Synthesis of Adamantane Derivatives; 48[1]. Synthesis of Some Novel 1,2-Fused Adamantane Azaheterocycles via 2-Oxoadamant-1-yl Isocyanate

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Although many examples of type **A** and **B** nitrogen heterocycles fused to the 1- and 2-positions of the adamantane nucleus have been reported[2], there are no reports describing synthesis of 1,2-fused adamantane azaheterocycles of type **C**, in which both C-1 and C-2 of adamantane are substituted with nitrogen atoms.

A **B** **C**

As a part of continuing efforts in our laboratory on the synthesis of adamantane-heterocycles[3], and in conjunction with our interest in their biological properties[4], we initiated a synthetic study on some nitrogen heterocycles fused to the 1- and 2-positions of the adamantane nucleus. In this paper we report the synthesis of 2-oxoadamant-1-yl isocyanate (**4**) and some of its reactions leading to novel, 1,2-fused adamantane azaheterocycles of the type **C**.

The readily accessible 2-oxoadamantane-1-carboxylic acid (**1**)[5] was converted to the corresponding acid azide **3** via the acid chloride **2**. Thermolysis of **3** in refluxing toluene afforded the isocyanate **4** as a colorless solid after sublimation in 75% overall yield from **1**.

Isocyanate **4** gave the corresponding ethylurethane **5** on treatment with ethanol but the corresponding *t*-butylurethane could not be obtained even on heating **4** in refluxing toluene/*t*-butanol (3:1 v/v) in the presence of potassium hydroxide or tin octylate as catalysts. The reaction of **4** with water in refluxing toluene gave urea derivative **6** in 59% yield.

Treatment of **4** with anhydrous ammonia in chloroform gave the very unstable ketourea **7** [$\nu_{C=O}$ = 1720 cm^{-1}]

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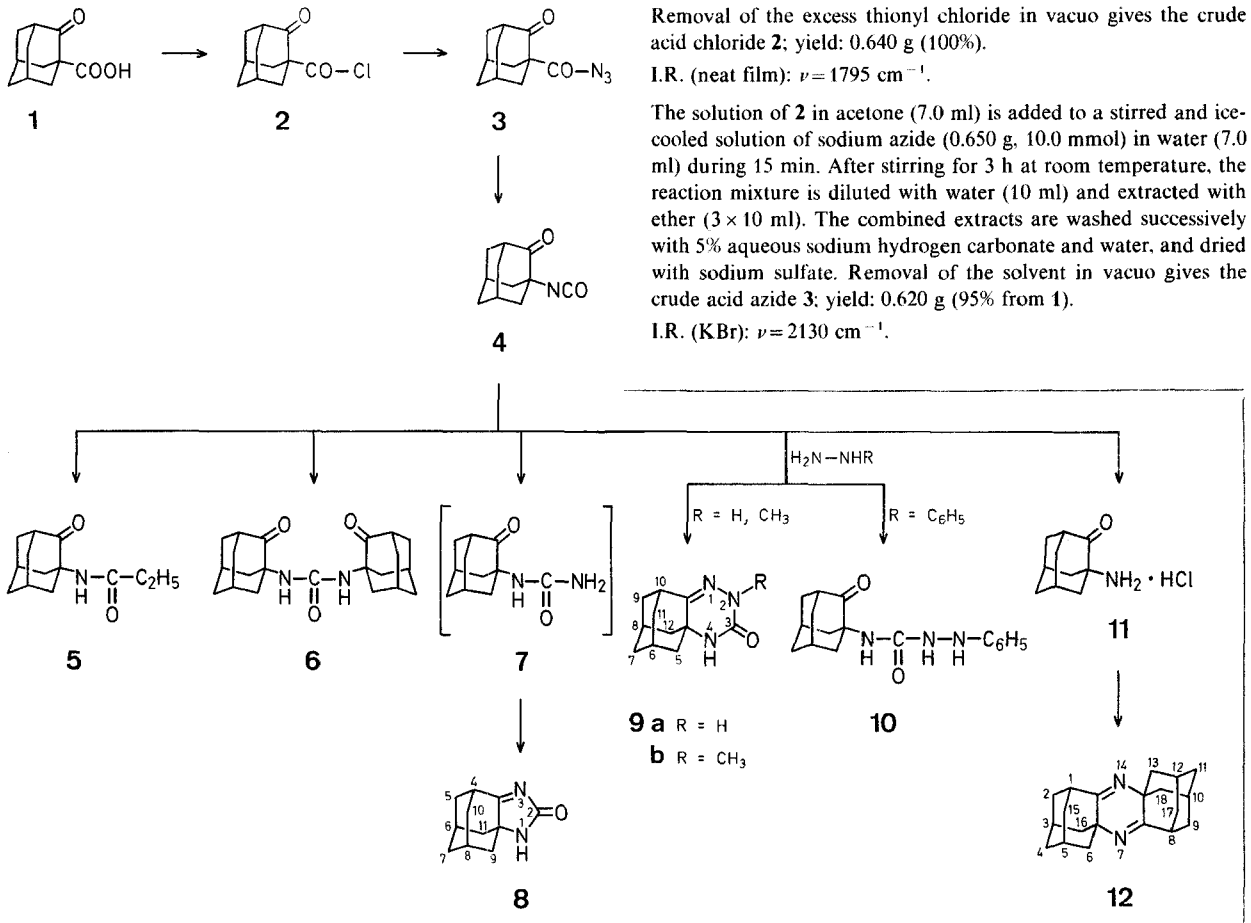
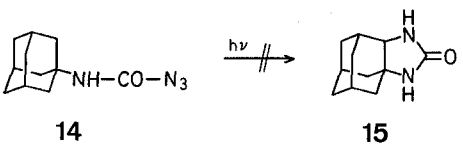


1 2 3 4 5 6 7 8 9a b 10 11 12 13

which cyclized spontaneously on heating to afford the imidazolin-2-one derivative **8** (71%). The reaction of **4** with hydrazine and methylhydrazine in ethanol directly afforded cyclized products, the triazin-3-one derivatives **9a** and **9b** in 72 and 80% yields, respectively, but the reaction with phenylhydrazine gave only the phenylsemicarbazide derivative **10**. Treatment of **4** with 10% aqueous hydrochloric acid afforded the aminoketone **11** as its hydrochloride in 95% yield. The free base of **11** afforded an intermolecular condensation product **12** on heating at 140–180 °C or in refluxing xylene in the presence of a catalytic amount of *p*-toluenesulfonic acid. The ^{13}C-N.M.R. spectrum of **12** revealed 7 lines (two singlets, two doublets, and three triplets), supporting the assigned structure **12** having a C_{2h} symmetry. The reduction of **12** with sodium cyanoborohydride gave the corresponding dihydro derivative **13** which had 10 lines in the ^{13}C-N.M.R. spectrum[6,7].

The relative ease with which **4** can be prepared by the route presented here[8] demonstrates the feasibility of extending this method to the synthesis of other 1,2-fused adamantane heterocycles. The facile formation of **8** and **9** is also of interest in view of nonformation of imidazolidin-2-one, **15** on photolysis of 1-adamantylaminocarbonyl azide (**14**)[9].



14 15

2-Oxoadamant-1-yl Isocyanate (4):
A mixture of 2-oxoadamantane-1-carboxylic acid[5] (**1**; 0.580 g, 3.00 mmol) and thionyl chloride (3.0 ml) is heated under reflux for 2 h. Removal of the excess thionyl chloride in vacuo gives the crude acid chloride **2**; yield: 0.640 g (100%).

I.R. (neat film): $\nu = 1795$ cm^{-1}.

The solution of **2** in acetone (7.0 ml) is added to a stirred and ice-cooled solution of sodium azide (0.650 g, 10.0 mmol) in water (7.0 ml) during 15 min. After stirring for 3 h at room temperature, the reaction mixture is diluted with water (10 ml) and extracted with ether (3 × 10 ml). The combined extracts are washed successively with 5% aqueous sodium hydrogen carbonate and water, and dried with sodium sulfate. Removal of the solvent in vacuo gives the crude acid azide **3**; yield: 0.620 g (95% from **1**).

I.R. (KBr): $\nu = 2130$ cm^{-1}.

To refluxing toluene (80 ml) is added the azide **3** in toluene (10 ml) during 0.5 h and the refluxing is continued for 5 h. Removal of the solvent by distillation gives the crude ketoisocyanate **4** which is purified by sublimation (120–140 °C/0.4 torr) to afford a colorless solid; yield: 428 mg (75% from **1**); m.p. 145–150 °C.

$C_{11}H_{13}NO_2$	calc.	C 69.09	H 6.85	N 7.32
(191.2)	found	69.26	7.03	6.98

I.R. (KBr): $\nu = 2940$; 2870; 2245; 2210; 1720 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.84$ (s, 1H); 2.4–1.5 ppm (m, 12H).

M.S. (70 eV): *m/e* (rel. intensity) = 191 (M^+, 52); 163 (40); 120 (100); 80 (43).

Ethyl *N*-(2-Oxoadamant-1-yl)-carbamate (5):
A mixture of **4** (50 mg, 0.26 mmol), ethanol (1.0 ml), and potassium hydroxide (2 mg) in toluene (3.0 ml) is heated under reflux for 4 h. Removal of the solvent in vacuo gives crude **5** which is purified by a Kugelrohr distillation (140 °C bath temperature/0.4 torr) to give an oil; yield: 52 mg (84%). See Table.

***N,N'*-Bis[2-oxoadamant-1-yl]urea (6):**
A mixture of **4** (100 mg, 0.52 mmol) in water (1.0 ml) and toluene (10 ml) is heated under reflux for 20 h. Removal of the solvent in vacuo gives a faintly yellowish solid which is recrystallized from aqueous methanol; yield: 55 mg (59%). See Table.

M.S. (70 eV): *m/e* (rel. intensity) = 356 (M^+, 13); 328 (13); 191 (26); 166 (30); 137 (59); 120 (44); 94 (100).

Table. Adamantane Derivatives **5**–**13** from 2-Oxoadamant-1-yl Isocyanate (**4**)

Product	Yield[a] [%]	m.p. [°C]	Molecular formula[b]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
5	84	oil[c]	$C_{13}H_{19}NO_3$ (237.3)	3400; 2990; 2970; 1725; 1700; 1500[d]	6.15 (s, 1H); 4.05 (q, J=7 Hz, 2H); 3.2–1.6 (m, 13H); 1.20 (t, J=7 Hz, 3H)
6	59	>300°	$C_{21}H_{28}N_2O_3$ (356.5)	3320; 2920; 2860; 1725; 1615; 1550	5.72 (s, 2H, NH); 3.3–1.5 (m, 26H)
8	71	237–239°	$C_{11}H_{14}N_2O$ (190.2)	3230; 2920; 2860; 1750; 1705; 1630	7.86 (s, 1H, NH); 3.22 (s, 1H); 2.5–1.6 (m, 12H)
9a	72	>300°	$C_{11}H_{15}N_3O$ (205.3)	3240; 3080; 2925; 2860; 1680	6.96 (s, 1H); 2.9–1.9 (m, 12H)[e]
9b	80	198–201°	$C_{12}H_{17}N_3O$ (219.3)	3200; 3080; 2920; 2860; 1665	7.00 (s, 1H); 3.50 (s, 3H); 3.08 (s, 1H); 2.8–1.9 (m, 12H)[e]
10	68	171–173.5°	$C_{17}H_{21}N_3O_2$ (299.4)	3340–3220; 2920; 2860; 1710; 1650; 745	7.9–6.7 (m, 5H); 7.25 (s, 1H, NH); 6.02 (s, 1H, NH); 5.78 (s, 1H, NH); 3.2–1.6 (m, 13H)
11	95	270–280° (dec.)	$C_{10}H_{16}ClNO$ (201.7)	3100–2600; 2930; 2860; 1720; 1505	8.55 (s, 3H); 2.7–1.8 (m, 13H)[f]
12	44	260–263°	$C_{20}H_{26}N_2$ (294.4)	2920; 2850; 1655; 1445	2.50 (s, 2H); 2.18 (s, 4H); 2.1–1.5 (m, 20H)
13	25	241–244.5°	$C_{20}H_{30}N_2$ (298.5)	3440; 2920; 2860; 1445	3.00 (s, 2H); 2.7–1.0 (m, 28H)

[a] Yield based on **4**.
[b] The microanalyses were in satisfactory agreement with the calculated values (C ±0.23, H ±0.22, N ±0.28).
[c] n_D^{20}: 1.5041.
[d] Neat film.
[e] CF_3COOH solution.
[f] $CDCl_3$/DMSO-d_6 solution.

Δ^3-Adamantano[2,1-*d*]imidazolin-2-one (8):
A mixture of **4** (96 mg, 0.50 mmol) and ammonia (13 mg, 0.75 mmol) in chloroform (1.2 ml) is stirred at room temperature for 4 h. Removal of the solvent and excess ammonia in vacuo gives **7** as a colorless solid; yield: 100 mg (96%).

I.R. (KBr): ν=1720, 1645 cm^{-1}.

Sublimation of **7** at 180–220°C/18 torr) affords crude **8** which is purified on an alumina (Wako, basic, grade II) column eluting with dichloromethane/methanol; yield: 68 mg (71%). See Table.

2,3,4,4a-Tetrahydroadamantano[1,2-*e*]1,2,4-triazin-3-one (9a):
A mixture of **4** (100 mg, 0.52 mmol) and hydrazine hydrate (30 mg, 0.62 mmol) in ethanol (10 ml) is stirred for 4 h at room temperature. Removal of the solvent in vacuo gives crude **9a** which is purified by recrystallization from methanol; yield: 77 mg (72%). See Table.

2-Methyl-2,3,4,4a-tetrahydroadamantano[1,2-*e*]1,2,4-triazin-3-one (9b):
A mixture of **4** (50 mg, 0.26 mmol) and methylhydrazine (12 mg, 0.26 mmol) in ethanol (10 ml) is treated as above for 12 h. Removal of the solvent gives the crude product which is purified by recrystallization from benzene; yield: 46 mg (80%). See Table.

4-(2-Oxoadamant-1-yl)-1-phenylsemicarbazide (10):
A mixture of **4** (50 mg, 0.26 mmol) and phenylhydrazine (30 mg, 0.28 mmol) in ethanol is treated as above for 10 h. Removal of the solvent gives the crude product which is recrystallized from benzene; yield: 53 mg (68%). See Table.

2-Oxoadamant-1-ylamine Hydrochloride (11):
A suspension of **4** (150 mg, 0.78 mmol) in 10% hydrochloric acid (5.0 ml) is stirred at room temperature for 20 h. A small amount of precipitated urea **6** is removed by filtration and the filtrate is evaporated in vacuo to give the crude aminoketone hydrochloride **11** which is purified by reprecipitation from methanol/ether; yield: 151 mg (95%). See Table.

6a,13a-Dihydrodiadamantano[2,1-*b*,2,1-*e*]pyrazine (12):
A solution of aminoketone hydrochloride prepared from **4** (290 mg, 1.50 mmol) and 10% hydrochloric acid (20 ml) is basified by addition of solid sodium hydrogen carbonate (2.4 g) and extracted with dichloromethane (3 × 10 ml). The combined extracts are dried with sodium sulfate and evaporated to give the free amine; yield: 195 mg (78% from **4**).

A solution of the free amine **11** (95 mg, 0.57 mmol) in xylene (10 ml) containing *p*-toluenesulfonic acid (5 mg) is heated under reflux for 30 h. Removal of the solvent in vacuo and purification on an alumina column (dichloromethane/methanol) affords the unreacted aminoketone (20 mg) and the dihydropyrazine **12** (38 mg, 57% for the reacted **11**). Heating the free aminoketone **11** in a sealed tube at 180°C for 4 h also gives **12** in 29% yield. See Table.

^{13}C-N.M.R. ($CDCl_3$): δ=175.2 (s, C-7a, C-14a); 56.3 (s, C-6a, C-13a); 46.8 (t, C-6, C-13, C-16, C-18); 43.3 (d, C-1, C-8); 38.7 (t, C-2, C-9, C-15, C-17); 35.5 (t, C-4, C-11); 29.2 ppm (d, C-3, C-5, C-10, C-12).

Diadamantano[1,2-*b*,1,2-*e*]piperazine (13):
Into a solution of **12** (50 mg, 0.17 mmol) in tetrahydrofuran (5.0 ml) is bubbled anhydrous hydrogen chloride gas. To the resulting mixture of **12** hydrochloride in tetrahydrofuran is added methanol (8.0 ml) and sodium cyanoborohydride (20 mg, 0.32 mmol) and the mixture is stirred at room temperature for 12 h. The mixture is basified with 1 normal potassium hydroxide (5.0 ml), diluted with water, and extracted with ether (4 × 10 ml). The combined extracts are dried with sodium sulfate and evaporated to give crude **13** which is recrystallized from benzene; yield: 24 mg (56%). See Table.

^{13}C-N.M.R. ($CDCl_3$): δ=58.3 (d, C-7a, C-14a); 51.2 (s, C-6a, C-13a); 44.8 (t, 2C); 38.1 (t, 2C); 37.7 (t, 2C); 35.0 (t, 2C); 34.3 (d, 2C); 30.4 (t, 2C); 29.9 (d, 2C); 29.3 ppm (d, 2C).

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[1] Part 47: T. Sasaki, S. Eguchi, N. Toi, *J. Org. Chem.* **44**, 3711 (1979).
[2] For examples of type **A**, see:
W. V. Curran, R. B. Angier, *J. Org. Chem.* **34**, 3668 (1968).
W. H. W. Lunn, W. D. Podomore, S. S. Szinai, *J. Chem. Soc.* [C] **1968**, 1657.

J. K. Chakrabarti, T. M. Hotten, D. E. Tupper, *J. Heterocycl. Chem.* **15**, 705 (1978) and preceeding papers.
W. L. F. Armarego, P. G. Tucker, *Aust. J. Chem.* **31**, 1769 (1978).
For examples of type **B**, see:
V. L. Narayanan, L. Setescak, *J. Org. Chem.* **36**, 4127 (1971).

[3] For example, see T. Sasaki, S. Eguchi, S. Hattori, *Heterocycles* **11**, 235 (1978) and previous papers.

[4] For a recent review, see R. C. Fort, Jr., *Adamantane: The Chemistry of Diamond Molecules*, in *Studies in Organic Chemistry*, Vol. 5, P. G. Gassmann, Ed., Marcel Dekker, Inc., New York, 1976.

[5] J. K. Chakrabarti, T. M. Hotten, D. M. Rackham, D. E. Tupper, *J. Chem. Soc. Perkin Trans. 1* **1976**, 1893.
M. L. Bagal, T. K. Klindukhova, V. I. Lantvoev, *Zh. Org. Khim.* **11**, 1645 (1975); *J. Org. Chem. USSR* **11**, 1633 (1975).
I. Tabushi, Y. Aoyama, *J. Org. Chem.* **38**, 3447 (1973).
J. A. Peters, J. D. Remijnnse, A. van der Wiele, H. van Bekkum, *Tetrahedron Lett.* **1970**, 3065.

[6] The stereochemistry of the reduction was not determined.

[7] The facile formation of dihydropyrazine derivatives was reported also in bicyclo[2.2.1]heptane ring system:
D. E. Applequist, J. P. Klieman, *J. Org. Chem.* **26**, 2178 (1961).
J. Meinwald, D. E. Putzig, *J. Org. Chem.* **35**, 1891 (1970).

[8] Although diphenylphosphoryl azide is known as a useful reagent for obtaining urethane derivatives directly from acid, treatment of **1** with DPPA in the presence of *t*-butanol and triethylamine afforded no urethane, instead, **12** was obtained in 3.4% yield.

[9] D. Lenoir, R. Glaser, P. Mison, P. v. R. Schleyer, *J. Org. Chem.* **36**, 1821 (1971).

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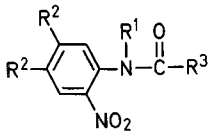
Errata and Addenda 1980

V. N. R. Pillai, *Synthesis* **1980** (1), 1–26;
The structure of compound **86** (p. 12) should be:

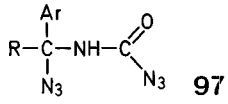


86

V. I. Cohen, *Synthesis* **1980** (1), 60–63;
The alternative name (in brackets) for compounds **1** (p. 62, first experimental procedure) should be ***S*-Methylpseudothiourea Hydroiodides.**

J. R. Mahajan, H. C. de Araújo, *Synthesis* **1980** (1), 64–66;
The authors have erroneously stated that "exaltolide" is a trivial name for pentadecanolide. In fact "exaltolide" is a trademark registered in the name of Firmenich SA, Geneva and should be designated as Exaltolide®.

V. I. Gorbatenko, L. I. Samarai, *Synthesis* **1980** (2), 85–110;
The structure of compound **97** (p. 99) should be:



97

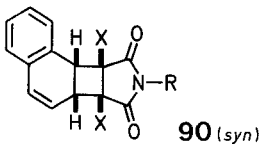
M. Mikołajczyk, P. Bałczewski, S. Grzejszczak, *Synthesis* **1980** (2), 127–129;
The correct name for compound **5a** (first procedure, p. 129) is **Diethyl 1-Phenylthioethanephosphonate.**

G. A. Olah, Y. D. Vankar, M. Arvanaghi, *Synthesis* **1980** (2), 141–142;
The correct name for compound **4** is ***N*-(Chlorosulfonyl)-dimethylsulfilimine.**

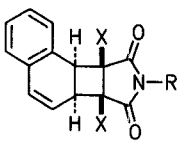
Abstract 5692, *Synthesis* **1980** (2), 159;
The title should be: **Phenols from Aryl Ethyl Ethers.**

Abstract 5698, *Synthesis* **1980** (2) 161;
The title should be: **Enals and Enones from Ketones.**

T. Wagner-Jauregg, *Synthesis* **1980** (3), 165–214;
The structures of compounds **90** (p. 175) should be:



90 (*syn*)



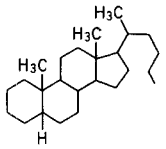
90 (*anti*)

The correct name for compound **251** (p. 188) is **2*H*-Cyclohepta[*gh*]pyrrolizin-Derivat.**

Abstract 5724, *Synthesis* **1980** (3), 254;
The title should be: **Carbamates, Thiocarbamates, and Carbonates from Alcohols or Thiols.**
The first line under the formula scheme should be: Y = O, S.

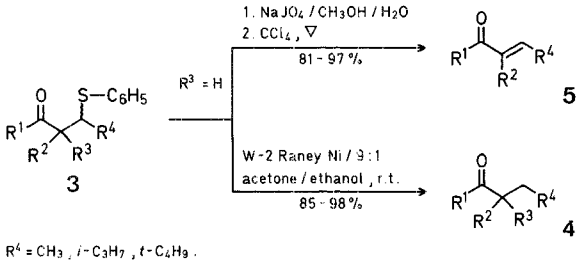
Abstract 5728, *Synthesis* **1980** (3), 256;
The title (and name for compound **3**) should be: ***N*-Sulphenylimines Derived from Amino Acids.**

C. R. Harrison, P. Hodge, *Synthesis* **1980** (4), 299–301;
The 3rd group in the Table, part B (p. 300) should have the structure:



Abstract 5745, *Synthesis* **1980** (4), 334;
The title should be: **Stereocontrolled *cis*-Addition of Organocopper Reagents to 2-Alkynals, 1-Alkynyl Ketones, 2-Alkynoic Acids, and 2-Alkynoic Esters.**

Abstract 5752, *Synthesis* **1980** (4), 336;
The title should be: **α-Alkylation and α-Alkylidenation of Carbonyl Compounds.**
The formula scheme for the conversion **3**→**4** or **5** should be:



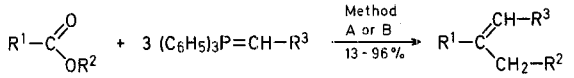
3 **5** **4**

R^4 = CH_3, *i*-C_3H_7, *t*-C_4H_9.

Abstract 5770, *Synthesis* **1980** (4), 342;
The title should be: **Claisen Rearrangement of Ketene Allyl Ethyl Acetals.**

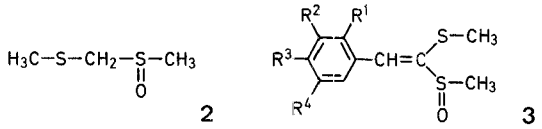
M. A. Alkhader, R. K. Smalley, B. Mohajerani, *Synthesis* **1980** (5), 381–383;
The correct name for compound **6** is **Indazolo[3,2-*b*]naphtho[2,3-*d*]-[1,3] oxazin-6-one.**

Abstract 5782, *Synthesis* **1980** (5), 418;
The formula scheme should be:



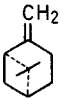
1 **2** **3**

Abstract 5799, *Synthesis* **1980** (5), 424;
The structures of compounds **2** and **3** should be:



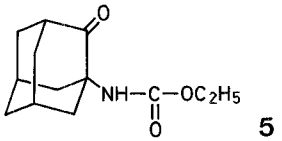
2 **3**

L. M. Harwood, M. Julia, *Synthesis* **1980** (6), 456–457;
The structure of compound (−)-**7** should be:



(−)-**7**

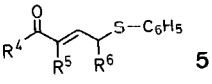
T. Sasaki, S. Eguchi, T. Okano, *Synthesis* **1980** (6), 472–475;
The structure of compound **5** should be:



5

Abstract 5804, *Synthesis* **1980** (6), 498;
The title should be: **Allylic Funtionalisation of Exomethylene Compounds.**

Abstract 5817, *Synthesis* **1980** (6), 503;
The structure of compound **5** should be:



5