One-Pot Synthesis of 7-Aryl-Octahydroazonino[5,4-*b*]indoles Based on the Fragmentation of Indolizino[8,7-*b*]indoles and the Insertion of Indoles and 3,4,5-Trimethoxyphenol

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Abstract: A series of 7-aryl-octahydroazonino[5,4-*b*]indoles were prepared in one pot via a three component reaction from indolizino[8,7-*b*]indoles, α-chloroethyl chloroformate (ACE-Cl) and activated arenes such as indoles and 3,4,5-trimethoxyphenol.

Key words: indolizino[8,7-*b*]indole, fragmentation, arene, insertion, 7-aryl-octahydroazonino[5,4-*b*]indole

Inspired by early model studies on vinblastine's hypothetical mechanism of action,[3] we turned our attention to the design of azonino[5,4-*b*]indoles in the hope to identify new cytotoxic agents. We surmised that a series of octahydroazonino[5,4-*b*]indoles **1** with an activated aryl group at the C7 carbon center might exhibit some of vinblastine's structural features required for cytotoxic activity. If we were to test this hypothesis, then access to a diverse set of the target compounds would require the synthesis of 7-aryl-octahydroazonino[5,4-*b*]indoles **2**, containing an activated aryl group at the C7 carbon center as well as a secondary N3 nitrogen center. Compound **2** would in turn result from the fragmentation of tertiary amine **3** (Figure 1).

The alkyl chloride induced quaternization of indolizino[8,7-*b*]indole **3** (R^1 = Ar) followed by reductive cleavage of the β-tetrahydrocarboline (β-THC) ring, could provide immediate entry to a number of 7-aryl-octahydroazonino[5,4-*b*]indoles **1** (R^1 = H, R^2 = alkyl, Ar = Ph, furyl, thienyl).[4] However, due to the small number of lower alkyl halides utilized in the quaternization of indolizinoindole **3** (R^1 = Ar), this fragmentation strategy could only lead to a restricted number of 3-alkyl-azonino[5,4-*b*]indoles. Dealkylation of the resulting 3-alkyl substrate to the corresponding azonine **2** (R^1 = H) may serve as an alternative method, which could offset this limitation, but this approach may prove cumbersome. Most importantly, this strategy lacks the ability to introduce the desired features of the target compounds, namely a C7 carboxymethyl group as well as an activated aryl group.

Access to the desired octahydroazonino[5,4-*b*]indole **2** would result from indolizino[8,7-*b*]indole **3** (R^1 = H, CO_2Me) via a chloroformate-induced fragmentation[5] of the β-THC ring, followed by insertion of an activated arene to the newly generated azonino ring (Figure 1). Although the insertion of anilines has been described,[6] the use of other activated arenes such as indoles and oxygenated aromatics has not yet been explored. Herein, we wish to report the results of our studies pertaining to the one-pot synthesis of 7-aryl-octahydroazonino[5,4-*b*]indoles with general structure **2**, resulting from the ACE-Cl-mediated fragmentation of indolizinoindole **3** (R^1 = H, CO_2Me) accompanied by the insertion of indoles and 3,4,5-trimethoxyphenol (Scheme 1).

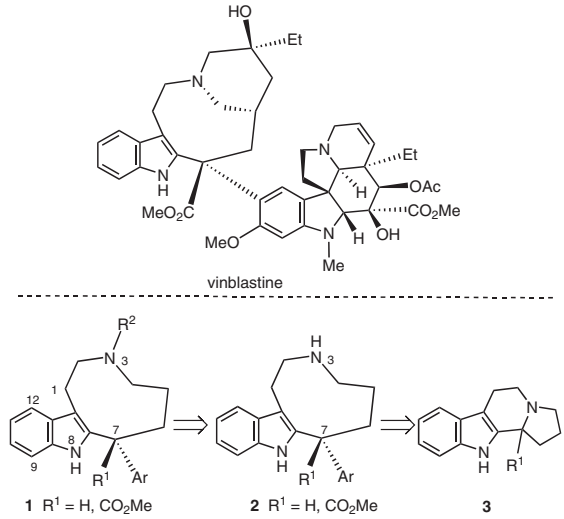

Figure 1 7-Aryl-octahydroazonino[5,4-*b*]indoles from β-THC scaffolds

Treatment of indolizinoindoles **3a** and **3b** with ACE-Cl could induce cleavage of the β-THC ring, providing a transient iminium ion which could generate adducts **4a** and **4b**, respectively, when trapped in the presence of an indole. Subsequent cleavage of the labile α-chloroethyl carbamate[7] would afford azonino[5,4-*b*]indoles **5** and **6** (Scheme 1). Indeed, when substrates **3a**[8] and **3b**[9] were treated at room temperature with ACE-Cl (1.2 equiv) in dichloroethane (DCE),[10] in the presence of an indole (1.1 equiv), the corresponding indole adducts **4a** and **4b** were produced. Addition of MeOH to the crude reaction mixture, followed by heating at 50 °C for one hour, led to carbamate cleavage and formation of 7-(1*H*-indol-3-yl)-octahydroazonino[5,4-*b*]indoles **5** and **6**, respectively.

A number of indoles with various substitution patterns were found to undergo an insertion reaction, resulting in

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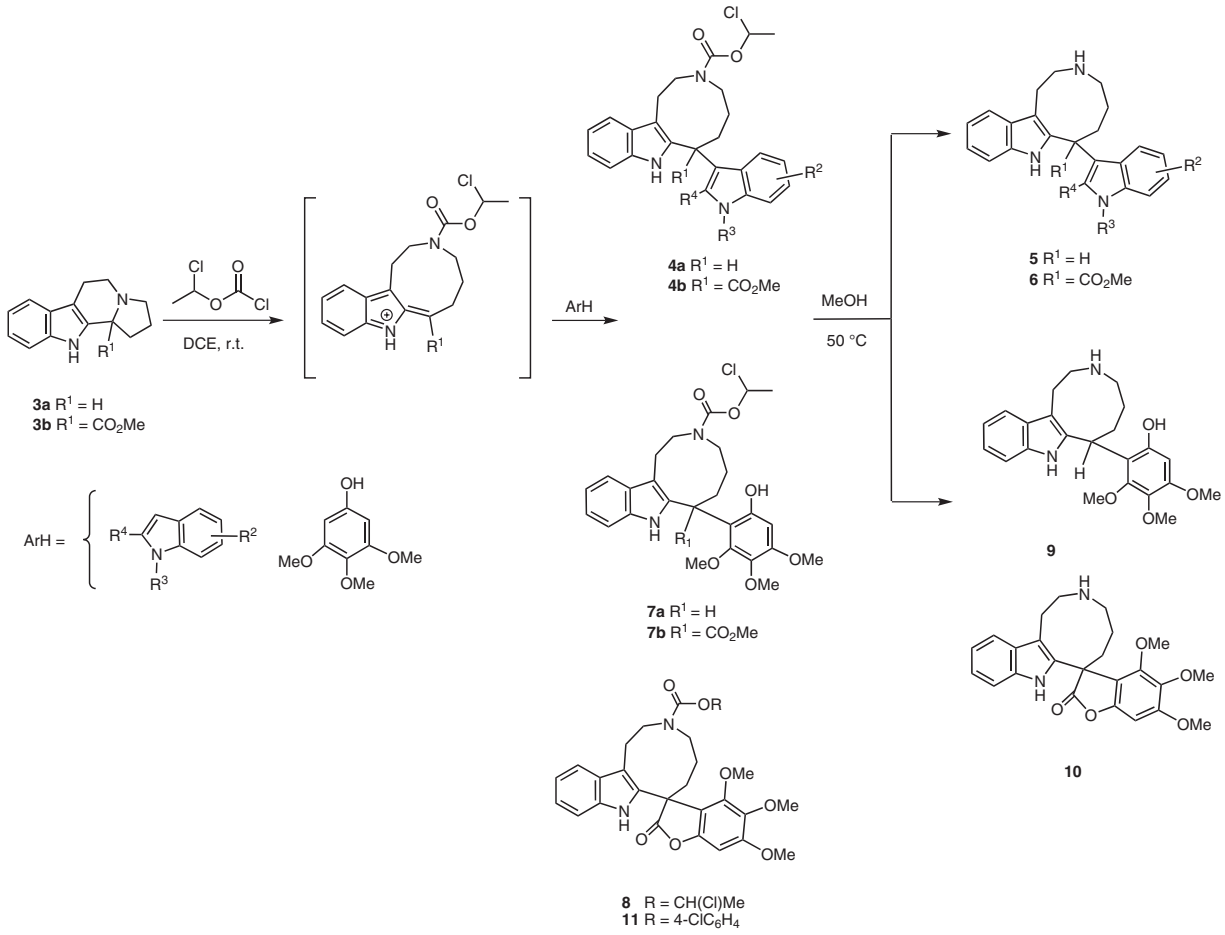
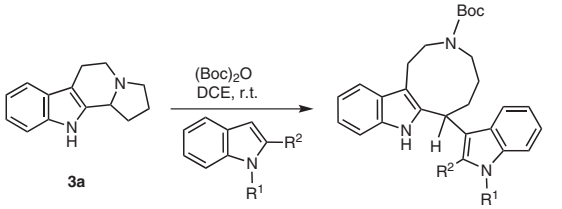


Scheme 1 Access to 7-aryl-octahydroazonino[5,4-*b*]indoles through the fragmentation of indolizino[8,7-*b*] indoles and the insertion of activated arenes

azonines **5** (Table 1, entries 1–7) and **6** (Table 1, entries 10–15) in moderate yields (21–46%). Attempts to improve the reaction yields utilizing an excess of ACE-Cl (2–3 equiv) and indole (2–3 equiv) were not fruitful given the inability to drive the fragmentation of indolizinoindoles **3a** and **3b** to completion. Both N–H and *N*-alkyl indoles were shown to be reactive, with the alkylation occurring exclusively at the β-indolic carbon. The presence of an electron-withdrawing carboxylate at the 2-position of the indole rendered the indole inactive and failed to give the desired product (Table 1, entry 8). However, the presence of a bulky phenyl group at the 2-position did not seem to affect the indole reactivity, as was witnessed by the formation of **5b** (Table 1, entry 2). Surprisingly, the 5-methoxy-2-methyl-indole failed to generate the desired product, presumably due to a competitive side reaction with ACE-Cl (Table 1, entry 9).

Amongst a series of oxygenated aromatics being tested,[11] 3,4,5-trimethoxyphenol was that found to insert to the azonino nucleus during the fragmentation of indolizinoindoles **3a** and **3b** (Scheme 1). Indeed, treatment of **3a** with ACE-Cl (1.2 equiv), in the presence of 3,4,5-trimethoxyphenol (1.1 equiv), gave phenol adduct **7a**. However, spirolactone **8**, instead of ester **7b**, was formed from substrate **3b** under the same reaction conditions. Attempts to generate compound **7b** were not fruitful and spirolactone **8** was obtained as the sole product, presumably via an intramolecular lactonization reaction between the C7 carboxymethyl group and the neighboring phenolic hydroxyl. Similarly, spirolactone **11** resulted from the reaction of **3b** with 4-chlorophenyl chloroformate and 3,4,5-trimethoxyphenol.[12] Subsequently, cleavage of the crude carbamates **7a** and **8** with MeOH at 50 °C afforded 3,4,5-trimethoxy-2-{octahydroazonino[5,4-*b*]indol-7-yl}phenol **9** (Table 1, entry 16) and 4′,5′,6′-trimethoxy-hexahydro-2*H*-spiro{azonino[5,4-*b*]indole-7,3′-[1]benzofuran}-2′-one **10** (Table 1, entry 17), respectively.

Furthermore, we found that treatment of **3a** with $(Boc)_2O$ (1.2 equiv) as the acylating agent,[13] in the presence of *N*-methyl indole as well as 2-(4-fluoro)phenyl indole (1.1 equiv), allowed access to the corresponding *N*-Boc-protected azonino[5,4-*b*]indoles **12** and **13**, respectively (Scheme 2). In contrast, ester substrate **3b** failed to undergo a ring expansion under the same reaction conditions and starting material was recovered. Should cleavage of the *tert*-butyl carbamates **12** and **13** occur under standard acidic conditions, it would serve as an alternative method for the synthesis of azonines **5a** and **5b**, respectively.



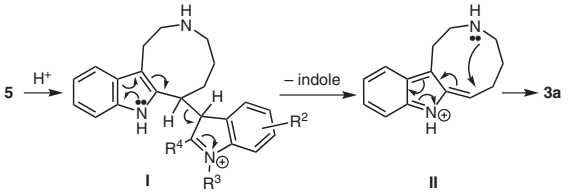
Scheme 2 *N*-Boc-azonino[5,4-*b*]indoles via the fragmentation of **3a** with $(Boc)_2O$

Table 1 One-Pot Synthesis of 7-Aryl-octahydroazonino[5,4-*b*]-indoles via a Three-Component Reaction

Entry	Compound	R^1	$R^{2,c}$	R^3	R^4	Yield (%)[a]
1	**5a**	H	H	Me	H	45
2	**5b**	H	H	H	4-FC_6H_4	30
3	**5c**	H	H	H	Me	41
4	**5d**	H	5-F	H	H	38
5	**5e**	H	7-Me	H	H	40
6	**5f**	H	4-MeO	Me	H	43
7	**5g**	H	7-Cl	H	H	42
8	**5h**	H	H	H	CO_2Et	0[b]
9	**5i**	H	5-MeO	H	Me	0[b]
10	**6a**	CO_2Me	H	Me	H	42
11	**6b**	CO_2Me	H	H	H	44
12	**6c**	CO_2Me	4-Cl	H	H	21
13	**6d**	CO_2Me	5-Cl	H	Me	39
14	**6e**	CO_2Me	H	Me	Me	38
15	**6f**	CO_2Me	6-MeO	H	H	40
16	**9**	H	–	–	–	45
17	**10**	–	–	–	–	31

[a] Isolated yields of purified products. All compounds produced satisfactory ^1H NMR, ^{13}C NMR, and mass spectra.[14]
[b] Trace amounts of product were detected by LC–MS.
[c] Numbering is based on the starting material indole.

When carbamates **12** and **13** were treated with a slight excess of TFA in DCE (6–8 equiv) or HCl (2 equiv) in dioxane, they failed to produce azonines **5a** and **5b**, respectively. Indeed, formation of **3a** was observed in all instances. The labile nature of **5a** and **5b**, when in the presence of acid, may account for the rise of **3a**.[15] The mechanism for the formation of **3a** may presumably involve protonation of **5** at the pendant indole to give indolium intermediate **I**. Indole release from **I** could generate iminium intermediate **II**, which could then be converted into indolizinoindole **3a** (Scheme 3).



Scheme 3 Acid-induced decomposition of azonino[5,4-*b*]indole **5**

The $(Boc)_2O$-induced fragmentation of indolizinoindoles might provide a complementary approach for the synthesis of several azonino[5,4-*b*]indoles. However, the lack of reactivity of ester substrate **3b**, coupled with the acid-labile nature of azonines **5**, kept us from pursuing this scheme any further. The chemistry depicted in Scheme 1 illustrates the one-pot synthesis of new versatile azonino[5,4-*b*]indole scaffolds from a common intermediate through a key-bond-breaking reaction, followed by the insertion of an aromatic nucleophile. Although the synthesis of these compounds is achieved in moderate yields, further elaboration of the secondary azonine nitrogen center as well as the C7 carboxymethyl group may lead to new chemotypes and thus enhance the search for new bioactive[16] azonino[5,4-*b*]indoles. The methods described here could also enable the high-throughput solution-phase synthesis of a diverse set of azonino[5,4-*b*]indoles desirable for drug discovery. The preparation of such screening libraries will be communicated in due course.

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References and Notes

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(3) Magnus, P.; Ladlow, M.; Elliott, J. *J. Am. Chem. Soc.* **1987**, *109*, 7929.
(4) (a) Houlihan, W. J.; Manning, R. E. US 3,478,051, **1969**. (b) Herbst, D. R.; Smith, H. US 3,943,148, **1976**. (c) Herbst, D.; Rees, R.; Hughes, G. A.; Smith, H. *J. Med. Chem.* **1966**, *9*, 864.
(5) (a) Calverley, M. J. *J. Chem. Soc., Chem. Commun.* **1981**, 1209. (b) Calverley, M. J.; Harley-Mason, J.; Quarrie, S. A.; Edwards, P. D. *Tetrahedron* **1981**, *22*, 1635. (c) Schill, G.; Priester, C. U.; Windhövell, U. F.; Fritz, H. *Helv. Chim. Acta* **1986**, *69*, 438.
(6) (a) Magnus, P.; Ladlow, M.; Elliott, J.; Kim, C. S. *J. Chem. Soc., Chem. Commun.* **1989**, 518. (b) Takahashi, T.; Inoue, H.; Horigome, M.; Momose, K.; Sugita, M.; Katsuyama, K.; Suzuki, C.; Nagai, S.; Nagase, M.; Nakamaru, K. EP 535529, **1997**.
(7) Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081.
(8) Corsano, S.; Algieri, S. *Ann. Chim.* **1960**, *50*, 75.

(9) Fokas, D.; Wang, Z. *Synth. Commun.* **2008**, *38*, 3816.
(10) Reaction was found to work equally well in other chlorinated solvents such as CH_2Cl_2 and $CHCl_3$.
(11) Attempts to achieve the same insertion reaction with 1,2 dimethoxybenzene as well as other less oxygenated phenols such as phenol, 4-methoxyphenol, 4-methylphenol, and 4-bromophenol, failed to generate the desired products.
(12) Compound **11** was isolated in 47% yield after purification by preparative TLC with EtOAc–hexanes (1:4) as the eluent: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, 2 H, *J* = 7.0 Hz), 7.24–7.02 (m, 5 H), 6.94 (d, 1 H, *J* = 7.0 Hz), 6.75 (d, 1 H, *J* = 7.4 Hz), 6.53 (s, 1 H), 4.10 (m, 1 H), 3.87 (s, 3 H), 3.79 (s, 3 H), 3.74 (s, 3 H), 3.64 (m, 2 H), 3.38 (m, 3 H), 2.80 (br s, 1 H), 2.20 (br s, 2 H), 2.10 (s, 1 H). MS (ES$^+$): *m/z* calcd for $C_{31}H_{29}ClN_2O_7$: 576.17; found: 577.10 [M + H]$^+$.
(13) For the reaction of **3a** with carboxylic acid anhydrides, see: (a) Schill, G.; Loewer, H.; Priester, C. U.; Windhöevel, U. F.; Fritz, H. *Tetrahedron* **1987**, *43*, 3729. (b) Harley-Mason, J.; Atta-ur-Rahman *Tetrahedron* **1980**, *36*, 1057. (c) Foster, G. H.; Harley-Mason, J.; Waterfield, W. R. *J. Chem. Soc., Chem. Commun.* **1967**, 21.
(14) **Typical Experimental Procedure for the Synthesis of 7-Aryl-octahydroazonino[5,4-*b*]indoles 5, 6, 9, and 10**
To a solution of indolizinoindole **3** (0.1 mmol) and aromatic nucleophile (1.1 equiv) in DCE at r.t., α-chloroethyl chloroformate (1.2 equiv) was added. The reaction mixture was stirred at r.t. overnight and then treated with MeOH (1 mL) at 50 °C for 1 h. The reaction mixture was then concentrated and the crude product was purified by silica gel column chromatography with CH_2Cl_2–MeOH (from 100:0 to 90:10) as the eluent.
Spectroscopic Data for Selected Compounds
Compound **5g**: ^{1}H NMR (400 MHz, CD_3OD): δ = 7.52 (m, 1 H), 7.26 (s, 1 H), 7.22–7.17 (m, 2 H), 7.07–7.02 (m, 3 H), 6.80 (t, 1 H, *J* = 7.8 Hz), 4.75 (t, 1 H, *J* = 9.0, 7.0 Hz), 3.55–3.38 (m, 3 H), 3.30–3.20 (m, 2 H), 3.10 (m, 1 H), 2.45 (m, 2 H), 1.93 (m, 1 H), 1.65 (m, 1 H). ^{13}C NMR (100.6 MHz, CD_3OD): δ = 138.1, 136.5, 134.1, 128.7, 127.6, 122.9, 121.3, 120.9, 119.5, 119.0, 117.9, 117.5, 117.2, 116.5, 111.0, 106.5, 46.9, 44.9, 33.9, 30.8, 23.7, 20.8. MS (ES$^+$): *m/z* calcd for $C_{22}H_{22}ClN_3$: 363.15; found: 364.08 [M + H]$^+$.
Compound **6a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70–8.80 (br s, 1 H), 7.42 (d, 1 H, *J* = 8.4 Hz), 7.35–7.17 (m, 5 H), 7.11 (t, 1 H, *J* = 7.7, 7.0 Hz), 7.07 (s, 1 H), 6.98 (t, 1 H, *J* = 7.7, 7.3 Hz), 3.76 (s, 3 H), 3.73 (s, 3 H), 3.50–3.25 (m, 6 H), 3.15 (m, 1 H), 3.00 (br s, 1 H), 2.85 (s, 1 H), 2.00 (br s, 1 H), 1.90 (s, 1 H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 174.5, 137.6, 134.8, 133.9, 127.8, 125.8, 122.7, 122.2, 120.1, 119.9, 117.9, 115.7, 111.6, 110.0, 109.8, 109.4, 53.2, 51.7, 46.8, 44.6, 33.2, 32.4, 23.6, 22.4. MS (ES$^+$): *m/z* calcd for $C_{25}H_{27}N_3O_2$: 401.21; found: 402.19 [M + H]$^+$.
Compound **9**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.17 (br s, 1 H), 7.35 (d, 1 H, *J* = 7.4 Hz), 7.25 (d, 1 H, *J* = 6.7 Hz), 7.07 (m, 2 H), 6.56 (s, 1 H), 4.97 (d, 1 H, *J* = 9.0 Hz), 3.98 (s, 3 H), 3.80 (s, 3 H), 3.76 (s, 3 H), 3.50–3.30 (m, 3 H), 3.25–2.95 (m, 3 H), 2.78 (br s, 1 H), 2.10 (br s, 1 H), 1.98 (s, 1 H), 1.78 (br s, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 152.9, 151.7, 150.6, 139.9, 136.4, 135.9, 129.6, 127.1, 122.1, 119.6, 117.5, 115.5, 111.3, 98.6, 62.0, 61.2, 56.1, 47.6, 46.2, 33.5, 31.7, 25.4, 21.5. MS (ES$^+$): *m/z* calcd for $C_{23}H_{28}N_2O_4$: 396.20; found: 397.04 [M + H]$^+$.
Compound **10**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.80 (br s, 1 H), 7.66 (br s, 1 H), 7.46 (d, 1 H, *J* = 7.4 Hz), 7.23–7.11 (m, 3 H), 6.60 (s, 1 H), 3.91 (s, 3 H), 3.82 (s, 3 H), 3.79 (s, 3 H), 3.70 (m, 1 H), 3.58 (br s, 2 H), 3.38 (s, 3 H), 3.17–2.82 (br s, 1 H), 2.80–2.50 (br s, 1 H), 2.35 (s, 1 H), 2.20 (s, 1 H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 176.1, 156.0, 150.2, 148.9, 138.8, 135.1, 129.2, 128.5, 123.4, 120.6, 118.1, 113.5, 112.1, 111.1, 92.2, 61.4, 61.1, 56.7, 47.1, 43.9, 36.6, 33.0, 23.9, 22.0. MS (ES$^+$): *m/z* calcd for $C_{24}H_{26}N_2O_5$: 422.18; found: 423.04 [M + H]$^+$.
(15) Indolylazonines **5** were found to be acid sensitive. They gradually decomposed when samples were dissolved in $CDCl_3$, presumably by traces of HCl present in the solvent. In contrast, no decomposition was observed when samples were dissolved in CD_3OD and stored at r.t. for over two weeks. Indolylazonines **6** were found to be stable when dissolved in $CDCl_3$.
(16) A series of 7-alkyl and 7-aryl-octahydroazonino[5,4-*b*]indoles have exhibited a wide range of biological properties as CNS stimulants, antidepressants, anti-inflammatories, diuretics, and anti-ulcer agents. For more information, see ref. 4 and 6b.