Org. Chem.*, **24**, 282 (1959).

(15) K. W. Rosenmund and G. Weiler, *Ber.*, **56**, 1486 (1923).

(16) This is a modification of the reduction procedure we described in paper IV of this series: T. L. Fletcher and M. J. Namkung, *J. Org. Chem.*, **23**, 680 (1958).

(17) To prevent possible ignition the metal powder is wet with alcohol in a small beaker and washed into the reaction flask with a stream of alcohol. The Raney nickel, stored under alcohol, is likewise washed in carefully from a spoonula to prevent its drying and sparking in the solvent vapors.

destroyed by adding a small amount of the Raney nickel described earlier[18] with additional boiling for 10 min. The mixture was then filtered through No. 3 Whatman paper and boiled down to a small volume and cooled. After separation, the crystalline product was recrystallized from methanol.

Method E.—Acetylation was carried out in benzene with acetic anhydride, and heating was continued for 10 min. on the steam bath. The product was recrystallized from alcohol.

2,7-(N,N′-Dibenzylidene)fluorenediamine.—To a hot solution of 3.9 g. (0.02 mole) of 2,7-fluorenediamine[16] in 120 ml. of alcohol, 4.6 g. (0.04 mole) of benzaldehyde was added slowly. A yellow precipitate came out immediately, and the mixture was heated on the steam bath for 10 min. and allowed to cool. Filtration and drying gave 7.1 g. (91%), m.p. 245–248°. One crystallization from toluene gave the pure product, m.p. 259–260°, lit.[9] m.p. 249–250°.

2,7-(N,N′-Di-*o*-chlorobenzylidene)fluorenediamine.—The foregoing procedure was used to obtain 97.5% of the crude product, m.p. 209–210°. One recrystallization from benzene (Darco) gave an analytically pure sample with the same melting point.

Anal. Calcd. for $C_{27}H_{18}Cl_2N_2$: C, 73.47; H, 4.11; Cl, 16.07; N, 6.35. Found: C, 73.33; H, 4.13; Cl, 16.10; N, 6.59.

2,5-(N,N′-Di-*o*-chlorobenzylidene)fluorenediamine.—A 99% crude yield (m.p. 148–150°) was obtained using the above procedure with 2,5-fluorenediamine.[16] Recrystallization from benzene (Darco) sharpened the melting point to 149–150°.

Anal. Calcd. as above. Found: Cl, 15.80; N, 6.17.

Triphenylphosphonium 2-nitrofluorenylide was made in the same way as the preceding fluorenylide using 9-bromo-2-nitrofluorene. The bromide was obtained in 87% yield. Upon treatment with NH_4OH, the dark purple ylide came out. The yield was quantitative, m.p. 291–292° dec., with slight softening at 290°. Recrystallization from toluene gave an analytical sample.

Anal. Calcd. for $C_{31}H_{22}NO_2P$: C, 78.97; H, 4.70; N, 2.97; P, 6.57. Found: C, 79.28; H, 4.38; N, 3.33; P, 6.79.

Infrared absorption bands showed C–NO_2, 1510 and 1340 cm.$^{-1}$; P–C_{aryl}, 1440 and 692 cm.$^{-1}$; P–C_{alkyl}, 718 cm.$^{-1}$.

Triphenylphosphonium 2-N,N-Dimethylaminofluorenylide.—An identical procedure starting with 9-bromo-2-N,N-dimethylaminofluorene hydrobromide[19] gave a quantitative yield of the bromide and 86% of the ylide, m.p. 275–280° dec.

Anal. Calcd. for $C_{33}H_{28}NP$: C, 84.41; H, 6.01; N, 2.98; P, 6.60. Found: C, 84.24; H, 5.88; N, 3.31; P, 6.59.

Infrared absorption bands showed C–N (vibrational band, *t*-amine), 1333 cm.$^{-1}$; P C_{aryl}, 1435 and 693 cm.$^{-1}$; P–C_{alkyl}, 720 cm.$^{-1}$.

9-*p*-Nitrobenzylidene-2-N,N-dimethylaminofluorene.—To a solution of 12 g. of 9-triphenylphosphonium 2-N,N-dimethylaminofluorenylide in 200 ml. of chloroform, 3.85 g. (an equimolar amount) of *p*-nitrobenzaldehyde was added. The mixture was refluxed for 30 min. and then boiled down to near dryness. The gummy mass was triturated with 20 ml. of ethanol until the dark purple product solidified. This was filtered off and dried giving 7.5 g. (86%), m.p. 125–127°. One recrystallization (Darco) from ethanol gave an analytical sample, m.p. 126–127°.

Anal. Calcd. for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.31; H, 5.41; N, 8.27.

Infrared absorption bands showed C–NO_2, 1510 and 1340 cm.$^{-1}$; C–NR_2, 1333 cm.$^{-1}$.

9-*p*-Nitrobenzylidene-2-nitrofluorene.—Reaction of 6 g. of 9-triphenylphosphonium 2-nitrofluorenylide with 1.93 g. of *p*-nitrobenzaldehyde in 100 ml. of chloroform as described in the preceding procedure gave 4.4 g. (100%) of a *cis–trans* mixture of 9-*p*-nitrobenzylidene-2-nitrofluorene,[20] m.p. 240–290°.

Biological Results.—None of the analogs of 9-*o*-chlorocinnamylidenefluorene, thus far submitted, show any antitumor activity. The latest data available from the Cancer Chemotherapy National Service Center, which sponsored the screening, show that the named compound had some activity against S180, having gone to multiple dose assay at two screening laboratories. This was not confirmed, however, and the compound is considered inactive. No activity was found against Adenocarcinoma 755 or leukemia L1210. Multiple dose assay at two laboratories is also being run with the KB cell culture system.

One of the new ylides described above also showed slight initial activity. 9-Triphenylphosphonium 2-N,N-dimethylaminofluorenylide is undergoing multiple dose assay tests against Cloudman melanoma and there is slight activity against the KB cell culture system. Initial activity against S180 was not confirmed.

(18) Ref. 16, footnote 18.

(19) T. L. Fletcher and M. J. Namkung, *J. Chem. Soc.*, 1400 (1961).

(20) E. Fischer and E. D. Bergmann [*Bull. Res. Council Israel*, **1**, 136 (1951)] reported the *cis* isomer, m.p. 251–252°; for the *trans* isomer, m.p. 287–288°. We prepared these (m.p. 238–290°) by condensing 2-nitrofluorene with *p*-nitrobenzaldehyde and then separating.

5-Methylpyrazole-3-carboxylic Acid. The Potent Hypoglycemic Metabolite of 3,5-Dimethylpyrazole in the Rat

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Biological evaluation of 3,5-dimethylpyrazole, a potent hypoglycemic agent (50 times tolbutamide) in the glucose-primed, fasted, intact rat suggested that this compound was active by virtue of its conversion to an active metabolite. Demonstration that the urine of treated rats possessed considerable hypoglycemic activity in the absence of detectable 3,5-dimethylpyrazole supported this hypothesis. A potent hypoglycemic metabolite (200 times tolbutamide in the rat) has been isolated from the urine of treated rats and identified as 5-methylpyrazole-3-carboxylic acid. Extensive studies of the urine from rats receiving 3,5-dimethylpyrazole indicate that this metabolite accounts for all of the urinary hypoglycemic activity.

A series of pyrazoles have recently been reported to possess considerable hypoglycemic activity.[1,2] The most active compounds of this series were those containing methyl groups in both the 3- and 5-positions. 3,5-Dimethylpyrazole (I) was the most active of the several pyrazoles tested. Studies, using eviscerate rats, aimed at defining the mechanism of hypoglycemic action of this compound suggested that the gastrointestinal tract and/or the liver was necessary for activity[2]; in this respect its behavior is similar to its close analog, 3,5-dimethylisoxazole.[3]

After oral administration of I to glucose-primed, fasted, intact rats, activity was apparent at 1 hr. and reached a maximum at 2 hr.; the response after intravenous administration, however, was not apparent until

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