SOME NEW ASPECTS OF THE CHEMISTRY OF TRIACETONEAMINE AND ITS SYNTHESIS

É. G. Rozantsev and V. P. Ivanov

UDC 547.824

Triacetoneamine (2,2,6,6-tetramethyl-4-oxopiperidine) is an important chemical intermediate. Its numerous derivatives are finding wide use in various fields of science and practice.

Numerous drugs have been created on the basis of triacetoneamine, which was discovered in 1874 [1]; they include α-eucaine [2], an effective preparation which, like cocaine, exhibits a local anesthetic action. Pyrilene, approved in the USSR for the treatment of hypertension and other vascular diseases, also is a triacetoneamine derivative (1,2,2,6,6-pentamethylpiperidine-p-toluene sulfonate [3]), while the recently synthesized 2,2,6,6-tetramethyl-4-methylene-(phenylpropylacetyl)-hydroxy-4-piperidine hydrochloride [4] has a pronounced antiviral effect. Many preparations of this series possess ganglioblocking [5] and spasmolytic activities [6]; a number of potential adrenolytics and cholinolytics have been synthesized [7].

In synthetic organic chemistry triacetoneamine is used for the production of varied derivatives of pyrroline, pyrrolidine [8, 9], and other heterocyclic compounds [10].

In the catalytic oxidation of triacetoneamine and some of its derivatives, stable nitroxide radicals can be obtained [11, 12]. More than 200 compounds of this class are now known. Studies conducted in recent years in the USSR and abroad have shown that stable nitroxide radicals are useful compounds for the solution of numerous problems arising in the course of chemical, physical, and biological experiments.

Stable nitroxide radicals have been used for the determination of the rate constants of the elementary events of reactions [13], as structural models in synthetic investigations [14], in the study of the structure and reactivity of molecules, and in the investigation of the microstructure of liquids [15, 16] and energetic and steric factors in kinetics [17]. They can be used as oxidizing agents and catalysts [18], and also as "spin markers" for establishing the three-dimensional configuration of molecules [19]. Nitroxides are working substances for the pickups of nuclear precession geomagnitometers [20], instead of unstable solutions of Fremy's salt. They can be used in quantum generators of the maser type as well [21]. There is information on the successful use of stable nitroxide radicals as inhibitors of polymerization reactions [22], antioxidants [23], and stabilizers of polymer materials [24, 25].

A number of compounds of this class have been tested as chemical mutagens [26], and preparations possessing antitumoral [27] and radiosensitizing [28] activities. Studies on molecular biology [29-31] in which nitroxides and their selective reactions without affecting the unpaired electron have been used [32] are widely known. Nitroxide radicals have been used in immunological investigations [33] and in the study of the supermolecular structure of nucleic acids [34].

The abundance of experimental and theoretical studies using nitroxide-free radicals has produced a genuine need for improving the existing methods of production of triacetoneamine. However, the development of the chemistry of triacetoneamine and nitroxide radicals is greatly inhibited by their high cost,* which in turn has determined the absence of reliable and convenient methods of synthesis of triacetoneamine and its derivatives.

*The cost of 125 mg of a preparation of a nitroxide radical is $200 [35].

Institute of Chemical Physics, Academy of Sciences of the USSR, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 5, No. 1, pp. 47-51, January, 1971. Original article submitted November 3, 1969.

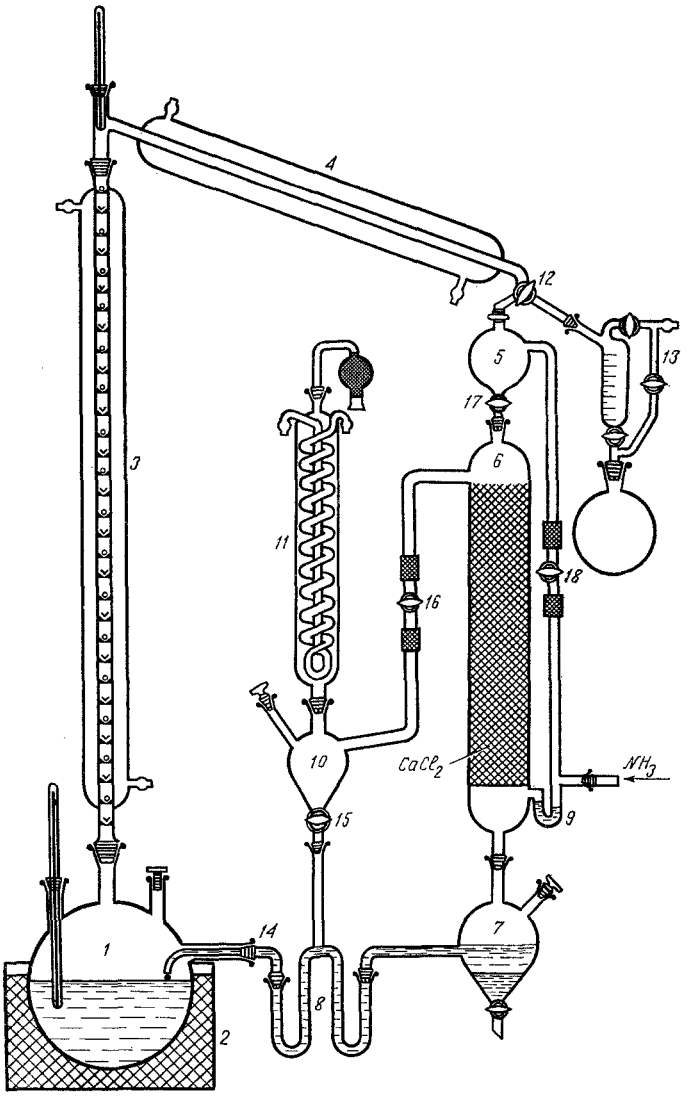
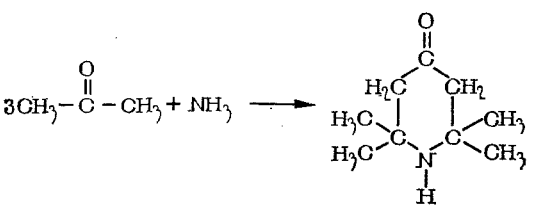


Fig. 1. Apparatus for the production of triacetoneamine by condensation of acetone with ammonia over calcium chloride. Explanations in text.

It has been shown [1] that triacetoneamine can be produced by the condensation of acetone with ammonia at increased temperature:



At room temperature the main product of condensation is diacetoneamine [36]. Subsequently, to remove the water obtained during the reaction and for better absorption of ammonia, calcium chloride was used [37, 38]. In this case the condensation proceeds in stages [39], through the intermediate stages of the formation of mesityl oxide and diacetoneamine.

According to one of the methods [40], triacetoneamine is produced by periodic passage of gaseous ammonia into a mixture of acetone and melted calcium chloride at room temperature. After alkaline treatment of the reaction mass, triacetoneamine is extracted with a yield of 15-20% of the theoretical. The

TABLE 1. Characteristics of Various Methods of Production of Triacetoneamine

Starting material	Yield (in %)	Duration (in days)	Literature
Phorone	68	1-2	[42-44]
2,2,4,4,6-Pentamethyl-2,3,4,5-tetrahydropyrimidine	60	2-3	[45]
Diacetone alcohol	48	6-7	[45]
Acetone	15-17	8-9	[40]
"	33-34*	9-10	[3]
"	15.5	9-10	[41]
"	40.0	2-3	[47]

*On unpurified triacetoneamine.

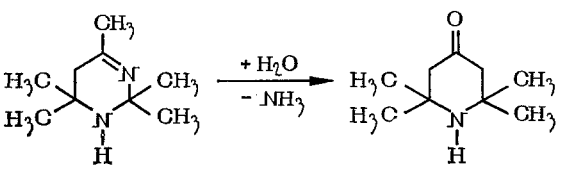
operation of saturation can be considered completed when the amount of absorbed ammonia reaches 100-105% of that necessary according to the reaction equation [3].

The yields of the final product can be increased to some degree, and they can be made more stable, through the use of liquefied ammonia [41] or the use of a preliminarily prepared ammine of calcium chloride; however, all these improvements do not introduce any radical improvements into the process.

Triacetoneamine can be produced from phorone and ammonia [42-44]. Evidently here the reaction is realized through a linear aminoketone, followed by intramolecular heterocyclization to triacetoneamine.

It is quite evident that the above-mentioned methods of production of triacetone amine are routine and inapplicable on an enlarged scale of production.

It has recently been shown [45] that triacetoneamine is smoothly formed in the disproportionation of 2,2,4,4,6-pentamethyl-2,3,4,5-tetrahydropyrimidine [46] and water in the presence of calcium chloride:



It has also been established [45] that the catalytic condensation of diacetone alcohol with ammonia leads to triacetoneamine with 48% yield.

In our opinion, a convenient laboratory method of synthesis of triacetoneamine is the catalytic condensation of ammonia with acetone in the apparatus proposed by Asinger et al. [47]. Repeated production of triacetoneamine using the apparatus that we modified and improved indicated that this method permits a reduction of the number of operations and a simplification of the stage of purification of the final product. We believe that the theoretical technological scheme in this variation (see Fig. 1) can be used in the construction of pilot plants and semi-industrial installations for the synthesis of this compound. The output of a small installation of this type, when it is properly operated, is approximately 0.15 kg/day (see experimental section).

In comparison of various methods of production of triacetoneamine (see Table 1), it is easy to see that the largest yield is achieved when phorone and ammonia are used as the starting materials; if we consider the comparative cost of the reagents, however, we should still give preference to the last method of those considered in the table.

We should mention, however, that the yield indicated by the authors of [47] was calculated on the basis of the reacted acetone, while the triacetoneamine obtained in this case requires additional purification.

EXPERIMENTAL

In a 3-liter four-necked round-bottomed flask (1) (see Fig. 1) we loaded 1980 g of acetone dried over calcium chloride and heated on an oil bath (2). The acetone was passed through a Vigre column (3), Liebig condenser (4), and a separatory funnel (5) into a reactor (6) filled with 600 g of granulated (with particle size 3-4 mm) fused calcium chloride. Five to nine hours after the beginning of irrigation of calcium chloride with acetone and delivery of ammonia to the reactor (6) downward through a bubble counter (9) filled with a concentrated solution of triacetoneamine in acetone, a saturated solution of calcium chloride collected in the lower portion of the separatory funnel (7) and was periodically run off. Triacetoneamine and the unreacted acetone were returned from the receiver (7) through a W-shaped tube (8) to the flask (1).

As a result of the reaction, the temperature in the reactor (6) rose to 50°, and the evaporated acetone, captured by a flow of gaseous ammonia, entered the condenser (11), where it was condensed and returned through the funnel (10) to the flask (1). The inlet of ammonia was regulated in such a way that only the inert gas contained in the ammonia passed out of the condenser (11). As soon as the temperature in the flask (1) reached 105-110° (after approximately 20 h), the delivery of ammonia was stopped, and heating of the flask (1) was continued for another 15-20 min, after which the reaction product was siphoned off with the stopcocks (15, 16, 17, and 18) closed, from the W-shaped tube (8) to the flask (1). The W-shaped tube (8) and connecting tube (14) were replaced by a glass stopper. The Liebig condenser (4) was connected through a three-way stopcock (12) to an Anschutz-Thiele adapter (13). The contents of the flask (1) were distilled under vacuum, collecting the fraction boiling in the range 52-60° (1 mm). The distillate was cooled and the precipitated crystals of triacetoneamine removed. After recrystallization fromn-hexane, triacetoneamine is in the form of colorless, readily subliming crystals, mp 35.5-36°. The yield of the product is about 400 g (28.8 g of the acetone used in the reaction).

LITERATURE CITED

1. W. Heintz, Justus Liebigs Ann. Chem., 174, 133 (1874).
2. C. J. Parsons, Am. Chem. Soc., 23, 885 (1901).
3. I. B. Simon and V. P. Vvedenskii, Med. Prom. SSR, No. 5, 9 (1963).
4. T. Kharizanova, Farmatsiya, No. 1, 45 (1965).
5. S. Cummings, S. Grace, and C. J. Latimer, Pharmacol. Exp. Ther., 141, 349 (1963).
6. N. Bikova and L. Zheleznyakov, Farmatsiya, No. 2, 81 (1965).
7. E. Mailey and A. Day, J. Org. Chem., 22, 1061 (1957).
8. H. Pauly, Justus Liebigs Ann. Chem., 322, 77 (1902).
9. H. Pauly and J. Rossbach, Ber. Dtsch. Chem. Ges., 32, 2000 (1899).
10. L. Orthner, Justus Liebigs Ann. Chem., 459, 217 (1927).
11. É. G. Rozantsev, Author's Certificate No. 166,032 (1962); Byull. Izobret., No. 21 (1964).
12. E. G. Rozantsev, Izv. Akad. Nauk SSSR Ser. Khim., 1669 (1963).
13. A. N. Plyuskin and N. M. Chirkov, Teoret. Éksper. Khimiya, 777 (1966).
14. A. L. Skripko, Dissertation, Moscow (1967).
15. V. Koltorer, M. Goldfeld, L. Hendel, et al., Biochem. Biophys. Res. Commun., 43, 421 (1968).
16. N. Bloembergen, E. Purcell, et al., Physiol. Rev., 73, 679 (1948).
17. L. A. Volodina, Dissertation, Moscow (1968).
18. W. Brackman and C. Gaasbeck, Rec. Trav. Chim. Pays. Bas., 85, 221 (1966).
19. É. G. Rozantsev and L. A. Krinitskaya, Izv. Akad. Nauk SSSR, Ser. Khim., 1137 (1967).
20. É. G. Rozantsev and A. P. Stepanov, Geofizich. Apparatura, No. 29, 35 (1966).
21. E. Allais, C. R. Acad. Sci. (Paris), 246, 2123 (1958).
22. M. B. Neiman, N. G. Karapetyan, A. S. Tarkhanyan, et al., Vysokomol. Soedineniya, 8, 1237 (1966).
23. M. B. Neiman and É. G. Rozantsev, Izv. Akad. Nauk SSSR, Ser. Khim., 1178 (1964).
24. É. G. Rozantsev, M. B. Neiman, and G. I. Likhtenshtein, Author's Certificate 166,133 (1962); Byull. Izobret., No. 15 (1964).
25. B. M. Kobarskaya, M. B. Neiman, V. V. Gur'yanova, et al., Vysokomol. Soedineniya, 6, 1737 (1964).
26. G. I. Efremova and É. G. Rozantsev, Genetika, No. 2, 63 (1965).
27. N. P. Konovalova, G. N. Bogdanov, V. B. Miller, et al., Dokl. Akad. Nauk SSSR, 157, 707 (1964).
28. P. Emmerson and P. Howard-Flanders, Radiat. Res., 26, 54 (1965).
29. S. Ogawa and H. McConnel, Proc. Nat. Acad. Sci. (USA), 58, 19 (1967).
30. J. Boegens and H. McConnel, ibid., 56, 22 (1966).

31. L. Berliner and H. McConnel, ibid., 55, 708 (1966).
32. E. G. Rozantsev, Free Nitroxyl Radicals, New York (1970).
33. L. Stryer and O. Gniffith, Proc. Nat. Acad. Sci. (USA), 54, 1787 (1965).
34. I. Smith and T. Yamanc, ibid., 58, 884 (1967).
35. Varian Instrument Application, 4, No. 1, 8 (1970).
36. E. Matter, Helv. Chim. Acta, 30, 114 (1947).
37. A. E. Everest, J. Chem. Soc., 115, 588 (1919).
38. F. Francis, ibid., 2897 (1927).
39. Heterocyclic Compounds [in Russian], Vol. 1 (1953), p. 502.
40. H. K. Hall, J. Am. Chem. Soc., 79, 5447 (1957).
41. L. Vanino, Handbuch der Präparat. Chemie, 3, 807 (1937).
42. J. Guareschi, Atti d. R. Acc. di Torino, 29, 680 (1894).
43. Idem, Ber. Dtsch. Chem. Ges., 28, 160 (1895).
44. C. Sandris and G. Quarisson, Bull. Soc. Chim. Fr., 345 (1958).
45. K. Murayama, S. Morimura, O. Amakasu, T. Toda, et al., Nippon Kagaku Zasshi., 90, 296 (1969).
46. R. B. Bradbury, N. C. Hancox, and H. H. Hatt, J. Chem. Soc., 1394 (1947).
47. F. Asinger, A. Saus, and E. Michel, Mh. Chem., 99, 1436 (1968).