DUAL REACTIVITY OF THE ALKALOID THEBAINE AND ITS DERIVATIVES TOWARDS ACETYLENES AND THE SYNTHETIC POTENTIAL THEREOF

I. V. Sandulenko*

Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, Moscow, 119991 Russia

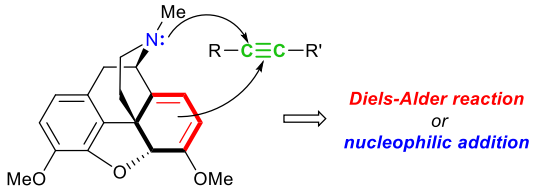
Cite this: *INEOS OPEN*, **2021**, *4 (2)*, 61–67
DOI: 10.32931/io2106r

Received 16 February 2021,
Accepted 23 March 2021

http://ineosopen.org

Abstract

A unique diene moiety of the alkaloid thebaine enables its successful application in the Diels–Alder reaction with ethylene derivatives for producing the adducts that can serve as precursors for a whole class of opioids used in medicine. The interaction of thebaine with acetylenes as an alternative approach to analogous adducts that offers an additional opportunity for their functionalization has received undeservedly little attention. The current review is devoted to these reactions and their synthetic potential.



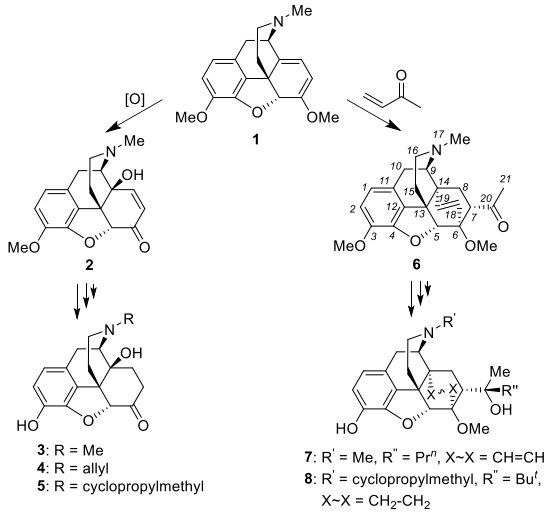
Key words: thebaine, [4+2]-cycloaddition, retro-Diels–Alder reaction, benzofuroazocine, fluorinated thevinols.

Introduction

The natural alkaloid thebaine (**1**) is a minor alkaloid of *Papaver somniferum* (the content in opium is about 0.3%) and the main alkaloid of *Papaver bracteatum* (the content in opium is 0.2–0.8% which composes up to 90% of the total content of alkaloids). A natural isomer, (-)-thebaine (**1**), is highly toxic but does not possess analgesic properties; like strychnine, it induces convulsions and is fatal in high doses [1]. Nevertheless, in very low content, it is included in a composition of the analgesic *omnopon* (medical opium).

However, thebaine is of paramount importance as a precursor for a variety of morphinan derivatives, in particular, a whole series of highly efficient synthetic analgesics and antagonists of opioid receptors that are used in medicine and veterinary [2, 3]. Nowadays, almost all thebaine is processed in two main directions depicted in Scheme 1. Both routes are premised on the presence of a unique electron-rich (owing to the presence of 6-MeO-substituent) conjugated diene moiety in the thebaine structure. Thus, the oxidation of this moiety with hydrogen peroxide or peroxy acids affords 14-hydroxycodeinone (**2**) [4]; further transformations of the latter yield highly important derivatives, such as oxymorphone **3**, naloxone **4**, and naltrexone **5** (Scheme 1). 14-Hydroxydihydromorphinone (oxymorphone) (**3**) is a narcotic analgesic that is 10 times more efficient than well-known morphine; it is produced in several formulations. Naloxone (**4**) and naltrexone (**5**) are the so-called pure opioid receptor antagonists. Unlike naloxone, the physiological effect of naltrexone is manifested slower but lasts for much longer. Furthermore, naltrexone exceeds naloxone in bioavailability, which enables its use in tablet formulations whereas naloxone is used only as injections.

The diene system of thebaine is also utilized in the reactions of cycloaddition with alkenes, which result in the derivatives of 6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine, for example, thevinone (**6**). Its following modification affords etorphine (**7**), buprenorphine (**8**) (Scheme 1), and other orvinol derivatives [5–8]. Etorphine (**7**) exhibits unprecedented analgesic efficiency (1000–3000 times higher than the activity of morphine) and is used in veterinary for immobilization of big animals. Buprenorphine (**8**) is a mixed agonist-antagonist (a partial agonist of μ- and antagonist of κ- and δ-opioid receptors); it exhibits a unique pharmacological profile. This drug exceeds morphine in analgesic activity approximately 30 times and is used in different formulations for acute and chronic pain relief.



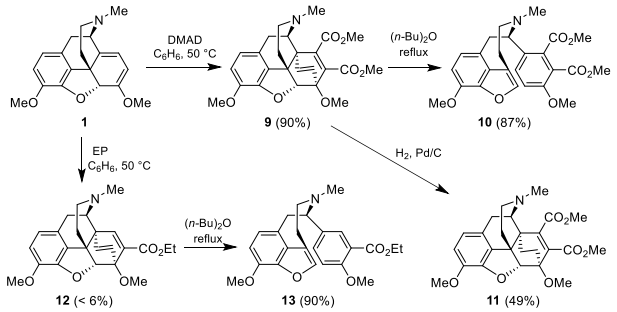
Scheme 1. Main directions of modification of thebaine (**1**) and atom numbering scheme for thevinone (**6**) (according to the common nomenclature).

It displays a relatively low level of side effects (tolerance and depression of a respiratory center) and now is the most widely used drug among orvinol derivatives.

Thebaine readily reacts with different dienophiles [9], resulting in cycloaddition that proceeds rather selectively. The dienophile approaches the diene system of thebaine from the side of a nitrogen atom, *i.e.*, from the more sterically unhindered site, and affords exclusively the *endo*-adducts. The reaction proceeds under electronic control (monosubstituted dienophiles form only C(7)-substituted adducts). As a rule, the reactions with ethylenes lead predominantly (or exclusively) to 7*α*-substituted derivatives. Numerous Diels–Alder adducts of thebaine (**1**) with ethylene derivatives have been reported to date [5, 10–14]. In contrast, [4+2]-cycloadducts of thebaine with acetylenes are scarcely reported since the desired cycloaddition competes with other reactions. This review describes the attempts to obtain such adducts and outlines the prerequisites for one or another process, with a focus on the possibility of production of the new derivatives of 4,5α-epoxymorphinan and other classes of the compounds that are of certain interest as potential physiologically active compounds.

Reactions of thebaine with acetylenes

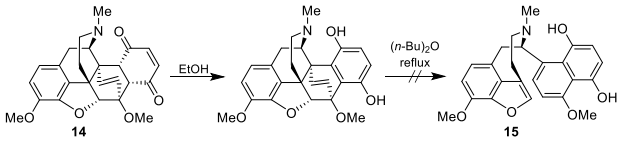
The interaction of thebaine (**1**) with electron-deficient dienophiles was studied for the first time by H. Rapoport and P. Sheldrick [15] as early as the beginning of the 1960s. It was shown that thebaine (**1**) smoothly reacts with dimethyl acetylenedicarboxylate (DMAD) at 50 °C in benzene; however, [4+2]-adduct **9** undergoes rearrangement by the retro-Diels–Alder reaction even upon short boiling in di-*n*-butyl ether, which affords thermally stable aryl-substituted benzofuroazocine **10**. At the same time, the product of reduction of adduct **9**, compound **11**, appeared to be thermally stable (Scheme 2).



Scheme 2

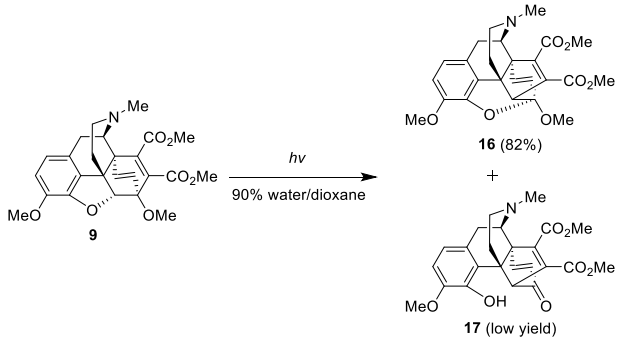
Unlike the reaction with DMAD, the cycloaddition of thebaine to ethyl propiolate (EP) proceeded with a low conversion; however, adduct **12** also readily underwent aromatization giving rise to benzofuroazocine **13** (Scheme 2).

It was suggested that the electron-withdrawing substituents at the C(7) and C(8) atoms of a [4+2]-cycloadduct must facilitate the thermal rearrangement into benzofuroazocines [15]. The authors explained this assumption by the fact that an adduct of thebaine and *para*-benzoquinone (**14**) does not undergo isomerization into compound **15** upon prolonged boiling in di-*n*-butyl ether (Scheme 3).



Scheme 3

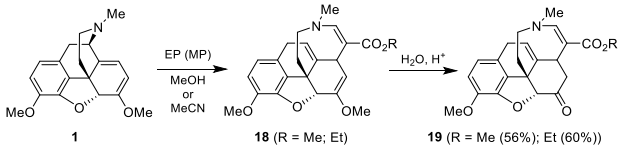
The report of H. Rapoport and P. Sheldrick [15] promoted further investigations of the behavior of thebaine adducts with acetylenes. It was revealed that, under irradiation with a high-pressure mercury lamp, an adduct of thebaine and DMAD (**9**) readily isomerizes to compound **16** which undergoes hydrolysis to afford **17** (Scheme 4) [16]. Compound **16** exhibited a low *in vivo* analgesic effect. Earlier a similar isomerization process that proceeds through an enolate anion was observed for thevinone (**6**) and its derivatives under the action of bases [17].



Scheme 4

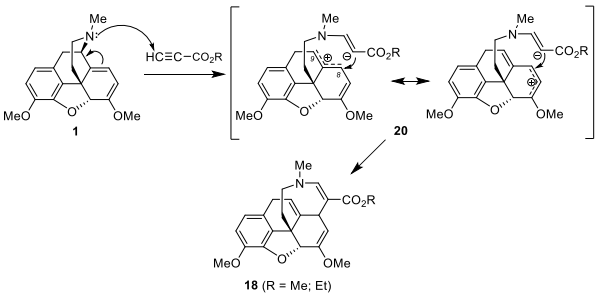
Rubinstein *et al*. [18] accomplished such a rearrangement (Scheme 4) upon irradiation of thermally stable compound **11** and confirmed the structures of rearrangement products **16** and **17**.

In polar solvents, thebaine (**1**) reacts with ethyl (EP) and methyl (MP) propiolates at room temperature in another way, affording products **18** (Scheme 5) in almost quantitative yields [19].



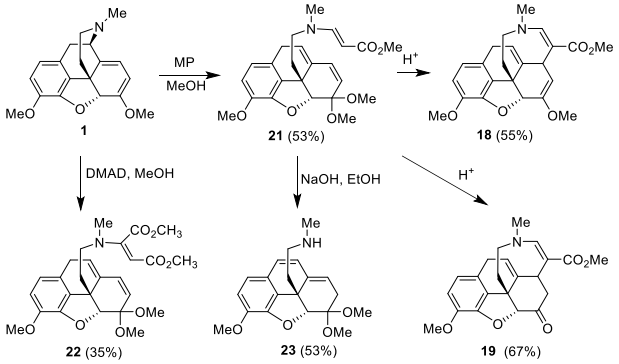
Scheme 5

The structures of products **18** were elucidated based on their spectroscopic data and the comparison of the latter with the corresponding data of the products of their mild hydrolysis **19**. Hayakawa *et al.* [19] suggested the following mechanism for this transformation (Scheme 6). The reaction is initiated by the nucleophilic attack of a thebaine nitrogen atom on the electron-withdrawing center of acetylene which is followed by the cleavage of the C(9)–N bond with the formation of zwitterion intermediate **20** and ring closure at the C(8) atom, resulting in the final reaction product. The polar solvent medium facilitates just this process with the formation of a zwitterion intermediate rather than the cycloaddition.



Scheme 6

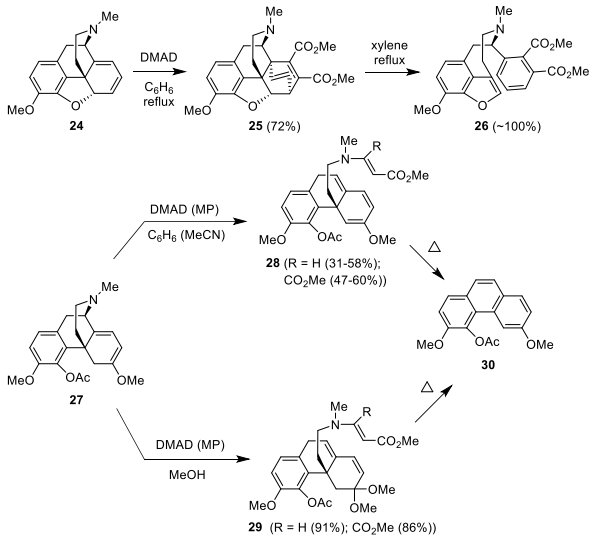
Subsequently it was established [20] that an intermediate of the aforementioned reaction in methanol is ketal **21** (or **22** in the case of DMAD) that readily converts to **18** under the action of hydrochloric or *para*-toluenesulfonic acid and further to **19** at the higher acid content (Scheme 7). The formation of ketals **21** confirms a stepwise mechanism of the nucleophilic attack (Scheme 6). It was also shown that the prolonged hydrolysis of **21** in an alcohol solution of an alkali leads to amine **23**.



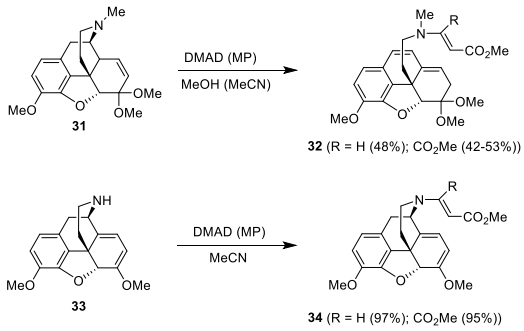
Scheme 7

A year later, two research groups simultaneously reported [21, 22] on the effect of solvent nature on the composition of products of the reactions of thebaine with acetylenes and confirmed two possible reaction pathways depending on the medium polarity: [4+2]-cycloaddition or nucleophilic attack of the nitrogen atom on the electron-deficient acetylene moiety followed by the cleavage of the C(9)–N bond. The dependence of the reaction direction on the diene structure was also revealed [21]. For example, 6-demethoxythebaine (**24**) does not react with DMAD in methanol and acetonitrile, whereas in boiling benzene it forms only the product of [4+2]-cycloaddition with DMAD (compound **25**) which upon heating to 140 °C undergoes the retro-Diels–Alder reaction (product **26**, Scheme 8). The interaction of *β*-dihydrothebaine acetate (**27**) with DMAD does not lead to the Diels–Alder product at all; instead it affords the products of nucleophilic attack of the nitrogen atom and subsequent cleavage of the C(9)–N bond (**28, 29**), which upon heating undergo aromatization to afford phenanthrene derivative **30** (Scheme 8) [21].

Similar products (**32**) were observed in the reaction of dimethyl ketal (**31**) with acetylenes (MP or DMAD) in polar solvents (Scheme 9). However, *N*-northebaine (**33**) furnishes the products of addition at the nitrogen atom but without the cleavage of the C(9)–N bond (**34**) [21].

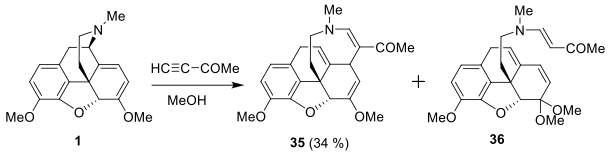


Scheme 8



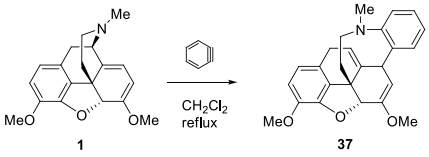
Scheme 9

Singh *et al.* [22] studied for the first time the interaction of thebaine with ethynyl methyl ketone in methanol, which resulted in enol **35** along with **36**. The yield of product **35** was enhanced to 46% by performing the reaction in THF (Scheme 10).



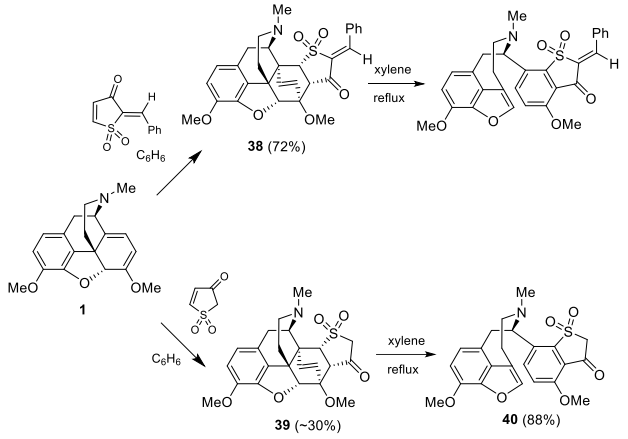
Scheme 10

At the beginning of the 1990s, exploring the new Diels–Alder reactions of thebaine with electron-withdrawing dienophiles, Pindur *et al.* performed the reaction with dehydrobenzene generated from *o*-diazobenzoic acid and isolated only product **37** in a low yield (6%), which resulted from the nucleophilic attack of the amine nitrogen atom of thebaine (**1**) on one of the aryne sp-centers of dehydrobenzene (Scheme 11) [23].



Scheme 11

It should be noted that the formation of such nucleophilic addition products is unique for acetylene derivatives as dienophiles and was not observed in the reactions of thebaine with ethylene dienophiles. However, another side reaction, the aromatization of [4+2]-cycloadducts, is feasible also in the case of thiolen-4-one 1,1-dioxide and 5-benzylidene-2-thiolene 1,1-dioxide dienophiles. The cycloadducts of these olefins with thebaine (**38** and **39**) readily undergo aromatization upon heating (Scheme 12) [24].



Scheme 12

Further modification of the molecule of benzofuroazocine derivative **40** afforded products **41**–**44** (Fig. 1) which exhibit different types of physiological activities (analgesic, antidepressant, and sedative [25]).

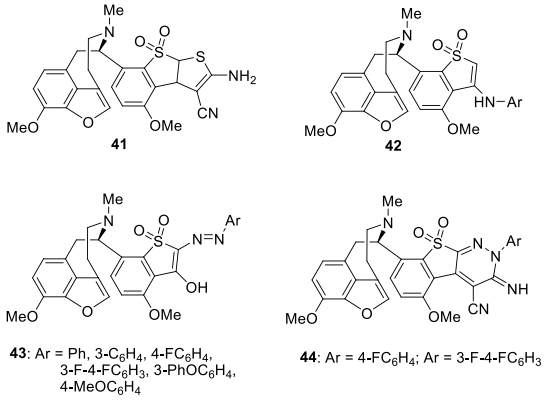
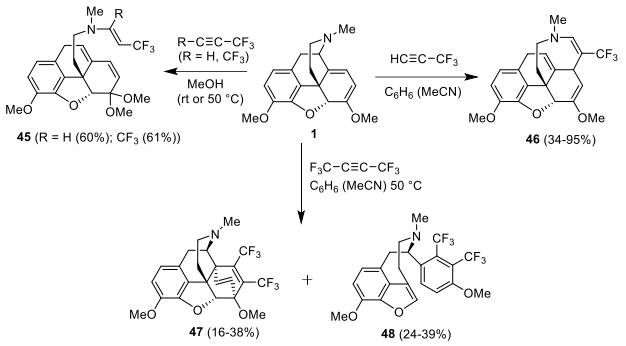


Figure 1

The appearance of fluorine-containing dienophiles provided new impetus to this area of thebaine chemistry. It is known that the introduction of fluorine atoms into the molecules of physiologically active compounds can strongly affect their properties owing to an increase in lipophilicity, conformational changes in the molecule, and enhanced stability to metabolic processes in the organism [26]. In the case of opioid ligands based on morphinans, this approach to modification of a pharmacological profile also appeared to be highly appealing [27, 28].

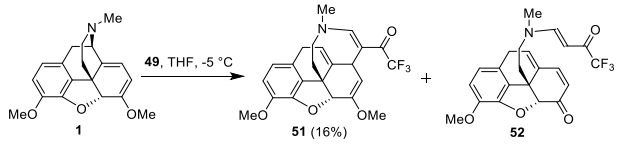
The first attempt to introduce a trifluoromethyl function into a morphinan framework using the reactions of thebaine with trifluoromethyl-substituted acetylenes was made in the 1990s [29]. The reaction with trifluoropropyne led to the products of the attack of a thebaine nitrogen atom on the acetylene moiety (**45, 46**). The Diels–Alder adduct (**47**) was obtained only in the case of hexafluorobut-2-yne in the corresponding solvents and only in a mixture with compound **48**—the product of the retro-Diels–Alder reaction of adduct **47** (Scheme 13).



Scheme 13

Target adduct **47** (the yields in benzene and acetonitrile were 38% and 16%, respectively), although contains a trifluoromethyl group, does not have other functionalities that would enable its further modification in order to provide series of derivatives, which is required to explore the structure–activity relationships.

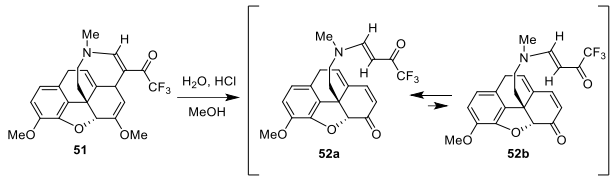
Unlike the adduct of thebaine with trifluoropropyne **47**, its analogs with trifluoroacetylethylene or trifluoroacetylacetylene (**49**) could serve as precursors for thevinols owing to a possibility of modification by the keto group at C(20) carbon atom. An attempt to obtain C(21)-fluorinated thevinols [30–33] using C(21)-fluorinated analogs of thevinone (**6**), namely, the adducts of thebaine with trifluoroacetylacetylene (HC≡C–CO–CF_3, **49**) and its Me_3Sn-substituted derivatives (Me_3Sn–C≡C–CO–CF_3, **50**) was reported [34]. Unlike its ethylene analog (CH_2=CH–CO–CF_3 [35]), trifluoroacetylacetylene (**49**) is an available reagent [36] and is highly reactive in the Diels–Alder reactions with nonfunctionalized dienes [36–39]. However, in the case of thebaine itself as a diene, the nucleophilic attack of an alkaloid nitrogen atom on the electron-deficient center in acetylene successfully competed with the desired [4+2]-cycloaddition and led to fluorine-containing ketone **51** as the main product (Scheme 14) [34].



Scheme 14

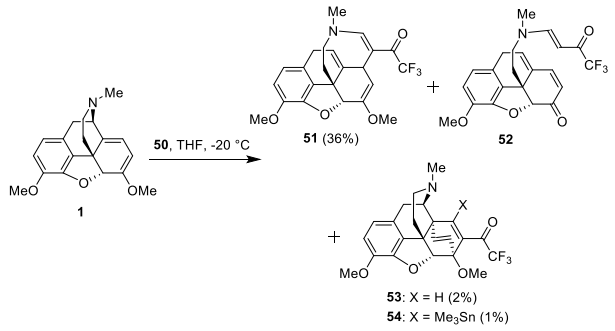
Besides ketone **51**, the reaction mixture contained traces of diketone **52**, which was also obtained in 30% yield upon acid hydrolysis of **51** (Scheme 15). Based on the mass and NMR (^{1}H, ^{13}C, and ^{19}F) spectroscopic data, in particular, the results of 2D NMR studies (COSY, HMQS, HMBC), it was shown that **52** exists in a solution in the form of two conformers **52a** : **52b** (2:1).

To direct the reaction of **1** with the fluorinated acetylene towards [4+2]-cycloaddition, the nucleophilic attack of a thebaine nitrogen atom on the acetylene dienophile was complicated by the application of acetylene **50** bearing a bulky



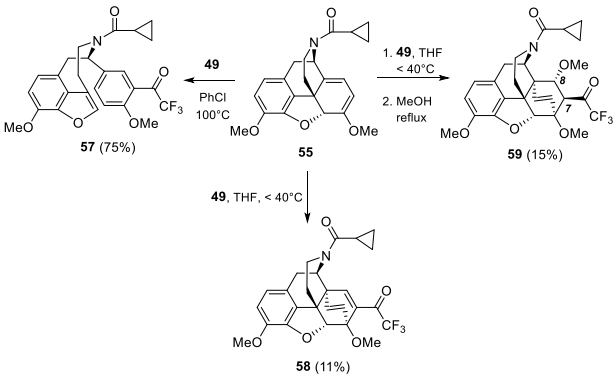
Scheme 15

Me_3Sn donor substituent as a dienophile [34]. Compound **50** can serve as a precursor for acetylene **49** and is less reactive in the Diels–Alder reactions than **49** [37]. The trimethylstannyl function could be removed or used for functionalization of the [4+2]-adduct by the C(8) atom [40]. However, the reaction of thebaine (**1**) with acetylene **50** (Scheme 16) led to already known compound **51** as the main product (yield 36%). Target [4+2]-adducts **53**, **54** were isolated in very low yields [34].



Scheme 16

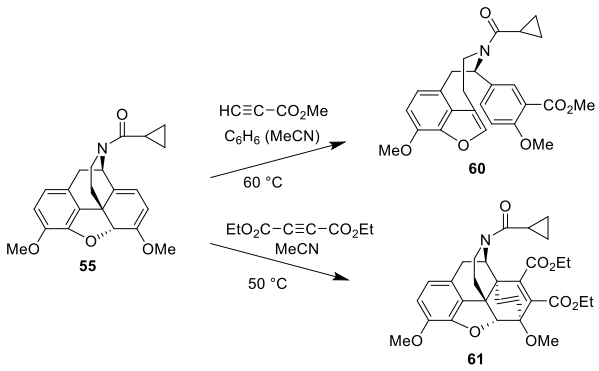
To achieve the desired result, the nucleophilicity of the nitrogen atom was reduced by the modification of diene **1** itself. The modification was accomplished by the substitution of a methyl group at the N(17) atom for an acyl one. The cycloadditions were performed using *N*-cyclopropylcarbonyl-*N*-northebaine (**55**) [41] and *N*-*tert*-butoxycarbonyl-*N*-northebaine (**56**) [42]. The reaction of *N*-cyclopropylcarbonyl-*N*-northebaine (**55**) with acetylene **49** (Scheme 17) upon heating in chlorobenzene afforded aromatic ketone **57** (yield 75%) as the main product, which resulted from the intramolecular rearrangement (the retro-Diels–Alder reaction) of the target [4+2]-adduct (**58**) [34].



Scheme 17

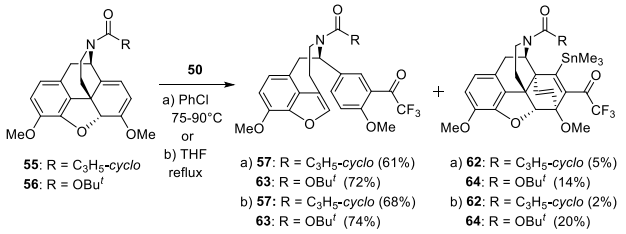
In THF the reaction of **55** with acetylene **49** led to target [4+2]-adduct **58** (11% yield). However, gentle evaporation of the solvent from the reaction mixture followed by crystallization of the product from methanol afforded compound **59**, which resulted from the Michael addition of methanol to the conjugated enone moiety of the initially formed product of [4+2]-cycloaddition (**58**) [34]. Unlike the well-studied biologically active structures of thevinol–orvinol series (for example, compounds **6**–**8**) that have α-orientation of the substituents at the C(7) atom, a trifluoroacetyl group in ketone **59** is in the β-position. Hence, this type of transformation opens the way to a series of C(8)-substituted derivatives of 7β-6,14-ethenomorphinans which have been scarcely studied to date [43].

The factors that affect the stability of [4+2]-adducts resulting from the interaction of acetylene dienophiles with amide derivatives of thebaine were determined [34]. Thus, upon the interaction of amide **55** with methyl propiolate in benzene or acetonitrile, the target [4+2]-adduct was not isolated since it completely underwent the retro-Diels–Alder reaction, giving rise to benzofuroazocine derivative **60** (Scheme 18). However, upon application of diethyl acetylenedicarboxylate, [4+2]-adduct **61** was formed in a good yield (77%) and did not undergo the aforementioned rearrangement even upon heating to 100 °C [34].



Scheme 18

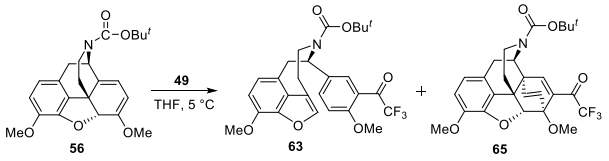
The reactions of amides **55** and **56** with disubstituted fluorine-containing acetylene **50** afforded, along with benzofuroazocine derivatives **57** and **63** as main products, [4+2]-adducts **62** and **64** in low yields (Scheme 19). A change of the solvent only insignificantly affected the ratio of the products. The reaction performed in THF afforded the highest yield of target adduct **64** (20%) [34].



Scheme 19

So far there is no clear answer to the questions when the Me_3Sn-function is lost to afford products **57** and **63** and what is the role of this group in the stabilization of products **62** and **64**, which are stable during storage at room temperature for a long time.

The reaction of *N-tert*-butoxycarbonyl-*N*-northebaine (**56**) with monosubstituted trifluoroacetylacetylene (**49**) in THF (Scheme 20) proceeded smoothly and afforded [4+2]-cycloadduct **65** as the main product (47% yield, a ratio of products [4+2]-adduct **65** : retro-adduct **63** = 11:3). However, as well as product **58**, compound **65** appeared to be thermodynamically unstable and during storage for several weeks at room temperature completely converted to benzofuroazocine **63** [34].



Scheme 20

Biological activity of the derivatives of 6,14-*endo*-ethano-6,14-dihydrothebaine and an alternative method for their synthesis

A survey of the patent literature on the synthetic opioids of a 4,5*α*-epoxymorphinan series revealed growing interest in the derivatives of 6,14-*endo*-ethano-6,14-dihydrothebaine, in particular, those containing the enone moiety (general formulae **66** and **67**, Fig. 2) [44, 45] in recent years in the search for new analgesic and antipruritic agents among selective ligands of *k*-opioid receptors.

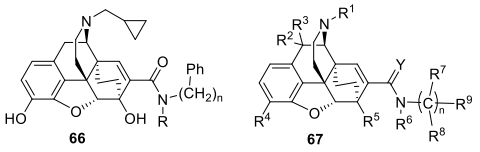
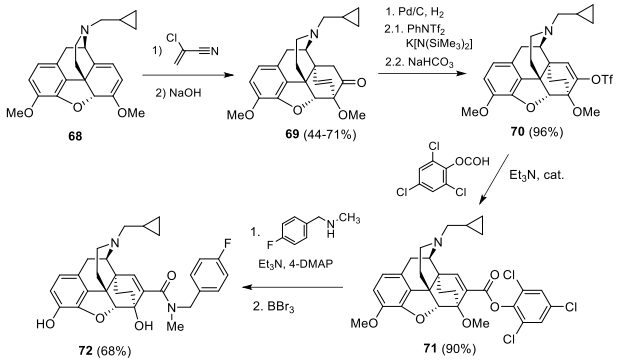


Figure 2

Although it is believed that the agonists of *μ*-opioid receptors are efficient analgesics, recently the selective agonists of *δ*- and especially *κ*-opioid receptors [46] demonstrated great potential since it is expected that the presence of analgesic and other useful effects of these ligands is accompanied by the reduced probability of the appearance of dangerous side effects, which are characteristic of *μ*-agonists.

Thus, *in vitro* screening of the structures with general formula **66** outlined a *κ*-agonist (compound **66** with R = Me, n = 1) with the high selectivity just to this type of opioid receptors [44]. According to the results of *in vivo* experiments, it exhibits some analgesic activity but does not exert an undesirable sedative effect. However, its insufficient metabolic stability stipulated to study an analogous series of structures with general formula **67**, among which there was revealed a range of highly active *κ*-agonists with metabolic stability that essentially exceeded the stability of the aforementioned drug compared to **66** (R = Me, n = 1) [45].

Although it was stated that the synthesis of series **66**, **67** (for example, compound **72**, Scheme 21) was carried out through ketone **69**, which results from the Diels–Alder reaction of *N*-cyclopropylmethyl-*N*-northebaine (**68**) with 2-chloroacrylonitrile [45, 47], the use of the approach described in the present review for the production of derivatives of 6,14-*endo*-ethano-6,14-dihydrothebaine (analogs of **66**, **67**) has much room for development.



Scheme 21

Conclusions

The search for new molecules as potential ligands for opioid receptors with improved pharmacological profiles and reduced side effects is still ongoing in many laboratories and diverse directions. The modification of natural alkaloids is one of the main trends in pursuit of new opioid ligands among 4,5*α*-epoxymorphinans, and thebaine is one of the main research objects in this field.

Thebaine can react with acetylenes in two directions: cycloaddition with the formation of [4+2]-cycloadducts or nucleophilic attack of an alkaloid nitrogen atom on the electron-deficient carbon atom of acetylene that result in the corresponding adducts. Based on the data on the diene structure, dienophile properties, and reaction conditions (polarity, medium, and temperature), one can predict the preferred reaction pathway. Anyway, both cases will afford adducts that can serve as precursors for new series of derivatives, and the initial acetylene can be used for the introduction of new functional groups into the adduct structures, including fluorine-containing ones, which holds great promise from the viewpoint of further modification of these molecules and their biological profiles.

The process of undesirable nucleophilic addition can be unambiguously prevented by protecting an amine function of thebaine. However, in this case, there remains a problem of instability of the target [4+2]-cycloadducts (especially in the case of the application of monosubstituted acetylenes as dienophiles) that often undergo thermal intramolecular rearrangement into the derivatives of benzofuroazocine, which, nevertheless are also potential physiologically active substances. The driving force for the aforementioned rearrangement (the retro-Diels–Alder reaction) is the transformation of a cyclohexadiene moiety in [4+2]-cycloadducts, which result from the reactions just with acetylene dienophiles, into an aromatic ring. Therefore, the investigation of the methods for preventing this process owing to the conversion of thermally instable moiety into cyclohexene (*via* selective reduction of double bonds or capture of the cycloadduct enone moiety with an appropriate nucleophile, opening the way, in particular, to unusual 8α,7*β*-disubstituted derivatives of 6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine) is still an urgent task.

Acknowledgements

This work was performed with financial support from the Ministry of Science and Higher Education of the Russian Federation.

Corresponding author

* E-mail: ira17.rock@mail.ru. Tel: +7(499)135-9314

References

1. J. W. Sloan, J. W. Brooks, A. J. Eisenman, W. R. Martin, *Psychopharmacologia*, **1962**, *3*, 291–301. DOI: 10.1007/BF00411369
2. S. Berenyi, C. Csutoras, A. Sipos, *Curr. Med. Chem*., **2009**, *16*, 3215–3242. DOI: 10.2174/092986709788803295
3. T. G. Tolstikova, A. V. Bolkunov, E. A. Morozova, S. E. Tolstikov, *Chem. Sustainable Dev*., **2009**, *2*, 115–133.
4. F. M. Hauser, T.-K. Chen, F. I. Carroll, *J. Med. Chem.*, **1974**, *17*, 1117. DOI: 10.1021/jm00256a019
5. K. W. Bentley, D. G. Hardy, *J. Am. Chem. Soc.*, **1967**, *89*, 3267–3273. DOI: 10.1021/ja00989a030
6. K. W. Bentley, D. G. Hardy, B. Meek, *J. Am. Chem. Soc*., **1967**, *89*, 3273–3280. DOI: 10.1021/ja00989a031
7. K. W. Bentley, D. G. Hardy, *J. Am. Chem. Soc.*, **1967**, *89*, 3281–3292. DOI: 10.1021/ja00989a032
8. S. M. Husbands, in: *Research and Development of Opioid-Related Ligands*, *ACS Symp. Ser*., *1131*, **2013**, 127–144. DOI: 10.1021/bk-2013-1131.ch007
9. G. R. Lenz, S. M. Evans, D. E. Walters, A. J. Hopfinger, *Opiates*, Acad. Press Inc., Orlando, London, **1986**, 101–165.
10. S. I. Kanevskaya, S. F. Mitryagina, *Zh. Obshch. Khim.*, **1947**, *17*, 1203–1207.
11. K. W. Bentley, A. F. Thomas, *J. Chem. Soc.*, **1956**, 1863–1867. DOI: 10.1039/JR9560001863
12. J. P. Cueva, C. Roche, M. Ostovar, V. Kumar, M. J. Clark, T. M. Hillhouse, J. W. Lewis, J. R. Traynor, S. M. Husbands, *J. Med. Chem.*, **2015**, *58*, 4242–4249. DOI: 10.1021/acs.jmedchem.5b00130
13. W. Li, J.-D. Long, Y.-Y. Qian, Y. Long, X.-J. Xu, Y.-J. Wang, Q. Shen, Z.-N. Wang, X.-C. Yang, L. Xiao, H.-P. Sun, Y.-L. Xu, Y.-Y. Chen, Q. Xie, Y.-H. Wang, L.-M. Shao, J.-G. Liu, Z.-B. Qiu, W. Fu, *ACS Chem. Neurosci.*, **2017**, *8*, 766–776. DOI: 10.1021/acschemneuro.6b00321
14. V. T. Bauman, E. E. Shul'ts, V. V. Kononchuk, I. Yu. Bagryanskaya, M. M. Shakirov, G. A. Tolstikov, *Russ. J. Org. Chem.*, **2013**, *49*, 1502–1513. DOI: 10.1134/S1070428013100175
15. H. Rapoport, P. Sheldrick, *J. Am. Chem. Soc*., **1963**, *85*, 1636–1642. DOI: 10.1021/ja00894a022
16. K. Kanematsu, T. Sasaki, *Chem. Commun.*, **1967**, 988–989. DOI: 10.1039/C19670000988
17. K. W. Bentley, D. G. Hardy, H. P. Crocker, D. I. Haddlesey, P. A. Mayor, *J. Am. Chem. Soc.*, **1967**, *89*, 3312–3321. DOI: 10.1021/ja00989a035
18. R. Rubinstein, R. Giger, D. Ginsburg, *Tetrahedron*, **1973**, *29*, 2383–2386. DOI: 10.1016/S0040-4020(01)93366-6
19. K. Hayakawa, S. Motohiro, I. Fujii, K. Kanematsu, *J. Am. Chem. Soc.*, **1981**, *103*, 4605–4606. DOI: 10.1021/ja00405a063
20. A. Singh, S. Archer, K. Hoogsteen, J. Hirshfield, *J. Org. Chem.*, **1982**, *47*, 752–754. DOI: 10.1021/jo00343a036
21. K. Hayakawa, I. Fujii, K. Kanematsu, *J. Org. Chem.*, **1983**, *48*, 166–173. DOI: 10.1021/jo00150a006
22. A. Singh, J. Hirshfield, K. Hoogsteen, S. Archer, *J. Org. Chem.*, **1983**, *48*, 173–177. DOI: 10.1021/jo00150a007
23. U. Pindur, D. Keilhofer, D. Schollmeyer, *Z. Naturforsch. B*, **1994**, *49*, 272–279. DOI: 10.1515/znb-1994-0220
24. G. A. Tolstikov, E. E. Shultz, L. V. Spirikhin, *Tetrahedron*, **1986**, *42*, 591–600. DOI: 10.1016/S0040-4020(01)87458-5
25. G. A. Tolstikov, E. E. Shults, T. Sh. Mukhametyanova, T. G. Tolstikova, V. G. Popov, A. F. Ismagilova, D. N. Lazareva, F. S. Zarudiy, *Khim.-Farm. Zh*., **1993**, *27*, 20–26.
26. E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.*, **2015**, *58*, 8315–8359. DOI: 10.1021/acs.jmedchem.5b00258
27. I. V. Sandulenko, A. A. Ambartsumyan, S. K. Moiseev, *Org. Biomol. Chem.*, **2020**, *18*, 5533–5557. DOI: 10.1039/D0OB00619J
28. J. P. Sorrentino, B. R. Ambler, R. A. Altman, *J. Org. Chem.*, **2020**, *85*, 5416–5427. DOI: 10.1021/acs.joc.0c00125
29. I. H. Jeong, Y. S. Kim, K. Y. Cho, *Bull. Korean Chem. Soc.*, **1990**, *11*, 258–260.
30. I. V. Sandulenko, E. S. Kovaleva, A. S. Peregudov, V. N. Kalinin, S. K. Moiseev, *ChemistrySelect*, **2016**, *1*, 1004–1005. DOI: 10.1002/slct.201600233
31. RU Patent 2503677, **2014**.
32. RU Patent 2503678, **2014**.
33. RU Patent 2506265, **2014**.
34. I. V. Sandulenko, D. V. Semenova, M. V. Zelentsova, S. K. Moiseev, A. B. Koldobskii, A. S. Peregudov, I. S. Bushmarinov, V. N. Kalinin, *J. Fluor. Chem.*, **2016**, *189*, 7–12. DOI: 10.1016/j.jfluchem.2016.07.015
35. M. Tordeux, C. Wakselman, *J. Fluor. Chem.*, **1982**, *20*, 301–306. DOI: 10.1016/S0022-1139(00)82221-6
36. N. P. Tsvetkov, A. B. Koldobskii, I. V. Korznikova, A. S. Peregudov, V. N. Kalinin, *Dokl. Chem*., **2006**, *408*, 87–89. DOI: 10.1134/S0012500806060012
37. A. B. Koldobsky, O. S. Shilova, V. N. Kalinin, *Mendeleev Commun.*, **2001**, *11*, 99–100. DOI: 10.1070/MC2001v011n03ABEH001401
38. N. P. Tsvetkov, A. B. Koldobskii, V. N. Kalinin, *Dokl. Chem*., **2005**, *404*, 174–177. DOI: 10.1007/s10631-005-0065-7
39. N. P. Tsvetkov, A. B. Koldobskii, I. A. Godovikov, V. N. Kalinin, *Dokl. Chem*., **2005**, *404*, 210–211. DOI: 10.1007/s10631-005-0074-6
40. A. B. Koldobskii, E. V. Solodova, P. V. Verteletskii, I. A. Godovikov, V. N. Kalinin, *Tetrahedron*, **2010**, *66*, 9589–9595. DOI: 10.1016/j.tet.2010.10.024
41. K. W. Bentley, J. D. Bower, J. W. Lewis, *J. Chem. Soc. C*, **1969**, 2569–2572. DOI: 10.1039/J39690002569
42. G. W. Kirby, D. C. McDougall, *J. Chem. Res.*, *Miniprint*, **1985**, *6*, 170–171(S).
43. J. Marton, Z. Szabó, S. Garadnay, S. Miklós, S. Makleit, *Tetrahedron*, **1998**, *54*, 9143–9152. DOI: 10.1016/S0040-4020(98)00551-1
44. US Patent 9963460, **2018**.
45. WO Patent 2019045006, **2019**.
46. H. Nagase, H. Fujii, in: *Chemistry of Opioids*, H. Nagase (Ed.), *Top. Curr. Chem*., **2010**, *299*, 29–62. DOI: 10.1007/128_2010_74
47. WO Patent 2020085234, **2020**.