SYNTHESIS OF OXYGEN AND NITROGEN HETEROCYCLIC RINGS FROM BROMONITROALKENES AND CYCLIC β-DIKETONES

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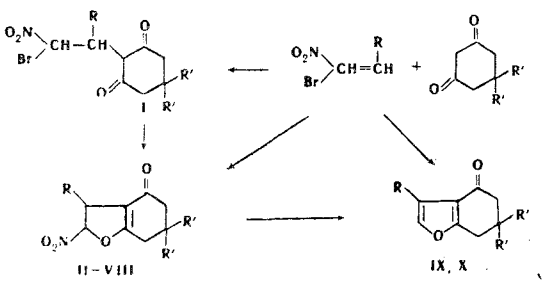
Condensing α-alkyl(aryl)-β-bromo-β-nitroethylenes with dimedon and dihydroresorcinol gives a number of derivatives of nitrohexahydrobenzofuran, reduced using Raney nickel catalyst, to substituted hexahydroindolones, boiling with the same catalyst in ethanol giving tetrahydroindolones. Acid hydrolysis of derivatives of nitrohexahydrobenzofuran gives monocarboxylic acids (only the furan ring being opened), or dicarboxylic keto-acids (both rings opened). Reaction of nitrohexahydrobenzofurans with p-nitrophenylhydrazine gives monohydrazones. 2-Nitro-3-(m-nitrophenyl)hexahydrobenzofurans, when boiled with excess triethylamine, lose nitrous acid to give 3-(m-nitrophenyl)tetrahydrobenzofurans.

In previous papers it was shown that reaction of 1-nitro-prop-1-ene, β-bromo-β-nitrostyrene, and α-(p-nitrophenyl)-β-bromo-β-nitroethylene with dimedon and dihydroresorcinol, in the presence of basic reagents (triethylamine, sodium methoxide), involves dehydrohalogenation, and leads to the formation of nitro derivatives of hexahydrobenzofuran [1–4]. The present work aimed to extend this reaction to a series of other α-alkyl(aryl)-β-bromo-β-nitroethylenes, and to study the chemical behaviors of the resultant products.

1-Bromo-1-nitroethylene and dimedon initially give the product of a Michael reaction, 2-(β-bromo-β-nitroethyl)-5, 5-dimethylcyclo-hexa-1, 3-dione (I) [5], converted to 2-nitro-4-oxo-6, 6-dimethyl-2, 3, 4, -5, 6, 7-hexahydrobenzofuran (II). 1-Bromo-1-nitroethylene reacts with dimedon to give immediately a cyclization product, 2-nitro-propyl-4-oxo-6, 6-dimethyl-2, 3, 4, 5, 6, 7-hexahydrobenzofuran (IV).



№	I	II	III	IV	V	VI
R	H	H	CH_3	n-C_3H_7	C_6H_5	C_6H_5
R′	CH_3	CH_3	CH_3	CH_3	CH_3	H

VII	VIII	IX	X
m-$NO_2C_6H_4$	m-$NO_2C_6H_4$	m-$NO_2C_6H_4$	m-$NO_2C_6H_4$
H	CH_3	H	CH_3

Condensation of α-(m-nitrophenyl)-β-bromo-β-nitroethylene with dihydroresorcinol or dimedon in benzene, in the presence of an equimolecular amount of triethylamine, is accompanied by dehydrohalogenation, and gives respectively 2-nitro-3-(m-nitrophenyl-4-oxo-2, 3, 4, 5, 6, 7-hexahydrobenzofuran (VII), and 2-nitro-3-(m-nitrophenyl)-4-oxo-6, 6-dimethyl-2, 3, 4, 5, 6, 7-hexahydrobenzofuran (VIII). With excess triethylamine, dehydrohalogenation is accompanied by denitration, and the end products are, respectively, 3-(m-nitrophenyl)-4-oxo-4, 5, 6, 7-tetrahydrobenzofuran (IX), and 3-(m-nitrophenyl)-4-oxo-6, 6-dimethyl-4, 5, 6, 7-tetrahydrobenzofuran (X). The structures of products II–VIII checked by their IR spectra,* which had absorption bands at 3430–3456 cm^{-1} and 3140–3230 cm^{-1}, corresponding to asymmetric and symmetric vibrations of the nitro group, and the frequencies, characteristic of the immobilized enol form of 1, 3-cyclohexanedione, 1640–1670 cm^{-1} [6, 7]. The latter were also found in the IR spectra of IX and X. Furthermore compounds IX and X show absorptions corresponding to the nitro group in the benzene ring, at 1525–1530 and 1348–1350 cm^{-1}, as well as absorptions in the 1550–1555 cm^{-1} region, corresponding to vibrations of C=C in the furan or benzofuran ring [8, 9].

When 2-nitro-3-phenyl-4-oxo-6, 6-dimethyl-2, 3, -4, 5, 6, 7-hexahydrobenzofuran (V) [1, 2] is reduced over Raney nickel in methanol under ordinary conditions, nitro group reduction is accompanied by re-heterocyclization, and conversion of V to 3-phenyl-6, 6-dimethyl-2, 3, 4, 5, 6, 7-hexahydroindol-4-one (XI), previously synthesized from 2-(α-phenyl-β-nitroethyl)-5, 5-dimethylcyclohexane-1, 3-dione (XXI) [10]. Compound XI is also obtained by reducing 4-phenyl-5-oxo-7, 7-dimethyl-5, 6, 7, 8-tetrahydro(1, 2, 4)benzoxazine-N-oxide (XIX). The latter is obtained from XXI by boiling in ethanol, or by treating an ethanol solution with a catalytic quantity of sodium methoxide, as well as by condensing β-nitrostyrene with dimedon, using the same catalyst. The IR spectra of XIX and 4-phenyl-5-oxo-5, 6, 7, 8-tetrahydro(1, 2, 4)benzoxazine-N-oxide (XX) [11] are the same, and they exhibit intense absorption bands, characteristic of benzoxazine-N-oxides [12]. Hydrogenation of 2-nitro-3-phenyl-4-oxo-2, 3, 4, 5, 6, 7-hexahydrobenzofuran (VI) [4] and XX over Raney nickel, gives 3-phenyl-2, 3, 4, 5, 6, 7-hexahydroindol-4-one (XII). Under similar conditions, compound IV was converted to 3-propyl-6, 6-dimethyl-2, 3, 4, 5, 6, 7-hexahydroindol-4-one (XIII), also obtained as the hydrochloride XIV. Reduction of 2-nitro-3-methyl-4-oxo-6, 6-dimethyl-2, 3, 4, 5, 6, 7-hexahydrobenzofuran (III) [3], followed by treatment of a

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Table 1

Derivatives of Hexa-and Tetrahydrobenzofuran*

Compound	Mp, ° C	IR spectrum, cm^{-1}			Formula	Found, %			Calculated, %			Yield, %
		C=O	NO_2	C=C benzofuran		C	H	N	C	H	N	
II	98—99**	1653	1365, 1570	—	$C_{10}H_{13}NO_4$	57.11 56.99	6.45 6.37	6.46 6.66	56.87	6.16	6.63	90
IV	81—82 (MeOH)	1670	1371, 1555	—	$C_{13}H_{19}NO_4$	61.11 61.26	7.72 7.62	5.82 5.78	61.66	7.56	5.53	37.6
VII	196—197 (MeOH)	1645	1563, 1370 1530, 1330	—	$C_{14}H_2N_2O_6$	55.30 55.54	4.19 4.23	9.36 9.34	55.26	3.94	9.21	71
VIII	177—177.5 (MeOH)	1670	1575, 1365 1538, 1355	—	$C_{16}H_{16}N_2O_6$	57.79 57.90	5.12 5.13	8.43 8.39	57.83	4.82	8.43	60
IX***	94—95****	1670	1525, 1350	1550	$C_{14}H_{11}NO_4$	65.26 65.55	4.19 4.14	5.66 5.51	65.37	4.28	5.44	60
X***	106—107 (MeOH)	1680	1530, 1348	1555	$C_{16}H_{15}NO_4$	67.35 67.65	5.33 5.41	5.16 5.12	67.36	5.26	4.91	62

* The synthesis of I, III, V, and VI have previously been described [1-4].

** Compound II was recrystallized from petrol ether containing a few drops of benzene.

*** Compounds IX and X formed brown crystals; all the other compounds were white.

**** Product IX was recrystallized from MeOH plus a few drops of dry $CHCl_3$.

Table 2

Derivatives of Hexahydroindol-4-one

Compound	Mp, ° C	IR spectrum, cm^{-1}, NH	Formula	Found, %			Calculated, %			Yield, %
				C	H	N	C	H	N	
XI	235 (MeOH)	3160	$C_{16}H_{19}NO$	79.75 79.86	8.21 7.74	6.11 6.17	79.61	7.94	5.81	80
XII*	194—195 (Dioxane)	3430 3175	$C_{14}H_{15}NO$	79.01 78.90	6.95 6.90	6.40 6.68	78.87	7.05	6.57	29
XIII	155 (H_2O-MeOH 1:1)	3450 3230	$C_{13}H_{21}NO$	75.65 75.28	10.48 10.21	7.05 6.99	75.36	10.14	6.76	73
XIV**	183—184***	—	$C_{13}H_{21}NO \cdot HCl$	64.02 64.08	9.21 9.08	5.95 6.05	64.07	9.03	5.75	88
XV****	229—230***	—	$C_{11}H_{17}NO \cdot HCl$	61.07 60.91	8.56 8.63	6.75 6.58	61.21	8.35	6.50	84

* Mixed mp shows it to be identical with the known compound [11].

** Found: Cl 15.00; 14.80%. Calculated: Cl 14.58%.

*** XIV and XV were recrystallized from dry ether + a few drops of MeOH.

**** Found: Cl 16.36; 16.31%. Calculated: Cl 16.47%.

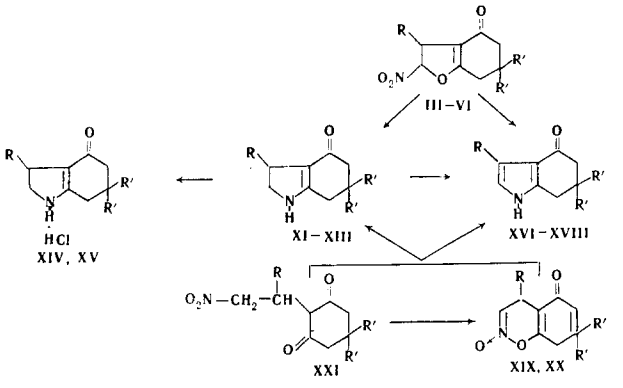
Table 3
Derivatives of Tetrahydroindol-4-one

Compound	Mp, ° C	Formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
XVI*	243—244 (MeOH)	$C_{16}H_{17}NO$	80.32 80.43	7.32 7.40	5.81 5.87	80.33	7.11	5.86	66
XVII**	234—235 (MeOH)	$C_{14}H_{13}NO$	79.77 79.91	6.46 6.49	6.55 6.71	79.62	6.16	6.63	30
XVIII	143—144***	$C_{13}H_{19}NO$	76.44 76.41	9.32 9.22	6.96 6.92	76.09	9.27	6.83	24

* IR spectrum of XVI, cm^{-1} : 3200 wide (NH), 1630 (C=O), 1603 (C=C pyrrole).
** Compound identical with authentic XVII [11], judging by mixed mp.
*** XVIII was recrystallized from aqueous EtOH 1:1.

methanol solution of the resultant base with hydrochloric acid, results in the synthesis of the hydrochloride of 3, 6, 6-trimethyl-2, 3, 4, 5, 6, 7-hexahydroinol-4-one (XV).

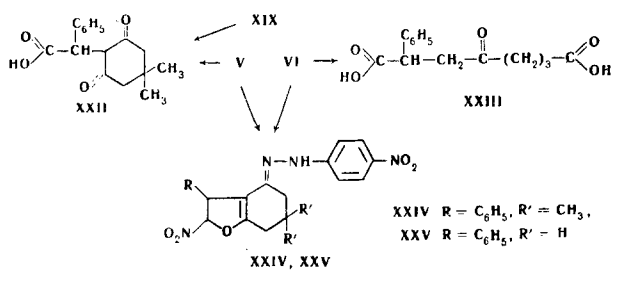
When compound XI is boiled with Raney nickel in ethanol, it undergoes dehydrogenation, giving 3-phenyl-6, 6-dimethyl-4, 5, 6, 7-tetrahydroindol-4-one (XVI), which is similarly obtained from V or XXI. In the same way VI is converted to 3-phenyl-4, 5, 6, 7-tetrahydroindolone (XVII), while XIII gives 3-propyl-6, 6-dimethyl-4, 5, 6, 7-tetrahydroindol-4-one (XVIII). The IR spectra of compounds XI–XIII are found to contain absorption bands characteristic of pyrrole [13] (free NH 3430–3456 cm^{-1} and associated NH 3140–3230 cm^{-1}). Hydrolysis of V with 36% hydrochloric acid is accompanied by opening of the dihydrofuran ring, to give α-(5, 5-dimethyl-1, 3-cyclohexanedion-2-yl)-α-phenylacetic acid, also obtained by hydrolyzing XIX. Acid hydrolysis of VI is accompanied by opening of both rings, and leads to synthesis of



№	XI	XII	XIII	XIV	XV
R	C_6H_5	C_6H_5	n-C_3H_7	n-C_3H_7	CH_3
R′	CH_3	H	CH_3	CH_3	CH_3

XVI	XVII	XVIII	XIX	XX	XXI
C_6H_5	C_6H_5	n-C_3H_7	C_6H_5	C_6H_5	C_6H_5
CH_3	H	CH_3	CH_3	H	CH_3

α-phenyl-γ-keto- suberic acid (XXIII). Obviously this difference in the behaviors of V and VI is due to the greater lability of the dihydroresorcinol as compared with the dimedon [14].



Condensation of V and VI with one or two molecules of p-nitrophenyl-hydrazine leads to the isolation of the respective monohydrazones: 4-(p-nitrophenylhydrazone)-2-nitro-3-phenyl-6, 6-dimethyl-2, 3, 4, 5, 6, 7-hexahydrobenzofuran (XXIV) and 4-(p-nitrophenylhydrazone)-2-nitro-3-phenyl-2, 3, 4, 5, 6, 7-hexahydrobenzofuran (XXV).

EXPERIMENTAL

2-Nitro-4-oxo-6, 6-dimethyl-2, 3, 4, 5, 6, 7-hexahydrobenzofuran (II). A solution of 0.2 g (0.0008 mole) I, 110 ml dry benzene, 3 ml MeOH, and 0.14 ml (0.001 mole) Et_3N was refluxed for 10 hr, then the MeOH distilled off. The $Et_3N \cdot HBr$ was separated off, the benzene evaporated, to give 0.13 g (90%) II.

2-Nitro-3-propyl-4-oxo-6, 6-dimethyl-2, 3, 4, 5, 6, 7-hexahydrobenzofuran (IV). A solution of 4.68 g (0.024 mole) 1-bromo-1-nitropent-1-ene in 10 ml dry methanol was prepared, cooled to 0° C, stirred, and a solution of 2.8 g (0.020 mole) dimedon in 25 ml MeOH and 0.46 g (0.020 g at) Na added. After holding at 0° for 1 hr, the products were poured into 300 ml cold water. The resultant oil quickly solidified. Yield 1.9 g (37.6%) IV.

2-Nitro-3-(m-nitrophenyl)-4-oxo-2, 3, 4, 5, 6, 7-hexahydrobenzofuran (VII). A hot solution was prepared consisting of 0.27 g (0.001 mole) dihydroresorcinol in 15 ml dry benzene, and 0.14 g (0.001 mole) added, then the whole refluxed for 1 hr. The product was isolated as described for II, yield 0.2 g (71%) VII.

Compounds VIII–X were synthesized similarly to VII (in preparing IX and X, a 4-fold excess of Et_3N was used, and the reaction mixture refluxed for 10 hr). X was obtained in the same way, from VIII (36% yield), by boiling with a 2-fold excess Et_3N in dry benzene for 20 hr.

3-Phenyl-6, 6-dimethyl-2, 3, 4, 5, 6, 7-hexahydroindol-4-one (XI). A solution of 1.22 g (0.0042 mole) V in 70 ml MeOH and 1 g Raney Ni was hydrogenated with vigorous shaking, under ordinary conditions. The calculated amount of hydrogen was taken up in 2 hr (4 mole H_2 per mole V calculated). The catalyst was filtered off, washed with MeOH, and the filtrate evaporated at 18°–20° C to give 0.8 g (80%) XI. A mixed mp and its IR spectrum showed it to be identical with authentic XI [10]. Similarly XI was obtained in 34% yield from XIX.

The syntheses of XII–XV were carried out similarly to that of XI (with XII and XIII hydrogenation was effected in EtOH). Hydrochlorides of XIV and XV were prepared by treating with conc. HCl the solutions of the bases obtained by reduction, then keeping the reaction mixtures for 5–10 hr, and lastly evaporating on a water-bath (Table 2).

3-Phenyl-6, 6-dimethyl-4, 5, 6, 7-tetrahydroindol-4-one (XVI). 2 g Raney Ni was added to a hot solution of 0.9 g (0.004 mole) XI in 45 ml 96% EtOH, and the whole refluxed for 5 hr. After filtering off the catalyst the EtOH was evaporated off at 18°–20°, and 0.6 g (66%) XVI obtained. In the same way XVI was obtained in 48% yield from V, and in 31% yield (18 hr boiling) from XXI. XVII and XVIII were prepared respectively from VI and XIII, similarly to XVI. Tetrahydroindol-4-ones (XVI–XVIII) gave the Erlich qualitative reaction for pyrrole [15] (Table 3).

4-Phenyl-5-oxo-7, 7-dimethyl-5, 6, 7, 8-tetrahydro-(1, 2, 4)benzoxazine-N-oxide (XIX). A solution of 0.42 g (0.003 mole) dimedon, 0.45 g (0.003 mole) β-nitro-

styrene, in 30 ml dry MeOH containing 0.2 ml 6% NaOMe, was kept for 22–25 hr. The MeOH was removed at 16°–20°, to give 0.5 g (62%) XIX, white plates, mp 159°–160° C (ex MeOH-H_2O 2:1). Found: C 71.05, 70.90; H 6.36, 6.55; N 4.85, 5.22%. Calculated for $C_{16}H_{17}NO_3$: C 70.85; H 6.27; N 5.16%. IR spectrum, cm^{-1}: 1646, 1390, 1161, 1030, 945. Compound XX: IR spectrum, cm^{-1}: 1646, 1388, 1164, 1000, 947 [11, 12]. Similarly, in the presence of 6% NaOMe, XXI gave a 39% yield of XIX. XIX was also synthesized by refluxing for 2 hr 0.22 g (0.0008 mole) XVI in 8 ml EtOH after which the solvent was removed at room temperature, yield 0.07 g (38%) XIX.

α-(5, 5-Dimethylcyclohexane-1, 3-dion-2-yl)-α-phenylacetic acid (XXII). A suspension of 1 g (0.0035 mole) in 14 ml 36% HCl was refluxed for 3 hr, and the tar filtered off from the hot solution. 0.1 g (11%) XXII separated from the filtrate, white crystals mp 196°–197° C (ex benzene plus a few drops of MeOH). Found: C 70.27; 70.08; H 6.80; 6.84%. Calculated for $C_{16}H_{18}O_4$: C 70.07; H 6.57%. XXII was obtained similarly from XIX, yield 13%, mp 196°–197°.

α-Phenyl-γ-ketosuberic acid (XXIII). This was synthesized by the method used for preparing XXIII, yield 23%, mp 146°–147° (ex water). Mixed mp showed it to be identical with authentic material [11].

Hydrazone (XXIV). Equimolecular amounts of V and p-nitrophenylhydrazine in EtOH containing a few drops of AcOH were boiled for 3 min, then the products allowed to stand for a few days. Yield of XXIV 18%, mp 202°–203° (ex EtOH). Found: N 13.43; 13.55. Calculated for $C_{22}H_{22}N_4O_5$: N 13.27%. The hydrazone XXV was prepared similarly to XXIV, yield 39%, mp 190°–191°. Found: N 14.02; 14.15%. Calculated for $C_{20}H_{18}N_4O_5$: N 14.21%.

The IR spectra were determined with a double beam IKS-14 spectrophotometer, in $CHCl_3$ solution (except VII, XI, and XII, for which vaseline mulls were used). The spectra of II, IV, VII–X, XIII, XVI, XIX, and XX were observed over the range 1800–660 cm^{-1}, using a NaCl prism, while XI, XII, XIII, and XVI were observed over the 4000–1700 cm^{-1} range, using a LiF prism.

REFERENCES

1. A. S. Sopova, V. V. Perekalin, and Ya. S. Bobovich, ZhOKh, **31**, 1528, 1961.

2. Ya. S. Bobovich, V. V. Perekalin, and A. S. Sopova, DAN, **134**, 1083, 1960.

3. A. S. Sopova, V. V. Perekalin, and V. M. Lebednova, ZhOKh, **33**, 2143, 1963.

4. A. S. Sopova, V. V. Perekalin, and V. M. Lebednova, ZhOKh, **34**, 2638, 1964.

5. A. S. Sopova, V. V. Perekalin, V. M. Lebednova, and O. I. Yurchenko, ZhOKh, **34**, 1185, 1964.

6. O. Ya. Neiland and G. Ya. Vanag, Usp. khim., **28**, 436, 1959.

7. O. Ya. Neiland, in collection: Cyclic β-Diketones [in Russian], Izv. AN Latv. SSR, **41**, Riga, 1961.

8. K. Nakanishi, Infrared Spectra and the Structures of Organic Compounds [Russian translation], IL, Moscow, 64, 1965.

9. L. J. Bellamy, The Infrared Spectra of Complex Molecules [Russian translation], IL, Moscow, 425, 1963.

10. V. V. Perekalin and K. S. Parfenova, ZhOKh, **30**, 388, 1960.

11. H. Stetter and K. Hockne, Chem. Ber., **91**, 1344, 1958.

12. V. A. Tartakovskii, B. G. Gribov, I. A. Savost'yanova, and S. S. Novikov, Izv. AN SSSR, OkhN, 1644, 1965.

13. L. A. Mironov, A. D. Miroshnichenko, R. P. Evstigneeva, and N. A. Preobrazhenskii, KhGS [Chemistry of Heterocyclic Compounds], 74, 1965.

14. I. N. Nazarov and S. I. Zav'yalov, ZhOKh, **25**, 508, 1955.

15. K. Bauer, Analysis of Organic Compounds [Russian translation], IL, Moscow, 156, 1953.

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