Dimeric Products from the Base-Catalyzed Condensation of Benzaldehyde with 2,3-Dihydro-1*H*-inden-1-one or 2-(Phenylmethylene)-2,3-dihydro-1*H*-inden-1-one

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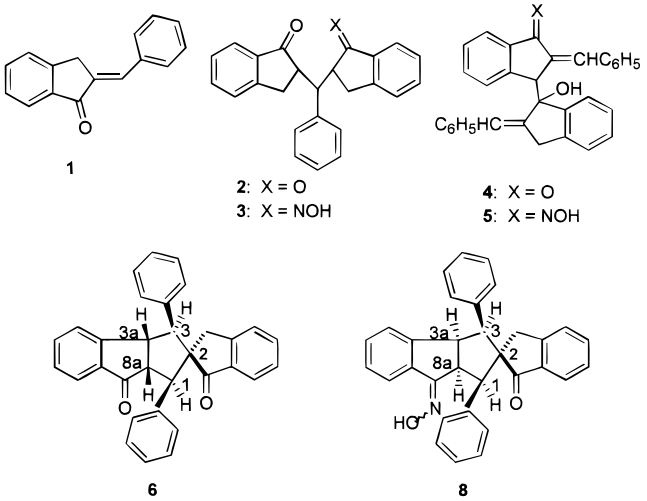
Introduction

In 1894, Kipping[1] reported that when an ethanol solution of benzaldehyde and 2,3-dihydro-1*H*-inden-1-one was treated with "a little alcoholic potash", a solid formed that upon recrystallization from ethanol gave the yellow 2-(phenylmethylene)-2,3-dihydro-1*H*-inden-1-one (**1**) and a white high-melting insoluble substance that was not further characterized.

Chatterjea and Prasad[2] repeated this work and isolated a solid with similar melting point (238−240 °C) that they proposed was probably (benzylidene-1-indanone) based on a carbonyl IR band at 5.95 μm and elemental analysis that agreed with a molecular formula of $C_{25}H_{20}O_2$. They also obtained a monooxime when the bis compound was treated with excess hydroxylamine hydrochloride in boiling ethanol. The IR of the oxime showed strong bands at 2.9, 6.0, and 6.25 μm that were assigned as OH, aromatic C═O, and C═N signals. An elemental analysis of the oxime was in agreement with an empirical formula of $C_{25}H_{21}O_2N$. Although the authors did not draw the structures for these products, we postulate they are **2** and **3** on the basis of the nomenclature, spectral data, and elemental analysis given in the publication.



Witschard and Griffin[3] reported that when **1** was treated with benzyltriphenylphosphonium chloride in ethanolic sodium ethoxide at room temperature or sodium hydride in refluxing glyme, the same high-melting dimer, which now analyzed for $C_{32}H_{24}O_2$, was formed in high yield. On the basis of infrared, ultraviolet, and ^{1}H-NMR data, the dimer was formulated as 2-benzylidene-3-(2-benzylidene-1-hydroxyindanyl)-1-indanone (**4**) with unassigned stereochemistry. Additional support for structure **4** was obtained when it gave a monooxime (**5**) that lacked a carbonyl infrared band. The authors state that the physical properties of **4** agree with those reported for compound **2** isolated by Chatterjea and Prasad, but did not attempt to reconcile the reported differences in empirical formulas.

More recently, Wendelin[4] and co-workers found that when **1** was treated with guanidine carbonate in dimethylformamide or a 1-propanol solution of thiourea in the presence of sodium propoxide, none of the expected heterocyclic systems were isolated. Instead, a $C_{32}H_{24}O_2$ dimer of **1** was obtained that on the basis of mass spectral, infrared, ^{1}H- and ^{13}C-NMR, and elemental analysis was concluded to be 1,3-diphenyl-3a,8a-dihydrospiro{cyclopenta[*a*]indene-2,2′(1H,3′H)-indene}-1′,8(3*H*)-dione (**6**). The stereochemical assignments between H-3a/H-3 and H-8a/H-1 in **6** were established as trans on the basis of a 400 MHz NOESY experiment, and a possible mechanism of formation was given. The authors commented that the dimer **4** reported by Witschard and Griffin had a similar melting point and a carbonyl band in the same region as **6**, but the two dimers could not be the same because of different ^{1}H-NMR data.

We have repeated the above authors[1−4] work and report here that the only high-melting product formed in the base-catalyzed condensation of benzaldehyde with 2,3-dihydro-1*H*-inden-1-one or 2-(phenylmethylene)-2,3-dihydro-1*H*-inden-1-one (**1**) is 1,3-diphenyl-3a,8a-dihydrospiro{cyclopenta[*a*]indene-2,2′(1*H*,3′*H*)-indene}-1′,8(3*H*)-dione with a cis stereochemical relationship between H-3a/H-3 and H-8a/H-1 (**7**).

Results

Treatment of an ethanol solution of benzaldehyde and 2,3-dihydro-1*H*-inden-1-one with a saturated solution of anhydrous potassium carbonate (potash) in 100% ethanol at room temperature for 48 h gave only **1** in 84% yield. No high-melting insoluble solid reported by Kipping[1] was found. When the same reaction conditions were repeated using a saturated solution of K_2CO_3 in 95% ethanol or 50% ethanol, no new product, as determined by TLC and MS, was detected.

Treatment of **1** according to the procedure of Witschard and Griffin[3] with benzyltriphenylphosphonium chloride in a solution of 0.25 M ethanolic sodium ethoxide at room temperature for 2 h or sodium hydride in glyme at reflux for *ca.* 20 h gave the same high-melting solid in 70% and 41% yields, respectively. The same solid was also obtained by treating **1** with ethanolic sodium ethoxide at room temperature for 2 h (11% yield) or anhydrous K_2CO_3 in refluxing DMF for 2 h (58% yield).

Mass spectral and elemental analysis of the high-melting solid agreed with an empirical formula of $C_{32}H_{24}O_2$, *i.e.* a dimer of **1**. The IR spectrum gave a strong band at 1703 cm^{-1}, and the UV showed maxima at 207, 248, and 296 nm, both of which are in agreement with the presence of a 2,3-dihydro-1*H*-inden-1-one system. The ^{1}H-NMR spectrum gave a 2H AB pair of doublets at δ 3.10, two 1H doublets at δ 3.85 and 4.15, respectively, and two 1H doublet of doublets at δ 4.00

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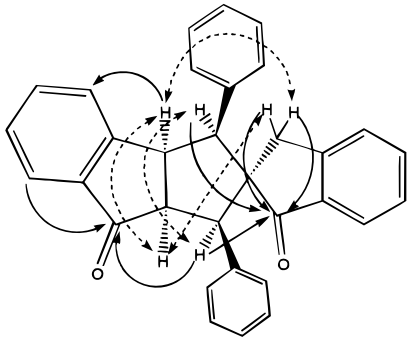


Figure 1. HMBC (→) and NOESY (<---->) connectivities for compound **7**.

and 4.60, respectively, together with 18 aromatic protons. The ^{13}C-NMR spectrum gave six signals between δ 28.86 and 69.22 that can be assigned to tetrahedral carbons and two signals at δ 205.92 and 207.86 that can be assigned to carbonyl groups. These data fail to support the proposed structures **2** and **4**, but are in agreement with a structure that contains a CH_2 group and four single H atoms on adjacent carbon atoms.

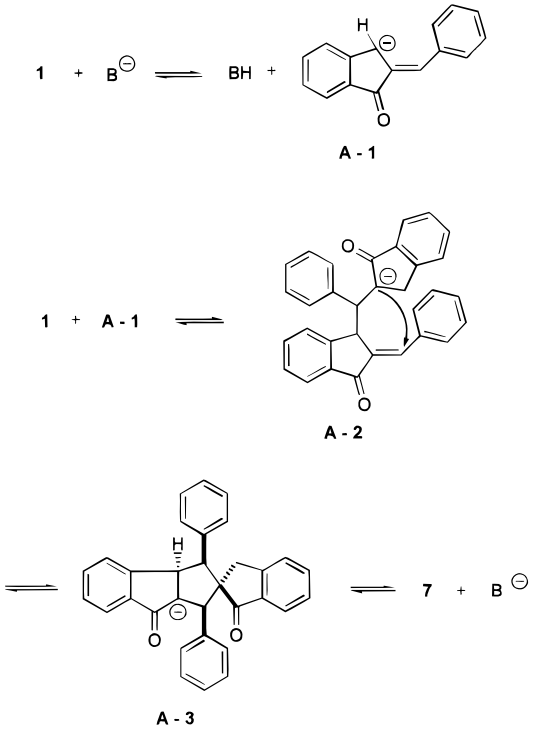
The structure assignment as **7** was based upon the heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple bonds correlation (HMBC) data. H-3′ was the only CH_2 group and assigned from the HMQC data. The H-1 proton was assigned on the basis of the HMBC correlations observed between the proton at 4.15 ppm and the two carbonyl's at 205 and 208 ppm (**7**). The HMBC correlations between the proton at 4.6 ppm and the three aromatic carbons led to the assignment of H-3a (Figure 1).

The stereochemistry of compound **7** is different than the previously proposed structure **6** where a trans relationship between H-3a/H-3 and H-8a/H-1 was assigned. Wendelin and co-workers interpreted the large apparent J values ($^3J_{\text{H-3/H-3a}}$ = 10.4 Hz and $^3J_{\text{H-1/H-8a}}$ = 10.8 Hz) to be indicative of an anti configuration. Stereochemistry of structure **7** was accomplished through the analysis of the NOESY data (Figure 1) and molecular modeling using PCMODEL. The two NOESY correlations of importance were H-3a/H-3′ and H-8a/H-3′. The observance of these correlations indicated that all the protons were on the same side of the spiro compound as shown in **7**. The model was in agreement with both the NOESY data and apparent J values.

Reaction of **7** with 6 equiv of hydroxylamine hydrochloride in refluxing ethanolic KOH resulted in the formation of a monooxime in 67% yield. The oxime was assigned as a syn and anti mixture (75:25) of 8-oxime **8** on the basis of the ^{1}H-NMR shifts observed at H-1 and H-8a of diketone **6**. The H-1 doublet located at δ 4.15 in **7** was shifted to δ 3.68 and 3.82 in a 25:75 ratio and the H-8a doublet of doublets at δ 4.00 was shifted to δ 4.25 and 4.38 in a 75:25 ratio. The H-3 and H-3a signals, which are more distant to C-8, were only slightly shifted and remained as one doublet and doublet of doublets, respectively. Failure of the carbonyl group at C-1′ to form an oxime is probably due to the steric shielding effects of the phenyl groups located at C-1 and C-3.

A possible mechanism for the formation of **7** is given in Scheme 1. The anion (**A-1**) resulting from the treatment of **1** with a base (**B**) undergoes a 1,4-conjugated addition (Michael addition) to a second molecule of **1** to form anion A-2. This then undergoes a second 1,4-conjugated addition to form A-3, which gives **7** and the base.

Scheme 1



Experimental Section

General. Melting points are uncorrected. Nuclear magnetic resonance (NMR) data for ^{1}H-NMR were taken at 300 MHz and ^{13}C-NMR at 75.5 MHz. Infrared (IR) spectra were determined using KBr pellets. Mass spectra (MS) were obtained by a desorption chemical ionization method using ammonia (or isobutane) as the reagent gas. Elemental analyses for carbon, hydrogen, and nitrogen are within ±0.4% of theory unless noted otherwise. If not otherwise specified, chemicals and reagents were obtained from the Aldrich Chemical Co. Solvents were of reagent grade and dried prior to use. Reaction progress and purity of final products were determined on E. Merck silica gel 60 chromatography plates.

NOESY and HMBC data were measured using an AM500 spectrometer with a proton frequency of 500.13 MHz and a carbon frequency of 125.77 MHz. The temperature of the sample was regulated at 305 K using $CDCl_3$ as the solvent and the internal reference (^{1}H, 7.25 ppm; ^{13}C, 77 ppm).

The proton and HMBC data were measured using a 3 mm inverse microprobe. The 90° ^{1}H pulse was 7.5 μs; the 90° ^{13}C pulse was 10 μs. The proton experiment was collected with a spectral width of 10000 Hz and an observation pulse of 2.8 μs. The HMBC data were collected with a spectral width of 6024 Hz in the ^{1}H dimension and 29410 Hz in the ^{13}C dimension. The recycle delay was set for 1 s, the $^1J_{\text{CH}}$ was 2.63 ms (180 Hz), and the evolution for long-range coupling was 50 ms. The data were recorded with 2048 data points in the ^{1}H dimension and 512 increments, 32 scans per increment, in the ^{13}C dimension. The data were processed in both dimensions using a sine-squared function that was shifted by 90°.

The carbon and NOESY data were measured with a 5 mm dual tuned probe (H, C). The 90° ^{1}H pulse was 13.3 μs; the 90° ^{13}C pulse was 3.3 μs. The carbon experiment was collected using a spectral width of 29 410 Hz and an observation pulse of 3.3 μs. The NOESY data were collected with a spectral width of 6024 Hz in both dimensions and TPPI phase cycling. The recycle delay was set for 1.5 s, and the mixing time was 0.9 s. The data were recorded with 2048 data points in the F2 dimension and 512 increments, 32 scans per increment, in the F1 dimension. The data were processed in both dimensions using a sine-squared function that was shifted by 90°.

Reaction of Benzaldehyde with 2,3-Dihydro-1*H*-inden-1-one in the Presence of Base. A. Potassium Hydroxide. A vigorously stirred solution of benzaldehyde (3.20 g, 0.03 mol) and 2,3-dihydro-1*H*-inden-1-one (4.00 g, 0.03 mol) at room temperature was treated with six drops of saturated ethanolic

potassium hydroxide. After ca. 15 min, a white solid mass formed that was allowed to stand an additional 0.5 h. The mixture was treated with 95% ethanol (15 mL), stirred for ca. 3 h, and filtered, and the solid was washed with 95% ethanol (5 mL). Crystallization from acetic acid gave 5.14 g (78%) of 2-(phenylmethylene)-2,3-dihydro-1*H*-inden-1-one (**1**): mp 109−110 °C (lit.[5] mp 109−111 °C); R_f 0.56 ($CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.10 (s, 2H), 7.35−7.74 (m, 9H), 7.94 (d, J = 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 32.47, 124.46, 126.19, 127.70, 128.95, 129.69, 130.74, 133.95, 134.65, 138.1, 141.5, 194.5.

B. Potassium Carbonate. A solution of benzaldehyde (1.06 g, 0.01 mol), 2,3-dihydro-1*H*-inden-1-one (1.23 g, 0.01 mol), and anhydrous potassium carbonate in 100% ethanol (25 mL) was stirred vigorously at room temperature for ca. 48 h. The light red mixture was treated with 37% hydrochloric acid (2 mL, 0.0242 mol), and a white solid was formed. The solid was filtered, washed with water (5 mL), and crystallized from acetic acid to give 1.85 g (84%) of **1**, mp 108−109 °C, TLC R_f 0.54 ($CHCl_3$). The ^{1}H-NMR and MS data were identical with those of **1** obtained from potassium hydroxide.

When the above reaction was repeated using 10 drops of saturated potassium carbonate in 95% ethanol or 50% ethanol, no reaction, as determined by TLC and MS, occurred after stirring at room temperature for ca. 48 h.

Reaction of 2-(Phenylmethylene)-2,3-dihydro-1*H*-inden-1-one (1) with Various Bases. C. Benzyltriphenylphosphonium Chloride and Sodium Ethoxide. The procedure described below is that reported by Witschard and Griffin.[3]

To a freshly prepared solution of 0.25 M ethanolic sodium ethoxide (100 mL anhydrous ethanol, 0.57 g, 0.025 mol sodium) under N_2 were added, each in one portion, **1** (5.50 g, 0.025 mol) and benzyltriphenylphosphonium chloride (9.72 g, 0.025 mol). The orange slurry was stirred at room temperature for 2 h and then treated dropwise with 48% hydrobromic acid (10.4 mL, 0.05 mol, HBr) followed by water (100 mL). After being stirred for ca. 0.5 h, the mixture was extracted with chloroform (100 mL) and separated. The chloroform layer was dried (anhydrous $MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo* to give a viscous light orange oil (17.3 g) that upon treatment with 95% ethanol gave a white solid. Crystallization from acetic acid gave 3.85 g (70%) 1,3-diphenyl-3a,8a-dihydrospiro[cyclopenta[*a*]indene-2,2′(1H,3′H)-indene]-1′,8(3*H*)-dione (**7**), mp 222−224 °C (lit.[3] mp 228−233 °C); R_f 0.22 ($CHCl_3$); MS (CI) 458 (100, M + NH_4^+), 441 (2.3, MH^+), 136 (33.4); ^{1}H NMR ($CDCl_3$) δ 3.10 (q, J = 17.0 Hz, 2H, H-3′), 3.85 (d, J = 10.1 Hz, 1H, H-3), 4.00 (dd, J = 10.5, 8.7 Hz, 1H, H-8a), 4.15 (d, J = 10.6 Hz, 1H, H-1), 4.60 (dd, J = 10.4, 8.7 Hz, 1H, H-3a), 6.91−7.80 (m, 18H); ^{13}C NMR (DMSO-*d*) δ 30.50 (C-3′), 46.70 (C-3a), 53.60 (C-8a), 54.80 (C-1), 59.80 (C-3), 70.00 (C-2), 122.72, 123.81, 125.01, 125.94, 126.87, 127.17, 127.23, 127.98, 128.05, 128.23, 128.31, 135.01, 135.15, 135.38, 136.17, 136.39, 136.99, 137.69, 152.64, 155.79, 205.92 and 207.86 (C-1′ and C-8); UV (95% EtOH) nm 207.4 (67, 129), 248.6 (24,779), 295.6 (4,854); IR ($CHCl_3$) cm^{-1} 1703 (C═O). Anal. Calcd for $C_{32}H_{24}O_2$: C, 87.25; H, 5.49. Found: C, 87.27; H, 5.44.

D. Sodium Ethoxide. To a freshly prepared solution of 0.25 M ethanolic sodium ethoxide (40 mL of anhydrous ethanol, 0.23 g, 0.01 mol Na) under N_2 was added **1** (2.20 g, 0.01 mol) in one portion. The orange mixture was stirred at room temperature for 2 h, treated dropwise with 48% hydrobromic acid (5 mL, 0.024 mol HBr), poured into water (50 mL), and then stirred at room temperature for ca. 0.5 h. The pale yellow solid was filtered off and crystallized from acetic acid to give 0.246 g (11%) of **7**, mp 231−232 °C. The TLC, MS, and ^{1}H-NMR data were the same as those for **7** obtained in procedure E.

E. Sodium Hydride. The procedure described below is that reported by Witschard and Griffin.[3]

To a stirred mixture of sodium hydride (60% in mineral oil, 0.40 g, 0.01 mol NaH) and anhydrous ethylene glycol dimethyl ether (glyme, 25 mL) under N_2 was added dropwise at room temperature a solution of **1** (2.204 g, 0.01 mol) in glyme (25 mL) over *ca*. 0.5 h. The mixture was refluxed for *ca*. 20 h, cooled to room temperature, treated dropwise with water (5 mL), and then poured into water (250 mL) and stirred at room temperature for *ca*. 3 h. The light tan solid was filtered off and crystallized from 95% ethanol/methylene chloride (9:1) to give 0.912 g (41%) of **7**, mp 220−221 °C. The TLC, MS, and ^{1}H-NMR data were the same as those for **7** obtained in procedure C.

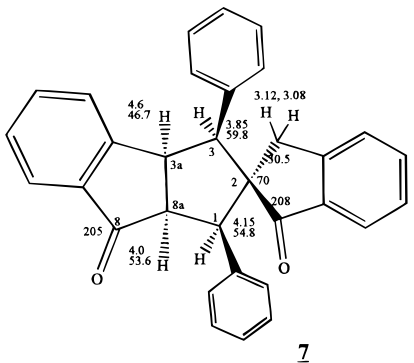
To a stirred mixture of sodium hydride (60% in mineral oil, 0.40 g, 0.01 mol of NaH) in anhydrous DMF (15 mL) under N_2 was added in one portion a solution of **1** (2.203 g, 0.01 mol) in DMF (25 mL). The mixture was heated to 60 °C for 2 h, allowed to cool to room temperature, and then poured into water (150 mL). A pale yellow solid was filtered off, washed with water (50 mL), and crystallized from acetic acid to give 0.500 g (23%) of **7**, mp 224−226 °C. The TLC, MS, and ^{1}H-NMR data were the same as those for **7** obtained in procedure C.

F. Potassium Carbonate. A mixture of **1** (2.20 g, 0.01 mol) and anhydrous potassium carbonate (2.07 g, 0.015 mol) in anhydrous DMF (75 mL) under N_2 was stirred and refluxed for 2 h. The mixture was allowed to cool to room temperature, poured into water (150 mL), treated with 37% hydrochloric acid (3.0 mL, 0.04 mol of HCl), and then stirred at room temperature for *ca*. 1 h. The solid was filtered off and crystallized from acetic acid to give 1.20 g (58%) of **7**, mp 226−227 °C. The TLC, MS, and ^{1}H-NMR data were the same as those for **7** obtained in procedure C.

Monooxime 8 of 7. The procedure given below is essentially that of Witschard and Griffin.[3]

A solution of **7** (1.00 g, 0.0023 mol), hydroxylamine hydrochloride (1.00 g, 0.014 mol), and potassium hydroxide (4.0 g, 0.071 mol) in 95% ethanol was stirred and refluxed for 2 h. The hot mixture was filtered to remove insoluble material (0.578 g, MS 115), and the filtrate was acidified with 10% hydrochloric acid (36.5 mL). The resultant solid was filtered off and crystallized from acetic acid and dried *in vacuo*[6] at 100 °C to give 0.703 g (67%) of **8**, the 8-oxime of **7**: mp > 250 °C; R_f 0.52, 0.61 ($CHCl_3$/C_2H_5OH, 95:5); MS 456 (MH^+, 100); IR (KBr) cm^{-1} 3398 (OH), 1716 (C═O), 1604 (C═N); ^{1}H NMR (DMSO-d_6) δ 3.05 (AB, J = 17.0 Hz, 2H H-3′), 3.68 and 3.82 (d, J = 10.6 Hz, 0.25- and 0.75H, H-1), 3.62 (d, J = 10.7 Hz, 1H, H-3), 4.25 and 4.38 (dd, J = 10.6, 8.7 Hz, 0.75- and 0.25H, H-8a), 4.65 (dd, J = 10.6, 8.7 Hz, H-3a), 6.83−7.35 (m, 16H), 7.46 and 7.49 (d, J = 7.0 Hz, 0.25- and 0.75H, H-7′), 7.65 and 8.46 (d, J = 7.0 Hz, 0.25- and 0.75H, H-7), 11.21 (br, 1H, OH); ^{13}C NMR (DMSO-d_6) δ 29.26 and 29.64 (C-3′), 46.08 and 46.18 (C-3a), 47.31 and 48.54 (C-8a), 57.49 and 59.77 (C-1), 61.45 and 61.61 (C-3), 67.75 and 68.40 (C-2), 120.98, 122.41, 123.78, 125.49, 125.60, 125.67, 126.30, 126.55, 126.68, 126.77, 126.83, 127.16, 127.38, 127.49, 127.66, 127.82, 127.91, 128.11, 128.28, 129.05, 129.38, 130.46, 132.51, 134.33, 133.43, 135.67, 136.39, 136.51, 136.72, 136.98, 138.63, 148.05 and 149.49 (C═NOH, 25:75 ratio), 152.60, 158.21 and 159.73 (C-3b, 75:25 ratio), 208.22 and 208.29 (C═O, 75:25 ratio).

Anal. Calcd for $C_{32}H_{25}NO_2$: C, 84.37; H, 5.53; N, 3.07. Found: C, 84.30; H, 5.58; N, 2.99.



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Supporting Information Available: PCMODEL of **7** (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(5) Hassner, A.; Cromwell, N. H. *J. Org. Chem*. **1958**, *80*, 893.

(6) When the compound was allowed to dry at room temperature, it retained 0.7 mol of acetic acid/mol of compound.