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2-BENZOPYRYLIUM SALTS. XXXI.[1]

ANALOGS OF REISSERT COMPOUNDS FROM 2-BENZOPYRYLIUM SALTS AND SODIUM CYANIDE

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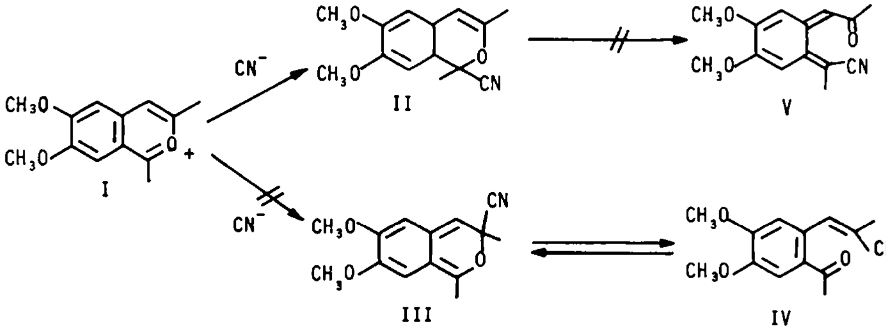
Abstract. *Nucleophilic addition of a cyanide anion to 2-benzopyrylium salts I takes place at the first position and leads to stable isochromenes II, which are oxygen analogs of Reissert compounds. The structure II was confirmed by IR, ^{1}H-NMR and ^{13}C-NMR spectra. The latter spectra reveal clearly the cyano group (which does not yield any observable stretching band) and give evidence for diastereotopic isopropyl carbons (unlike ^{1}H-NMR spectra).*

INTRODUCTION

The interaction between monocyclic pyrylium salts and alkali cyanides with attack in α-position, leading to ring-opened *cis*-cyanoalkadienones, was described.[2,3]

Since the cyanide anion is a mild C-nucleophile and since its addition product to the pyrylium cation does not recyclize to a pyridine or benzenoid ring as it happens with primary or secondary amines and with alkali hydroxides,[4] it was interesting to check the reaction of 2-benzopyrylium salts and sodium cyanide. This mild nucleophile (unable to deprotonate alkyl side-chains and devoid of mobile hydrogens) might add either to the 1st or to the 3rd position ; in the latter case a kinetically controlled reaction would have a larger activation barrier, but the intermediate product III might then ring-open to a benzenoid system IV, whereas the addition product II to position 1 would have no such alternative, because its ring-opened valence isomer V would be *ortho*-quinonoid (although it might recyclize to an α-cyanonaphthalene). The regioselectivity of the nucleophilic attack will be dictated by charge densities in positions 1 and 3.[5]



This investigation seemed also interesting because of the unusual behaviour of 2-benzopyrylium salts in reactions with various N- and O-nucleophiles under different conditions[6,7] and because the interaction with C-nucleophiles has been little investigated.

CNDO/2 CALCULATIONS OF CHARGE DENSITIES

Recent quantum chemical calculations by CNDO/2 method using a standard geometry for 6,7-dimethoxy-1,3-dimethyl-2-benzopyrylium cation (Ib) are in good agreement with the previous Del Bene-Jaffe method[8] and reveal that differences in charge densities between positions 1 and 3 are smaller than it was reported earlier by means of an approximate model.[5] The molecular diagram for the salt Ib is illustrated in Fig. 1.

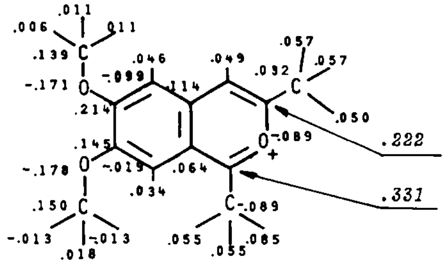


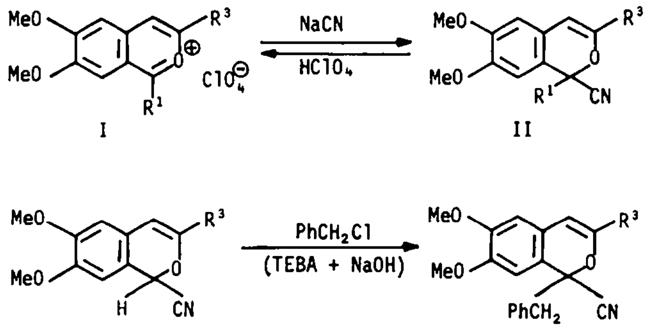
Figure 1.
Charges in Ib calculated with CNDO-2 method for standard geometry.

The ^{13}C-NMR spectrum of this compound is also in a good correlation with literature data.[9] The assignments are to be seen in Table 2 in accordance with the molecular diagram for the cation. The chemical shifts differing from earlier data[9] are marked with an asterisk.

RESULTS

The reaction between isobenzopyrylium salts Ia-g and sodium cyanide under conditions described for monocyclic salts[2] gives stable, colourless products which are pure according to TLC control. Their IR spectra revealed the absence of any nitrile band at 2200 - 2300 cm^{-1} and showed characteristic bands at 1675 and 1620 cm^{-1} for products from 3-alkyl-substituted salts Ia-e and at 1635 and 1600 cm^{-1} for products from 3-aryl-substituted salts If, g ; these bands at 1675 - 1600 cm^{-1} in IR spectra cannot be assigned to carbonyl groups. At the same time the data of elemental analysis showed nitrogen in these compounds in amounts just suitable for the presence of one cyano group in the molecule.

These facts indicate that the reaction between 2-benzopyrylium salts and sodium cyanide was stopped at the stage of the cyanide addition to the heterocycle and was not accompanied by ring opening. The stability of the addition products supports the nucleophilic attack to position 1 with cyanoisochromenes IIa-g as the result :



I II

IIa,g IIe,h

I,II	R^1	R^3
a	H	Me
b	Me	Me
c	iPr	Me
d	Et	Me
e	$PhCH_2$	Me
f	Me	Ph
g	H	$3,4-(MeO)_2C_6H_4$
h	$PhCH_2$	$3,4-(MeO)_2C_6H_4$

The band at 1675 or 1635 cm^{-1} in the IR spectra apparently is a C=C bond stretching vibration and is in a good correlation with the nature of the substituent in position 3 of the heterocycle.[10] The absence of a C≡N stretching band in the IR spectra was mentioned also for Reissert compounds[11] and cyanohydrines,[12] but no satisfactory explanation of this interesting fact has been given. Since 1-cyanoisochromenes IIa-g are oxygen analogs of Reissert compounds, this "rule" obviously applies to them as well as to 1-cyanoisochromanes[13] and to the only example of 1-cyano-1-N-R-amidoisochromenes.[14]

NMR SPECTRA

The ^{1}H-NMR spectra of the new compounds precisely confirm their structure as 1-cyano--isochromenes (TABLE 1).

TABLE 1. ^{1}H-NMR spectra of isochromenes IIa-h in $CDCl_3$ (δ, ppm).

Compound	R^1	R^3	6,7-$(CH_3O)_2$	H-4*	H-5, H-8
IIa	5.95 (1H,s)	2.02 (3H,s,b)	3.92 (6H,s)	5.80 (s,b)	6.60 (1H,s) 6.73 (1H,s)
IIb	2.05 (3H,s)	1.95 (3H,s,b)	3.87 (6H,s)	5.75 (s,b)	6.53 (1H,s) 6.73 (1H,s)
IIc	1.11(6H,d,CH($\underline{CH_3}$)$_2$) 2.55(1H,m,$\underline{CH}$(CH_3)$_2$)	1.62 (3H,s,b)	3.85 (6H,s)	5.53 (s,b)	6.46 (1H,s) 6.77 (1H,s)
IId	1.50 (3H,t,$\underline{CH_3}CH_2$) 3.43 (2H,q,$CH_3\underline{CH_2}$)	1.93 (3H,s,b)	3.83 (6H,s)	5.68 (s,b)	6.57 (1H,s) 6.77 (1H,s)
IIe	3.33 (2H,s,$\underline{CH_2}$Ph) 7.20 (5H,s,CH_2Pb)	1.95 (3H,s,b)	3.73 (3H,s) 3.87 (3H,s)	5.60 (s,b)	6.48 (2H,s)
IIf	2.17 (3H,s)	6.73-7.23 (5H,m)	3.88 (6H,s)	6.50 (s)	6.73 (1H,s) 6.83 (1H,s)
IIg	6.46 (1H,s)	3.92 (6H from 12H,s) 6.93-7.23 (3H arom.,m)	3.92 (6H from 12H,s)	6.01 (s)	6.73 (1H,s) 6.77 (1H,s)
IIh	3.53 (2H,s,$\underline{CH_2}$Ph) 7.30 (5H,s,$CH_2\underline{Ph}$)	3.88 (3H,s,CH_3O) 3.92 (3H,s,CH_3O) 6.90-7.13 (3H,atom.,m)	3.77 (3H,s) 3.84 (3H,s)	6.43 (s)	6.73 (2H,s)

*Abbreviation : b = broad

For the case of 3-methyl-substituted compounds IIa-d,a long-range interaction between H-4 and the 3-methyl group protons takes places leading to broadened singlets. The chemical shift for H-4 is strongly dependent on the nature of the substituent R^3 : when R^3 is an alkyl group (as in IIa-e), the H-4 peak appears at δ = 5.5-5.8 ppm, whereas when R^3 is aromatic (as in IIf-h) the H-4 peak is deshielded to 6.0-6.5 ppm owing to the ring current in R^3 which is coplanar with the chromene system.

The diastereotopic protons of IId, e, h or the diastereotopic methyls of IIc do not give rise to any observable chemical shift non-equivalence, but we shall see later that IIc has magnetically non-equivalent isopropyl methyls in the ^{13}C-NMR spectrum.

The quantum chemical calculations by the CNDO-2 method with standard geometry for the model compound of 1-cyano-6,7-dimethoxy-1,3-dimethylisochromene give the charge distribution and are presented on the molecular diagram in Fig. 2. The ^{1}H-NMR chemical shifts of 1-cyano-isochromene IIa are in good agreement with charge densities in this model.

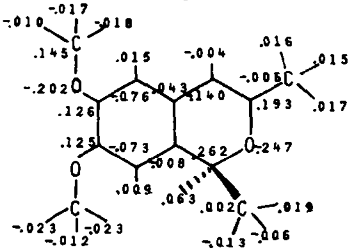


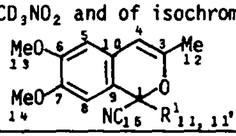
Figure 2.

Charges in IIb calculated with CNDO-2 method for standard geometry.

This fact and the good correlation of the CNDO/2 method with the ^{13}C-NMR data for the 2-benzopyrylium salt Ib made it possible to apply the ^{13}C-NMR spectroscopy also for investigation of 1-cyanoisochromenes. The main purpose of this examination was to provide spectral evidence for the cyano group in compounds having such a "hidden" group (invisible by IR or ^{1}H-NMR methods), e.g. Reissert compounds. So far, no report on the use of ^{13}C-NMR spectroscopy has appeared for Reissert compounds[15] or their oxygen analogs.[13,14]

The ^{13}C-NMR spectra of isochromenes IIa-d are given in TABLE 2 ; for compound IIb, Fig. 3 is also presented.

TABLE 2. ^{13}C-NMR spectra of salt Ib in CD_3NO_2 and of isochromenes IIa-d in $(CD_3)_2CO$ (δ, ppm).



Carbon	Ib (R^1=Me)	IIa (R^1=H)	IIb (R^1=Me)	IIc (R^1=iPr)	IId (R^1=Et)
1	181.04	66.08	73.46	81.73	77.65
3	165.29	151.71	151.48	151.35	151.42
4	107.01*	103.17	103.31	101.99	102.69
5	107.71	108.48	108.45	108.65	108.68
6	164.26	151.14	150.97	150.10	150.50
7	154.40	149.43	149.46	149.18	149.41
8	120.78*	109.58	108.45	109.80	108.83
9	116.42*	115.29	119.75	118.12	118.77
		(22.8)†	(32.3)†	(16.7)†	(29.3)†
10	143.00	124.62	124.78	124.89	124.99
		(21.0)†	(21.9)†	(22.4)†	(40.4)†
11	19.93	-	24.80	27.87	31.19
11'	-	-	-	17.72, 16.53	8.34
12	20.46	19.16	19.23	19.14	19.21
13	57.68	59.17	56.05	56.09	56.11
14	58.85	56.41	56.51	56.65	56.59
15	-	118.20	120.57	119.15	119.82
		(11.0)†	(12.4)†	(11.0)†	(17.0)†

*Assigments corrected on the basis of the CNDO/2 method in comparison with data.[9]
†Intensity of the signal.

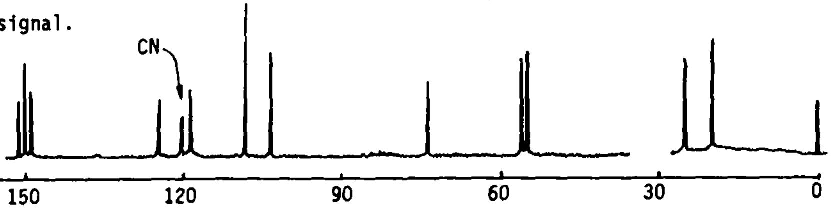


Figure 3.

^{13}C-NMR spectrum of IIb in $(CD_3)_2CO$

Assignments of carbon atom signals are based on data of quantum chemical calculations and on comparisons with literature values for isoquinolines[16] and vinyl ethers[17] with a good agreement of the result. The number of signals corresponds to the number of carbon atoms in 1-cyanoisochromenes IIa-d. One may see, however, that the isopropyl methyls of IIc are magnetically non-equivalent because they are diastereotopic, being bonded to a chirotopic carbon atom. Apparently the cyano group may be one from the three signals in the range 121-115 ppm. The choice between the CN group and atoms C-9 and C-10 in accordance with values of their charges was made on the basis of the signal intensities : these must be similar for both atoms C-9 and C-10. The signal of the CN group with a larger relaxation time is less intense and appears at 120.57-118.20 ppm for isochromenes IIa-d (just between signals of atoms C-9 and C-10). Thus the application of ^{13}C-NMR is successful as spectral evidence for the existence of a cyano group in compounds IIa-g.

ALKYLATION OF ISOCHROMENES IIa AND IIg

Since 1-cyanoisochromenes are analogs of Reissert compounds, it seemed interesting to check the ability of compounds IIa,g to give carbanions with sodium hydride and to undergo alkylation with alkyl halides.[18] This property is known to be important and useful in the chemistry of Reissert compounds.

Initial attempts to alkylate 1-H-1-cyano-3-methylisochromene IIa with ethyl iodide in the presence of sodium hydride were unsuccessful, similarly to reports on 3-methyl-containing Reissert compounds ;[19] however, the phase-transfer method of alkylation in the presence of triethyl-N-benzylammonium chloride (TEBA) described earlier for other compounds (N-acyl-dihydroisoquinaldonitriles[20]), gave good results. Thus, the interaction between compounds IIa, g and benzyl chloride in the presence of TEBA under alkaline conditions gave products of 1-alkylation, namely 1-cyano-1-benzylisochromenes IIe,h. The ^{1}H-NMR spectral data of the newly prepared compound IIh are presented in TABLE 1.

The application of these alkylation reactions may lead to various 1-cyano-1-alkyl(aryl)-isochromenes, which are easily converted with perchloric acid into corresponding 2-benzopyrylium salts, important intermediate products in the synthesis of isoquinolines.

Currently, the behaviour of cyanoisochromenes IIa-h in the presence of alkali hydroxides is under investigation.

EXPERIMENTAL PART

IR spectra were determined with a Jena U. R. 10 IR instrument. ^{1}H-NMR spectra were recorded on a Varian A-60 A spectrometer in $CDCl_3$. ^{13}C-NMR spectra were recorded on a Varian XL spectrometer equipped with a Varian 620 L computer in trideutero-nitromethane. Both noise-decoupled and off-resonance decoupled spectra of compounds IIa-d were recorded to facilitate assignments.

1-Isopropyl-6,7-dimethoxy-3-methyl-2-benzopyrylium perchlorate (Ic) was obtained as it was described in[21] through acylation of 3,4-dimethoxyphenylacetone with isobutyric anhydride in the presence of 70% $HClO_4$ (80% yield). M.p. 202° (from glacial acetic acid). The IR spectrum has characteristic bands of isobenzopyrylium perchlorate.[5] ^{1}H-NMR spectrum in CD_3NO_2 : δ = = 1.52 (3H, s, $CH(C\underline{H}_3)_2$) ; 1.63 (3H, s, $CH(C\underline{H}_3)_2$) ; 2.83 (3H, s, 3-CH_3) ; 4.10, 4.23 (7H, 2s , and m, $2CH_3O$ and $C\underline{H}(CH_3)_2$) ; 7.50 , 7.73 and 7.80 ppm (3H, m, H arom).

Reaction of 2-benzopyrylium salts (IIa-g) with sodium cyanide. The 2-benzopyrylium perchlorate (1 mole) was shaken at room temperature for 3-8 hrs with 15-20% aqueous sodium cyanide (2 moles) in the presence of ethyl ether to assist separation of products. When salts Ia-d,f were completely dissolved, the upper brownish-yellow layer was separated, washed with water, dried ($CaCl_2$) and ethyl ether was removed in vacuum. The isochromenes IIa-d,f were obtained with yields 70-80%.

1-H-Cyano-6,7-dimethoxy-3-methylisochromene (IIa), m.p. 95°.

1-Cyano-6,7-dimethoxy-1,3-dimethylisochromene (IIb), m.p. 84°.

1-Cyano-1-isopropyl-6,7-dimethoxy-3-methylisochromene (IIc), m.p. 92°.

1-Cyano-1-ethyl-6,7-dimethoxy-3-methylisochromene (IId), m.p. 73-5°.

1-Cyano-6,7-dimethoxy-1-methyl-3-phenylisochromene (IIf), m.p. 129°.

1-Cyano-6,7-dimethoxy-3-(3,4-dimethoxyphenyl)isochromene (IIg), insoluble in ether, was prepared in the absence of ether and separated from the mixture by filtration, washed with water, dried and recrystallized from n-propanol, m.p. 165°.

1-Cyano-1-benzyl-6,7-dimethoxy-3-methylisochromene (IIe) was obtained by the same way, but after filtration and washing with water it was dried and then washed first with ether and then extracted into chloroform, followed by filtration. The small amount of residue after this procedure, containing nitrogen according to data of elemental analysis, is now under investigation. The pure isochromene IIe was obtained after evaporating the chloroform with yield 55%, m.p. 164°. From the yellowish ethereal solution 1-benzylidene-6,7dimethoxy-3-methylisochromene was obtained with yield 15% and identified according to its melting point, IR and ^{1}H-NMR spectra obtained in [10].

1-Cyano-1-benzyl-6,7-dimethoxy-3-(3,4-dimethoxyphenyl)isochromene (IIh) was obtained by alkylation [20] of isochromene IIg with benzyl chloride in 50% aqueous sodium hydroxide solution in the presence of catalytic amounts of TEBA. The mixture was stirred for 2 hrs, diluted with double volume of water, filtered off, carefully washed with water, dried and purified from ethanol (yield 90%, m.p. 172°).

1-Benzyl-1-cyano-6,7-dimethoxy-3-methylisochromene (IIi was obtained both from Ie with sodium cyanide, and by alkylation of 1-cyanoisochromene IIa with benzyl chloride in the presence of sodium hydroxide and TEBA (in the latter case the yield was 80%). The comparison of melting points and the ^{1}H-NMR spectra gave no difference with the same characteristics of isochromene, obtained from the salt Ie.

The IR spectra (in $CDCl_3$) of the newly prepared compounds have characteristic bands at 3050—2850, 1680, 1580, 1280 and 1150 cm^{-1} for isochromenes IIa-d and at 3050-2850, 1635, 1600, 1580, 1280 and 1050 cm^{-1} for isochromenes IIf-h.

REFERENCES

1. Part XXX, I.V. Shcherbakova, L. Yu. Ukhin, V.N. Komissarov, E.V. Kuznetsov, A.V. Polyakov, A.I. Yanovskii and Yu. T. Struchkov, *Khim. Geterotsikl. Soedin.*, 1986, in press.
2. A.T. Balaban and C.D. Nenitzescu, *J. Chem. Soc.*, 3566 (1961).
3. A.T. Balaban, T.H. Crawford and R.H. Wiley, *J. Org. Chem.*, 30, 879 (1965).
4. A.T. Balaban, A. Dinculescu, G.N. Dorofeenko, G.W. Fischer, A.V. Koblik, V.V. Mezheritskii and W. Schroth, *"Pyrylium Salts. Syntheses, Reactions, and Physical Properties", Adv. Heterocyclic Chem.* Suppl. Vol. 2, Academic Press, New York, 1982.
5. G.N. Dorofeenko, E.I. Sadekova and V.M. Goncharova, *Khim. Geterotsikl. Soedin.*, 1308 (1970).
6. G.P. Safarjan, I.V. Shcherbakova, G.N. Dorofeenko and E.V. Kuznetsov , *Khim. Geterotsikl. Soedin.*, 1608, (1981).
7. I.V. Korobka, A.I. Voloshina and E.V. Kuznetsov, *Khim. Geterotsikl. Soedin.*, 1472 (1984).
8. J. Del Bene, and H.H. Jaffe, *J. Chem. Phys.*, 48, 1807 (1969).
9. M. Farkas, W. Voelter and M. Vajda, *Acta Chim. Hung.*, 96, 373 (1978).
10. I.V. Korobka, I.V. Shcherbakova and E.V. Kuznetsov, *Khim. Geterotsikl. Soedin.*, 1184 (1982).
11. F.D. Popp, *"Reissert Compounds", Adv. Heterocyclic Chem.*, Academic Press, 9, 1 (1968).
12. W.E. McEwen and R.L. Cobb, *Chem. Rev.*, 55, 511 (1955).
13. M. Boehme and K. Linderberg, *Arch. Pharm. (Weinheim)*, 301, 544 (1968).
14. G.W. Kirby, S.L. Tan and B.C. Uff, *J. Chem. Soc. Chem. Commun.*, 1138 (1970).
15. F.D. Popp and B.C. Uff, *Heterocycles*, 23, 731 (1985).
16. E.Pretsch, T. Clerc, J. Seibl and W. Simon, *"Tabellen zur Strukturaufklärung organischer Verbindungen mit spektroskopischen Methoden"*, Springer Verlag, Berlin, 1976, p. C160.
17. Idem, *ibid.*, p. C40.
18. F.D. Popp, *"Developments in the Chemistry of Reissert Compounds (1968-1978)", Adv. Heterocyclic Chem.*, Academic Press, 24, 187 (1979).
19. H.W. Gibson, *J. Heterocycl. Chem.*, 7, 1169 (1970).
20. M. Makosza, *Tetrahedron Lett.*, 677 (1969).
21. S.V. Krivun, V.I. Dulenko, L.V. Dulenko and G.N. Dorofeenko, *Doklady Akad. Nauk.*, 166, 359 (1966).