UDC 547.74 + 542.95

SYNTHESIS OF CHALCONE ANALOGS CONTAINING A PYRROLE RING

S. V. Tsukerman, V. P. Izvekov, and V. F. Lavrushin

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 1, No. 4, pp. 527-530, 1965

Crotonaldehyde-type condensation in alkaline medium of 2-acetylpyrrole or pyrrole-2-aldehyde with aromatic or heterocyclic aldehydes and methyl ketones gives a number of hitherto undescribed pyrrole analogs of chalcone, and their 2, 4-dinitrophenylhydrazones are prepared.

The first pyrrole analog of chalcone, 1-(pyrryl-2')-3-phenylpropene-3-one, was prepared by crotonaldehyde-type condensation of 2-acetylpyrrole with benzaldehyde [1]. An isomer of it, corresponding to the propene-1-one-3, mp 138-139°, was similarly synthesized by E. Lyubrzhinskaya [2], from pyrrole-2-aldehyde and acetophenone; subsequently this compound was stated to have mp 133-134° [3]. Some derivatives of 1-(pyrryl-2')-3-phenylpropenes with p-methyl, p-methoxy, m- and p-nitro, p-dimethylamino groups and certain other substituents have been described [4, 5]. At present analogs of chalcone with the pyrrole nucleus and the furan and thiophene rings all present simultaneously, are known [6-8]. Papers by A. Ponomareva relate to synthesis of vinylogous pyrrole analogs of chalcone [9].

The present aim was systematic synthesis of a series of chalcone analogs, containing the pyrrole ring and having the carbonyl group in various positions, with a view to further study of their spectral characteristics, halochromic properties, physiological action, etc. The route chosen for preparing the requisite α, β-unsaturated ketones was crotonaldehyde condensation of 2-acetylpyrrole or pyrrole-2-aldehyde with the appropriate aromatic or heterocyclic aldehydes, and methyl ketones, the equations being

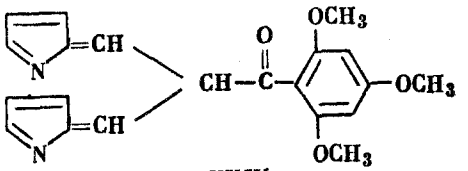
I, III, V, VII, IX, XI, XIII, XV, XVII, XIX, XXI, XXII

II, IV, VI, VIII, X, XII, XIV, XVI, XVIII, XX, XXI, XXIII

R = phenyl (I, II), 4-methylphenyl (III, IV), 4-chlorophenyl (V, VI), 4-nitrophenyl (VII, VIII), 4-methoxyphenyl (IX, X), 2, 4-dimethoxyphenyl (XI, XII), 4-dimethylaminophenyl (XIII, XIV), 4-diphenylyl (XV, XVI); 2-furyl (XVII, XVIII), 2-thienyl (XIX, XX), 2-pyrryl (XXI), and 2-quinolyl (XXII, XXIII).

Reaction proceeds readily in aqueous alcohol, on adding a few drops of alkaline condensing catalyst, 10% sodium hydroxide, and only in a few cases was it necessary to reflux for 2-15 hr.

It was also desired to prepare the product of crotonaldehyde condensation between 2-pyrrole aldehyde and 2, 4, 6-trimethoxyacetophenone. However, despite attempts to prepare it under various conditions, among them in glacial acetic acid containing acetic anhydride [10], it proved impossible to isolate the corresponding chalcone analog. Prolonged refluxing (15 hr) of the reactants in alkaline medium gives a crystalline product whose elementary analysis is that of a compound formed by reaction of two molecules of the pyrrole aldehyde with one of 2, 4, 6-trimethoxyacetophenone. It is known that pyrrole-2-aldehyde can react in the hydroxymethylene form [2], and it was recently shown [8] that this latter form with 2-hydroxyacetophenone gives a product from 2 molecules of aldehyde and one molecule of ketone, so that by analogy the compound here obtained is assigned the structure 1, 3-di(pyrrylidene-2')-2-(2", 4", 6"-trimethoxybenzoyl)-propane (XXIV).



XXIV

It is of interest that, as was shown by two of the present authors, 2, 4, 6-trimethoxyacetophenone does not undergo crotonaldehyde condensation with 5-nitro-2-thiophene aldehyde [10] or 5-nitrofurfural [11]. Apparently this is connected with an accumulation of methoxy groups in the acetophenone molecule affecting its reactivity. It may be mentioned that crotonaldehyde condensation could not be effected between 2-acetylpyrrole and 2, 4, 6-trimethoxybenzaldehyde.

Table 1

Pyrrole Analogs of Chalcone

Compound no.	Mp, °C	Ketone form and color	Formula	N, %		Yield, %
				Found	Calc.	
I	141*	Colorless parallelepipeds	$C_{13}H_{11}NO$	—	—	76
II	134*	Green plates	$C_{13}H_{11}NO$	—	—	73
III	156*	Colorless plates	$C_{14}H_{13}NO$	—	—	95
IV	160	Yellowish-green prisms	$C_{14}H_{13}NO$	6.70; 6.82	6.63	70
V	161,5	Colorless needles	$C_{13}H_{10}ClNO$	6.03; 6.02	6.06	70
VI	183	Yellow plates	$C_{13}H_{10}ClNO$	6.32; 6.09	6.06	97
VII	207*	Green parallelopipeds	$C_{13}H_{10}N_2O_3$	—	—	86
VIII	193	Orange needles	$C_{13}H_{10}N_2O_3$	11.80; 11.75	11.55	50
IX	138*	Colorless needles	$C_{14}H_{13}NO_2$	—	—	53
X	167	Yellowish-green plates	$C_{14}H_{13}NO_2$	6.13; 6.27	6.16	50
XI	114	Yellowish-green cubes	$C_{15}H_{15}NO_3$	5.20; 5.16	5.44	60
XII	126	Dark green needles	$C_{15}H_{15}NO_3$	5.51; 5.20	5.44	41
XIII	205*	Yellow prisms	$C_{15}H_{16}N_2O$	—	—	30
XIV	207	Yellow needles	$C_{15}H_{16}N_2O$	11.75; 11.75	11.66	25
XV	190	Colorless prisms	$C_{19}H_{15}NO$	5.23; 5.12	5.12	36
XVI	208	Yellow needles	$C_{19}H_{15}NO$	5.23; 5.06	5.12	40
XVII	133*	Colorless prisms	$C_{11}H_9NO_2$	—	—	55
XVIII	169	Yellowish-green needles	$C_{11}H_9NO_2$	7.41; 7.41	7.48	53
XIX	154*	Green plates	$C_{11}H_9NOS$	—	—	75
XX	149*	Orange prisms	$C_{11}H_9NOS$	—	—	90
XXI	172**	Yellowish-green plates	$C_{11}H_{10}N_2O$	—	—	30
XXII	250	Colorless plates	$C_{16}H_{12}N_2O$	11.44; 11.16	11.25	95
XXIII	189	Yellow needles	$C_{16}H_{12}N_2O$	11.18; 11.15	11.25	72

*In the main the mp corresponds to the literature values [1-8].

**Mp 153° after recrystallizing from aqueous methanol.

All the pyrrole analogs of chalcone prepared in the course of the present work (see Table 1) are solids which crystallize well, and which are usually soluble in alcohol, sparingly soluble in ether and benzene, and insoluble in water. They all have halochromic properties, and in 15% sulfuric acid-glacial acetic acid darken to an orange-reddish-violet color, while solutions in sulfuric acid resinify in time.

2-4-Dinitrophenylhydrazones of the pyrrole chalcones form with difficulty when prepared by the usual methods [12, 13], the ketones resinifying rapidly in acid, so that in some cases they could not be obtained (see Table 2).

Table 2

2, 4-Dinitrophenylhydrazones of Ketones

Compound no.	Mp, °C	λ_{max}, mμ*	Formula	N, %	
				Found	Calculated
I	230	432	$C_{19}H_{15}N_5O_4$	18.70; 18.69	18.56
II	256	435	$C_{19}H_{15}N_5O_4$	18.73; 18.75	18.56
III	236	435	$C_{20}H_{17}N_5O_4$	18.05; 17.95	17.90
VII	236	434	$C_{19}H_{14}N_6O_6$	20.01; 19.65	19.90
IX	234	444	$C_{20}H_{17}N_5O_5$	17.34; 17.23	17.19
X	214	434	$C_{20}H_{17}N_5O_5$	17.23; 17.06	17.19
XI	232	440	$C_{21}H_{19}N_5O_6$	16.11; 15.90	16.05
XVII	235	434	$C_{17}H_{13}N_5O_5$	18.70; 18.58	18.56
XIX	243	434	$C_{17}H_{13}N_5O_4S$	18.33; 18.27	18.27

*Measured in chloroform solution, with a SF-2M spectrophotometer.

Experimental

Pyrrole-2-aldehyde was prepared by the method of [14], mp 44-45°, and 2-acetylpyrrole was prepared by the method of [15], mp 90°.

Crotonaldehyde condensation. Equimolecular quantities of the appropriate aldehyde and methylketone (0.01 mole) were dissolved in a minimum amount of methanol (5-30 ml), and a 10% solution (1.5-4 ml) of sodium hydroxide slowly dropped in. The resultant solution was left for a few hours at room temperature. The crystalline precipitate formed was filtered off, washed with water containing alcohol, and recrystallized from methanol, aqueous methanol, or benzene to constant melting point. With ketones XIII, XIV, XV, and XVI, refluxing for 2-15 hr was used in condensation.

2, 4-Dinitrophenylhydrazones of ketones I-III, XI, XVII were prepared by the method of [12], those of ketones VII, IX, X, XIX, by the method of [13] and they were recrystallized from benzene, chlorobenzene, or chloroform.

1, 3-Di(pyrrylidene-2')-2-(2", 4", 6"-trimethoxybenzoyl)propane (XXIV) was prepared similarly to XVI. Yield 20%, yellow, long needles, mp 226° (from alcohol). Found: N 7.60, 7.90%. Calculated for $C_{21}H_{20}N_2O_4$: N 7.69%.

REFERENCES

1. G. Ciamician and M. Denstendt, Gazz. Chim. ital., 15, 12, 1885.
2. E. Lyubrzhinskaya, ZhRFKhO, 49, 244, 1917.
3. W. Herz and J. Brasch, J. Org. Chem., 23, 1513, 1958.
4. H. Fischer, H. Beyer, and E. Zaucker, Ann. chim., 486, 55, 1931.
5. N. Maxim and J. Copuzeanu, Bull. Soc. Chim., 5, 3, 2251, 1936.
6. C. Finzi and E. Vecchi, Gazz. Chim. ital., 47, 11, 10, 1917.
7. J. Tirouflet and A. Corvaisier, Compt. Rend., 250, 1276, 1960.
8. A. Corvaisier, Bull. Soc. Chim., 528, 1962.
9. A. A. Ponomarev, Z. V. Til, and V. V. Zelenkova, ZhOKh, 20, 1085, 1950.
10. S. V. Tsukerman, V. M. Nikitchenko, and V. F. Lavrushin, ZhOKh, 32, 2328, 1962.
11. V. F. Lavrushin, S. V. Tsukerman, and A. I. Artemenko, ZhOKh, 32, 1331, 1962.
12. W. Johnson, R. Shennan, and R. Reid, Organic Reagents for Organic Analysis [Russian translation], IL, Moscow, 1948.
13. G. D. Johnson, J. Am. Chem. Soc., 73, 5888, 1951.
14. R. M. Silverstein, E. E. Ryskiewiez, C. Willard, and R. C. Kochler, J. Org. Chem., 20, 668, 1955.
15. G. N. Dorofeenko, A. P. Kucherenko, and N. V. Prokof'eva, ZhOKh, 33, 586, 1963.

5 March 1964

Gor'kii Khar'kov State University