ACADEMICIAN V. M. RODIONOV AND HIS RESEARCH ON THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS (1878-1954) — ON HIS 100TH BIRTHDAY

N. N. Suvorov

It has been 100 years since the birth and 25 years since the death of Academician Vladimir Mikhailovich Rodionov, the outstanding specialist in organic chemistry. Rodionov originated three of the most important branches of the fine-organic-synthesis industry in our country, viz., the pharmaceutical-chemical industry, the aniline-dye industry, and the production of perfumes. It is characteristic that he was awarded three State Prizes of the USSR for his fundamental research on β-amino acids and his achievements in the industrial synthesis of perfumes and industrial products and dyes.

Academician Rodionov was born in Moscow, where, except for the years spent studying in the Dresden Polytechnic Institute, he lived for his entire life. After his brilliant graduation in 1906 from the Moscow Higher Technical School, he began his practical scientific research in the chemistry and technology of synthetic dyes and intermediates.

During World War I, Russia found herself in a very grave situation with respect to the supplying of medications. The Russian pharmaceutical-chemical industry was developing very weakly, and medicinal preparations were being imported from Germany. The war made importation impossible, and Russian medicine remained virtually without medical preparations, including analgesics. Striving to find a way out of this situation, Academician Rodionov was the first to organize the production of opium alkaloids from the Central Asian poppy [1]; in 1917 under his supervision an alkaloid plant that provided the country not only with morphine but also with other plant preparations — caffeine, theobromine, atropine, and strychnine — as well as pyrazolone analgesics, was created in Moscow.

In 1915 in his post as technical supervisor of the Moscow plant Trigor, Academician Rodionov began his research on the creation of industrial methods for the preparation of the most important intermediate products of the aniline dye industry (naphthols, naphthylamines, etc.) and dyes. He developed these research trends successfully after the October Revolution as technical director of the Aniline Trust of the Supreme Council of the National Economy and head of the department of the chemistry of dyes of the Moscow Textile Institute [2]. In 1939 he participated actively in the creation of the Soviet synthetic perfume industry and supervised the scientific research in this field [3].

Although Academician Rodionov successfully headed a number of purely scientific and scientific-industrial collectives, including the laboratory of heterocyclic compounds of the All-Union Institute of Experimental Medicine, his principal research was conducted in the departments of the colleges of the country. The characteristic style of the pedagogical talent of this outstanding scientist and educator was to attract youth to independent research in the most timely fields of science.

In 1916 Academician Rodionov strove to organize the first department of the chemistry and technology of pharmaceutical-chemical preparations at Moscow Higher Technical School. After the October Revolution, he successfully directed through theoretical research on the methylation of phenolic bases and amines of quaternary alkoxides and esters of aromatic sulfonic acids and research on aromatic aldehydro acids [1] in the department of the chemistry of alkaloids, which he had founded, in the second Moscow State University. Prior to his death, he was the head of the department of organic chemistry at D. I. Mendeleev Moscow Institute of Chemical Technology and at the second Moscow Medical Institute. It was precisely in these institutes that Academician Rodionov conducted his classic research on the chemistry of β-amino acids and heterocyclic compounds.

The Rodionov reaction — a method for the preparation of β-amino acids — was discovered in 1926. A low yield of an unsaturated compound had been obtained in the synthesis of β-

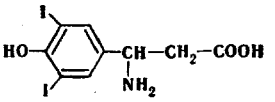
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 267-273, February, 1979.

0009-3122/79/1502-0227$07.50

piperonylacrylic acid by the Knoevenagel method (condensation of piperonal with malonic acid under the influence of an alcohol solution of ammonia). Academician Rodionov proposed that this was due to the formation of a water-soluble substance and established that the aqueous phase contains β-piperonyl-β-aminopropionic acid hydrochloride.

A thorough study of this process (particularly detailed research was carried out from 1942 to 1954) made it possible to establish that the reaction is a general one, i.e., that it is applicable to aldehydes of the aromatic [5-8], aliphatic [9-12], alicyclic [13, 14], and heterocyclic [10, 15-17] series, to aromatic aldehydo acids [18], and some diketones [19]. In place of malonic acid one can use malonic ester [20] and malonic half-ester [21], monoalkylmalonic acid or its esters [22, 23] can be subjected to the reaction, and ammonia can be replaced by methylamine [4, 24]. High yields of acids are obtained when ammonium acetate in ethanol [25], n-butyl alcohol [26], or acetic acid [6] is used or simply when the reagents are fused [17].

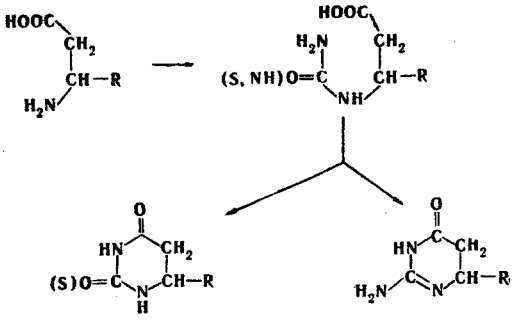
β-(4-Hydroxy-3,5-diiodophenyl)-β-alanine (I), which is an analog of natural diiodotyrosine, was synthesized on the basis of the discovered reaction.



I

The technology for the production of this compound was developed [26, 27], and a preparation called Betazine was incorporated in medical practice for the treatment of thyrotoxicoses [28].

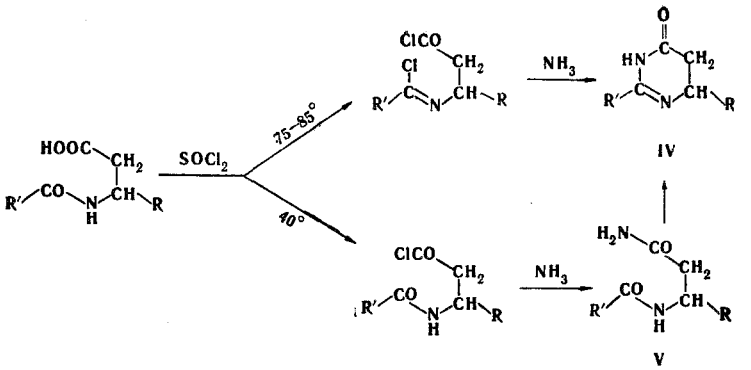
Academician Rodionov regarded β-amino acids as convenient starting substances for the synthesis of heterocyclic compounds, mainly pyrimidines and imidazoles. One should note the syntheses of dehydrouracils, thiodihydrouracils (II), and dihydroisocytosines (III) by reaction with potassium cyanate, aryl isocyanates [29] or urea [30], potassium thiocyanate and aryl isothiocyanates [30], and O-methylisourea [31], respectively, with subsequent cyclization of the intermediate β-ureido, β-thioureido, and β-guanidino acids.



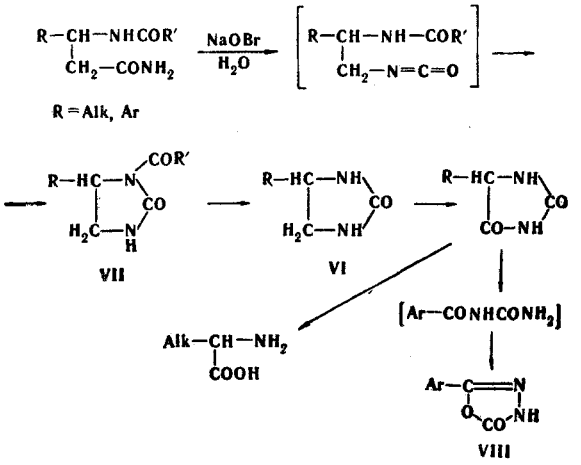
II III

With his brilliant perspicacity Academician Rodionov assumed that processes of this sort could be realized in nature. This was, in fact, confirmed completely. It is now known that the biosynthesis of uridine 5'-monophosphate, the progenitor of pyrimidine nucleotides, proceeds from aspartic acid through carbamoyl aspartate [32].

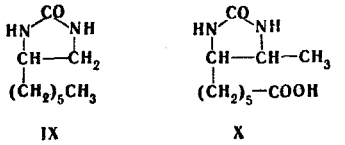
2,4-Dialkyl(aryl)-6-oxotetrahydropyridimidines (IV), which can be obtained from β-acylamino acids by the successive action of thionyl chloride and ammonia, [33], constitute another class of pyrimidine compounds.



Academician Rodionov demonstrated that amides V undergo cyclization to pyrimidines IV (with partial transacylation, i.e., with replacement of R' by CH_3) when they are heated with acetic anhydride. The application of the Hofmann reaction to amides of N-acyl-β-amino acids leads to mixtures of substances, among which 5-aryl(alkyl)glyoxalidones (VI)* and their N-acyl derivatives (VII) predominate [34]:



By selecting the appropriate conditions one can obtain aryloxadiazolones (VIII) or accomplish the conversion from β- to α-amino acids. The Curtius reaction proceeds more unambiguously. N-Benzoylglyoxalidones, which are readily saponified to free cyclic ureas, are formed in the case of N-benzoyl-β-amino acids [35]. Hexylglyoxalidone (IX) is the structural analog of desthiobiotin (X), and the character and magnitude of the biological activity are almost the same as in the case of the latter.

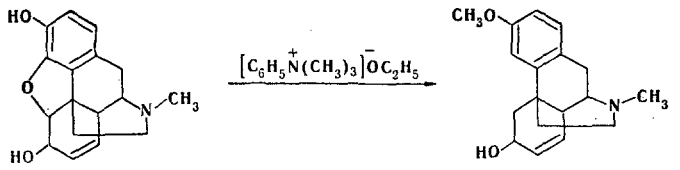


The principal research of Academician Rodionov on β-amino acids and pyrimidine and imidazole derivatives and a detailed review of this research are given in [36].

We have already stated that Academician Rodionov began his research on alkaloids in order to solve the problem of providing our country with the preparations necessary for medicine. Within the framework of this paper we will mention only the principal theoretical research that he carried out in this area. His research on the methylation of phenolic bases serves as a clear example. It was undertaken to create an industrial method for the conversion of morphine (XI) to codeine (XII). The methylation of the phenolic hydroxyl group, which, at first glance, seems to be a trivial task, proved to be exceptionally difficult: The usual methylating agents led to quaternization of the tertiary nitrogen atom, and the subsequent alkalization necessary for the isolation of the base caused far-reaching processes,

*The nomenclature adopted by the authors is used here and subsequently.

as a result of which the yield usually did not exceed 50% of the theoretical value. This problem was solved brilliantly by the application of a new methylating agent — trimethylphenylammonium ethoxide — which is very easily obtained from the methyl esters of arenesulfonic acids and dimethylaniline with subsequent treatment with sodium ethoxide.

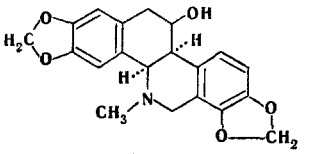


XI XII

The yield reached 85% of the theoretical value [37]. The method was incorporated in industry and is still the best method for the preparation of codeine.

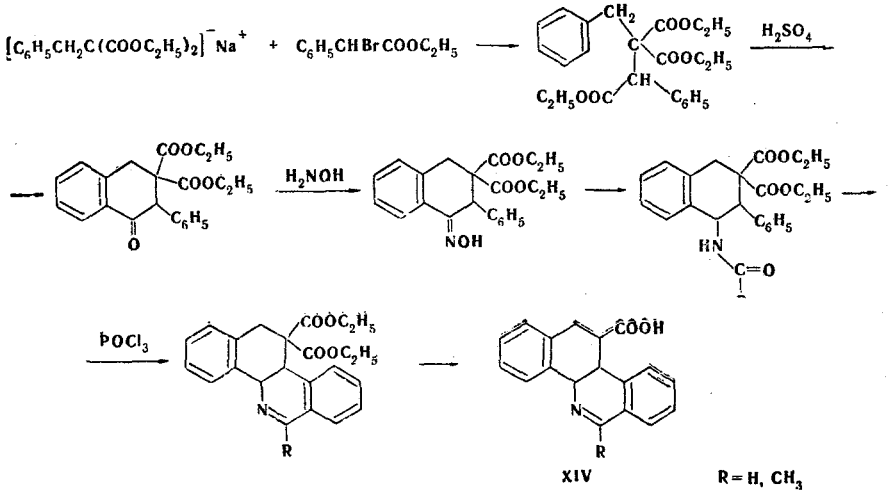
A method for the industrial production of antipyrine and pyramidone (amidopyrine) was developed by means of esters of benzene- and p-toluene-sulfonic acids [37, 38]; the conversion of narcotine to narceine and of hydrastine to methylhydrastine is based on the same principle [37]. The classical research by Academician Rodionov on aromatic aldehydo acids [1], which began with the practical task of using opianic acid, which is a side product in the production of cotarnine from narcotine, is also intimately related to the chemistry of alkaloids. Here, one should also include the synthesis of analogs of the alkaloid damascenine [39].

Academician Rodionov displayed particular interest in the alkaloid-bearing plants of non-chernezem soils, primarily to the celandine Chelidonium majus L., which is a well-known agent of national medicine, assuming that the alkaloids of the latter may have antitumorigenic activity. The study of the alkaloid composition of the Central-Russian celandine was begun in 1939 [40], and in the postwar years research on the synthesis of chelidonine (XIII) and its analogs was developed in the department of organic Chemistry of D. I. Mendeleev Moscow Institute of Chemical Technology.



XIII

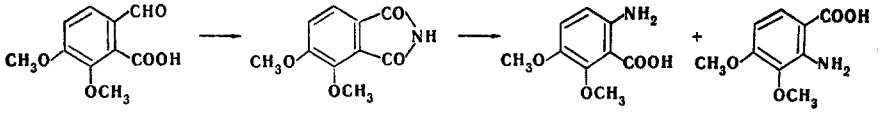
At the start of these studies not one of the benzophenanthridine alkaloids of the celandine had been synthesized and no approaches at all to the synthesis of chelidonine existed. The stereochemistry of the alkaloid also had not been studied. The synthesis of model structures, e.g., from benzylmalonic ester and α-bromophenylacetic ester to give XIV, was therefore accomplished initially [41-43]:



Unfortunately, these studies were discontinued in 1952 for a number of reasons. However the synthesis of chelidonine was accomplished only after 20 years in Switzerland [44]. The foresight of Academician Rodionov was brilliantly confirmed: Benzophenanthridine alkaloids displayed high antileukemic and antitumorigenic activity (see [45]).

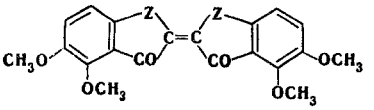
The principal research of Academician Rodionov on alkaloids and a review are presented in [47].

In connection with his research on alkaloids and the chemistry of dyes, Academician Rodionov became interested in the chemistry of indole. In an attempt to find a practical application for opianic acid (XV), he converted it to hemipinimide (XVI), which, via the Hofmann reaction, gave a mixture of two dimethoxyanthranilic acids:



XV XVI XVII

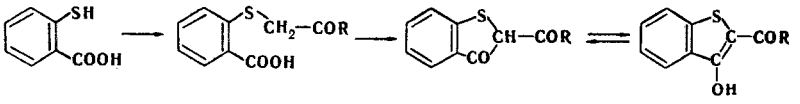
Of these acids, only isomer XVII reacted with chloroacetic acid, and this made it possible to synthesize a number of indigoid dyes (XVIII) [48].



XVIII

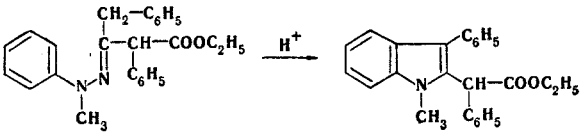
Z=NH, S

A preparative method for the synthesis of 2-acyl-3-hydroxythionaphthenes (XIX) was subsequently worked out in the department of dyes of the Moscow Textile Institute [49]:



XIX

Academician Rodionov had a clear conception of the general biological significance of indole derivatives, particularly tryptophan. He therefore, carried out experiments in the Mendeleev Moscow Institute of chemical Technology to obtain β-tryptophan. These experiments were initially unsuccessful, and the synthesis of this amino acid was accomplished only after his death [16]. Finally, in the course of his studies of the synthesis of benzophenanthridine derivatives he observed the fact of the unusually facile and quantitative Fischer reaction in the reduction of the methylphenylhydrazone of α,γ-diphenylacetoacetic ester [50]:



This discovery, first of all, led to the publication of the first detailed review of research on the Fischer reaction [51] and, second, stimulated further research on the synthesis of indolylbutyric acids [52, 53] in the department of organic chemistry of Mendeleev Institute of Chemical Technology. It should be pointed out that Rodionov's interest in the synthesis of plant-growth stimulators had arisen prior to this time in connection with his detection of the growth-stimulating properties of phthalimidineacetic acid [54].

Within the framework of the present review it is not possible to even list the numerous studies by Academician Rodionov dealing with the chemistry of heterocyclic compounds. Among these, one must, nevertheless, note the preparative methods for the production of quinoline- and isoquinolinealdehydes by oxidation of the corresponding methyl-substituted compounds with selenium dioxide [55-57], his research on the synthesis of sulfanilamide derivatives of pyra-

zolone [58], and his expansion of the range of application of the Skraup [59] and Bischler—Napieralski [60, 61] reactions. Many of these studies are genetically related to the principal trends of the scientific endeavor of Academician Rodionov: Thus the bridge between aldehydeo acids and quinazolones was spanned [62], and the research on β-amino acids stimulated the study of 5-alkyl-1,3,4-oxadiazolones, which in turn were used for an elegant approach to β-semicarbazido acids [63].

The multifaceted and tireless activity of Academician Rodionov with respect to the chemistry of heterocyclic compounds would not be adequately illuminated if we forgot to mention his splendid basic papers on the chemistry of alkaloids [64, 65] and the fact that he was the science editor of fundamental handbooks in this field [66, 67].

The fruitful scientific and pedagogical endeavors of Academician Rodionov were successfully combined with an enormous amount of public activity: He was president of the Mendeleev All-Union Chemical Society, vice president of the technical council of the Ministry of the Chemical Industry of the USSR, a member of many scientific councils, etc. In 1939 he was elected a corresponding member of the Academy of Sciences of the USSR, and in 1943 he was named an academician. The merits of Academician Rodionov were held in high esteem by the nation. He was awarded the Order of Lenin, the Order of the Workers' Red Banner (on two occasions), and a number of medals.

Academician Rodionov won universal recognition even in his own lifetime. Thus, for example, the American scientist T. Johnson proposed his own modification of the Rodionov reaction and, acknowledging the priority of the Soviet scientist, used it extensively in the synthesis of pyrimidine derivatives.

Academician Rodionov died in the full bloom of his powers and creative abilities, leaving a large collective of students and followers, who in various cities and countries continue the research begun by him and are engaged in developing its scientific trends. In Novosibirsk Corresponding Member of the Academy of Sciences of the USSR V. P. Mamaev has created his own school, which is successfully studying the chemistry of pyrimidines. The chemistry of indoles has become the principal topic in the department of organic chemistry of Mendeleev Moscow Institute of Chemical Technology. The Bulgarian Academician B. I. Kurtev is doing research on the chemistry of amino acids. In Moscow V. M. Belikov is also studying the chemistry of amino acids, while N. A. Kravchenko is investigating the chemistry of polypeptides, V. K. Antonov is doing research on enzymes, and N. N. Bezinger is studying the heterocyclic compounds of petroleum. The ideas of Academician Rodionov have also undoubtedly had an effect on the profound research of Academician A. S. Sadykov and his school on the complex utilization of the alkaloids of Central-Asian plants. The endeavors of Academician Rodionov, a splendid scientist and human being, are an example for all those engaged in scientific research in our country.

LITERATURE CITED

1. A. M. Fedorova, "Research by V. M. Rodionov on aromatic aldehydo carboxylic acids and their derivatives," in: V. M. Rodionov. Selected Works [in Russian], Izd. Akad. Nauk SSSR, Moscow (1958), p. 123.
2. B. M. Bogoslovskii, "Research by V. M. Rodionov on the chemistry of intermediates and dyes," in: V. M. Rodionov. Selected Works [in Russian], Izd. Akad. Nauk SSSR, Moscow (1958), p. 271.
3. V. N. Belov, "Research by V. M. Rodionov on synthetic and natural perfumes," in: V. M. Rodinov. Selected Works [in Russian], Izd. Akad. Nauk SSSR, Moscow (1958, p. 677.
4. V. M. Rodionov and E. F. Malevinskaya, Ber., 59, 2952 (1926).
5. V. M. Rodionov and A. M. Fedorova, Arch. Pharm., 266, 116 (1928).
6. V. M. Rodionov and N. A. Kravchenko, Dokl. Akad. Nauk SSSR, 82, 269 (1952).
7. V. M. Rodionov and B. I. Kurtev, Izv. Akad. Nauk SSSR, Ser. Khim., 113 (1952).
8. V. M. Rodionov, A. A. Dudinskaya, V. G. Avramenko, and N. N. Suvorov, Zh. Obshch. Khim., 28, 2242 (1958).
9. V. M. Rodionov and V. K. Zvorykina, Izv. Akad. Nauk SSSR, Ser. Khim., 216 (1943).
10. V. M. Rodionov and N. G. Yartesva, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk Ser. Khim., 103 (1952).
11. V. M. Rodionov, V. K. Zvorykina, and N. E. Kozhevnikova, Zh. Obshch. Khim., 23, 1794 (1953).
12. V. M. Rodionov and V. K. Zvorykina, Zh. Obshch. Khim., 26, 793 (1956).

13. V. M. Rodionov and T. S. Kiseleva, Izv. Akad. Nauk SSSR, Ser. Khim., 278 (1952).
14. V. M. Rodionov and L. V. Antik, Izv. Akad. Nauk SSSR, Ser. Khim., 253 (1953).
15. N. N. Suvorov, V. P. Mamaev, and E. M. Rokhlin, Dokl. Akad. Nauk SSSR, 101 269 (1955).
16. V. P. Mamaev and L. S. Sandakhchiev, Zh. Vses. Khim. Obshch., 6, 350 (1961).
17. A. G. Balabushevich, Author's Abstract of Master's Dissertation, Moscow (1976).
18. V. M. Rodionov and A. M. Fedorova, J. Am. Chem. Soc., 52, 368 (1930).
19. V. M. Rodionov and A. M. Fedorova, Izv. Akad. Nauk SSSR, Ser. Khim., 247 (1950).
20. V. M. Rodionov and A. M. Fedorova, Ber., 60, 804 (1927).
21. V. M. Rodionov and N. N. Bezinger, Izv. Akad. Nauk SSSR, Ser. Khim., 96 (1952).
22. V. M. Rodionov and E. A. Postovskaya, J. Am. Chem. Soc., 51, 841 (1929).
23. V. M. Rodionov and K. P. Preobrazhenskaya, Zh. Obshch. Khim., 24, 1971 (1954).
24. V. M. Rodionov and E. V. Yavorskaya, Zh. Obshch. Khim., 23, 983 (1953).
25. T. B. Johnson, J. Am. Chem. Soc., 58, 299 (1936).
26. V. M. Rodionov, N. N. Suvorov, V. G. Avramenko, and L. M. Morozovskaya, Zh. Obshch. Khim., 27, 2234 (1957).
27. N. N. Suvorov and V. G. Avramenko, Khim.-Farm. Zh., No. 9, 18 (1968).
28. M. D. Maikovskii, Medicinals [in Russian], Part 1, Medgiz, Moscow (1977), p. 555.
29. V. M. Rodionov and S. A. Vyazkova, Zh. Obshch. Khim., 3, 628 (1933).
30. V. M. Rodionov and B. I. Kurtev, Izv. Akad. Nauk SSSR, Ser. Khim., 268 (1952).
31. V. M. Rodionov and O. S. Urbanakaya, Zh. Obshch. Khim., 18, 2023 (1948).
32. J. Davidson, The Biochemistry of Nucleic Acids [Russian translation], Mir, Moscow (1976), p. 231.
33. V. M. Rodionov and V. K. Zvorykina, Izv. Akad. Nauk SSSR, Ser. Khim., 330 (1948).
34. V. M. Rodionov and V. K. Zvorykina, Izv. Akad. Nauk SSSR, Ser. Khim., 608 (1950).
35. V. M. Rodionov and N. N. Bezinger, Izv. Akad. Nauk SSSR, Ser. Khim., 962 (1952).
36. V. M. Rodionov, Selected Works [in Russian], Izd. Akad. Nauk SSSR, Moscow (1958)., p. 327.
37. V. M. Rodionov, Bull, Soc. Chim. France, 39, Ser. 4, 305 (1926).
38. V. M. Rodionov and V. E. Vvedenskii, Zh. Khim. Prom., 7, 11 (1930).
39. V. M. Rodionov and A. M. Fedorova, Izv. Akad. Nauk SSSR, Ser. Khim., 501 (1937).
40. V. M. Rodionov and Yu. S. Shidlovskaya-Ovchinnikova, Zh. Prikl. Khim., 16, 152 (1943).
41. V. M. Rodionov and N. N. Suvorov, Dokl. Akad. Nauk SSSR, 69, 189 (1949).
42. V. M. Rodionov and N. N. Suvorov, Dokl. Akad. Nauk SSSR, 75, 43 (1950).
43. V. M. Rodionov, N. N. Suvorov, and L. B. Shagalov, Dokl. Akad. Nauk SSSR, 82, 731 (1952).
44. W. Oppolzer and K. Keller, J. Am. Chem. Soc., 93, 3836 (1971).
45. G. Cordell and N. Farnworth, Heterocycles, 4, 393 (1976).
46. N. N. Suvorov, L. V. Sokolova, Zh. D. Ovchinnikova, V. S. Murasheva, and V. A. Yaroslavtseva, Med. Prom. SSSR, No. 2, 7 (1958).
47. V. M. Rodionov, Selected Works [in Russian], Izd. Akad. Nauk SSSR, Moscow (1958), p. 13.
48. V. M. Rodionov and B. M. Bogoslovskii, Zh. Obshch. Khim., 7, 2685 (1937).
49. V. M. Rodionov, B. M. Bogoslovskii, and Z. S. Kazakova, Izv. Akad. Nauk SSSR, Ser. Khim., 536 (1948).
50. V. M. Rodionov and N. N. Suvorov, Zh. Obshch. Khim., 20, 1273 (1950).
51. N. N. Suvorov, V. P. Mamaev, and V. M. Rodionov, "Synthesis of indole derivatives from arylhydrazones," in: Reactions and Methods for the Investigation of Organic Compounds [in Russian], B. 8, Goskhimizdat, Moscow (1958), p. 9.
52. N. N. Suvorov and V. K. Antonov, Dokl. Akad. Nauk SSSR, 84, 1952 (1952).
53. N. N. Suvorov, V. P. Mamaev, and L. B. Shagalov, Dokl. Akad. Nauk SSSR, 101, 103 (1955).
54. V. M. Rodionov and E. I. Chukhina, Zh. Obshch. Khim., 14, 325 (1944).
55. V. M. Rodionov and M. A. Berkengeim. Zh. Obshch. Khim., 14, 330 (1944).
56. A. M. Sultanov, V. M. Rodionov, and M. M. Shemyakin, Zh. Obshch. Khim., 16, 2072 (1946).
57. V. M. Rodionov, E. N. Alekseeva, and G. Vleudts, Zh. Obshch. Khim., 27, 734 (1957).
58. V. M. Rodionov and A. M. Fedorova, Izv. Akad. Nauk SSSR, Ser. Khim., 1049 (1952).
59. V. M. Rodionov and L. V. Antik, Zh. Obshch. Khim., 11, 423 (1941).
60. V. M. Rodionov and E. V. Yavorskaya, Zh. Obshch. Khim., 11, 446 (1941).
61. V. M. Rodionov and E. V. Yavorskaya, Zh. Obshch. Khim., 13, 491 (1943).
62. V. M. Rodionov and A. M. Fedorova, Zh. Obshch. Khim., 13, 249 (1943).
63. V. M. Rodionov and V. K. Zvorykina, Izv. Akad. Nauk SSSR, Ser. Khim., 70 (1953).
64. V. M. Rodionov, Izv. Akad. Nauk SSSR, Ser. Khim., 385 (1953).
65. V. M. Rodionov, Usp. Khim., 22, 628 (1953).
66. A. P. Orekhov, The Chemistry of Alkaloids [in Russian], Izd. Akad. Nauk SSSR (1955).
67. T. A. Genri, The Chemistry of Plant Alkaloids [in Russian], Goskhimizdat, Moscow (1956).