The Synthesis of Quinolines from *N*-Alkylformanilides and Activated Acetic Acids[1]

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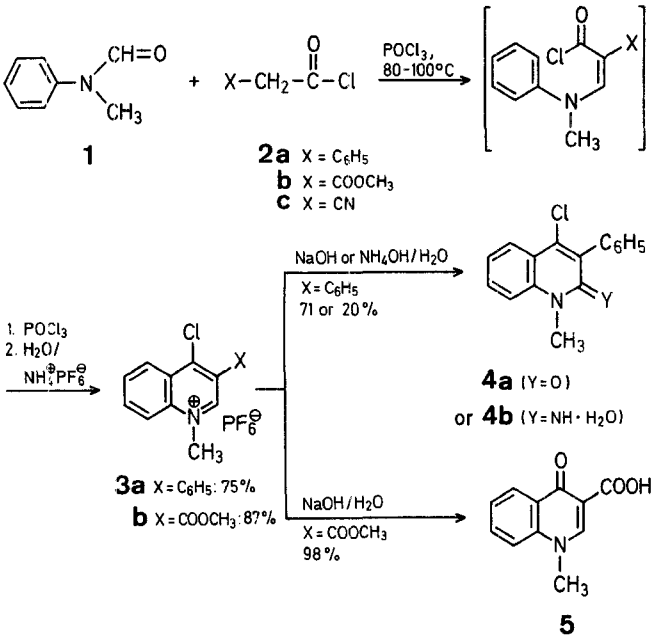
The action of phosphoryl chloride and *N*-methylformanilide on activated acetic acids (X—CH_2—COOH) or acetyl chlorides (X—CH_2—CO—Cl), where X = aryl, cyano, or methoxycarbonyl, yields *N*-methylquinolinium salts or quinolones in good yields.

Formylation of reactive aromatic compounds is routinely conducted utilising dimethylformamide and phosphoryl chloride, the Vilsmeier-Haack reaction. Principally due to the labours of Arnold and his co-workers a wide variety of functions have also been efficiently formylated[2] including acetic acid derivatives. These systems yield malonaldehydes, 3-dimethylaminoacroleins, and trimethinium salts[2].

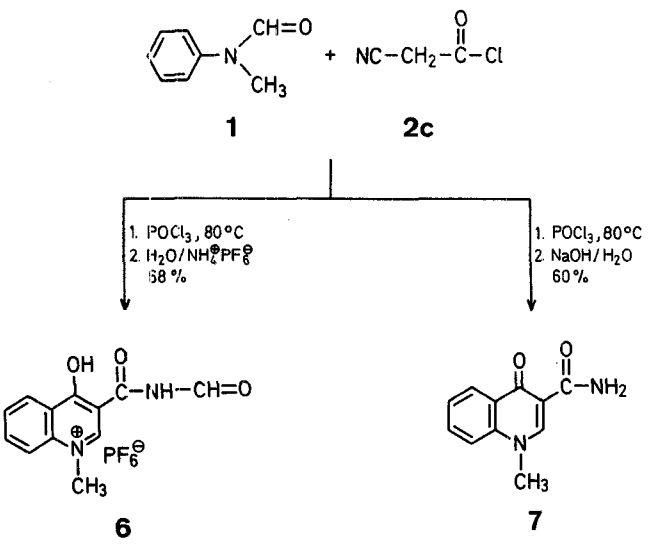
Using *N*-methylformanilide (**1**) as the acylating agent it is now found that a variety of activated acetic acids, acid chlorides, or anhydrides are readily transformed into quinolinium salts and their derivatives in good yield (Scheme **A**)[3].



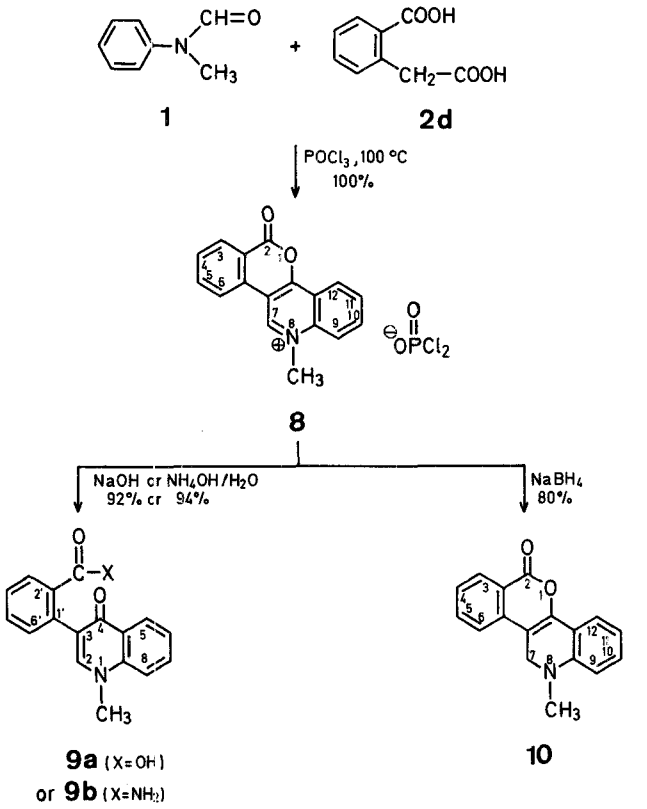
Scheme **A**

In this way, reaction of **1** with phenylacetyl chloride (**2a**) gave the salt **3a** in 75% yield, while reaction of methyl malonyl chloride (**2b**) gave the salt **3b** (87%) (Scheme **A**). Cyanoacetyl chloride (**2c**) and **1** gave the salt **6** (68%) in which a second formylation at the cyano group occurred[3] (Scheme **B**), while from homophthalic acid (**2d**) or its anhydride and **1** the salt **8** was obtained in 10 minutes at 100° C in 94% yield (Scheme **C**).

If the reactions are worked up by alkali instead of by ammonium hexafluorophosphate addition, quinolones are obtained. Thus, from **3a** using aqueous alkali the quinolone **4a** was obtained (71%) while with ammonium hydroxide, the corresponding imine **4b** was formed (20%), both products resulting, surprisingly, by attack at the α-position rather than hydrolysis of the halogen (Scheme **A**). The salt from the cyanoacetyl chloride reaction with alkaline work-up gave the



Scheme **B**



Scheme **C**

4-quinolonecarboxamide **7** (60%) (Scheme **B**) while that from methyl malonyl chloride gave the corresponding acid **5** (98%) (Scheme **A**).

The salt **8** showed kinetic preference for attack at the quinoline α-position giving, for example, with sodium borohydride the fluorescent orange product **10** (80%). However, thermodynamic preference is shown in cleavage of the ester linkage, hot water yielding the acid **9a** (92%) while ammonium hydroxide gave the amide **9b** (94%) (Scheme **C**).

4-Chloro-1-methyl-3-phenylquinolinium Hexafluorophosphate (3a): *N*-Methylformanilide (**1**; 3.00 g, 0.22 mmol) in phosphoryl chloride (5 ml) is heated at 80° C for 3 min, then phenylacetyl chloride (**2a**;

1.55 g, 0.10 mmol) is added in phosphoryl chloride (1 ml), and the solution heated for 2 h at 80° C. The solution is poured into ice/water (100 ml), extracted with ether (3 × 50 ml), and the aqueous phase treated with ammonium hexafluorophosphate (1.40 g, 8.6 mmol). After 5 min stirring, the off-white solid **3a** is washed with water, ether, and air dried; yield: 2.96 g (75%). An analytical sample is obtained by recrystallisation from acetic acid as cream plates; m.p. 201–203° C.

$C_{16}H_{13}ClF_6NP$	calc.	C 48.08	H 3.28	N 3.50
(399.7)	found	48.28	3.30	3.63

^{1}H-N.M.R. (CF_3COOD): $\delta = 4.77$ (s, 3 H, CH_3); 7.63 (s, 5 H, C_6H_5); 8.0–8.6 (m, 5,6,7-H's); 8.87 (br.d, $J = 9$ Hz, 8-H); 9.12 ppm (2, 1 H, 2-H).

I.R. (Nujol): $\nu = 840\ cm^{-1}$ (PF_6).

4-Chloro-3-methoxycarbonyl-1-methylquinolinium Hexafluorophosphate (3b):

Methyl malonyl chloride (**2b**; 1.37 g, 10 mmol) is added to a premixed solution of **1** (3.00 g, 22 mmol) and phosphoryl chloride (6 ml) and heated for 1 h at 80° C. The pale orange solution is poured into ice/water (100 ml) to give a clear solution. Addition of ammonium hexafluorophosphate (1.5 g, 9.2 mmol) gives, after 0.5 h stirring, the salt **3b** as a yellow solid; yield: 3.30 g (87%); which is recrystallised as white needles from acetonitrile/ethylacetate; m.p. 190–192° C.

$C_{12}H_{11}ClF_6NO_2P$	calc.	C 37.77	H 2.91	N 3.67
(381.6)	found	37.76	2.82	3.71

^{1}H-N.M.R. (CF_3COOD): $\delta = 4.25$ (s, 3 H, OCH_3); 4.81 (s, 3 H, NCH_3); 8.2–8.7 (m, 5,6,7-H's); 9.01 (d, $J = 9$ Hz, 8-H); 9.78 ppm (s, 1 H, 2-H).

I.R. (Nujol): $\nu = 1725$ (CO); $840\ cm^{-1}$ (PF_6).

4-Chloro-1-methyl-2-oxo-3-phenyl-1,2-dihydroquinoline (4a):

When the above reaction mixture from **1** and **2a** is poured into ice/water (100 ml), extracted with ether (3 × 50 ml), the aqueous phase basified with aqueous sodium hydroxide solution, and stirred for 1 h, a solid precipitates. This is purified by chromatography on silica with chloroform as eluant to give **4a** [yield: 1.67 g, (71%)] which is recrystallised from ethyl acetate and petroleum ether as colourless needles; m.p. 126–127° C (Lit.[3], m.p. 120–121° C).

$C_{16}H_{12}ClNO$	calc.	C 71.25	H 4.48	N 5.19
(269.7)	found	71.42	8.80	5.28

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.72$ (s, 3 H, CH_3); 7.2–7.5 (m, 4 H_{arom}); 7.5–7.8 (m, 3 H_{arom}); 8.52 ppm (dd, 2 H_{arom}).

I.R. (Nujol): $\nu = 1620\ cm^{-1}$.

1-Methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (5):

The above reaction mixture of **1** and **2b**, after pouring into ice/water (100 ml), is made alkaline with aqueous sodium hydroxide solution. After 2 h stirring the clear solution is acidified, the precipitate filtered, washed with water, and dried over phosphorus pentoxide under vacuum to give **5** [yield: 2.00 g, (98%)] which is recrystallised from acetic acid as cream needles; m.p. 295–296.5° C (Lit.[5], m.p. 296–297° C).

$C_{11}H_9NO_3$	calc.	C 65.02	H 4.46	N 6.89
(203.2)	found	64.76	4.32	6.77

^{1}H-N.M.R. (CF_3COOD): $\delta = 4.61$ (s, 3 H, CH_3); 7.9–8.7 (m, 5,6,7-H's); 8.90 (d, $J = 9$ Hz, 8-H); 9.53 ppm (s, 1 H, 2-H).

I.R. (Nujol): $\nu = 3500$-2500 (br., OH); 1700-1600 cm^{-1} (br., CO).

3-Formylaminocarbonyl-4-hydroxy-1-methylquinolinium Hexafluorophosphate (4):

Pure, dry cyanoacetic acid (0.85 g, 8.2 mmol) and phosphorus pentachloride (2.25 g, 10.8 mmol) are mixed together for 3 min and the solution added to **1** (3.00 g, 22 mmol) in phosphoryl chloride (5 ml) prepared as above. After 0.75 h at 80° C, the mixture is worked up as above giving the salt **6** as a yellow solid; yield: 2.19 g (68%). The salt is recrystallised from acetonitrile/ethyl acetate as pale yellow needles; m.p. 280–283° C.

$C_{12}H_{11}F_6N_2O_3P$	calc.	C 38.31	H 2.95	N 7.45
(376.2)	found	38.57	2.69	7.60

^{1}H-N.M.R. (CF_3COOD): $\delta = 4.55$ (s, 3 H, CH_3); 8.0–8.6 (m, 5,6,7-H's); 8.87 (br. d, $J = 9$ Hz, 8-H); 9.51, 9.54 ppm (2 s, 2 H, 2-H and CHO).

I.R. (Nujol) = $\nu = 3500$-2400 (br., OH, NH); 1740-1600 (br., CO); 835 cm^{-1} (PF_6).

1-Methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide (7):

From the above reaction mixture of **1** and **2c**, after pouring into ice/water (100 ml) and basifying with aqueous alkali with ice cooling, a yellow crystalline mass precipitates. After 10 min the material is filtered, water washed, and dried over phosphorus pentoxide under vacuum to give **5**; yield: 1.2 g (60%). Recrystallisation from ethanol gives yellow needles; m.p. 280–283° C (Lit.[4], m.p. 276–278° C).

$C_{11}H_{10}N_2O_2$	calc.	C 65.34	H 4.99	N 13.85
(202.2)	found	65.06	4.80	13.53

^{1}H-N.M.R. (DMSO-d_6): $\delta = 4.11$ (s, 3 H, CH_3); 7.5–8.0 (m, 6,7,8-H's); 8.42 (d, $J = 9$ Hz, 5-H); 9.01 (s, 1 H, 2-H); 9.34 (d, $J = 10$ Hz, 1 H, NH); 12.48 ppm (bd, 1 H, NH).

I.R. (Nujol): $\nu = 3300$, 3180 (NH_2); 1645, 1600 cm^{-1} (CO).

12-Methyl-6-oxo-6*H*-[2]benzopyrano[4,3-*c*]quinolinium Phosphorodichloridate (8):

Homophthalic acid (**2d**; 1.80 g, 10 mmol), **1** (1.50 g, 11 mmol), and phosphoryl chloride (4 ml) are heated at 100° C for 10 min and then poured into ice/water (100 ml). The white solid is filtered, air dried and recrystallised by dissolving in a little acetic acid and adding the filtered solution to ethyl acetate giving **8** as white needles; yield: 3.71 g (95%); m.p. 291–293° C. Curiously, this material is now cold water soluble but has the same I.R. spectrum as the crude product. This change occurs on air drying the crude material.

$C_{17}H_{12}Cl_2NO_4P$	calc.	C 51.54	H 3.05	N 3.54
(396.2)	found	51.27	2.90	3.57

^{1}H-N.M.R. (CF_3COOD): $\delta = 4.88$ (s, 3 H, CH_3); 7.9–8.8 (m, 3,4,5,6,10,11,12-H's); 9.00 (d, $J = 9$ Hz, 9-H); 10.13 ppm (s, 1 H, 9-H).

I.R. (Nujol): $\nu = 1750\ cm^{-1}$ (CO).

3-(2-Carboxyphenyl)-1-methyl-4-oxo-1,4-dihydroquinoline (9a):

The salt **8** (1.00 g, 2.6 mmol) in water (50 ml) is heated under reflux for 5 min (during which white needles precipitate), then cooled, filtered, and the residue dried to give pure **9a**; yield: 0.65 g (92%); m.p. 185–187° C.

$C_{17}H_{13}NO_3 \cdot {}^1/_3H_2O$	calc.	C 71.57	H 4.83	N 4.91
(285.3)	found	71.40	4.80	4.96

^{1}H-N.M.R. ($CDCl_3$ and DMSO-d_6): $\delta = 3.88$ (s, 3 H, CH_3); 7.25–8.0 (m, 6,7,8,3',4',5',6'H's); 7.80 (s, 1 H, 2-H); 8.49 ppm (dd, $J = 9$ Hz, 2 Hz, 5-H).

I.R. (Nujol): $\nu = _{max}$: 3540, 3460, 3200-2200 (b, OH); 1680, 1615 cm^{-1} (b, CO).

3-(2-Aminocarbonylphenyl)-1-methyl-4-oxo-1,4-dihydroquinoline (9b):

The salt **8** (1.00 g, 2.6 mmol) in water (50 ml) is treated with aqueous ammonium hydroxide (10 ml, 25%). An exothermic reaction occurs and the clear solution becomes yellow. On boiling the colour disappears and white needles precipitate. Recrystallisation from water gives **9b** as white needles; yield: 0.67 g (94%); m.p. 141–142° C.

$C_{17}H_{14}N_2O_2 \cdot {}^2/_3H_2O$	calc.	C 70.33	H 5.32	N 10.07
(290.3)	found	70.32	5.17	9.82

^{1}H-N.M.R. (DMSO-d_6): $\delta = 3.85$ (s, 3 H, CH_3); 7.0 (b, 2 H, NH_2); 7.2–7.9 (m, 6,7,8,3', 4',5',6'-H's); 8.05 (s, 1 H, 2-H); 8.33 (d, $J = 9$ Hz, 5-H).

I.R. (Nujol): $\nu = 3280$, 3150 (NH_2); 1650, 1600 cm^{-1} (CO).

12-Methyl-6-oxo-11,12-dihydro-6*H*-[2]benzopyrano[4,3-*c*]quinoline (10):

The salt **8** (1.00 g, 2.6 mmol) in water (50 ml) and ethyl acetate (100 ml) is cooled in ice and treated with sodium borohydride (0.20 g, 5.3 mmol) little by little with stirring. The mixture immediately becomes fluorescent orange and, after 1 min, is separated, the organic phase is washed with water, dried with magnesium sulphate,

and evaporated to give **10** as an orange solid; yield: 0.53 g, (80%). Recrystallisation from methanol gives yellow needles; m.p. 154–155°C.

$C_{17}H_{13}NO_2$	calc.	C 77.57	H 4.94	N 5.32
(263.3)	found	77.25	4.90	5.37

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.80$ (s, 3H, CH_3); 4.37 (s, 2H, CH_2); 6.3–8.4 ppm (m, 8 H_{arom}).

I.R. (Nujol): $\nu = 1715$, 1700 (CO); 1640 cm^{-1} (C=C).

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[1] Part 14 in the series A Versatile New Synthesis of Quinolines and Related Fused Pyridines. Part 13: Meth-Cohn, O. *Tetrahedron Lett.* **1985**, *26*, 1901.
[2] For a thorough review see: Jutz, C. *Adv. Org. Chem.* **1976**, *9*, 225.
[3] Ahlbrecht, H., Vonderheid, C. *Chem. Ber.* **1975**, *108*, 2300.
[4] Kozello, A.I., Khmelevski, I.V., Gazena, A.Ya. *Khim.-Farm. Zh.* **1971**, *5*, 24; *Pharm. Chem. J. U.S.S.R. (Engl. Trans.)* **1971**, *5*, 21.
[5] Hughes, G.K., Neill, K.G. *Aust. J. Sci. Res. Ser. A.* **1949**, *2*, 429.

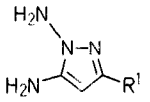
Errata and Addenda 1986

I. Ganboa, C. Palomo *Synthesis* **1986**, 52. The ^{1}H-NMR data for compounds **2d** and **2e** in the Table (p. 53) should be, respectively: 8.13 (d, 2 H_{arom}); 7.46 (d, 2 H_{arom}); 7.3 (s, 5 H_{arom}); 5.73 (m, 1 H, C–H); 5.26 (s, 2H, CH_2–$C_6H_4NO_2$); 4.9 (m, 1H, C–H); 3.7 (m, 2H, CH_2–CO–NH); 3.3 (m, 2H, S–CH_2); 2.13 (s, 3H, CH_3). 7.33 (s, 5 H_{arom}); 7.3 (s, 5 H_{arom}); 5.76 (m, 1 H, C–H); 5.2 (s, 2H, C_6H_5–CH_2); 4.9 (m, 1 H, C–H); 3.63 (s, 2 H, CH_2–CO–NH); 3.3 (m, 2H, S–CH_2); 2.13 (s, 3 H, CH_3).

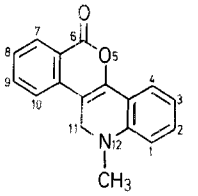
The ^{1}H-NMR data for compound **6** (p. 54) should be:
^{1}H-NMR ($CDCl_3$/TMS_{int}): δ = 8.03 (d, 2 H_{arom}); 7.43 (d, 2 H_{arom}); 5.65 (s, 1 H, CH); 5.23 (s, 2 H, CH_2); 4.5 (s, 1 H, NH); 1.53, 1.35 ppm (2 s, 6 H, 2 CH_3).

K. Tanaka, H. Yoda, K. Inoue, A. Kaji *Synthesis* **1986**, 66. The $[\alpha]_D^{25}$ value for compound **2e** in Table 1 (p. 67) should be:
$-28.2°$ (1.80).

D. R. Sliskovic, M. Siegel, Y. Lin *Synthesis* **1986**, 71. The structures for compounds **6a, b** (p. 73) should be:

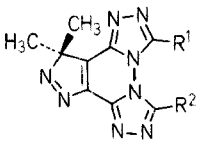


O. Meth-Cohn *Synthesis* **1986**, 76. The correct numbering for compounds **8** and **10** (p. 76) is as illustrated below for compound **10**:



10

B. Furlan, B. Stanovnik, M. Tišler *Synthesis* **1986**, 78. The double-bond arrangement of compounds **3, 6,** and **7** (pp. 78, 79) should be:

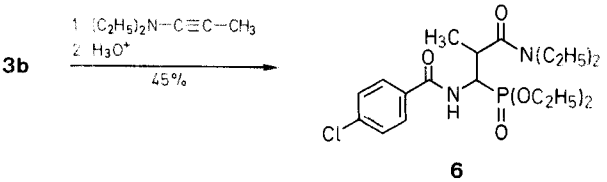


N. Petragnani, H. M. C. Ferraz, G. V. J. Silva *Synthesis* **1986**, 157. The authors wish to include the following pertinent references:
R. M. Adlington, A. G. M. Barret *Tetrahedron* **1981**, *37*, 3935.
R. M. Adlington, A. G. M. Barret *J. Chem. Soc. Perkin Trans. I* **1981**, 2848.
R. M. Adlington, A. G. M. Barret *J. Chem. Soc. Chem. Commun.* **1981**, 65.
R. M. Adlington, A. G. M. Barret *J. Chem. Soc. Chem. Commun.* **1979**, 1122.

A. J. Fatiadi *Synthesis* **1986**, 249. The heading for the first experimental procedure on p. 268 should be:
2,6-Diphenyl-4-(2,3,3-tricyanoallylidene)pyran (201)[354]:

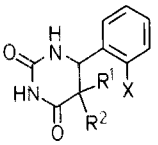
D. P. Matthews, J. P. Whitten, J. R. McCarthy *Synthesis* **1986**, 336. The headings for the first and last experimental procedures should be, respectively:
***N*^{1},*N*^{3}-Bis(2,2-dimethoxyethyl)oxaldiamidine Dihydrochloride (2):**
2-(2-Imidazolyl)-4-methoxy-4,5-dihydroimidazole (5):

T. Schrader, R. Kober, W. Steglich *Synthesis* **1986**, 372. The last equation in the formula scheme (p. 372) should be:

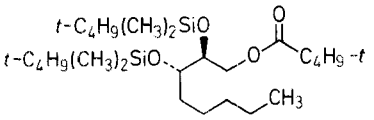


6

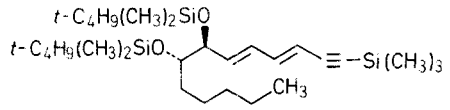
D. N. Dhar, K. S. K. Murthy *Synthesis* **1986**, 437. The heading for Table 2 (p. 440) should be:
4-Aryl-2(1*H*)-quinazolines **(13)** and 4-Aryl-1*H*-2,1,3-benzothiadiazine 2,2-Dioxides **(14)**
The names of compounds **13a** and **14a** in the experimental procedure on the same page should be corrected accordingly.
For compounds **60** and **61** (p. 445) R^3 = H, SO_2Cl.
The product in the lower, left reaction scheme on p. 446 should be:



K. C. Nicolaou, S. E. Webber *Synthesis* **1986**, 453. The structures of compounds **8** (p. 454) and **16** (p. 455) should be:



8

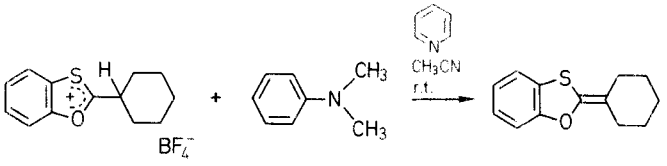


16

E. Dalcanale, M. Foà *Synthesis* **1986**, 492. In the reaction scheme, products **4** and **5** are obtained in 33 and 8%, respectively, a ratio of 80:20.

W. G. Dauben, J. M. Gerdes, G. C. Look *Synthesis* **1986**, 532. In the experimental procedure headings (p. 534), the names of compounds 3, 5, 7, and 9 should read:
(3,3-Ethylenedioxybutyl)triphenylphosphonium Bromide (3)
6-*t*-Butyldimethylsiloxy-3,7-dimethyl-1,6-octadiene (5)
5-[1,1-Bis(ethoxycarbonyl)ethyl]bicyclo[3.3.0]octan-2-one (7)
2,2-Ethylenedioxy-1,3,3-trimethylbicyclo[2.2.1]heptane (9).

S. Cadamuro, I. Degani, R. Fochi, A. Gatti, V. Regondi *Synthesis* **1986**, 544. Formula Scheme **B** should be:



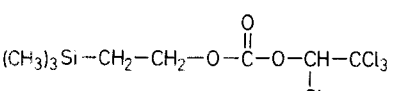
1c **2** **5**

H. M. R. Hoffmann, K. Giesel, R. Lies, Z. M. Ismail *Synthesis* **1986**, 548. The heading for the last experimental procedure (p. 551) should be:
Cycloadditions; 4-Oxatricyclo[7.2.1.0^{3,8}]dodeca-3,10-dien-2-one (11e):

Abstract 7330, *Synthesis* **1986**, 599. The structure of compound **7** should be: CH_2=C(R^6)R^7.

Abstract 7333, *Synthesis* **1986**, 600. Line 2 of the text should read: dimenthyl succinate **(1)** with lithium 2,2,6,6-tetramethylpiperidide reacts...

G. Barcelo, J. P. Senet, G. Sennyey, J. Bensoam, A. Loffet *Synthesis* **1986**, 627. The structure of compound **1k** (p. 630) should be:



D. Achet, D. Rocrelle, I. Murengezi, M. Delmas, A. Gaset *Synthesis* **1986**, 642. The last word of the title should be: **Sulfate**