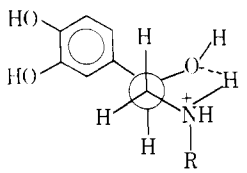
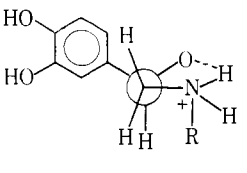
hydrogen bonded in a manner similar to the ephedrines. For example, epinephrine and norepinephrine might be expected to reside mainly in *gauche* or partially staggered conformations (VIII and IX, respectively). While the nonbonded interactions are



VIII



IX

minimized in VIII, the latter rotamer (IX) is also a possibility since the internal hydrogen bond in IX would be stronger due to the shorter distance between the donor proton and acceptor group. This could compensate for the greater steric interaction due to partial staggering. No significant partial eclipsing was observed in the ephedrines because of the severe interaction which would be created between the phenyl and methyl groups. Internal bonding may not only stabilize these amines in a conformation favorable to amine–receptor association, but also would render the hydroxylic proton more acidic and consequently promote stronger hydrogen bonding with the receptor.

The ephedrine isomers are known[2e] to show only very minor differences in central stimulant activity. It recently has been reported[38] that there is little, if any, direct action associated with these compounds. The fact that pipradrol possesses stereospecificity[39] and a high degree of direct action has led to the generalization[40] that the receptors involved in direct central action possess greater steric demands than do the sites associated with the release of endogenous catecholamines. Consequently, the conformational requirements for the indirect action of these compounds in the CNS may not be very critical.

(38) H. H. Wolf, D. E. Rollins, and C. R. Rowland, 114th Meeting of the A.Ph.A. Academy of Pharmaceutical Sciences, 1967, Abstracts, p 92.

Experimental Section

All spectra were obtained with a Varian A-60 nuclear magnetic resonance spectrometer at an operating frequency of 60 Mc/sec. Chemical shifts are considered accurate to ±0.02 ppm and the spin–spin coupling constants were within ±0.1 cps of the mean values reported. Each sample was run as a 10% (w/v) solution. The probe temperature was 37 ± 1°.

Ephedrine was obtained from a commercial source (Merck) as were ψ-ephedrine (Burroughs Wellcome) and *trans*-3-methyl-2-phenylmorpholine (Geigy). *cis*-3-Methyl-2-phenylmorpholine was prepared according to the method of Clarke.[21]

Acknowledgment.—The author is indebted to Mr. Kenneth Stenglein for preparing *cis*-3-methyl-2-phenylmorpholine and to Dr. Norbert Gruenfeld of Geigy Research Laboratories for supplying the *trans* isomer. This work was supported by Public Health Service Grant GM 09402 from the National Institute of General Medical Sciences.

(39) The term "stereospecificity" signifies that pharmacological activity resides only in one isomer, while "stereoselectivity" implies that activity is found predominantly in one isomer, though not exclusively. This definition is adapted from E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 436.

(40) P. S. Portoghese, T. L. Pazdernik, W. L. Kuhn, G. Hite, and A. Shafi'ee, *J. Med. Chem.*, in press.

Reaction of Cyclic β-Diketones with 3,4-Dihydroisoquinolines and Related Compounds. Preparation and Anticancer Activity of 2-Substituted 1,3-Cyclohexanediones

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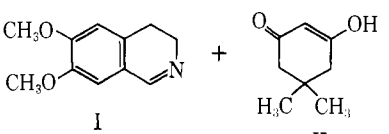
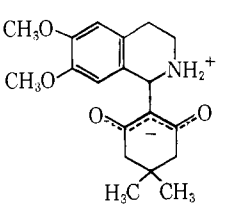
Received June 15, 1967

1,3-Cyclohexanediones add readily to 3,4-dihydroisoquinolines, 3,4-dihydro-β-carbolines, and quinazoline. Some of the resulting 2-substituted 1,3-cyclohexanediones are active in experimental tumor systems.

Recently, we have described a synthesis of benzo[*a*]-quinolizines[1] by the reaction of linear β-diketones with 3,4-dihydroisoquinolines. The present communication concerns the reaction of cyclic β-diketones with 3,4-dihydroisoquinolines and other partially reduced heterocyclic nuclei having an activated C=N function.[2] The reaction is characterized by rapid rate and high yields. For example, addition of 6,7-dimethoxy-3,4-dihydroisoquinoline (I) to dimedone (II) produced



I II



III

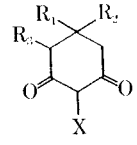
within seconds a crystalline precipitate of III in 95% yield. Compounds prepared by this method are summarized in Table I.

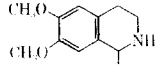
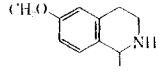
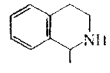
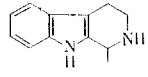
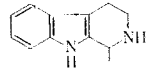
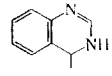
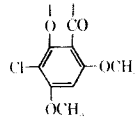
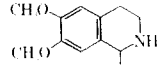
(1) M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., *J. Org. Chem.*, **31**, 797 (1966).

(2) Related reactions of corresponding carbinolamines such as cotarnine (1-hydroxy-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline) and hydrastine (1-hydroxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline) with compounds having activated methylene groups have been described by C. Liebermann and K. Kropf, *Ber.*, **37**, 211 (1904).

TABLE I

2-SUBSTITUTED 1,3-CYCLOHEXANEDIONES



Compd	R_1	R_2	R_3	X	M.p., °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
III·HCl	CH_3	CH_3	H		125–127	$C_{14}H_{20}NO_4^a \cdot HCl$	62.03	7.12	3.80	61.83	7.27	3.50
IV	CH_3	CH_3	H		192–196	$C_{15}H_{23}NO_3$	71.73	7.69	4.65	71.85	7.85	4.86
V	CH_3	CH_3	H		188–189	$C_{17}H_{21}NO_2$	75.24	7.80	5.16	75.07	7.90	4.88
VI	CH_3	CH_3	H		218–219	$C_{19}H_{22}N_2O_2$	73.52	7.14	9.02	73.50	7.41	8.84
VII	H	H	H		201–203	$C_{17}H_{18}N_2O_2$	72.32	6.43	9.92	72.05	6.62	9.99
VIII	CH_3	CH_3	H		156–158	$C_{16}H_{18}N_2O_2 \cdot C_2H_5OH$	68.33	7.65	8.85	68.40	7.60	8.70
IX·HCl	CH_3	H			152 dec	$C_{17}H_{23}NO_5Cl^b \cdot HCl \cdot 0.5C_2H_5OH$	57.40	5.58	2.35	57.19	5.83	2.18

[a] *Anal.* Calcd: Cl, 9.64. Found: Cl, 9.39. [b] *Anal.* Calcd: Cl, 11.89; Cl^-, 5.94. Found: Cl, 11.74; Cl^-, 5.72.

TABLE II

RESULTS OF THE TISSUE CULTURE[a] SCREENING FOR CYTOLOGICAL EFFECTS (CCNSC TEST NUMBER 520D)[4]

Compd	ED_{50}, $\mu g/ml$[b]	Slope[c]	ALD_{50}[d]
III·HCl	18.0	...	>1000
IV	17.0	−0.81	...
V	27.0	−0.84	>1000
VI	2.8	−0.88	>1000
	3.5	−1.26	
	5.6	−1.62	
	2.2	−0.94	
VII	1.0	−0.62	>1000
	4.0	−0.97	
VIII	59.0	−0.49	>1000

[a] KB cell culture. [b] Dose that inhibits growth to 50% of control. [c] Change of response for each tenfold change of dose. [d] Approximate LD_{50} (mg/kg *po* in mice) determined at Warner-Lambert Research Institute.

TABLE III

EVALUATION OF III·HCl[a] AGAINST HUMAN SARCOMA (HS1) GROWN IN EMBRYONATED EGGS (CCNSC TEST CODE 8-H1)[4]

Dose, mg/egg	Survivors	T/C, %[b]	Stage index[c]	Status
20	00/06			Toxic test
5	03/06			Toxic test
5	06/06	24	0.24	Stage 1
5	04/06	85	0.20	Stage 2
5	02/06			Toxic test
5	05/06	28	0.05	Stage 3
5	05/06	5	0.05	Confirmation
5	04/06	50	0.55	2nd confirmation
5	05/06	23	0.78	Activity confirmed (Av T/C = 26%)

[a] 1-(4,4-Dimethyl-2,6-dioxo-1-cyclohexyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride. [b] Ratio of tumor weight in test animals to that in control animals. [c] Cumulative product of T/C values (expressed as decimals) through sequential screen (stage 1–3) and cumulative sum of T/C values (expressed as decimals) through the three confirmation tests. Compound is considered active when stage index is $\leqq 0.63$ at stage 1, $\leqq 0.19$ at stage 2, $\leqq 0.08$ at stage 3, and the average of the three successive confirmation tests is T/C $\leqq$ 42%.

The zwitterionic structure of the products, as represented by III, is supported by the relatively high melting points, low solubility in ethanol, and spectral data. The infrared spectra are devoid of the typical carbonyl bands. Instead, intense, broad bands are visible in the 1480–1510-cm^{-1} area and bands of weak to medium strength in the 1570–1590-cm^{-1} region. In contrast, the spectrum of III·HCl shows a broad carbonyl band at 1610 cm^{-1} which is characteristic of the enolized β-diketone such as dimedone. The nmr spectra display a four-proton singlet at 2.1 ppm indicating that the methylene groups next to the carbonyl are equivalent.

Anticancer Evaluation.—Literature reports[3] on anticancer properties of 2-substituted 1,3-cyclohexanediones suggested an evaluation of our compounds in experimental tumor systems. The test results provided by the Cancer Chemotherapy National Service Center (CCNSC) are summarized in Tables II and III.

In tissue culture[4] the β-carboline derivatives VI and VII showed limited activity. Compound VI passed the two-stage testing system and the confirmation test. While these tests were being conducted, the criteria were tightened to select only materials with $ED_{50} \leqq 1$ $\mu g/ml$. This resulted in termination of further evaluation of VI and VII. Compound III·HCl, found inactive in tissue culture, displayed activity in tests against human sarcoma (HS1) grown in eggs (code 8-H1).[4] Since III·HCl passed the sequential screen and the three confirmation tests, it was placed on the list of potential candidates for further preclinical evaluation. However, III·HCl was assigned a low priority because of its lack of activity against leukemia L1210, Dunning leukemia, lymphosarcoma P1798, and because of the seemingly poor correlation between the activity in the 8-H1 system and clinical usefulness.[5]

The griseofulvin derivative IX·HCl was inactive *in vitro* against *Staphylococcus aureus*, *Escherichia coli*, *Proteus vulgaris*, *Candida albicans*, and *Trichophyton mentagrophytes*.

Experimental Section

Melting points were determined using the Thomas–Hoover capillary melting point apparatus which was calibrated against known standards. The ultraviolet and infrared spectra were obtained, respectively, with a Beckman DK-1 spectrophotometer and a Baird Model 455 double-beam instrument. Unless otherwise stated, the former were determined as solutions in 95% EtOH and the latter as Nujol mulls.

General Procedure.—Ethanolic solutions of 0.1 mole of base and 0.1 mole of diketone were combined and heated on steam bath for 5–20 min. The crystalline precipitate (85–95% yield) was filtered off and recrystallized from ethanol.

Compound III·HCl was obtained in 90% yield by recrystallization of 2 g of III from 20 ml of 2 *N* HCl.

Griseofulvic acid[6] was used as the starting material for IX. Compound IX·HCl was obtained in 50% yield by dissolving IX in ethanolic HCl, concentrating *in vacuo*, and crystallizing the glassy residue from 2-propanol. The physical constants and analytical values are reported in Table I.

Spectral data for compounds III–IX·HCl are as follows: III·HCl, λ_{max} ($m\mu$ (ϵ)) 228 (10,500), 280 (18,900); ν_{max} 720 (mw), 785 (mw), 825 (mw), 865 (m), 975 (mw), 1015 (ms), 1095 (m), 1120 (ms), 1195 (ms), 1230 (s), 1260 (s), 1310 (ms), 1515 (ms), 1610 (s) cm^{-1}; IV, λ_{max} ($m\mu$ (ϵ)) 225 (10,750), 281 (22,600); ν_{max} 840 (ms), 1002 (m) 1140 (ms), 1240 (ms), 1500 (s), 1580 (m), 1590 (m), 1651 (m) cm^{-1}; V, λ_{max} ($m\mu$ (ϵ)) 281 (19,400); ν_{max} 745 (m), 1005 (m), 1140 (ms), 1260 (ms), 1500 (s), 1570 (m), 1585 (m) cm^{-1}; VI, λ_{max} ($m\mu$ (ϵ)) 223 (34,100), 279 (26,100); ν_{max} 745 (ms), 905 (mw), 1010 (mw), 1085 (m), 1145 (m), 1175 (m), 1225 (m), 1265 (ms), 1310 (m), 1415 (m), 1495 (vs) cm^{-1}; VII, λ_{max} ($m\mu$ (ϵ)) 227 (33,500), 276 (29,200); ν_{max} 735 (m), 870 (w), 995 (mw), 1090 (mw), 1140 (m), 1170 (ms), 1225 (mw), 1300 (ms), 1490 (s), 1580 (m), 3300 (mw) cm^{-1}; VIII, λ_{max} ($m\mu$ (ϵ)) 220 (22,200), 280 (23,400); ν_{max} 750 (ms), 1035 (m), 1145 (m), 1255 (ms), 1585 (m), 1630 (m), 1670 (ms), 3150 (m) cm^{-1}; IX·HCl, λ_{max} ($m\mu$ (ϵ)) 232 sh (23,000), 289 (38,250); ν_{max} 1510 (m), 1590 (ms), 1610 (s), 1650 sh (m), 1700 (m) cm^{-1}.

Acknowledgment.—We wish to thank the Cancer Chemotherapy National Service Center (CCNSC) for the anticancer evaluation and the test data. We are indebted to Mr. A. Lewis and his associates, Mrs. U. Zeek and Mr. R. Puchalski, for analytical and spectral data. We wish to express our gratitude to Dr. A. W. Ruddy and his associates, Messrs. F. McMillan, J. Genzer, G. Conrad, and R. Novack, for large-scale preparation of starting materials.

(3) (a) T. Ukita, Y. Kato, M. Honi, and H. Nishizawa, *Cancer Chemotherapy Rept.*, **13**, 211 (1961); (b) P. E. Papadakis and G. Haven, *J. Pharm. Sci.*, **55**, 1016 (1966).

(4) For detailed description of the test procedures see *Cancer Chemotherapy Rept.*, **25**, 1 (1962).

(5) Private communication by J. M. Venditti, Asst. Chief, Drug Evaluation Branch, CCNSC, National Cancer Institute.

(6) A. E. Oxford, H. Raistrick, and P. Simonant, *Biochem. J.*, **33**, 240 (1939).