MONOARYLHYDRAZONES OF DI- AND TRICARBONYL COMPOUNDS IN THE KNORR SYNTHESIS OF PYRROLES

V. I. Shvedov, L. B. Altukhova, and A. N. Grinev

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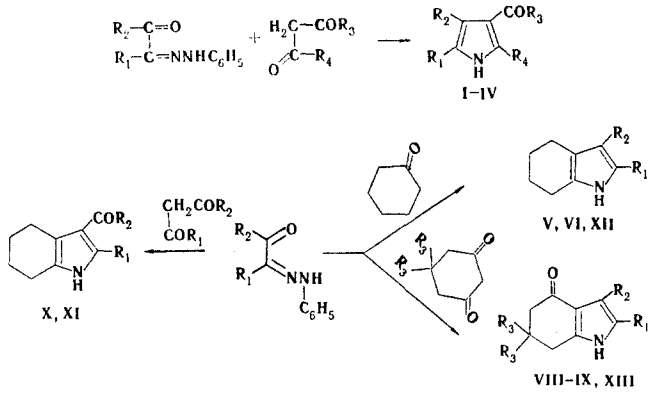
A method was developed for the preparation of various pyrrole, tetrahydroindole, and octahydrocarbazole derivatives from the monophenylhydrazones of di- and tricarbonyl compounds. As a rule, the yields of the substituted pyrroles obtained were higher than those obtained via the Knorr method using isonitroso ketones.

In a continuation of our investigations [1], we synthesized pyrrole derivatives containing CHO, COR, and COOR groups in the α position. The Knorr method is used most frequently for the synthesis of such pyrrole derivatives. According to one of the variants of this method, 1,3-dicarbonyl compounds are condensed with isonitroso ketones [2]. The synthesis of isonitroso ketones is fraught with certain difficulties in the case of cyclic mono- and diketones [3-6]. The yields of isonitroso ketones in the nitrosation of aliphatic ketones are far from being always satisfactory [7]. Since the nitrosation of ketones and the reduction of isonitroso derivatives under the conditions of the Knorr reaction are often carried out in a single step, the yields of substituted pyrroles are usually low [8, 9]. The possibility of using monoarylhydrazones of polycarbonyl compounds instead of isonitroso ketones in the Knorr synthesis of pyrroles was used for the synthesis of 2,4-dimethyl-3,5-dicarbethoxypyrrole from phenylazoacetoacetic ester [10]. However, this reaction has not undergone further development. In connection with the fact that the monoarylhydrazones of α-dicarbonyl compounds are widely available [11], we decided to use them in place of isonitroso ketones in the Knorr synthesis of pyrroles. Our preliminary experiments demonstrated that substituted pyrroles



I R_1=$COOC_2H_5$, R_2=R_3=R_4=CH_3; II R_1=$COCH_3$, R_2=R_3=R_4=CH_3; III R_1=$COCH_3$, R_2=R_4=CH_3, R_3=OC_2H_5; IV R_1=$COCH_3$, R_2=R_4=CH_3, R_3=NHC_6H_5; V R_1=$COOC_2H_5$, R_2=CH_3; VI R_1=$COCH_3$, R_2=CH_3; VII R_1=$COOC_2H_5$, R_2=CH_3, R_3=H; VIII R_1=$COOC_2H_5$, R_2=R_3=CH_3; IX R_1=$COCH_3$, R_2=R_3=CH_3; X R_1=CH_3, R_2=OC_2H_5; XI R_1=R_2=CH_3; XII R_1R_2=$(CH_2)_4$; XIII R_3=CH_3, R_1R_2=$(CH_2)_4$

are generally obtained in higher yields if monophenylhydrazones of α-dicarbonyl compounds are used in the reaction instead of isonitroso ketones.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow.
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TABLE 1. Pyrrole Derivatives

Compound	Mp, °C	Yield, %
I	143—144 (143—144[15])	60
II	135—136 (134—135[8])	67,4
III	139—140 (139—140[16])	64,2
IV	285—286 a	85,5
V	110—111 (110[3])	74
VI	149—150 (149—150[3])	57
VII	167—168 (163—164[9])	65
VIII	169—170 b	51,5
IX	185—186 c	51
X	132—133 (132—133[17])	52
XI	202—203 (201—202[3])	44
XII	97—98 (97[18])	60
XIII	203—204 d	66,6

[a] Found: C 7.03; H 6.5; N 10.9%. $C_{15}H_{16}N_2O_2$. Calculated: C 70.3; H 6.3; N 10.9%.

[b] Found: C 67.6; H 7.4; N 5.8%. $C_{14}H_{19}NO_3$. Calculated: C 67.4; H 7.7; N 5.6%.

[c] Found: C 71.4; H 7.7; N 6.4%. $C_{13}H_{17}NO_2$. Calculated: C 71.2; H 7.8; N 6.4%.

[d] Found: C 77.8; H 8.6; N 6.5%. $C_{14}H_{19}NO$. Calculated: C 77.4; H 8.8; N 6.5%.

Tetrahydroindole (X, XI) and octahydrocarbazole (XII, XIII) derivatives were obtained from cyclohexane-1,2-dione monophenylhydrazone. It should be noted that we introduced considerable simplifications and refinements into the synthesis of cyclohexane-1,2-dione monophenylhydrazone. The sodium salt of formylcyclohexanone, obtained in the reaction of cyclohexanone with ethyl formate in alcoholic sodium ethoxide, was coupled with benzenediazonium chloride and the product was used without isolation.

The synthetic method that we developed is especially interesting in connection with the fact that several of the tetrahydroindole and octahydrocarbazole derivatives are starting compounds for the preparation of biologically active substances [9, 12, 13].

EXPERIMENTAL

Cyclohexane-1,2-dione Monophenylhydrazone. An alcohol solution of sodium methoxide, prepared from 4.6 g (0.2 g-atom) of sodium and 45 ml of methanol, was added with stirring to a cooled (5°) mixture of 19.6 g (0.2 mole) of cyclohexanone and 22.2 g (0.3 mole) of ethyl formate. The precipitated sodium derivative of formylcyclohexanone was allowed to stand for 5-6 h at room temperature and was then dissolved in 100 ml of cold water. The cooled (to 0-5°) solution was added to an aqueous solution of benzenediazonium chloride, prepared in the usual manner from 9.3 g (0.1 mole) of aniline, 30 ml of concentrated HCl, and 6.9 g (0.1 mole) of sodium nitrite and brought up to pH 5-6 by the addition of sodium acetate. The precipitated crystals were removed by filtration, washed with cold water, and dried to give 18.0 g (90%) of cyclohexane-1,2-dione monophenylhydrazone with mp 184-185°.

General Method for the Preparation of Substituted Pyrroles. Zinc dust (30 g) was added in portions to a heated (to 60°) mixture of 0.1 mole of the monophenylhydrazone of a dicarbonyl or tricarbonyl compound, 0.1 mole of cyclohexanone or a dicarbonyl compound,* 10 g of anhydrous sodium acetate, and 100 ml of acetic acid. The reaction mixture was refluxed with stirring for 1 h and decanted from the sediment into 500 ml of cold water. The sediment was washed with hot acetic acid (four 15-ml portions), and the acetic acid solutions were also diluted with water. The resulting precipitate was removed by filtration and recrystallized from alcohol. Data on the pyrrole derivatives obtained are presented in Table 1.

* In the case of dimedone and dihydroresorcinol, 0.2 mole of each per 0.1 mole of monophenylhydrazone was used. The phenyliminodimedone or phenyliminodihydroresorcinol that are formed as side products are easily separated from the tetrahydroindole derivative by recrystallization.

LITERATURE CITED

1. V. I. Shvedov, L. B. Altukhova, and A. N. Grinev, Khim.-Farmats. Zh., No. 3, 25 (1967).
2. E. Baltazzi and L. Krimen, Chem. Rev., 63, 511 (1963).
3. A. Treibs and D. Dinelli, Ann., 517, 152 (1935).
4. W. Dieckmann and A. Groeneveld, Ber., 33, 595 (1900).
5. W. Dieckmann, Ber., 33, 579 (1900).
6. A. Treibs and R. Zinsmeister, Ber., 90, 85 (1957).
7. R. Adams (editor), Organic Reactions, Vol. 7, Wiley (1951-1959).
8. H. Fischer and M. Neber, Ann., 496, 25 (1932).
9. R. Moffett, J. Med. Chem., 11, 1251 (1968).
10. A. Treibs, R. Schmidt, and R. Zinsmeister, Ber., 90, 79 (1957).
11. R. Adams (editor), Organic Reactions, Vol. 10, Wiley (1951-1959).
12. S. Hauptmann and M. Martin, Z. Chem., 8, 334 (1968).
13. Belgian Patent No. 670,798 (1966); Chem. Abstr., 65, 7148 (1966).
14. H. Fischer, E. Baumann, and H. Riedl, Ann., 476, 238 (1929).
15. H. Fischer and H. Orth, Chemie des Pyrrols, Johnson Reprints (1969).
16. A. Treibs, Ann., 524, 285 (1936).
17. A. N. Kost and I. I. Grandberg, Zh. Obshch. Khim., 26, 565 (1956).