7. H. G. Rajaharison and C. M. Roussel, European Patent 69,641; Chem. Abs., 101, 23334 (1984).
8. M. Bkhaumik, Dissertation, Moscow State University (1985), p. 95.
9. P. J. von Rijn, Rec. Trav. Cheim., 45, 267 (1926).
10. E. Profft and F. Melichan, J. Prakt. Chem., 274, 87 (1955).

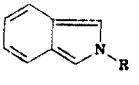
ISOINDOLES FROM PHTHALIMIDINES. N-ARYLISOINDOLES

V. A. Kovtunenko, T. T. Kucherenko,
M. Yu. Kornilov, A. K. Tyltin,
A. V. Turov, and F. S. Babichev

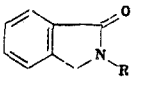
UDC 547.759.4.07:542.942.4:
543.422.25

A convenient method was developed for the preparation of N-arylisoindoles by the reduction of the corresponding phthalimidines.

Several methods have been described for the preparation of N-arylisoindoles I, but none of them can be considered satisfactory [1]. Thus, we could not reproduce the synthesis of compound Ib via N-(4'tolyl)isoindoline N-oxide by the Polonskii reaction described in a brief communication [2]. Then we attempted to carry out the method of Wittig et al. [3], consisting in the reduction of phthalimidines IIa-d by lithium aluminum hydride. However, the main products of the reduction were the corresponding isoindolines, and the formation of trace amounts of isoindoles could be determined only chromatographically.



I



II

I, II a R=C_6H_5, b R=4'-$C_6H_4CH_3$, c R=4'-BrC_6H_4, d R=CH_3

We were able to obtain isoindoles Ia-d by the reduction of phthalimidines IIa-d with lithium bis(2-methoxyethoxy)aluminum hydride [4] used as a solution in benzene or toluene. As a rule, as a side product in the reaction, from 5 to 10% of the corresponding isoindoline was formed, which could be avoided by using its solubility in cold ether, which is better than that of isoindoles. N-arylisoindoles Ia-d could be obtained in yields from 70 to 80% by the proposed method (Table 1). All the synthesized isoindoles are colorless crystalline substances, and Ia-c are much more stable than Id.

In the proton NMR spectra of isoindoles Ia-d (Table 1), the 1,3-H protons gave a somewhat broadened singlet. The 4,7-H and 5,6-H protons in the spectrum gave two multiplets (Fig. 1). The components of one of them, located in a weaker field, were somewhat broadened because of interaction with 1,3-H protons (spin-spin coupling constant of 1 Hz [5]). We carried out a calculation with the PANIC iteration program to determine the values of the spin-spin coupling constants and to verify the indicated assignment of the proton signals (Fig. 1). The best correspondence between the calculated and experimental spectra was found with the chemical shifts indicated in Table 1 and the following values of the spin-spin coupling constants: $J_{1-7} = J_{3-4} = 0.8$; $J_{4-5} = J_{6-7} = 9$; $J_{5-6} = 6.3$; $J_{4-6} = J_{5-7} = 0.9$; $J_{4-7} = 0.77$ Hz. As shown by experiments, the nature of the substituent at the nitrogen atom of isoindole has practically no effect on the values of the spin-spin coupling constants of the protons of the isoindole fragment. As was accepted in [6], we tried to use the above-determined values of the spin-spin coupling constants of the vicinal protons of the carbocyclic part of isoindole as the aromaticity index. Our value of $J_{rel} = (J_{5-6}/J_{4-5}) = 0.7$ corresponds to the data for 2-methyl- and 1,3-diphenyl-2-methylisoindoles [1] and indicates partial localization of the bonds in the carbocyclic part of the molecule of the N-arylisoindoles.

The N-arylisoindoles have four absorption bands (Fig. 2), whereas the N-methyl derivative has only two distinct ones. In all the isoindoles, the long-wave absorption band at

T. G. Shevchenko Kiev State University, Kiev 252017. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1629-1631, December, 1987. Original article submitted July 23, 1986; revision submitted April 15, 1987.

 0009-3122/87/2312-1308$12.50

TABLE 1. Constants and Spectral Characteristics of Compounds Ia-d

Compound*	T_{mp}, °C** (with decomp.)	ΔpK_a	Proton chemical shifts				IR spectra, cm^{-1}				Found, %			Empirical formula	Calculated, %			Yield, %
			1-H, 3-H (s)	4-H, 7-H (q)	5-H, 6-H (q)	2-R	ν_{C-H} (weak)	stretching vibrations of ring system	$\nu_{C=N}$ (strong)	ν_{C-H}	C	H	N(Br)		C	H	N(Br)	
Ia	143–144 (143–143.5 [3])	5.9	7.80	7.52	6.88	7.74 s	3130, 2910, 3060, 2860, 3030	1630 m, 1595 s, 1460 s, 1365 s, 1540 m, 1435 s, 1340 s, 1505 vs	1220, 1200 (bend)	1050, 795 m, 1030, 755 vs	87.3	5.9	7.0	$C_{14}H_{11}N$	87.0	5.7	7.2	80
Ib	170–171 (173.4 [2])	5.8	7.76	7.52	6.87	7.76 d 7.35 d 2.37 s	3120, 2910, 3060, 2860, 3030	1630 m, 1560 m 1485 m, 1617 s, 1367 s, 1520 vs, 1440 s, 1345 s.	1218, 1200	1055, 825 s, 1022, 760 vs.	86.3	6.4	6.7	$C_{15}H_{13}N$	86.9	6.3	6.8	65
Ic	178–180	6.7	7.82	7.52	6.89	7.75 s	3130, 2910, 3065, 2860, 3030	1630 m, 1590 s, 1440 s, 1365 s, 1545 m, 1415 m, 1345 s, 1503 vs.	1214, 1200	1053, 830 s, 1013, 765 vs.			5.2 (29.3)	$C_{14}H_{10}BrN$			5.2 (29.4)	70
Id	90 (90–91 [11])	1.2	7.19	7.43	6.78	3.94 s	3110, 2940, 3060, 2850, 3030	1640 m, 1545 m, 1477 s, 1625 s, 1365 s 1520 vs 1413 s, 1335 s.	1237, 1203	1023, 815 m. 760 vs.	81.9	7.0	10.6	C_9H_9N	82.4	6.9	10.7	70

*N-(4-Anisyl)isoindole was also synthesized in 61% yield, mp 177-178°C (with decomposition); according to the data of [2], mp 175-176°C; found ΔpK_α 5.5.

**All the isoindoles were purified by recrystallization from 2-propanol.

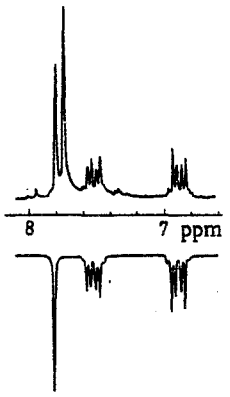


Fig. 1

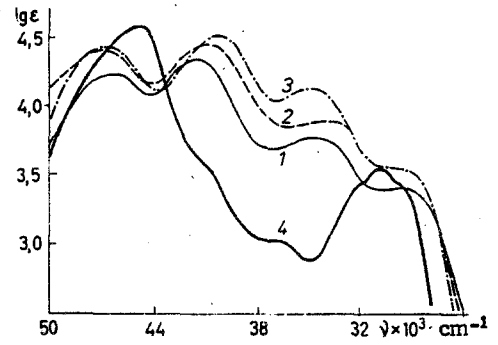


Fig. 2

Fig. 1. Fragment of the experimental proton NMR spectrum of 4-(4-bromophenyl)isoindole Ic in DMSO-D_6 (above) and the same area of the spectrum of isoindole fragment Ic calculated according to the PANIC program for the AA'BB'CC' system.

Fig. 2. UV spectra of isoindoles Ia-d (in alcohol): 1) Ia; 2) Ib; 3) Ic; 4) Id.

320-370 nm is due to the presence of an o-quinoid chromophore in their structure [7]. The bending vibrations of the C–H bonds (near 800 cm^{-1}) should probably be assigned to out-of-plane vibrations, as was done in [8], and the absorption bands near 1000 cm^{-1} should probably be assigned to breathing stretching vibrations of the ring system of Ia-d, very characteristic of compounds with a high degree of symmetry [9].

We investigated the basicity of compounds Ia-d by potentiometric titration in a nitromethane medium. The relative measure of the basicity was the value of ΔpK_a, equal to the difference of pK_a of diphenylguanidine (the standard) and pK_a of the substance being tested [10]. An analysis of the obtained results (see Table 1) shows that the N-arylisoindoles are five to six orders less basic than N-methylisoindole, and for the series of N-(4-R-aryl)isoindoles (R = H, Me, OMe, Br) the values of ΔpK_a depend linearly on the values of the Hammett σ-para constants.

EXPERIMENTAL

The melting points were measured on a Boetius heating unit. The purity of the substances was monitored by thin-layer chromatography on Silufol UV-vis plates. The UV spectra were recorded for 0.00005 M solutions of the substances in alcohol on a Specord UV-vis instrument. The IR spectra were recorded for tablets with KBr on a Pye-Unicam SP3-300 instrument. The proton NMR spectra of the substances (in DMSO-D_6) were recorded on a WP-100SY instrument, and the internal standard was TMS. The basicity constants were measured in nitromethane, and the relative measure of the basicity was the value of ΔpK_a, equal to pK_a of diphenylguanidine minus pK_a of the substance being tested. The value of pK_a was determined graphically from the potentiometric-titration curves of 0.0025 M solutions of the substances with a solution of perchloric acid in nitromethane as the pH at the half-neutralization point.

Isoindoles Ia-d. In an argon stream, 7 ml of a 60% toluene solution of the reducing agent was added dropwise to a solution of 10 mmoles of the corresponding phthalimidine IIa-d [12] in 2.8 moles of dry toluene at 20°C. The reaction mixture was stirred at 20°C for 2-3 h. The obtained light-green solution was treated with 6 ml of 25% alkali. The organic layer was separated, dried with magnesium sulfate, and removed at reduced pressure. The solid residue was transferred to a filter and washed with the minimum amount of ether, after which it was crystallized from 2-propanol.

LITERATURE CITED

1. F. S. Babichev and V. A. Kovtunenko, Isoindole Chemistry [in Russian], Naukova Dumka, Kiev (1983), p. 280.
2. R. Kreher and J. Seubert, Angew. Chem., 78, 984 (1966).

3. G. Wittig, G. Closs, and F. Mindermann, Ann. Chem., 594, 89 (1955).
4. M. Černy, J. Málek, M. Čapka, et al., Coll. Czech. Chem. Commun., 34, 1033 (1969).
5. M. H. Palmer and S. M. F. Kennedy, J. Chem. Soc., Perkin 2, No. 1, 81 (1976).
6. P. Crews, R. R. Kinter, and H. C. Padgett, J. Org. Chem., 38, 4391 (1973).
7. V. A. Kovtunenko, Z. V. Voitenko, V. L. Sheptun, A. K. Tyltin, and A. I. Chernega.
8. C. O. Bender and R. Bonnett, J. Chem. Soc., C, No. 24, 3036 (1968).
9. L. Bellamy, New Data on the IR Spectra of Complex Molecules [Russian translation], Mir, Moscow (1971), p. 318.
10. C. A. Streuli, Anal. Chem., 31, 1652 (1959).
11. B. Zeeh and K.-H. König, Synthesis, No. 1, 45 (1972).
12. V. A. Kovtunenko, A. K. Tyltin, T. T. Dobrenko, and F. S. Babichev, Ukr. Khim. Zh., 49, 1099 (1983).

SYNTHESIS OF HETEROCYCLES ON THE BASIS OF IMINOTETRAHYDROCARBAZOLES.

1. 3-BENZYL-8-METHYL-2-OXO-2,3,3a,4,5,6-HEXAHYDRO-1H-PYRAZINO[3,2,1-j,k]-CARBAZOLE

A. I. Bokanov, P. Yu. Ivanov, T. V. Akalaeva, G. A. Bogdanova, and V. I. Shvedov

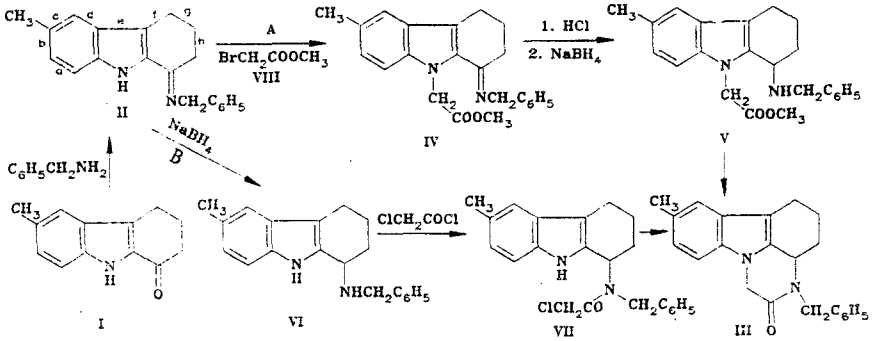
UDC 547.759.2'863.07:543.422

The reaction of 6-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole and benzylamine gave 1-benzylimino-6-methyl-1,2,3,4-tetrahydrocarbazole, which was converted by two methods to a pyrazinocarbazole derivative. The promising character of the use of iminotetrahydrocarbazoles for the synthesis of more complex heterocyclic systems was thereby demonstrated.

6-Methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (I) is an intermediate in the manufacture of the antidepressant pirazidol [1]. The chemical transformations of ketone I were described in [2-4], but the reactions with primary amines were not studied. We have established that 1-benzylimino-6-methyl-1,2,3,4-tetrahydrocarbazole (II) is formed in high yield when a mixture of ketone I and benzylamine in xylene is refluxed.

3-Benzyl-8-methyl-2-oxo-2,3,3a,4,5,6-hexahydro-1H-pyrazino[3,2,1-j,k]carbazole (III) was synthesized via two pathways on the basis of iminocarbazole II.

Pathway A includes alkylation, reduction, and cyclization steps, and the overall yield of pyrazinocarbazole III is 43% based on iminocarbazole II. Pathway B includes reduction, acylation, and cyclization steps, and the overall yield is 42%. It is appropriate to note that an attempt to obtain a 2-oxopyrazino[3,2,1-j,k]carbazole derivative via a different scheme [5] (not through the iminotetrahydrocarbazole) was unsuccessful.



Iminocarbazole II was alkylated with methyl bromoacetate (VIII) in benzene—50% aqueous NaOH solution in the presence of tetrabutylammonium bromide. The optimum time of the pro-

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow 119815. Translated from Khimiya Geterosiklicheskikh Soedinenii, No. 12, pp. 1632-1635, December, 1987. Original article submitted July 2, 1986.

0009-3122/87/2312-1311$12.50