Electron Impact Induced Fragmentation of Some 7-(*o*- and *p*-R-Benzylidene)-3-(*o*- and *p*-R-Phenyl)-3,3a,4,5,6,7-hexahydro-2*H*-indazoles. I

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The mass spectral fragmentation patterns of ten 7-(*o*- and *p*-R-benzylidene)-3-(*o*- and *p*-R-phenyl)-3,3a,4,5,6,7-hexahydro-2*H*-indazoles, I, obtained by electron impact have been studied. All the spectra analyzed contain molecular ions and the principal fragmentation routes take place either from the molecular ion, or from (M^+ -1) ion. Likewise, our investigation of the mass spectra of these compounds revealed interesting relationships between the substitution pattern in the framework of I and the fragmenation pathways.

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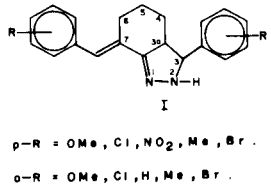
In the course of our mass spectrometric and synthetic investigations of compounds with possible pharmacological activity, we undertook the study of the 2*H*-indazoles of general formula I (Scheme I) since several reports [3] indicated that they exhibited antiinflammatory activity and a CNS depressant profile [4].



I

p–R = OMe, Cl, NO_2, Me, Br.

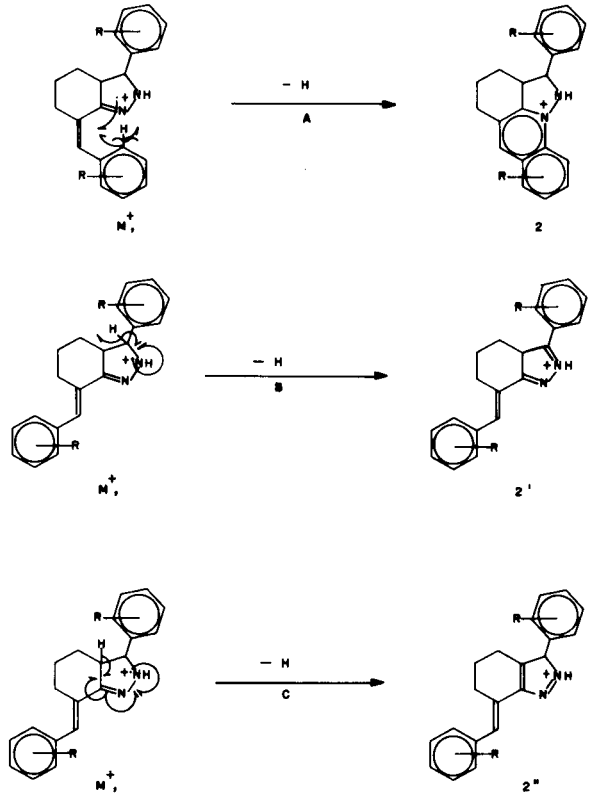
o–R = OMe, Cl, H, Me, Br.

Scheme I

In this paper we described the elucidation of fragmentation patterns and mechanisms of I. The relative abundances of relevant ions obtained as primary fragmentation products and discussed in this paper are reported in Table 1 and the proposed fragmentation patterns in Schemes 2-7. These latter have been justified by the existence of metastable ions and by comparison with the fragmentation patterns of known compounds.

The molecular ions, (M^+), **1**, were clearly observed in the electron impact mass spectra of all ten derivatives. A striking feature of the spectra of the ten 2*H*-indazoles, I, is a large peak at m/e (M^+-1), **2**. Based on the behaviour under electron impact of benzylidenecyclohexanone oximes [5] and on the careful examination of relative abundance listed in Table 1, which show that: a) For the compounds with the R-substituent of the 7-benzylidene group on *para* position the relative abundance of **2** is the base peak for all the compounds; b) In the case of compounds with the R-substituent of the 7-benzylidene group on *ortho* position, the relative abundance of **2** ion is less abundant than 100%, three pathways are feasible for the formation of the ion **2** from the molecular ion conforming with the view that loss of a hydrogen atom is less favorable in the *o*-R-derivatives than in the *p*-R-compounds and one of them invoking an *ortho* interaction of the *o*-R-substituent on the 7-benzylidene group with the 1 ring nitrogen atom of 2*H*-indazoles.

In one pathway, loss of an *o*-hydrogen atom from the 7-(*p*-R-benzylidene)-substituent leads to the (M^+-1) ion, **2**, which is depicted as a dihydropyrazole-tetrahydroacridine cation (A, Scheme 2). In this pathway, a prior *E* to *Z* isomerization is necessary before the intramolecular substitution can occur and the high relative abundance of **2** for *para*-R-compounds is explained by the presence of the R substituents on the *para* position which permits the possibility of loss easily of any one of the *o*-hydrogens.



Scheme 2

Table 1

Relative Abundance of Principal Fragments of I (Figures in parentheses indicate the nature of the ions)

Compound No.	R	m/e M$^+$ (1)	M$^+$-1 (2)	M$^+$-R (3)	(183 + R) (2a)	(181 + R) (2b)	(103 + R) (2c)	(90 + R) (4)	182 (3a)
1	H	35.7	100.0	—	7.3	30.40	9.80	23.9	30.40
2	*p*-OMe	50.0	100.0	—	12.2	19.51	7.31	14.63	2.43
3	*p*-Cl	51.1	100.0	—	16.09	47.90	19.5	31.70	18.3
4	*p*-NO_2	37.4	100.0	—	—	12.2	6.1	—	9.8
5	*p*-CH_3	55.1	100.0	—	14.90	27.0	6.1	4.90	6.1
6	*p*-Br	24.4	100.0	—	6.10	14.70	14.63	8.60	14.63
7	*o*-OMe	23.2	14.7	100.0	2.5	8.60	2.5	13.0	54.5
8	*o*-Cl	60.97	70.00	100.0	4.9	26.83	13.0	26.83	91.70
9	*o*-CH_3	35.4	46.90	100.0	7.31	21.95	7.31	6.09	4.44
10	*o*-Br	21.95	26.82	36.1	2.43	11.0	100.0	12.20	100.0

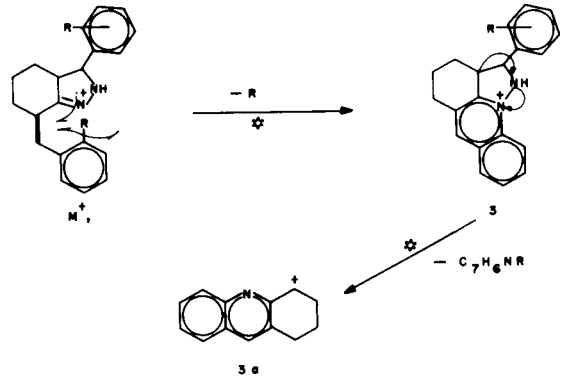
Table 2

Analytical and Physical Data for Compounds I

Compound No.	R	Mp °C	Yield %	Molecular Formula	Analyses, % C	H	N
1 [a]	H	67-69	72.0	$C_{20}H_{20}N_2$	83.29 (83.26)	6.99 (7.01)	9.71 (9.74)
2 [a]	*p*-OMe	78-80	72.9	$C_{22}H_{24}N_2O_2$	75.83 (75.80)	6.94 (6.99)	8.04 (8.00)
3	*p*-Cl	106-109	56.52	$C_{20}H_{18}Cl_2N_2$	67.23 (67.21)	5.07 (5.01)	7.84 (7.87)
4	*p*-NO_2	186-188	45.72	$C_{20}H_{18}N_4O_4$	63.48 (63.50)	4.79 (4.82)	14.80 (14.85)
5	*p*-CH_3	78-81	63.00	$C_{22}H_{24}N_2$	83.50 (83.53)	7.64 (7.66)	8.85 (8.87)
6	*p*-Br	110-112	58.50	$C_{20}H_{18}Br_2N_2$	53.83 (53.80)	4.06 (4.10)	6.28 (6.30)
7	*o*-OMe	82-84	65.0	$C_{22}H_{24}N_2O_2$	75.83 (75.88)	6.94 (7.00)	8.04 (8.11)
8	*o*-Cl	84-86	41.96	$C_{20}H_{18}Cl_2N_2$	67.23 (67.21)	5.07 (5.12)	7.84 (7.90)
9	*o*-CH_3	88-90	66.75	$C_{22}H_{24}N_2$	83.50 (83.52)	7.64 (7.70)	8.85 (8.90)
10	*o*-Br	108-111	86.90	$C_{20}H_{18}Br_2N_2$	53.83 (53.81)	4.06 (4.11)	6.28 (6.30)

[a] Prepared by A. K. El-Shafei [6].

Contrary to what has been observed in the *para*-R-compounds, I, the loss of an *o*-hydrogen atom from the molecular ion in the *ortho*-R-compounds, appear to be inhibited by the presence of these bulky groups. This indicates that the major part of **2** ion on the *para*-R-derivatives are due to the elimination of one *ortho*-hydrogen atom and that in the case of *ortho*-R-compounds would be proposed a second pathway. In this pathway the lost of the 3-hydrogen atom from **1** by a β-rupture with respect to the 2 ring nitrogen of 2*H*-indazole moiety yields **2′** as shown in Scheme 2, B. On the other hand, elimination of 4-hydrogen atom of 2*H*-indazole framework (C, Scheme 2) cannot be excluded.

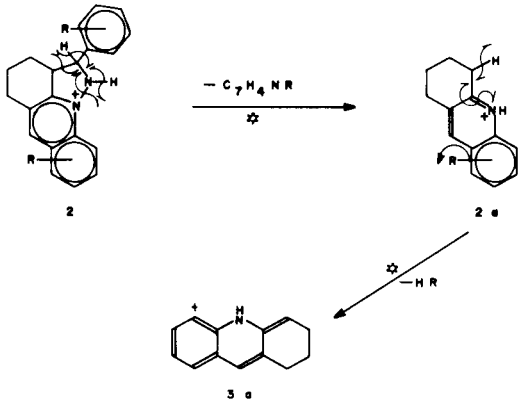


Scheme 3

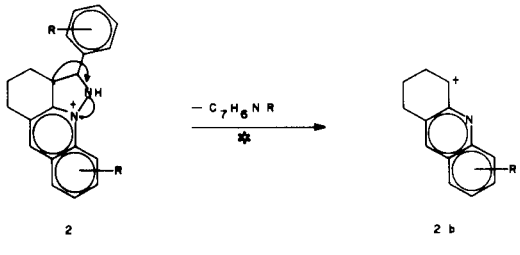
One major fragmentation route from the molecular ions of *ortho*-R-compounds studied involves the loss of the R-substituent which gives rise to an ion at m/e (M^+-R), **3**, base peak for the compounds with *o*-R = -OMe and Me-. The (M^+-R) peak is either absent or its intensity negligible in all the *para*-R-compounds analyzed.

This **3**, ion, presumably has the dihydroindazole-tetrahydroacridinium structure and is formed by a loss of the *ortho*-R-substituent after *E* to *Z* isomerization has occurred. This fragmentation is favored since in the *Z* isomer the *ortho*-R-substituent and the 1 ring nitrogen of indazole moiety are in close proximity and loss of the *ortho*-R-substituent is favored. This situation is quite impossible, however, for *para*-R isomers. Likewise, this fragmentation pathway supports the fragmentation pattern mechanism proposed above for the loss of one *ortho*-hydrogen atom (see Scheme 2, A) in the *ortho*-R-2*H*-indazoles, I. In another hand, the loss of a C_7H_6NR unit from **3** gives the ion of m/e 182, **3a** (Scheme 3).

Other fragmentations observed in the mass spectra of almost all the 2*H*-indazoles, I, studied arising from **2**. Fragmentation of **2** proceeds along three pathways; in one pathway **2** gives rise to m/e (183 + R), **2a**, in one step by the loss of a R-benzonitrile molecule together with the transfer of two hydrogen atoms as shown in Scheme 4. Expulsion of the R-substituent as HR from **2a** leads to the formation of hexahydro acridinium ion **3a**.

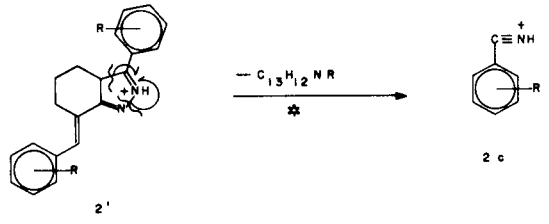


Scheme 4



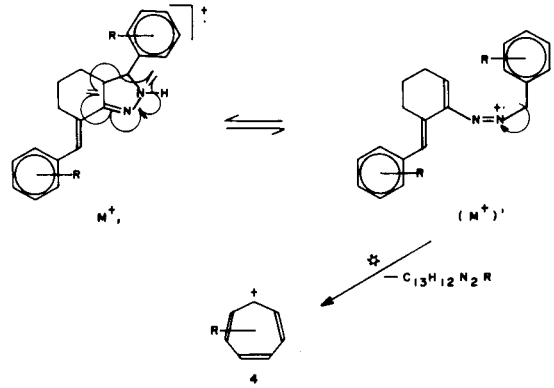
Scheme 5

In another pathway, derived from breakdown of the pyrazole ring, elimination of a benzylimine unit (C_7H_6HR) from **2** affords an ion at m/e (181 + R), **2b** (Scheme 5). In the third pathway (Scheme 6) loss of a $C_{13}H_{12}NR$ moiety from **2′** yields the ion **2c** of m/e (103 + R).



Scheme 6

In addition to the fragments discussed above, the mass spectra of I has also exhibited another characteristic fragment at m/e (90 + R), **4**, which arising from cleavage of the heterocyclic C_3-C_4 bond to form the $(M^+)'$ which undergoes β-cleavage with respect to the N-1 to form **4** (Scheme 7).



Scheme 7

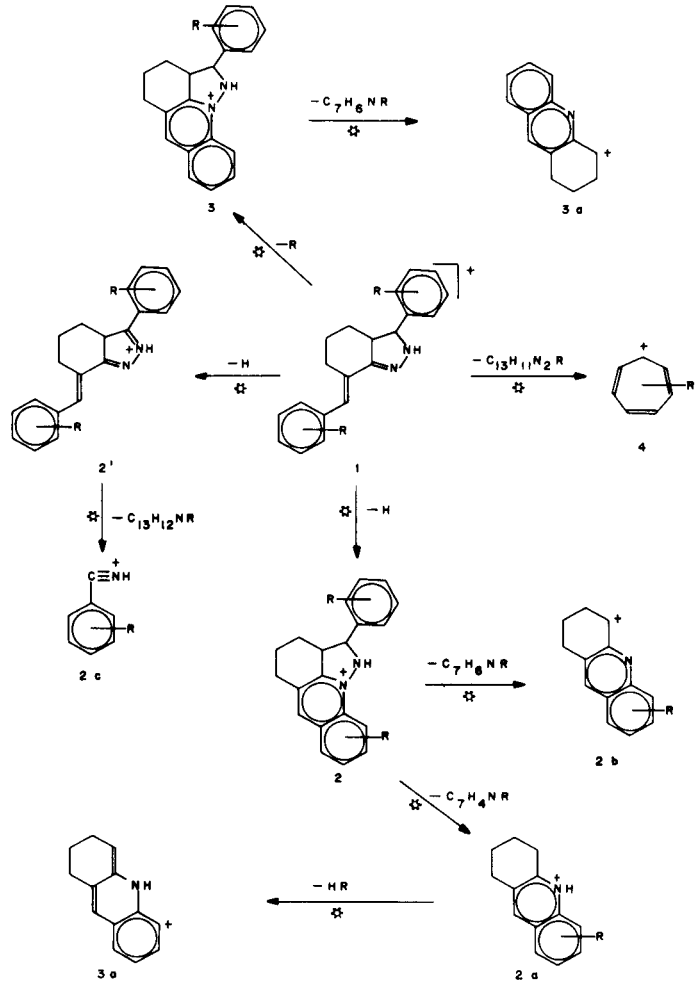
In conclusion, the fragment **2,2′,2a,2b,2c,3,3a** and **4** may be considered as characteristic peaks of patterns of fragmentation of 2*H*-indazoles (I), (Scheme 8).

EXPERIMENTAL

The compounds were synthesized following reported procedures [6] with some modifications. The structures of compounds **1** to **10** were supported by ir and ^{1}H-nmr spectral data.

The ir spectra (Nujol) for all compounds showed bands at 3250-3200 (m, -NH); 1600 (w, C=N); 1590, 1500, 750-730 (-C=C) cm^{-1}. Besides these, bands for the R substituents are also shown.

The ^{1}H-nmr spectra (deuteriochloroform) of compound **1** (R = H) had signals at 7.6-7.1 ppm (11H, m, Ar and 1H, =CH-), 4.45 (1H, d, J = 14 Hz, N-CH), 6.1-5.9 (1H, bs, -NH), 3.2-1.25 (7H, m, aliphatic). The ^{1}H-nmr spectra of the other compounds analyzed also showed these characteristic signals with modifications on their chemical shifts due to the *ortho* and *para*-R-substituents.



Scheme 8

Melting points are uncorrected. The ir spectra were recorded on a Perkin-Elmer 283-B spectrophotometer. The ^{1}H-nmr spectra were recorded on a Varian FT-80A spectrometer operating at 80 MHz in deuteriochloroform solution containing tetramethylsilane as internal standard with chemical shifts (δ) expressed downfield from TMS. Mass spectra were obtained with a Perkin-Elmer RMU-7H double focusing mass spectrometer and a Hewlett Packard 59854-A quadropole mass spectrometer using the direct inlet system. The samples were recorded at an ionization chamber temperature of 210° and operating at 70 eV.

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REFERENCES AND NOTES

[1] To whom correspondence should be addressed.

[2] Contribution No. 719 from Instituto de Química.

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