

*Dedicated to Professor Dumitru Oancea
on the occasion of his 75th anniversary*

QUATERNIZATION OF N-METHYLATED PHENYL-BENZIMIDAZOLE AZOMETHINES TO BENZIMIDAZOLIUM SALTS

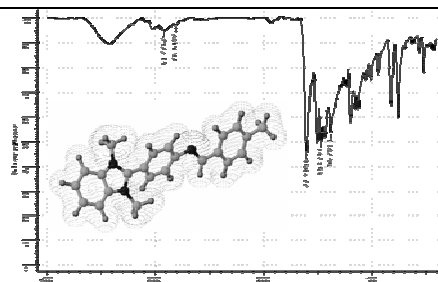
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Received December 21, 2015

In order to extend the benzimidazole derivatives series, previously described,^{1,2} the quaternization reaction of N-methyl-phenyl-benzimidazole azomethines (more suitable for such reaction) with methyl iodide, under pressure, has been tested in order to obtain polar benzimidazolium salts with azahemicyanine dye structure. The obtained quaternary salts were characterized by melting points, elemental analysis and FT-IR, UV-Vis and NMR spectroscopy.



INTRODUCTION

The phenyl benzimidazoles are already known for their biological effects such as: analgesic,³ anti-inflammatory,³ anti-helminthic, antimicrobial^{4,5} and antispastic^{6,7} activities. Some benzimidazole derivatives act as central nervous system regulators.⁸ Recent literature data indicate the inhibiting action of the 2-(aminophenyl)-benzimidazoles on cancer cells⁹⁻¹¹ as well as of drugs against malignant and non-malignant proliferating diseases¹² or against those causing immunodepression in transplants.¹³

We were interested in the study of aminophenyl benzimidazoles, which, due to their aromatic structure, are suitable for numerous reactions,

some of them being not investigated until now. A difficulty arose in their obtaining. Since the existing procedures are rather few and laborious¹⁴⁻¹⁹ we managed to develop a simple and efficient method. After numerous trials we obtained 2-(4'-aminophenyl)-benzimidazole by the reduction of the corresponding nitro derivatives with Na₂S and NaHCO₃.²⁰

Next, the 2-(4'-aminophenyl)-1-methyl-benzimidazole was submitted to a great number of condensation reactions with aromatic aldehydes, thus resulting azomethines exhibiting prolonged and sometimes conjugated chains.² The colour depends on the conjugated system extension and also on the substituent group in the aromatic carbonylic component.¹

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The synthesis of quaternary salts that is, in theory, a simple methylation is very difficult to realize practically due to the molecule inertia. The reaction occurs in an autoclave, at 6 at, under heating and stirring. The preliminary studies to establish a successful method for the synthesis of the compounds presented in this paper were very laborious and often were trial and error experiments.

EXPERIMENTAL PROCEDURE

Melting points were measured using an electro-thermal apparatus (Boetius hot stage microscope BM2) and are uncorrected. Elemental analysis was performed with a Carlo Elba Model M-1106. IR spectra were recorded on a Fourier Transform Digilab Scimitar Series spectrometer, in KBr pellets in the range 4000-400 cm^{-1} .

Synthetic methods were carried out as follows:

The azomethines previously obtained from 1-methyl-2-(4'-aminophenyl)-benzimidazole² have been treated with methyl iodide, at 1:1.5 molar ratio, in methanol.

The mixture has been heated in a steel autoclave, for 4 hours at 130-140°C. By vaporization under vacuum, a solid separated that has been purified from an ethanol-water mixture.

Thus, the impure solid was solved in ethanol and precipitated in water, followed by solving it again under heating. Under these conditions, the quaternary iodide separated from the sparingly soluble periodide.

These quaternary salts are all original compounds, never having been synthesized before.

RESULTS AND DISCUSSION

In connection with the synthesis of azomethines containing either free or methylated -NH groups, presented in another paper² we found interesting to carry out their quaternization to iodomethylated derivatives.

The reaction scheme applied is detailed in Fig. 1.

The previously prepared N-methylated derivatives² were chosen as substratum since the quaternization proceed better that for the non-methylated azomethines.

Following this reaction, the molecule becomes more polarized and might gain new physical, including photo physical, properties. The possibility of azomethine quaternization is not mentioned in literature.

The azomethine was suspended in methanol, and then treated with excess of methyl iodide and the mixture heated in autoclave, for 4 hours. The separated solid was purified by solving in methanol and precipitation in water, followed by solving again under heating. Under these conditions, the quaternary iodide separated from the sparingly soluble periodide.

The azomethines thus quaternized and some of their characteristics are presented in Table 1.

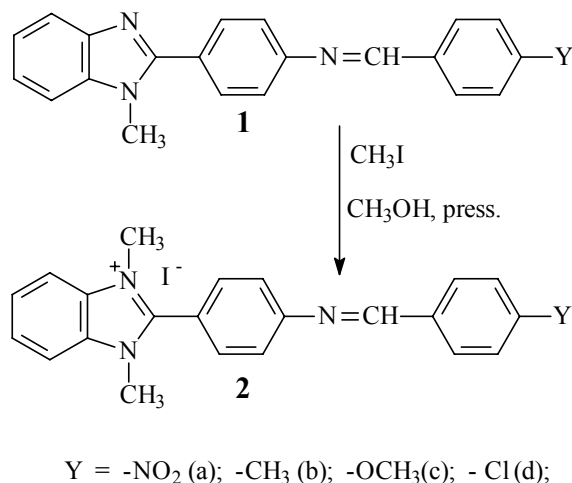


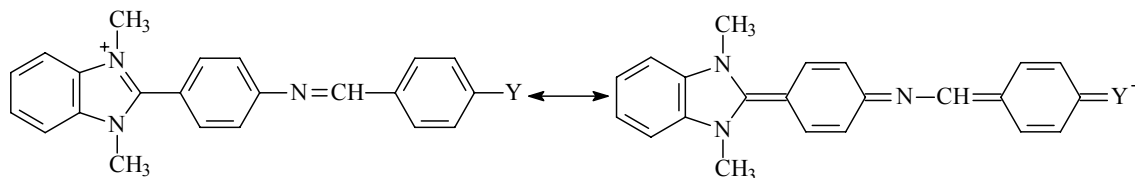
Fig. 1 – Quaternization of the N-methyl phenyl benzimidazole azomethines.

Table 1

Quaternized azomethines and some of their characteristics

Comp.	Y	M.p., °C	Molecular Formula	Analysis %					
				C %		H %		N %	
				calc.	exp.	calc.	exp.	calc.	exp.
2 a	NO ₂	285-290	C ₂₂ H ₁₉ IN ₄ O ₂	53.01	52.88	3.82	3.97	11.24	11.36
2 b	CH ₃	265-268	C ₂₃ H ₂₂ IN ₃	59.10	59.02	4.71	4.85	8.99	9.13
2 c	OCH ₃	278-280	C ₂₃ H ₂₂ IN ₃ O	57.14	57.06	4.55	4.62	8.69	8.82
2 d	Cl	254-256	C ₂₂ H ₁₉ ClIN ₃	54.15	54.01	8.97	9.05	8.61	8.75

The salts containing an electron-donor substituent are the most interesting since the delocating electrons proceed in a single direction, to the nitrogen atom positively charged.



Azomethine benzimidazolium salts have the structure similar to azahemicyanine dyes **3**, also being cationic dyes, showing photosensitive properties.

The structure of the compounds **2** was confirmed by the IR spectra (Table 2, Fig. 2-5).

In Fig. 2 is presented the IR spectrum for the quaternary salts **2c** (Y = OCH₃).

From the values listed in Table 2 and highlighted in Figs. 2-5 we mention the absorption generated by the $\nu\text{C}=\text{N}$ vibrations can be seen at 1625 cm⁻¹ (**2a**, **2c**) and at about 1650 cm⁻¹ (**2b**, **2d**).

The substituent in *para* position is identified by their specific bands²¹. Thus, NO₂ group (**2a**) is

The positive charge on the nitrogen atom induces a p- π electrons transfer that moves the positive charge on the electrono donor group in *para* position to the azomethine bond, thus resulting the following polar limit structure:

identified through the bands at 1340 cm⁻¹ and 1537 cm⁻¹.

The methyl groups (**2b**, **2c**) give rather weak absorptions between 2820-2866 cm⁻¹ and about 2925 due to the aliphatic $\nu\text{C-H}$ valence vibrations. In addition to that, intense bands are to be found at 1381 cm⁻¹, 1467 and 1473 cm⁻¹ due to the deformation vibration δCH_3 .

The halogen atom is identified by the stretch bands found at 748.30 cm⁻¹ and 821.67 cm⁻¹.

The four compounds structures have been confirmed by ¹H-NMR spectroscopy. The spectra obtained are presented in Table 3 and Fig. 3 (for the quaternary salt **2c**).

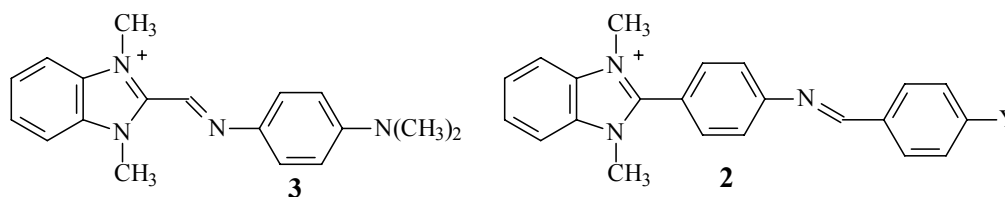


Table 2

Main IR bands for the quaternized azomethines

Comp.	Characteristic Bands (cm ⁻¹) and their intensity (VS=very strong, S=strong; M=medium; W=weak; VW=very weak)
2 a	420.48 W, 443.63 W, 505.35 VW, 526.57 W, 565.14 VW, 594.07 VW, 632.65 W, 671.23 VW, 694.37 W, 738.73 M, 761.88 M, 829.39 S, 883.40 W, 921.97 W, 945.12 W, 962.48 W, 1012.63 W, 1060.85 W, 1128.35 W, 1155.36 W, 1201.65 M, 1230.58 W, 1278.80 M, 1340.52 VS, 1384.89 W, 1438.89 W, 1458.18 M, 1475.54 M, 1512.19 VS, 1537.26 VS, 1600.91 VS, 1625.36 M, 1649.13 W, 2858.50 VW, 2924.08 VW, 3024.38 W, 3101.53 VW.
2 b	416.62 M, 439.77 M, 470.63 M, 514.99 M, 526.57 M, 559.36 W, 594.07 W, 615.29 W, 630.72 W, 671.23 W, 748.38 M, 821.67 M, 941.26 W, 1014.55 W, 1101.35 M, 1124.50 M, 1163.07 M, 1197.79 M, 1226.72 M, 1257.59 M, 1278.80 M, 1381.03 S, 1438.89 S, 1467.83 S, 1508.33 S, 1604.77 VS, 1649.13 M, 2829.57 W, 2926.01 W, 3103.46 W, 3419.78 S, 3647.38 VW.
2 c	426.27 W, 447.48 W, 482.20 W, 526.57 M, 563.21 W, 615.29 W, 634.58 W, 673.16 W, 702.09 W, 759.95 S, 823.60 S, 941.26 M, 1010.70 M, 1060.85 M, 1128.35 S, 1155.36 S, 1201.65 S, 1232.51 M, 1255.66 M, 1286.52 M, 1382.96 S, 1436.96 S, 1473.61 VS, 1506.40 VS, 1546.91 M, 1604.77 VS, 2819.92 VW, 2922.15 VW, 3020.52 VW, 3091.88 VW.
2 d	418.55 M, 437.84 M, 480.27 M, 513.06 M, 526.57 M, 559.36 M, 615.29 M, 634.58 W, 690.51 M, 748.38 S, 821.67 S, 898.83 M, 943.19 M, 1010.70 M, 1087.85 S, 1128.35 S, 1163.07 S, 1195.86 S, 1226.72 M, 1257.59 S, 1284.59 M, 1340.52 S, 1375.24 S, 1465.90 S, 1514.12 VS, 1604.77 VS, 1656.85 M, 1695.43 W, 1789.94 VW, 2763.99 W, 2866.21 W, 2927.94 W, 3032.09 W.

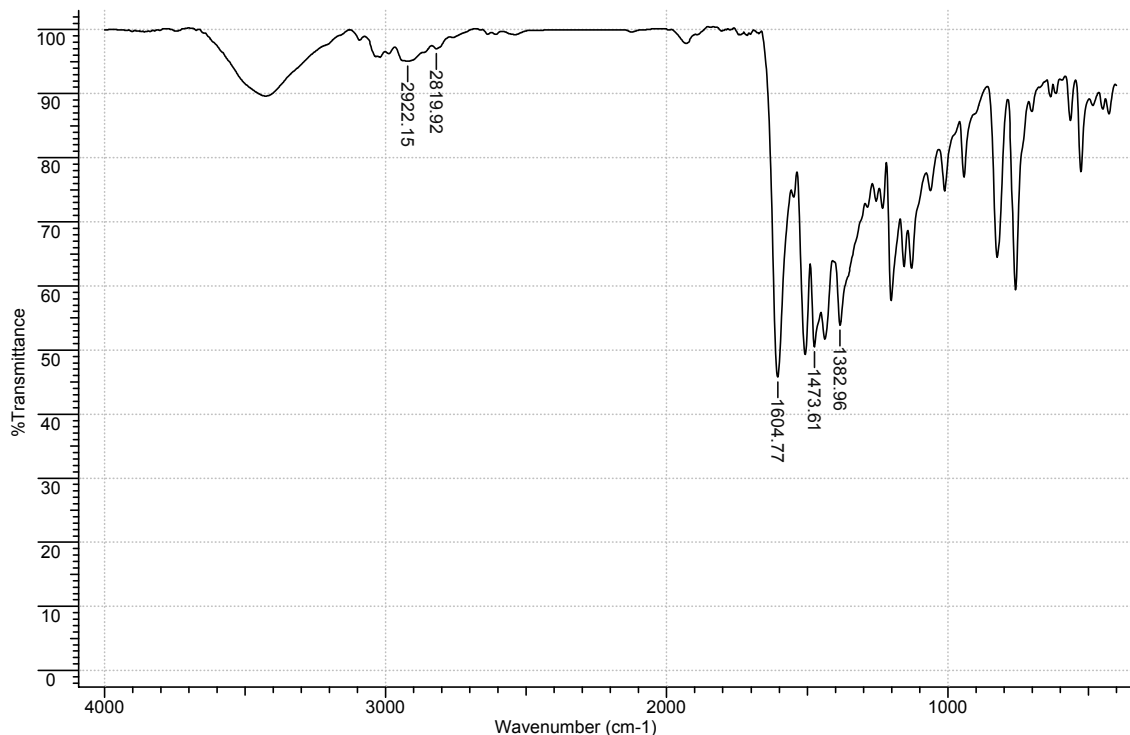
Fig. 2 – IR spectrum for quaternary salt **2 c** (Y=OCH₃).

Table 3

¹H-MNR Spectra for quaternary salts **2a-d**

Comp.	Characteristic bands DMSO, δ (ppm), J(Hz)
2 a	3.95 (s, 6H, N-CH ₃); 7.25 (m, 6H, H-5, H-6, H-3', H-5', H-2', H-6'); 7.40-7.43 (d, 2H, H-4, H-7, J _o =8.475); 8.11-8.13 (d, 2H, H-2'', H-6'', J _o =8.734); 8.26-8.28 (d, 2H, H-3'', H-5'', J _o =8.899); 8.62 (s, 1H, N=CH).
2 b	2.39 (s, 3H, CH ₃); 3.38 (s, 3H, N1-CH ₃); 3.87 (s, 3H, N3-CH ₃); 7.14-7.15 (d, 2H, H-3'', H-5''); 7.23-7.35 (m, 4H, H-5, H-6, H-3', H-5', J _o =8.26, J _o =6.75); 7.74-7.83 (m, 6H, H-2', H-6', H-2'', H-6'', H-4, H-7, J _o =8.55, J _o =6.75, J _o =8.26); 8.45 (s, 1H, N=CH).
2 c	3.33 (s, 3H, O-CH ₃); 3.81 (s, 3H, N1-CH ₃); 3.87 (s, 3H, N3-CH ₃); 7.04-7.08 (d, 2H, H-3'', H-5''); 7.24 (m, 2H, H-5, H-6); 7.35-7.39 (d, 2H, H-2'', H-6'', J _o =8.46); 7.65 (m, 2H, H-4, H-7); 7.84-7.88 (d, 2H, H-3', H-5', J _o =6.78); 7.89-7.92 (d, 2H, H-2', H-6', J _o =6.48); 8.56 (s, 1H, N=CH).
2 d	3.32 (s, 3H, N1-CH ₃); 3.88 (s, 3H, N3-CH ₃); 7.24-7.27 (m, 2H, H-5, H-6, J _o =8.18); 7.41-7.45 (d, 2H, H-3', H-5', J _o =8.20); 7.57-7.61 (d, 2H, H-3'', H-5'', J _o =8.35); 7.63-7.67 (d, 2H, H-2', H-6', J _o =8.44); 7.87-7.91 (d, 2H, H-2'', H-6'', J _o =8.28); 7.95-7.99 (d, 2H, H-4, H-7, J _o =8.29); 8.71 (s, 1H, N=CH).

The peak for the methylene protons usually appears at low δ values. Aromatic protons appear according to the different effect of substituent for the final phenyl ring.

For three of the quaternary salts UV-Vis spectra were registered using methanol as solvent. The main bands are presented in Table 4.

From Table 4 it is observed that the quaternary salts have three spectral fields

The type, number and position of substituent in the benzimidazole ring also influence the position of all the absorption bands. In this case, the H bond between the methanol (solvent) and the heteroatom from the quaternary salts is proved by a hypsochromic shift for the minimum energy adsorption band III.

Thus, the quaternary salts with electron donor group (methoxy, **2 c**) have the absorption maximum at higher values compared to the compounds with methyl group in *para* (**2 b**) that have higher values compared to the salt with electron withdrawing group (nitro, **2 a**).

According to the literature regarding compounds with similar structure, the obtained quaternary salts have potential applications as photosensitizers for polymers and biopolymers.

Preliminary tinctorial tests show that the new compounds could be used as cationic dyes for poly acrylonitrile fibres, studies that will be continued and detailed in the future.

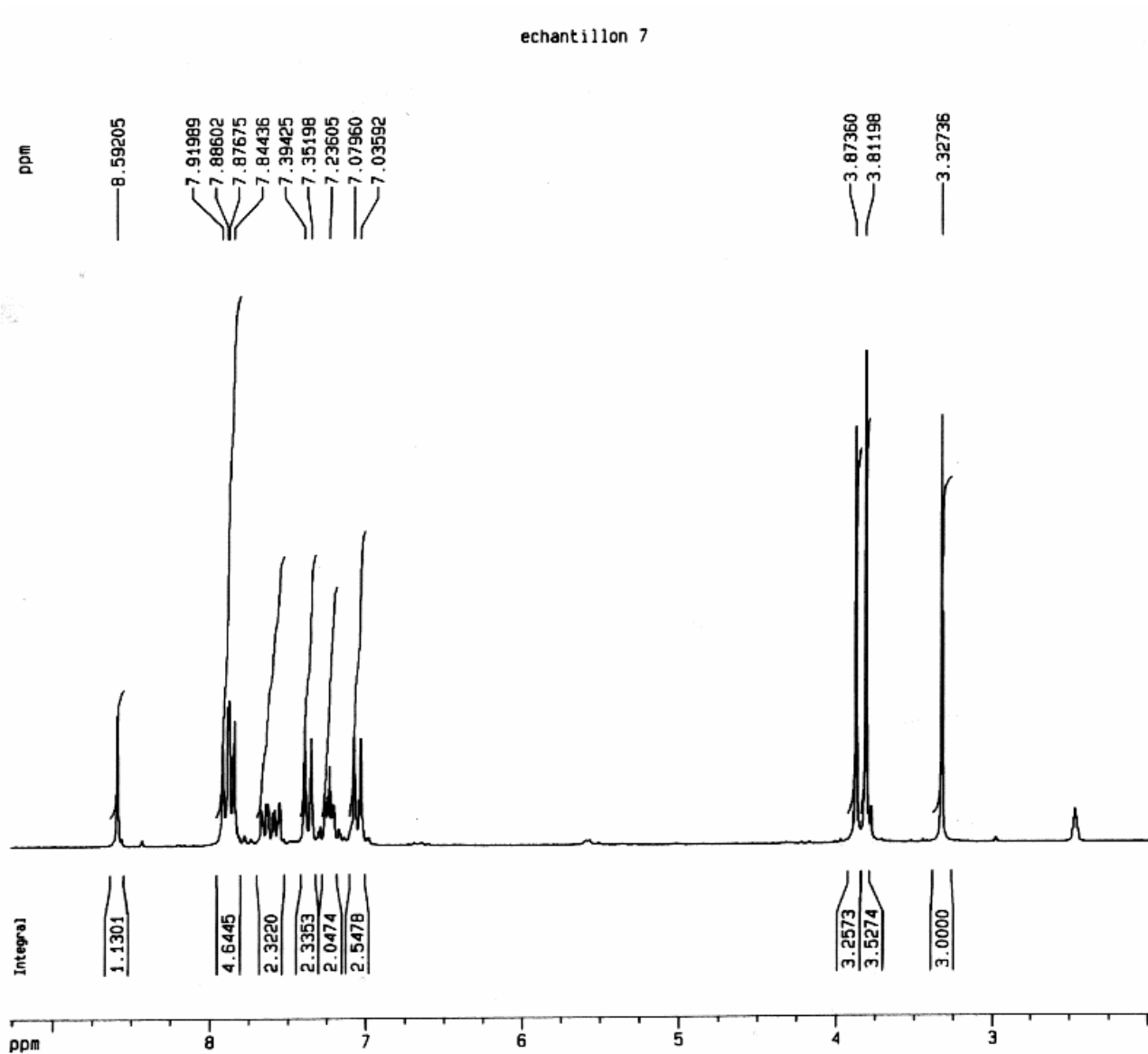
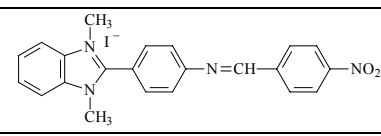
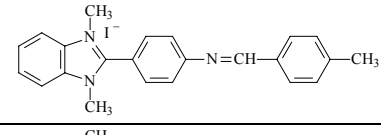
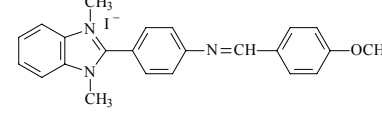


Fig. 3 – NMR spectrum for quaternary salt **2c** (Y=OCH₃).

Table 4

UV-Vis Spectral characteristics for the quaternary salts **2a-c** (solvent: methanol)

Comp.	Structure	Wavelength λ_{\max} , nm, (log ϵ)		
		Band I	Band II	Band III
2 a		230 (4,39)	250 (4,36)	343 (4,324)
2 b		231 (4,33)	249 (4,343)	334,5 (4,40)
2 c		230 (4,22)	281 (4,415)	326 (4,18)

It will also be interesting to test the biological activity of the quaternary salts obtained, being well known the pharmacophore action of benzimidazole derivatives. Next we will explore if they have or not biological activity, if they have photosensitivity.

Also, future studies will focus on the possibility to use these compounds as cationic dyes for textile fibres and we intend to study the resistance of the dyed fibre at washing and UV rays' action.

CONCLUSIONS

A series of four quaternary salts have been obtained from p-substituted phenyl-4'(2''-benzimidazole-1''-methyl)phenyl azomethines with methyl iodide, under pressure, at 130°C and 4 hours. The obtained compounds have been purified by recrystallization and characterized by elemental analysis and FTIR spectra.

These four quaternary salts are original compounds, never being synthesized before because the synthesis is very difficult to realize, even if chemically the reaction is just a methylation process.

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