Lake [13] who investigated the formation constants of adducts formed by Nb(V) and Ta(V) chlorides with soft ligands as benzene. In a similar way, Figure 2 shows that bromides are softer than the corresponding chlorides; this was discussed above in terms of symbiotic effect.

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134. Synthesis of some Indanones having Nitrogen-containing Substituents

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(28. III. 74)

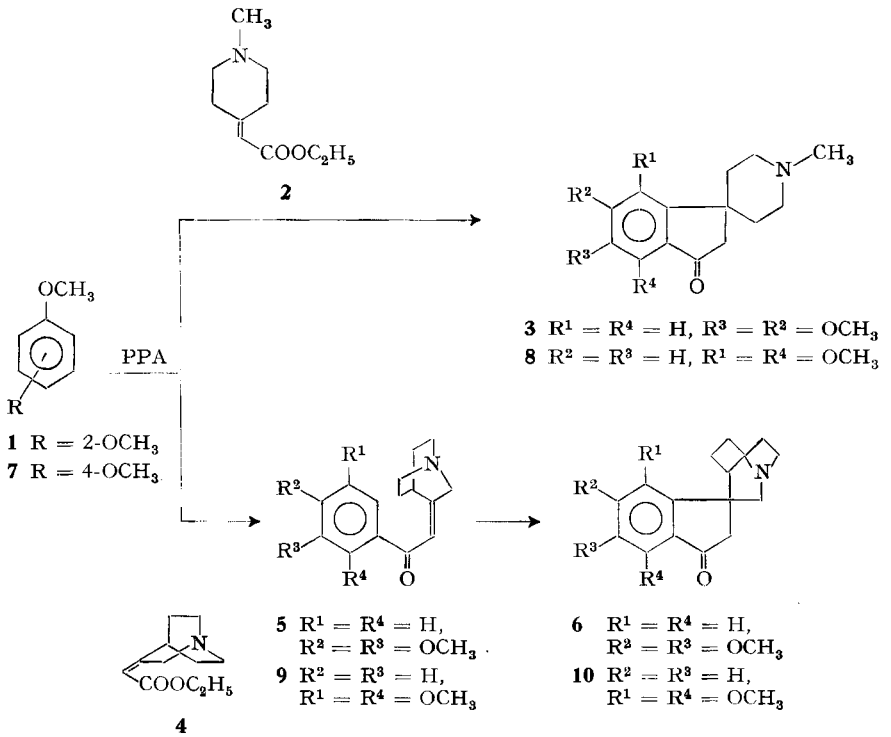
Summary. The title compounds have been synthesized by a *Friedel-Crafts* acylation-alkylation between aromatic ethers and α,β-unsaturated carboxylic acids (or esters) having nitrogen-containing substituents. Polyphosphoric acid was used as condensing agent.

Introduction. – There have been a number of reports concerning the preparation of indanones by condensing an α,β-unsaturated carboxylic acid or derivative with an aromatic nucleus. Aluminum chloride [1], hydrogen fluoride [2] and polyphosphoric acid [3] have been used most frequently as condensing agents.

In this paper we describe the cyclisation between some α,β-unsaturated carboxylic acids or esters, having nitrogen-containing substituents, and aromatic ethers. Polyphosphoric acid was used as medium in these reactions. Indanones having nitrogen-containing substituents were obtained in moderate yields, and they were easily separated from their by-products or starting materials. In one case a β-hydroxy carboxylic acid was used instead of an α,β-unsaturated carboxylic acid.

Results. – When veratrole (**1**) was treated with ethyl (1-methyl-4-piperidylidene)-acetate (**2**) [4] in polyphosphoric acid (PPA), spiro[(5,6-dimethoxyindan-1-one)-3,4′-(1′-methylpiperidine)] (**3**) was obtained. Yields were optimal when the temperature was maintained at 135° for 40 minutes. The NMR. spectrum of **3** showed a singlet at δ 2.5 ppm, corresponding to the equivalent protons in the α position of the carbonyl group. This peak disappeared when **3** was refluxed for a few minutes in D_2O/tetrahydrofuran (THF) containing a small amount of NaOH.

Veratrole and ethyl 3-quinuclidylidene-acetate (**4**) [5] heated with PPA at 115° gave as intermediate product the quinuclidylidene-acetophenone **5**, which was cyclised when heated in PPA at 135° to give spiro[(5,6-dimethoxyindan-1-one)-3,3′-quinuclidine] (**6**). The indanone **6** was also produced directly by treating the α,β-unsaturated carboxylic ester **4** with veratrole and PPA at 135°. In the NMR. spectrum of **6**, the non-equivalent α-hydrogen atoms appeared as two doublets centered at δ 2.5 and δ 3.2 (J = 18 Hz). In analogy to the product **3** above these peaks disappeared when **6** was treated with NaOH in D_2O/THF.

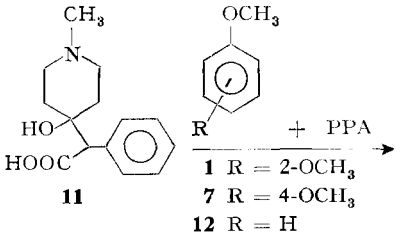


The fact that the α,β-unsaturated ketone **5** could be isolated was probably due to the β-position in compound **4** being more strongly hindered than the corresponding β-position in compound **2**.

Similarly, spiro[(4,7-dimethoxyindan-1-one)-3,4′-(1′-methylpiperidine)] (**8**) was prepared from hydroquinone dimethyl ether (**7**) and compound **2** in PPA at 130°. This reaction gave lower yields of indanones, due to the lower reactivity of **7** compared

with that of veratrole. The lower reactivity is illustrated by the condensation of the α,β-unsaturated carboxylic ester **4** with **7**, which led to the intermediate quinuclidylidene-acetophenone **9**. In contrast to veratrole where cyclisation took place, no cyclised product (**10**) could be isolated, even when the temperature of the reaction was raised to 180°.

In an analogous manner, the free base or the hydrochloride of α-phenyl-α-(1-methyl-4-hydroxy-4-piperidyl)-acetic acid (**11**) [6] reacted with veratrole, hydroquinone dimethyl ether or anisole (**12**) in PPA, affording the corresponding indanones **13**, **14** and **15**.



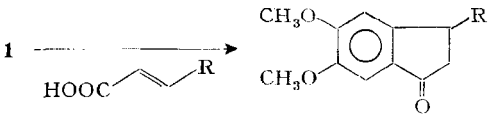
11

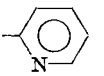
13 $R^1 = R^4 = H$, $R^2 = R^3 = OCH_3$

14 $R^2 = R^3 = H$, $R^1 = R^4 = OCH_3$

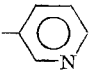
15 $R^1 = R^3 = R^4 = H$, $R^2 = OCH_3$

The 3-pyridylindanones **16**, **17** and **18** were prepared by the same procedure from the corresponding pyridylacrylic acids **19** [7], **20** and **21**, respectively.

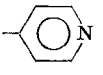


19 R = 

16 = R – 

20 R = 

17 R = 

21 R = 

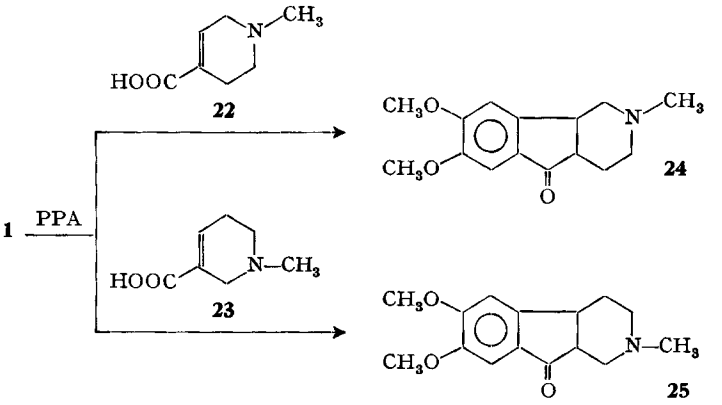
18 R = 

The two tetrahydropyridine-carboxylic acids **22**[1]) and **23**[2]), in the form of their hydrochlorides, and veratrole in PPA afforded, respectively, the indano[1,2-*c*]piperidin-5-one **24** and the indano[2,1-*c*]piperidin-9-one **25**. A few attempts were made to prepare the indanones **24** and **25** from the ethyl ester of **22** and the methyl ester hydrochloride of **23**, respectively, but these were unsuccessful.

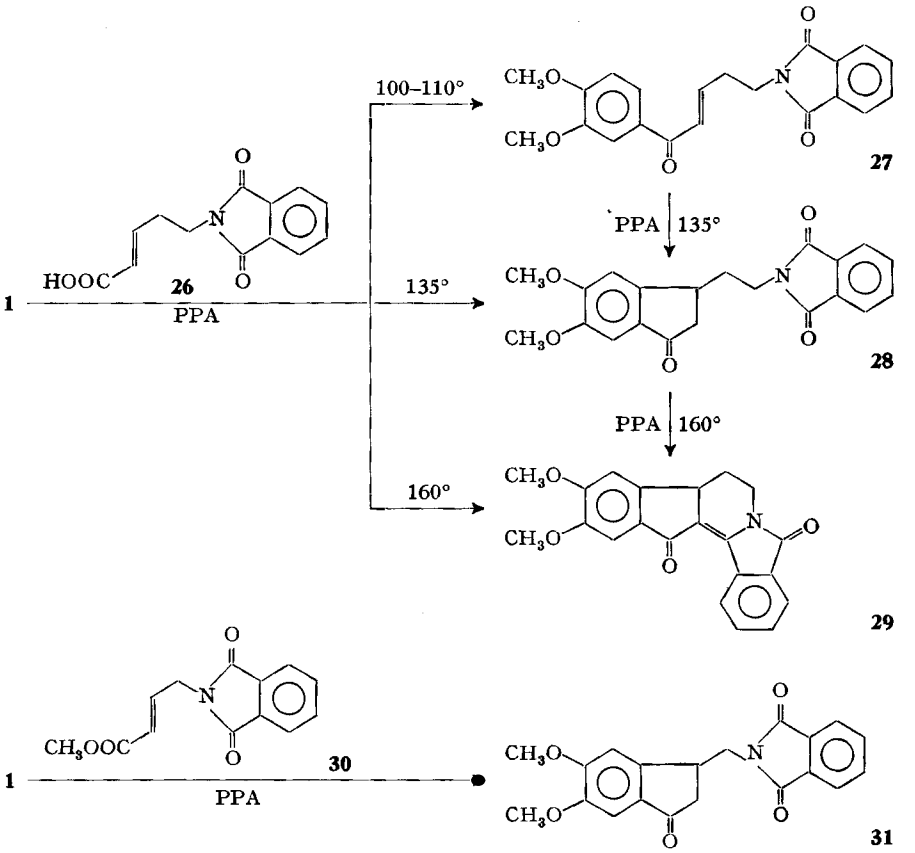
When 5-phthalimido-2-pentenoic acid (**26**) [9] was heated with veratrole and PPA between 100 and 110° for 30 minutes, the intermediate α,β-unsaturated ketone **27** was isolated as the main product. When the reaction mixture was heated at 135° for 15 minutes the phthalimidoethyl-indanone **28** was obtained in good yield. Further

[1]) For preparation of the ethyl ester of **22** see [8]; the hydrochloride of the acid **22** (dec. 245°) was obtained by hydrolysis of that ester.

[2]) The hydrochloride of the carboxylic acid **23** was produced by hydrolysis of its methyl ester hydrochloride (*Fluka*).



cyclisation occurred when the reaction mixture was heated at 160° for 20 minutes, a yellow product containing five fused rings (**29**) being isolated. Compound **29** could also be obtained either from **27** or **28** by heating at 160° in PPA.



Finally methyl 4-phthalimidocrotonate (**30**) [10] was cyclised with veratrole to yield phthalimidomethyl-indanone **31**.

Experimental Part

General. NMR. spectra were taken at 60 MHz with tetramethylsilane as an internal standard, using a *Varian* T-60 high-resolution NMR. spectrometer. In the case of salts, a sample of the free base was prepared and used in $CDCl_3$. Abbreviations: *s* = singlet, *d* = doublet. – Analytical results obtained for the indicated elements were within ± 0.4% of the theoretical values.

Spiro[5,6-dimethoxyindan-1-one)-3,4'-(1'-methylpiperidine)] hydrochloride (**3**). In a 1 l wide-necked conical flask are mixed together veratrole (20.7 g, 0.15 mol) and ethyl (1-methyl-4-piperidylidene)-acetate (**2**) [4] (18.3 g, 0.10 mol). Then polyphosphoric acid (*Fluka*) (400 g) is added and the mixture is thoroughly stirred with a glass rod and finally heated in an oil bath at 135° for 45 min, with occasional stirring. The hot, reddish reaction mixture is poured slowly into 3 l of stirred water; the solution is then cooled with ice and extracted with chloroform to remove the excess of veratrole.

The acidic solution is made alkaline (pH 12–13) with a 30% sodium hydroxide solution; ice is added again to keep the temp. below 30°, and the indanone is extracted with portions of chloroform (3 × 300 ml). Anhydrous sodium sulfate, ether (200 ml) and charcoal (20 g) are added to the combined chloroform extracts; the mixture is boiled under reflux for 10 min and then filtered and evaporated to dryness. – The resulting oil is dissolved in abs. ethanol and acidified by addition of a 5N ethanolic hydrogen chloride solution (20 ml). Ether is added until the solution becomes slightly turbid, and the hydrochloride is allowed to crystallise. The product is recrystallised by dissolving it in a minimum of water, adding abs. ethanol and then ether. Yield 20.5 g of **3** (66%), m.p. 240–242° (dec.). – NMR. ($CDCl_3$), δ (ppm): 2.35 (*s*, 3 H, NCH_3); 2.55 (*s*, 2 H, CH_2CO); 3,9 (*s*, 3 H, OCH_3); 3.95 (*s*, 3 H, OCH_3); 7.0 (*s*, 1 H, arom); 7.15 (*s*, 1 H, arom). – $C_{16}H_{22}ClNO_3$: C, H, N.

The following products were prepared, using the same general procedure:

3-[(3,4-Dimethoxybenzoyl)-methylene]-quinuclidine (**5**) *hydrochloride.* Veratrole (20.7 g, 0.15 mol), ethyl 3-quinuclidylideneacetate (**4**) [5] (19.5 g, 0.10 mol), polyphosphoric acid (400 g). Heating for 40 min at 115°, yield 19.1 g of **5** (59%), m.p. 259–262° (dec.). – NMR. ($CDCl_3$), δ (ppm): 4.15 (*d*, J = 3 Hz, 2 H, N–CH_2–C=); 6.9 (*d*, J = 3 Hz, 1 H, olefinic); 7.6 (*s*, 1 H, arom). – $C_{17}H_{22}ClNO_3$: C, H, N.

Spiro[5,6-dimethoxyindan-1-one)-3,3'-quinuclidine] (**6**) *hydrochloride.* – *a) From ethyl 3-quinuclidylideneacetate* (**4**). Veratrole (20.7 g, 0.15 mol), ethyl 3-quinuclidylideneacetate (**4**) [5] (19.5 g, 0.10 mol), polyphosphoric acid (400 g). Heating for 2 h at 145°, yield 10 g of **6** (31%), m.p. 228–240° (dec.). – NMR. ($CDCl_3$), δ (ppm): 2.5 (*d*, J = 18 Hz) and 3.2 (*d*, J = 18 Hz), both CH_2CO. – $C_{17}H_{22}ClNO_3$: C, H, N.

b) From 3-[(3,4-dimethoxybenzoyl)-methylene]-quinuclidine (**5**) *hydrochloride.* **5** hydrochloride (32.4 g, 0.10 mol), polyphosphoric acid (350 g). Heating for 2 h at 145° gives 19.5 g of **6** (60.5%), m.p. 228–240° (dec.).

Spiro[(4,7-dimethoxyindan-1-one)-3,4'-(1'-methylpiperidine)] (**8**). Hydroquinone dimethyl ether (20.7 g, 0.15 mol), ethyl (1-methyl-4-piperidylidene)-acetate (**2**) [4] (18.3 g, 0.10 mol), polyphosphoric acid (400 g). Heating for 2 h at 130°. The brownish hydrochloride is converted to the free base by 1N sodium hydroxide. After extraction with chloroform, drying and evaporation, the product is recrystallised from chloroform/ether (4,4 g, 16%), m.p. 156–158°. – NMR. ($CDCl_3$), δ ppm: 2.6 (*s*, 2 H, CH_2CO); 6.8 (*d*, J = 10 Hz, 1 H, arom); 7.1 (*d*, J = 10 Hz, 1 H, arom). – $C_{16}H_{21}NO_3$: C, H, N.

3-[(2,5-Dimethoxybenzoyl)-methylene]-quinuclidine (**9**) *hydrochloride.* Hydroquinone dimethyl ether (20.7 g, 0.15 mol), ethyl 3-quinuclidine-acetate (**4**) [5] (19.5 g, 0.10 mol), polyphosphoric acid (400 g). Heating for 4 h at 120°, yield 20.5 g (63%) of **9**, m.p. 193–196°. – NMR. ($CDCl_3$), δ (ppm): 4.05 (*d*, J = 3 Hz, 2 H, N–CH_2–$\overset{|}{C}$=); 7.0 (*s*, 1 H, arom). – $C_{17}H_{22}ClNO_3$: C, H, N.

Spiro[(5,6-dimethoxy-2-phenyl-indan-1-one)-3,4'-(1'-methylpiperidine)] (**13**). Veratrole (20.7 g, 0.15 mol), α-phenyl-α-(1-methyl-4-hydroxy-4-piperidyl)-acetic acid (**11**) [6] (24.9 g, 0.10 mol), polyphosphoric acid (450 g). Heating for 50 min at 130°. The free base is recrystallised from chloroform/ether (31.5 g, 89.5%), m.p. 189–191°. – $C_{22}H_{25}NO_3$: C, H, N.

Spiro[(4,7-dimethoxy-2-phenyl-indan-1-one)-3,4'-(1'-methylpiperidine)] (**14**). Hydroquinone dimethyl ether (20.7 g, 0.15 mol), α-phenyl-α-(1-methyl-4-hydroxy-4-piperidyl)-acetic acid (**11**) [6]

(24.9 g, 0.10 mol), polyphosphoric acid (450 g). Heating for 45 min at 140°. The free base is recrystallised twice from chloroform/ether (24.5 g, 69.5%), m.p. 152–153°. – NMR. ($CDCl_3$), δ (ppm): 3.8 (*s*, 1 H, CHCO). – $C_{22}H_{25}NO_3$: C, H, N.

Spiro[(5-*methoxy-2-phenyl-indan-1-one*)-*3,4'-*(*1'-methylpiperidine*)] (**15**) *hydrochloride.* Anisole (16.2 g, 0.15 mol), α-phenyl-α-(1-methyl-4-hydroxy-4-piperidyl)-acetic acid (**11**) [6] (24.9 g, 0.10 mol), polyphosphoric acid (400 g). Heating for 45 min at 140° gives 10.8 g (30%) of **15**, m.p. 253–255° (dec.). – NMR. ($CDCl_3$), δ (ppm): 3.8 (*s*, 1 H, CHCO); 7.8 (*d*, J = 8 Hz, 1 H, arom). – $C_{21}H_{24}ClNO_2$: C, H, N.

5,6-Dimethoxy-3-(*2-pyridyl*)*-indan-1-one* (**16**) *hydrochloride.* β-(2-Pyridyl)-acrylic acid (**19**) [7] (14.9 g, 0.10 mol), veratrole (20.7 g, 0.15 mol), polyphosphoric acid (350 g). Heating for 45 min at 120°, yield 21.0 g (69%) of **16**, m.p. 190–205° (dec.). – NMR. ($CDCl_3$), δ (ppm): 3.2 and 2.8 (two double *d*, J_{AB} = 18 Hz, J_{AX} = 7 Hz, J_{BX} = 4 Hz, $-CH_2CO$); 4.7 (double *d*, J_{AX} = 7 Hz, J_{BX} = 4 Hz, 1 H, benzylic). – $C_{16}H_{16}ClNO_3$: C, H, N.

5,6-Dimethoxy-3-(*3-pyridyl*)*-indan-1-one* (**17**). β-(3-Pyridyl)-acrylic acid (**20**) (*Aldrich*) (14.9 g, 0.10 mol), veratrole (20.7 g, 0.15 mol), polyphosphoric acid (350 g). Heating for 40 min at 130°. The free base is recrystallised from chloroform/ether (19.7 g, 73%), m.p. 137–139°. – $C_{16}H_{15}NO_3$: C, H, N.

5,6-Dimethoxy-3-(*4-pyridyl*)*-indan-1-one* (**18**) *hydrochloride.* β-(4-Pyridyl)-acrylic acid (**21**) (*Fluka*) (14.9 g, 0.10 mol), veratrole (20.7 g, 0.15 mol), polyphosphoric acid (350 g). Heating for 45 min at 130° gives 18.3 g (60%) of **18**, m.p. 190–208° (dec.). – $C_{16}H_{16}ClNO_3$: C, H, N.

7,8-Dimethoxy-2-methyl-1,2,3,4,4a,9b-hexahydro-indeno[*1,2-*c]*pyridin-5-one* (**24**). Veratrole (41.4 g, 0.30 mol) and polyphosphoric acid (600 g) are mixed and heated together at 135°; then 1-methyl-1,2,5,6-tetrahydro-pyridine-4-carboxylic acid (**22**) hydrochloride[1]) (17.7 g, 0.10 mol) is added with mechanical stirring. The mixture is heated for a further 20 min. The free base is recrystallised from chloroform/ether (10.8 g, 41%), m.p. 141–142°. – $C_{15}H_{19}NO_3$: C, H, N.

6,7-Dimethoxy-2-methyl-1,2,3,4,4a,9a-hexahydro-indeno[*2,1-*c]*pyridin-9-one* (**25**). Veratrole (41.4 g, 0.30 mol) and polyphosphoric acid (600 g) are mixed and heated together at 135°; then 1-methyl-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (**23**) hydrochloride[2]) (17.7 g, 0.10 mol) is added with mechanical stirring. The mixture is heated for a further 20 min. The free base is recrystallised from chloroform/ether (9.9 g, 38.2%), m.p. 154–155°. – $C_{15}H_{19}NO_3$: C, H, N.

1-(*3,4-Dimethoxyphenyl*)*-5-phthalimido-2-penten-1-one* (**27**). Veratrole (15.2 g, 0.11 mol), 5-phthalimido-2-pentenoic acid (**26**) [9] (24.5 g, 0.10 mol), polyphosphoric acid (400 g). Heating for 30 min at 100–110°. The reaction mixture is poured into water, but the resulting acidic solution is not made alkaline. The residue from the chloroform extract after evaporation is recrystallised from chloroform/petrol-ether to give 18.5 g (50%) of pentenone **27**, m.p. 137–139°. – $C_{21}H_{19}NO_5$: C, H, N.

N-[(*5,6-Dimethoxy-1-oxo-indan-3-yl*)*-ethylene*]*-phthalimide* (**28**). Veratrole (16.6 g, 0.12 mol), 5-phthalimido-2-pentenoic acid (**26**) [9] (24.5 g, 0.10 mol), polyphosphoric acid (400 g). Heating for 20 min at 135°. The reaction mixture is poured into water, but the resulting acidic solution is not made alkaline. The residue from the chloroform extract after evaporation is recrystallised from chloroform/ether to yield 30 g (82%) of indanone **28**, m.p. 204–205°.

This compound can also be prepared from **27** by treatment with polyphosphoric acid at 135° for 20 min, followed by a similar working-up (yield 80%). – $C_{21}H_{15}NO_5$: C, H, N.

*10,11-Dimethoxy-7,8,8a,13-tetrahydro-5*H*-indeno*[*2',1':3,4*]*pyrido*[*2,1-*a]*isoindole-5,13-dione* (**29**). Veratrole (20.7 g, 0.15 mol), 5-phthalimido-2-pentenoic acid (**26**) [9] (24.5 g, 0.10 mol), phosphoric acid (450 g). Heating for 30 min at 160°. The reaction mixture is poured into water, but the resulting acidic solution is not made alkaline. The residue from the chloroform extract after evaporation is recrystallised from chloroform/ether to yield 14 g (40%) of bright yellow needles, m.p. 275°.

This compound can also be obtained from **27** or from **28** by treatment with polyphosphoric acid. Yields are 40% and 51% respectively. – $C_{21}H_{17}NO_4$: C, H, N.

N-[(*5,6-dimethoxy-1-oxo-indan-3-yl*)*-methylene*]*-phthalimide* (**31**). Veratrole (20.7 g, 0.15 mol), methyl 4-phthalimidocrotonate (**30**) [10] (24.5 g, 0.10 mol), polyphosphoric acid (450 g). Heating

for 30 min at 135°. The reaction mixture is poured into water, but the resulting acidic suspension is not made alkaline. The residue from the chloroform extract after evaporation is recrystallised from chloroform/ether to give 10.5 g (29%) of **31**, m.p. 227–228°. – $C_{20}H_{17}NO_5$: C, H, N.

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135. Intramolekulare *Diels-Alder*-Additionen von 1,2-Dihydropyridinen

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(15. III. 74)

Summary. Reduction of the pyridinium salts **1b-f** in methanolic sodium hydroxide solution with sodium borohydride gave the dimeric dihydropyridine derivatives **3b-f**. Heating these dimers in hydrocarbon solvents at 110–207° resulted in the formation of the tricyclic amines **4c–f**, which were shown to bc products of an intramolecular *Diels-Alder* addition within the intermediate dihydropyridines **2c–f**. The structures of **4c–f** were deduced from spectroscopic, mainly NMR. data.

Über die Addition reaktiver Dienophile an 1,2-Dihydropyridine in einer *Diels-Alder*-Addition ist bereits mehrfach berichtet worden (vgl. die in [2] zitierte Literatur). Im Rahmen unserer Arbeiten über intramolekulare Diensynthesen [3] erschien es daher von Interesse, die Möglichkeit intramolekularer *Diels-Alder*-Additionen von 1,2-Dihydropyridinen zu untersuchen.

Bei der Reduktion von 1-Methyl-4-cyanopyridiniumjodid (**1a**) mit Natriumborhydrid in methanolischer Natronlauge erhielten *Liberatore et al.* [4] *via* das intermediäre, nicht isolierbare Dihydropyridin **2a** die dimere Verbindung **3a** (R=CH_3). Da es möglich schien, Verbindungen des Typus **3** durch Thermolyse wiederum in die reaktiven Dihydropyridine **2** zurückzuführen, haben wir die Dimeren **3b–f** synthetisiert. Die bei deren Thermolyse entstehenden N-Alkenyl-dihydropyridine **2b–f** könnten nach Schema 1 eine intramolekulare Diensynthese eingehen.

Die Pyridiniumsalze **1b–e** wurden durch Umsetzung von 4-Cyanopyridin mit Allylbromid, But-3-enylbromid, 2-Methylen-but-3-enylbromid (vgl. [3c]) bzw. Pent-4-enylbromid in siedendem Acetonitril in 50–70% Ausbeute erhalten. Bei der Umsetzung eines 2:3- (oder 3:2-) Gemisches von *cis*- und *trans*-3-Methyl-penta-2,4-