

Jan Bergman

Department of Organic Chemistry, Royal Institute of Technology,  
S-100 44 Stockholm, Sweden

Received June 5, 1984

Indole and *N*-methylindole react with oxa stabilized carbocations generated *in situ* from orthoformates to yield tris(3-indolyl)methane. The unsymmetrical isomers, e.g. 2-(*N*-methyl-3-indolyl)di(*N*-methyl-3-indolyl)methane (**4**), were not formed as established by an independent synthesis. *N,N*-Dimethylacetamide dimethylacetal reacted with 2-alkyl substituted indoles to produce 1,1-bis(3-indolyl)ethanes (**3**).

*J. Heterocyclic Chem.*, **22**, 341 (1985).

### Introduction.

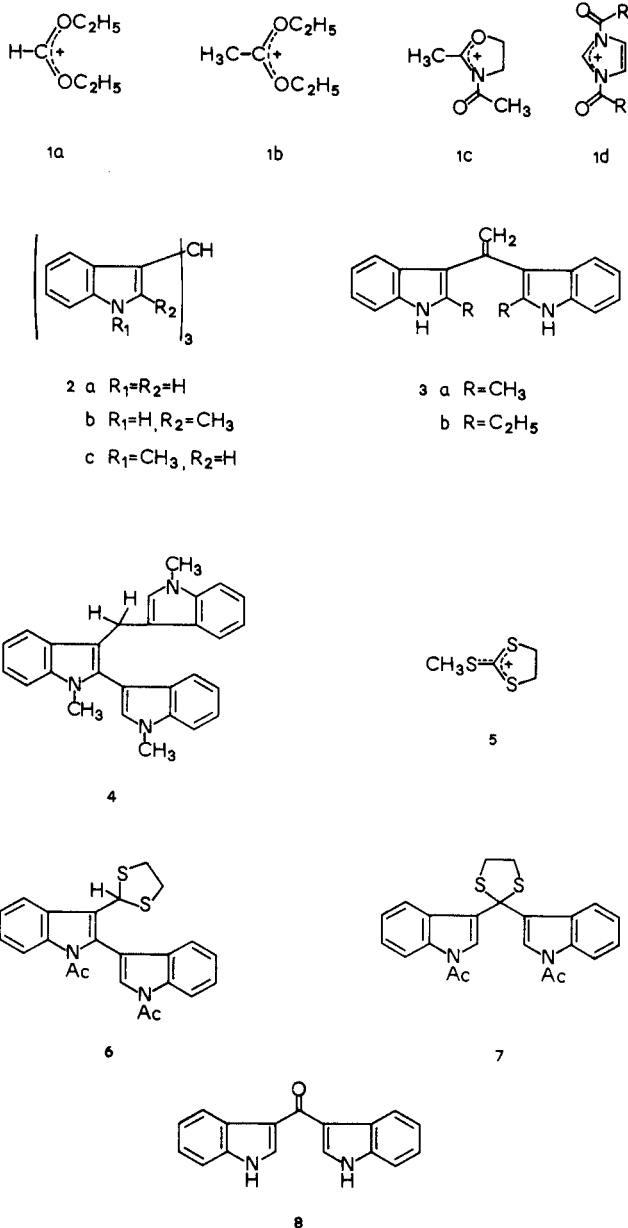
It has been known [1] since 1929 that indoles will readily condense with orthoformate under acidic conditions to yield tris(3-indolyl)methanes **2**, a class of compounds known [2] since 1909 (for a short review see ref [3]). Since 1929 this condensation has been studied by several authors under a variety of conditions [4-10]. Condensations of orthoacetates with indoles were first studied by Kiang and Mann [7] who isolated 1,1-bis(2-methyl-3-indolyl)ethene from the condensation of ethyl orthoacetate with 2-methylindole.

These results are readily explained in terms of the formation of oxa stabilized carbocations, *viz* **1a** and **1b**. Similar reactions involving aza stabilized species (e.g. **1c** and **1d**) have recently been studied by Bergman *et al.* [11,12]. However it is not self-evident that products incorporating three units of indoles and one carbon atom from the orthoformate must have structure **2**, because as indicated in Scheme 1, the introduction of the second unit must not necessarily occur at position A, as position B should clearly be an alternative site for a nucleophilic attack.

### Results and Discussion.

In a recent paper, Pindur *et al.* [13] reported the isolation of compound **2c** from the condensation of *N*-methylindole with ethyl orthoformate in hot methanol in the presence of *p*-toluenesulfonic acid. This compound was reported to melt with decomposition at 150° [13a]. The authors, however, failed to recognize that a compound with structure **2c**, prepared by a condensation between *N*-methyl-3-formylindole and two molecules of *N*-methylindole, had been reported [14] earlier to have mp 268-270°. Consequently after reading Pindur's paper we believed that a) the compounds are different and b) that one of the compounds should be assigned structure **2c** and the other structure **4**.

In this connection another problem from the literature is of interest to consider. In his thesis, Kutter [15] describ-

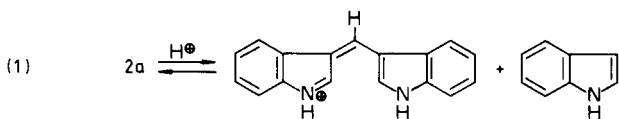


ed a condensation between indole and the *S*-stabilized carbocation **5**. The product was considered to have either structure **6** or structure **7**. In a following paper [16] the structure **7** was preferred, however without sufficient evidence. Structure **7** has now been established by hydrolysis to the known [17] carbonyl compound **8**.

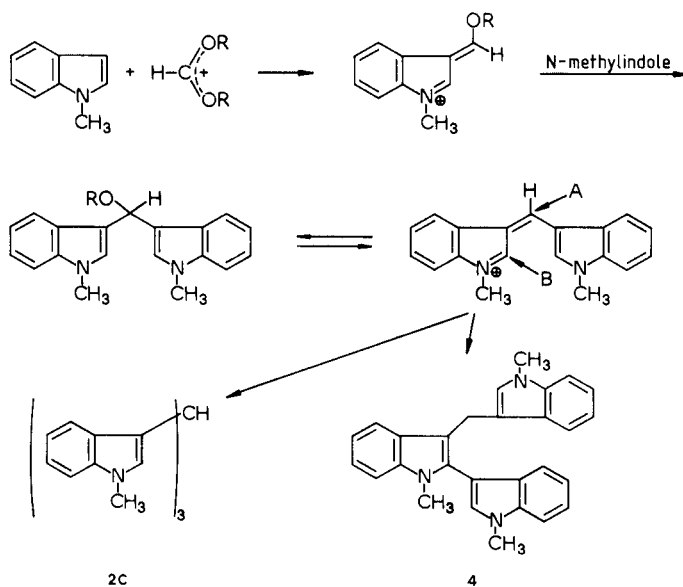
We have now repeated Pindur's experiment and we conclude that the products are identical and have the structure **2c**. This compound could also be readily obtained by methylation [18] of **2a**. Furthermore, compound **4** was prepared [19] as outlined in Scheme 2 and this compound was found to be absent in all the reactions under discussion. Although compound **2c** is sensitive to light it is thermally less sensitive than one might expect and the compound can be melted for some time without appreciable decomposition. The compound can even be distilled. However prolonged heating above the melting point will result in a cleavage reaction, yielding *N*-methylindole. Similar cleavage reactions have been used by Bergman *et al.* in connection with the synthesis of ellipticine, girinimbine and related indole alkaloids [20].

Dr. Pindur *et al.* [13] also reported the preparation of 3-benzoylindole and 2-methyl-3-benzoylindole by the condensation of the appropriate indoles with trimethyl orthobenzoate. The authors did not, however, acknowledge the fact that both compounds had previously been reported in the literature and that their melting points (215° with decomposition for 3-benzoylindole) was considerably lower than those reported in the literature (*e.g.* mp 241-243.5° [21] see also refs [22-25]). We have repeated the reported preparations of 3-benzoylindole and 2-methyl-3-benzoylindole and have confirmed that the compounds are identical.

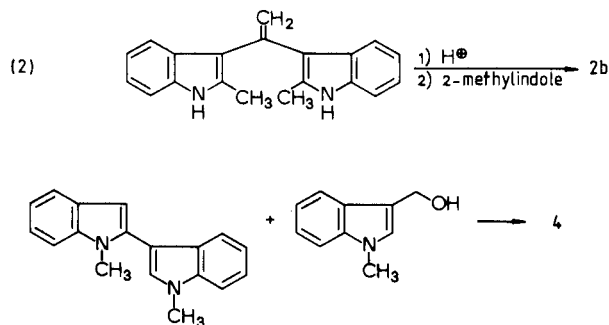
Tris(3-indolyl)methanes (*e.g.* **2a**) are readily cleaved by acids as a consequence of the equilibrium [1] and in an early study of the interaction of tris(3-indolyl)methanes with acid König [26] did isolate indolidene-3-indole (as the perchlorate).



Indoles do not react [5,6] with orthoformates without addition of an acid catalyst, whereas *N,N*-dimethylformamide now has been found to readily react to produce a mixture of indole oligomers and derivatives of tris(3-indolyl)methanes. The reaction seems to be of negligible synthetic interest. *N,N*-Dimethylacetamide acetals on the other



hand gave with 2-substituted indoles as reactants, 1,1-bis(3-indolyl)ethenes **3** in high yields. Addition of acids to the 1,1-bis(3-indolyl)ethanes, followed by the appropriate indole resulted in the formation of tris(3-indolyl)methanes as indicated in equation (2) (*cf.* ref [7]).



## EXPERIMENTAL

### Tris(*N*-methyl-3-indolyl)methane (**2c**).

All three descriptions [13,14] in the literature were repeated and all products were shown to be identical (mixed mps, ir). The same compound was also obtained by methylation of the tris(3-indolyl)methane (see below).

### Trismethylation of Tris(3-indolyl)methane (**2a**).

Tris(3-indolyl)methane [14] (3.61 g, 10 mmoles), dimethyl oxalate (3.54 g, 30 mmoles) and potassium *t*-butoxide (3.36 g, 30 mmoles) were heated (nitrogen) in DMF (50 ml) under reflux (3 hours). After addition of water the product was collected, dried and recrystallized from pyridine, yield 3.90 g (97%), mp 268-270° (lit [14] mp 268-270°).

### 1,1-Bis(2-ethyl-3-indolyl)ethene (**3b**).

A solution of 2-ethylindole (2.90 g, 20 mmoles), *N,N*-dimethylacetamide dimethylacetal (1.33 g, 10 mmoles) in *N,N*-dimethylacetamide (DMF)

(15 ml) was heated (3 hours, 135°) whereupon the solvent was evaporated and the residue crystallized from methanol, yield 2.60 g (83%), mp 195-196°; ir (potassium bromide): 3398, 3382, 3051, 2965, 2929, 2918, 1462, 1440, 1433, 1322, 1313, 749, 742, 733 cm<sup>-1</sup>; pmr (DMSO-d<sub>6</sub>): δ 10.62 (s, 2H, NH), 7.4-6.7 (m, 8H, arom H), 4.03 (s, 2H, olefinic CH<sub>2</sub>), 2.7 s (q, 4H, 2CH<sub>2</sub>), 2.46 (t, 6H, 2CH<sub>3</sub>).

Anal. Calcd. for C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>: C, 84.04; H, 7.05; N, 8.91. Found: C, 84.13; H, 7.09; N, 8.75.

#### 1,1-Bis(2-methyl-3-indolyl)ethane (3a).

The same procedure as above was used. The crude product was crystallized from toluene, yield (70%) mp 202-202°, (lit [7] mp 201-203°).

#### 2-(N-Methyl-3-indolyl)di(N-methyl-3-indolylmethane (4).

To a solution of *N,N*-dimethyl-2,3-biindolyl [28] (260 mg, 1 mmole) and *N*-methylindole-3-carbinol [29] (161 mg, 1 mmole) in methanol (4 ml) and dioxane (4 ml) was added concentrated hydrochloric acid (2 droplets) at 50°. A semisolid started to form within 2 minutes. After 30 minutes the mixture was cooled and the semi-solid dissolved in hot acetonitrile. The crystals formed were collected after 1 hour, yielded 300 mg (80%), mp 212-213°; <sup>13</sup>C nmr (DMSO-d<sub>6</sub>): δ 20.5 (t, CH<sub>2</sub>), 30.5 (q, NCH<sub>3</sub>), 32.0 (q, NCH<sub>3</sub>), 32.6 (q, NCH<sub>3</sub>). The aromatic carbon atoms resonated between 104.3 and 137.1 ppm.

Anal. Calcd. for C<sub>25</sub>H<sub>19</sub>N<sub>3</sub>: C, 83.11; H, 5.25; N, 11.63. Found: C, 83.08; H, 5.30; N, 11.61.

#### 3-Benzoylindole.

All five procedures [11,13,21,22,24] in the literature were repeated and all products were shown to be identical (mixed mps, ir).

#### Hydrolysis of 2,2-Di(*N*-acetyl-3-indolyl)-1,3-dithiolane (7).

Compound 7 [16] (2.10 g, 5 mmoles) in acetone (15 ml) and DMF (10 ml) was added to a stirred, refluxing suspension of cupric oxide (0.48 g, 6 mmoles) and anhydrous cupric chloride (1.61 g, 12 mmoles) in acetone (50 ml). The mixture was refluxed for 2 hours and filtered hot. The insoluble part was extracted with hot acetone and combined with the filtrate, which upon concentration and cooling deposited 3,3'-carbonylindole (8), yield, 0.85 g (65%), mp 301-302° (lit [17] mp 301-302°).

#### Tris-3-(2-methylindolyl)methane.

A solution of 1,1-bis(2-methyl-3-indolyl)ethene (286 mg, 1 mmole) and 2-methylindole (131 mg, 1 mmole) in ethanol (10 ml) containing 0.1 mg hydrogen chloride was refluxed for 1 hour. The solid formed was collected upon cooling, yield 375 mg (90%), mp 319-320° lit [14] mp 319-320°.

## REFERENCES AND NOTES

- [1] C. D. Nenitzescu, *Bul. Soc. Chim. Rom.*, **11**, 37 (1929).
- [2] A. Ellinger and C. Flamand, *Hoppe-Seylers Z. Physiol. Chem.*, **62**, 276 (1909).
- [3] H. Eckau, *Diss. Köln*, 1971, p 24.
- [4] J. Harley-Mason and J. D. Bullock, *Biochem. J.*, **51**, 430 (1952).
- [5] J. R. Majer, *Tetrahedron*, **9**, 106 (1960).
- [6] J. R. Majer, *Tetrahedron*, **9**, 111 (1960).
- [7] A. K. Kiang and F. G. Mann, *J. Chem. Soc.*, 594 (1953).
- [8] H. von Dobeneck and H. Prietzel, *Hoppe-Seylers Z. Physiol. Chem.*, **299**, 214 (1955).
- [9] I. Maas, *Diss. München*, 1954.
- [10] H. Budzikiewics, H. Eckau and M. Ehrenberg, *Tetrahedron Letters*, 3807 (1972).
- [11] J. Bergman, H. Goonewardena and B. Sjöberg, *Heterocycles*, **19**, 297 (1982).
- [12] J. Bergman and B. Sjöberg, *Heterocycles*, **19**, 301 (1982).
- [13] E. Akgün, U. Pindur and J. Müller, *J. Heterocyclic Chem.*, **20**, 1303 (1983).
- [13a] Editor's note: After correspondence with Dr. Pindur, he acknowledged an error in typing the original manuscript which was not detected by reviewers, authors or editorial staff. Dr. Pindur's observed mp was 250°.
- [14] J. Bergman, *J. Heterocyclic Chem.*, **8**, 329 (1971).
- [15] E. Kutter, *Diss. Stuttgart*, 1964.
- [16] R. Gompper and E. Kutter, *Chem. Ber.*, **98**, 1365 (1965).
- [17] J. Bergman, R. Carlsson and B. Sjöberg, *J. Heterocyclic Chem.*, **14**, 1123 (1977).
- [18a] In this connection the new method, [18b], for methylation with potassium *t*-butoxide and dimethyl oxalate was found to be particularly expedient.
- [18b] J. Bergman and P. Sand, *Tetrahedron Letters*, 1957 (1984).
- [19] In this connection it was established that *N,N*-dimethyl-2,3-biindolyl is attacked much more readily by electrophilic reagents than *N*-methylindole. *N,N*-dimethyl-2,2-biindolyl, in contrast, is less reactive than *N*-methylindole towards electrophiles.
- [20] J. Bergman and R. Carlsson, *Tetrahedron Letters*, 4055 (1978).
- [21] W. C. Anthony, *J. Org. Chem.*, **25**, 2049 (1960).
- [22] B. Oddo and F. Sessa, *Gazz. Chim. Ital.*, **41**, 243 (1911).
- [23] P. Stütz and P. A. Stadler, *Helv. Chim. Acta*, **55**, 75 (1972).
- [24] P. Stütz and P. A. Stadler, *Org. Synth.*, **56**, 8 (1977).
- [25] J. Szmuszkovicz, *J. Org. Chem.*, **27**, 511 (1962).
- [26] W. König, *J. Prakt. Chem.*, **84**, 194 (1911).
- [27] H. Fischer and K. Pistor, *Ber.*, **56**, 2315 (1923).
- [28] J. Bergman and N. Eklund, *Tetrahedron*, **36**, 1445 (1980).
- [29] E. Leete, *J. Am. Chem. Soc.*, **81**, 6023 (1959).